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Optical microscopy: the resolution revolution

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Throughout the 20th century it was widely accepted that a light microscope relying on conventional optical lenses cannot discern details that are much finer than about half the wavelength of light (200-400 nm), due to diffraction. However, in the 1990s, the viability to overcome the diffraction barrier was realized and microscopy concepts defined, that can resolve fluorescent features down to molecular dimensions. In this lecture, I will discuss the simple yet powerful principles that allow neutralizing the limiting role of diffraction^{1,2}. In a nutshell, feature molecules residing closer than the diffraction barrier are transferred to different (quantum) states, usually a bright fluorescent state and a dark state, so

that they become discernible for a brief period of detection. Thus, the resolution-limiting role of diffraction is overcome, and the interior of transparent samples, such as living cells and tissues, can be imaged at the nanoscale.

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Biosensors – towards frictionless management of health

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A frictionless approach to health management would empower users with the data and information they require to efficiently manage their health anywhere and anytime, while providing them with confidence in the integrity of data and the security of any automated actions. Implicit in this vision is the ability to supplement advanced information management with real-time measurements of both individuals and their immediate environment. The recent boom in wearable sensors may not have delivered the consumer revolution that investors had hoped for, but it has highlighted the potential of continuous measurement and the appetite amongst users for personalized information. Arguably, the major bottleneck at the current time is the availability of reliable sensors that directly measure key biochemical parameters. Most current devices have ingeniously exploited physical sensors that were readily available and used these to infer relevant secondary information. Chemical sensors and biosensors present greater challenges in sample acquisition, but the direct molecular information that they can deliver is essential to higher level algorithms for personalised management of health.

Biosensors, as classically defined, incorporate biological or biologically derived sensing elements that harness the exquisite specificity and sensitivity of living systems in conjunction with electronic transducers and processors, to either provide data or to directly actuate an appropriate response. The most powerful example to date, has been the evolution of the artificial or “bionic” pancreas. Enzyme electrodes were first successfully launched commercially in decentralised analyzers in 1975, and then for use by people with diabetes in their home in 1987. The first wearable continuous glucose monitors appeared in 2005. In 2012, some degree of automation was approved, first in Europe and then USA, allowing the biosensors to be used to shut off insulin delivery from an insulin pump to reduce the risk of hypoglycaemia. On 28th September 2016, Medtronic announced that it had received FDA approval for the world’s first closed loop insulin delivery system, the MiniMed 670G™, which became available in the USA under a limited access program in Spring 2017. This automatically adjusts the delivery of basal insulin in response to a subcutaneous glucose sensor.

While glucose biosensors have been the highest profile success so far, they are far from the only example and biosensors have been widely commercialized for use in medicine, process monitoring, food quality control, environmental

monitoring, defence and law enforcement. A few years ago, one may have been forgiven for considering the area as a mature field with diminishing prospects for innovation. However, the recent convergence of thinking around the escalating cost of delivering healthcare, the opportunities offered by mobile health and the demand for more personalized medicine has reignited enthusiasm for novel interdisciplinary solutions based on biosensors. In addition, new areas have evolved where biosensors are now recognized to have a potential pivotal role such as in robotic surgery, tissue engineering and the production of biologics.

With the demand now so clearly in focus, the challenge is to harness the tens of thousands of research reports to hone products that can meet these needs. On the one hand, we now have technology that can probe single biomolecules and begin to unravel the natural heterogeneities that may be the key to many important biological questions [1]. Such new, inexpensive approaches will underpin new digital diagnostics, personalized medicine and fundamental biochemical research. Emerging advanced materials are providing tools to fabricate systems with improved performance [2,3], while areas such as printed electronics can show us the way to mass produce integrated systems at the right cost and with form factors that meet the rapidly evolving requirements for sensing interfaced with telecommunications [4,5]. The future importance of biosensors in clinical diagnostics, health management and research in the life sciences is clear and we need to bring engineers, clinicians and management together to implement effective ways forward.

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Relevance of multi-scale dosimetry for targeted radionuclide therapy optimization

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I. INTRODUCTION & AIM

Targeted radionuclide therapy (TRT), is the therapeutic field of nuclear medicine. TRT represents about 10% of Nuclear Medicine procedures in the EU, but is in expansion. In the past, TRT was essentially confined in the treatment of thyroid diseases with iodine 131. However, TRT is now increasingly been used, as new radiopharmaceuticals emerge in clinical practice (and are approved by regulatory agencies such as FDA or EMA).

At the basis of TRT is the identification of a vector that will specifically target a receptor on the target cell. If the vector is labelled with short-range radioactive isotopes, it is possible to concentrate radiation on the target whereas sparing surrounding tissues. Most often the isotope is a beta emitter, and therefore pronounced absorbed dose gradients can be observed within mm of the emission point, thereby insuring specific irradiation. There are examples of very short-range emitters used in the context of TRT: Alpha emitters or even Auger emitters have been proposed, and some (ex. Xofigo™) are on the market.

This presentation will present the current status of TRT, while promoting the role of the physicist in optimising the safety and efficacy of the procedure. Namely the relevance of dosimetry will be discussed, at various scales.

II. RELEVANCE OF DOSIMETRY IN TRT

The current status of TRT is that of “radioactive chemotherapy”, where patients are being given the same amount of drug (activity) in a “one size fits all” approach. Activity administration (in Bq, or Bq/kg) is defined after escalation “dose” clinical trials that assess the toxicity of the drug. However, most often the fact that a radiolabelled compound is being used means that it is possible to follow the fate of the radiolabelled vector in the patient. In addition, it has been demonstrated in most situation that the pharmacokinetics of a radiolabelled compound varies from a patient to another, thereby calling for patient-specific administrations of the drug.

The biological effect of procedures involving ionizing radiation can be evaluated in the light of the energy delivered to the tissues. The absorbed dose (energy/unit mass, in J/kg or Gy) is an objective index of the irradiation pattern. The relevance of dosimetry in TRT relies on the assumption that an absorbed dose – effect relationship (ADER) can be put in evidence and used to monitor and optimise therapy.

In 2014 the EANM dosimetry committee reviewed published ADER evidences¹. Conclusions were that:

- ADER can be found whenever they are looked for in a rational way.
- Absorbed dose calculation is only one side of the ADER. The biological/clinical end-point should be carefully designed.
- There is no and there won't be a generic clinical dosimetry procedure. “Dosimetry that works” is disease/application specific.
- Assessing errors and uncertainties is the current new frontier in radiopharmaceutical dosimetry.

However, an important point to consider is that ADERs should be looked for at various scales, as the clinical observation (at the scale of the tissue or organ) derives from phenomena that occur at the microscopic scale (cellular or even infra-cellular). Approaches that are able to give account of ADERs at various scales are therefore needed².

CONFLICT OF INTEREST

M Bardiès is a consultant for IPSEN, BTG and Roche

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Organ-on-a-Chip: merging microfluidics with analytics to transform *in vitro* technology

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Engineering cellular microenvironments that more accurately reflect the *in vivo* situation is now recognized as being crucial for the improvement of the *in vitro* viability and *in vivo*-like function of cells or tissues. Microfluidic technologies have been increasingly applied since the late 1990's for this purpose, with a growing number of examples of perfused cell and tissue cultures in microfluidic chambers and channels. The well-defined solution flows provided by microfluidics mean enhanced cell growth and function through improved nutrient delivery and waste removal. Additional benefits include the implementation of well-defined temporal and spatial (bio)chemical gradients, and mechanical signals that cells experience in their natural environment. Because the ability to culture cells and tissue under such controlled conditions leads to cellular function that is distinctly more organ-like, the microfluidic systems used are now referred to as "organs-on-a-chip" or "microphysiological systems".

Reported organ-on-a-chip systems are as diverse as the biological models they have been designed to study. Most examples are based on cell culture models, which involve seeding cells into a chip with the eventual formation of a 2D or 3D tissue-like structure. The biological approach in these cases could be regarded as "bottom-up". Less common are the "top-down" biological approaches, in which organotypic tissue samples are directly obtained from mammals or human subjects for further study. Regardless of biological model, there is an inherent need in these systems to monitor cell growth and behaviour under controlled conditions.

This presentation will focus on examples from our labs in which we have designed "top-down" and "bottom-up" organ-chips incorporating means to both monitor culture conditions and quantify cell behaviour. In a "top-down" example, a microfluidic device was designed for perfusion culture of precision-cut organ slices. Metabolic studies employing precision-cut liver slices and on-line HPLC analysis were successfully demonstrated with this device, as was a multi-

organ slice experiment showing regulation of bile acid synthesis in the liver by the intestine.

Our "bottom-up" example constitutes the culture and investigation of primary human endothelial cells in microfluidic devices. Here we present a new approach for real-time, non-invasive, label-free monitoring of cellular micromotion in endothelial cell cultures. Cells are cultivated in a microcuvette formed by etching through the silica and waveguiding layers of a solid-state device. Light (638 nm) is directly coupled into the cell monolayer from an integrated waveguide, and forward-scattered light is recorded as a measure for cellular micromotion. Motion behaviour could serve as a readout for changes in the cytoskeleton caused by various chemical and physical factors. Observation of cytoskeletal changes indicative of inflammatory status using this approach could therefore prove useful for the investigation of the role of endothelial cells in the onset of cardiovascular diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Light emitting fabric for photodynamic therapy

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I. INTRODUCTION & AIM

Light delivery is one of the major concerns in PDT (Photodynamic Therapy). However, commercial light sources used for the photodynamic treatment of skin lesions for example are usually planar while the surfaces to be treated are mainly curvy. The integration of Side Emitting Optical Fibers (SEOF) into flexible fabric structures by knitting or weaving processes is a way to overcome the lack of homogeneity of the light distribution in PDT. Since 2011, our group develops Light Emitting Fabric (LEF) [1]. This paper aims to present the last developments and some examples of clinical applications of this innovative light source.

II. METHODS

LEF are made of polyester yarn and require 37 Plastic Optical Fibres/cm. LEF does not need any pre or post treatment of optical fibers because the weaving parameters provide the diffusion of light. LEF can be connected to any laser source and consequently can deliver light from 350 nm up to 1200 nm. Irradiance up to 50 mW/cm² can be delivered without any temperature elevation of the LEF.

III. RESULTS & DISCUSSION

A specific device based on LEF (FLEXITHERALIGHT®) and dedicated to the treatment of AKs of the scalp by PDT was developed. Thanks to the extreme flexibility, it was possible to design a cap fitting totally with the scalp. Both ends of optical fibers were gathered into metallic connectors and illuminated by a 635 nm light source. Its efficiency have been assessed in a comparative, randomized (split intra individual), phase II study which aimed to compare the clinical results obtained with a conventional LED panel to those obtained with the FLEXITHERALIGHT® device. The clinical results clearly show that the FLEXITHERALIGHT® device was at least as effective as the conventional LED panel, but with pain scores similar to those experienced by patients during PDT with daylight [2]. Similarly, it was possible to use this new technology to treat vulvar Paget's disease with PDT

[3]. A dedicated LEF has been designed, flexible and adaptable to the vulvar anatomy. The LEF was connected to a laser (635nm) with an irradiance of 6 mW/cm² during 1h43 minutes to deliver the total light dose recommended of 37 J/cm²

IV. CONCLUSIONS

The extreme flexibility ensures to LEF to fit with non-planar anatomical surfaces, such as the scalp, and corporal extremities without any impact on light delivery and proves that LEF can adapt to the human morphology. A LEF production has been realized using an adapted textile-weaving loom, which enables relatively easy scale up (no size limitation for length). Large (500 cm²) LEF could be used in peritoneal or pleural cavities. They could be a cheap alternative as light source for PDT.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Smartphone-based digital phenotyping

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I. INTRODUCTION & AIM

Recent advances in biomedicine and technology are beginning to change the priority in biomedical research towards phenotyping, which refers to the collection and analysis of various traits of organisms, such as their anatomy, enzyme activity, and behavior. Many investigators have promoted the role of large-scale phenotyping as the natural complement to genome sequencing as a route to advances in biomedical sciences, but behavior continues to present special challenges to phenomics because of its temporal nature and context dependence. We believe that the ubiquity and capability of smartphones to collect social and behavioral data can contribute to the phenotyping challenge via objective measurement, especially in neuropsychiatric conditions. We have defined *digital phenotyping* as the “moment-by-moment quantification of the individual-level human phenotype *in situ* using data from personal digital devices,” in particular smartphones [1, 2]. The collected data, when coupled with appropriate data analysis methods, enable the study of behavioral patterns, social interactions, physical mobility, gross motor activity, and speech production among other phenotypes.

II. METHODS

We have developed a research platform, called Beiwe, for smartphone-based high-throughput digital phenotyping. The Android and iOS smartphone apps that constitute the front-end of the configurable platform collect various types of active data, such as surveys and audio diary entries, and passive data, such as GPS and accelerometer data in their raw (unprocessed) form. The Beiwe back-end, which is based on Amazon cloud computing infrastructure—making it both scalable and globally accessible—collects, stores, and processes the collected data.

III. RESULTS & DISCUSSION

I will provide an overview of our Beiwe platform for smartphone-based digital phenotyping and the associated

data analysis pipeline. I will also share some results from our ongoing studies. While smartphone-based data collection is getting easier, digital phenotyping in biomedical and clinical research requires research quality data, which is a considerably higher standard than those used in most wellness and mHealth applications. In a typical study, approximately 1GB of data is collected per patient-month, although the volume of collected data depends entirely on the data collection settings, which themselves are driven by specific scientific questions. The high-dimensional and longitudinal nature of the data emphasizes the need for novel statistical and computational methods, development of which is our current research focus. Briefly, the Beiwe pipeline converts raw smartphone sensor and usage data into daily summary statistics, which can then be investigated further in a supervised or unsupervised learning context. In the former, a typical goal might be to associate passively collected smartphone data with clinical or patient-reported outcomes of interest, such as GPS-based mobility of brain tumor patients as a function pain levels surrounding surgery. In the latter, a typical goal might be to detect social and behavioral anomalies in neuropsychiatric patients, which can sometimes be so subtle that they remain unnoticeable to patients themselves.

ACKNOWLEDGMENT

The author is grateful to all colleagues and collaborators who have contributed to our ongoing efforts in smartphone-based digital phenotyping.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Bio-responsive hybrid materials for regenerative medicine and biosensing

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Bio-responsive hybrid materials are of growing importance with potential applications including drug delivery, diagnostics and tissue engineering. A disagreeable side effect of longer life-spans is the failure of one part of the body – the knees, for example – before the body as a whole is ready to surrender. The search for replacement body parts has fuelled the highly interdisciplinary field of tissue engineering and regenerative medicine. This talk will describe our research on the design of new hybrid (nano)materials and nanomaterials to direct stem cell differentiation for regenerative medicine. We have also designed and developed porous silicon “nanoneedles” capable of efficiently, rapidly and safely delivering sensitive

biocargoes to cells and tissues *in vivo* as well as interfacing with cells to inform intracellular pH and high-resolution demarcation of tumorous region boundaries. This talk will also provide an overview of our recent developments in the design of materials for ultrasensitive biosensing. We are applying these nanomaterial-based approaches both in high throughput drug screening and to diagnose diseases ranging from cancer to global health applications.

CONFLICT OF INTEREST

Prof Stevens holds several patents in the area of biomaterials for regenerative medicine and nanoparticle-based diagnostics.

Stimulating and measuring the human brain

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I. INTRODUCTION

The weak electric currents that mediate neuronal signaling can be measured and manipulated by electromagnetic fields; this allows a bidirectional coupling to the brain. In transcranial magnetic stimulation (TMS), a strong magnetic pulse induces electric currents in the brain, changing transmembrane voltages and triggering action potentials in neurons. With navigated TMS (nTMS), one can selectively excite, inhibit, or modulate activity in small patches of the cortex. Less specific stimulation is possible with transcranial electrical stimulation (TES). Magnetoencephalography (MEG) is the opposite of TMS; electric currents due to neuronal activity is measured. MEG signals can be recorded by superconducting quantum interference devices (SQUIDs) extracranially. The corresponding electric measurement is called electroencephalography (EEG).

II. METHODS

We are taking the first steps toward electronically targeted brain stimulation, developing multi-locus TMS (mTMS). This allows feedback-controlled shifting of stimulated targets within milliseconds after responses measured from muscles or from the brain. To improve MEG, we are building a highly sensitive multi-SQUID device with which both the structure and function of the brain can be measured. Using the same SQUID sensors for concurrent recording of MEG and magnetic resonance imaging (MRI) signals, brain can be very accurately located.

III. RESULTS

We have demonstrated the necessary technology for multi-coil TMS (mTMS) with a two-coil device and electronics with fine control of the magnetic-field and the induced electric-field (E-field) waveform. The new device can electronically shift the locus of the stimulating E-field with delays below a millisecond. For the improvement of MEG, we have built a head-shaped MEG–MRI array and demonstrated its ability to measure both MEG and MRI signals. We have started work towards the next-generation MEG–MRI in the European BREAKBEN project and suggest that ultra-low-field MRI may enable the imaging of the current distribution in the human brain due to weak currents fed through the head

via scalp electrodes. This would allow the accurate determination of the conductivity values of tissues and lead to more accurate source determination.

IV. CONCLUSIONS

Electromagnetic stimulation and measurement techniques are undergoing major advances that will improve the accuracy and reliability of locating brain activity and will enable feedback-controlled brain stimulation paradigms that may be useful in neuroscientific research, in diagnostics, and in therapy.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The author is advisor and minority shareholder of Nexstim Plc.

Communication with neurons – new materials and new dimensions

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Electrical communication with neuronal systems enables us to both monitor and modulate function.

These abilities are important in studying disease development and perhaps developing innovative interventions. Such communication with stem cells provides avenues to control neuronal development.

In recent years the materials inventory available for such purposes has expanded dramatically. In particular, organic conductors have been shown to bring some unique attributes to this venture.

Here, we will use examples wherein organic conductors - either graphene or organic conducting polymers are used to stimulate and/or record activity from neuronal systems. The ability to influence stem cell development into neurons using these organic conductors will also be illustrated. Another intriguing finding is that organic conducting polymer platforms may inherently facilitate communications between neurons.

Neural systems are, of course, three dimensional so we will also explore the ability to create interconnected 3D structures containing neurons using 3D bioprinting. We will discuss our most recent advances in recording from and/or stimulating such structures.

We have come along way since the pioneering studies of Luigi Galvani.

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028 - Preliminary results of the Design and Construction of a low cost Humid chamber and Temperature Controller for a Fluorescent Microscope to study Biological Samples

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I. INTRODUCTION & AIM

In several biological experiments samples used to be kept at certain temperatures. One problem we faced when trying to study activated *Taenia solium* oncospheres under the microscope were that they get cold fast, thus we cannot observe their specific characteristics that appears only if maintained at 37 °C such as the secretion of vesicles [1]. Companies offer such incubator chambers but they are so expensive for us. Thus, we designed to build our own low cost system to perform our experiments.

II. METHODS

We used a Nikon Eclipse E600 fluorescent microscope. It has been designed and adapted a humid chamber with its electronic temperature controller.

For the chamber It has been used grease to fix the cover slip to the microscope slide and to maintain humidity in the biological sample between them. inside using a cover slide design

In order to kept the slide around 37 ± 1 °C, a Peltier we used that heat the microscope base and a temperature sensor coupled with a comparator circuit with hysteresis that switch on/off the Peltier cell.

In order to visualize internal proteases in oncospheres, the fluorogenic peptide z-Phe-Arg with and without E64 inhibitor were incubated with activated *Taenia solium* oncospheres.

III. RESULTS & DISCUSSION

We could identify in pictures under visible light and UV light certain fluorescent vesicles at the surface and inside *T. solium* oncospheres.

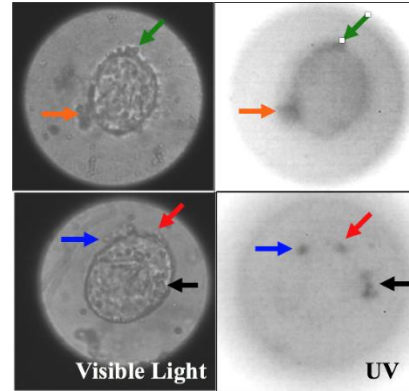


Figure 1 *T. solium* oncospheres vesicles with Cathepsin L-like activity.

IV. CONCLUSIONS

Our data provides preliminary results about the identification of specific proteases inside *Taenia solium* oncospheres compartments. More importantly, our preliminary data using E64 inhibitor identified for the first time that that cathepsin L-like proteases seems to be in oncospheres secretory vesicles.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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030 - 3D Laser printing of biomaterials and living cells

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For 3D printing of biomaterials and scaffold generation, we apply two-photon polymerization (2PP) technique, which allows writing CAD structures directly into the volume of photosensitive polymer solutions. The polymerization occurs in the laser focus only. Thereby, resolutions below the diffraction limit down to the sub-100-nanometer range have been achieved. Scaffolds from different biomaterials like organic-Inorganic Sol-Gel-Composites (e.g., zirconium-hybrids), biodegradable polymers (e.g., polylactic acid (PLA), polycaprolactone (PCL), polyethylene glycol (PEG)), and hydrogels (e.g., gelatin, hyaluronic acid, chitosan, alginate, gellan gum) or hydrogel blends, have been generated with this technique. The effect of the micro-structure on cell behavior will be discussed. For arranging cells in 3D patterns, laser-assisted bioprinting (LAB) based on the laser-induced forward transfer process is

used. Different cell types, including primary cells and stem cells embedded in hydrogels as extra-cellular matrix, have been printed. Thereby, 3D stem cell grafts, skin tissue, and cell patterns for studying cell-cell interactions have been generated.

Both 2PP and LAB techniques are capable of advancing 3D cell culture towards CAD defined and precisely arranged 3D cell models and “organ-on-chip” systems. Such innovative 3D cell models could provide new insights in understanding of cell behavior, tissue functions and their regeneration. Printed tissue, for example skin, can be used for analyzing the effect of agents like pharmaceuticals or cosmetics *ex vivo* and, by applying human primary cells, it might be applied instead of animal tests

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032 - Controlled release of exosomes by a photo-triggerable hydrogel enhances the healing in a diabetic wound animal model

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I. INTRODUCTION & AIM

Above 25 billion dollars are spent annually in complications related to chronic wounds. The incidence of this type of wounds is expected to increase dramatically in the coming years due to the increased incidence of diabetes and obesity, combined with the aging of the population. Advanced therapies to heal chronic wounds have been developed in the last years, including the use of topic growth factors (e.g. PDGF_{BB}) and cell-based therapies. In this last case, several studies indicate that cell-based therapies act by paracrine effect, i.e., by factors secreted by the cells. Unfortunately these advanced therapies show limitations because they are approved for certain chronic wound applications (e.g. PDGF_{BB}), they show low survival and engraftment (e.g. stem cells), and in most cases are very expensive. The hypothesis of this work is that vesicles secreted by cells, specifically exosomes, might have skin healing properties. However, to maximize its therapeutic effect we need to develop exosome controlled release systems.

II. METHODS

Exosomes were isolated from the conditioned media of human umbilical cord blood mononuclear cells by sequential ultra-centrifugation and characterized by DLS, Zeta potential, TEM and expression of surface markers.

III. RESULTS & DISCUSSION

Our *in vitro* results show that exosomes enhanced endothelial and keratinocyte survival under ischemic conditions, fibroblasts proliferation, fibroblast and keratinocyte wound healing rate in a scratch assay and endothelial tube formation in Matrigel. Importantly, exosomes administered daily in diabetic mice acute wounds accelerated significantly the healing of the

wounds. This therapeutic effect was confirmed in diabetic (type I and II) and non-diabetic mice. In case of exosomes administered in a single dose at the beginning of the treatment the healing was similar to the control condition (treated with PBS). Our results indicate that the bioactivity of exosomes was mediated by miRNAs because if we inhibit the miRNA processing machinery we loose their bioactivity. miRNA composition of the exosomes was further studied by RNA deep sequencing and qRT-PCR and the most important miRNAs validated by functional *in vitro* and *in vivo* tests.

To reduce the number of applications of exosomes in the wound, we have developed a photo-triggerable gel formed by hyaluronic acid (HA) crosslinked with a light-degradable linker. The controlled release of exosomes was demonstrated by exposing the hydrogel to sequential blue light irradiations of two minutes each. The release of exosomes increased while irradiating the gel and reached a plateau after 5 irradiations. The impact of a photo-triggerable gel to release exosomes was demonstrated in a diabetic type 1 full-thickness wound animal model. The significant acceleration of the wound closure was observed in early stages. After 5 days, while the control group still presented an open wound (96% wound area), the groups treated with HA gel + exo + light presented wound areas of 50%. Importantly, wounds treated with HA gel + exo + light, had superior healing as compared to the bi-daily treatment with exosomes. FRET studies indicate that the stability of exosomes in the gels is superior in the wound. In summary, a new platform to delivery therapeutic exosomes was successfully developed. Overall, our work developed for the first time an exosome delivery hydrogel for regenerative medicine, specifically in the context of wound healing.

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035 - Biodegradable and self-healing hydrogels with fast gelation as promising biomaterial for tissue engineering application

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I. INTRODUCTION

Chitosan is the second most abundant natural biopolymers and is an attractive biomaterial due to its excellent biocompatibility, biodegradability and antimicrobial properties [1]. However, the poor water solubility of raw chitosan at physiological pH (~7.4) hindered its further applications [2].

II. MATERIALS AND METHODS

In this work, we prepared a zwitterion water-soluble chitosan (WSC) by grafting a small anionic natural amino acid (L-glutamic acid) by a one-step EDC reaction [3]. Using this WSC as a base material (amino-group) together with aldehyde terminated star-PEG, the reversible (i.e. schiff-base linkages) cross-linked hydrogels were synthesized within ~<60 s, under ambient conditions [4]. The whole gel formulation does not need any external toxic catalyst and at the same time the hydrogel is injectable due to the dynamic nature of such linkages, thus being unique.

III. RESULTS AND DISCUSSION

The XRD/DSC characterization provide a proof for the decrease in the crystallinity of WSC chitosan after modification. Simultaneously the FTIR and NMR analyses indicated the successful grafting of amino acid through amide bond formation. Moreover, the hydrogels showed self-recovery ability during a mechanical compression testing at a specific crosslinker concentration and total solid mass (i.e. T ~1%). These hydrogel shows accelerated degradation during a month period in PBS at two different pH (i.e. 6.5 and 7.4).

The biocompatibility of these hydrogel systems was tested by live/dead assay of fibroblast cell culture for 3 days, which

shows good cytocompatibility. Therefore, these dynamic hydrogels can be a potential therapeutic agent for any kind of drug/protein delivery.

IV. CONCLUSIONS

Dynamic hydrogels obtained from renewable resources are attractive candidates of being inert and injectable, thus could provide a reasonable alternative for the delivery of therapeutic agents. Being degradable, the hydrogel would not leave any residual matter after achieving the targeting function i.e. the delivery of proteins or drugs. Hence, these hydrogel systems would be promising biomaterials for the delivery of growth factor or any other proteins to the cell.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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036 - Carbon nanofibers based wearable patch for bio potential monitoring

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We fabricated a wearable patch including novel patch type flexible dry electrode based on carbon nanofibers (CNFs) and silicone-based elastomer (MED 6215) for long-term bio potential monitoring. There are many methods to make flexible conductive polymer by mixing metal or carbon based nanoparticles. In this study, CNFs are selected for conductive nanoparticles because carbon nanotubes (CNTs) are difficult to disperse uniformly in elastomer compare with CNFs and silver nanowires are relatively high cost and easily oxidized in the air. Wearable patch is composed of 2 parts that dry electrode parts for recording bio signal and sticky patch parts for mounting on skin. Dry electrode parts were made by ultrasonic wave and baking in prepared mold. To optimize electrical performance and diffusion degree of uniformity, we developed unique mixing and baking process. Secondly, sticky patch parts were made by patterning and detaching from smooth surface substrate after spin-coating soft skin adhesive. In this process, attachable and detachable strength of sticky patch are measured and optimized them for using a monitoring system. Manufactured two parts are aligned and make a hole in center point of them. To connect easily with conventional signal processing system without any adapters, we insert conventional snap into the hole. Assembled patch is flexible, stretchable, easily skin mountable and connectable directly with system. To evaluate performance of electrical, mechanical and adhesive characteristics, wearable patch were tested by changing concentrations of CNFs and thickness

of dry electrode. The performances of electrodes were evaluated by using 9 types of electrodes with different concentrations of CNF and thickness. Also ECG (Electrocardiography) signals, motion artifact and sweat effect were tested by using 9 types of electrodes to evaluate performance of bio potential electrodes.

In this results, the CNF concentration and thickness of dry electrodes were important variables to obtain high-quality ECG signals without incidental distractions. Cytotoxicity test are conducted to prove biocompatibility and long-term wearing test showed no skin reactions such as itching or erythema. To sum up, we could fully utilize fabricated wearable for the long-term bio potential monitoring easily.

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CONFLICT OF INTEREST

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039 - In Silico Modeling Meets IPS Cardiac Cells: an Overview on Computational Methods for Drug Effect Assessment

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I. INTRODUCTION & AIM

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are a powerful tool for drug proarrhythmic risk assessment. Nevertheless, they presents challenges: i) *how similar is their response to drugs to adult cardiomyocytes?* or ii) *how to manage their electrophysiological variability?* We reply to these questions by (i) developing a hiPSC-CM *in silico* model, (ii) testing drug effects with comparison to adult models and (iii) creating a population of *in silico* hiPSC-CM models.

II. METHODS

We developed a biophysically-detailed hiPSC-CM *in silico* model calibrated on a set of patch-clamp data [1] and compared it to the O'Hara-Rudy model of human adult cardiac cell [2], upon the block of eight ionic currents. We then used an experimentally calibrated population of hiPSC-CM models to reproduce the action potential (AP) biomarker variability observed in experiments from different laboratories. Finally, we investigated how the phenotypical variability affects the hiPSC-CM responses to a strong (90%) block of the rapid delayed rectifying K^+ current (I_{Kr}), and the appearance of arrhythmogenic events.

III. RESULTS & DISCUSSION

Qualitatively, the hiPSC-CM and the adult cardiomyocyte models respond similarly to current blocks, consistently with experiments. Nonetheless, quantitatively, hiPSC-CMs are more sensitive to blocks of the L-type Ca^{2+} current (I_{CaL}) and of the inward rectifying K^+ current (I_{K1}). The hiPSC-CM *in silico* population covers the biomarker space derived by joining datasets from different laboratories, selecting 1463 models and

reproducing the experimental variability (e.g. $APD_{90} = 378 \pm 85$ ms, AP amplitude = 111 ± 9 mV). In response to I_{Kr} block, 838 models produce normal spontaneous AP, 115 generate early afterdepolarizations and 510 fail to repolarize. To assess the mechanisms underlying such behaviors, we compared the three classes and obtained significant differences for I_{CaL} , I_{Kr} , I_{K1} , the slow delayed rectifying K^+ current (I_{Ks}), the Na^+/Ca^{2+} exchanger (I_{NCX}) and the Na^+/K^+ pump (I_{NaK}).

IV. CONCLUSIONS

In silico hiPSC-CMs and adult cardiomyocytes exhibit a similar response to selective current blocks but greater sensitivity, which may facilitate the *in vitro* identification of drug-induced effects. Extrapolation of drug effects from hiPSC-CM to adult cardiomyocytes and proarrhythmic risk assessment can be facilitated by *in silico* predictions. In case of high experimental variability, a population of *in silico* hiPSC-CMs allows more comprehensive and realistic simulations of the hiPSC-CM response to drugs.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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047 - Honeycomb films in retinal tissue engineering

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I. INTRODUCTION & AIM

Honeycomb-like porous films can be prepared under the influence of a humid airflow by the breath figure (BF) method. Biodegradable honeycomb films hold great promise as semi-permeable scaffold materials for the transplantation of retinal pigment epithelial cells in patients suffering from degenerative eye diseases such as age-related macular degeneration (AMD) [1]. The aim of this work was to investigate the potential use of honeycomb films as semi-permeable supportive materials for human embryonic stem cell-derived retinal pigment epithelial (hESC-RPE) cells, enabling cell survival, proliferation and function.

II. METHODS

Honeycomb films were prepared by the BF method using 96/4 PLDLA [1,2]. Before cell culture, honeycomb films were either dip-coated with collagen I/IV, or double-coated by Langmuir-Schaefer (LS) technology using the sequential deposition of collagen type I and type IV. Materials were characterised and used as cell-culture materials for hESC-RPE [1,2].

III. RESULTS

PLDLA films were significantly porous. However, nanometre-thick collagen layers formed by LS deposition completely covered the pores, which contrasted with the uncovered pores of the dip-coated controls. The surface of LS-honeycomb films also became markedly more hydrophilic. hESC-RPE proliferated on all films, but the increased hydrophilicity and decreased roughness of LS-coated films evidently favoured cell spreading

and retention of the typical RPE morphology, as well as the expression of RPE-specific markers. Cells cultured on dip- and LS-coated materials were effective in carrying out phagocytosis of outer segments.

IV. CONCLUSIONS

Surface properties of the PLDLA honeycomb films can be significantly modified by the collagen deposition method. The combination of BF and LS technologies enabled the production of biodegradable, semi-permeable materials that hold great promise for RPE replacement therapy in the treatment of degenerative eye diseases such as AMD.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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048 - Severity of individual obstruction events in diagnosis of sleep apnea – adjusted AHI

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I. INTRODUCTION & AIM

Estimation of the severity of obstructive sleep apnea (OSA) is currently based on number of obstruction events (apnea-hypopnea index, AHI) and the severity of individual obstruction events is ignored [1]. We aimed to include the severity of individual obstruction events to diagnosis of OSA and investigate the factors affecting severity of individual events. We hypothesized that the severity estimation of OSA is enhanced by considering also characteristics of individual obstruction events.

II. PATIENTS AND METHODS

Ambulatory polygraphies of 2057 patients were retrospectively reanalyzed. Subgroups of this population were used in development of the novel parameters (e.g. *obstruction severity and adjusted-AHI*) in which a sum of products of breathing cessation event duration and related desaturation event area are normalized by index time [2, 3] and to investigate their potential to enhance estimation of the severity of OSA by conducting retrospective follow-up studies (average follow-up time over 16 years) [2, 4]. Furthermore, based on these registrations, effects of gender [5], sleeping position [6], BMI, and age on the severity of individual obstruction events were explored. The Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland has given a favorable statement on the study protocol (127/2004 and 24/2013).

III. RESULTS

We have shown in our latest publications that the severity of OSA may be estimated more accurately by considering also obstruction event characteristics as obstruction severity and adjusted-AHI parameters were more strongly linked to increased mortality and cardiovascular morbidities than AHI [2, 4, 7]. Apneas and desaturations were more severe in men than women [5] and while sleeping in supine compared to non-supine position [6] especially in moderate and severe OSA categories. Durations of apneas, hypopneas and desaturations were

prolonged by increasing age while increase in BMI led to decrease in the event durations.

IV. CONCLUSIONS

The estimation of association of OSA with mortality and cardiovascular morbidities could be improved by considering the severity of obstruction events and thus, it is important to be aware on the factors affecting the event characteristics. As adjusted-AHI seems to estimate the severity of OSA better than AHI, it could be beneficial if this parameter would available for clinicians. Therefore, our novel tool enabling clinical calculation of adjusted-AHI could help to discriminate OSA patients with increased risk for OSA related health outcomes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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050 - A Bioengineered 3-Dimensional Model of Human Tuberculosis to Dissect Host-Pathogen Interactions

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I. INTRODUCTION

Standard cell culture models do not reflect the complexity of 3-dimensional interactions that take place between cells and extracellular matrix in vivo. These cell-cell and cell-matrix interactions may significantly modulate cellular physiology and we hypothesised that studying biology in 3-dimensional cell culture systems will reflect conditions more accurately in humans. We used human tuberculosis as a disease model. Tuberculosis (TB) is a globally important disease caused by *Mycobacterium tuberculosis* (Mtb) and characterized by multicellular granuloma formation and matrix destruction.

II. AIM

To develop a 3-dimensional cell culture model based on bio-electrospray technology and use it as a model system to investigate the effect of the matrix on the host-pathogen interaction in Mtb infection.

III. METHODS

We incorporated primary human cells, extracellular matrix components within an alginate matrix and live Mtb to mimic early infection using bio-electrospray technology.

IV. RESULTS & DISCUSSION

We have demonstrated phagocytosis of Mtb by macrophages, aggregation of cells to form a granuloma, leading to differential secretion of cytokines and metalloproteinases by Mtb infected cells. By incorporating multiparameter readouts of cellular viability, matrix breakdown, bacterial growth and secretion of inflammatory mediators, we have demonstrated the applicability of the model in studying antimicrobial testing, host-directed therapy assessment and immunoaugmentation. Overall, incorporation of collagen in the matrix alters

host-pathogen interaction, favoring the host over the pathogen.

V. CONCLUSIONS

We have developed a 3D cell culture system that permits interrogation of the host-pathogen in Mtb infection longitudinally in the context of extracellular matrix. We have also elucidated that a bioengineered 3-dimensional model culture system is more relevant to human disease and has potential applications for a variety of infectious, inflammatory and malignant conditions.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. For analysis of blood from health donors and healthy TB exposed individuals, ethics was acquired from the local ethical clearance committee. In all instances, cones from anonymized donors for National Blood Service was used.

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051 - Switching monopolar mode in radiofrequency assisted hepatic resection: A computational model

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I. INTRODUCTION & AIM

In many studies about radiofrequency (RF) assisted hepatic resection the objective is to achieve sufficiently deep thermal lesion [1]. Although RF-based bipolar devices are commonly used to coagulate, and hence minimize blood loss during hepatic resection [2], they have two main disadvantages: 1) They create a highly superficial coagulation zone (CZ), and 2) both electrodes must always be in contact with the tissue, which is not possible under certain conditions, such as in the laparoscopic approach. Our aim was thus to: A) build a computational model to assess whether using the bipolar device with a switching monopolar mode (i.e. the roles of the active and dispersive electrodes change intermittently between the two electrode tips) would increase CZ depth and reduce contact problems, and B) determine the optimal terms of use for the device in the switching monopolar mode, such as the applied voltage or switching frequency.

II. METHODS

RF heating in liver was modeled using a bipolar device formed by a plastic handle and two cylindrical electrodes (radius 1.5 mm, length 20 mm) topped off by spherical tips of radius 1.5 mm. We implemented two modes, bipolar and switching monopolar, and compared their results. In both models, we assessed CZ depth and temperature profiles during a period of 16 s of RF heating, varying the applied voltage and the switching frequency in the case of the switching monopolar mode. We also vary the angle to introduce the electrode with respect to the tissue 10, 20 and 30°, respect to the perpendicular initial position. We made an experimental *ex vivo* setup in order to validate the modeling results.

III. RESULTS

Applying a voltage of 65 V and a switching frequency of 4 commutations/minute we obtained the deepest CZ in the switching monopolar mode. In the bipolar mode the deepest CZ is

obtained for a voltage of 50 V. Comparing these optimal cases for both modes we obtained 41% greater CZ depth in the switching monopolar mode than in the bipolar mode. Lower switching frequencies in the switching monopolar mode produce a shallower CZ, which moreover is not symmetrical in the space between both of the device's electrodes. Experimental results ratify the computational ones.

IV. CONCLUSIONS

The switching monopolar mode can increase coagulation zone depth and reduce contact problems between electrodes and tissue.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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054 - Double-arm optical manipulator with a microlens array for flexible patterning of microbeads

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I. INTRODUCTION & AIM

Dynamical arrangement of microbeads or individual cells offers great flexibility and potential as platforms for various biomedical applications such as bio-MEMS and Lab-on-a-Chip [1]. To realize the potential of dynamic arrays, precise micromanipulation technique which allows us to transport the specified micro-objects and to dynamically immobilize them at the desired positions or pattern is essential. Multi-beam optical tweezers is one of the most suitable techniques for assembling the dynamic arrays. In order to promote the use and application of such dynamic arrays in various scientific fields as well as biomedical fields, we have recently developed a double-arm optical manipulator system (two-beam optical tweezers) with a simple and inexpensive optical configuration using a single commercially available microlens array and two 2-axis scanning mirrors for assembling large-sized dynamic arrays [2]. In order to evaluate the patterning performance of this double-arm optical manipulator with a microlens array, here we demonstrate the periodic patterning of microbeads with various properties.

II. EXPERIMENTAL SYSTEM

The developed double-arm optical manipulator (that is, non-contact micromanipulation system) has not only a simple and inexpensive optical configuration (see the figures in Ref. 2 for the detailed hardware configuration) but also suitable properties for handling large-sized dynamical arrays as compared to the conventional time-shared scanning (TSS) optical tweezers. This system can manipulate the several tens of microbeads at once; the resulting TSS manipulation of microbeads enables us to arrange them into the arbitrary periodic pattern, like as Escher's paintings, around the prime lattice points (O_1 , O_2 , etc.) of the microlens array. The principle of the proposed patterning method using our optical manipulator is briefly mentioned as follows: the microbeads (P_1 , P_2 , ..., P_n) are arranged on the desired closed curve surrounding one prime lattice point O_1 using the TSS technique of optical tweezers; the periodic replicas of

optical traps are produced around the others (O_2 , O_3 , etc.); consequently, periodic pattern of microbeads with arbitrary shape is formed.

RESULT & DISCUSSION

In the demonstrations, microbeads with different properties (size, color, and fluorescence) as well as uniform properties were dynamically arranged into the specified patterns (for example, alphabetic, stripes, etc.) on a microscope's cover glass, using a computer's 3-button mouse for user interface.

In the poster of EMBEC'17, we will show the Roman alphabet patterns with homogeneous microbeads (2 μm) formed around the lattice points. We will also show that heterogeneous microbeads (three kinds of microbeads with different properties: 3 μm blue, 3 μm red, and 2 μm white polystyrene beads) can be arranged in periodic triangles and squares.

These results demonstrate the possibility of the automated and simultaneous cell-clustering by the optical method. It is expected that the double-arm optical manipulator with a microlens array becomes a useful tool for the precise patterning and simultaneous manipulation of numerous cells as well as microbeads.

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CONFLICT OF INTEREST

I declare that I have no conflict of interest.

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059 - *In vitro* neuronal networks for closed-loop electrophysiology

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I. INTRODUCTION & AIM

Starting from the 20s, researchers have begun to explore the possibility to create *in vitro* systems at the interface between neuroscience and robotics, thus providing an excellent test bed for modulation of neuronal tissue and forming the basis of future adaptive, bi-directional Brain Machine Interfaces and Prostheses [1]. The first-ever *in vitro* closed-loop system consisted of a lamprey brainstem bi-directionally connected to a small wheeled robot [2]. Inspired by that pioneering study, we developed a bi-directional system involving neocortical networks grown on Micro Electrode Arrays (MEAs) and a small robot (i.e. ‘neurorobotic’ experiment). The realized software architecture guarantees a bi-directional exchange of information between the natural and the artificial part by means of simple linear coding/decoding schemes. We used a similar closed-loop paradigm for developing a ‘brain-prosthesis’, aimed at restoring damaged neuronal connections in an *in vitro* model of brain injury [3]. The perspectives and applications of the above systems will be discussed, as potential proofs of principle for novel electroceutical-based devices for treating neurological diseases [4].

II. METHODS

A. Neuronal cultures

Our closed-loop architecture was based on a neural controller bi-directionally connected to a virtual robot, characterized by proximity sensors and wheels. As neural controller, we used cortical or hippocampal cultures dissociated from embryonic rats (E18) and kept alive over MEAs for 3-4 weeks. All procedures involving experimental animals were approved by the Italian Ministry of Health and Animal Care (authorization ID 023, April 15th, 2011).

To implement the brain-prosthesis, the culture of neurons was bi-directionally connected to a neuromorphic board based on an FPGA, able to perform real-time event detection (e.g. spike detection) and trigger consequent electrical stimulation to one or more electrodes of the MEA.

III. RESULTS

First, we were interested in characterizing the electrophysiological behavior of our *in vitro* cultures, both during spontaneous and evoked activity. Then, by selecting specific ‘input’ (sensory) and ‘output’ (motor) areas in each network, we were able to successfully interface it with an artificial agent in a bi-directional way. We will present two examples of bi-directional communication: a biological network connected to (1) a real/virtual robot (neurorobotic experiment) and (2) a computational model, implemented in the FPGA (brain-prosthesis experiment).

IV. CONCLUSIONS

Our closed-loop experimental framework can be exploited (and potentially translated to *in vivo* systems) to study the mechanisms of neural coding and the computational properties of cell assemblies with the final goal to facilitate progress in understanding neuropathologies, designing innovative prosthetics, and creating different types of artificial intelligence.

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060 - Modelling Ion Channel Blocking Using Multiple Parameter Sets for Ventricle Monophasic Action Potential of Guinea Pigs

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I. INTRODUCTION & AIM

The effects of novel drugs on cardiac ion channels are critically important to drug development, as they can lead to arrhythmias such as torsade de pointes, constituting a major cause of sudden cardiac death. To predict arrhythmic risk in humans, candidate drugs are normally administered to animals such as guinea pigs and the resulting ECG traces are used to identify possible abnormalities, like QT interval prolongation which indicates a risk of torsade de pointes. In order to improve speed and reduce animal testing, computational models can be used to help with this process.

Many mechanistic cardiac cellular-level models exist which can be used to reproduce action potentials that can be measured in vivo. The aim of this work is to use one such model (LuoRudyI[1]) and data from Monophasic Action Potential (MAP) measurements in guinea pigs to examine ion channel blocking, which can be used for drug safety assessment. This is achieved by producing all possible ranges of action potentials based on valid parameter sets of each subject's baseline condition.

II. METHODS

The values presented here are obtained by parameter scanning between 10 times higher and lower than literature values using quasi-Monte Carlo Sobol sequences. A chi-squared confidence ($p < 0.05$) is used on the global fit of the baseline conditions to demonstrate there is insufficient information in these alone to determine the results of ion channel blocking, showing

there are multiple possible parameter sets that are valid for each baseline MAP. Using the chi-squared confidence in conjunction with the parameter scans provides us with sample valid parameters covering the entire parameter space. This also allows a map of the entire valid parameter space for several individual subjects to be produced.

III. RESULTS & DISCUSSION

Given a certain amount of ion channel blocking, it is shown that different baseline parameters within each valid set produce different resulting action potentials. This could be used to simulate the effects of drugs being applied to subjects based on their known ion channel blocking.

In addition, the parameter maps provide a complete set of resulting action potentials so no results are missed, and allow further valid parameter sets to be sampled for future work.

CONFLICT OF INTEREST

This post-doctoral fellowship was funded entirely by AstraZeneca.

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062 - Biopsy needle with local bioimpedance measurement and real-time tissue classification

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I. INTRODUCTION & AIM

Tissue samples, biopsies, are necessary for accurate diagnosis of malignancies and cancer. Local tissue identification from the tip of biopsy needle might ease the procedure and enhance the sample and treatment quality. We aim to study the possibility of using bioimpedance in core needle biopsy for the real-time identification of the tissue type. Here computer simulations and animal experiment are utilized.

II. METHODS

Injeq IQ-Biopsy needle measures complex bioimpedance from the tip of the needle, and subsequent classification algorithm transforms this information into tissue type information. IQ-Biopsy was simulated with 3D finite element method (Comsol Multiphysics, Stockholm) in block with 0.1 S/m conductivity, representing liver. The block also contained membrane or small target with other conductivity. The aim was to verify 18G-sized IQ-Biopsy resolution and the ability to detect membranes and small targets. The needle was moved through targets with conductivities of 0.01-1.0 S/m and impedance calculated for each step.

Focused local sensitivity distribution is desired property of the measurement. However, it may cause variation to the measurement signal, since all actual tissues are inhomogeneous. The needle was therefore also tested *in vivo* with porcine model to verify the real-time performance in actual tissue. The animal study was authorized by Southern Finland Regional State Administrative Agency (ESAVI/4389 /04.10.07/2015) and an experienced veterinarian monitored the porcine during the study. Fat, muscle, blood, spleen and liver of the anesthetized porcine was punctured in visual control. In total 21 punctures with 7 needles were made to each tissue. Tissue classification algorithm was created and tested with 7-fold, needle-specific cross-validation based on the gathered data.

III. RESULTS & DISCUSSION

Simulations showed good resolution to measure correctly even small targets. Membranes of 1 mm thickness and targets of 1x1x1 mm³ provided signal that differed less than 10% from signal that would have been obtained from significantly larger target with corresponding conductivity in all tested conductivities.

Animal study provided data for classifier creation and verification of the feasibility *in vivo*. According to the cross validation, approx. 90% total accuracy (correct classifications per all classifications) was achieved with the created classifier. When the needle was in liver, the classification algorithm occasionally detected other tissues, especially blood. Because liver is well vascularized, it is likely that blood classifications in liver originate from blood.

Our results showed that IQ-Biopsy is able to detect even small targets. The method showed feasibility also *in vivo*. Ultrasonography (US) provides macroscopic image about the organs and guide the directions where to proceed, but US has limited resolution and precise location of the needle tip is difficult to interpret from the image. IQ-Biopsy can complement US by providing local tissue type information to the physician, and by these means enhance obtaining a representative tissue sample.

ACKNOWLEDGMENT

MSc(Eng) Petri Ahonen provided geometry of the biopsy needle for the simulations. Animal study was conducted under DVM Sari Ilivitzky-Kallioma supervision.

CONFLICT OF INTEREST

SMH, JJAK and KEK are employees of Injeq Ltd. KEK and JAKH are stakeholders of Injeq Ltd.

063 - Novel tools for longitudinal simultaneous fMRI/EEG studies of the brain in small animals

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I. INTRODUCTION

Simultaneous EEG-fMRI is a valuable tool in the clinic as it provides excellent temporal and spatial information about normal and diseased brain function. In pre-clinical research with small rodents, obtaining simultaneous EEG-fMRI in longitudinal studies faces a number of challenges, including issues related to longitudinal study design with chronically implanted electrodes, magnetic susceptibility artifacts and anesthesia.

II. METHODS & RESULTS

We have developed number of different novel fMRI approaches to overcome these challenges. Here, we demonstrate a method for permanent MRI RF-coil and EEG electrode implantation in rats that is suitable for long-term chronic follow-up studies in both stimulus and resting-state fMRI paradigms (1). Furthermore, we demonstrate that with proper habituation protocol resting state fMRI data can be collected from completely awake rats. Stress level of the animals, as measured by plasma corticosterone level was comparable to anesthetized animals. Data from awake animals shows strong thalamo-cortical functional connectivity which is suppressed with most anesthetics in rats. We have also developed non-BOLD zero-echo time fMRI approach using multi-band SWIFT (Sweep Imaging with Fourier Transformation) pulse sequence (2), with high tolerance for magnetic susceptibility, making it especially useful for studies combining deep brain stimulation (DBS) and fMRI. Our SWIFT DBS/fMRI results show similar activated areas and relative signal changes during stimulation as BOLD fMRI, with no magnetic susceptibility related image distortion from metallic stimulation leads used for DBS (3). The fMRI contrast is dependent on flip angle and thus has likely

a contribution from in-flow effect of blood, however the origin of the SWIFT fMRI contrast requires future detailed investigation. As SWIFT also is inherently quiet pulse sequence, it is also optimal for fMRI studies of awake animals.

III. COMPLIANCE WITH ETHICAL REQUIREMENTS

The authors declare that they have no conflict of interest. All animal procedures will be carried out under licenses approved by the Animal Ethics Committee of the Provincial Government of Southern Finland and in accordance with the guidelines of the European Community Council Directive 2010/63/EU.

IV. CONCLUSIONS

Our novel toolbox of pre-clinical fMRI techniques opens up new longitudinal study designs and makes it possible to obtain fMRI data with excellent translational value to human studies.

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068 - Experimental and numerical assessment of MRI-induced temperature change and SAR distributions in phantoms

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I. INTRODUCTION

During an MRI procedure, most of the transmitted RF power is transformed into heat within the patient's tissue and device implants as a result of resistive losses. This is referred to as the specific energy absorption rate (SAR) (1). The European committee for electrotechnical standardization (CENELEC) has mandated that all scanners must measure the specific absorption rate of radiofrequency in patients and develop system safeguards to ensure that the limits set out IEC 60602-3-33 are not exceeded. Accurate estimation of SAR is critical in safeguarding unconscious/sedated patients, patients with compromised thermoregulation, implant patients, pregnant patients and neonates who require an MRI procedure. The increased static field strength and RF duty cycle capabilities in modern MRI scanners means that systems can easily exceed safe SAR levels (2). Internationally accepted MRI quality assurance protocols routinely used to establish quality assurance (QA) protocols do not offer advice on the testing of SAR levels in MRI and thus it is not routinely measured in annual medical physics QA. Aim of this research is to develop a protocol to verify the SAR delivered to a patient's head.

II. METHODS

There are a number of experimental approaches to verify SAR however these methods broadly fall into three categories; phantoms, mathematical modelling and MR thermography. To ensure these methods are accurate for actual MRI coils, however, it is necessary to validate models experimentally. To determine the RF power deposition and its thermal effects in tissue we will use a T1 doped MR phantom in 4 channel head coil where the only source of heat is the radiofrequency fields produced by the imaging coil. The temperature changes in the phantom will be determined using three independent measurements, embedded fibre optic thermometry, thermal imaging, and MR thermometry

SAR is equivalent to the heating source created by the electric field in the tissues. The SAR is defined

$$SAR = \frac{\sigma}{\rho} E^2 [W/kg]$$

where σ is the conductivity of the tissue [S/m], ρ is the density of the tissue kg/m³, and E is the electric field (rms) [V/m]. The

tissue heating effects will vary over the whole body with the greatest effects at the periphery and least at the centre. As there is negligible contribution from thermal conduction in our SAR assessment and the phantom is nonperfused. We can determine SAR at discrete points in the observation plane by the following equation

$$SAR \approx c \frac{\Delta T}{\Delta t} [W/kg]$$

where c (J/kg K) is the specific heat of the phantom, ΔT [K] is the temperature rise, and Δt [s] is the exposure time. The specific heat and emissivity of the phantom based on our material properties of dissolving agar (7 g/L), NaCl (10 g/L), and CuSO₄ (1 g/L) in distilled water is 3850 J/kg K and 0.97, respectively. The T1 properties of the phantom were determined at room temperature using a STIR sequence over times ranging from 50-2000ms.

III. RESULTS

A standard Brain protocol acquisition following a baseline GRE sequence was applied over the whole phantom. This included localizer, T2 axial TSE, FLAIR axial TSE, T1 sagittal and Flair Sagittal. Following a standard brain protocol a further GRE sequence was acquired. Throughout all the scanning thermal images were captured and fibre optic thermal measurements were taken continuously. The highest temperature rise was at the periphery of the phantom with a ΔT of 3°C degrees and less than 1°C degree over the whole phantom.

IV. DISCUSSION

We have developed an open source phantom that can independently verify the temperature rise associated with SAR.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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070 - Healthcare Technology - Compete or Collaborate? - How key stakeholders can to support each other to mutual benefits

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Patients, carers and clinicians face many challenges in modern healthcare. Some of these challenges could be addressed with new technologies¹ but often, indeed usually, the people on the front line don't know what technological advancement exist or might be developed to help them.

Researchers in academia are often at the frontiers of science and engineering, developing new all kinds of new technologies. Some of these new technologies have the potential to revolutionise healthcare, but often, indeed usually, the researcher don't appreciate the real challenges are face patients and healthcare workers.

Even when researcher and healthcare come together and do address the real challenges with the right potential technological advancement, they often fail to understand how to develop that technology into a healthcare-ready solution and how best to get it adopted widely.

The Med Tech industry knows how to make healthcare-ready technologies and to get them adopted into clinical practice, but they don't always pick the best technology or address the most important clinical challenges³

These three partners – healthcare, academia and industry – might be driven by different motivations, but they essentially all share the same goal: getting the best innovative healthcare technology adopted for patient benefit. They have different skills and experience but all are needed if we are to bring about a genuine step change in healthcare provision. How can these three partners be brought together to work collaboratively for patient benefit?

Professor Clark will discuss these issues and show how, HTA as a discipline is a core field for all three and deployed effectively can bind the three partners together in mutually beneficial collaborations.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest

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075 - Gender differences in severity of desaturation events following hypopnea and obstructive apnea events

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I. INTRODUCTION

Severity estimation of obstructive sleep apnea (OSA) is currently based on apnea hypopnea -index (AHI) [1], which ignores the individual breathing cessation event characteristics. Even though women with OSA have been shown to have lower AHI compared to men [2], it is not clear whether the physiological effect of individual breathing cessations differs between genders. The aim of this work was to evaluate gender differences in the severity of peripheral oxygen desaturation events following obstructive apneas and hypopneas.

II. PATIENTS AND METHODS

Type I polysomnographic recordings of 220 males and 175 females were retrospectively analyzed. All obstructive apnea and hypopnea events from these patients were divided into eight different durational categories: from 10 to 45s with 5s interval and >45s. The severity (median duration, area and depth) of desaturation events following obstructive apneas or hypopneas were compared between genders within these durational categories. Ethical approval was given by the Institutional Human Research Ethics Committee (Princess Alexandra Hospital, Brisbane, Australia) (HREC/16/QPAH/021).

III. RESULTS

Desaturations following obstructive apneas with duration of 30-45s were substantially more severe ($p < 0.05$, Mann-Whitney U) in females compared to males. In contrast, areas of desaturations following hypopneas were smaller in females compared to males. In both genders the mixed model

analysis of all events adjusted for sleep stage, sleeping position, age and BMI showed that duration of both hypopneas and obstructive apneas were strongly associated with desaturation duration ($p \leq 0.001$), desaturation area ($p \leq 0.001$) and desaturation depth ($p \leq 0.001$), longer events causing more severe desaturations.

IV. CONCLUSIONS

In females longer obstructive apneas (>30s) could be more detrimental compared to those of males. The gender differences in relationship between breathing cessation event duration and related desaturation event characteristics could mean that the severity of OSA is different in males and females despite of similar AHI.

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081 - Modelling of Time-varying HRV using Locally Stationary Processes

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I. INTRODUCTION & AIM

Estimates of heart rate variability (HRV), and particularly parameters related to high frequency HRV (HF-HRV), are increasingly used as a proxy of cardiac parasympathetic nervous system regulation. Reduced HF-HRV is related to attention deficits, depression, various anxiety disorders, long-term work related stress or burnout, and cardiovascular diseases [1,2]. In this work, a stochastic model, known as *Locally Stationary Processes*, [3], is applied to HRV data sequences from 47 test participants. The model parameters are estimated with a novel inference method and regression using a number of available covariates is used to investigate their correlation with the stochastic model parameters.

II. METHODS

A. Test Description

The test participants (TP) were told not to ingest food, caffeine, or tobacco during the 2 h before the experiment or alcohol the day before lab visit. Patients using medicines or suffering from any disease known to affect the cardiovascular system were not included. ECG and respiration were recorded at 1 kHz. ECG was assessed using disposable electrodes and respiration using a strain gauge over the chest. 5 min of data were recorded when the TP was breathing in accordance with a time-varying metronome beginning at 0.12 Hz and ending at 0.35 Hz.

B. Data Preprocessing

The raw data sequences (respiratory data and HR data) were downsampled to 4 Hz, i.e. in total 1200 samples for each sequence. After adjusting to zero-mean, both respiratory and HR data were filtered with a band-pass FIR-filter of length 256 of 3 dB-bandwidth 0.1-0.5 Hz. The first and last data samples were corrupted from the transient of the filter and as data for the further analysis, the middle 960 samples (4 minutes) were

used.

C. Stochastic model and regression

The stochastic model considered, known as *Locally Stationary Processes (LSP)*, is based on the modulation in time of a stationary covariance function. A novel inference methodology based on the separability properties possessed by the model covariance is used to estimate the model parameters for every participant in the study. A generalised linear model with the LSP parameters as response is fitted to investigate their correlation with a number of covariates, including age, gender, height, weight, BMI, and stress level.

COMPLIANCE WITH ETHICAL REQUIREMENTS

Data collection took place at the Department of Laboratory Medicine, Division of Occupational and Environmental Medicine, Lund University. The study was approved by the central ethical review board at Lund (Dnr 2013/754) and was conducted in correspondence with the Helsinki declaration. All participants signed an informed consent that clearly stated that participation was voluntary and could be discontinued at any time.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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083 - 3D visualization of intraoperative stimulation test results in deep brain stimulation

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I. INTRODUCTION

Deep brain stimulation (DBS) is a treatment for movement disorders such as Essential Tremor (ET). The implant position of the electrode is crucial. After preoperative surgical planning and intraoperative tests, the collected data is only “mentally” visualized and analyzed by the physician to decide on the optimal implant position of the DBS lead. We propose a method to combine and visually present this multitude of data for surgical decision making using patient-specific simulations of the electric field (EF) distribution, intraoperative accelerometry based tremor evaluations and direct-targeting technique of DBS.

II. METHOD

Five ET patients participating in a clinical study (Ref: 2011-A00774-37/AU905, CPP Sud-Est 6, Clermont-Ferrand, France; written informed consent) were included in the presented protocol in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Patients underwent routine stereotactic bilateral implantation of the DBS electrodes in the ventro-intermediate nucleus of the thalamus (VIM) [1]. During planning, the target structure and the anatomical neighbours were outlined on patient images and an anatomical target was selected. Two microelectrodes were intraoperatively inserted per hemisphere on parallel trajectories. Stimulation tests were performed on 5 to 10 positions per trajectory with several stimulation amplitudes per position to evaluate side effects and changes in tremor using an accelerometer fixed to the patient's wrist [2]. To estimate the extension of the stimulation, the EF was simulated using a finite-element model for several amplitudes per position related to different tremor improvements [3]. To identify the optimal implant position for chronic stimulation, we summarized all data in “Improvement Maps” by assigning to each voxel in the stimulation test region the highest

improvement in tremor. Improvements were visualized on the patient-specific anatomical outlines using a green color scale and simulations of side-effects in red (Paraview, Kitware Inc). Postoperatively the optimal implant positions with the highest improvement were identified for the five patients.

III. RESULTS

The clinical teams were able to identify the optimal implant positions with more ease and in less time compared to the routine discussion using pen and paper. Additionally, for 7 out of the 9 improvement maps, the highest improvement region was found to be in the posterior subthalamic area inferior and posterior to the surgical target, the VIM.

IV. CONCLUSIONS

Visual analysis of the results of intraoperative stimulation tests in form of improvement maps assists the clinicians in determining the optimal implant location of the chronic DBS lead and in comparing results between patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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084 - Electrospray - A versatile tool for physical targeted gene- and chemotherapy

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I. INTRODUCTION

In gene therapy today a major issue is to overcome the cell membrane, enabling therapeutic plasmid to enter the interior of cells. State-of-Art approaches using viral and nonviral vectors often lead to immune response or provide poor efficiency. Similar requirements are identified in chemotherapy, where a targeted delivered therapeutics will avoid adverse effects and may increase the delivered dose locally. Therefore, a tool providing physical targeted delivery will provide significant improvement for chemotherapy and genetherapy in clinical applications. In this work we present electrospray as versatile tool to deliver liquid therapeutics for physical targeted gene- and chemotherapy.

II. ELECTROSPRAY DEVICE

Electrospray is based on Coulomb repulsion, generated through electrical fields, and enabling a liquid to disperse into small droplets and accelerate them toward the targeted tissue. Our device consists of a stainless steel capillary, providing the liquid therapeutics, connected to high voltage, and acting as driving electrode. In working distance, the targeted tissue is placed, connected to ground, and acting as counter electrode. To assure a well-defined distance both electrodes are placed within a single housing, forming the tip of our electrospray device and enabling a design as a bipolar single port instrument, suitable for minimal invasive access to the human body. The current rigid device is designed with an outer diameter of 10 mm, working distances adjustable (1 to 10 mm), providing an acceleration voltage up to 6 kV and enabling a volume flow more than 20 $\mu\text{l}/\text{min}$.

III. RESULTS

For gene therapy, we characterized our electrospray device by delivering eGFP reporter gene on alveolar epithelial cells (A549) in vitro and evaluating transfection efficiency (FACS).

A set of optimized parameters like working distance (4 mm), applied voltage (3 kV), flow rate (20 $\mu\text{l}/\text{min}$), delivered volume (3x25 μl), and procedure was obtained, resulting in a transfection efficiency up to (58.6 \pm 2.6)% using eGFP diluted in sucrose solution (370 mOsm; 75 μl). For cancer treatment, the effect of two times within 7 days electrospray mediated delivery of Cisplatin and Methotrexate on the growth of a subcutaneous lewis lung carcinoma in a mouse model in vivo was observed. Applying identical parameters the tumor size growth was retarded to (43 \pm 16) mm^3 for Cisplatin and (22 \pm 12) mm^3 for Methotrexate, while control tumor obtained a volume of (514 \pm 104) mm^3 .

IV. CONCLUSION

In conclusion, we successfully demonstrated the feasibility of electrospray for targeted delivery of plasmids in vitro and chemotherapeutics in vivo, indicating the versatility of this concept towards further applications.

COMPLIANCE WITH ETHICAL REQUIREMENTS

All animal experiments were performed in accordance with the standards of the European Convention of Animal Care. The University of Bern Animal Study Committee approved the study protocol.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

085 - Using Bayesian networks to synthesize evidence on human reliability into clinical validity for the assessment of pH strips in nasogastric tube feeding

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Nasogastric-tubes are commonly used for feeding or medication. The location of blindly inserted tubes requires confirmation to ensure patient safety. This is most commonly done by using pH strips which test the acidity level of tube aspirates. The current safety guideline in England prescribes feeding if the pH is below 5.5. Chest x-rays should be used if pH is observed to be at or above the cutoff. Our previous research demonstrated risks associated with the use of various bedside tests [1]. The main issue with the pH test is that whilst the test is relatively specific, and can exclude feeding into the lung, the pH test is not sensitive to include all stomach tubes especially when patients are being fed or on antacids medication. Chest x-rays are more accurate but are also more expensive. Large number of unnecessary x-rays result in huge waste of resources. We are working with a Scottish company to develop new generation of pH strips. The strips are innovative in the sense that it can adjust for the unwanted influences of feeding and medication. We have carried out a pilot clinical study and human factor studies. We found that pH readings varied depending on the reader (72 laypersons versus 72 experts) and conditions (ideal versus otherwise). We also found errors when pH is measured by litmus paper in contrast to pH meter. We employed Bayesian networks to incorporate these uncertainties in our assessment of the new test. Bayesian networks are graphical tools for reasoning with uncertainties [2]. Within a BN, each node represents an uncertain event; arrows connect the nodes, indicating the presence and the direction of dependence. We show how Bayesian networks can be used to illustrate the logical relationship amongst technology validity, measurement uncertainty

and human reliability. We express this by a chain of uncertain quantities. Important for decision-making is the ability of the pH to predict ‘tube sites’. Using Bayesian networks, we demonstrate how the confidence of making such predictions vary under different conditions and their influences on the cost-effectiveness of the new generation of pH strips. This approach can be used to promote shared understanding between stakeholders and to carry out sensitivity analyses incorporating variables that are not routinely considered relevant for health economics..

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CONFLICT OF INTEREST

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087 - Rotational electrical impedance tomography of hydrogel phantoms

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I. INTRODUCTION & AIM

New tools to image three dimensional (3D) cell cultures are needed in the fields of regenerative medicine and tissue engineering. [1] Electrical impedance tomography (EIT) is an emerging medical imaging method used for example to monitor lung function. [2] It is a high speed, non-invasive technique that could provide a functional imaging tool for 3D cell culture analysis.

We *aim* to build an EIT setup able to provide information of cell viability and distribution in the 3D scaffold. Here we demonstrate that the novel rotational EIT setup can provide good image quality with very limited amount of electrodes.

II. METHODS

In EIT, the electrical conductivity of the sample is visualized based on electrical measurements on the sample using several electrodes. In our setup the sample is rotated, thus we can obtain EIT using just few electrodes. To test the proof of concept of the rotating EIT, we performed measurements of gelatin phantoms with insulating objects, which mimic living cells. Images were reconstructed using EIDORS [3] with some modifications to account for the sample rotation and unusual electrode configuration.

III. RESULTS

Gelatin phantoms with different sizes of resistive objects were measured and images reconstructed. The reconstructed images depicted even the smallest objects with 5% of the whole sample area. To study how much the number of rotations af-

fects the EIT reconstruction, rotational EIT was carried out using a few different rotation numbers. The results show improvement in the image resolution as number of rotations is increased up to 64.

IV. CONCLUSIONS

Rotational EIT using only eight fixed electrodes around rotating sample proved to be effective. This method could provide a long-term monitoring tool for cell cultures *in vitro*.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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088 - Vibration stimulator for imaging mechanotransduction based cell responses

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I. INTRODUCTION & AIM

Studying of the cellular mechanics and mechanobiology more reliably requires a platform, where cells can be simultaneously monitored and mechanically manipulated or stimulated *in vitro*. Here we developed for a purpose a high frequency (HF) vibration stimulation system, which can be combined with live cell high resolution microscopy. The system can be used to investigate how the cells and microtissues respond to vibration stimulus.

II. METHODS

A loudspeaker ($\phi=5$ cm, Partco Oy) moved horizontally a 3D printed (polylactid acid, Ultimaker Original) sample vehicle, tailored for the microscopy unit, with miniaturized railroad cars (Roco). Maximum G_{peak} -magnitudes of the HF stimulation, measured with a commercial accelerometer (3-axis, ADXL325, Analog Devices), were tested for a continuous sinusoidal waveform. For the live cell imaging, MDCK cell line was plated on a collagen-coated cover slip assembled to a metallic holder (Airekacells), and the effects of the HF ($0.2 G_{\text{peak}}$; 30 Hz; 45 min) vibration loading to cell morphology and nuclei were imaged (Zeiss LSM 780 LSCM, Carl Zeiss Microscopy GmbH).

III. RESULTS

Low magnitude ($1 < G_{\text{peak}}$; 30 Hz, 100-300 Hz) and even high magnitude ($1 \geq G_{\text{peak}}$; 40-90 Hz) HF vibration stimulation is

produced accurately. The horizontal vibration does not cause any detectable sample drift or movement and preserves well the microscope imaging field. The initial results suggest that the stimulus alters the nucleus, but not the cellular, morphology.

IV. CONCLUSIONS

The designed low-cost stimulator performs well in producing the continuous HF vibration stimulation for different loading parameter combinations. It enables us to image different mechanotransduction -related cell physiology processes in living cells.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

090 - Evaluation of the effects of intra-cortical micro-stimulation on functional connectivity: implications for neuro-rehabilitation studies

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I. INTRODUCTION & AIM

Enhancing functional motor recovery after localized brain injury is a widely recognized priority in healthcare as disorders of the nervous system causing motor impairment, such as stroke, are among the most common causes of adult-onset disability. Restoring the physiological function of a dysfunctional brain to improve the quality of life is a primary challenge in scientific and clinical research and will be driven through innovative therapeutic approaches. Recent studies [1, 2] demonstrated that intracortical microstimulation can be successfully used to manipulate neuronal functional connectivity, thus representing a potentially powerful tool to steer neuroplasticity occurring after brain injury. Activity-dependent stimulation (ADS), in which the activity recorded from a single neuron is used to trigger stimulation at another cortical location, is able to potentiate cortical connections between distant brain areas. Here, we investigated the ability of ADS vs. open-loop random stimulation to induce changes in functional connectivity in chronically implanted Long-Evans rats.

II. METHODS

For this study we used $n=6$ adult, male chronically implanted Long-Evans rats (weight: 350-400 g, age: 4 mo). Stimulation was delivered to forelimb (FL) somatosensory cortex during awake recordings, using either randomly-generated stimulus pulses (RS) or ADS triggered from rostral forelimb area (RFA) neural activity.

For both groups, recording followed one-hour and twenty minutes period of stimulation separated and surrounded by twenty-minute periods of no stimulation, for a total of approximately two hours of recorded data per day. The animals underwent the experimental procedure for 21 consecutive days in order to quantify cumulative effects of the stimulation (if any), the persistence of the effect (if present) and its extinction rate and the speed of re-establishment of such an effect, when a washout period is present.

III. RESULTS & CONCLUSIONS

All stimulation protocols transiently (within-day) affect the spontaneous activity within RFA. In particular, both protocols induced reversible changes in neuronal firing activity, consisting of (i) decrease of firing rate, (ii) variation of firing patterns as measured by the increase of the Local Variation with Refractoriness constant (LvR, see [3]), (iii) decrease of pairwise cross-correlations. Consequently, each neuron's coupling to the network activity (as measured by the population coupling metric, see [4]) also changes because of stimulation. For each used metric, ADS induced greater changes than open-loop random stimulation, further strengthening the idea that Hebbian-inspired protocols might potentiate cortico-cortical connections between distant brain areas. These investigations are thus critical for inspiring new neurorehabilitation therapies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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095 - Egg Yolk Plasma as a 3D Cell Culturing and 3D Printable Biomaterial

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I. INTRODUCTION & AIM

Extrusion-based bio-printing involves the combination of a biocompatible material, cells and a 3D printer to produce a 3D structure. Granted simple gels exist for this purpose [1], more intricate gels better resembling human tissues are desired. The avian egg is the source of our novel biomaterial for 3D culturing and bio-printing of human cells. A fraction of the yolk named the egg yolk plasma (EYP) is described here as a novel biological biomaterial usable for 3D culturing and 3D bio-printing.

Salivary hypofunction (dry mouth) is considered a frequent side effect of medications [2]. Bio-printing functional salivary secreting organoids could be used in pre-clinical drug testing to evaluate this outcome. With salivary cells in the EYP, we wish to bio-print salivary gland (SG) organoids. For this, mechanical and biocompatible properties of the EYP are evaluated.

II. METHODS

Primary human fibroblasts (SG biopsy) and human NS-SV-AC acinar cell line (saliva producing cells) were grown in the EYP. Cells seeded in non-printed viscous EYP were benchmarked every 5 days to 2D cultures (>20 days). High content screening with Live/Dead and Hoechst were used to quantify. For bio-printing, the EYP was gelled and the material's stiffness was measured using a rotational rheometer. Manual mixing of the cells into the gel and bio-printing of the cell laden EYP was performed.

III. RESULTS & DISCUSSION

In 2D, cells grow and live in a 2D sheet conformation. In viscous non-bio-printed EYP, 3D spherical growth of the cells occurs with morphological properties specific to each cell type. Fibroblasts live, proliferate slowly but form distinctive spheres (~50 cell) with major attachment points. The acinar cells live, proliferates very fast and form relatively large 3D agglomerates (> 500um in diameter at 21 days) without major anchor points. The manually mixed cells in the gelled EYP produce a homogeneous distribution; it can be printed with precision in well plates and cells maintain their 3D conformation.

Non-gelled viscous EYP is a promising alternative for spheroid growth because of its abundance, inexpensiveness, developmental stimulating environment and easy production method. Also as a tunable gel, EYP can be used as a bio-ink for 3D bio-printing where the precise positioning of multiple cell types is maintained for the formation of miniature tissue mimics.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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096 - Snapshot of medical informatics research in Japan

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Abstract—This paper is to provide snapshot of medical informatics research in Japan. Rapid advancement and rapid introduction of information and communication technologies into clinical field and medical research is drastically changing clinical activities and medical research. Automation of clinical activity recording enables detailed analysis of clinical activities, and the national level databases ease population wide epidemiology. On the other hand, privacy concerns spread among the society. Thus, regulations for medical data treatment is now underway.

Keywords— Medical Informatics, Japan, Population-wide epidemiology, Automatic Recording, Privacy concerns.

I. INTRODUCTION

The recent advancement and introduction of information and communication technologies (ICTs) is reforming clinical activities and researches. This paper quickly describes current Japanese condition around medical informatics research.

II. MEDICAL DATA RECODING AND PRIVACY CONCERNS

As the Japanese healthcare insurance system based on activity based coding (fee for service), all the activity performed within hospital should be recorded. Additionally, national healthcare insurance system fully covers clinical costs of Japanese citizens. Therefore, the pile of reimbursement request provides demographical view of clinical activities. The National Database of Health Insurance Claims and Specific Health Checkups (NDB) recording whole reimbursement is opened for researchers of epidemiology and several outcomes are coming [1]. On the other hand, the NDB does not include clinical outcomes such as test results or summary documents. The introduction of electronic health records (EHR) is expected and innumerable trials to emerge them [2].

Auto-ID / barcode enabled medication administration (ABMA) systems, which are originally designed to secure medication, enables semi-automatic recording, and introduction of position tracking technologies enables fully automatic recording of four-Ws (who, where, when, and what) and one-H (how) of clinical activities [3]. Once they are free from recording the sensory data, electronic medical records (EMR)

may become record of clinicians' recognitions, whereas the sensory records may be the records of facts. It is just as airplanes' black-box, the cockpit voice recorder for recognitions and the flight data recorder for facts. This separation of records may ease analysis of the records, and, consequently, enriches the value of EMR and EHR.

Introduction of daily recording sensors such as wearables [4] adds daily health conditions of patients through personal health records (PHRs). They will provide more detailed clinical data for further data-based clinical researches.

The high compilation of medical data arouses social privacy concerns. Japan renews the privacy protection act in the end of May 2017 which follows the European general data protection regulation (GDPR). Within the modification of relating regulations, Japanese government try enabling clinical data analysis for social and academic use.

III. CONCLUSIONS

The social reform following ICTs is still underway. Both the way of data handling and social system is rapidly changing. We need to discuss faithfully the expected outlook of future clinical medicine of the information age.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

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104 - Motor evoked potentials induced by biphasic paired-pulses

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I. INTRODUCTION & AIM

When transcranial magnetic stimulation (TMS) is focused on the primary motor cortex, it evokes a sequence of descending waves, called the I-waves (typically I2- and I3-waves) initiating from the cortical neuronal complex. The characteristics of these waves can be studied with paired-pulse TMS in which the second pulse is timed at the peak of an I-wave. Until now, the paired-pulses had to be applied with monophasic stimulation due to technical limitations, and thereby the characteristics of biphasic I-waves have not been widely studied. [1]

The aim of this study was to evaluate the characteristics of biphasic I-waves, and their facilitatory effects.

II. METHODS

I-waves were evaluated in 15 healthy subjects with biphasic paired-pulse sequences. The inter-pulse interval varied between 1.2 and 8.0ms, and altogether 30 different intervals were tested. Furthermore, a single-pulse sequence was applied. Sequences contained 20 repetitions between 4–6s and the first pulse was given with an intensity of 110% of resting motor threshold (rMT) and the second with 90% of rMT. I-wave characteristics were measured from the motor evoked potentials (MEPs) of the target muscle. A prototype stimulator producing biphasic paired-pulses was used (Nexstim Plc) with neuronavigation. The measurements were done in accordance with the Helsinki Declaration.

III. RESULTS

Biphasic paired-pulses seemed to induce I-waves up to I6-waves. In some subjects the earlier waves were the most prominent whereas in others, the later ones.

IV. DISCUSSION

The use of biphasic paired-pulses might open novel possibilities for studying neurophysiology and for clinical applications, especially with the focus on cortical physiology.

CONFLICT OF INTEREST

GJ and JK are employed by Nexstim Plc, manufacturer of the neuronavigated TMS systems. PJ has received unrelated consulting fee from Nexstim Plc.

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110 - Data warehouse System conjunction with Cohort Data and Clinical Data

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I. INTRODUCTION

Recently, reuse of medical information and big data analysis using clinical information are receiving attention. In Japan, several projects of medical big data analysis using artificial intelligence has been promoted by the support of the Ministry of Health, Labor and Welfare. Unfortunately, there are several problems to analyze using clinical data, because medical information is not stored and managed for reuse in a general hospital. In order to solve this problem, Kyoto University Hospital developed a data warehouse system that conjunction with cohort information and clinical information. In this paper, we introduce the function of this data warehouse.

II. CONSTRUCTION

About three thousands of outpatients come every day in Kyoto University Hospital. Therefore, the number of patients are about seventy-five thousand in a year. In this decade, we recorded every data of in patients and outpatients as the electronic medical records (EMR). In addition, in June of 2016, a medical examination center was established in the hospital. This center is named as preemptive medicine and lifestyle related disease research center. We had been not collect the data from healthy subjects, because the Kyoto university hospital is the advanced research oriented hospital. We have been able to collect the data from healthy subjects as the result of the establishment this research center. Furthermore, in October of 2016, we constructed data warehouse system integrated these clinical data from patients and examination data from healthy people. This data warehouse system is constructed four major parts. They are an ETL system that extracts data from EMR, a database DB2 made by IBM, an analysis tool MD-View that improved IBM COGNOS-BI tool, and CPDP that also analyzes time series data.

III. OPERATION

This data warehouse system provided as a WWW application on the hospital information system called KING6. Therefore, every user of KING6 system can use this data warehouse system from own desk top machine. Data acquired through diagnosis and health checkups are updated once a day, and the user can always perform analysis using the latest data. Since a comprehensive consent to the use of the data has been acquired at the time of visit the hospital, there is no need to obtain individual consent. Types of data are diverse, they are personal data such as ID, name, date of birth, and disease related data such as examination data, pathological data, prescribed drug, in addition, social data such as zip code, occupation smoking history, and so on. By using this data warehouse, it is possible to compare dosage of medicine and multiple examination results side by side as time series data. Therefore, retrospective study on drug side effects are currently being attempted, using clinical data. In addition, we are trying to develop an algorithm to predict the state of kidney dysfunction from changes in renal function test results.

IV. CONCLUSION

We reported the data warehouse system in the Kyoto university hospital in Japan. This data warehouse system is expected that there is a possibility of changing medical care in Japan.

CONFLICT OF INTEREST

Part of the preemptive medicine and lifestyle diseases research center is donated by Resorttrust Co, Ltd.

113 - Hydrazone crosslinked hyaluronan hydrogels combined with collagen I for the treatment of corneal stromal defects

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I. INTRODUCTION

Currently there is a great need for new treatment methods for corneal stromal defects, which could replace the use of corneal keratoplasty and lessen the need for corneal donors. Regenerative medicine aims to improve tissue growth through biodegradable material mimicking the features of native cornea. Hydrogels are promising as corneal stromal biomaterials due to their favorable properties, such as efficient nutrient diffusion, transparency, injectability and softness.

The aim of this study was to form transparent hydrazone crosslinked hyaluronan (HA)-based hydrogels combined with collagen I, the predominant type of collagen in the cornea, and to study the effect of collagen and different hyaluronan modifications for the properties of hydrogels. The potential of hydrogels as a cell delivery vehicle to the corneal stroma was also evaluated.

II. MATERIALS & METHODS

In this study, two types of injectable hydrazone crosslinked HA-based hydrogels (HALD-HAADH and HAALD-HACDH) were fabricated. Hydrogels were also combined with human collagen I through imine formation. The chemical structure of the hydrogels and their rheological, mechanical, swelling, biodegradation and optical properties were characterized. The cytocompatibility of the hydrogels was determined using human adipose stem cells (ASCs).

III. RESULTS

The results showed that HAALD-HACDH hydrogel had improved stability, and higher complex modulus and stiffness

compared to HALD-HAADH hydrogel. The refractive index was also higher and closer to the native cornea with HAALD-HACDH hydrogel. The addition of collagen lowered the swelling ratio and increased the stiffness of HAALD-HACDH hydrogel. The transparency of hydrogels was not visibly affected by the addition of collagen. The inferior stability of HALD-HAADH hydrogels was observed during the cytocompatibility tests. Instead, HAALD-HACDH-hydrogels maintained the hASC viability and showed elongated cell morphology.

IV. CONCLUSION

In summary, HAALD-HACDH hydrogels showed good cytocompatibility with hASCs. The hydrogels were transparent and the refractive indexes were close to the native cornea. The injectability of the hydrogels enables the injection of cells to the damage site during the gelation. Hydrazone crosslinking is a simple gelation method that enables the gelation in short time without any harmful reagents, side-products or heating. The polymers used are also biodegradable. Therefore, we propose these HA-based hydrogels combined with collagen I as a potential material for ASC delivery to treat corneal stromal defects.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

114 - Early Health Economic evaluation via MAFEIP tool: the Warwick Experience. L. Pecchia^{1*}

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According to WHO, “the ‘problem’ of the assessments is considered only when the technology is close to its placing on the market and not during R&D process [1]. Consequently, innovative medical technologies having good potential to improve quality of life do not arrive on the market because they fail to prove their cost-effectiveness. In the past few years, the main contribution of biomedical engineering (BME) research in health technology assessment (HTA) has been in developing methods and tools for early HTA (eHTA). At this regard, the IFMBE HTA Division organized several training events on eHTA and published an eLearning platform that is freely available online with several learning modules on this emerging topic (i.e., <http://htad.ifmbe.org/>), proving the growing interest for eHTA among BMEs. This talk will present a case study of eHTA for the prediction of imminent falls due to standing hypotension in older citizen. This case study was conducted using the MAFEIP tool to calculate the incremental cost effectiveness ratio, with a threshold at £30k per qaly.

In the past two years, intensive researches were carried out in order to investigate the associations among physiological signals[2] and risk of falling and predict major drops of blood pressure (i.e. standing hypotension), which are considered to be one of the main causes for indoor falls in later life. Further details can be read in published journal papers [3, 4]. However, significant literature demonstrating how many falls could have been predicted with such a model was not available. Therefore, a survey was designed, piloted and administered among the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) experts of falls. This survey aimed to define: the % of falls that are really due to standing hypotension and, among those, the % of falls that could have been avoided if predicted. Health economic data were collected from scientific literature in order to initialize a 3 state Markov Model[5] aiming to predict the cost-effectiveness of a wearable device warning the patient if rising while a major drop in blood pressure was expected. This model was then used to identify: 1) [*best-*

case scenario] the cost-effectiveness of such a device, assuming correct lab data and the predicted cost; 2) [*worst case scenario*] the minimum level of effectiveness that the device should achieve to meet the UK willingness to pay threshold; 3) the maximum reimbursable cost, in the best and in the worst case scenarios; 4) the uncertainty of those predictions.

The results demonstrated that in the device would have been cost-effective in the best case. The worst-case analysis demonstrated that the device would meet the willingness-to-pay threshold even with a significant drop in its capability to correctly predict events. The max reimbursable cost was estimated in both best/worst scenarios and was considered convenient to continue this research. The uncertainty estimation proved that the uncertainty was small enough to avoid rank reversal problem (i.e. device not cost-effective in the best case).

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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117 - An overview of methods for multi-criteria decision analysis to support new product development in healthcare

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I. INTRODUCTION & AIM

Multi-criteria decision analysis (MCDA) has been increasingly applied in healthcare. MCDA can aid decision makers in comparing the value of alternative technologies for healthcare, while taking into account multiple, and even conflicting, decision criteria. It is useful for the early assessment of the value of innovations for healthcare, even when the performance of the technological innovation is still uncertain. Experts can express their expectations on the performance and future possibilities of the alternative technologies to apply, and the uncertainty in their expectations can be visualized. The outcomes can support decisions about the further development and application of new technologies for healthcare.

II. OVERVIEW OF METHODS OF MCDA

An overview will be presented of the most commonly used methods for MCDA, including direct rating, AHP, MACBETH, and more. These methods are not only presented in a theoretical context, but will be illustrated using an example

within the context of healthcare. These illustrations provide a basic understanding of the types of decisions in healthcare MCDA can support, as well as its support to group decision making on the development and market positioning of innovations for healthcare.

III. CONCLUSIONS

There are different methods of MCDA that can support NPD in healthcare, ranging from simple approaches to approaches that are more complex. These methods can help the developers to screen for relevant opportunities for healthcare innovations, to prioritize user requirements, and to assess the value of prototypes to healthcare. There is no gold standard in MCDA, the method selected should be appropriate for the intended goal, and fit the personal preferences of the decision makers.

CONFLICT OF INTEREST

The author declares to have no conflict of interest.

123 - Response characteristics of radiochromic film at CT radiation quality

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I. INTRODUCTION & AIM

Radiochromic films (RF) have been developed for measurement of the absorbed dose of low-energy photons. RF are self-developing and radiation sensitive, and the amount of darkening is proportional to the absorbed dose. RF are easy to handle due to their insensitivity to interior room light. In this study, energy and directional responses of GAFCHROMIC XR-QA2 film (XR-QA2) were evaluated to obtain an accurate measurement of CT dose.

II. METHODS

The measured dose and energy range of the XR-QA2 was designed to be 2-500 mGy and 20-200 kVp. XR-QA2 is a reflective-type film, and a flatbed scanner was used for the measurement of image density. To obtain the calibration curves, XR-QA2 were irradiated at 0 to 200 mGy (air-kerma) using 80, 100, 120, and 140 kVp (45~65 keV). Direction characteristics were evaluated by irradiating at a constant X-ray dose (120 kV, 5 mGy) at an incidence angle of 0 to 180 degrees at intervals of 2.5 to 10 degrees under conditions of in the air, on the phantom, in the phantom. For image density acquisition, XR-QA2 were scanned before and after irradiate using a flatbed scanner (Epson GS-11000) in RGB (48 bit) mode, 150 dpi.

III. RESULTS

The calibration curves varied according to the tube voltage. The energy response was best at 80 kVp and decreased according to increase tube voltage. In the directional characteristics, the sensitivity decreased at 90 degrees where the incident angle became parallel to the film plane, 76% in the air, 75% on the phantom and 18% in the phantom.

IV. CONCLUSIONS

The dose differences were around 10% at 80-140 kVp. This indicated that single calibration curve is not adequate for CT dosimetry performed at different energies. To obtain an accurate measurement of CT dose, calibration curve has to make base on used energy. In the X-ray CT examination, since the X-ray is incident from the 360-degree direction, even if the 100% sensitivity decreases at 85 to 95, 265 to 275 degrees, the influence exerted is 6% or less. Therefore, it is unnecessary to consider correction of the direction characteristic only for the X-ray CT examination.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

125 - Decision-Oriented HTA for Comparing Three-Dimensional (3D)/Two-Dimensional (2D) Laparoscopic Display Systems

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I. INTRODUCTION

Videolaparoscopy born as a diagnostic examination to view organs and tissues through the insertion into the abdominal cavity of a laparoscope. This technique is nowadays used in many fields (as gynecology, urology, general surgery and other specialized surgery) for both diagnosis and surgical treatment of diseases of intraperitoneal organs [1]. Traditional, 2D, video systems for laparoscopy provide the surgeon a two-dimensional image. The lack of information on spatial depth can be derived only from secondary spatial depth cues and experience, that eventually translates into greater complexity and longer execution time of interventions. Although the advantage of stereoscopy for surgical task efficiency has been clearly shown, there isn't yet a validated assessment and a common agreement about the advantages of 3D systems into clinical routine.

II. METHODS

The assessment of 3D display systems was performed with the Decision-oriented HTA (DoHTA) method [2], a method that integrates the EUnetHTA CoreModel©[3], and Analytic Hierarchy Process (AHP)[4]. This method aims to deliver valued, contextualized and shared outputs to direct and support health care decision-making especially in the hospital. Following AHP mathematical methods, a global score is determined delivering a consequent ranking between the alternatives. Finally, sensitivity analysis was performed to test the stability of the alternatives' ranking. Indeed, this work illustrates how the

sensitivity analysis could improve decision makers' knowledge and drive them towards the best performing alternative.

III. RESULTS AND CONCLUSION

DoHTA results of 3D system have highlighted the most relevant characteristics of 3D system compared to conventional 2D system, hence reporting the potential benefits and challenges of this new technology as well as the potential implications of incorporating this system into surgical practice (in a variety of pediatric surgical procedures).

Moreover, sensitivity analysis has also confirmed that the doHTA results associated to the best technology (3D laparoscopic system) are robust; this has led to a confident decision for recommending it in the hospital

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126 - Microfluidic Neurochips for Axonal Studies

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I. INTRODUCTION & AIM

Axon degeneration is a characteristic event in neurodegenerative conditions including stroke, Alzheimer's diseases and traumatic brain injuries. These rank among the most significant causes of mortality and reduction in the quality of life and they are expected to become increasingly relevant as the population ages. Miniaturization can lead to substantial reductions in consumption of time, reagents and test animals and allows novel experimental set-ups that mimic features of the central nervous system [1]. Key steps include axonal isolation and manipulation through utilization of microfluidic channels, surface functionalization for increased neurocompatibility and electrical and electrochemical characterization. This paper summarizes our work on combining optogenetics and patch clamp electrophysiology to axonal isolation as well as development of carbon based microelectrode arrays for neuronal sensing.

II. METHODS

The polydimethylsiloxane (PDMS) protocols and culture protocols for cultivating primary rat hippocampal neurons, lentiviral infections and optogenetic techniques can be found in previous publications [2,3,4]. The custom microelectrode arrays were made in similar external dimensions to commercial MED64 chips. The handling and use of animals was done according to the guidelines approved by EU and the animal ethics committee of the University of Helsinki. All animal experiments are approved by The National Animal Experiment Board of Finland. The sputtered carbon films were fabricated based on a previously published protocol [5].

III. RESULTS AND DISCUSSION

PDMS based microfluidic networks were utilized for axonal isolation of rat hippocampal neurons. The axonal isolation was combined to whole cell patch-clamp recordings by utilizing a modular chip that could be switched from a cultivation mode to an electrophysiology mode [2]. The chip was combined to optogenetic techniques to study the effect of kainate type glutamate receptor variants to synaptic development [3]. Results

obtained with the chips revealed that calcium permeable variants of low affinity GluK1-3 subunits were associated with increased synaptic density and transmission efficacy.

Carbon based materials were studied for electrical and electrochemical measurements. A conductive nanocrystalline carbon film was fabricated by unbalanced magnetic sputtering. We developed plasma etching processes for this carbon material and optimized the power, pressure and the process gas ratios. The sputtered carbon film was found to promote neuronal cell maturation by inducing an early increase in low frequency spontaneous intracellular calcium oscillations, which resulted in increased arborization. The optimized etching process was utilized to fabricate microelectrode arrays out of the sputtered carbon.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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129 - Re-engineered regulation of medical devices. What role for in silico trials?

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I. INTRODUCTION

Demonstrating the safety and efficacy of novel medical devices is challenging, highly uncertain and resource-consuming. To date, the only way to generate such evidence is by extensive testing on animals and humans through in vivo pre-clinical and clinical research. However, despite being unavoidable, the actual evidence generation paradigm often results in high development costs and may even lead to suboptimal innovation rates, costlier technologies to health-care systems and prolonged time before patients get access to valuable innovations.

In recent years there has been a growing interest in the use of in silico trials as a way to integrate and refine clinical and pre-clinical testing. At their core, in silico trials make use of computer modelling and simulation to inform product design and predict how a novel medical product would perform in a specific clinical setting.

The potential of in silico trials is underpinned by the increased acceptance by regulatory bodies such as EMA and FDA which are promoting research agendas, and reviewing their regulatory processes in order to accommodate in silico designs alongside traditional in vitro and in vivo studies.

II. AIM

To discuss how in silico trials can assist pre-clinical and clinical research in order to better inform regulatory pathways for medical devices, speed up access, reduce costs and improve population health outcomes.

III. METHODS

Building on previous work done on the different characteristics of medical devices compared to pharmaceuticals, we explored how the use of in silico trials may address specific challenges in the evaluation of medical devices for regulatory and reimbursement purposes.

IV. RESULTS

In silico trials may prove to be a valuable tool for both the design and assessment of MDs. The possibility to provide a deeper understanding of the mechanical properties of devices and their interaction with the physiology of patients early in the development phase may contribute to improve research efficiency and inform better-designed evidence generation programs throughout the whole product life-cycle. In addition, by estimating which patients' subgroups are likely to benefit the most from a novel technology, in silico trials can contribute to the design and implementation of adaptive licensing and reimbursement pathways, where access and coverage are first limited to narrower indications and then widened as the evidence base evolves, and benefits are demonstrated for wider portions of patients.

V. CONCLUSIONST

The use of in silico trials for the development and evaluation of medical devices represents a promising shift in the evidence generation paradigm. Further research is needed to improve acceptance, reliability and diffusion, and to better understand the potential impact on licensing and reimbursement decisions.

136 - Assessment of a simultaneous measurement of cardiomyocyte contraction using video image-based block matching methods and calcium imaging

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I. INTRODUCTION & AIM

Cardiovascular diseases are the leading cause of death in the world. Induced pluripotent stem cell derived cardiomyocytes (CM) provide a platform for studying CM functionality *in vitro*. Traditionally, CMs have been measured using electrophysiological methods or with fluorescent dyes, e.g. Ca²⁺ measurements. Video microscopy image analysis has enabled non-invasive measurement of CM biomechanics [1].

CM contraction-relaxation cycle is modulated by Ca²⁺. Imaging using Ca²⁺ sensitive dyes provides a way to measure the cellular Ca²⁺ fluctuations. A simultaneous measurement of Ca²⁺ transient and CM contraction from stem cell derived CM could allow the study of interaction between Ca²⁺ and mechanical function. Fluorescence in Ca²⁺ analysis changes pixel intensity potentially hindering video analysis. Thus, simultaneous Ca²⁺ and video microscopy measurements have not been conducted previously.

The aim of the study is to demonstrate simultaneous Ca²⁺ imaging and CM contraction analysis using minimum quadratic difference (MQD) based particle image velocimetry (PIV) [1] and to assess the effect of a concurrent fluorescent Ca²⁺ measurement to PIV measurement.

II. METHODS

Videos of beating CMs were recorded with concurrent imaging of Fluo-4 Ca²⁺ indicator. Ca²⁺ imaging was done with and without background light. Interlaced with Ca²⁺ imaging frames, normal brightfield microscopy was conducted. This enabled the comparison of contraction signals from videos with and without fluorescence as well as simultaneous comparison of PIV with Ca²⁺ imaging.

The videos were analyzed with MQD PIV using our previously developed method [1] that puts equal weight to all image pixels. Contractions and Ca²⁺ transients were characterized by calculating transient width parameters from one-beat long correlation-based averaged waveform templates [2]. Linear regression was used for comparing contraction duration parameters. The magnitudes were compared using symmetric mean

absolute percentage error. The time difference between the onsets of Ca²⁺ and contraction were measured from the simultaneous recording.

III. RESULTS & DISCUSSION

Motion signals measured from videos with and without Ca²⁺ fluorescence were very similar in waveform and amplitude, as shown by high ($R^2 > 0.95$) linear regression of contraction duration. The mean time interval between Ca²⁺ and contraction was 163 ms and SD of 132 ms, indicating a large variance between the cells. The difference in magnitude was measured to be 5.0% with a SD of 3.9%.

The presence of fluorescent Ca²⁺ dye has a negligible effect on motion analysis of CMs when using MQD PIV methods. This study demonstrates that CM motion can be measured synchronously with Ca²⁺ imaging and possibly other types of fluorescent dyes as well. This opens new avenues to study cellular ionic functions in combination with biomechanical measurements.

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CONFLICT OF INTEREST

The first, third and last author have a patent application related to the field. The second author has no conflict of interest.

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137 - Real-time Macro Sleep Stages Estimation using Audio Analysis

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I. INTRODUCTION

Sleep can be divided into three states: rapid eye movement (REM), non-REM (NREM), and wake, collectively named macro-sleep stages (MSS). Previously [1] we demonstrated that epoch-by-epoch (30 sec) MSS estimation is feasible using breathing and body movement sound analysis yielding matching and even superior performances compared with actigraphy-based technology. In the current study, we explored the possibility of MSS estimation in a real-time manner; this can be used, for example, for "smart-watch alarm".

II. METHODS

We acquired sleep data from 120 patients (>18 years) who were referred for routine PSG study at the Sleep-Wake Disorder Unit at Soroka University Medical Center. Patients were recorded with a digital audio recorder and an ambient microphone attached to the ceiling and one meter above the subject's head. We arbitrarily divided our data into design ($n=60$) and validation datasets ($n=60$). The MSS estimation procedure relies on a streamed audio signal of the sleeping patient, and contains several steps including: noise reduction, breathing and body movement detection, MSS feature extraction, and MSS classification. At first, the streamed audio signal is enhanced (signal-to-noise manner) by an adaptive noise reduction algorithm [2]. This step is crucial since breathing sounds can be very quiet and frequently below the background noise level. In the next step of detecting breathing and body movement sounds we used our previously designed detectors [2]. Once breathing and body movement sounds are located, nine acoustic features [1] are calculated from a 30s time window (at a 30s epoch resolution). MSS classification was performed by using an ensemble of five time-series classifiers to produce MSS estimation for epochs 1–10, 11–20, 21–50, 51–100, and >100. Each sub-classifier was designated for MSS estimation on a particular epochs range (solely), using the information hidden on the previous

epochs (previous feature vectors). For example, the sub-classifier for epochs 21–50 uses the information from the previous 20 epochs; the sub-classifier for epochs 1–10 uses no prior information at all. The sub-classifiers used in this work were neural-network models with 10, 20, 50, 100, or 200 neurons in each layer, respectively. The output of the system is a stream of 3D scores representing the MSS to occur throughout the night at a 30s resolution.

III. RESULTS AND CONCLUSIONS

Based on the validation dataset ($n=60$), for each subject, we compared epoch-by-epoch MSS between our approach and the PSG annotated sleep stages. An overall accuracy rate of $73\pm 13\%$ was registered, with Cohen's kappa coefficient of 0.39 ± 0.20 . These performances are very encouraging, showing that MSS can be reliably estimated in a real-time manner using non-contact microphone and audio signal analysis.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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140 - A Novel Measure of Instantaneous Baroreflex Sensitivity

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I. INTRODUCTION & AIM

Various time- and frequency-based approaches have been proposed to measure baroreflex sensitivity. All these methods are block-based ones. This study proposes a novel instantaneous measure of baroreflex sensitivity that enables the investigation of frequency domain characteristics of baroreflex sensitivity.

II. METHODS

This study was performed using the EUROBAVAR dataset, which consists of 10-12 minute recordings (in both supine and standing positions), acquired from 21 patients (age: 20-68 yrs.; 4 men). The data was obtained non-invasively from the subjects (healthy subjects and unhealthy ones with problems such as hypertension, heart transplant, and diabetes), and consists of the beat-to-beat interval, systolic, diastolic and mean blood pressure values. Instantaneous baroreflex sensitivity was obtained for each subject using a 15-second sliding window, by analyzing the ration between standard deviation of the inter-beat intervals and systolic blood pressure. Frequency characteristics of the instantaneous baroreflex sensitivity was then evaluated using power spectrum analysis.

III. RESULTS & DISCUSSION

Power spectrum analysis indicated that the percentage of total power of the instantaneous baroreflex sensitivity was concentrated more in the very-low frequency band [0.003 Hz - 0.04 Hz], than the ultra-low frequency band [0.0 Hz - 0.003 Hz], (respectively 71 ± 9 and $15\pm 10\%$). The average peak frequency was 0.0193 ± 0.008 Hz confirming the existence of an oscillation in the very-low frequency band. Furthermore, significant difference was found between the healthy and unhealthy populations. The proposed instantaneous baroreflex sensitivity measure is simply defined and computed. Results suggest that baroreflex sensitivity presents quasi-periodic fluctuations, an observation in accordance with the pioneering work of D. Eckberg [1].

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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141 - A Non-linear Filter to Detect Atrial Activation from Intracardiac Electrograms

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I. INTRODUCTION & AIM

Atrial activation (AA) detection during atrial fibrillation (AF) can be considered as a first step in estimating AF characteristics such as the AF cycle length. The detection of AA from intracardiac electrograms (EGM) remains challenging due to the constant variation in amplitude and duration of atrial EGM. This study is aimed at developing a robust detection of AA based on a novel non-linear filtering technique.

II. METHODS

Three consecutive patients (62-64 yrs.) with persistent AF (sustained AF duration 9-25 months) underwent catheter ablation (CA). Before CA, multipolar catheters were sequentially placed within the four pulmonary veins and the left atrial appendage for a duration of one minute. Sliding short- and long-term signal energies were measured for each sample in the EGM. A coefficient signal was then created as the ratio between the corresponding short- and long-term energies. Filtering was carried out by multiplying the coefficient signal to the EGM. Since AA have relatively higher amplitude than that of the noise and other EGM activities, the coefficient signal values are close to one where AA take place, while insignificant otherwise. Performance of the algorithm was measured with respect to activations manually annotated by a clinical expert.

III. RESULTS & DISCUSSION

For a total of 5216 annotated activations, our method achieved a 99.6% detection rate, 99.8% specificity and 99.8% positive prediction value (PPV), against a state-of-the-art approach [1] with 93.6%, 94.6% and 98.9% of detection rate, specificity and PPV respectively. These preliminary results indicate that the non-linear filter efficiently detects AA. This method is implementable by using two simple filters, avoids excessive use of arbitrary thresholds while incorporating physiological constraints. It offers low computational complexity, which makes it suitable approach for real-time/online scenarios.

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142 - Can one detect atrial fibrillation using a wrist-type photoplethysmographic device?

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I. INTRODUCTION & AIM

The potential of wearable photoplethysmographic (PPG) – based devices as diagnostic tools to detect arrhythmias is still partly unexplored. This study aims at evaluating the ability of a wrist-type PPG device to detect atrial fibrillation (AF), which could offer in the future many possibilities to improve ambulatory screening of AF. In addition to some inter-beat interval (IBI) derived features, we propose a set of innovative features consisting of complexity/organization measures and evaluate their discriminative performance between AF and other rhythms (sinus rhythm (SR) and ventricular arrhythmias (VA)).

II. METHODS

ECG and PPG signals were acquired on 16 consecutive patients during catheter ablations of cardiac arrhythmias. PPG signals were recorded with a wrist-based device embedding reflective infrared sensors (sampling rate of 21.33Hz) and a 3-D accelerometer, used to remove PPG segments corresponding to motion artifacts. Reference ECGs were annotated for all 10-second epochs belonging to the following types of rhythm: SR (381 epochs), AF (1370 epochs), and VA (415 epochs). The following features were derived from the PPG signal in these epochs: adaptive organization index [1,2], variance of the slope of the phase difference between fundamental and first harmonic components [2], permutation entropy, spectral entropy, fractional spectral radius, spectral purity index, mean, standard deviation, median, interquartile range and minimum IBI values.

III. RESULTS & DISCUSSION

Classification of AF against SR and AF against VA using decision trees (5-fold cross-validation) resulted in accuracy of 97.8/94.9%, specificity of 92.1/89.6% and sensitivity of 99.3/96.5%, respectively. Interestingly, the complexity/organization features alone performed better than the classical IBI-based features alone. These encouraging results suggest that subtle changes occurring in the PPG waveform during AF can be exploited to develop robust classification schemes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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144 - Hospital-Wide Equipment Upgrade Implementation – Perspectives from a Canadian Tertiary Pediatric Hospital

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I. INTRODUCTION & AIM

Hospital-wide equipment change management is cost- and resource-intensive, often with unrealistic lead-time expectations. It can be even more challenging in children's hospitals where equipment is often not designed specifically for pediatric population [1].

Patient monitors are one such example. Commonly there are 3 configuration profiles for settings: adult, pediatric, and neonatal. At Children's Hospital of Eastern Ontario (CHEO), the best practice guidelines divide the population to 9 age groups: neonate 1 day, neonate 4 days, infant 1 month, infant 3 months, infant 1 year, child 2 years, child 7 years, and adolescent. The design of the monitor creates the dilemma on how to standardize profiles, and forces clinical users to adapt to the limitations.

The objective of this paper is to present a successful implementation of enterprise-wide patient monitor replacement and upgrade in a pediatric hospital, and to share the lessons learned.

II. METHODS

In 2016, the hospital upgraded a fleet of 250 patient monitor devices within 5 days, while all the equipment remained in-use in a live environment. The team had a limited 3 months to prepare and execute the project with the following key components:

1. Understand the existing use cases at the hospital, and create adaptations due to the limitation of the equipment, including alarm management settings.
2. Provide hospital-wide clinical staff training to update the user competency, and fit it into regular staff rotations.
3. Assess the inventory, and implement hardware & software changes on the end-user devices in the patient care areas.
4. Update IT infrastructure, and ensure monitor data continues to flow into Electronic Medical Record.

III. RESULTS & DISCUSSION

The team was able to accomplish all the key steps within the short timeframe. Post implementation, the project team continues to collaborate with clinical teams to fine-tune the monitor settings to reduce alarm fatigue. It is an ongoing process.

IV. CONCLUSIONS

Key lessons learned from this project include the need for dry runs prior to the Go-Live, in order to minimize interruptions/errors to users, fine-tune implementation process, analyze critical pathways, and create risk mitigation strategy. Contingency plans should also be prepared to address any issues surfacing during and after the Go-Live period.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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146 - Liver-lobule-on-a-chip microfluidic device for long-term maintenance of human hepatocytes

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I. INTRODUCTION & AIM

The pressing need for *in vitro* micro-physiological platforms for drug discovery and development has given rise to the emergence of organs-on-a-chip (OOC) microfluidic devices. The possibility of reproducing the native niche of each organ in a dynamic microenvironment offers advantages over current static 2D and 3D cell culture techniques [1]. Constant removal of waste products and metabolites from the culture while providing a continuous flow of growth media is one of the major benefits of dynamic OOC systems. Additionally, physiological flow conditions can be introduced to the system allowing for reproduction of the vasculature parameters of organs *in vitro*. The liver is the main organ in the body for drug clearance and detoxification. The key role of the liver in the metabolism system of the human body makes it an interesting target organ to mimic in the dynamic OOC systems. Here we present a PDMS-based liver-lobule-on-a-chip microfluidic device [2] designed to reproduce the geometrical as well as convection-diffusion mass transport aspects of the classic liver lobule.

II. LONG-TERM CULTURE OF HUMAN HEPATOCYTES

We cultured human induced pluripotent stem cell (hiPSC)-derived hepatocytes (CDI) in honeycomb cell culture chambers with involvement of two different extra-cellular matrix (ECM) materials. In the first approach, microfluidic devices were pre-treated with rat-tail collagen I and cell suspension was seeded in the devices afterwards. Cells were seeded in the devices with the supplemented plating medium (RPMI) and culture for 5

days. The medium was changed to the supplemented maintenance media (RPMI) thereafter and replaced every other day. In the second approach, we mixed the cell suspension with 20% diluted Geltrex™ (15 mg/ml) in a 1:1 ratio. Cells were seeded in the supplemented plating media (RPMI) and were kept under conditions identical to approach one during the hepatocyte maturation period. After day 5, however, the formulation of maintenance media was changed to supplemented DMEM/F12. Cultures were kept viable and functional for at least three weeks. In both scenarios cells formed 3D tissue-like structures and formation of bile canaliculi network was observed in the devices versus 2D static cultures. The compatibility of the device for drug toxicity applications and multi-cellular *in vitro* organotype construction is currently under exploration.

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151 - Can we link biophysics and physiology in transcranial brain stimulation?

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I. INTRODUCTION & AIM

Transcranial magnetic brain stimulation (TMS) is a versatile tool to non-invasively modulate and shape brain activity. In neuroscience research, it is a valuable complement to neuroimaging methods, as it allows demonstrating causal relationships between brain function and structure. It is further promising as a novel treatment option for some neuropsychiatric diseases such as depression. However, it is still hampered by a limited understanding of its mechanism of action.

Here, I aim to demonstrate that integrating electric field modelling with electrophysiological measurements can improve our understanding of how TMS acts on brain activity.

II. METHODS

I will report on three recent studies, which combined electrophysiological measurements of muscle responses to monophasic TMS pulses with realistic estimates of the induced electric field [1], [2], based on the finite-element method and MRI-derived individual head models. In the first study [3], the orientation of a standard figure-8 coil was systematically varied and the field changes in different subparts of the motor cortex were compared with the electrophysiological threshold changes. In the second study, three figure-8 coils having different field decays were used and the differences in the electrophysiological thresholds for current direction posterior-to-anterior (PA) were correlated with the differences in the calculated field distributions. Finally, the last study tested the correlation between the field in the motor cortex and the onset delays of the muscle responses for anterior-to-posterior (AP) current orientation.

III. RESULTS

The first two studies consistently show that TMS stimulates the region around the gyral crown and that the maximal electric field strength in this region is significantly related to the electrophysiological response. In the third study, the same part of the motor cortex exhibits a significant negative correlation between the onset delays and the field strength.

IV. CONCLUSIONS

Our studies are among the most extensive comparisons between FEM-based field calculations and physiological TMS effects so far. The gyral crown is identified as preferred TMS target, suggesting that TMS at the optimal current orientation mainly stimulates subarea 4a of the motor cortex. In addition, in those subjects in which lower field strengths are sufficient to induce a motor response for current orientation AP, later I-waves are recruited. This suggests that local interindividual differences in cortical organization in the upper part of M1 might underlie the observed latency differences.

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152 - Towards combined MEG and MRI

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I. INTRODUCTION & AIM

In magnetoencephalography (MEG), weak magnetic fields are measured outside the scalp to locate brain activity. For data interpretation, accurate structural knowledge about the head is needed from magnetic resonance imaging (MRI). However, since MRI and MEG are measured with different instruments, their coordinate systems may be misaligned, causing errors in locating the neuronal activity. MEG has been performed since early 1970's with superconducting quantum interference devices (SQUIDs). SQUIDs can be used also to measure MRI at very low magnetic fields (~100 microtesla); this technique is called ultra-low-field MRI (ULF MRI). ULF MRI is possible thanks to the extremely good frequency-independent sensitivity of the SQUID and the prepolarization technique, in which the head is subjected to a relatively strong field (~100 mT) before the MRI field manipulations and signal detection at lower fields [1].

Our goal is to develop hybrid MEG–MRI technology to enable concurrent measurement of MEG and MRI with the same SQUID sensors. Advantages are improved workflow, elimination of the coregistration error, and new measurement modalities such as injected-current-density imaging (CDI). CDI would inform us about tissue conductivities, improving the accuracy and reliability of inverse-problem solutions of MEG.

II. METHODS

Continuing from the prototype MEG–MRI system (Vesänen et al., *Magn. Res. Med.* 2012) developed by Aalto University, Elekta Ltd., VTT Technical Research Centre of Finland and

Helsinki University Hospital, we are building a second-generation system to enhance the MRI power signal-to-noise ratio by about three orders of magnitude, aiming at a practical device ready for neuroscientific and clinical testing.

III. RESULTS

Progress in SQUIDs, low-noise liquid-helium dewars, electronics, MRI magnets etc. seem to make our aim achievable.

IV. CONCLUSIONS

The current status of MEG–MRI technology development and its intended benefits will be discussed.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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153 - Connectomics and ZEISS MultiSEM – the fastest scanning electron microscope in the world enables extreme-scale electron microscopy

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I. INTRODUCTION & AIM

Connectomics is a still new discipline in the Neurosciences to study complex synaptic networks assembled by billions of neurons with the ultimate goal of a better understanding of neuronal functions. One way to shed some light on the structural and therefore functional organization of these networks is serial array tomography. Ultrathin slices are prepared from blocks of tissue embedded in resin, followed by imaging these series of sections using scanning electron microscopes (SEM). After aligning and merging all acquired section images into a 3D volume, human trained computer algorithms delineate and visualize the fine structure of neurons. The result is a detailed 3D map of the brain: the Connectome. However, at a sufficient resolution, the imaging might take more time than most researchers can dedicate to a single experiment or project, as current single beam SEMs are limited in their ultimate data acquisition rate at a given resolution by electron interactions and detector bandwidth. Scanning multiple electron beams in parallel circumvents the limitations in scan speed of single beam SEMs. Such a multi-beam SEM can image areas of several mm² at nanometer pixel size within hours. The dramatic increase of imaging speed opens the door for electron microscopy to applications where both high resolution and large scan area are of key importance. The presentation will give an overview of the current state of the technology, its potential application space and the challenges in data handling imposed by the enormously increased data rate.

II. METHODS

With the advent of automated sample preparation devices [1] and the first commercially available multi-beam SEM [2], dense reconstructions of larger brain volumes at nanometer resolution are now within reach. Whereas the imaging of one mm³ of tissue with the required pixel resolution would take ~6 years with a conventional single-beam SEM, the 61-beam ZEISS MultiSEM 505 could do the same task in merely 4 months. A second variant of the multi-beam SEM from ZEISS with 91 beams and a higher current per beam [3] increases the imaging

throughput even further. A net acquisition rate of up to two TeraPixel per hour is now achievable, therefore enabling extremely large-scale imaging experiments.

III. RESULTS

We expect first results in the field of connectomics based on MultiSEM data being published within the next coming months. Given the extremely large amount of data, suitable processing and analysis tools need to be developed first and in some cases even from scratch. However, another ongoing application development in bone research already lead to a study published in 2016 [4]. A large-area data set acquired from a selectively etched surface of a human femur allowed for the quantitative analysis of different cell states and their localization with respect to other bone constituents.

IV. CONCLUSIONS

The ability to acquire much larger data sets in shorter time enables better qualitative assessments due to more contextual data, as well as real quantitative statistics, as compared to sparse sampling. Ultimately, this opens up new perspectives for scanning electron microscopy in biomedical research.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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158 - Effective dose display system for patients undergoing X-ray screenings for gastric cancer

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I. INTRODUCTION

There are few articles that calculated the effective dose of the gastric cancer screening [1, 2]. The effective dose is calculated based on actual measurements using a dosimeter and a standard phantom (human body model) or using a software. The phantom-based effective dose values represent the amount of exposure for a standard human rather than the individual effective dose for each subject and are practically not very useful.

Furthermore, because these methods require a certain amount of time for calculation, they are unable to instantly, i.e. in real time, provide the effective dose of the test subject on completion of gastric cancer X-ray screening.

The purpose of this study was to develop an 'gastric cancer X-ray screening effective dose display system' to display, in real time, the effective dose of a test subject post an X-ray screenings for gastric cancer.

II. SUBJECTS AND METHODS

The subjects comprised 499 individuals who underwent screenings for gastric cancer at three institutions. At each institution, the dose area product (DAP) (cGycm^2) for each examination obtained using DIAMENTOR M4-KDK (PTW, Freiburg, Germany) was entered into the software PCXMC ver2.0.1.3 (STUK-Radiation and Nuclear Safety, Helsinki, Finland) for calculation of the effective dose (mSv). A regression formula for the relationship between DAP (mGycm^2) and the effective dose was derived. A programming software was then created to display the effective dose.

This study obtained approval of the study Ethical Review Board of the Osaka Centre for Cancer and Cardiovascular Disease Prevention.

III. STATISTICAL ANALYSES

The regression equation of the effective dose and DAP conducted a regression analysis. These statistical analyses were

performed using PASW Statistics 18 for Windows (IBM SPSS Japan Inc., Tokyo, Japan).

IV. RESULTS

The mean DAP was 17388.46 mGycm^2 and effective dose was 7.13 mSv. The regression formula was as follows:

$$(i) \quad Y = 0.737 + 0.0003676X,$$

wherein Y is the dependent variable (mSv), X is the independent variable (mGycm^2), 0.737 is the constant and 0.0003676 is the coefficient. The effective dose at the end of the examination was displayed on the computer screen.

V. CONCLUSION

It was possible to display the effective dose (mSv) of subjects undergoing X-ray screenings for gastric cancer examination for gastric cancer instantly after the completion of an X-ray examination.

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CONFLICT OF INTEREST

The authors hereby declare that they have no conflict of interest.

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162 - High Frequency QRS analysis for detection of Stress-Induced Ischemia

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I. INTRODUCTION & AIM

To this day, the most common test for diagnosing Ischemic Heart Disease (IHD) is the exercise ECG test mainly due to its availability, safety and its low cost. However, it is widely recognized that its accuracy is too low with sensitivity of 45%-50% [1]. Previous studies have shown that High Frequency QRS analysis (HFQRS) which uses information from the depolarization phase of the cardiac cycle is more accurate and sensitive for the detection of stress-induced ischemia compared to changes in the repolarization phase (mostly ST segment deviations) [2],[3]. However, it has required a sampling rate of 1 kHz, which is not common in most ECG devices. In this study, we aim to examine the potential of the HFQRS analysis in diagnosing IHD patients using a standard ECG device with sampling rate of 500 Hz.

II. METHODS

A group of 98 patients (54 men) who underwent a bicycle stress ECG test was selected from the Finnish Cardiovascular Study (FINCAVAS) database [4] to comprise three equally sized subgroups of patients classified according to their gold standard (GS): Coronary Artery Disease (CAD) (32), No-CAD (33) and Low-Likelihood CAD (LLC) (33). Coronary angiography used as the GS [4]. All files were recorded at 500 Hz with *CardioSoft* exercise ECG system (GE Healthcare, Freiburg). Prior to the HFQRS analysis the raw data files were interpolated to 1 kHz and thereafter analyzed by a commercial software called *HyperQ* (BSP, Tel Aviv) using standard parameters [2]. In contrast to previous HFQRS studies that typically analyzed the band of 150–250 Hz, the upper part of this band was not available in this study due to the limited sampling rate. Exclusion criteria were QRS duration ≥ 120 ms and noisy tests (7 and 5 patients respectively). In addition, patients who did not reach their target heart rate and have not manifest significant HFQRS changes were excluded as well (15 patients).

III. RESULTS & CONCLUSION

We compared the diagnostic performance of the HFQRS analysis to a computerized ST analysis. First, we examined the 43 patients with angiography results (19 CAD and 24 no-CAD). This comparison showed the HFQRS analysis is significantly more sensitive (84% VS 37%, $p < 0.01$) and preserves reasonable specificity which was lower but not statistically significant (67% VS 75%, $p = 0.65$). Then, we also included the LLC subgroup as No-CAD (19 CAD and 52 no-CAD). This affected only the specificity, which did not change significantly with *HyperQ* at 73% VS 79% for ST ($p = 0.75$). All P-values were calculated using the two-tailed Fisher's exact test.

These results suggest that much of the required energy used for HFQRS analysis exists even in the limited frequency band. HFQRS may be applied to existing ECG devices, and contribute to improved diagnosis of IHD.

CONFLICT OF INTEREST

NO, YG and SA are employees of BSP. All other authors declare that they have no conflict of interest.

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165 - Rotating Frame Relaxation Time Mapping for Cardiac Magnetic Resonance Imaging

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I. INTRODUCTION AND AIM

Magnetic resonance imaging (MRI) is a golden standard to measure cardiac functional parameters. Late gadolinium enhanced (LGE) images are typically acquired to visualize fibrotic areas in myocardium. The non-contrast agent alternative for LGE is rotating frame longitudinal relaxation time $T_{1\rho}$ mapping. So far, $T_{1\rho}$ is used mostly in preclinical studies, since relatively high specific absorption rates (SAR) has limited its clinical applicability. Relaxation Along Fictitious Field (RAFF) [1] and further development RAFF in n^{th} rotating frame [2] are rotating frame type relaxation time measurements, where spin-locking field contains fictitious component allowing the lower SAR compared to $T_{1\rho}$ while maintaining the spin-locking field. RAFFns were applied originally for brain imaging, but in the current work, the application for cardiac imaging is studied.

II. METHODS

Mouse models of myocardial infarct (MI) by ligation of left anterior descending coronary artery, and mild and severe hypertrophic cardiomyopathies by transverse aortic coarctation (TAC) were applied to demonstrate the RAFFn contrasts in pathologic myocardium. In vivo and ex vivo experiments were done using quadrature volume transceivers at 9.4 T and 7 T. All relaxation time data was acquired using electrocardiogram and respiratory triggered pulse sequences with rotating frame relaxation preparations. Both MI and TAC mice were followed up by MRI and the mice were sacrificed and prepared for histology

after the follow up period. All experiments were done in accordance of Helsinki Declaration and approved by the Finnish Committee for the use and care of laboratory animals.

III. RESULTS

The RAFFn and $T_{1\rho}$ relaxation time mappings showed elevated relaxation times in infarct areas and the similar infarct areas were detected in LGE and in histology images. Increased RAFFn relaxation times and $T_{1\rho}$ in chronic infarct and moderately increased in acute infarct were seen. Increased RAFFn and $T_{1\rho}$ relaxation times were detected in severe hypertrophic cardiomyopathy compared to mild one and normal myocardium. Masson's trichrome stained histology sections confirmed increased fibrosis in severe model compared to mild one.

IV. CONCLUSIONS

The RAFFns provide a low SAR alternative without contrast agent for $T_{1\rho}$ and LGE to visualize fibrosis in myocardial infarct and in hypertrophic cardiomyopathy.

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166 - Nanofibers doped with functionalized nanodiamonds for treatment of non-healing wounds

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I. INTRODUCTION

According to the data from WHO [1], there are 8.5 % of diabetic people among adults globally. Non-healing wounds are one of the common complications of diabetic patients, which highly affect the quality of their life. However, appropriate treatment has not yet been established. One cause of a non-healing wound are increased levels of matrix metalloproteinases (MMPs), enzymes responsible for degradation of extracellular matrix during wound healing process [2]. Higher levels of MMPs can be decreased using local delivery of small interfering RNA (siRNA) by RNA interference [3]. This siRNA can be tracked and delivered into cells by fluorescent nanodiamonds.

Electrospun nanofiber materials are being widely tested as a scaffold system for drug loading. It has been proven that nanofibers are suitable material for use in the treatment of non-healing wounds [4].

The aim of our work is to create a wound dressing for non-healing wounds by incorporating siRNA-functionalized fluorescent nanodiamonds inside core/shell nanofibers.

II. METHODS

For delivery of the siRNA inside cells responsible for high MMP levels, we employed a biocompatible fluorescent nanodiamond carrier (ND). We treated the surface of the nanodiamond with polyethylenimine to establish the electrostatic binding of siRNA. We used zeta potential measuring to prove the proper functionalization of fluorescent nanodiamonds by siRNA. We monitored the entry of functionalized nanodiamonds inside cells by confocal microscope. ND-siRNA complexes were incorporated into nanofibers from highly biocompatible materials: polyvinyl alcohol (PVA) and poly-ε-

caprolactone (PCL). To visualize nanofibers with encapsulated nanodiamond complexes we used confocal microscopy. Real-time PCR was used to assess the silencing effect of ND-siRNA complex *in vitro* on 3T3 murine fibroblasts

III. RESULTS AND DISCUSSION

We created ND carriers with surface siRNA functionalization, which are capable of local delivery and decreasing MMP levels. We performed encapsulation of NDs into nanofibers to produce a wound dressing applicable *in vivo*.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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171 - Development of novel 3D histopathological methods for osteoarthritis

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I. INTRODUCTION

Osteoarthritis is the most common musculoskeletal disease worldwide. Despite extensive research, etiology of osteoarthritis is still poorly understood. Histopathological grading of osteochondral tissues is widely used as the gold standard in osteoarthritis research, and it is also relatively common approach in post-surgery *in vitro* diagnostics. However, relying on thin tissue section, conventional histopathological grading includes a number of limitations, such as: (i) destructiveness, (ii) sample processing artefacts, (iii) a few 2D sections are limited to evaluation of local degeneration only, (iv) 2D section does not represent spatial 3D structure and composition of the tissue, and (v) the final outcome is subjective.

II. OBJECTIVES

There are following objectives in this study:

1. To establish and validate the very first 3D histopathological grading of osteoarthritis based on micro-computed tomography (micro-CT) technologies.
2. To use the established method to clarify the beginning phases of OA.
3. To validate the developed 3D histopathological grading method for *in vivo* use.

III. METHODS

A large amount of human osteochondral samples from patients undergoing total knee arthroplasty, as well as from healthy cadavers, have been collected under the permissions from the institutional ethical boards. All the participating patients were

given informed consent. Furthermore, tissue samples from experimental animal models (bovine, rabbit) were utilized in the project. All the samples were imaged *in vitro* with micro-CT, and some of them also with clinical high-end extremity CT, using specific contrast agents to quantify tissue composition and structure in 3D within a large volume.

IV. RESULTS AND CONCLUSIONS

In this talk, recent results and conclusions from this ongoing ERC Starting Grant project will be reviewed. The special emphasis of the talk will be to introduce novel semi-quantitative and quantitative approaches for quantifying structure and composition of osteochondral tissues in 3D. The associations between quantitative parameters and conventional histopathological evaluation of progressive phase of osteoarthritis will be also presented. Finally, some approaches to translate these findings *in vivo* will be discussed.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The author declare that he has no competing conflicts of interest.

172 - Design and Evaluation of a Mandible Endoprosthesis System

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I. INTRODUCTION & AIM

The gold standard for reconstruction of mandibular defects is the fibula free flap approach. However, this strategy remains to be associated with various disadvantages. Patient may suffer from donor site morbidity [1-2], which requires longer hospitalization stay and rehabilitation. Our goal is to develop an alternative strategy to replace the diseased mandible bone upon segmental resection.

In this study, we aim to design an endoprosthesis system that can provide a stable reconstruction of a segmental jaw defect in a preclinical animal model. A monkey model will be selected due to its close anatomical similarity to humans. The load-bearing capability of the endoprosthesis system will be evaluated using a finite element (FE) model prior to *in vivo* implantation.

II. METHODS

Mandibles from euthanized monkeys were harvested in compliance with the Institutional Animal Care and Use Committee at Singhealth, then imaged using a computed tomography (CT) scanner. The CT scans were used to visualize the monkeys' teeth and bone anatomical structures; Physical measurements were made on the cross-sections of the harvested mandible bones using vernier calipers in order to determine the appropriate height, thickness and stem diameter of the endoprosthesis. To simulate performance of the implanted titanium-based endoprosthesis under a maximum loading force of 700N during short and long term implantation, explicit dynamics and static FE analyses were performed respectively. Various endoprosthesis configurations were designed and 3D printed, then compared based on their ease of clinical use and ability to withstand repetitive bite forces without device loosening and fatigue failure.

III. RESULTS & DISCUSSION

Based on the selected endoprosthesis design, results showed a maximum relative movement of 3-5um at the interface of the implanted endoprosthesis stem within the mandibular stump. This micromotion at the bone-implant interface is considered minimal, and likely favorable for osseointegration to take place during the initial phase upon implantation. Upon osseointegration, simulations of the rigid bone-implant body revealed a maximum von Mises stress profile of 459-666MPa at the endoprosthesis stems. This is within an allowable stress range that the mandible bone can withstand.

IV. CONCLUSIONS

Results of the FE analysis showed promise. The functionality of the titanium-based endoprosthesis will be further validated using mechanical testing methods and implanted in a segmental monkey jaw defect model for 6 months. If proven to be successful, this mandible endoprosthesis system is expected to provide patients with better clinical outcomes and quality of life.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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173 - Spheroid-based bio-lead with PC12 cells for development of neuronal stimulation electrodes

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I. INTRODUCTION & AIM

When a metal electrode implanted into the tissue, microglia become activated and migrated to the site of implantation, and they are located next to the electrode interface. After those responses, the reactive astrocytes encapsulate the implanted electrode. Since the encapsulation response increases impedance, it is hard to stimulate from neuronal region [1]. In addition, an implanted electrode causes an induced current by electromagnetic field so that the generation of induced current increases possibilities of tissue damage. Therefore, we propose the technology procedures and concept of development: Spheroid-based bio-lead with PC12 (rat adrenal medulla cell line, ATCC) cells for development of neuronal stimulation electrodes. Compared with the implantable electrodes that mentioned above, the newly developed bio-lead will enable stimulating the neuronal tissues without tissue encapsulation responses.

II. METHODS

Prior to form neuronal-like spheroid structure, we examined using the PC12 cells cultured in the collagen coated dish with 200ng/ml NGF (Nerve Growth Factor) for confirmation of cellular differentiation. Because NGF promoted an apparent morphological transformation of PC12 cells. We fabricated PDMS-based microwells (400 μ m diameter), by using soft-lithography and photo-lithography techniques. PC12 spheroids were generated concave microwell arrays made using meniscus of the PDMS prepolymer [2]. This PDMS-based microwells offer substantial advantages for formation and harvesting of 3D micro-tissue. This PDMS-based microwells offer substantial advantages for formation and harvesting of 3D micro-tissue. PC12 cells seeded into these microwells and cultured for several days. Differentiated PC12 cells maintained in the RPMI 1640 media with N2-supplement. PC12 spheroids from 400 μ m diameter concave wells seeded to a micromold having 600 μ m diameter wells for formation like bio-lead.

III. RESULTS & DISCUSSION

Upon exposure to NGF in microwells, PC12 cells gradually initiate to differentiate after 2 to 3 days. In this study, we used immunofluorescence microscopy to investigate the microtubule cytoskeleton protein (MAP-2) during the development of spheroids culture. In addition, immunostaining of spheroids for MAP-2 and β 3-tubulin to investigate possible neuronal differentiation effects showed that spheroid-based model positively affected growth and neuronal differentiation of PC12 cells. It appears that spheroid-based bio-lead with PC12 cells may offered as a better technique for future neuronal tissue engineering investigations such a development of neuronal stimulation electrodes. After procedures of verification that the bio-lead can be used, we will perform whether the spheroid-based bio-lead is suitable for electrodes. In addition, the proposed spheroid-based models can have a possibility to apply for studies on investigation of neural prostheses and electrical stimulation therapies.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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174 - The Contribution of Tracheal Sound Signals to sleep apnea diagnosis

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I. INTRODUCTION

Combining an acoustic sensor and a suprasternal pressure sensor, the PneaVoX technology could be used as a threefold sensor: an oro-nasal respiratory flow sensor, a snoring monitoring sensor and a respiratory effort monitoring sensor.

II. OBJECTIVE

The objective of this study is to show the importance of the PneaVoX technology in the diagnosis of sleep apnea syndrome.

III. METHODS

PneaVoX measurements were performed using CID102L8D and CIDLX (Cidelec, France). In addition to the usual polysomnography (PSG) sensors, esophageal pressure was recorded as well. Only data from ventilatory signals was analyzed. The respiratory events that were identified were sleep apnea and hypopnea as well as increased respiratory efforts.

IV. RESULTS

PneaVoX measurements were performed using CID102L8D and CIDLX (Cidelec, France). In addition to the usual poly-

somnography (PSG) sensors, esophageal pressure was recorded as well. Only data from ventilatory signals was analyzed. The respiratory events that were identified were sleep apnea and hypopnea as well as increased respiratory efforts.

V. CONCLUSIONS

The PneaVoX technology has the potential for detecting apnea, hypopnea, snoring and respiratory efforts. Associated with other PSG sensors, the PneaVox technology is a valuable solution for the detection of respiratory events during sleep diagnostic studies. Added to the AASM recommended sensors, the PneaVoX technology can only make pathophysiological information more reliable and improve sleep studies.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The author declares that he is a full-time employee at the company CIDELEC.

178 - Remote optical assessment of *in-vivo* skin: methods, prototype devices and clinical applications

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I. INTRODUCTION

A brief overview on optical techniques for non-contact skin assessment, developed at the Biophotonics Laboratory, University of Latvia, is presented. Three imaging modalities have been exploited – multispectral reflectance imaging, autofluorescence photobleaching rate imaging and photoplethysmography imaging. Clinical potential of these approaches has been evaluated.

II. THE PROTOTYPE DEVICES

Operation principles and designs of three groups of laboratory-developed prototype devices are discussed:

- Smartphone add-on devices for spectral imaging, skin chromophore mapping, erythema assessment and mapping of autofluorescence photobleaching rates,
- Photoplethysmography imaging devices for local anesthesia monitoring,
- Multimodal imaging devices for mapping of skin chromophores, fluorophores and blood perfusion.

III. CLINICAL VALIDATION

All prototypes passed preliminary clinical validation at hospitals and clinics in Riga: Latvian Oncology Center, Riga Eastern University Hospital, Hospital of Traumatology and Orthopedics, Laser Plastic Clinic and Health Center – 4. Typically, 20-50 volunteers participated at each trial. The obtained diagnostic maps of clinically significant parameters agreed well with the physiological models, so confirming the expected functionality of the prototypes; more details in [1-5].

IV. CONCLUSIONS

The developed portable optical imaging devices have demonstrated potential for clinical applications in dermatology, oncology and anesthesiology. The revealed specific features for bedside applications will be taken into account in the further designs. Activities toward commercialization of the devices are in progress [6].

ACKNOWLEDGMENT

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179 - Transcranial magnetic stimulation device with electronic targeting

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I. INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method. A TMS device produces a brief magnetic field pulse, which induces electric fields and currents in neuronal tissue. Focal stimulation can be obtained with a (hand-held) figure-of-eight coil; to change the stimulation target, the coil must be moved. The physical movement of the coil is inherently slow, which rules out any quick adjustment to the stimulation target. To overcome this limitation, an array of small coils has been suggested for electronic stimulation targeting [1–2]. Such an array would, however, require a large number of channels and much more power than conventional TMS—to our knowledge—no such device has ever been built.

II. METHODS

We introduce a practical approach for electronically controlled stimulation targeting. Our approach requires only a few channels to control the locus of stimulation: already with two channels, the target can be moved steplessly along one dimension. We will demonstrate this with electric field measurements with our TMS-coil characteriser [3] and *in vivo*.

III. RESULTS

We designed and built a two-channel TMS device in which the locus of stimulation can be adjusted electronically. The de-

vice comprises a two-channel TMS transducer with a minimum-energy figure-of-eight coil and an overlapping oval coil. The figure-of-eight coil alone would stimulate a target underneath the transducer centre; when both coils are driven simultaneously, the stimulation target in the cortex can be translated within a 30-mm-long line segment along a desired axis.

ACKNOWLEDGMENT

The coil former parts for the transducer were manufactured by Enna Rane (Aalto University Design Factory).

CONFLICT OF INTEREST

The authors are inventors on related patent applications. R.J.I. is advisor and minority shareholder of Nexstim Plc.

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180 - Development of a dual mode marker for navigated dental implant surgery

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I. INTRODUCTION & AIM

Oral Implantology is a growing field for rehabilitation of missing teeth. Dental implants are in 96% positioned free hand but risks of suboptimal placement have been reported. A 3D real time navigation system has been developed by fixing two stereo cameras to the drill to guide the surgeon during implant insertion. To follow the actual drill position on the Cone Beam CT (CBCT) planning images, a marker had to be developed being precisely identifiable on CBCT images as well as via an optical pattern by the cameras. The aim of the present study was the development of such a dual-mode and sterilisable marker.

II. METHOD

An optical pattern was laser engraved on a ceramic substrate with two asymmetrically positioned holes allowing the identification of substrate position and orientation on CBCT images. Substrate and optical pattern dimensions were verified using a micro-gauge and optical microscope images respectively. Six markers were cleaned and steam sterilized 20 times. The surface was analysed by optical and scanning electron microscope images including energy dispersive X-ray spectroscopy (EDX).

III. RESULTS

Substrate dimension were of 15.008 ± 0.003 mm, 10.002 ± 0.004 mm and 2.022 ± 0.008 mm for length, height and

thickness respectively and remained within the specified tolerances (height, length: 0.05 mm; thickness: 0.1 mm) as well as the angular error of the optical pattern on the marker ($<0.25^\circ$). Only its position on the marker revealed a systematic error up to 0.1mm. No changes in contrast or surface deteriorations were observed after 20 cleaning and sterilisation cycles. EDX results show some fluctuations in the relative occurrence of the different elements especially for carbon.

IV. CONCLUSIONS

We developed a highly precise and sterilisable dual-mode marker with a high contrast optical pattern. The remaining systematic error of the position of the pattern on the substrate can be corrected by optimizing the positioning of the substrate during the laser engraving process. Changes in the carbon concentration on the surface can be due to the steam sterilization process and do not seem to have any influence on the contrast of the optical pattern on the substrate. First tests of the overall tracking precision of the system within its whole working room have confirmed the expected overall submillimetric precision.

CONFLICT OF INTEREST

F. Berlinghoff is CEO, M. Breitenstein Quality and Product Manager, S. Böhringer responsible for R&D, P. Jürgens CMO and E. Schkommodau co-founder at Mininavident AG.

183 - Multi days' classification of hand motions: Daily assessment based on surface electromyography (EMG)

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I. INTRODUCTION

Considerable work has been done on pattern recognition methods for classifying user motion intent based on surface electromyography (EMG) under controlled laboratory conditions. However, these methods are still not clinically viable for upper limb prostheses control due to their limited robustness in user's daily life situations. In this study, we investigated the variation in EMG classification performance over the course of seven consecutive days in order to account for changes in accuracies induced due to non-stationarity of EMG signal and quantify the degree of variation in classification performance over time. This study will provide insight to the design of long-term myoelectric control applications.

II. METHODOLOGY

The experiment was performed on ten able-bodied subjects (all male, age range: 18-38 yrs., mean age 24.6 yrs.). Six bipolar Ag/AgCl electrodes were used to record surface EMG targeting the following muscles: Extensor carpi radialis, Extensor digitorum muscle, Extensor carpi ulnaris, Flexor carpi radialis, Palmaris longus and Flexor digitorum superficialis. Subjects were prompted to execute five comfortable and sustainable contractions corresponding to 11 classes containing 10 active motions (open hand OH, close hand CH, wrist flexion WF, wrist extension WE, pronation PR, supination SU, side grip SG, fine grip FG, agree AG, pointing PO) and resting state (NM). Eight time domain features : mean absolute value (MAV), zero crossings (ZC), slope sign changes (SSC), root mean square (RMS), Willison amplitude (WAMP), waveform length (WL), myopulse rate (MYOP), cardinality (CARD)

were computed. Physical and physiological conditions were tried to keep consistent during the experiment such as electrode shift, inter-electrode distance and muscle fatigue. The classification error (ratio between misclassifications and total classifications) was used as the performance measure. Data from each day was classified separately without adding the data from remaining days. Linear discriminant analysis (LDA) was applied for classification due to its high performance on EMG signal and low computational cost.

III. RESULTS

Average classification error was 5.37 ± 2.69 % for all 11 motions on first day, which increased to 8.94 ± 8.22 % on fourth day. From fifth until seventh day, error reduced marginally by 1.1% to 7.84 ± 6.70 %. Thus, a plateau was observed after day four. In six out of ten subjects, average error on seventh day was equal or less than error on first day. Nevertheless, if only seven functional motions including rest were tested, average error reduced significantly to 1.51 ± 1.56 % on first day increasing to 4.78 ± 7.07 % on seventh day.

IV. DISCUSSION

Results show that able-bodied subjects are capable of maintaining classification performance within 4 percentage points in a course of 7 days. Decreasing the number of classes significantly improves performance, however with similar trend in degradation of classification accuracy. Future investigation will involve performance across days.

184 - MIDAS EU Project– Meaningful Integration of Data Analytics and Services

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I. INTRODUCTION & AIM

In the current information driven society, large amounts of data are available to support the decision-making, but in practice, the decisions are still often made with limited data, or narrow perspectives on details. The MIDAS EU project will bring policy makers, data owners and scientists together to develop a decision support system (DSS) for health policy making at regional and national level. An efficient usage of data can create new opportunities to improve healthcare, quality of life and develop personalized medicine. Currently, the main limitations for data driven decision making in healthcare are in legislation and heterogeneous data management. For example, using healthcare records together with biobank registers and hospital management data requires significant amount of paperwork and in some cases, the aimed study can even turn out to be prohibitively difficult to carry out due to the involved bureaucracy.

One central aim of the MIDAS project is to act as a proof of concept (PoC) of a national DSS to show the possibilities if the regulations would allow a broader range of data integration. The final system will support the decision makers like ministry and government to make information-based decisions for health policies. With traditional data management approaches, it is challenging to study how different policies are affecting each other and what practical consequences they might have: there are no efficient forecasting tools available for policymaking. Policies are always affecting on populations, and thus MIDAS project concentrates on larger cohorts instead of single subjects.

II. IMPLEMENTATION

MIDAS will utilize citizen data from MyData together with social media like Twitter and open data. These are used to enrich the controlled healthcare system data, which is provided in Finland from University of Oulu (UO), City of Oulu (CO) and National Institute for Health and Welfare (THL). The data integration is based on state of the art data virtualization, which is bundled with Apache Spark framework. The CO provides up-to-date data from regional healthcare related services and THL provides corresponding data from national level. The Oulu Cohort data from UO will be used to test and develop the system dynamic models. The used forecasting models will be based on the interviews of key personnel in healthcare together with big data analytics of connected key factors. Social media and news analytics supports the social evaluation of impact models.

The data analytics implementation of MIDAS is based on Apache Spark framework, which supports state-of-the-art data analytics tools from e.g. Python, R and Scala. The model-based forecasts are implemented with Simantics server software. All analytics will use dedicated user interface (UI). The UI will include a fully customizable dashboard where users can add, remove and modify different analytics and visualizations. The dashboard UI will also include personalization options and options to share, publish or send the created dashboard to other users. Based on initial interviews three main types of users will be catered for: high-level policy makers (predefined dashboards); supporting personnel (creators of the dashboards); and research oriented users (developers of new analytics).

III. RESULTS & DISCUSSION

The first policymaker interviews in Oulu revealed the initial topics for the Finnish pilot: Prevention of mental health problems, wellbeing of young people and wellbeing of elderly people. After interviews for wider scope of potential end-users and policymakers, the focus in Finnish consortium evolved to a combination of the original topics: the mental health and wellbeing of young people. This topic was emphasized in most of the interviews. By applying efficient preventive policies for problems existing with the focus group, significant long-term impacts can be archived. The interviews with owners of controlled data have shown that legislation and data sensitivity will force the project to develop separated anonymized secured datasets from each source separately, and only these preprocessed datasets can be connected to MIDAS data virtualization system. This limits the data integration and sets new perspective for data analytics. Even with the limitations, MIDAS can still provide the functional PoC for national DSS for policy making in health. The project was started in November 2016 and will last 40 months. The MIDAS system will be implemented in parallel for four EU sites: Finland, Northern Ireland, Republic of Ireland and Basque Country.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

188 - A Study to find the Optimal Imaging Condition and Evaluation of the Usefulness of the PROPELLER DWI on Pediatric Ear 1.5T MR Examinations

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I. INTRODUCTION & AIM

Recently, the usefulness of non-echo-planar imaging (EPI) diffusion-weighted imaging (DWI) for detection of cholesteatoma is reported in many studies [1]. On MR examinations, there are prominent geometric distortions from the susceptibility effect at the border between the skull base and the air in the paranasal sinus or other structures. Also, periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) MRI is characterized technique by greatly reduced sensitivity to various sources of image artifacts [2]. The aim of this study is to find the optimal PROPELLER DWI condition on 1.5T MR examinations of pediatric ear.

II. MATERIALS & METHODS

Experiment 1 : We measured the signal-to-noise ratio (SNR) of the PROPELLER DWI acquired with 8 channel brain coil. We evaluated the SNR by use of the subtraction method (NEMA standard). We changed only the slice thickness (3mm or 6mm) and matrix size (96×96, 128×128, 192×192, or 256×256).

Experiment 2 : We measured the distortion in spin echo imaging, PROPELLER DWI and EPI DWI using the polyvinyl alcohol gel brain phantom in 8 channel brain coil. Using Image J software, we measured the length of the phantom-center (=L mm) in the phase direction and calculated the ratio of absolute difference between the two diameters to the real phantom diameter (=200mm) in each condition (the ratio = $|(200-L)|/200$). We compared each ratio.

III. RESULTS

As the matrix size increased, SNR decreased. As the slice thickness increased, the SNR increased. The signal intensity was equal among different matrix size even if slice thickness changed. The noise intensity increased as matrix size increased. The distortion in axial plain images was approximately equal between spin echo imaging and PROPELLER DWI. The distortion in axial plain in EPI DWI was higher than in PROPELLER DWI. The distortion in coronal plain in PROPELLER DWI could not be measured because only axial plain and oblique axial plain were available in PROPELLER DWI.

IV. CONCLUSIONS

From these results, we judged that it is proper to use slice thickness (3mm) and the matrix size (96×96) in the clinical settings. PROPELLER DWI was considered to be useful in the pediatric ear MR examinations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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192 - Dynamic Volume Scan Using an Electrocardiography Synchronization System with 320-Detector-row Computed Tomography for Pediatric Tracheal Bronchus

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I. INTRODUCTION & AIM

A 320-detector row computed tomography (CT) enables scanning of a maximum length of 160 mm using volume scan. Dynamic volume scan (DVS), which dynamically scans using the volume scan, enables the scanning of the four-dimensional (4D) dynamic image. Furthermore, 4D DVS imaging enables the accurate observations of the dynamics of the trachea associated with respiratory kinetics and may also reveal the dynamic mechanism of the trachea.

In DVS for infants, who naturally breathe with high breathing rates, scanning two accurate respiratory cycles is difficult and thus requires additional scan time. For subjects with rapid and strenuous breathing, imaging may be difficult for temporal resolution. Therefore, we performed dynamic scanning using an electrocardiography (ECG)-gated system to achieve accurate imaging of the respiration phase in DVS.

II. MATERIALS AND METHODS

All examinations were performed using a 320-row multidetector CT scanner (Aquilion One, Toshiba Medical Systems, Otawara, Japan). In dynamic scanning using DVS with an ECG-gated system, ECG-gated imaging was performed by transmitting electrocardiographic signals via an external pacemaker according to the breathing rates. For evaluating ECG-gated imaging, a test bag equipped with an elemental diet tube was attached to an artificial respirator to prompt breathing movements to serve as dynamic phantoms. ECG-gated imaging was performed by transmitting ECG signals via the dynamic phantom, at the same number as the breathing rates of the artificial respirator. The scanning parameters were as follows: tube voltage, 80 kV; tube current, 50 mA; collimation, 160 × 0.5 mm; and rotation time, 0.35-0.5 s. Retrospective ECG-gated segment reconstruction and half reconstruction were performed on the obtained images, which had slice thickness and interval

of 0.5 mm. The dynamic images were evaluated on the basis of accurate breathing images and the presence/absence of motion artifact and loss of image.

III. RESULT

Based on ECG signals, images can be acquired with accurate respiratory rates using synchronized imaging. With regard to higher respiratory rates, images can be reconstructed with less motion artifact, loss of image, and impact of motions by adopting a segmented reconstruction compared with images obtained using normal imaging.

IV. CONCLUSION

DVS with the ECG synchronization system for pediatric tracheal bronchus is useful for improvement of dynamic image ability and radiation dose reduction.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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193 - Bioactive glass scaffolds: understanding the *in vivo* effects of morphology

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I. INTRODUCTION & AIM

Research into bioactive glass scaffolds for bone repair has grown immensely in the last ten years. Researchers aim to create 3D scaffolds, which will guide cell growth, stimulating the formation of fully vascularised bone tissue [1]. Until 2011, scaffold topography focused upon foamed based structures mimicking that of cancellous bone [2]. These ‘cancellous mimicking’ scaffolds were limited by their low mechanical properties due to their high porosities and glasses brittle nature. In 2011, Fu *et al.* [3] utilised the additive manufacturing technique direct-ink writing to produce bioactive scaffolds with aligned struts and square pore geometries creating scaffolds with mechanical properties up to 10 times that of their foamed equivalents. Within this study, we have produced comparative bioactive scaffolds via direct-ink writing and adapted gel-cast foaming, and have analysed their ability to stimulate bone growth *in vivo* over 12 weeks.

II. METHODS

Scaffolds were produced via direct-ink writing, and the adapted gel-cast foaming process from melt derived ICIE16 bioactive glass (49.46 mol% SiO₂, 36.6 mol% CaO, 6.6 mol% Na₂O, 1.07 mol% P₂O₅, 6.6 mol% K₂O). Scaffolds were produced with comparative interconnects of 150 μm with porosities of 40 ± 0.2 and 70 ± 0.4 % respectively [4]. Scaffolds were implanted in a 6.5 mm critical sized femoral head defect within a rabbit model for 4 and 12 weeks. Regeneration was quantified via x-ray tomography and histological analysis.

A. Statement of Human and Animal Rights

All animal procedures were approved and conducted in accordance with institutional, University of Ulster, animal care committee and United Kingdom Home Office guidelines.

III. CONCLUSIONS

Scaffolds produced from ICIE16 bioactive glass had the ability to stimulate bone growth regardless of scaffold topography within this defect site in rabbits. However, results show that the foam architecture produced by the adapted gel-cast process stimulated greater bone growth by both the 4 and 12 week timepoints compared to the comparative 3D printed scaffolds. Here we discuss various hypothesis to understand the results obtained and where this could lead the future of scaffold design for bone regeneration.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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194 - National Institute for Health and Care Excellence Guidance Development for Medical Devices and Diagnostics in the UK: A NICE approach to picking winners

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The National Institute for Health and Care Excellence (NICE) has bespoke programmes for non-drug technologies which focus on medical devices and diagnostics. These complement the existing drug appraisals and the quasi-regulatory programme on safety and efficacy of interventional procedures. Over the past 7 years we have published guidance (Medical Technologies Guidance and Diagnostic Guidance) on more than 50 technologies and advice on more than 100¹. Of the 32 published medical technologies guidance (MTG), 25 have positive recommendations and 6 recommend further evidence generation².

The assessment of value in these programmes follows NICE principles for guidance development. There is always an independent assessment of the clinical and economic evidence by an external group. Contributions are invited from expert and patient advisers including technical and scientific experts (e.g. biomedical engineers). The recommendations are drafted using structured decision-making by an independent advisory committee.

The medical technologies evaluation programme which develops MTG has a number of unique features within NICE which have been tailored for the development of guidance on non-drug technologies^{3,4}. The evidence considered by the committee is broad, including grey literature and sometimes technical assessments. For MTG development the technology must be cost-saving and the economic evaluation uses a cost

consequences approach. Within NICE, we provide advice to companies with early-stage technologies on the evidence requirements and we work with companies following guidance publication to facilitate development of data collection or research in response to these type of guidance recommendations. Future developments for MTG include a review of the processes of topic selection and guidance development and consideration of digital technologies.

Dr Dillon will present an overview of the NICE programmes for non-drug technologies highlighting the approach taken and the value this brings to developers and to the NHS.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest

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196 - Sodium Magnetic Resonance Imaging of Cartilage at 7 Tesla

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I. INTRODUCTION & AIM

Magnetic resonance (MR) imaging allows a non-invasive *in vivo* evaluation of tissue molecular composition. Although most MR imaging methods are based on an interaction between hydrogen nuclei and the magnetic field, sodium nuclei can also be used for MR imaging. This abstract provides a short overview on sodium MR imaging of articular cartilage.

II. CHALLENGES AND STRATEGIES FOR SODIUM MR IMAGING

Articular cartilage contains mainly water (~70%), macromolecules, such as collagen and proteoglycans (PG), electrolytes and a small number of chondrocytes. The relationship between water, electrolytes and PGs is responsible for unique cartilage properties such as compressive stiffness. Since sodium concentration is directly proportional to the amount of PG in cartilage, sodium imaging is an accurate and robust method for non-invasive monitoring of PG content and cartilage quality. Previous studies showed that sodium imaging is able to evaluate the performance of different cartilage repair techniques and can offer new insights into the evaluation of osteoarthritis [1, 2].

Sodium nucleus has specific MR properties such as spin number of 3/2 and a quadrupole moment. The latter is responsible for very short longitudinal (20-62 ms) and transverse (0.5-28 ms) relaxation times modulated by the molecular environment of sodium [3]. Due to low MR sensitivity and low concentration in cartilage, the sodium signal-to-noise ratio (SNR) in cartilage is about 3400 times smaller than that of the proton MR imaging. In order to improve SNR, sodium images are acquired with lower spatial resolution (2-5 mm), and longer measurement times (10-30 min) than common morphological proton MR images.

Strategies for increasing SNR in sodium images include sequences allowing imaging with short echo times (TE) that minimize signal loss caused by the fast transverse relaxation. Ultra-short echo time MR sequences sample the k-space from the center toward the periphery using radial or spiral trajectories

and can acquire images with TE below one millisecond [2]. The cartesian gradient echo sequence with variable TE train is a robust sequence capable of acquiring images with short TE (1-2 milliseconds) [1]. An additional increase of SNR in sodium images can be achieved by using dedicated phased-array knee coils and 7 Tesla MR systems [3].

Quantitative evaluation of cartilage in low-resolution sodium images is prone to errors caused by partial volume effects arising from synovial fluid and bone. Imaging techniques with fluid suppression [2], quantum-filtered sequences and signal correction in post-processing based on cartilage thickness [1] were used to mitigate errors due to partial volume effects. Finally, by adding calibration phantoms to *in vivo* measurements, sodium signal intensities from cartilage can be converted into sodium concentration [3].

III. CONCLUSIONS

Sodium MR imaging is a very promising tool for noninvasive evaluation of cartilage. Recent hardware and software advances led to the increased spatial resolution and SNR in sodium images. However, further software and hardware improvements are needed to translate sodium imaging into a clinically feasible method for 3 Tesla MR systems.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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202 - Magnetic fields in enhancing radiotherapy

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I. INTRODUCTION TO THE CONCEPT

Cancer is the leading cause of death globally [1]. Typical treatment options for cancer include surgery, chemotherapy, radiotherapy (RT), and hormonal therapy. RT damages DNA of the cancerous tissue, either directly or indirectly via radicals, leading to cell death. Unfortunately, normal tissues are also damaged and the toxicity of radiation to normal tissues can still be a limiting factor for delivering curative radiation doses to the tumour.

Because magnetic fields (MFs) alone are generally thought not to be genotoxic [2], our research group has focused on experimental studies evaluating combined effects of MFs with other physical or chemical agents. We have also conducted a meta-analysis of studies that have combined MFs with other agents, including ionising radiation [3]. The majority of the studies reviewed were positive, which is a surprising finding in contrast to the largely negative and inconsistent literature on weak MFs. Later, our studies showed that pre-exposure to 50 Hz MFs at 100-300 μ T modified the responses of cultured cells to menadione, an agent damaging DNA and stimulating cellular radical production (mechanisms similar to RT). In the first study [4], changes were seen in cell cycle arrest and apoptosis. Pre-exposure to MF was also found to increase the level of DNA strand breaks immediately after menadione treatment [5]. In our more recent study [6], MF exposure was found to increase the level of radicals, which might explain our previous findings. Our most recent results also indicate that MF exposure can alter the G1 checkpoint response and that the p21 protein may be involved in early responses to MF exposure [7]. Also possible harmful effects of combined RT and MF exposure have to be taken into account.

II. CONCLUSIONS

Therefore, based on the studies by others and us, MFs as a supplementary modality in combination with RT could offer an

easy and efficient way to enhance the tumour cell death caused by RT. Combining RT treatments with MFs could allow the use of lower radiation doses with the same radiobiological damage to the tumour cells and reduced probabilities of side effects.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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212 - Advanced preprocessing pipeline for cleaning TMS–EEG data

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I. INTRODUCTION

Transcranial magnetic stimulation (TMS)-evoked electroencephalography (EEG) data suffer often from noise and artifacts due to the strong magnetic pulse that easily interacts with scalp and muscle tissues as well as with measurement instruments. We present an efficient signal-processing pipeline to clean TMS–EEG data with minimal human intervention.

II. METHODS

Conventionally, data have been visually inspected to reject contaminated trials from further analysis. However, a faster and less heuristic approach is to cross-validate signals across the trials to determine the noise-level in each epoch. One can then, *e.g.*, define a noise threshold for labeling data segments as either accepted or rejected, or alternatively, emphasize trials based on the specific noise levels when estimating TMS-evoked responses by weighted averaging.

TMS can generate a lot of measurement noise, *e.g.*, by polarizing skin–electrode interfaces. We suggest a *source-utilized noise discarding* algorithm (SOUND) to suppress this noise. SOUND utilizes anatomical information of the head to cross-validate the data between the sensors. As a result, we are able to identify the noise level in each channel and clean the data accordingly by successive inverse and forward calculations.

It is common that TMS activates cranial muscles, producing large signal artifacts. We show that these muscle artifacts can

be projected out from the multisensory TMS–EEG data by using a *signal-space-projection* (SSP) operator [1] obtained from high-pass-filtered data [2]. SSP introduces distortions in the signals of interest, but these unwanted changes can be corrected with *source-informed reconstruction* (SIR) [3].

III. CONCLUSIONS

We show how TMS–EEG data can be cleaned efficiently and accurately from many TMS-elicited artifacts. The developed methods broaden the possibilities of future TMS–EEG experiments.

CONFLICT OF INTEREST

RJI is advisor and minority shareholder of Nexstim Plc. The other authors declare no conflict of interest.

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224 - Correlation of Mayer waves in retinal vessel diameter and arterial blood pressure

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I. PURPOSE

Static and dynamic retinal vessel analysis are promising tools for the early risk evaluation of cardiovascular diseases. Mayer waves are cyclic biological variations visible in retinal vessel diameter [1] and lead to uncertainties in this analysis. A correlation to blood pressure is described in literature and commonly demonstrated by discrete measurements with a sampling rate in the minute range. We investigated the temporal correlation of retinal vessel diameters and arterial blood pressure in the range of the very low frequency and low frequency waves in a multimodal measurement study to gain an understanding of the temporal relation.

II. METHODS

In a study in accordance with the Declaration of Helsinki we performed measurements on 15 young and healthy subjects. Within a time period of 90 minutes, six repeated measurements with a duration of six minutes each were conducted.

Retinal vessels were recorded by Dynamic Vessel Analyzer (IMEDOS Systems UG, Jena). Simultaneously, the arterial blood pressure was recorded by means of a continuous blood pressure measurement device (Finapres Medical Systems B.V., Amsterdam, NL). From the retinal vessel diameters, the equivalent values of arterial and venous vessel diameters CRAE and CRVE were calculated and the Mayer waves around 0.05Hz as well as 0.1Hz were extracted by filtering. Temporal dependencies were determined by cross correlation and the time values of the minimum and maximum correlation were extracted in each measurement. The median values, the quartiles, and the interquartile range (IQR) were calculated for the whole dataset.

III. RESULTS AND CONCLUSIONS

Cross correlation yielded clear dependencies in most of the 90 datasets. The strongest correlations are in the frequency range around 0.05Hz: minima of arteries: median

-3.83 s, IQR 3.38, minima of veins: median -6.03 s, IQR 3.94 and around 0.1Hz: minima of arteries: median -4.01 s, IQR 1.90, minima of veins: median -0.16 s, IQR 0.86. Negative time lags mean signal of blood pressure is in advance of retinal vessel diameter signal. Distribution of the time shifts around 0.1Hz is much narrower than around 0.05Hz. Most of the outliers are shifted by one period. Correlation Coefficients range up to 0.83 for frequencies around 0.05Hz and up to 0.96 around 0.1Hz, randomly shifted outliers have lower correlation coefficients up to 0.4. Most outliers are concentrated on a few subjects. Outliers for arterial and venous correlation are not necessarily related.

The measurements show clear dependencies between Mayer waves in retinal vessel width and arterial blood pressure. The best correlation can be seen around 0.05Hz on minima of arteries and veins and around 0.1Hz on minima of arteries and maxima of veins, yielding the smallest variation and the smallest number of outliers.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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225 - Application of Classification Tree for Quality Estimation of Textile Electrodes based ECG

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I. INTRODUCTION & AIM

Wearable biomedical devices industry market is increasing and the foremost parameter of a wearable system becomes the reliability of the gathered data. Electrocardiographic (ECG) signal brings significant information and can be acquired by wearable devices using smart textile electrodes. Textile electrodes are comfortable for the consumers but also they should satisfy high requirements for signal quality. The signal quality question is also important in clinical physiologic monitoring devices [1]. The aim of this research was to develop and benchmark a single channel ECG signal quality estimation algorithm that could be applied in wearable devices and be compatible with low power embedded systems. The algorithm is based on the classification tree [2] that uses statistical parameters of the ECG signal.

II. DATA AND METHODS

The data for the algorithm development and testing was used from three sources: 1) recordings of six volunteers (9 records) recorded with textile and ordinary (for reference) electrodes using proprietary ECG recording device; 2) ProSim 8 Vital Signs Patient Simulator (Fluke Biomedical) simulated data; 3) 3 noisy records from MIT-BIH database (www.physionet.org).

Seven signal quality indices (SQI) based on statistical analysis were used to train and test the algorithm [3, 4]: 1) signal variance; 2) excess kurtosis; 3) skewness; 4) mobility (squared root of the ratio of the variance of the first derivative of the signal to the variance of the original signal); 5) complexity (ratio of the mobility of the first derivative of the signals to the mobility of the signal itself); 6) root mean squared value; 7) zero crossing rate. These SQI were chosen based on good performing characteristics and low calculation demand.

SQIs of all signals were calculated in sliding time windows and were used as input parameters for the classification tree. Part of the signals was used for the training of the classification tree and another – for the testing (cross-validation was applied). The output of the classification tree is the answer to the question: is the signal quality enough for the heart rate calculation

or not. The ordinary electrode's records (for volunteer recordings) or annotations (for MIT-BIH database) were used for the signal quality reference. To optimize (in respect of R wave detection) the decision tree stepwise logical sequence of procedures was made optimizing time window length and overlap, discretization frequency, used number of SQIs, signal preprocessing and decision tree pruning.

III. RESULTS AND CONCLUSIONS

The optimized decision tree is able to annotate ECG signal quality and, based on it, applying R wave detection algorithm, detect heart rate in qualitative signal episodes. Exclusion of non-qualitative signal episodes leads to the reliable heart rate estimation. The final decision tree size is eight branches using six SQIs (except mobility), using preprocessing with base line removal and 40 Hz lowpass filtering, using window length of 4 s with overlap of 1.8 s. The sensitivity for R wave detection 0.985 and precision 0.988 was achieved. Optimized algorithm remained compatible with cheapest modern embedded systems and can be implemented as system firmware update in electrocardiograph.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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226 - How to involve citizens and patients in HTA: the experience of Cittadinanzattiva

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I. INTRODUCTION

The involvement of citizens, as individuals, communities, patients and caregivers, in processes of HTA is raising increasing interest in the field of public health policies in several Countries. This is due to the fact that the economic crisis and the reduction of resources impel decision-makers to delicate choices, which require a discussion with communities and patients. In support of this involvement there are a literature and experiences (e.g. in Australia, Canada, United Kingdom, Scotland), from which barriers to the participation of citizens and patients still emerge. Although in Italy a national system on HTA has been in place for some years, a solid experience in involving citizens and patients in HTA doesn't exist.

II. AIM, METHODS AND RESULTS

In order to fill this gap, Cittadinanzattiva since 2012 has organised 4 training initiatives, through which about 100 people have been trained. In the first 3 Summer Schools the target was represented by leaders of patients' and citizens' associations, but in the last edition, an Autumn School held in 2016, the target was **purposely mixed**, including managers and operators of healthcare services, in order to encourage interaction and promote co-working. The distinguishing features of the last edition are: **focus** on Patients' Involvement, **de-centralization** of the training in favour of the territory (north-east of Italy), **mixed target** and a **project work** (an example of a "citizens' and patients' involvement Plan"). For the **Project Work**, participants were divided into groups, with the following tasks: presenting a document

during the Concluding Day and discuss it with institutional interlocutors about the "feasibility" of the idea. The topic was citizens', patients' and users' involvement in the following issues chosen by the groups: **purchasing process** of medical devices, introduction of **beds for intermediate care**, design of a **Path Diagnostic Therapeutic Care for ADHD** (Attention-Deficit/Hyperactivity Disorder).

III. CONCLUSIONS

The **format** thus designed has more chances to **produce change** in the reality. We are going to monitor in the next years the impacts of these experience on the the decision-making system. At the conclusion of the training, the following results have emerged: 1) the three **project works**, if improved with regard to methodology, could be **implemented** in the areas concerned. Of particular interest is the project on the purchasing processes at a regional level, which shows that patients' evidence and users' evaluations of medical devices could contribute to take more informed decisions; 2) regarding the recommendations on patients' involvement addressed to administrations, we adopted the document "**Values and quality standards for patient involvement in HTA**", outcome of the "Interest Sub-Group for patient/Citizen involvement in HTA" of HTA International, integrated with elements emerged during the School; 3) as concerns the identification of the **patients' associations to involve**, emerged the need of promoting also smaller associations with expertise to share.

CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

228 - The test and simulation of aortic valve leaflets with shape memory alloy fibers

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I. INTRODUCTION

In the previous work [1] the principles for the fabrication of a new class of materials on the basis of shape memory alloys SMA and polymer composites have been developed. This composite was fabricated by using 3D printing technics. The SMA pseudoelastic fibers can imitate natural collagen properties in aortic valve leaflets, which are responsible for blood flow from the heart. The differential blood pressure causes the opening and closing of the valve by appropriate leaflets deformation. The anatomy of a leaflet is very important in this process. The excellent mechanical properties of collagen-based tissues allow for the proper operation of the heart valve and has been the subject of studies for many years [2]. An example is a paper [3] where authors mapped collagen fibers network and performed the numerical analysis.

II. EXPERIMENTAL AND NUMERICAL SIMULATION

In the order to verify the operation of the aortic valve with new leaflets material, was develop a test stand, which allows to visualize the operation of opening and closing of the valve leaflets and compare results for the different type of leaflets. In contrast to the professional test stands, the medium for exciting the leaflets is air. This allows to perform quality tests of leaflet models in low-pressure condition and have a significant influence on the usability. The main use of the stand is the possibility of recording the leaflets deformation with the high-speed camera with minimum rate of 1000 Hz and resolution of 1600 x 1200 pixels. For this purpose, the aortic valve stent was fixed to the transparent cylinder.

The simulation of aortic valve leaflets behavior was done in LS-Dyna by using the Smoothed Particle Hydrodynamic (SPH) method. Preliminary a constant pressure difference of 60 mmHg at the aortic side was assumed. For SPH elements the properties of human blood were taken. Through the contact between meshless SPH elements and shell elements of leaf-lets the Fluid Structure Interaction (FSI) with dynamic effect was observed.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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232 - Combining Haar wavelets with Karhunen Loève transform for the effective representation and comparison of physiological time series

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I. INTRODUCTION & AIM

This work proposes a methodology for the effective representation and analysis of physiological time series, through the description of a time series by means of a reduced set of parameters. The methodology combines the Haar wavelet decomposition [1], in which signals are represented as linear combinations of a set of orthogonal basis, with the Karhunen Loève transform [2], which allows for the optimal reduction of that set of basis. This representation enables to achieve a compact representation of a physiological signal, as well as to efficiently evaluate the similarity between physiological time series. Additionally, to address the similarity indexing problem an iterative scheme is introduced for computing the coefficients associated with each basis, leading to a significant reduction in the computational complexity of the scheme [3].

Given the characteristics of the proposed strategy, two main applications are considered in this work. The first one uses the capacity of describing a signal by means of a reduced set of coefficients, to implement a specific compression scheme, particularly appropriated to deal with trends. The second application exploits the fact that the coefficients embody the dynamic behaviour of the physiological signal. As result, these coefficients can be efficiently used in the assessment of the similarity between biosignals (computed from the coefficients instead of directly from the original signals). Additionally, through pattern recognition techniques, these coefficients can be used to group physiological signals into classes that present similar behaviours, enabling to discriminate distinct clinical conditions.

II. RESULTS

The efficiency of the methodology was assessed through its performance analysis, namely by computing the compression rate when representing a physiological signal and by evaluating the complexity (number of operations) for the similarity indexing problem, i.e., when searching subsequences of a time series that are similar to a given template. In particular, the scheme achieved a compression rate of $CR=N/(2\log 2N)$, where N represents the length of the time series, and a complexity of order $O(N(\log 2N)^2)$ and $O(N \log 2N)$, respectively, for the representation of a biosignal and for the comparison of two biosignals.

For these experiments, data daily collected during the telemonitoring MyHeart study was used [4]. The clinical study was carried out during some months with 148 patients from six clinical centres in Germany and Spain. During the clinical study patients were requested to daily measure body weight, blood pressure, and, using a vest, heart rate and bio-impedance, as well as breathing rate and activity during the night by means of a bed sensor.

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233 - Measurement of breathing during sleep - advanced solutions

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I. INTRODUCTION

Measurement of respiration during sleep is a key feature in the diagnosis of sleep related breathing disorders (SRBD). Depending on morbidity of patients and country-specific regulations, recordings are going to be performed either in-lab by attended polysomnography or unattended at patients' home. Based on actual guidelines [1] a number of different signals (e.g. respiratory flow, respiratory effort, blood oxygen saturation, snoring) have to be measured continuously during sleep. It allows to identify different pattern of disturbed breathing during sleep (e.g. apneas, hypopneas) with good accuracy, although this technique has a number of limitations. Especially in-lab recordings need excessive personnel resources that make it cost-intensive and prohibits widespread use. Moreover, the different sensors attached to the body could disturb sleep of subjects and in addition, artefacts due to body movements etc. superimpose signals. This limits the interpretability of results in a number of cases and does not favour the use in a long term-fashion, e.g. during several subsequent nights. As a result, further development of existing technologies is needed.

II. RECENT DEVELOPMENTS

Currently a number of new developments focus on contactless techniques for measuring SRBD. In subjects being investigated, these allow identification of apneas and hypopneas with high comfort and without any disturbance of sleep. Furthermore, long-term monitoring in distinct patient groups, e.g. therapy control, becomes available. One type of contactless solution measures respiratory signals by tracking body movements with mechanical sensors attached under the mattress. Different sensors are available, e.g. electromechanical film sensors, piezoelectric sensors, and static charge-sensitive sensors. While most of them are capable to detect respiratory events qualitatively [2], others allow detection of respiratory effort in addition [3]. Another promising approach for contactless measurement of SRBD are camera-based systems which combine consumer 3D sensors with three-dimensionally image processing algorithms. Recently it was shown that they are capable to detect limb movements during sleep [4]. Currently high effort is taken to apply this movement pattern analysis for tracking of respiratory activity. Others have developed systems using radar technology. These approaches utilize changes in reflection induced by body movement. By digital filtering of signals, one could get an estimate of respiration and of SRBD [5]. Another topic of research is the combined measurement of different physiological signals within one single sensor. An example is the measurement of breathing sounds, suprasternal pressure, and snoring by a small sensor which contains a pressure transducer and a microphone attached to the suprasternal notch. It seems that this none-obtrusive

sensor is capable to track for SRBD with high reliability [6]. Other research is focusing on cardiovascular and autonomic consequences of apneas in order to get an estimate of SRBD severity. Beside of heart rate analysis [7] especially the finger pulse wave analysis has become a promising tool. One application for SRBD detection in a single finger probe is the analysis of sympathetic mediated changes of peripheral arterial tone in combination with oxygen desaturation analysis [8]. Similarly, evaluation of pulse rate and pulse wave morphology parameters by Neuro-Fuzzy classification are used to assess cardiac risk related to SRBD [9].

III. SUMMARY

For the detection of SRBD advanced technologies become available. They aim to measure pattern of disturbed breathing during sleep in a none-obtrusive fashion either by new contactless technologies or by small sensors capable to monitor several physiological parameters together. In addition, they could provide information on the interaction of SRBD with the autonomic and cardio-circulatory system thus allowing a better estimate of the disease severity. These new technologies may be capable to diagnose and monitor SRBD more widespread, with less effort, and high accuracy. Further research in large patient groups have to proof their ability to distinguish different SRBD pathologies.

CONFLICT OF INTEREST

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234 - Exploring Arrhythmias after Hospital Discharge in Post-Myocardial Infarction Patients – the MADDEC project

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I. INTRODUCTION

Patients with acute myocardial infarction (MI) have exceptionally high mortality rates exceeding 10% during the first year post-MI. The incidence of sudden cardiac death after acute MI is the same with ST-elevation and non-ST elevation MI. The risk of disabling stroke and sudden cardiac death is high especially during the first months after myocardial infarction. Subjects in later working age, below 65 years, may also be subject to disabling stroke after MI increasing the societal burden. Preventing these outcomes is of high priority, considering the fact that the quality of life can remain high in these patients, if serious adverse events can be avoided. The high mortality and comorbidity rates among cardiac patients provide an opportunistic environment for testing the utility of data integration and resulting mass data. Long follow-up times are not required, which facilitates the linking of potential risk factors with outcome.

II. AIM

The prospective part of the MADDEC (MAss Data in Detection and prevention of serious adverse Events in Cardiovascular disease) project aims at exploring mechanism of sudden death in the first month after a MI and at detecting arrhythmias heralding life-threatening arrhythmias. Additionally, the project will define the incidence of new atrial fibrillation post MI. The events to be predicted are cardiovascular mortality, mortality from other causes, and re-hospitalization from any cause.

Based on the study protocol, it could be possible to identify novel explanatory factors for the high rate of sudden death post-MI with potential for cost savings in health care.

III. METHODS

Prospective home monitoring of patients after ST-elevation or non-ST elevation MI will commence in May 2017 and continue until the end of 2019. For arrhythmia detection, two different methods will be used: 12-channel Holter recording (GE Seer 12[®], GE Healthcare Finland) and the eMotion Faros[®] device (Bittium Biosignals Ltd/Mega Electronics Ltd, Finland). The aim is to record continuous 12-channel Holter data from 200-250 patients with ST-elevation MI. Exclusion criteria are short life expectancy, unwillingness to participate and need for permanent institutional care. The first 48-hour recording will commence at hospital discharge or transferal to another health care unit. The second recording will take place two weeks after the index event. As a part of the protocol, the subjects will also perform simple tests measuring their functional status and possible disability at study enrollment. All accrued ECG-data will be integrated into a research database for further analysis, linking it with outcome data. The Faros 360 mobile device will also enable recording patient activity, such as movement and respiratory rate, simultaneously using an accelerometer.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

235 - Assessment of Abdominal Muscles Thickness Symmetry during Movement Performance Testing Using Double Probe Ultrasound Scanner

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I. INTRODUCTION & AIM

Musculoskeletal disorders are one of the causes of long-term pain [1]. The diagnosis and therapy of the musculoskeletal disorders mainly rely on the physiotherapist's subjective evaluation lacking for instrumental methods. Visualization and biofeedback of muscles activities can be done using electromyography and ultrasound (US) [2]. The latter technology has advantage for the assessment of internal muscles [3]. The objective of this work was to evaluate methodology based on the double probe US scanner for the assessment of abdominal muscles thickness symmetry during diagnostic movement performance test.

II. DATA AND METHODS

MicrUs EXT-1H US scanner with double linear probe LV8-4L65S-3 (UAB Teled, Vilnius, Lithuania) working at 8 MHz was used to assess the thickness symmetry and temporal activation of abdominal muscles: external oblique (EO), internal oblique (IO) and transverse abdominis (TA) during sling suspension exercise test (Neurac method, Redcord, Staubo, Norway). Low profile US probes were placed symmetrically on the volunteer's abdomen, adjusted to visualize EO, IO and TA muscles and fixed by the wide elastic textile band with Velcro around abdomen. Then the exercise using sling system was performed. The exercise involved patient lying on the horizontal base on the back and lifting up one leg to match other leg, which is hold by the sling as well as lifting up pelvis to straighten body.

US video at 12 frames/s of left and right sides of the abdomen was acquired simultaneously by double probe scanner software. US video data was processed off-line using Matlab (The MathWorks, Inc., Natick MA, USA) to present visually muscle thickness symmetry and temporal activation during test exercise. For this, the edges of EO, IO and TA were extracted and used to: calculate thickness of the muscles; represent time course of the muscles activities; calculate statistical parameters

for muscle activation symmetry evaluation: mean, standard deviation values, cross-correlation, frequency domain analysis, temporal distribution of statistical values, and symmetry coefficients based on calculated parameters. In addition, various visualization ways were tried for representation of the results to physiotherapist or patient.

III. RESULTS AND CONCLUSIONS

Muscle thickness variation over time extracted from processed video data showed abdominal muscles thickness dynamics on the right and left sides during test exercises and were interpreted by the physical therapist. The muscle thickness symmetry indicates neuromuscular activation patterns and double probe US imaging allows to visualize them.

Statistical parameters characterizing temporal symmetry of muscles thickness can be used for the quantitative evaluation of the test, however the usage of particular indices should be investigated more to be used in practice. Simultaneous visualization of the different muscles on both sides of the abdomen during exercise gives powerful visual tool for the physical therapists for the qualitative evaluation of the musculoskeletal system and for the patients as biofeedback.

Experience of the performed tests showed that care should be taken by arranging probe setup on the patient and positioning US probes for the best visualization of muscles.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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237 - The effect of borosilicate glasses and glass dissolution products on human adipose stem cells

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I. INTRODUCTION & AIM

Despite the good performance of silicate bioactive glasses in bone tissue engineering (TE) applications, there is a considerable potential to further enhance their properties by chemical modifications. For example, silicate can be partially replaced with borate, thus providing the glass with boron, which is suggested to have beneficial effects on bone formation.

The aim of this study was to evaluate the cellular response of human adipose stem cells (hASCs) upon direct culture on S53P4-based borosilicate glass discs. The cellular responses were also assessed in glass ions containing extract media.

II. METHODS

Cell viability, attachment and proliferation were evaluated on the different culture conditions. To analyze osteogenic commitment alkaline phosphatase (ALP) activity, osteogenic marker gene expression, mineralization as well as the production of bone-associated proteins osteocalcin and collagen-I, were assessed.

III. RESULTS & DISCUSSION

Our results indicate that despite the good viability of hASCs on all the culture conditions, the borosilicate glasses had a re-

ducing effect on cell proliferation. With respect to the osteogenic commitment, the ALP activity was evidently reduced in the presence of boron but in contrast to this, the expression of osteogenic marker genes *RUNX2a*, *OSTERIX*, *DLX5* and *OSTEOPONTIN*, was upregulated in both direct culture and in borosilicate glass extract media. There was also a borosilicate-induced increase in osteocalcin protein production. Borosilicate extracts containing osteogenic supplements significantly increased the mineral production when compared to the glass ion free osteogenic medium control. Our results reveal that S53P4-based borosilicate glasses enhance the osteogenic differentiation of hASCs as observed in both direct contact culture and in glass extract medium, thus supporting the utilization of these glasses in bone TE applications.

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CONFLICT OF INTEREST

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241 - A Clinical Decision Support System for a Holistic Approach to Dementia Diagnosis

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I. INTRODUCTION & AIM

Diagnosing complex diseases, such as dementia, is challenging. Clinicians need to mentally combine a wide range of information sources (ranging from brain scans to neurophysiological tests and laboratory data) to consider a high number of possible reasons behind clinical symptoms. They need to take into account background information and, finally apply knowledge about economical and feasibility constraints when deciding what tests should be acquired next. This complexity easily leads to less-than-optimal decision making, even if profound clinical expertise is available. Clinical decision support systems (CDSS) based on principles of data-driven medicine potentially make the process more quantitative and objective.

II. IMPLEMENTATION

In the EU-funded project VPH-DARE@IT [1], the Patient Care Platform (PCP) implements a CDSS integrating biomarkers from medical images, neuropsychological tests and other measurements. It helps form a holistic view of a patient's status based on the principles of data-driven medicine. It uses an approach where large databases of previously diagnosed patients are used to build models of several dementing diseases, such as Alzheimer's disease (AD), frontotemporal dementia (FTD), vascular dementia (VaD) and dementia with Lewy bodies (LBD). When a new patient arrives at a clinic, tests are done, after which all available patient data are compared with the disease models, revealing the most likely reasons for dementia. The software architecture enables access to heterogeneous patient data from several data sources.

The PCP functionality hinges on two main components: automatic segmentation and quantification of brain images [2] and a supervised machine learning method for assessing the state of a disease in the patient. First, fully automated image processing methods derive volumetric measures from brain MR images. Second, the quantified imaging data are combined with all other available data, including demographic information, neuropsychological test results, blood test analysis,

CSF (cerebrospinal fluid) analysis and the patient's genetic profile. A machine-learning paradigm, the Disease State Fingerprint [3], is able to take all patient data and compare it to previously diagnosed patients, providing an index of similarity with each disease profile. Moreover, it provides an interactive visual representation of the holistic patient state, allowing the clinician to understand which variables contribute how to the decision suggestion.

III. RESULTS & DISCUSSION

The methods have been shown, using cross-validation, to reach a classification accuracy of 78% when discriminating patients between 5 different memory problems, ranging from Mild Cognitive Impairment to Alzheimer's disease. The clinical decision support tool using these methods is being validated with prospective patients, to see how it performs, both quantitatively and from a usability perspective, with real users at 4 memory clinics across Europe [4].

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CONFLICT OF INTEREST

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4. PredictND at <http://www.predictnd.eu/>

244 - Optical Guidance for Brain Tumor Stereotactic Biopsy

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I. INTRODUCTION & AIM

In the routine of stereotactic biopsy on tumors located deep in the brain or patients with multiple lesions, tissue samples are harvested using a biopsy needle from pre-calculated positions based on the preoperative radiologic images to determine the type of tumor malignancy. Due to the brain shift or ambiguity in the radiologic images, in some cases sampling becomes less accurate or result in non-diagnostic samples as a result of which repetition of the procedure from a different insertion path becomes necessary. To provide guidance for targeting diagnostic tissue and avoiding vessel rupturing, two optical systems were implemented using an application specific fiber optic probe during surgery.

II. MATERIAL AND METHODS

The setup incorporated an in-house developed fluorescence spectroscopy system¹ for 5-aminolevulinic acid (5-ALA) induced protoporphyrin IX (PpIX) detection in the tumor and laser Doppler flowmetry system (Perimed AB, Sweden) for measurement of blood perfusion². The custom-made fiber optic probe was connected to both systems. The probe was used together with a Leksell® stereotactic frame (Elekta AB, Sweden) and a mechanical insertion device for being placed precisely at the pre-calculated positions. Fluorescence and blood flow were recorded millimeter-wise towards the precalculated target. All together 107 fluorescence spectra and 182 laser Doppler signals were recorded along three trajectories in three patients. The patients were given 20 mg/kg body weight of 5-ALA prior to the surgery. The recorded signals were compared to the histopathology of the tissue samples (n = 12) removed from the pre-calculated positions in the tumor.

III. RESULTS

On all occasions, strong PpIX fluorescence was visible during real-time guidance. The tumors were all diagnosed as glioma WHO grade IV. Comparing the tumor marginal zone with the tumor, the PpIX (142 vs. 702 a.u., [0 - 1790], $p < 0.05$) was significantly higher in tumor. The autofluorescence was smaller than the surrounding normal brain but

was not significantly different in between the tumor margin and the tumor (93 vs. 44 a.u., [0 - 442], $p > 0.05$). Blood perfusion did not show any remarkable trend in the tumor compared to the surrounding brain; however, a few slightly increased perfused spots were detected. No hemorrhage was observed in the postop radiology images in the measured trajectories.

IV. CONCLUSIONS

In conclusion, the optical guidance probe makes real-time detection of tumor possible during the biopsy procedure and gives a preliminary feedback on the malignancy. Moreover, the PpIX fluorescence, autofluorescence and blood perfusion in the tumor could be studied at precise positions in the brain and the tumor.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The study was performed under ethical approval No. 2015/138-32. Written informed consent was received from the patients.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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250 - Simulation of Neuron-Astrocyte Network Interactions

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I. INTRODUCTION & AIM

Astrocytes are a type of glia cells known to affect the blood flow, as well as the processing, transfer and storage of information by the nervous system by releasing gliotransmitters, which influence neuronal function [1], [2]. Here, we show *in silico* how adding astrocytes can change the behavior of a neuronal network.

II. METHODS

The basis of the model was the spiking neuronal network model INEX [3] which simulates a network of inhibitory and excitatory neurons. To model the effects of astrocytes on tripartite synapses, where the astrocyte is able to modulate neuronal signaling, we used a modified version of presynapse astrocyte interface by De Pittà et al. through which the astrocytes were able to join with the excitatory synapses [4]. In order to combine the effect of synaptic inputs as seen by each astrocyte from all the excitatory synapses it modulates, the local astrocytic responses to each synapse were summed into a whole cell astrocyte calcium response. The propagation of calcium in the astrocyte network was then modeled according to the simplified UAR calcium signaling model by Lallouette et al. [5]. Astrocytes, when activated, release glutamate as a one off event to the synapses it modulates and inducing a tonic inhibition in its local area by GABA release for the duration it is activated.

We run and compared simulations with different setups to see the effects of added astrocytes. For each, we calculated the spike and burst rate, burst duration, and average number of spikes per bursts using a modified version of the burst analysis algorithm by Kapucu et al. [6].

III. RESULTS & DISCUSSION

Our results show that astrocytes can alter the signaling behavior of a neuronal network. The overall activity is reduced since the release of astrocytic GABA in response to high activity. While the spike rate is decreased, the burst rate remains the same and we see less interburst spiking which implies a more synchronous bursting than in pure neuronal populations.

Our model is the first biologically inspired neuron-astrocyte network model with astrocyte network effects on neuronal behavior. As expected, the overall neuronal network activity is reduced when astrocytes are presented since the release of astrocytic GABA in response to high activity reduces the overall activity [1].

IV. CONCLUSIONS

We showed using our computational neuron-astrocyte network model that including astrocytes to the neuronal networks leads to regulation of the neuronal network towards increased spike frequency and less interburst spiking.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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252 - Multi-scale Simulation of Spontaneous Calcium Release Events in the Human Atria

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V. INTRODUCTION & AIM

Atrial tachy-arrhythmias, such as atrial tachycardia (AT) and fibrillation (AF), are the most common sustained cardiac arrhythmias globally. Recent years have seen significant progress in the understanding of the mechanisms underlying arrhythmic electrical dynamics in the human atria, in particular pertaining to the vulnerability to and spatio-temporal dynamics of self-perpetuating re-entrant excitation. However, the multi-scale mechanisms underlying the development and propagation of spontaneous activity, mediated by sub-cellular release events and conjectured to play a major role in AT and AF initiation, are still to be elucidated. The aim of this study was to develop a multi-scale mathematical model of the human atria, which reproduces stochastic spontaneous calcium release events at the sub-cellular, cellular, and organ scales.

VI. METHODS

A previously developed model of the human atrial action potential [1] was integrated with a newly developed model of spatio-temporal sub-cellular calcium handling [2,3]. The model accounts for stochastic dynamics in key calcium handling regulatory proteins, regional heterogeneity in electrophysiology, and electrical and calcium system remodeling associated with long term AT or AF [1].

A rapid pacing protocol (~ 3 Hz) was applied to promote intracellular calcium overload and study the emergence of spontaneous release events under control and remodeling conditions. A large volume of simulations were run to provide well described probability density functions pertaining to the timing of spontaneous release events.

A tissue model was created using a reconstruction of whole human atrial anatomy [1]. Our previously developed multi-scale integration approach [4] was implemented to model spontaneous release events at the whole organ scale associated with rapid pacing.

VII. RESULTS

Under rapid pacing and beta stimulation, whole-cell spontaneous release events were observed. Calcium remodeling pro-

moted spontaneous release events, whereas chronic AF electrical remodeling inhibited this activity but promoted sustained re-entry. In single cell, triggered activity (spontaneous action potentials) was observed under some conditions, in particular in the pulmonary vein model. In tissue, spontaneous release events manifested as conduction block and premature excitation with the potential to develop into re-entry. The pulmonary vein region of the left atrium and crista terminalis region of the right atrium demonstrated the largest vulnerability to the propagation of sub-cellular release events in tissue.

VIII. CONCLUSIONS

Mathematical modelling has been used to study organ-scale arrhythmic dynamics and the underlying cellular mechanisms of spontaneous calcium release events in the human atria. The results demonstrate that spontaneous calcium release events can account for the development and recurrence of tachycardia and fibrillation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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255 - Bismuth-Oxo-Clusters for Soft Tissue Staining

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I. INTRODUCTION & AIM

Currently, X-ray absorption-based MicroCT is successfully used in material science investigations as well as in non-destructive testing enabling 3D imaging of these materials with micrometer resolution.[1] However, the application of MicroCT for biological sample screening (e.g. *ex vivo* screening of biopsies) is limited by the missing contrast of soft tissue, which is important to visualize microscopic structures.[2] Novel specific and functional contrast agents (stains) and staining protocols are essential to achieve the 3D visualization of specific cellular or sub-cellular structures (e.g. nucleus or cytoskeleton).

In order to overcome these limitations, we developed a novel staining method in order to enhance the contrast in X-ray imaging. Importantly, this method still allows compatibility with conventional histological examinations, i.e. the possibility of counter staining by the histologist.

II. METHODS

The bismuth-oxo-clusters were synthesized following a procedure described earlier.[3] The bismuth-oxo-clusters were filtered hot and the filtrate was kept for a minimum of 6 hours to allow cluster formation. Fixated mouse liver samples were stained for 24 hours with the prepared bismuth-oxo-clusters. The stained tissue samples were investigated with the ZEISS Xradia Versa 500 (commercially available machine) above ethanol vapor or as critically point dried samples. Furthermore, the anatomical structures were validated using conventional histological methods and light microscopy.

The internal animal protection committee approved the project 'CONSALT'; the projects internal reference number is 4-005-09 and all procedures were in accordance with the laws of animal experimentation issued by the German federal government. The institutional and national guide for the care and use of laboratory animals was followed. All laboratories are inspected for accordance with the OECD principles of good laboratory practice.

III. RESULTS & DISCUSSION

The results obtained provide a remarkably improved contrast of the stained soft tissue sample by our staining method when using the novel bismuth-oxo-clusters. Substructures are clearly visible and assignable that cannot be visualized without the staining. Correlation and validation of the X-ray data with conventional histological methods is presented.

IV. CONCLUSION

Currently available staining agents for microscopic imaging techniques are often toxic or inhibit subsequent histological treatment. The presented novel bismuth-oxo-clusters overcome these challenges and allow for a fast penetration of the stain through the soft tissue not compromising homogeneity. This study further demonstrates the effect of contrast enhancement through localized concentration of the high atomic number element bismuth within one molecule.

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CONFLICT OF INTEREST

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256 - A Computational Study on the Role of N_2O_3 in Enhancing Nitric Oxide from Deoxyhemoglobin Nitrite Reduction

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The production of nitric oxide (NO) by the nitrite reductase activity of deoxygenated hemoglobin (deoxyHb) has been proposed as a major mechanism in hypoxic vasodilation. Infusions of nitrite into the bloodstream have been shown to cause vasodilation, reduce hypertension, and protect from ischemia-reperfusion injury in animal and human experiments [1]. A major challenge to the deoxyHb nitrite reductase hypothesis is to explain how nitrite-derived NO escapes scavenging by hemoglobin [1]. It has been hypothesized that a stable intermediate species, dinitrogen trioxide (N_2O_3), is generated during nitrite reduction which can diffuse away from erythrocytes and release NO in smooth muscle cells (SMC) [2]. We developed a mathematical model for an arteriole and surrounding tissue to investigate the potential for this pathway to enhance SMC NO, based on rate constants in the literature for production and homolysis of N_2O_3 .

Coupled partial differential equations for an arteriole model were written in cylindrical coordinates and solved to steady state by finite element numerical methods using COMSOL v5.2 (COMSOL, Inc., Burlington, MA). NO was produced by the endothelium through shear stress and O_2 -dependent endothelial nitric oxide synthase, and deoxyHb reduction of infused nitrite was modeled using the Monod-Wyman-Changeux allosteric equation [3]. The model predicts how N_2O_3 produced in the blood by deoxyHb nitrite reductase diffuses away from the erythrocyte trap, and is homolyzed in tissue to release NO. The effect of the N_2O_3 pathway on SMC NO from infused nitrite was simulated for different conditions of blood flow and oxygen level.

Our simulations predict that without the N_2O_3 pathway, nitrite reduction by deoxyHb results in negligible NO elevation. For simulations without the N_2O_3 pathway, a decrease in blood PO_2 is predicted to decrease average SMC NO. With the N_2O_3 pathway, moderate levels of nitrite infusion can compensate for this lost NO with significant elevation of vascular wall NO dur-

ing hypoxic conditions. The enhancement of SMC NO increases with more severe hypoxia, reaching a maximum at the lowest blood PO_2 , and increases nonlinearly with increasing nitrite concentration [4]. This effect is consistent at different flow rates, but the relative elevation is higher at low flow rates due to lower baseline NO.

Our model demonstrates that under certain conditions, the N_2O_3 pathway can significantly preserve the NO produced by blood infusions of nitrite and elevate SMC NO. The model predicts minimal effects at normoxia or lower nitrite concentrations. This model does not fully explain how low levels of nitrite can still elicit vasodilation as observed *in vivo*, and more detailed modeling of secondary pathways are required for future studies. Nevertheless, these results provide insight into the mechanisms by which nitrite infusion can cause vasodilation despite the NO-scavenging environment of RBC hemoglobin.

The authors declare that they have no conflict of interest.

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257 - Different proliferation and osteogenic potential of human adipose tissue-derived stem cells influenced by fibroblast growth factor 2

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I. INTRODUCTION & AIM

Human adipose tissue-derived stem cells (ASCs) are a promising source for bone tissue engineering. An osteogenic differentiation of these cells can be induced relatively easily *via* osteogenic medium. This medium is usually supplemented with dexamethasone (DXM), β -glycero-phosphate (BGCP), ascorbic acid (AA), variably also by L-glutamin (L-GLU) and vitamin D3 (vit. D3). Fibroblast growth factor 2 (FGF2) has a positive effect on ASCs growth and proliferation. Lim et al. 2016 [1] reported a positive effect on osteogenic stimulation of ASCs when pre-treated with FGF2, but the role of FGF2 during osteogenic differentiation is ambiguous, and it has been evaluated in various ways in the literature. Some studies have reported a positive effect [2], but others have reported a negative effect [3] of FGF2 on osteogenic differentiation. In the present study we investigate the impact of FGF2 and various medium supplements on osteogenic stimulation of ASCs.

II. METHODS

ASCs were isolated from lipoaspirate obtained from the thigh area of a patient (woman, 46 years old). The ASCs were isolated in accordance with the ethical standards of the responsible committee on human experiments and in accordance with the Helsinki declaration. Written informed consent was obtained from patient before liposuction. Nine different compositions of the medium, with the combination of osteogenic supplements DXM (100 nM), BGCP (10 mM), AA (150 μ M), L-GLU (2 mM), vit. D3 (1 μ M) and either without or with FGF2 (5 or 10 ng/mL), were applied to the cells for a study of their influence on osteogenic differentiation. On days 6, 13, 20, and 27, we performed a resazurin assay, an ALP activity assay, a calcium (Ca) deposition assay and immunofluorescence staining of type I collagen and osteocalcin in order to assess the osteogenic differentiation of the ASCs.

III. RESULTS AND DISCUSSION

The results showed significantly higher cell proliferation and metabolic activity in cells incubated with osteogenic supplements on days 13 and 20. Surprisingly, as the cells were confluent, higher proliferation and metabolic activity of the cells depended more on the osteogenic supplements than on the addition of FGF2. The ALP activity increases in time, the highest levels were obtained in cells treated with osteogenic supplements and without FGF2. Interestingly, the highest levels of Ca deposition in the initial intervals were found in cells treated with FGF2 (10 ng/mL).

IV. CONCLUSIONS

A study was made of the influence on ASCs of treatment with FGF2 and osteogenic supplements. Significantly higher proliferation and metabolic activity were measured in the cells treated with osteogenic supplements. The cells treated without FGF2 showed higher ALP activity. However, the cells treated with FGF2 initially showed the highest Ca levels. The authors declare they have no conflict of interest.

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258 - Integrated superconducting quantum interference device magnetometers with sub-micron Josephson junctions for ultra-low-field magnetic resonance imaging

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I. INTRODUCTION

The combination of magnetic resonance imaging, performed at ultra-low magnetic fields (ULF MRI), with magnetoencephalography (MEG) in a single instrument is a feasible concept for improving the accuracy of MEG. A demonstrator was built [1] as a result of an active collaboration with Aalto University, VTT, Elekta Oy, Aivon Oy and HUS in a former MEGMRI – project funded by EU. Currently, the technology is being pushed forward in a BREAKBEN –project [2]. In the heart of the imaging system lie superconducting quantum interference devices (SQUIDs) cooled to liquid helium temperature. For decades, SQUIDs have been used for measuring MEG signals, especially due to their superior sensitivity at low frequencies. Thus, it has been natural to develop new magnetic sensors [3] that are suitable for both imaging modalities. Yet, one of the key issues with ULF MRI, before commercially viable, is the improvement of image quality. This is often characterized with the voxel $SNR \propto B_p/(S_B t)^{1/2}$, where S_B is the magnetic field noise power of the sensor, t the measurement time and B_p the pre-polarization field used for boosting the signal before the measurement. Thus, a very-low-noise and high-field-tolerance sensor is a must, with the relevant sensor performance criteria specified as $B_p > 100$ mT and $S_B^{1/2} < 1$ fT/Hz^{1/2}.

II. DEVICE

To address these issues, we have implemented a new interated SQUID magnetometer resembling those presented in [4], [5]. The device was fabricated with a lately developed process based on cross-type Josephson junctions, enabling sub-micron features in size. The small junction area is expected to lead to lower capacitance of the junctions and, hence, better energy resolution of the sensors. Furthermore, problems related to the flux trapping after large magnetic fields are expected to be alleviated [3]. In comparison with their wire-wound counterparts, all-thin-film sensors are easier to mass-produce and place as a part of large sensor arrays.

III. RESULTS AND DISCUSSION

The device contains 16 gradiometric SQUIDs connected in series, yielding a dynamic resistance of 130 Ω at the output and, hence, improving the noise matching to the amplifier. Critical current of about 8 μ A was measured for the junctions of size 0.6 μ m, leading to a voltage swing of 1.5 mV. The SQUID array is coupled to a pickup loop (size 28 \times 28 mm²) through a multiloop flux transformer [5], yielding a mutual inductance of $\Phi_0/5.6$ μ A between the SQUID loop and the input coil. Here Φ_0 is the flux quantum. Components without the pickup loop have reached flux noise of 2 μ Φ_0 /Hz^{1/2} and < 0.2 μ Φ_0 /Hz^{1/2} at 10 Hz and in the white part of the spectrum, respectively, and have recovered spontaneously from magnetic pulses up to 8 mT. The upcoming tests in the magnetically shielded environment will reveal the full potential of the magnetometers, determining their applicability for ULF MRI purposes.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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259 - Quantitative high field *ex vivo* MRI of articular cartilage

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I. INTRODUCTION

Ex vivo magnetic resonance imaging (MRI) at high field strength provides experimental means for exploring new potential techniques that could be applied *in vivo*. The higher signal-to-noise ratio of the experimental devices is often a key feature for identifying properties of new methods, which can then be transferred to clinical use. This paper summarizes some recent high field findings for articular cartilage.

II. METHODS

Different types of cartilage samples were investigated: human specimens from knee replacement surgeries [1], enzymatically degraded bovine specimens [2] and rabbit arthritis-model [3]. Furthermore, the orientation dependence of these parameters was investigated [4]. The parameters included T_1 , T_2 and contrast enhanced T_1 relaxation times, and several rotating frame parameters: continuous wave (CW)- $T_{1\rho}$, adiabatic $T_{1\rho}$ and $T_{2\rho}$ and T_{RAFF} . The experiments were done at 9.4 T, using a 19-mm volume coil. For reference, the samples were also measured using semiquantitative histology and mechanical testing.

III. RESULTS

The samples represent various degrees of tissue damage from intact to advanced degeneration. The mechanical stiffness (Young's modulus) of the samples ranged from 0.2 to 1.26 MPa and reduced histological staining for proteoglycans and changes in the collagen fiber meshwork were noted with degeneration. The MRI parameters showed variable sensitivity: adiabatic $T_{1\rho}$ and $T_{2\rho}$ and classical T_2 relaxation times were

generally sensitive to degeneration. CW- $T_{1\rho}$ was almost as sensitive, but dependent on the chosen spin-locking power. Classical T_1 relaxation time was also found sensitive. Contrast enhanced T_1 showed variable sensitivity to degeneration. The investigated parameters exhibited a full range of orientation sensitivity from nearly orientation-independent to strongly dependent, with T_1 and adiabatic $T_{1\rho}$ the least sensitive and T_2 the most sensitive.

IV. CONCLUSIONS

A range of sensitivities of high field quantitative MRI parameters to cartilage degeneration *ex vivo* were found. The high field experiments allow careful investigation of the parameters and thus pave way for future clinical implementations and provide information directly applicable to interpretation of already clinically-used MRI parameters.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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264 - Correlation time determined in cartilage by MRI T1rho relaxation dispersion

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I. INTRODUCTION & AIM

Water dynamics are affected by macromolecular environment and can be characterized by the correlation time of molecular processes (τ_c). τ_c could therefore provide information about ordered biological tissues, such as cartilage that could be calculated from noninvasive MRI measurements. The aims of this study were: (i) to calculate τ_c in visually intact bovine cartilage using $T_{1\rho}$ relaxation dispersion measurements; and (ii) to use τ_c for comparison between healthy and damaged cartilage in an equine surgical defect – repair model.

II. METHODS

The study was approved by the local ethics committee. All $T_{1\rho}$ dispersion measurements were performed at 9.4 T (Oxford instruments Plc, Witney, UK). For intact bovine patellar cartilage, $T_{1\rho}$ dispersion measurements with 22 spin-lock frequencies ($\omega_{SL} = 10\text{-}2500$ Hz) were acquired. In equine model, surgically created lesions in femoral cartilage of mature Shetland ponies were filled with different hydrogel-cell combinations and left to heal for 12 months [1]. The animals were sacrificed and osteochondral specimens ($n = 13$) were collected. $T_{1\rho}$ dispersion measurements with nine spin-lock frequencies ($\omega_{SL} = 100\text{-}2000$ Hz) were acquired from all samples. Mean τ_c values were calculated in the repair tissue, in region next to the repair site, and in visually intact cartilage. Cartilage layers (superficial, transitional and deep zones) were distinguishable both in the intact equine cartilage region and in the bovine specimen in $T_{1\rho}$ images. All correlation time maps were obtained by fitting function (1) to the measured set of $T_{1\rho}$ data points:

$$1/T_{1\rho} = 3A\tau_c/(1 + 4\omega_{SL}^2\tau_c^2) + B \quad (1)$$

where A, B, and τ_c are the fitted parameters [2,3]. The normalized RMSE (nRMSE) was calculated and used to assess the goodness of fits. Statistical differences were tested using Kruskal-Wallis post-hoc test.

III. RESULTS & DISCUSSION

Correlation time maps were fitted based on relaxation dispersion values for bovine and equine cartilage specimens (nRMSE = 0.020 ± 0.014). In bovine cartilage, τ_c values in superficial (5% of total cartilage thickness), transitional (20%) and radial zone (75%) were $943 \mu\text{s}$, $1827 \mu\text{s}$ and $775 \mu\text{s}$, respectively. Low spin-lock frequencies ($\omega_{SL} < 600$ Hz) were found to affect the fitting τ_c values more than the high frequencies. In equine cartilage, τ_c values were significantly shorter in the damaged (188 ± 38 ms, $p = 0.003$) and repaired regions (179 ± 40 ms, $p < 0.001$) compared to control region (318 ± 104 ms), suggesting that τ_c can be sensitive to degenerative changes in cartilage.

The proposed τ_c -based contrast was able to differentiate between different structural zones of cartilage in intact bovine cartilage and was sensitive to structural and biochemical alterations in equine articular cartilage. Further experimental evidence is needed to validate τ_c as a new MR contrast for cartilage imaging.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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267 - Assessment of the Effects of Radiofrequency Radiation at Different Frequencies and Exposure Duration on Human Colorectal Carcinomas Cells

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I. INTRODUCTION

Wireless communication technologies based on radiofrequency (RF) energy and the possible health effects of non-ionizing electromagnetic (EM) radiation emitted from the devices used RF technology on both public and environment are one of the essential and private issues and open discussion. Therefore, over the last few decades scientists have focused on the hypothesis whether the rapid growth and intensive use of the artificial EM field sources in our daily lives can make contribution to rising rate of cancer cases. However; some studies in literature have showed that EM radiation can be a quite effective adjuvant treatment for cancer cases. Consequently, the possible effects of RF radiation at different frequency and different exposure duration on caspases-dependent apoptosis in human colorectal carcinomas (HT-29) cell lines were investigated in the present study.

II. METHODS

Human colon epithelial cells (HT-29) were exposed to 1800 MHz (2G), 2100 MHz (3G) and 2600 MHz (4G) radiofrequency fields for three different exposure duration (3h continuous exposure; 6h intermittent exposure [3h RF exposure setup on/1h RF exposure setup off/3h RF exposure setup on]; 6h continuous exposure). Cell viability was measured by using Trypan Blue cell viability assay. The gene expression analysis of Caspase-8, Caspase-9, Caspase-3 and Caspase-12 were performed using quantitative SYBR green real-time polymerase chain reaction assay.

III. RESULTS

Cell viability of the human colon epithelial cells decreased significantly under 2100 MHz and 2600 MHz RF radiation for

three different exposure duration with respect to their sham and control groups ($p < 0.05$). However, 1800 MHz GSM like signal did not change cell viability of human colon epithelial cells (3h continuous exposure; 6h intermittent exposure with respect to their sham and control groups ($p > 0.05$)). Caspases (8, 9, 3 and 12) were not affected by exposure to 1800 MHz and 2600 MHz RF radiation for three different exposure durations with respect to their sham and control groups ($p > 0.05$). Caspase-8 and Caspase-9 increased significantly under 2100 MHz RF radiation (3h continuous exposure; 6h intermittent exposure) with respect to their sham ($p < 0.05$) and control groups ($p < 0.05$). Caspase-3 increased significantly under 2100 MHz RF radiation (6h continuous exposure) with respect to their sham ($p < 0.05$) and control groups ($p < 0.05$).

IV. CONCLUSIONS

Exposure to the frequency band of second generation (2G) digital systems (1800 MHz RF radiation) and to the frequency band of fourth generation (4G) of wireless technology (2600 MHz RF radiation) might not induce apoptosis neither intrinsic mitochondrial pathway nor extrinsic pathway. Furthermore, endoplasmic reticulum stress may not be responsible for the possible induction of caspase-dependent apoptosis under RF radiation. Stability in the gene expression level of Caspase -12, which is a key mediator of endoplasmic reticulum stress, induced apoptosis is the main indicator for evaluation the possible effects of RF radiation on HT-29 cells. The frequency band (2100 MHz RF radiation) of third generation (3G) wireless communications is highly effective for 3h and more than 3h exposures on caspases-dependent apoptosis of HT-29 cells. Therefore, the regulation of apoptotic pathways and the detection of caspases' activation involved actively in these apoptotic pathways may be referred to as targeted cancer therapy.

268 - Risk stratification in hypertrophic cardiomyopathy using ECG-based clustering and personalized computer simulations

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I. INTRODUCTION & AIM

Hypertrophic cardiomyopathy (HCM) is a common cardiac genetic disease and a leading cause of sudden cardiac death (SCD) in young adults. Yet, most patients remain asymptomatic and identifying high-risk patients to provide them with appropriate treatment is therefore critical [1]. It remains a challenge as the current electrocardiogram (ECG) biomarkers are not specific [2].

II. METHODS

12-lead Holter ECG recordings for 86 HCM patients were analyzed. We developed signal processing and mathematical modelling techniques to extract morphological biomarkers from the ECG waveforms, and identified subgroups in the HCM population by clustering. We then compared left ventricular structure from cardiac magnetic resonance (CMR) imaging and arrhythmic risk for each group. In order to investigate the influence of HCM structural and electrophysiological abnormalities on the ECG, we developed a whole-body personalized modelling framework allowing the simulation of the ECG from CMR images using 3D volumetric meshes.

III. RESULTS

Four distinct ECG phenotypes were identified, including Group 1A (n=21), with primary repolarization abnormalities (normal QRS with inverted T waves), and Group 3 (n=22), with QRS abnormalities and upright T waves. Interestingly, Group 1A had increased HCM Risk-SCD score [3] compared to other groups (3.8%, p=0.0004), and a trend to increased non-sustained ventricular tachycardia (NSVT). Group 3 had similar

maximum wall thickness to 1A (21±6mm) but no increase in Risk-SCD or NSVT. The simulations based solely on cardiac anatomy led to normal QRS in Group 3 and upright T waves in Group 1A, showing that hypertrophy alone does not account for the identified ECG abnormalities but other structural changes may play a role. Current work focuses on integrating fiber disarray based on diffusion-tensor imaging to explain QRS abnormalities, and modelling conduction delays in areas of hypertrophy to investigate mechanisms of inverted T waves.

IV. CONCLUSIONS

These results suggest that computational ECG phenotyping can become a novel risk factor for stratification in HCM, and highlight the potential of personalized high performance computing simulations in understanding cardiac mechanisms.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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269 - A Novel Model of Human Cardiac Purkinje Action Potential

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I. INTRODUCTION & AIM

Cardiac Purkinje cells (PCs) play a crucial role in arrhythmogenesis, since differences in electrophysiological properties make them more prone than ventricular cells (VCs) to develop abnormalities, i.e. early and delayed after-depolarization (EADs and DADs). Computer models are a useful tool to investigate pro-arrhythmic mechanisms. However, the most updated human PC action potential (AP) model [1] lacks representation of known intracellular compartments as well as integration of new experimental data.

The aim of this work is to develop a novel AP model of human cardiac PC.

II. METHODS

A novel AP model of human PC was developed, building on the most updated human VC [2] and canine PC [3] models, human Purkinje voltage-clamp data and AP recordings acquired from human PCs at 1Hz pacing. To induce EADs, the model was paced at 0.25 Hz with 85% hERG block. To induce DADs, the model was paced at 3 Hz with RyRs hypersensitivity

III. RESULTS & DISCUSSION

The human PC model reproduces all the key electrophysiological features reported experimentally, and is in range with human experimental AP data for all biomarkers, e.g., AP duration and upstroke velocity. At slow pacing rates and with hERG

block, the model shows EADs, due to the re-activation of calcium current. At high frequency, the human PC model displays calcium alternans and, when also including RyRs hypersensitivity, DADs.

IV. CONCLUSIONS

We developed a novel biophysically detailed model of human PCs AP that can be used to investigate the specific role of PCs in arrhythmogenesis.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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271 - Comparison of dose calculations with two Monte Carlo-based codes in external beam small-field radiotherapy

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I. INTRODUCTION & AIM

The use of small-field techniques in external beam radiotherapy (RT), e.g. in stereotactic radiotherapy (SRT), has increased in recent years. With SRT, a highly localized and conformal treatment is achieved, but challenges are met with dosimetry and dose calculation [1]. Monte Carlo (MC) calculation methods provide efficient way to investigate dosimetry in RT and they are considered to be the most accurate methods [2]. In this study, the dose calculations with two user codes of MC software package *EGSnrc* were compared: *DOSRZnrc* and *egs_chamber* [3]. With the *DOSRZnrc*, the dose is scored in a cylindrical geometry while in the more recent *egs_chamber* code a library with versatile geometries is supported.

II. METHODS

Dose calculations were compared through single volume, percentage depth dose (PDD), and profile calculations. Calculations were performed for 6 MV photon beam ranging from 4 to 40 mm in diameter transported to a large water phantom. All calculations were performed with both user codes. In order to verify the accuracy of MC calculations, PDD and profile calculation results were also compared with measurements performed by micro-ionization chamber.

III. RESULTS

In single volume calculations, the maximum difference of 0.2% was found. The largest and mean statistical uncertainties

were 0.2% and 0.1%, respectively. Profile and PDD calculations were in good agreement, with maximal difference of 0.5% and distance-to-agreement (DTA) of 0.6 mm. The maximum difference between measured and calculated results was 1.0% and the maximum DTA was 1.5 mm. In the measurements, the broadening of the penumbra in dose profile was recognized.

IV. CONCLUSIONS

As a conclusion, the results of dose calculations computed with two user codes were in good agreement. This encourages the use of the *egs_chamber* over more traditional *DOSRZnrc*, as it enables more realistic geometry models, which are not restricted to a cylindrical geometry only.

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276 - Experiences and benefits of wireless monitoring of significant cardiac events with modern pacemakers

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I. INTRODUCTION & AIM

In the era of modern communication technology, options for remote monitoring are now available for following-up patients implanted with pacemakers and defibrillators. These devices have wireless capabilities that communicate automatically with home transmitters, which then relay data to the physician using the GSM network, thereby allowing remote patient follow-up and monitoring. These systems are currently being widely used in all centers performing follow-up in patients with pacing devices.

II. METHODS

Remote monitoring has proven to be optimal mechanism for performing intensive device and patient surveillance and relieving the burden of routine follow-up performed by device clinics. With wireless technology remote follow-up involves scheduled automatic device interrogation, which replaces in-office visits aimed at assessing device function and data for patient's normal heart rhythm variability and arrhythmias. Remote monitoring involves automatic unscheduled transmission of alert events (e.g. atrial and ventricular fibrillation, device integrity etc.). Patient initiated interrogations are non-scheduled follow-ups initiated manually by the patient as a result of a real or perceived clinical event (e.g. palpitations, fainting etc.). The remotely acquired data are processed and made accessible to the physician on a secured webpage. The types of events which trigger an alert can be customized for each patient.

The upcoming fifth generation (5G) mobile communication promises better coverage, faster response times and increased bandwidth over existing networks [1]. These advances will allow more data to be transmitted and increase the potential of advanced, cloud-based analysis of recorded events [2].

III. CONCLUSION

The benefits of remote monitoring has been shown in randomized and controlled studies [3]. Therefore, remote monitoring has the potential to offer improved patient safety and quality of care.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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282 - Novel Cap Concepts for Rapid EEG with Dry Multipin Electrodes

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I. INTRODUCTION

Dry electrode technologies can improve the viability of electroencephalography (EEG) acquisitions, contributing to an increased use in established and emerging fields of application for EEG. We recently developed and successfully validated a novel polymer-based flexible dry multipin electrode [1]. Dry electrodes rely on a direct, stable contact to the scalp and therefore pose specific requirements for the used cap or helmet system. Our investigations emphasize the need for adaptive EEG caps ensuring both easy, comfortable application and reliable adduction within a pre-defined force range. Here, we propose a novel modular, adaptable cap system for rapid EEG, implementing the specific requirements of dry electrodes.

II. MATERIALS AND METHODS

Our proposed cap system is based on two independent components: a headband and a butterfly-shaped central cap module. The headband enables adaption to the individual head circumference, integrating frontal, temporal and occipital electrodes. The central module enables adaptation to sagittal and coronal width as well as height of the head, carrying central and parietal electrodes. The modules are based on a semi-flexible, washable textile. 64 electrodes are arranged in a quasi-equidistant layout to allow application of state-of-the art methods for artifact removal [2] and source localization.

III. RESULTS

We present our assessment of electrode and cap requirements, the cap design and preliminary results of the concept validation on multiple subjects. For our proposed electrode shape, we've identified an optimal adduction force between 2-3 N. Adapted pin height at frontal and frontal-temporal areas contribute to improved wearing comfort. The cap system enables rapid application with preparation times below 10 min. The separate modules enable adaptation of the cap to different head shapes.

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284 - Addressing the biocompatibility of photo-crosslinkable hyaluronic acid hydrogels

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I. INTRODUCTION & AIM

Cell culture scaffolds organize cells into a three-dimensional architecture, which will stimulate and direct cell growth [1]. Hyaluronic acid (HA) is a polysaccharide found in the extra cellular matrix of different tissues [2]. HA cross-linked hydrogels have been achieved by several chemical modifications [3]. However, cells poorly adhere to hydrogel scaffolds composed of only very hydrophilic HA, which limits the cells' proliferation in pure HA scaffolds [2].

The aim of this work is to increase cell adhesion (biocompatibility) of photo-crosslinkable hyaluronic acid for 3D cell culture scaffolds. Two different approaches were used to modify the HA: 1) physical addition of gelatin into the photopolymerized HA matrix and 2) chemically attachment of RGD peptides to the HA chains of the matrix.

II. METHODS

HA-am was synthesized by reacting the carboxylic acid group of high molecular weight HA and the amino group of an aminoethyl acrylate linker. Cross-linked HA was formed by placing a solution of HA-am and Irgacure 2959 (0.4 % w/v) in a silicon mold (100 μm height) covered with a glass coverslip and exposing the solution to UV light. HA-am+gelatin scaffolds were prepared by adding gelatin to the HA-am solution and cross-linking by UV light as describe above. HA-am-RGD scaffolds were prepared by soaking cross-linked HA-am hydrogels in a RGDSC-5FAM solution and subsequently exposing to UV light through a photomask. The modified hydrogels were then seeded with bEnd.3 cells to investigate the hydrogels' biocompatibility.

III. RESULTS

Exposure of HA-am liquid solution to UV light triggers the polymerization of acrylamide groups on HA-am derivative resulting in a 100 μm thin gel film as determined by the thickness of the silicon mold. Cross-linked HA-am+gelatin scaffolds

were achieved by addition of gelatin to the pre-gel HA-am solution, resulting in the physical entrapment of gelatin within the scaffold. It was found that a gelatin to HA w/v % ratio of 1:1 was maximal for the successful photo-crosslinking of the HA. RGD peptides were selectively coupled onto the HA scaffold via thiol-ene addition reaction in the areas exposed to UV light for the second time. We assume that only a part of the acrylamide groups were cross-linked during the first exposure to UV light so that residual acrylamide groups further participate in the thiol-ene addition reaction with the cysteine residue of the RGDSC-5FAM peptide. The attachment of the peptide was visualized under a fluorescent microscope using Ex 465-495, BA 515-555 filter. Cell adhesion to HA-am+gelatin and HA-am-RGD scaffolds was assessed by Live/Dead staining assay.

IV. CONCLUSIONS

In this work we show two methods to modify the biocompatibility of high molecular hyaluronic acid.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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285 - Microfluidic Multi-compartment Structures for Neuronal Co-culture Studies

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I. INTRODUCTION & AIM

Microfluidic organ-on-chip (OOC) devices are currently under active research in order to provide in vitro models which better mimic normal and pathophysiological conditions in humans. These advanced in vitro models are aimed for studying disease mechanisms and toxicity assessment and efficacy screening of new drugs [1]. Microfluidic organ-on-chip devices have been demonstrated for several different cell types including simplified models for cardiovascular, respiratory, nervous and digestive systems [2]. The current trend is towards multi-compartment structures with different cell types cultivated in a single device. The OOC devices typically use either cell lines or primary rodent cells, but the use of cells derived from human stem cells is still in its infancy. In this paper, we present results on microfluidic multi-compartment structures for human pluripotent stem cell derived neuronal co-cultures. The focus is on structures and case studies aimed for myelination and epilepsy research.

II. RESULTS

The basic structural elements in our myelination and epilepsy models are multiple cell cultivation compartments, micro-tunnels and microfluidic perfusion and drug supply channels. Neuronal cells are grown in the compartments which are connected by the micro-tunnels. The micro-tunnels separate neurites from somata in order to provide distinct neuronal cultures which are connected by the neurites. In our studies, a special emphasis has been placed on designing micro-tunnels which support the neurite separation of human-origin neuronal cells. The structures have been fabricated from polydimethylsiloxane (PDMS) using SU-8 molds. Before cell seeding, the structures have been coated with laminin to facilitate cell growth. Different neuronal cells of human origin, such as human embryonic and human induced pluripotent stem cells have been successfully cultivated in the devices and the micro-tunnels have been shown to efficiently separate neurites from somata. Furthermore, the structures have significantly improved the network activity and cultivated cells have been exposed to

pharmacological substances with expected functional responses.

In addition to the multi-compartment structures, we have developed various integratable microfluidic and biosensing functionalities such as CO₂ and O₂ supply, medium and drug delivery, recording of electrical activity and oxygen monitoring. In the system designs, finite element modelling has been used for guaranteeing properly functioning systems [3]. Using the designed CO₂ supply system for example, the electric activity of neuronal cells has been recorded for several days instead of the typical 20 minutes [4]. Custom-made micro electrode arrays (MEAs) have been fabricated and used for recording cell signaling [5]. In addition to the CO₂ control, the gas supply system has been used for creating hypoxic conditions. The dissolved oxygen concentration has been measured using an optical phase-sensitive fluorimetric sensor where fluorescent dyes were embedded in a polystyrene thin-film.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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288 - 'Hospital Design Week': releasing the design potential of clinical staff

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I. INTRODUCTION & AIM

Here we present the concept and initial experiences of 'Design Week' in a large acute teaching hospital. Design Week is an opportunity for hospital clinical staff to work with engineering and design students on design problems put forward by the staff themselves. The objectives of the week are: (i) to help discover clinical problems that may be amenable to designed solutions; (ii) to help promote a creative, solution-focused hospital culture, and (iii) demonstrate the application of design methods to clinical staff. Clinical staff are often best placed to see where good design could improve existing equipment/processes [1]. However, day to day pressures and lack of formal exposure to design methodologies result in this resource being largely untapped. Design Week for St. James's Hospital (SJH) Dublin was developed by the Medical Physics and Bioengineering Dept. in collaboration with the Medical Device Design M.Sc. at the National College of Art and Design (NCAD), Dublin and has been implemented in 2015, 2016, and 2017.

II. METHODS

A call is put out to all staff, to respond with ideas they have that would help improve patient or staff experience with a focus on design. The ideas are then reviewed and shortlisted by a panel, with consideration for suitability of submissions and capacity. Those who submit the ideas ('Ideators') are paired with 3-4 students each to work intensely on the design challenge for 1 week. Students use a design iterative process to carry out user research in the clinical environment, followed by sketching up concept designs which they receive feedback on from their Ideator and fellow staff. These designs are then combined and amended by each of the teams to produce a final design that is presented to a hospital-wide forum. A judging panel is utilised to determine a winner from the presenting teams, formulated to consist of representatives from a variety of backgrounds – e.g. charitable sector, enterprise, innovation, and nursing. Finally, a

student from the winning group is invited for a further 12 weeks as their final MSc thesis project to create a more robust design concept.

III. RESULTS

In 2016, 54 members of staff replied with their ideas. Design ideas came from a wide range of disciplines not just engineering. These were shortlisted to 11 ideas paired to teams of 4 students. The winning team presented a design concept for a fast patient admission trolley to increase the overall quality of admissions. A design student from this team completed a final thesis project in Sept 2016 working closely with the Ideator and clinical team. The design was developed and refined, producing an in-depth process map of ward admissions. The design is being pursued for manufacturing into a prototype.

IV. DISCUSSION AND CONCLUSION

The Design Week experience signposts one approach to helping provide hospital staff an opportunity to be involved in improving equipment and process design. A very encouraging aspect of the experience has been the eagerness of clinical staff from across a wide range of disciplines to become involved. As implemented, Design Week requires only limited staff time, yet effectively promotes and values the application of a design approach across the hospital. The challenge now is to continue to develop the Design Week model for maximum and sustained impact.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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290 - Development of a chair-based cuffless blood pressure monitor for home healthcare systems

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I. INTRODUCTION

We have attempted a new model of healthcare that involves monitoring physiological parameters to improve team-based healthcare. This study examined a new intervention system based on unobtrusive monitoring. In this report, we have attempted to develop the cuffless blood pressure monitor and evaluated accuracy and validation of the device.

II. SYSTEM DESIGN

An unobtrusive blood pressure (BP) estimation system was designed with a cuffless BP monitor combined with electrocardiography (ECG) and photoplethysmography (PPG). The system is mainly composed of an ECG with three electrodes is adopted with two electrodes at the left sides linked together to obtain a balanced touch sense for the left and right sides, a PPG sensor with a green lighting LED and a photodetector, a control circuit with a Bluetooth module, and a high capacity battery. The PPG sensor and ECG electrodes were mounted on the right armrest. The cuffless BP has been that was developed in the 2000s [1,2] and approved as a standard by the Institute of Electronics and Electrical Engineers (IEEE) in 2014 [3]. BP is related to the stiffness of blood vessels and the pulse transit velocity based on the R wave of the electrocardiograph (ECG) and the associated peak of the pulse wave are related to the BP. If we know the calibrated BP, calibrated systolic blood pressure (SBP_{CAL}), and calibrated pulse transit time (PTT_{CAL}) at SBP_{CAL} , the estimated systolic (SBP_{EST}) and diastolic (DBP_{EST}) blood pressures can be obtained [4].

The comparison study between cuff-based and cuffless BP monitors were performed by healthy young adults (11 males, including a subject with hypertension of 144/91 mmHg, and one female). The continuous every-day monitoring was performed at six month. The experiment was approved by the ethics committee of each institution. Following a detailed explanation of the investigation objective, informed

consent was obtained from each subject.

III. RESULT

The mean differences (MD) of the estimated SBP and DBP were 0.2 ± 5.8 mmHg and 0.4 ± 5.7 mmHg, respectively. The validation of this device accepts AAMI standards for cuff blood pressure.

IV. CONCLUSIONS

We proposed a team-based healthcare system. The core technologies operated smoothly. The next step will involve testing the entire system in a home-based healthcare setting.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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298 - Future prospects of research in non-contact ballistocardiography and sleep analysis

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I. INTRODUCTION

Ballistocardiogram (BCG) was studied several decades up until 1970's for its clinical value related to several cardiac diseases and conditions. It is stated that almost every heart and circulatory disease causes visible changes to BCG. The technology seemed promising, as measurement could be done in simple and routinely applicable fashion, and it provided a considerable body of useful information not otherwise obtainable [1]. Thousands of scientific papers were published, but eventually electrocardiogram (ECG) took de facto position as diagnostic tool.

Now, at the new millennia, new sensor technology and advanced signal and data processing tools offer wide and deep perspective to BCG, and we have seen newly refreshed interest towards BCG. New methods enable easy measurements, which can be done easily each and every day/night, in the confines of patients own home, without the presence of medical staff, factor which avoids the stress of measurement itself, and enables easy longitudinal studies [2]. This new approach may open completely new paradigm for detecting and treating certain conditions early on, maybe even before their actual onset.

II. APPLICATIONS OF BCG WITH EMFIT QS

Emfit QS is a non-invasive wireless device, whose sensor installs under the bed mattress, and picks up the BCG signal, and derivatives of it, such as heart rate, heart rate variability, respiration rate and movement level. This data can be used to measure sleep quantity and quality, stress and fitness levels, and identify some medical conditions, such as inflammations and onset of flu or fever (e.g. by detecting elevated heart or respiration rate).

Also some heart rate variability (HRV) indices are extracted from BCG signal, and these can be used to quantify stress/training load, recovery, and central nervous system status, enabling to prevent burnout, to optimize physical training regimen, pre-

vent overtraining condition, and indices can provide useful information also in pain management. Raw BCG signal also enables physicians to visually detect sleep apneas and snoring.

At Emfit we have re-identified wide clinical possibilities based on morphological analysis of the BCG signal, in a similar fashion as early researchers proposed already in the 50's. As studies show, shape and amplitude analysis of BCG can be used to detect several cardiac problems e.g. coronary artery disease, angina pectoris, myocardial disease and heart failure, valvular disease, arteriosclerosis and coarctation of the aorta, and abnormalities in aortic flow [2,3]. Other applications of analysis of BCG include optimization of medication dosing and cardiac re-synchronization therapy, determination of physiological age of the heart, and extending even to persons physical fitness level tracking.

III. CONCLUSIONS

We believe that contemporary signal and data processing approaches enhanced with artificial intelligence offer means to detect several medical conditions reliably and in an automated fashion, early on, possibly before their actual onset. Further, morphological analysis of the BCG signal may lend itself to as a practical means to evaluate individuals physical fitness level, and physiological age of heart. All these features can be incorporated into Emfit QS system, thus offering environment capable of monitoring slow, longitudinal changes in cardiac function associated with a number of cardiovascular diseases.

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299 - Signal Processing to Assess Atrial Fibrillation Complexity

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I. INTRODUCTION & AIM

Atrial fibrillation (AF) is a common cardiac arrhythmia, characterized by irregular electrical activation of both atria. AF often increases in complexity over time and is associated with increased risk of stroke. Current AF treatment has limited long-term success rates, partly since the mechanisms driving AF are not completely understood and common clinical markers poorly describe progression of AF complexity. Here we outline how advanced signal processing improves (non-) invasive characterization of the electrical substrate and the quantification of complexity of fibrillation patterns during AF.

II. METHODS AND RESULTS

A. Invasive signal complexity

Unipolar electrograms (EGM) were recorded using high-density contact mapping in a goat model of AF and AF patients undergoing cardiac surgery. All animal procedures conformed to US National Institutes of Health guidelines. All animal and human protocols were approved by our institutional ethical committee. Patients undergoing cardiac surgery provided written informed consent.

Conduction patterns during AF were reconstructed using a probabilistic activation detection and wave reconstruction algorithm. AF complexity was higher in patients with persistent AF (n=9) compared to acute AF (n=11): left atrial number of waves per cycle: 17.9 vs. 8.5, $p < 0.001$. Simultaneous mapping of the epi- and endocardial wall in goats revealed epi-endocardial dissociation and transmural conduction as important determinants of AF complexity (% of breakthrough waves: 2.1% (acute AF, n=7) vs. 14.2% (6 months AF, n=7), $p < 0.001$). The phenomenon of epi-endo dissociation during AF was replicated in equivalent recordings in patients (n=8). Analysis of conduction in a goat model of persistent AF and MRI-derived fiber orientation showed that after structural remodeling epicardial conduction aligns more to epicardial fiber direction (directional

correlation $R_N = 0.66$) instead of endocardial bundle direction ($R_N = 0.34$, $p < 0.001$).

B. Noninvasive signal complexity

Electrocardiograms (ECG) were recorded in patients undergoing treatment of AF, by pharmacological (n=221) or electrical cardioversion (CV) (n=502), or catheter ablation (n=93). Atrial activity was extracted from standard 12-lead ECGs and high-density body surface potential maps (BSPM), and noninvasive AF complexity parameters were computed and combined with clinical patient phenotype data to develop treatment outcome prediction models.

ECG parameters improved prediction of treatment outcome compared to common clinical parameters, for instance when predicting pharmacological CV success: area under the receiver operating characteristics curve 0.68 (using clinical parameters) vs. 0.81 (clinical & ECG), $p < 0.001$. Analysis of signal-averaged P-waves, as computed from high-resolution BSPMs, identified higher P-wave complexity (defined as the number of distinct peaks) as an independent predictor of a history of AF in a cohort of patients with (n=123) and without a history of AF (n=137): average P-wave complexity 2.9 (AF) vs. 2.5 (no AF), $p < 0.001$.

III. CONCLUSIONS

Signal processing of atrial EGMs provides novel insights into possible mechanisms initiating and perpetuating AF. There is strong empirical evidence that noninvasive quantification of AF complexity from the ECG provides valuable additional information that can be used to predict treatment outcome and stratify patients according to non-invasively determined complexity. Future work will aim at tightening the link between noninvasively measured complexity and the underlying AF substrate complexity and driving AF mechanisms.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

305 - Multiscale Methods for Definition of Ionic Variables in Electrophysiological Models

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I. INTRODUCTION

Models of gating currents are usually built by fitting the expression of individual gating variables to experimental data, thus considering each gate as independent of others. In this work, we present a methodology to fit ionic currents while considering the interaction with other elements defining the current as well as the effects at cell and tissue levels.

II. METHODS

The Carro-Rodríguez-Laguna-Pueyo (CRLP) human ventricular action potential (AP) model [1] was used as the basis for this study. In silico simulations of experimental protocols were run to optimally define voltage-dependent L-type calcium (I_{CaL}) current inactivation gates (f, f_2). The parameters describing steady-state gating inactivation were identified by solving an optimization problem using a response surface methodology [2]. A number of constraints were considered, and each result validated, at the ionic level, based on experimental evidence: steady-state voltage-dependent I_{CaL} inactivation was required to decrease monotonically for negative voltage values and have only one inflection point. The effects of introducing those changes in the model were evaluated at cell and tissue level. In this regard, a set of arrhythmic risk markers, including systolic and diastolic intracellular calcium concentration ($[Ca^{2+}]_i$), AP duration (APD), AP triangulation and the slow time constant of APD adaptation to abrupt cycle length changes (τ_{slow}) were required to lie within experimental ranges.

III. RESULTS

The redefined I_{CaL} current satisfactorily reproduced experimental observations, with mean square errors between simulated and experimental steady-state inactivation current values

being 20% lower than for the original CRLP model. At cell and tissue levels, APD, Triangulation and τ_{slow} lay within physiological ranges, and systolic and diastolic $[Ca^{2+}]_i$ values were of the same order than for the original CRLP model.

IV. CONCLUSIONS

The methodology proposed in this study can greatly help to define ionic current models in good concordance with experimental results. To avoid model overfitting, validation at all involved scales is advised.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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307 - A novel system for continuous non-invasive blood pressure monitoring

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I. INTRODUCTION

Winmedical developed a wearable CE marked and modular medical device, called WinPack, able to continuously monitor several physiologic signals through its sensor modules. All data are transmitted via wireless communication. The sensor modules are plug and play making easy to customize the device based on clinical and patient needs. Winmedical is developing a new sensor module (cNIBP) to continuously monitor blood pressure avoiding the use of inflatable cuffs. Part of the development includes a clinical trial (NCT02934386) assessing the performance of a Pulse Arrival Time (PAT) based-estimation of blood pressure. Accordingly, the cNIBP is intended to synchronously acquire ECG, PPG and tonometric signals.

II. MATERIALS AND METHODS

The abovementioned clinical trial aims to assess the accuracy of the cNIBP sensor module extracting BP estimates, when compared to gold-standard BP devices (NIBP100D by BIOPAC Systems) in compliance with IEEE 1708:2014 standards. During the trial, 50 volunteers performed in one hour timeframe various activities (mental, leg isometric and aerobic exercises) in order to induce blood pressure changes. The cNIBP sensor module acquired continuous 2-lead ECG signals, transmission PPG (Photoplethysmography) signals at the fingertip and four tonometric signals at the radial artery at a sampling rate of 500 samples/s. The recorded signals were used to extract two estimates of PAT: one at the radial artery (PAT1) and one at the fingertip (PAT2). PAT estimation was done based on the ensemble averaging of arterial pulsatility signals as described in [2]. Automatic quality indexes of both ensemble averaging and PAT calculation were generated to discard unreliable PAT estimates. Time series of both PAT1 and PAT2 estimations were further transformed into Systolic Blood Pressure (SBP) values according to [3], and compared to reference SBP time series in terms of Mean Absolute Difference (MAD) values, as defined in IEEE1708:2014 standard.

III. RESULTS

Preliminary analysis of the recorded data consisted on evaluating the best achievable performance when using PAT2 time

series to predict reference SBP time series. Accordingly, a linear calibration-function relating both time series was estimated for each subject using all available data points. The statistical analysis of the obtained MAD performances showed an average MAD of 4.7 mmHg, with a 95% confidence interval ranging from 4.23 to 5.22 mmHg. These results suggest the cNIBP module falling within IEEE 1708 Standard Grade A, when an optimal patient-dependent calibration function is available..

IV. CONCLUSION

Due to its widely-accepted usability and based on presented preliminary performances, the cNIBP sensor module by WinMedical is suggested as a new promising solution to continuously monitor blood pressure in sub-acute hospital settings.

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CONFLICT OF INTEREST

The authors of the paper are employer of the WinMedical s.r.l. that developed the WinPack and CSEM, part of the consortium in the WBPS project.

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309 - A multiscale approach to bone damage and fracture

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I. INTRODUCTION & AIM

Bone is a smart composite construction material, and a fascinating biological tissue. It has the ability to renew and repair itself without leaving a scar. Its hierarchically optimized structure based on an inorganic stiff mineral (hydroxyapatite) and a more flexible organic collagen results in a tissue that in a healthy state is able to withstand surprisingly high loads without fracturing. However, when affected by degenerative diseases, its strength and fracture resistance diminish substantially [1]. The quality of bone, or its fracture resistance, is related to a combination of factors, including geometry, composition and structure, accumulation of micro-damage, and cellular activity. Thus, it is essential to understand how bone behaves under loading on different length scales separately, to understand by which mechanisms it fails and fractures. This presentation will discuss our combined effort to understand bone strength and its damage mechanisms on multiple length scales going from macro- to micro- to nano-scale, using a combined experimental, *in situ* imaging, and numerical approach.

II. METHODS AND RESULTS

Today, bone density is used to diagnose patients with osteoporosis and high fracture risk, but it has been shown that finite element (FE) analysis can explain 20% more of the variance in strength than only bone mineral density [2]. Experimental characterization of human hip (femur) bones using mechanical testing in combination with digital image correlation (DIC) has allowed us to understand the deformation patterns and strains at failure [3]. Moreover, it serves as ground for validation of finite element models that can predict yield and fracture pattern in the bone [4].

On the microscale, state-of-the art includes FE modeling based on high-resolution microCT images. However, validation with full-field data spatially and temporally using high-resolution imaging with *in situ* mechanical testing, followed by 3D-volumetric DIC analysis is still largely missing. We have performed fast high-resolution tomographic imaging of bone

microstructure *in situ* (compression or tension) at TOMCAT beamline, Swiss Light Source, PSI, Switzerland, to resolve these questions.

The nanoscale in bone is of particular interest since the initial damage starts with separation at the mineral-collagen level. We have performed high-resolution tomographic imaging of cortical bone samples, followed by small and wide angle X-ray scattering (SAXS and WAXS) with *in situ* tensile loading and DIC of the surface, to characterize the strains in the collagen and mineral compartments of the material and tissue. This work has been carried out at I911-4 beamline at the Max-II ring (Max-IV, Lund, Sweden). Importantly, this allows us to link the strain in the tissue constituents (nanoscale) to the micro- and the macro-strains at failure.

III. DISCUSSION

Ongoing work is combining the work from different length scales into computational models, which may improve our understanding of bone mechanics and tissue behavior under critical loading, and enable us to improve the prediction of bone fracture risk and future diagnostics of osteoporosis.

ACKNOWLEDGMENT

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314 - Repolarization Heterogeneity Measured with T-Wave Area dispersion in Standard 12-Lead Electrocardiogram Predicts Sudden Cardiac Death in General Population

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I. INTRODUCTION & AIM

Identifying patients at elevated risk for sudden cardiac death (SCD) remains a clinical dilemma, especially in the setting of general population, where the majority of SCDs occur [1]. Widespread use of standard 12-lead electrocardiogram (ECG) offers a low-cost and easily accessible platform for noninvasive identification of patients at risk for SCD.

We developed a novel electrocardiographic (ECG) marker, T-wave area dispersion (TW-Ad), which measures repolarization heterogeneity by assessing interlead T-wave areas during a single cardiac cycle [2], and tested whether it can identify patients at risk for sudden cardiac death (SCD) in the general population.

II. WRITING THE PAPER

TW-Ad was calculated (as shown in equation 1) from standard digital 12-lead ECG in 5,618 adults (46% men; age 50.9±12.5 years) who took part in the Health 2000 Study, an epidemiological survey representative of the Finnish adult population. During the follow-up (7.7±1.4 years), 72 SCDs occurred. The measurements were validated in 6,160 subjects (45% male; age 49.2±13.1 years) drawn from another general population sample, the Mini Finland Health Survey. In this database, 310 SCDs occurred during the follow-up (25.6±9.6 years). Both studies were performed according to the Declaration of Helsinki and written informed consent was obtained from all subjects.

$$TW-Ad = \frac{1}{N} \sum_{i=1}^N \frac{Area_i}{\max(Area_{i,N})}, i \in \{V_4-V_6\} \quad (1)$$

III. RESULTS

Decreased TW-Ad, was univariately associated with SCD (0.32±0.36 vs. 0.60±0.19; P<0.001). In Cox proportional hazards model, TW-Ad (≤0.46) was associated with a 10.8-fold risk (95% confidence interval [CI]: 6.8 - 17.4; p<0.001) for SCD. When adjusted with clinical risk markers, including age, sex, body mass index, systolic blood pressure, total cholesterol/HDL ratio, arterial hypertension, current smoking, diabetes, coronary artery disease and previous myocardial infarction, it remained as an independent predictor of SCD with 4.6-fold adjusted relative risk (95% CI: 2.7 - 7.4; p<0.001). In the Mini Finland Health Survey TW-Ad was the best ECG-based predictor of SCD with 1.9-fold adjusted relative risk (95% CI: 1.5 - 2.4; p<0.001).

IV. CONCLUSIONS

The results of our study indicate that decreased values of TW-Ad are associated with increased risk for SCD in the general population and convey predictive information beyond that of conventional risk markers as well as other ECG-based risk markers. Future research should assess the predictive power of this index in other populations as well as other modalities of ECG measurement.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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315 - New EEG Forward Solution

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I. INTRODUCTION & AIM

Well-established EEG forward modeling routines require numerical integration, on which most of the computation time is spent. Recently, the Method of Fundamental Solutions has been proposed as the integral-free forward EEG solver [1]. However, it places the sources on a fictitious boundary and the solution accuracy could be very sensitive to the position of the sources. In this paper, we propose a method where source and collocation points coincide and both are placed directly on the real boundary of the domain. Hence, we calculate charges that accumulate at all the locations where conductivity changes inside a volume conductor [2]. The importance of the field created by surface charge accumulation at conductivity interfaces is only rarely studied [3]. We remove singularities replacing the concentrated point sources by uniformly distributed sources over mesh elements belonging to the boundary of the compartment. This technique can be applied to an arbitrary shaped geometry. We demonstrate the precision of this EEG forward solver using known analytical formulas of the electric scalar potential when considering a one-layer spherical model of the head.

II. METHODS

An ideal current dipole \vec{d} at a position \vec{r}_0 is considered as a neuronal source inside a real head model containing M isotropic compartments of conductivities σ_i , $i = 1, \dots, M$. We discretize M boundary layers using triangle meshes containing N_i , $i = 1, \dots, M$, triangle elements at each boundary layer i . The electric scalar potential at any point \vec{r} can be represented as a sum of electric scalar potentials of the current dipole placed in an infinite homogeneous medium of conductivity of the innermost compartment σ_1 and a correction scalar potential produced by surface charges occurring at the boundaries of the different head compartments:

$$\varphi(\vec{r}) = \frac{\vec{d} \cdot (\vec{r} - \vec{r}_0)}{4\pi\sigma_1|\vec{r} - \vec{r}_0|^3} + \sum_{i=1}^M \sum_{j=1}^{N_i} \frac{Q_j^i}{4\pi\epsilon_0|\vec{r} - \vec{r}_j^i|}, \quad (1)$$

where Q_j^i and \vec{r}_j^i of point source j at the boundary layer i represent the accumulated charge and its position vector, respectively. Satisfying the Neumann boundary condition, $\vec{E}_j^i \cdot \hat{n}_j^i = Q_j^i / (S_j^i \epsilon_0 (1 - \sigma_{i+1}/\sigma_i))$, at the centroids of the triangles of surface S_j^i and unit normal vectors \hat{n}_j^i , charges are determined.

III. RESULTS & DISCUSSION

In order to verify the accuracy of the present method, we use the homogeneous spherical head model as a simple test case where an analytical solution exists. We consider a sphere of radius $a = 0.1$ m filled with a homogeneously conducting material of conductivity $\sigma = 0.33$ S/m. Quantification of the numerical error in the computed EEG's is done using the relative difference measure (RDM) and the magnitude error (MAG). A tangential dipole produces MAG between 0.997 and 1.025 and RDM between 0.07 % and 2.9 % for $0 < r_0 < 0.98a$. A radial dipole has MAG between 0.994 and 0.957 and RDM 0.026 % and 2.7 % for $0 < r_0 < 0.95a$.

IV. CONCLUSION

First numerical results show that our proposed method is capable of fast and satisfactory accurate forward EEG calculations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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316 - State-of-art musculoskeletal imaging of osteoarthritis

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I. INTRODUCTION

The demand for clinically specific detection methods for diagnosing osteoarthritis (OA) and other joint-related diseases and dysfunctions is increasing due to greater demand further in life. A high percentage (13–20%) of adults suffer from OA, so that over 50% of them are limited in their activity [1]. Currently, medication is able to relief pain, but is unable prevent progression of the condition towards complete joint impairment. At that point, only option is to replace joint with an implant. Majority of hip and knee replacement surgeries are done to correct joint damage caused by OA [1]. To prevent or delay progression of OA to that severe level, it is imperative to develop imaging techniques that are able to detect the onset of OA. It would be even more important, albeit more challenging, to develop methods of prevention able to predict the onset of OA in people with high risk, e.g., due to obesity or trauma. In my presentation, I will review the current efforts made to reach such ambitious goals in musculoskeletal imaging towards early detection or prediction of OA.

II. CURRENT STATUS

Even though, plain radiography is most often clinically used for OA diagnostic imaging, magnetic resonance imaging (MRI) and ultrasound (US) are gaining popularity due to their own specific advantages, i.e. MRI for its tissuespecificity and US for its low cost.

Currently, studies on contrast enhanced radiological imaging, MRI, US imaging and testing as well as computational methods present various novel potential solutions for detecting the onset of OA, and hypothetically predicting OA. The yearly number of studies on OA imaging is constantly increasing [2]. The general direction in research is to achieve direct measures with physical meaning to update multiple arbitrary biomarkers. Conebeam computed tomography (CBCT) has gained interest

in musculoskeletal imaging. CBCT can be applied for loaded and unloaded joints, and it requires lower radiation dose than conventional CT, but it also has limitations [2]. Low-field MRI has been applied successfully for musculoskeletal imaging in supine and upright positions to image loaded and unloaded joints. High-field 7T MRI instead can applied for detecting fine structural changes related to OA, and holds great potential for compositional tissue quantification.

Modern approach is also to use statistical shape to apply the 3D information in MRI to provide accurate quantification [3]. These and other novel approaches will be reviewed in my presentation, and overall future directions discussed. At present, several techniques are under development, and some are in translational stage. Further development is indeed required, but promising steps have been taken towards the ultimate goal of beating OA.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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320 - Changes in EEG directional connectivity during a slow induction of propofol anesthesia

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I. INTRODUCTION & AIM

The analysis of brain connectivity in general anaesthesia has the potential to shed light on the still unclear mechanisms of anaesthetic induced loss of consciousness (LOC) and is of great interest both for anaesthesiologists and neuroscientists [1]. A series of neuroimaging studies have contrasted brain activity in wakefulness with anaesthesia [2][3] to explore neural correlates of consciousness; a disruption of long-range connectivity and changes in fronto-posterior coupling have been reported as important mechanisms. The majority of these studies used functional magnetic resonance or combined transcranial magnetic stimulation and EEG approaches, however EEG presents a series of practical advantages [4]. The aim of this work is to assess EEG directional connectivity using Directed Coherence (DC)[5] during a slow induction of propofol anaesthesia and identify network features that reliably reflect anaesthetic LOC at cohort and individual level.

II. METHODS

The study was approved by the Southampton and Southwest Hampshire Research Ethics Committee and involved ten patients. The experimental protocol consisted of a slow induction of general anaesthesia with propofol after a baseline recording, using a computer-controlled infusion to achieve brain effective site concentration (ESC) of 2, 3, 4 $\mu\text{g ml}^{-1}$. During the experiment 32 channels EEG was collected at different ESC levels. Effective connectivity was assessed (and statistically validated) on 60 s EEG epochs using the DC estimator, that provide information about the strength, direction and spectral content of multivariate linear dependencies between EEG channels. Capitalizing on our previous work on NREM sleep [6], we have focused the analysis on long-range connectivity and proposed an index quantifying the dominant direction of information flow on the fronto-posterior axis.

III. RESULTS

The most characteristic changes observed in anaesthesia are a significant decrease in the average strength of long-range DC links and a switch in the direction of information flow, from markedly posterior-frontal in wakefulness to fronto-posterior in anaesthesia. These changes occur at the onset of light anaesthesia and remain constant in deeper sedation identifying a step change with anaesthesia and appear to be consistent at individual level.

IV. CONCLUSIONS

We investigated changes in EEG directed connectivity features during a slow induction of propofol anaesthesia and identified significant changes in DC long-range connectivity strength and direction with the onset of anaesthesia as compared to wakefulness. These findings are in line with previous works and are particularly interesting in terms of a physiological interpretation of anaesthetic induced LOC.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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322 - Examination of biopolymer silica nanoparticle composites

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I. INTRODUCTION

In recent years there is an increasing interest to develop biopolymer-based films due to their outstanding properties such as biodegradability, biocompatibility and low toxicity. Capsulation of polymer matrices can open doors to developing self-healing coatings and can be useful for controlled drug release. The dispersability of capsules in the polymer matrix is a crucial requirement for these applications.

II. AIM

The aim of our work was to study the dispersibility of silica nanoparticles in biopolymer matrices (like chitosan, gelatin and their mixtures) and to get information about important parameters which can influence the aggregation phenomena.

III. METHODS

The biopolymer and composite coatings were prepared on glass substrates from aqueous polymer solutions and polymer-silica dispersions by dip coating technique. The transmittance of biopolymer and composite coatings was measured by optical spectroscopy method. The optical measurements provided information about layer thickness and also gave indirect information about the aggregation of silica particles. Dispersibility of nanoparticles in the coatings was directly studied by high resolution optical microscopy. The interfacial tension of the solutions was measured by pendant drop method. The viscosity of the solutions was investigated by capillary viscometer method. Coatings were deposited at different value of pH of dispersion phase.

IV. RESULTS

It was found that the dispersibility of silica nanoparticles is highly dependent on the composition of biopolymer matrix. For chitosan-gelatin-silica composites the dispersibility was even dependent on the mixing order of components. It was also revealed that the pH of precursor liquids also influenced the degree of dispersity.

V. CONCLUSIONS

Analysing the experimental results we came to the conclusion that aggregation of silica particles took place during the film deposition process. Nevertheless, number of questions remained unanswered. The main question for the future whether the polymer segment-segment or polymer segment-silica particle interactions control the dispersity degree of particles in the investigated polymer matrices.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

325 - Heart cell beating force measurement using piezoelectric PVDF sensor platform

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I. INTRODUCTION & AIM

Human stem cell based tissue and organ models are developed as alternatives for animal experimentation to study toxicology and disease models. Polyvinylidene fluoridene (PVDF) is a transparent and flexible piezoelectric film sensors [1] has been previously used for physiological measurements [2], as well as in touch panel [3] and energy harvesting [4] applications. Here, heart cells were cultured directly on the fabricated sensor array platform that was composed of PVDF film and Au electrodes.

II. SENSOR ARRAY FABRICATION

A commercial piezoelectric 110- μm -thick PVDF film was purchased from Measurement Specialties, Inc. Electrodes were fabricated on PVDF by using e-beam evaporation. The 100-nm-thick gold (Au) electrodes were patterned on both sides of PVDF by using a mechanical laser-cut stencil as evaporation masks. The arrays of four PVDF sensors per substrate were then used for cell culturing directly on top of the electrodes.

In the heart cell beating force measurements the sensor array is connected into a measurement computer through an in-house built USB charge amplifier measurement card. During the monitoring of the heart model pulsing, the data was collected from four PVDF sensors simultaneously in parallel and data was saved for further analysis.

III. CELL CULTURING

Human embryonic stem cells (hESCs) were cultured and differentiated on plates coated with vitronectin, which is an extracellular matrix protein. The media used in culturing were Essential 8 Flex Medium and PSC Cardiomyocyte Differentiation Kit (Thermo Fisher), both xeno-free and serum-free. The differentiation process proceeded according to instructions given by manufacturer for the differentiation kit, with a small change in the schedule. This change was done, because during optimization of the differentiation process it was noticed that it lead

to quicker and more effective differentiation of the cells used in this study. During differentiation process the morphology of the cells first changed from clumps of round cells typical to stem cells to migrating elongate, fibroblast-like cells. Then the amount of these elongate cells grew, after which the cells, assumedly precardiomyocytes, started forming strong, easily distinguishable structures. Those structures eventually started beating synchronically and regularly. Results so far show that hESCs differentiate to beating cells with these methods and form larger entities of electrically continuous areas, visible both microscopically and in microelectrode array (MEA) measurements.

IV. CONCLUSIONS

The PVDF sensor array was found biocompatible substrate for cell culturing and in-vitro pulsing force measurement. The heart organ model beating force measurements are still ongoing, but earlier results have shown that sensitivity of PVDF sensors is enough for this type of measurements.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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328 - Towards the introduction of phase contrast breast tomography into clinical practice

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I. INTRODUCTION

In the framework of breast imaging, to overcome the limitations of mammography, commonly used in large scale screening programs, x-ray phase-contrast imaging techniques, which are able to measure the effects of x-rays refraction in the body, have shown promising results for refining breast cancer diagnosis.

These techniques permit the visualization of soft-tissue structures that are not detectable by use of conventional x-ray radiographic methods, and also hold the potential to reduce the radiation dose delivered to the patient [1,2]. The purpose of this work is to highlight benefits and advantages of phase contrast tomography and their implications for breast cancer diagnosis with respect to conventional absorption based methods.

II. METHODS

We analyzed 15 breast tissue samples containing various cancer types (such as in situ carcinoma, infiltrating ductal carcinoma, papillary and invasive lobular carcinoma), using synchrotron propagation-based phase contrast CT (PB-CT). The resulting images were compared with conventional absorption based techniques in terms of quantitative quality parameter and based on the opinion of expert radiologists.[3,4].

III. RESULTS

It has been demonstrated that images obtained with synchrotron PB-CT have significantly higher radiological quality than images obtained with conventional techniques. First

because of the higher spatial resolution, then because the application of phase retrieval processing in PB-CT can decrease the impact of noise and increase the Contrast to Noise ratio in the reconstructed images. These characteristics allow to better evaluate and differentiate diverse features of the lesion that are fundamental for an accurate diagnosis (i.e. edge sharpness, evolution of speculations, texture inside the cancerous area).

IV. CONCLUSIONS

The main conclusion drawn from this study is that our optimized PB-CT method has proven to produce images with a significantly higher diagnostic power than conventional images obtained delivering the same x-ray dose.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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330 - Eye movements estimate time awake

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I. INTRODUCTION & AIM

Sleep deprivation impairs human cognitive functions and performance which increases the probability of human errors and accidents [1]. Therefore a reliable, practical and objective metrics for estimating the sleepiness would be valuable [2,3]. Sleep deprivation affects individuals differently and the cognitive and attentional deficits differ between individuals but are rather stable with-in individuals [3,4,5]. Saccadic eye movements, have been used to study attentional functions [4] and the number of errors in response execution (omissions) have been reported to increase in a saccade task during sleep deprivation in a laboratory study [6]. Omissions in the saccade task are potentially result of attention lapses and microsleeps caused by wake state instability [1].

Our aim is to study if the saccades measured with electro-oculography (EOG) outside the laboratory could be used to estimate the time awake.

II. METHODS

The number of executed saccades was measured in 11 subjects during an 8-minute saccade task. The saccades were recorded outside the laboratory (Naval Academy, Bergen) using EOG every 6th hour until 54 hours of time awake. The measurements were done on two occasions separated by 10 weeks. Five subjects participated in both measurement weeks. This study adhered to the Declaration of Helsinki and all participants gave written informed consent.

III. RESULTS & DISCUSSION

The number of saccades decreased during sustained sleep deprivation for all subjects. Subjects made on average 24%

(range: 8-56%) less saccades in the last (54 hour) than in the first (6 hour) measurement. The decrease in eye movements was a result of increased time between saccades suggesting that attentional lapses and/or microsleeps have occurred. The performance differed between subjects but was stable within subjects. The correlation coefficient between study weeks was higher than 0.6 for all subjects (N=5) (range: 0.62-0.96).

The results imply that saccades measured with EOG can be used as a time awake metric outside the laboratory.

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The authors declare that they have no conflict of interest.

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331 - Soft Robotic Sock for Robot-Assisted Ankle Dorsiflexion-Plantarflexion and Eversion-Inversion Rehabilitation Exercises

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I. INTRODUCTION

Most stroke patients suffer lower limb paralysis, and are usually bedridden during the initial recovery phase. This immobility leads to detrimental complications such as deep vein thrombosis (DVT) and ankle joint contracture. Current methods for prevention of DVT (e.g. intermittent pneumatic compression devices, compression stockings) and ankle contracture (e.g. rigid ankle exerciser devices) remain controversial in their efficacy [1,3]. In this study, we present the design and characterization of a soft robotic sock for early on-bed rehabilitation of stroke patients by assisting with ankle dorsiflexion-plantarflexion and inversion-eversion, which is not achievable by current mechanical prophylaxis.

II. METHODS

We fabricated the soft extension actuators with silicone material casted onto a 3D-printed fish-bone design mold; this creates a fish-bone pneumatic network that allows for longitudinal expansion. The soft robotic sock comprises of two extension actuators (connected to a pump-valve control system) placed on lateral and medial sides of the shank, and connected to the foot with nylon straps. When both actuators inflate and extend, they pull the foot into dorsiflexion. If the lateral or medial actuator is activated, the foot will undergo eversion or inversion respectively. To characterize this actuator design, the actuator was inflated at fixed pressures of 30-60kPa and the final actuator length was measured. At the same fixed pressures, we also measured the force output using a digital spring gauge. Moreover, ten healthy human subjects gave informed consent to evaluate the functionality of soft robotic sock in a gait analysis laboratory.

III. RESULTS

The actuators extended from 45.0 ± 1.0 mm (22.5%) at 30kPa to 111.7 ± 0.6 mm (55.9%) at 60kPa. For the force-pressure relationship, the actuators exhibited an average maximum pulling force of 16.6 ± 0.4 N at 30kPa, up to 29.8 ± 0.4 N at 60kPa. The soft robotic sock assisted the subjects with $10.2 \pm 3.2^\circ$ (22.1%) of dorsiflexion-plantarflexion motion and

$19.7 \pm 6.6^\circ$ (45.6%) of inversion-eversion motion, as compared to the active range of motion of $46.2 \pm 13.9^\circ$ and $43.2 \pm 16.1^\circ$ respectively.

IV. CONCLUSIONS

One key feature of the soft robotic sock was the ability to assist the ankle with two planes of motion. Stroke patients who underwent dorsiflexion-plantarflexion exercises are less likely to develop ankle joint contracture within six months of stroke [2]. Therefore, it is important to conduct early ankle rehabilitation to prevent ankle contracture. With the soft robotic sock, the therapist does not have to assist the patients manually with ankle exercises, and can rely on multiple socks to robot-assist multiple patients at one go, thus saving both time and manpower. Future design iterations will consider strengthening the actuator force output and varying the actuation rate so as to provide a more functional assisted range of motion. Thereafter, we will test the sock with stroke patients to assess efficacy in preventing DVT and ankle contracture through robot-assisted ankle exercises.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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332 - From planar absorptiometry to three-dimensional finite element modeling: A short history of noninvasive assessment of bone strength

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Bone densitometry based on dual-energy X-ray absorptiometry (DXA) has been the mainstay of clinical and scientific bone research since late 80's. In the near future, however, the progress and broader access to three-dimensional (3D) imaging of clinically relevant bones (proximal femur and lumbar vertebrae) is expected to diminish the present predominance of DXA-measured areal bone mineral density (aBMD) – a trait that is not only ambiguous but also subject to substantial inaccuracy at the individual level. Both the clinical and scientific focus will be more on 3D imaging of bone structure and subsequent finite element (FE) analyses of bone strength in different loading situations. Obviously, no real progress can be achieved as long as the obstinate reliance on DXA-measured aBMD continues. While old methods die hard, there is now a good prospect that the paradigm shift is really happening.

At present, several feasible 3D imaging and analysis methods are available while relevant structural data on different bones from various clinical populations and study settings are accumulating. Exploded interest in DXA-based hip structural analysis (HSA) in the beginning of this millennium over the conventional BMD can be regarded as a turning point in the field of clinical bone densitometry and also the start of broader-scale mechanical thinking. Therefore, the recent evolution and applications of quantitative computed tomography (QCT) and its peripheral (pQCT) and high resolution modalities (HR-pQCT) as well as corresponding magnetic resonance imaging (MRI and HR-MRI) methods hold much more promise in this

respect. Furthermore, these methods permit feasible *in vivo* applications also to clinically relevant proximal femur and lumbar vertebral sites, more sophisticated analyses of cortical and trabecular structural traits, and above all, construction of the 3D bone model and implementation of FE analysis.

Biomechanical approach based on the FE analysis of 3D model of bone to assessing the bone strength is expected to improve evaluation of treatment-effects, identification of high-risk individuals and provide more reliable estimate of risk of fragility fractures than obtained from conventional aBMD data. While the 3D structural assessments or FE analyses have not yet consistently shown essential improvement in the clinical fracture prediction beyond DXA-measured aBMD, these approaches rely on solid biomechanical grounds and will yield more meaningful information on bone fragility and its susceptibility to fracture, as some pivotal clinical findings have already shown. More clinical evidence is obviously needed to corroborate the true clinical value of FE approaches. In the end, bone fragility and related fractures are a problem of an *individual* patient, and all novel prognostic approaches should truly facilitate the decision making of practicing doctors and ultimately enhance the clinical outcome of each individual patient.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

334 - Saliva as a non-invasive sample matrix: collection and handling for point-of-care diagnostics

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I. INTRODUCTION & AIM

Saliva is an attractive and analytically interesting sample matrix for point-of-care (POC) diagnostics as there are many analytes present in saliva that are comparable to blood and in reasonable concentrations. Saliva is a non-invasive and easily available sample fluid. In a small scale salivary POC assay pilot study, we found that 80 % of participants (n=40) preferred to give saliva samples instead of blood. Standard procedures and collection tubes exist for blood sampling that verify the correct handling of sample collection whereas saliva collection and handling methods are diverse and in some cases improper handling may remove the analyte of interest from saliva before it can be measured. Therefore, correct selection of the type of device used needs to be made with care. Within this presentation, we introduce basic methods for saliva collection and handling, emphasizing issues that needs to be considered when choosing the right methods and insights to procedures that can be used to eliminate the matrix effect of saliva.

II. METHODS

In the simple “passive drool” method saliva is collected directly into a tube. Salivary mucins and large glycoproteins can cause saliva to be viscous and “sticky” and difficult to handle. Relatively simple treatments can be applied to make saliva easier to handle without changing its molecular content. These include freezing, heating and sonication that can break down the viscous molecular network. For some analytes this is enough but in many cases further treatment is needed to eliminate the saliva matrix effect completely. Saliva dilution is commonly used but the choice of diluent is important. In some cases it is beneficial to fractionate saliva or remove the heterogenous part of saliva. Large particles are removed by centrifugation (16 000 x g for 30 minutes). More specific treatments were investigated to eliminate saliva’s matrix effect including filtration with syringe filter (0.45 µm) or molecular size cut off centrifugal filter (10 KDa). Additives like protease inhibitor or enzymes were found beneficial when saliva proteases or glycoproteins contribute to the saliva matrix effect. Precipitation of carbohydrates with FeCl₃ or detergent treatment were effective when

saliva polysaccharide fraction was responsible for its matrix effect.

III. RESULTS & DISCUSSION

Freezing, heating and sonication treatments make saliva easy to handle, however, further treatment was needed to eliminate the matrix effect. Centrifugation was effective with small peptide analyte, ghrelin, and 86 % response was achieved. Filtering eliminated both cortisol and ghrelin matrix effect and over 90 % responses were achieved. Aprotinin is protease inhibitor and treatment with it was able to eliminate ghrelin matrix effect moderately, 72 % response was achieved compared to buffer. Leptin shows strong matrix effect and without treatment no response was observed from saliva. Enzymatic treatment gave 68 % response in saliva but treatments with FeCl₃ and cationic detergent treatment improved detection and 79 % and 70 % responses were observed, respectively

IV. CONCLUSION

In general it can be noted that different analytes gave different matrix effect behavior and required different treatments for its elimination. After saliva matrix effect is removed with correct treatment, saliva is a preferable choice for POC diagnostics

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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336 - Saliva matrix effect elimination by detergents

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I. INTRODUCTION & AIM

The use of saliva as a non-invasive and painless sample material has attracted an increasing interest in health and wellbeing applications and multiple biosensors have been developed to measure salivary analytes. Saliva is a complex matrix that can have a strong effect on signal intensity and in the worst case it can inhibit signal completely. Cortisol is a hydrophobic steroid hormone with small 362 Da molecular size. Leptin on the other hand it is a 16000 Da peptide hormone and in saliva we would assume would behaved completely differently compared to cortisol in its interaction with saliva and displayed matrix effect characteristics. Here we present how detergents can be used to eliminate saliva matrix effect in immunoassays of two different salivary model analytes, cortisol and leptin.

II. METHODS

When salivary cortisol was measured using a colorimetric competitive direct immunoassay, a moderate amount of matrix effect was detected and only 60 % of the response was achieved compared to buffer. To eliminate the saliva matrix effect, different detergents were tested including non-ionic Triton X 100, anionic SDS (sodium dodecyl sulfate) and sodium deoxycholate, cationic CTAB (cetrimonium bromide) and zwitterionic detergent CHAPS (3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate). Leptin gave no response in colorimetric immunoassay in saliva. Detergents SDS, Triton X 100, Tween 20, deoxycholate and CTAB were all tested with competitive indirect leptin immunoassay to eliminate strong matrix effects.

III. RESULTS & DISCUSSION

With cortisol, Triton X 100 and CTAB were the most effective and high colorimetric response was achieved in saliva. CTAB was more effective with lower concentrations and in 0.32 % solution already 97 % response was reached whereas with Triton X 100 91 % colorimetric response was achieved with 2.5 % concentration. Triton X 100 affects lipid-protein interactions and CTAB to polysaccharides indicating that in case

of cortisol multiple factors contribute to saliva matrix effect but these can be almost completely removed by correct detergent treatment. Deoxycholate eliminated matrix effect but it also decreased the maximum response in buffer and therefore was not beneficial. Likewise SDS and CHAPS eliminated the response both in buffer and saliva when higher concentrations were used, with SDS this decrease in response was seen already in concentrations as low as 0.05 %.

Saliva eliminates response from leptin immunoassay completely and from tested detergents, only CTAB had an effect and 70 % response was achieved from saliva compared to buffer. Again SDS eliminated the response in buffer and saliva when higher concentrations were used. A possible reason why CTAB was effective could be the positive charge of the molecule that has been found to denature macromolecules like polysaccharides and glycoproteins. Saliva is rich in these molecules and if CTAB treatment eliminates this fraction, it enables antibody binding to leptin. Although the CTAB treatment did not eliminate the matrix effect completely, calibration curve in saliva was constructed and compared to a curve determined in buffer and it gave promising results. In buffer, the limit of detection was 9.4 ng/ml and linear range 23.7–1400 ng/ml whereas in saliva, detection limit was 21.5 ng/ml and linear range 54–3740 ng/ml.

IV. CONCLUSION

Our results demonstrate how simple treatment with detergents can eliminate the matrix effect almost completely and also emphasize how important it is to find the correct treatment for each analyte, since the analyte properties effect on the strength of the matrix effect and on which treatment is the most effective.

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CONFLICT OF INTEREST

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340 - UHF RFID Monitoring of Assistive Technologies beyond the Clinic

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I. INTRODUCTION & AIM

Professionals currently have little or no information about how the Assistive Rehabilitation Technology (ART) patient uses their equipment outside the clinic on a daily basis. This leads to sub-optimal outcomes for the patient themselves and inefficient use of resources [1]. This paper outlines multidisciplinary work creating a low energy, long-term UHF RFID (Ultra High Frequency Radio Frequency Identification) based sensing platform to provide information for the clinician, the carer, and the end-user.

II. RFID MONITORING

To provide monitoring, label based sensors are being developed to mount on assistive equipment, and for the user, tattoo transfer RFID tags with accelerometers and energy harvesting capability are being created [1]. These tags in association with Commercial Off The Shelf (COTS) smart beam switching UHF RFID readers will enable indoor location of identifiable tags to be tracked over time. Together with the accelerometer epidermal tags, it will be possible to assess small-scale movements and possibly tremors in addition to larger scale positional information. The advantage of exploiting passive backscatter based RFID assisted by energy harvesting is that the need for routine battery recharge and replacement is eliminated allowing the tags to be worn for extended periods.

The reader used in this study is a ceiling mounted Impinj xArray 52 beam warehouse asset tracking device which is able to return x and y floor position to a stated lowest accuracy of 1.5 m [2]. Preliminary studies indicate that when mounted at domestic ceiling height (around 1.6 m) the reader routinely returns positional accuracies of 0.5 m or better within a coverage

radius of 3 m, making it suitable for general domestic location monitoring. As the tag reader is ceiling mounted it is possible to create tags with some directionality in the antenna beam. This is to overcome the inherent radiation efficiency limitations of epidermally worn tags [3]. Presented results will show a clear interaction between the user and the assistive equipment.

III. CONCLUSIONS

These technologies could make available data for activity signature identification enabling professionals and users to more effectively exploit their assistive technologies such as walking frames, rollers, wheelchairs or prosthetic limbs.

The authors declare that they have no conflict of interest. The anonymous volunteers gave informed consent and the study was carried out in accordance with the authors' institutional ethical framework.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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344 - Modern ECG algorithms for ECG monitoring at the hospital

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I. INTRODUCTION

ECG is one of the most important but also a very challenging monitoring measurements. The Interest is in small signals at μV level, while environmental aspects are causing challenges in terms of electrical or mechanical interference causing artifacts to a signal, multiple times stronger than ECG signal itself. Artifacts are also often present during clinical events as a result of patient's cramping. Waveforms, in such as very poor signal condition due to heart failure, causes extra challenges. Artifacts may occur only in some of the leads and they may mimic real arrhythmias. Arrhythmias on the other hand may at the same time be clearly notable in some of the leads but very shallow in the other leads at the same time. Due to these reasons multi-lead algorithms provide significant benefits when monitoring patients with cardiac problems. Over the past 10 years, multi-lead algorithm technology has been further developed to better select relevant leads for analysis using real-time correlators. This is especially important to be able to reliably differentiate arrhythmia mimicking artifacts, that may be seen only in some of the leads, between real arrhythmias not clearly detectable in some of the leads.

II. AIM

Database of 461 ICU patients was collected in UCSF hospital, containing ECG waveforms from each hospitalized patient during one month. GE monitors in hospital included EKPro arrhythmia algorithm technology from 2003. Aim of this study is to evaluate improvement of algorithms to present day and to analyze methods and reasons behind those differences. Main interest is to evaluate false alarm rates of arrhythmia calls including cardiac standstill, and ventricular tachy arrhythmias.

III. METHODS AND RESULTS

Database was tested by feeding signals in to the algorithms and comparing results with the ones from data collection. Events were annotated by clinical experts of the hospital during the data collection. The result show that the latest revision of the algorithm performed much better than the algorithm used in the UCSF hospital. 75% reduction of false alarm rate was recorded. Most significant improvement is 84% reduction of false cardiac standstill alarms. This is due to improvements in QRS detection related to low amplitude (<0.5mV) QRS. Also, improvements in analyzing multiple ECG signals simultaneously have major impact. This is due to fact that often artifacts are connected by motion or noise through one single electrode causing only some of the ECG leads to get noisy, while others remain with good signal quality. As result of these improvements, 54% reduction of false ventricular tachycardia or fibrillation alarms was detected. In addition, 10% increase of real arrhythmias was detected as a result of better noise tolerance and beat detection.

IV. CONCLUSIONS

75% performance improvement was measured with latest algorithm technology compared to older versions of algorithm. Usage of multi-lead detection technology allows high performance level of arrhythmia detection.

CONFLICT OF INTEREST

Author declare that he has no conflict of interest.

345 - Detection of Atrial Fibrillation via MEMS accelerometers and gyroscopes

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I. INTRODUCTION

Atrial fibrillation (AF) is a very common cardiac rhythm abnormality. Due to failure of the atrium to contract effectively, a blood clot may form within, which may enter blood flow at a later time and in some cases block a blood vessel in the brain, resulting in a stroke. Up to 30 percent of all strokes are caused by AF. AF sometimes begins as asymptomatic ("silent AF"), in which case an otherwise healthy patient remains unaware of the condition. Our aim is to provide simple and cost-effective means for detecting AF (including the "silent AF"). Since many existing mobile devices, such as smartphones, are today equipped with accelerometers and gyroscopes (IMU), they can be used for monitoring the operation of the heart. The purpose is to prevent the consequences of undetected AF with early prevention.

II. METHODS

We have performed two separate clinical trials to investigate AF detection from wearable devices equipped with accelerometers and gyroscopes. The first included 13 paroxysmal AF patients and the data was collected using custom-made data collection unit equipped with ECG, accelerometer and gyroscope. The second trial, which used smartphone only solution to detect AF, included 16 chronic AF patients and additional 20 recordings from healthy volunteers. In first trial, seismocardiogram was taken in supine position simultaneously with the ECG assessment during AF as well as sinus rhythm from 13 patients. Measurement data was saved to a SD memory card and analyzed retrospectively with a computer. An SCG-based AF-detection algorithm was developed and its performance tested with the acquired clinical data. In the second trial, a smartphone device was placed on the chest of the patient, and an accelerometer and gyroscope measurement recording was taken from the subject. The procedure was simple and fast. An automated algorithm extracts features such as autocorrelation and spectral entropy from the pre-processed (FFT filtering and potential noise exclusion) IMU data. A machine learning algorithm, which operates based on the extracted fea-

tures, is used for classification. We used state-of-the-art machine learning methods such as SVM (Support Vector Machine), Kernel SVM (KSVM) and Random Forest (RF) classifier. The data from each person was divided into 10 second non-overlapping segments for feature extraction and classification. The learning part was implemented in desktop environment and the critical data acquisition was implemented on a smartphone.

III. RESULTS & DISCUSSION

In first trial with custom-made data logger we used linear classification of the spectral entropy and a heart rate variability index computed from the MEMS cardiac signals. Using a majority voting scheme which takes 5 randomly selected segments from a signal and classifies these segments using the proposed algorithm, we obtained an average true positive rate of 99.9% and an average true negative rate of 96.4% for detecting atrial fibrillation in leave-one-out cross-validation. In second trial using smartphone, we used 10-fold cross validation to verify classifier performance. The best performing classifier was KSVM with sensitivity of 98.5% and specificity of 95.2%. Out-of-bag classification error for RF was 4.95% (200 grown trees).

IV. RESULTS & DISCUSSION

The presented work facilitates adoption of MEMS-based heart monitoring devices for arrhythmia detection.

CONFLICT OF INTEREST

The first and last author are shareholders of Precordior Oy.

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349 - Multimodal Imaging of Silver Nanoclusters

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V. INTRODUCTION

X-ray Microtomography (μ CT) is a non-invasive and non-destructive imaging technique which provides high spatial 3D images of the object [1][2]. Optical Projection Tomography (OPT) is known as an equivalent of μ CT in which image is formed by optics [3]. In this study, the fluorescent silver nanoclusters (AgNCs) [4] were analyzed by both imaging modalities.

In this work we aim to show for the first time the possibility of fluorescent silver nanoclusters as contrast agent in OPT and X-ray microtomography and dual functionality of silver nanoclusters in light and X-ray absorption for both imaging methods. AgNCs can be used to highlight low contrast samples such as cells in biological imaging. The purpose of the study is to find out what is the correlation between different concentrations of silver nanoclusters and image contrast and the possible effect of the light exposure and X-ray on optical properties of the samples.

VI. METHODS

Both bright-field and fluorescent mode of optical imaging were used in this study. 400 projection images were obtained by OPT during 360-degree rotation with 10 X magnification and 650 nm pixel size with the same exposure time of 3 seconds and source current 500 mA in fluorescent imaging and different exposure time were applied in bright-field mode. In μ CT, samples were imaged by 20 X magnification and image pixel size of 1.13 μ m with 1600 images obtained during 360-degree rotation, the source voltage and current were set to 40 kV and 10 W, respectively and exposure time of 14 seconds. For each sample, fluorescent imaging took 30-40 minutes and bright-field imaging lasted for 10 minutes roughly while for μ CT imaging acquisition took around 22 hours for each imaging session. Eventually, graphs were created based on the values from microCT and OPT images to evaluate the relation between image contrast and AgNC concentration.

VII. RESULTS & DISCUSSION

In this study, we could detect both fluorescent and X-ray absorption from data obtained from images and display that there is a linear correlation between the absorption of light and X-ray versus different concentrations of silver in samples. However, most of the samples get darker due to exposure, specifically during fluorescent imaging. Fluorescent imaging of some samples lead to intensive cloudy structures after light absorption, while some samples formed the granular structures and some samples did not show any structure or darkening. Furthermore, microCT images represented different grayscale levels which images of samples with higher concentration looked brighter due to more X-ray absorption. The microCT images after reconstruction displayed ring artifact due to imperfection of optic and images were included noise which deteriorated the grayscale background.

In sum, darkening of samples during fluorescent imaging can be caused by either photo-bleaching or due to chemical changes. Moreover, the novel silver nanoclusters can be substituted as labelling in bioimaging since they show contrast for optical imaging and X-ray microtomography.

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350 - Read Directivity of Epidermal Tags for Future Medical and Social Care Monitoring Systems

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I. INTRODUCTION

AART-BC [1] is a European funded consortium composed of members of the broadband and wireless group at the University of Kent (UoK) and six other project partners from academia with expertise in the fields of RFID, Biomedical Engineering, Rehabilitation, Biomechanics and Orthopedic technologies. As a group, we are investigating the patients use of Assistive Technologies (AT) when beyond the clinic to ascertain whether the AT is being used correctly, if at all, allowing measures to be put into place to modify their AT and improve the patient's rehabilitation as required. The main focus for the group at the UoK is to provide a wireless system which provides a patient's position and movement data within its wireless coverage footprint. At the same time further developing body worn (tattoo) [2] and equipment mounted RFID tags, with some offering additional functionality beyond the usual tag identification, utilizing such technologies as energy harvesting of the RFID carrier to supply very low power sensors such as accelerometers.

Although originally developed for applications such as inventory management and toll collecting RFID offers great potential beyond that. The systems are relatively low cost and unobtrusive and can be easily deployed in a patient's home or living environment with a single ceiling mounted antenna providing coverage of the space to be monitored. This could potentially be expanded upon for larger spaces. A body of research has been carried out into developing additional functionality to RFID reader systems, particularly in tag design [3] either by adapting readily available RFID semiconductor devices or the development of application specific ones.

II. MEASUREMENTS AND RESULTS

The efficiency of RFID tags drops markedly when placed upon or close to the skin. Radiation efficiencies of -20dB or so

are typical when compared to the same tag in air. An effect of placing a slot tuned dipole based RFID tag upon the skin is that its current concentrates at the feed and skews the radiation pattern towards the feed-point, where maximum radiation would be expected at 90° to the tag rather than from 0-30° as experienced with on-body measurements using the Voyantic UHF RFID measurement system.

III. CONCLUSIONS

The efficiency of on-body mounted RFID tags is markedly reduced. Measurements have shown that the tag radiation pattern is skewed in favor towards its feed-point in the case of the slot fed RFID tag. The skewing of the radiation pattern provides directivity of some 4.5dB giving useful directive gain. With correct placement of the tag in relationship to the RFID reader this can be exploited to improve read ranges for body worn tags.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. The anonymous volunteers gave informed consent and the study was carried out in accordance with the authors' institutional ethical framework.

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351 - The effect of sample duration on the robustness of pulse-pressure variation during ongoing surgery

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I. INTRODUCTION & AIM

Intraoperative hemodynamic optimization using goal-directed volume expansion reduces postoperative morbidity and hospital stay. To guide volume expansion and predict fluid responsiveness, pulse pressure variation (PPV), derived from the arterial blood pressure (ABP), has been proposed [1]. Clinical practice has adopted PPV algorithms with extended pulse-pressure sample durations spanning multiple ventilation cycles [2,3]. The validity of these PPV algorithms to predict fluid responsiveness under stable hemodynamic conditions is well established. However, little is known about their performance in the face of rapid-changing blood pressure, which often occurs during ongoing surgery. In this paper, we study the effect of the sample duration on the robustness of the PPV algorithm during ongoing surgery.

II. METHODS

Invasive ABP signal was continuously recorded at the radial artery with a catheter (Philips Heartstart MRx monitor). A total of 91.2-hour data from 29 patients undergoing major abdominal surgery was used for the analysis. We identified a common pattern in the PPV values that concerning the robustness of PPV algorithm. This pattern is a short-term elevation of the PPV values: a 10-40 second increase in median PPV values larger than 2 percentage points compared to the PPV values in preceding 40 seconds and following 40 seconds. This temporal deviation originates from the PPV calculation formula. When the pulse pressure gradually changes over a time span of several ventilation cycles, the difference between the pulse pressure extrema is artificially amplified, leading to temporarily elevated PPV values. Thus, this no longer reflects true volume status and may confuse clinicians. To investigate how this pattern affects PPV calculation, we computed the occurrence rate of this event as indicators inversely related to the performance. We considered three algorithms that all shared the structure of the original definition: the formula to calculate raw PPV, three-

point mean filter to post-process raw PPV. The tested algorithms only differed in sample duration: one ventilation cycle, eight seconds, and ten seconds.

III. RESULTS

The occurrence rates of short-term elevations for the PPV algorithms are 1.9, 2.4, and 2.6 times per hour, for sample durations of 1 ventilation cycle, 8 seconds, and 10 seconds, respectively.

IV. CONCLUSIONS

Extended sample durations increase the occurrence rate of temporal elevations of the PPV during ongoing surgery. This happens when the pulse pressure gradually changes over a time span of several ventilation cycles. Such short-term elevations that may complicate clinical decision making on fluid loading in the operating room.

CONFLICT OF INTEREST

W.H. Peeters, R. Bezemer, X. Long, I. Paulussen, and R.M. Aarts are employed by Philips, and G.J. Noordergraaf is a consultant for Philips. S. Sun is financially supported by a grant from China Scholarship Council (CSC).

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352 - Electrorotation of zebrafish embryo: a potential tool for toxicological assays

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I. INTRODUCTION & AIM

The electrorotation (ER) is a ponderomotive technique based on the polarization of a particle under a rotational electric field, very useful for non-invasive manipulation, separation, detection and characterization of tiny bioparticles in suspension. Although ER has been mainly applied in the micro- and nano-scale, it is also suitable for larger particles, up to 1000 μm , despite its application over mm-sized particles has been scarce [1, 2]. This paper shows the application of the ER technique to the dielectric characterization of mm-sized embryos of the zebrafish (*Danio rerio*). The electrical parameters are obtained by fitting the experimental ER spectra to those provided by simulation using a multilayer spherical model. The analysis of the spectra of embryos exposed to a contaminant agent of various concentrations, shows that the ER technique might be a very useful tool in toxicological assays.

II. METHODS

The single zebrafish embryos (ZFe) were subjected to a rotational electric field through planar electrodes over a glass substrate. Two layers of metals were deposited over the glass by Joule effect evaporation (Cr/Au, 10nm/140 nm respectively) drawing eight electrode tips arranged around a circle of 1.25 mm of diameter. The glass chip is hosted in a printed circuit board (PCB) over a drilled hole opened for microscope observation. Two parallel series of 4 pogo-pins were symmetrically arranged on the interior edges of the hole for the electrical connection of the chip, and four 90°-phase-shifted sinusoidal signals of 15 Vpp were driven through a connected multiplexing PCB from the output of the signal generator.

Control ZFe and exposed to ethanol ZFe (3%, 5% y 16% (v/v)) were suspended in 12 μl of egg water (with several conductivities) over the ER receptacle, and their ER behavior from 1 kHz to 20 MHz were recorded and processed for obtaining the corresponding ER spectra. A simplified analytical three-shell particle model has been used for the dielectric characterization of the ZFe, according to its structural compartments: yolk core, yolk envelope, perivitelline space and chorion.

III. RESULTS & DISCUSSION

In general, the ER behavior of control zebrafish embryos presents a **clear** dependence on the conductivity of the external medium. However, the ER response of the embryos seems to be reproducible only under specified experimental conditions (stage of development, spatial orientation of the embryo on the ER chamber ...). The ER spectra of control ZFe in different conductivity media were fitted through the spherical three-shell model, and the dielectric parameters were extracted. The differences found for the ER responses of the ZFe exposed to ethanol were likely related to the diverse ethanol tissue absorption. These results pointed out the electrorotation of ZFe as a useful tool for toxicity testing and it is worth for further investigation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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353 - High resolution functional magnetic resonance imaging using parallel detection

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I. INTRODUCTION & AIM

Typical functional magnetic resonance imaging (fMRI) [1] using blood oxygenation level dependent (BOLD) contrast [2, 3] detects hemodynamic responses secondary to neuronal events with the spatial resolution in a few millimeters and the temporal resolution in seconds. This spatiotemporal resolution limits the sensitivity at high fields (≥ 3 T), the ability of detecting neuronal timing information, the opportunity to explore the interactions between brain areas at higher frequency, and functional specificity. To address these challenges, we propose to exploit the high SNR offered by a coil array to provide high temporal or spatial resolution imaging [4] of human brain function.

II. METHODS

Enabled by a multi-channel coil array and inspired by electroencephalography (EEG) or magnetoencephalography (MEG) sensor systems using highly parallel signal detection to obtain spatial information, inverse imaging (InI) [5] can estimate brain hemodynamic responses at the 10-Hz sampling rate (repetition time TR = 0.1 s) with whole-brain coverage and isotropic 5-mm spatial resolution using a 32-channel head coil array at 3T [6].

III. RESULTS & DISCUSSION

We will present studies using InI to monitor and to suppress physiological noise caused by heart beating and breathing and to detect fine timing (in a few hundreds of milliseconds) as well as high frequency (above 1 Hz) features inside the hemodynamic responses. InI also allows us to get EEG data minimally contaminated by the MRI gradient coils during concurrent EEG-fMRI recording, because fMRI only samples in a temporally sparse pattern (0.1 s for every 2 s). The same InI protocol also allows us to integrate TMS inside MRI with very little constraint in TMS pulse scheduling and fMRI data acquisition.

Multi-channel coil array with high sensitivity also allows us to perform high spatial resolution fMRI to improve the functional specificity. To this end, we first developed a 24-channel

array tailored to the human temporal lobe. Together with acquisitions with the 1.5 mm isotropic resolution, this coil array was used to characterize tonotopic representations, tuning widths, and their variabilities at the auditory cortex using laminar analysis [7]. We will report both intra- and inter-subject variabilities in both frequency preference and tuning width across cortical depths. Results suggest that the intermediate layers have the least inter-subject variability and the largest correlation between frequency preference and tuning width.

Taken together, we are convinced that multi-channel coil array enables the unprecedented spatial and temporal resolution in fMRI. This tool can disclose physiological and pathophysiological information about human brain function and dysfunction with high sensitivity and specificity.

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CONFLICT OF INTEREST

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356 - Multi-parameter Sensing Platform in ESS-H and E-care@home

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I. INTRODUCTION

Considering the population of ageing, health monitoring of elderly at home have the possibility for a person to keep track on his/her health status, e.g. decreased mobility in a personal environment. This also shows the potential of real-time decision support, early detection of symptoms, following of health trends and context awareness [1]. The ongoing projects Embedded Sensor for Health (ESS-H)¹ and E-care@home² are focusing on health monitoring of elderly at home. This paper presents the implementation of multi-parameter sensing on an Android platform. The objectives are, both to follow health trends and to enabling real time monitoring.

II. MATERIAL AND METHODS

The Shimmer platform³ is used for wireless data acquisition and real-time monitoring. The parameters/sensors included in this implementation are body and skin temperature, photoplethysmography (PPG), skin conductance, pulse, respiratory rate, body movement, accelerometer, magnetometer, gyroscope, oxygen saturation, heart rate, electrocardiography (ECG), and electromyography (EMG) [2]. Java/Android API helps to develop apps on the Android platform in order to stream health parameters directly to the Android devices and forward it further to the ESS-H and E-care@home databases (RDMS MySQL), both locally and in the cloud. In this case, a maximum of seven health parameters can be measured simultaneously with the limit of Bluetooth communication, depending on sampling frequency, signal types and processor of the mobile device. Maximum battery consumption is achieved by the ECG shimmer node around 10 hours, however, it can adjust by controlling the writing/transmitting alternatives [3]. There are three

identified user groups: care providers, elderly patients with chronic obstructive pulmonary disease and co-morbidity, and elderlies in better health but who are afraid of or at risk for falls.

III. CONCLUSIONS

A multi-parameter sensing platform is implemented in ESS-H and E-care@home projects based on Bluetooth communication and Android operating system. The functionalities of the platform are: real-time measurement, state-of-the-art communication protocols, high-level analysis of data from various types of sensors, interpret, store, and visualization several health parameters both in real-time and offline by different user groups i.e. patients, nurses and doctors.

ACKNOWLEDGMENT

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¹ <http://www.mdh.se/forskning/inriktingar/2.4200/ess-h>

² <https://ecareathome.se/>

³ <http://www.shimmersensing.com/>

358 - *In vivo* measurement of ocular microtremor using *i*-tremor instrument

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I. INTRODUCTION & AIM

Ocular Microtremor (OMT) is a minuscule (12 to 216 μ rad) and high frequency (20 to 150Hz) physiological tremor of the eye [1]. This ever-present tremor is the smallest component of the involuntary eye movements that are seen in the normal human eye. The frequency of OMT correlates well with levels of consciousness; for example, the tremor slows under anesthesia [2] and in coma [3], providing clinical value for determining status of awareness.

Here we introduce *i*-tremor, a non-eye-contacting, easy to use OMT measurement device with the potential to expedite uptake of OMT in clinical setting. The device has been developed from many years of clinical and technical research on OMT at Trinity College Dublin and St. James's Hospital in Dublin, Ireland. In the recent development, a non-invasive optical OMT measurement technology using laser speckle metrology was introduced [4] and laid the foundation for the currently developed hand-held *i*-tremor tool. We report the results from a small-scale investigation assessing the utility and usability of a prototype *i*-tremor device for measuring OMT in a cohort of healthy volunteers.

II. METHODS & RESULTS

A group of 12 healthy volunteers from a local sports club were recruited for this study. All participants were males aged 20-23 with a mean age of 21 years. Ethics approval for this study was received from St. James's/AMNCH Research Ethics Committee and written informed consents were sought from all study participants. Measurements were taken before routine team training sessions over two consecutive days (5 subjects on day one and 7 on day two).

The mean peak frequency for the 12 subjects as estimated from peak counting was 73.6 \pm 5.4 Hz and 80.2 \pm 5.2 Hz in vertical and horizontal directions respectively. These results match

closely to the results reported by earlier studies using both contact (84 Hz [1]) and non-contact (78 \pm 3.9 Hz [5]) measurement techniques. Spectral analysis of recorded OMT traces contained features consistent with typical OMT signal. A characteristic rise of power in the band of expected OMT peak frequency (the region around 80 Hz) was observed in both vertical and horizontal signal components.

III. CONCLUSIONS

Our investigation has revealed that the prototype *i*-tremor device utilizing non-contact configuration is feasible in practical use. The convenience of a short set-up and measurement time was noted by the investigators and study participants alike. Further work is ongoing to optimize the proposed hand-held design and ensure its robustness for use in clinical applications.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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359 - Analytical method for calculating drug outflow in multi-infusion: outlook and future perspectives

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I. INTRODUCTION

One of the highest technology associated risks in critical care is infusion technology [1]. There are many reasons why intravenous infusion therapy is challenging. For example, limited vascular access and a high risk of systemic infections typically require clinicians to connect multiple infusion pumps to one multiple-in, single-out infusion set and catheter. This technique is called multi-infusion. However, over the past years, ample evidence has been gathered that multi-infusion is associated with dosing errors due to ambiguous physical effects, caused by the complex nature of multi-infusion systems [2,3]. For this reason, we aimed to develop a model capable of predicting the drug dosing rate outflow during infusion therapy.

II. METHODS

Using Mathematica 10 (Wolfram® Inc., USA), we derived explicit expressions to describe drug outflow of multi-infusion setups after interventions such as flow rate changes. Our approach incorporates the mechanical/physical properties of the infusion hardware, i.e. mechanical compliances and flow resistances of the syringes, tubes, filters etc. Subsequently, a Z-transform was used to model the contents of the ‘dead volume’, this is the common volume where the drugs from the various different pumps mix until the distal outflow point at the catheter tip. The model considers a laminar Poiseuille flow, which is appropriate for the flow rates typically used in critical care. Consistency of the analytical expressions was tested for limiting cases using several *in vitro* experiments.

III. RESULTS

For the various cases tested, the model was able to predict the *in vitro* measurement within a 13%-14% standard deviation. The model is capable of distinctly presenting the various factors affecting the dosing errors, that is, the Poiseuille flow profile, resistance and internal volume of the tubing, and mechanical compliances (mostly in the syringes) [4]. This helps clinicians to gain insight in the often counter-intuitive results of clinical interventions with regard to infusion therapy. Moreover, we propose that the performance of existing as well as

hypothetical medical pumps, incorporating feed-forward and feed-back technologies, may be improved by the incorporation of our model. Ultimately, the model may improve patient safety.

IV. CONCLUSIONS

Our model is capable of describing the drug outflow of multi-infusion setups using explicit expressions. This allows clinicians to improve their understanding of multi-infusion therapy and support the development of new technical innovations.

COMPLIANCE WITH ETHICAL REQUIREMENTS

Statement of Informed Consent and Human and Animal Rights

No human or animal subjects nor any biological materials were involved in this study. Informed consent was therefore not applicable.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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361 - Monitoring sleep through smart devices: different scenarios and analysis protocols

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I. INTRODUCTION & AIM

The last years witnessed the growing interest of the scientific community in sleep studies. From a clinical point of view, sleep quality and sleep disturbances have been related to many different dysfunctions, ranging from neurological, psychiatric, cardiac, metabolic and others. Sleep total duration and quality have been recognized as an important factor in the assessment of the general conditions in elderly people and, in general, it is recognized that quality of sleep is related to quality of life. This justifies the efforts in proposing innovative devices for monitoring sleep in alternative to clinical polysomnography (PSG), which still remains the golden standard, but, for its costs in terms of technological and human resources, is not feasible for continuous monitoring or for home solutions [1-3]. Many of the proposed solutions address very specific sleep disturbances, thus proper signal processing modules and analysis schemas are required. In the following, different scenarios are presented requiring different protocols and feedback strategies [4].

II. DIFFERENT SCENARIOS FOR SLEEP MONITORING

Non-intrusiveness is one of the main characteristics of the proposed systems. This means that in many cases EEG is not recorded, while sleep assessment is based on other physiological signals, among them the most common are heart rate and heart rate variability, respiratory activity and movements. Proper signal processing pipelines, including automatic signal quality check, feature extraction and classification, can provide reliable sleep scoring, sleep apnea detection, and estimation of total sleep time, sleep efficiency, number of microarousals, etc. According to the needs, three common scenarios are listed below, which require different analysis procedures and report strategies.

- Supervised sleep monitoring for health care units and nursery homes, as an alternative to the expensive PSG-based sleep exam. Unobtrusive sleep monitoring is intended for screening of sleep and cardiac disorders and for follow-up of sleep apnoea therapy, detection of cardiac episodes, risk stratification. Data are collected on a server for automatic scoring and are available for clinicians.

- Supervised use for tele-monitoring purposes at home and follow-up of therapy in different pathologies. Results obtained are stored on a server for off-line analysis to be used/checked by physicians. Risk conditions and worsening in respect to baseline conditions are automatically detected and alarms are generated.
- Non-supervised use for well-being, sleep quality monitoring, stress and lifestyle management. Results are immediately shown to the user next morning in reports comprehensible for non-experienced and non-clinical users.

III. CONCLUSIONS

The presented list is not exhaustive of all the possible cases in which sleep monitoring can be applied, on the other hand it is clear that proper processing procedures and data management are a fundamental aspect for the correct use of the devices and the specific applications.

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CONFLICT OF INTEREST

The author declares that she has no conflict of interest

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365 - Robust control of extracorporeal gas exchange

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I. INTRODUCTION

As one of the last options in treating severe respiratory disorders the respiratory gas exchange can be augmented by extracorporeal membrane oxygenation (ECMO). A typical setup of such a system consists of cannulas for extracting blood out of the venous (or arterial) system, a blood pump and a hollow fibre oxygenator, where the gas exchange takes place between blood and fresh-gas. In order to enable more autonomous operation of such systems, the authors have been active in the automation of the therapy systems involved to allow for a less demanding supervision and operation of the systems. Starting from isolated control of the extracorporeal gas exchange [1] we extended the system to use less sensor information using Kalman filters [2]. First approaches to include artificial ventilation into the control system were made in [3].

As the processes involved in ECMO gas transfer show significant nonlinearities and a large degree of parameter uncertainty, controllers are typically tuned weak to generate practical stability. In order to improve performance and to guarantee robust stability in all operating points and parameter uncertainties, we derive a new decoupling of the MIMO system and design a robust H_∞ controller.

II. METHODS

Describing the model of an ECMO system with the human body from a high abstraction level, some core components are needed: gas exchangers and storage as well as transport media. Both in the lungs and the oxygenator the gas transfer is determined by diffusion between gas phase and blood across a diffusion barrier. This is described by partial differential equations but can be reduced to models with concentrated parameters following [4] and [5]. Transport processes in the circulation are typically described by transport delays. The extensive process model consists in total of 26 differential equations with the same number of internal states. To design the controllers, we have reduced the model to the most significant time constants and nonlinearities, which yields a total of 4 differential- and 18 static equations with only 6 states. Based on that, we calculated a decoupling inverse function for the ECMO circuit to separate O_2 and CO_2 gas transfer.

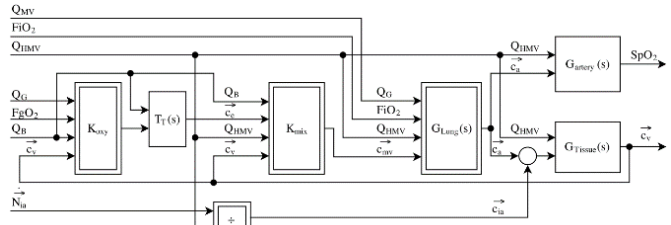


Figure 1: Structure of the robust control scheme

With that we then determined the parameter uncertainty sensitivities in the system, which we used to design the H_∞ controller. We used different approaches for controller synthesis, including fixed-structure-, mixed sensitivity- and signal based procedures. The goal for the controller synthesis was to achieve good disturbance rejection and acceptable reference tracking. Control performance was subsequently evaluated using the extended model with varying parameters and noise at the output of the control loop. So far we could prove sufficient performance with robust stability with increased performance in comparison to our previous controller implementation [2]. The control has been evaluated in first animal experiments and shows adequate and stable performance in vivo.

ACKNOWLEDGMENT

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367 - Using facial electrodes for sleep-wake classification in home recordings

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I. INTRODUCTION & AIM

Accurate sleep stage classification is important part of sleep disorder diagnosis and of health and wellness monitoring. Clinical sleep stage monitoring involves multiple electrodes placed by trained nurses [1]. Most long-term home monitoring systems are based on surrogate measures of sleep including activity and heart rate monitoring.

We have developed an accurate and automatic sleep stage classification algorithm based on facial electrodes measuring brain, muscle activity, and eye movements in a simple setup [2]. Facial electrodes outside hairline enables self-applicable home recordings over multiple nights. One version of the algorithm is based on single channel (two electrode) input [3]. Recently it has been tested on sleep apnea patients for binary sleep-wake classification [4]. In this study, we tested this algorithm on different electrode configurations outside hairline in home recordings.

II. METHODS

Total of 109 overnight recordings from 38 healthy subjects (age range 21-46 years, 25 females) were analyzed. Full polysomnography was used for visual sleep staging [1]. Sleep stages R, N1, N2, N3 were combined into single sleep stage S this study. Different bipolar montage combinations including EOG (left E1, right E2) and mastoid electrodes (left M1, right M2) were calculated offline and analyzed by the earlier developed automatic algorithm. Number of overlapped 2 s segments with DFT power 18-45 Hz below threshold was calculated for every 30-s epoch. If this density (0-100 %) was above another threshold, sleep was assumed and otherwise wake [3,4]. Leave-one-out cross validation (LOOCV) was used to determine these two threshold parameters resulting in highest Cohen's Kappa.

III. RESULTS

Highest Cohen's Kappa agreement between visual sleep staging and automatic algorithm using two electrodes infor-

mation was 0.69 for E2-E1 (electrodes eye to eye), followed by 0.62 for E2-M2 (electrode above right eye referenced to ipsilateral mastoid) and E2-M1 (electrode above right eye referenced to contralateral mastoid). With E1-M2 (electrode below left eye referenced to contralateral mastoid) and E1-M1 (electrode below left eye referenced to ipsilateral mastoid) agreement were 0.60 and 0.59. Lowest agreement was 0.54 for M2-M1 (electrodes mastoid to mastoid) configuration.

IV. DISCUSSION

The results confirm the usefulness of the standard EOG configuration E2-E1 for automatic sleep analysis using simple algorithm. Algorithm can be extended to cover different sleep stages [3].

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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371 - Screening sleep-related breathing disturbances in stroke patients using the Emfit ferroelectret film sensor and the oximeter

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I. INTRODUCTION & AIM

Sleep-related breathing disturbances (SDB) are present in 50 – 70 % of stroke patients and can have a negative effect on the recovery. Therefore, screening for SDB in all stroke patients is recommended. Continuous positive airway pressure (CPAP) is the recommended treatment [1]. Screening of all stroke patients for SDB by standard is typically not possible due to the lack of staff resources implying a need for a less laborious screening method.

The aim of the study was to evaluate if Emfit sleep mattress (Emfit Ltd, Vaajakoski, Finland) and oximeter (Nox Medical, Reyjavik, Iceland) could be used as a screening method to identify stroke patients with suspected moderate or severe sleep apnea.

II. METHODS

We studied a group of 41 patients, who were hospitalized for stroke and had not been diagnosed with sleep apnea before. These patients underwent simultaneous respiratory polygraphy and Emfit mattress measurement during the night. The standard polygraphy included respiratory inductance plethysmography, oximeter, nasal flow measurement and EKG. Emfit mattress measurement included a ferroelectret film sensor which was positioned under the bed mattress and the oximeter signal from polygraphy measurement.

Polygraphy was scored automatically using Noxturnal (Nox Medical, Reyjavik, Iceland) Respiratory Cannula Flow analysis and visually according AASM criteria (=golden standard). Emfit data was scored automatically using Noxturnal modified flow analysis.

The patients were classified into four categories according to the automatic scorings of Apnea-Hypopnea Index. The categorizations obtained from both methods were compared using receiver operating characteristics curves. We also evaluated the concurrence and consistency of events (desaturation, hypopnea or apnea) in both methods.

III. RESULTS & DISCUSSION

Comparison of automatic analyses revealed that 89 % of Emfit events were overlapping with polygraphy events. However, only 46 % of them were classified similarly. When compared to visual scoring polygraphy had sensitivity of 92 % and specificity of 79 %, Emfit mattress had sensitivity of 100 % and specificity of 82 %.

IV. CONCLUSIONS

The Emfit mattress and oximeter seems to be promising method to screen out stroke patients with moderate and severe sleep apnea. However, the automatic analysis must be improved to be more accurate. Improving the accuracy of the automatic analysis is the aim of the following study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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374 - Development of fabrication methodology for a silicon armpit rehabilitation device for Burns patients

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I. INTRODUCTION

Scars across joints can impede recovery of functional range of motion. Many authors have shown silicon pressure garments to prevent abnormal scar formation, resulting in scar contraction improvement. However, standard silicone sheeting does not achieve a good fit in concave areas of the body and therefore require custom fabricated pressure application [1]. The aim of this work is to develop a methodology using 3D scanning and printing technology for the production of patient-specific silicone devices for burn wound healing and functional rehabilitation.

II. METHODS

A four-step process for creating the inflatable bladder system was implemented.

1. *Development of a virtual anatomical armpit model:* A 3D digital model of the patient's armpit was obtained using a 3D scanner. This technique provides the ability to capture 3D shapes without any patient contact and without the use of conventional medical imaging modalities
2. *Create a 3D printed PLA (Polylactic acid) mold from the virtual anatomical armpit model:* With the use of Meshmixer software, a 3D printable negative mold for casting was generated from the anatomical armpit model.
3. *Casting of the inflatable bladder system layers:* RTV liquid silicone was poured into the mold. This was then cooled to obtain a single layer of the inflatable bladder system. After curing for 24 hours at room temperature the silicone layer was stripped from the mold. This solid Silicone casting process was performed twice to fabricate the two layers of the inflatable bladder system.
4. *Assembly of the inflatable bladder system:* The two silicone layers, pump and release valve were assembled together to create the inflatable bladder system

III. CONCLUSIONS

The methodology described is an early-stage fabrication feasibility study.

Although the 3D scanner used had limited resolution, it enabled us to obtain a digital model of the patient's armpit sufficiently accurate to generate the virtual anatomical model required.

The surface of the 3D printed mold was found to be insufficiently smooth to accurately cast the anatomical negative. Consequently, alternate mold finishing processes are to be investigated [2].

The complex geometry of the anatomy and the limitations associated with the 3D printing process meant it was not possible to build a single piece mold cavity. The current multi piece mold casting process resulted in a bladder layer lacking in the thickness uniformity required. This can be improved by modifying the structure of the multi piece mold. Commercial silicone was used during the fabrication process. Mechanical properties and biocompatibility have to be evaluated for material selection.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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376 - Ambulatory assistive device for early mobilization of critically ill patients

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I. INTRODUCTION

Lack of physical activity and prolonged bed rest after thoracic surgery can lead to muscle atrophy and weakness; in turn, this can prolong patient recovery and extend hospitalization time. Some authors have shown that early mobilization (EM) may attenuate this neuromuscular weakness [1].

Ambulation is one of the most adopted EM techniques in critical care units. Standard hospital ambulation assisting devices provide essential utility, however are often not ideal for the safe and effective patient rehabilitation. Nesbitt et al. have shown that modern ambulation methods based on custom-made walkers improved patient satisfaction and the postoperative outcome [2]. Furthermore, this ambulation method has proven effective at reducing the medical staff during the patient mobilization and consequently the healthcare costs.

II. AIM & METHODS

In this work, we propose a new ambulatory device for assisting post-operative patient rehabilitation. It is intended to reduce the number of tasks required from accompanying medical staff assisting the patient and managing auxiliary equipment during exercise. Ultimately, this can help to improve patient comfort and safety by allowing more staff attention to be focused on the patient needs.

The proposed device consists of a trolley for carrying various items of medical equipment and attachments necessary during ambulation, e.g. oxygen cylinder, external pacemaker, infusion devices, mobile suction unit, chest drain etc. In addition, it incorporates a distance measurement feature allowing convenient way for tracking distance walked by the patient while exercising. This solution consists of two parts: a distance-measuring sensor and a data acquisition system. The distance-measuring sensor is composed of a 3D printed slotted index disc and photo interrupter mounted on the trolley wheel for capturing

the rotation. The data acquisition system consists of an ATmega 328P microcontroller and a display. The controller receives a signal from the photo interrupter and calculates distance travelled which is then displayed on the screen.

III. CONCLUSIONS

Although, various ambulatory assistive device for early mobilization have been described in the literature previously, none have included an embedded distance measuring system [1,2]. Our first prototype was built using mostly recycled hardware while in-house 3D printing was used to manufacture the necessary customized parts. Similarly, all the electronics was built in-house using low cost components. The prototype device has received a very positive feedback from the clinicians, especially on the ability to measure distance walked by the patient during mobilization as it provides them with a clinically relevant information [3]. In future development, a sensor for peripheral capillary oxygen saturation (SpO_2) is proposed to be integrated in the current data acquisition system to allow convenient measurement of the patient's oxygen saturation during exercise.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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380 - Entropy in analysis of hemodynamic response on tilt test in Patients with syncope

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I. INTRODUCTION & AIM

A syncope is defined as a temporary self-regressing loss of consciousness. The direct cause of a syncope is the short-term reversible global cerebral hypoperfusion. There are three types of a syncope: cardiac, orthostatic and neuro-cardiogenic. We are interested in neuro-cardiogenic type of the syncope named as the vasovagal syncope. The etiology and the mechanism of it are still unknown [1]. In our investigation, we try to add additional characteristic of that kind of syncope.

We propose an example of nonlinear analysis of four signals: ECG (RR interval (RRI) extracted from it), SBP (systolic blood pressure), dBP (diastolic blood pressure) and ICG (SV (stroke volume) extracted from it). The signals were measured simultaneously with the head up tilt test (HUTT) performed with Task Force Monitor device. We examined patients recommended to diagnosis of vasovagal syncope (VVS). Sample Entropy (SampEn) of measured signals was used for description of the mechanism of VVS [2].

II. METHODS AND RESULTS

In the investigation we examined 57 patients, that had the faint episode and were recommended to tilt table test. The test was performed according to the modified Westminster protocol. All examined patients fell in the syncope during the test. For each patient there were recorded (with beat-to-beat method) the values of RRI, sBP, dBP and SV. We extracted 250 points from each signal in three phases of the test: in supine position (I), after tilt (II), before the syncope (III). We analyzed the data in each phase and with sliding windows of width of 100 beats. We determined Sample Entropy (SampEn) for each phase and each window and afterwards we performed multiple comparison of the results. In the phase I mean values of:

SampEn (RRI), SampEn (sBP), SampEn (dBP) and SampEn (SV) are in arrange 0.8 - 1.3. In the phase II they are in arrange 0.76 - 0.86 and in phase III are in arrange 0.36 - 0.95.

The comparison of SampEn between phases I, II, III shows, that there is a statistically significant difference between entropy in phases: I and II, I and III for the RRI. In case of sBP and dBP there are significant difference between the phases: I and II, II and III. The comparisons of the entropy for SV data shows, that there is statistically significant difference between phases: I and II as well as II and III.

The results obtained in sliding windows, show that the values of entropy of RRI, sBP, sBP and SV decrease before the syncope. The changes of complexity of SV are not such meaningful as in case of sBP, dBP and RRI but in many cases they appear at first. The results suggest that the syncope relates to the minimum value of the entropy of SV and sBP but it needs further investigation.

III. CONCLUSIONS

The complexity of heart rhythm, blood pressure and stroke volume decreases before syncope occurs. We conclude that the decreasing of Sample Entropy before the syncope could detect a development of a neuro-cardiogenic reaction.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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381 - Developing impedance pneumography towards clinical use in childhood asthma

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I. INTRODUCTION & AIM

Lung function testing is essential in diagnosis and monitoring of asthma. However, young children and infants are incapable of performing the normal test, spirometry, due to lack of co-ordination and co-operation. Here we present technological development of a new impedance pneumography (IP) -based measurement method alongside with its first clinical studies in young children with asthma symptoms.

II. METHODS

Methodological/technological studies:

- First demonstration of deriving tidal breathing flow rate signal from IP [1]
- Developing a signal processing method that attenuates cardiogenic part of the IP signal [2]
- Developing a novel strategy for placing the skin electrodes for IP recording [3]
- Development of a small wearable IP recorder [4]

Clinical evaluation studies for the method:

- Validation of IP-derived tidal flow rate signal in adults during expiratory loading [5]
- Validation of IP-derived tidal flow rate signal in pre-school children during methacholine challenge test [6]
- Validation of IP-derived tidal flow rate signal in infants during methacholine challenge test [7]
- Assessment of clinical value of overnight IP measurement in young children with asthma symptoms [8]

All studies were approved by ethics committees and all participants gave written informed consents.

III. RESULTS & DISCUSSION

IP has been found to accurately derive tidal breathing flow rate signal in adults and young children. Novel indices of overnight variability of tidal flow rate variability were found to associate with risk of having persisted asthma in children.

The presented method based on principle of IP holds a promise for convenient lung function testing for young children with asthma symptoms. The method has been commercialized and is currently available for clinical studies.

CONFLICT OF INTEREST

V.-P. Seppä and J. Viik are shareholders in Tide Medical Oy that holds patents relating to impedance pneumography. V.-P. Seppä is an employee of Revenio Group Oyj that commercializes impedance pneumography technology.

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384 - Collaboration in the Triangle: Biomedical Engineering Research - Industry - Hospital

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I. INTRODUCTION

A research project, that can rely on an intensive collaboration between a centre of Biomedical Engineering, a company of medical systems and a hospital with expert physicians is obviously most successful. But to assure a good collaboration is not an easy job. Academic partners need publications and industrial partners need exclusive know-how and patents – so the objectives of the project are not 100% identical. Biomedical engineers use different journals and conferences as compared to medical partners. Who is the first to publish the results, who is second? Who is the first author, who is the last? The largest roadblock is the contract. Three legal departments are often involved. Who will be the owner of the intellectual property? But also the clinical data need special care. Who is the owner of the clinical data? Can the clinical data be used in other research projects? This contribution is based on personal experience and is aiming at avoiding pitfalls.

II. PATIENT DATA

Most often during the course of a joint research project patient data have to be exchanged. Several items have to be made clear in the beginning of the project. Who is the “owner of the data”? Often it is the principal investigator at the hospital. In case a clinical study is sponsored by a company, there will be a contract between the hospital and the company, in which the ownership is defined. In any case the “owner of the data” has to agree that the patient data can be used in the research project. It should be declared that the medical partner is responsible for ethical requirements, the informed consent of the patient and the anonymous transfer of data. It must be agreed upon, that

patient data have to be handled with special care by all partners: they must be protected against unintended transfer to anybody else who is not explicitly named as a project partner.

III. PUBLICATIONS

Both, the medical partner and the partner from biomedical engineering research have a strong interest in publications. Sometimes it is even mandatory, e.g. in case of a link to a research project funded by public agencies or in case a master or PhD thesis is supposed to be published in the end. The industrial partner most often is not interested in publications or even wants to hinder a publication of the results. It should be agreed upon a publication strategy in the beginning of the project. Sometimes the problem shows up: who is the first to publish the results, the medical partner or the biomedical engineering side? Obviously, the partners must agree in a friendly manner. Same is true for the question, who is the first and who is the last author in the author-list. There is no general rule to solve these problems. Mutual trust is the best advice.

IV. KNOW-HOW AND PATENTS

The industrial partner has a justified interest in claiming the rights on know-how and patents (“intellectual properties”) if financial resources come from industry. Patents should not be rated as a disadvantage from the research side: the researcher becomes an “inventor” and the chance for a follow up project are significantly increased. A contract should always make clear how the gratifying event is handled if the partners make a collaborative invention.

386 - Online EEG data analysis with MNE-CPP

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I. INTRODUCTION

Multichannel electroencephalography (EEG) is widely used in clinical investigations and basic neuroscience research [1]. There is a growing interest in online EEG data processing for brain-computer-interfaces (BCI) and neurofeedback applications. Moreover, online processing of EEG data provides a faster and more intuitive insight on instantaneous brain functions.

II. SOFTWARE FRAMEWORK MNE-CPP

We present recent advances of the open-source MNE-CPP project. It offers a framework to develop online as well as offline data analysis and processing software for EEG/MEG. MNE-CPP supports online data acquisition for several EEG amplifiers (e.g. ANT eegospots) and MEG systems (e.g. Elekta Neuromag Vectorview). MNE-CPP is structured into libraries, which guarantee a modular and easily extendable architecture. The included libraries support the Fiff and FreeSurfer data format. External dependencies are kept to a minimum, namely Qt. MNE-CPP includes a variety of noise reduction tools (SSP, synthetic gradiometers, temporal filtering, spatial filtering with SPHARA [2]) being applied directly to the incoming EEG/MEG data stream, providing a processed data stream for subsequent steps.

III. EXAMPLE APPLICATION

We developed online source estimation procedures aiming at source-level BCI [3]. We implemented a BCI based on steady-state-visual-evoked-potentials (SSVEP) for an online spelling application. We successfully tested the acquisition and

online processing of EEG data, recorded with a newly supported eegospots amplifier and a dry electrode cap setup [4].

IV. CONCLUSIONS

The proposed novel online data processing framework MNE-CPP (www.mne-cpp.org) will enable new fields of application – like brain-computer-interfaces and neurofeedback for patient treatment and rehabilitation.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

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387 - Intra- and inter-observer variation in depth of penetration of ultrasound scanners

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I. INTRODUCTION & AIM

Ultrasound (US) is one of the most used imaging methods in clinical practice. Even though the ultrasound is widely used, it does not have clear standards for performance testing. The problem of the quality control reliability is that the results can lead to an undesirable level of intra-observer and inter-observer variation. The measurements should be user independent as much as possible. The aim of the study was to detect intra- and inter-observer variations in depth of penetration, using phantom based B-mode ultrasound imaging quality control (QA). The depth of penetration should remain constant over time.

II. MATERIALS AND METHODS

The entire study included measurements of repeatability of depth of penetration, vertical and horizontal distance accuracy, axial and lateral resolution and anechoic object imaging at different depths, obtained for three scanners and two linear transducers. In this study two General Electric Logiq E9 ultrasound scanners and 9L-D linear transducer were used. The operators were two hospital physicists. In case a) a three years old scanner was tested by three instantly repeated measurements, while in case b) four measurements were made within one year for a new scanner. Intra – observer and inter – observer variations were evaluated in depth of penetration.

The tests were performed using the CIRS Model 040GSE Multi-Purpose phantom. Gain and depth of penetration were selected so that background texture echoes were visible to as

deep as possible. The transducer was located orthogonally to the phantom. Focus was set to the deepest possible level. Attenuation area of 0.7dB was used. All the improving and enhancing instrument settings and the frequency were adjusted to be at the minimum. The measurements were performed in PACS (Picture archiving and communication system) in Tampere University Hospital.

III. RESULTS & DISCUSSION

Study showed that the depth of penetration (DOP) range was between 73.0–79.8 mm (case a) and 69.2–82.2 mm (case b). In inter-observer study case a) mean DOP was 76.2 mm, SD 3.1, CV% 4.1 and in case b) mean DOP 74.7 mm, SD 5.3, CV% 7.1. Intra-observer results in case a) mean DOP 73.5 mm, SD 0.5, CV% 0.7 and in case b) mean DOP 71.2 mm, SD 1.8, CV% 2.5. Average DOP deflection in all 14 measurements made inside one year was 0.8 cm (range 0.2 cm–1.3 cm), mean DOP was 75.4 mm, SD 3.2 and CV% 4.3.

It can be concluded that the depth of penetration is a subjective parameter. Changes in depth of penetration should be evaluated not only quantitative but also by comparing the control images among each other to see if the variation depends on the operator judgement or a real change in scanner performance.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

391 - Development of a 3D patient-specific model for atrial fibrosis assessment in patients with atrial fibrillation

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I. INTRODUCTION & AIM

Atrial fibrillation (AF) is the most common arrhythmia and its treatment remains suboptimal. Catheter ablation is a promising AF therapy whose success is limited by uncertainty in the mechanisms sustaining arrhythmia. Recently, delayed enhancement magnetic resonance imaging (DE-MRI) has been proposed to optimize AF diagnosis and treatment through the assessment of atrial fibrosis, which is considered an arrhythmogenic substrate. Several studies [1,2] report that fibrotic tissue distribution on the atrial wall is an independent predictor of arrhythmia recurrences after the ablation procedure.

In this study, we developed a fully-automated 3D patient-specific left atrium (LA) model with pulmonary veins (PVs) integrating anatomical and structural information, in order to assist the electrophysiologist in patient selection for the ablation procedure.

II. METHODS

MRA and DE-MRI in five patients with AF were acquired pre-ablation. A 3D patient-specific anatomical model was derived from the MRA data, applying a fully automated segmentation algorithm based on a level set approach guided by a phase-based edge detector. The initialization of the level set function was obtained by applying Otsu's method [3] resulting in a rough detection of LA boundaries. The atrium was automatically selected applying morphological operators and considering the size of the atrium and its position in the image. The distance function of the selected region was built and its zero level was used as the initial condition for the evolution of the level set function. An affine registration based on mutual information was applied to register MRA into the spatial domain of DE-MRI. Once affine registration parameters were obtained, the grey level intensity from DE-MRI was used as a texture for the 3D LA patient-specific model, allowing the 3D visualization of LA fibrosis location and extent. A thresholding algorithm [4] based on the normalized voxel intensity was optimized and applied for the fibrosis quantification.

III. RESULTS & DISCUSSION

The fully-automated approach was feasible in all patients. Time required for the analysis is compatible with the ablation procedure one and is about 25 minutes for each patient. Based on fibrosis quantification, one patient was in class Utah 2 (fibrosis percentage: 19.4%), two were classified Utah 3 (25.8%, and 24.3%) and two were in class Utah 4 (38.6%, and 50.2%).

LA volumes were computed not considering the PVs and the values were: 160 ml, 126ml, 86ml, 87ml, 55ml. Preliminary results at four months follow-up showed no AF recurrence in any patient.

The 3D LA patient-specific model including anatomical and structural information was developed. The implemented workflow is fully-automated because no prior information is required. The obtained model seems a promising tool for a correct fibrosis localization and quantification, potentially able to optimize patient selection for AF ablation.

CONFLICT OF INTEREST

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396 - Novel Sensor Technologies for a more Functional and Accurate EEG Acquisition

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I. ABSTRACT

EEG is nowadays the most widely used brain imaging technique, due to an excellent time-resolution of the brain signal, cost effectiveness and straightforward application, especially when compared to competing state of the art technologies like fMRI (functional magnetic resonance imaging) and MEG (magnetoencephalography). The conventional biopotential acquisition setup relies on the use of the standard silver/silver chloride (Ag/AgCl) wet electrodes that, despite the unique signal transduction characteristics, display important disadvantages that limit the EEG application. The authors have been working in alternative electrode technologies aiming to improve the EEG acquisition and reliability.

Dry electrodes are one of the most relevant alternatives to the Ag/AgCl wet electrodes. The fabrication and performance of Ag/AgCl coated dry polyurethane multipin electrodes, which recently reached the marketplace will be described [1]. However, even though dry electrodes can work almost as plug-and-play devices, they are more easily afflicted by movement artifacts than wet electrodes.

Therefore, we also proposed an alternative bioelectrode that combines the advantages of the wet and dry technologies, namely generating a low contact impedance while dispensing with the gel paste. The proposed bioelectrode works like a felt pen, relying on a pin-shaped polymer wick coupled to a sponge swollen with a hydrating fluid to keep the scalp hydrated, for a low scalp impedance [2]. In-vivo tests showed that it was possible to achieve impedance values and EEG signals similar to those obtained with the conventional electrodes in psychophysiology applications [2].

A third solution will be presented that could be more easily adapted to the conventional existing technology, including electrodes and caps. It consists of an alginate-based gel that can be injected into the electrode cap cavities, like a normal electrolytic gel, but undergoes gelation within a few minutes after injection, forming a solid hydrogel. This hydrogel is removed at the end of the exam in about 5 minutes, without leaving residues in the hair or scalp. Besides the cleaning advantages, our preliminary results show that EEG signals are indistinguishable from conventional signals [3].

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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397 - Skin movement tracking with a low-cost optical navigation sensor

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I. INTRODUCTION & AIM

Optical navigation sensors are widely used in modern IT peripherals, most notably optical mice, printers and digital pens. They are typically manufactured as single chip units with built-in imaging sensor, light source and DSP for real-time tracking of direction and distance of motion. Their solid-state durability and low cost (typically under €10 at low volume) also make them an attractive option for navigation applications beyond the traditional IT gadgets.

Our aim is to investigate the utility of a conventional optical mouse sensor for measurement of movement directly from the surface of human skin. If successful, these single-chip sensors may provide a low cost solution for non-contact measurement of heart rate, respiration, tremors and other types of motion that translate to skin movement in human body. Some research has already been carried out on the measurement of certain movements in the body using conventional optical mouse hardware. For surface movements, however, it would typically involve placement of a patch (e.g. paper) covering the area where the measurement is required [1]. This helps to eliminate *biospeckle* [2,3] which can cause interference in biological surface motion measurements

II. METHODS

In this work, we utilized a standard optical navigation sensor from PixArt Imaging Inc. with a resolution of 12000 CPI (Part #: PMW3360DM- T2QU). By design, this chip is intended for gaming applications requiring high precision navigation. Its high resolution capacity allows detection of movements in the micro-meter range with a theoretical limit of 2 μ m. Such resolution is well suited for measuring movements invisible by naked eye, e.g. wrist pulse beat on the surface of the skin, with amplitudes of approximately 40-50 μ m as reported previously (4).

A test rig was built utilizing the LabVIEW measurement and automation platform. A peripheral hardware interface module (NI USB-8451) was used to facilitate communication between

the chip mounted on a purpose made breakout PCB and a PC via 4-wire SPI link.

For proof of concept, we set up a test rig to measure heart rate from the surface of human skin. The sensor was placed 2mm away from the skin covering the right common carotid artery and a 20s trace of skin movement was recorded. A clinical heart rate monitor was used simultaneously for validation purpose.

III. RESULTS

Upon inspection of the recorded skin movement trace, a 1Hz pulsation was evident corresponding to a 60bpm average heart rate. A clinical heart rate monitor measured identical average heart rate value over the same 20s measurement period.

IV. DISCUSSION

Initial testing has revealed that a standard configuration optical mouse hardware is capable of tracking movements directly from the surface of skin and may provide a low cost solution for non-contact measurement of motion in the human body. It is foreseen that modifications to the light source and re-arrangement of optics for light collection on the sensor may be required to optimize motion tracking from the skin, as biological surfaces are inherently challenging for speckle metrology.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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398 - Cardiac risk stratification using the V-index

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I. INTRODUCTION

An augmented spatial heterogeneity of ventricular repolarization (SHVR) is supposed to increase vulnerability to ventricular arrhythmia, including lethal ones. Thus, the non-invasive assessment of SHVR would be of paramount importance to screen those patients at higher risk of ventricular arrhythmia. Combining a statistical model of spatial repolarization times with a biophysical model of the ECG, we recently developed a new metric, called V-index [1], which estimates SHVR by evaluating the standard deviation of the repolarization times from multi-lead ECG recordings. In this abstract, we review the performance of V-index both in measuring arrhythmic effects [2] and in the stratification of cardiovascular risk in two populations: Chagas disease [3] and with symptoms suggestive of Acute Myocardial Infarction (AMI) [4] patients.

II. METHODS AND RESULTS

The derivation of V-index is based on the observation that the morphology of T-wave is described by a linear combination the myocytes' transmembrane potentials and its derivatives $\varphi(t) = \mathbf{w}_1 T_d + \mathbf{w}_2 \dot{T}_d + \dots$ where T_d is known as "Dominant T-wave" and where \mathbf{w}_1 and \mathbf{w}_2 are the lead vectors. We showed [1] that the ratio between the standard deviation of \mathbf{w}_2 and \mathbf{w}_1 computed across beats is an estimator of the standard deviation of repolarization times. This ratio was named V-index.

V-index and arrhythmogenicity. Moxifloxacin and sotalol are two drugs known to alter ventricular repolarization and to prolong QT_c intervals. Coherently we observed that V-index increased during sotalol (27.8 ± 4.9 vs 60.1 ± 18.5 ms, placebo vs. drug, $p < 0.05$, 39 subjects) and moxifloxacin administration (30.70 ± 8.32 vs. 40.48 ± 7.61 ms; $p < 0.05$, 68 subjects). Also, we verified that these changes were larger, in percentage, than in QT_c.

V-index in Chagas Disease. In 113 Chagas disease patients, the value of V-index was found to be statistically different between survivors (S) and non-survivors (NS) (S: 31.2 ± 13.3 ms vs NS: 41.2 ± 18.6 ms, Wilcoxon rank sum test: $p < 0.05$). A

V-index value larger than 36.3 ms, evidenced an elevated risk of death in a univariate Cox proportional hazards analysis (HR = 5.34, $p < 0.01$). Interestingly, multivariate analysis showed that V-index is a predictor of mortality independently of other clinical parameters such as Left Ventricular Ejection Fraction, QRS duration and T-Wave Variability. Thus, the V-index captures prognostic information not immediately available from other established risk factors.

V-index and AMI. The V-index predicts mortality in patients suspected AMI independently of age and hs-cTnT, and it increases the sensitivity of the traditional ECG-criteria in the early diagnosis of AMI. In fact, in a prospective study composed by 582 patients presenting to the emergency department with suspected non-ST elevation myocardial infarction (NSTEMI), the use of the V-index in addition to conventional ECG-criteria improved the overall diagnostic accuracy (from 0.66 to 0.73 ROC AUC, $p = 0.001$) and sensitivity (from 41% to 86%, $p < 0.001$). After adjustment for age and ECG and clinical parameters, the V-index remained an independent predictor of all-cause mortality in a 24 months follow up.

III. CONCLUSIONS

This abstract reviews the application of V-index and evidences its relevance as new and independent predictor of mortality in cardiac disease patients.

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405 - Development of an Intelligent Patrol Robot System for Home Healthcare

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I. ABSTRACT

With the advancement in human machine interaction, image-based object recognition, sensor networks, real-time communications, intelligent path planning and remote control, robotic technology and applications have been developed rapidly in many fields. Intelligent robot systems can now perform a very wide variety of tasks to replace human and in places where humans cannot effectively fulfil the requirements such as in dangerous or hazardous environments and situations humans cannot reach. One fast growing application area is about assistive robotic systems given the widespread problem of ageing worldwide and the infirmary in need of support.

This paper presents the design, implementation and testing of an intelligent autonomous robot that can patrol in a home environment. Aiming to provide some fundamental home healthcare assistance, the robot performs tasks such as remote

surveillance of the environment, basic service and interactions in real time over the internet for security monitoring and assistance to elderly and infirm people. A mobile robot is adopted for hardware development along with a Raspberry Pi for the control. Numerous types of sensors are used to detect the surroundings including video camera, human infrared sensor, light sensor, humidity sensor, temperature sensor and ultrasonic sensor. Path planning is performed in both known and unknown environments with obstacle avoidance functions. Contemporary techniques of artificial intelligence and machine learning are applied in an effective way to implement the functions required. The robotic system has been tested through simulations and in physical environments. Initial results demonstrate good potential for real-life applications and for further development. Future work will include further study of user requirements, experience and acceptance, and functionality enhancement.

408 - Integrating *in vitro* neuronal cultures in machine learning applications

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I. INTRODUCTION

The current performances of computers being similar to humans on executing "mental tasks that can be achieved in less than a second" [1], the criteria of energy consumption is introduced for improving machines. The recent advances in neuromorphic chips gives the possibility for machine to reduce their energy consumption while computing in similar ways than networks of neurons.

This abstract first presents a short review of neuromorphic hardware for the real-time execution of simulation models of neurobiology, i.e. Spiking Neural Networks (SNNs). Secondly, an overview of studies on learning using Multi-Electrode Arrays (MEAs) is presented. Finally, a vision on future research for the integration of *in-vitro* cultures of neurons as components of machine learning applications is given as conclusion.

II. NEUROMORPHIC CHIPS

Neuromorphic chips are different from conventional hardware as, similarly to human brains, they use only short-peaks of potential for encoding and transmitting information. Three notable neuromorphic chips are presented here: IBM TrueNorth [2], the SpiNNaker chip [3] and the HICANN chip[4]. TrueNorth was developed for the execution of preliminary trained artificial neural networks on an energy efficient chip, therefore it has only binarised synapses. For computational and energy efficiency, this chip is based on Leaky-Integrate-and-Fire neuron (LIF). TrueNorth is highly efficient in machine vision and in energy consumption. The SpiNNaker chip is used in the Human Brain Project to simulate multi-scale models of the human and rat cortex. It has an abstraction interface allowing the execution of SNNs written with PyNN (different types of neurons and learning synapses). Models executed with SpiNNaker can be simulated in real-time. HICANN is developed at University of Heidelberg is optimized for the speed of execution of simulations (can run simulation 10^4 faster than real biological time). However, communication on HICANN is static for reasons of speed efficiency.

III. STUDIES ON LEARNING WITH MEAS

We consider here the pioneering works realized with the development of the Neurally controlled animats and Hybrots [5].

More recent work present strong ground for the viability of inter-communication between a SNN and *in-vitro* cell assemblies [6].

IV. CONCLUSIONS

This abstract has presented initial grounds for the potential development of chips integrating biological components. In such chip, biological neuronal networks and SNNs would interact in symbiosis to compute cognitive tasks, e.g. tasks related to machine vision and pattern recognition. Such hybrid bio-hardware dedicated for the execution of machine learning tasks should achieve very low energy consumption.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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414 - Generation of Matrix Elasticity Gradients for Cellular Engineering

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I. INTRODUCTION & AIM

Matrix elasticity has recognized as a vital factor in regulating both the migration and differentiation behavior of mesenchymal stem cells (MSCs). While MSCs exhibit active migration under 0.1-1 kPa [1], through the establishment of stiffness gradients on hydrogels within this range, it is believed that a specific durotactic control over MSCs can be investigated. More importantly, by observing the corresponding migration behavior of MSCs, sorting of MSCs can be possibly achieved. The study aims to fabricate a stiffness gradient embedded hydrogel through the utilization of gradient films. Subsequently, by evaluating the constructed stiffness gradient, MSCs can be transplanted to the hydrogel for further investigation.

II. METHOD

To generate stiffness gradients, 20% PEGDA (20kDa), 5% alginate, 0.136% UV initiator (Irgacure 2959) were mixed with DI water uniformly. Meanwhile, a layer of circular gradient film was printed. The film was in a circle shape with a diameter of 4cm, whose transparency decrease from center (100%) to periphery (0%) in a radial gradient. After that, the pregel was injected into a cylinder mold and covered by the gradient film. Such a setting was later exposed to 16.2 mW cm⁻² UV light for 10 min. After gelatinization, atomic force microscopy (Nano ii, JPK, DE) was used to measure the Young's modulus of the hydrogel. After being stuck onto the petri dish, the sample was tested by a processed cylinder tip (csg-01, NT MTD Co.,RU). Five sample groups varying in the distance from the center were selected while 6 points were tested within each group. Hertz model was applied for the calculation of Young's Modulus. One-way ANOVA was used for data analysis.

III. RESULTS & DISCUSSION

The results of AFM testing showed that there was a significant difference in Young's modulus between the central and the

peripheral ($p < 0.05$). The Young's moduli of the five selected points (1, 3, 5, 7 and 9mm away from the center) were 2.372, 2.088, 2.019, 1.785 and 1.306 kPa respectively, which demonstrates the formation of the continuous stiffness gradients. Despite the precise resemblance between the gradient width in stiffness of the fabricated hydrogel and the width of MSCs' dynamic migration, accurate level of ranging has not been achieved yet. Though reducing the concentration of PEGDA participated in hydrogel formulation, the level of stiffness gradient can possibly be suppressed. Moreover, the scope of gradient can be promoted under fine adjustments on the gradient film in the sake of sorting cell with a larger variation.

IV. CONCLUSION

A hydrogel with significant stiffness gradients is developed by controlling the intensity of the UV light propagated with a gradient film. The range of the matrix elasticity gradient formed corresponds to the extracellular matrix where MSCs have the best mobility. Such a design is likely to assist the future research on stem cell migration.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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416 - Design, fabrication and characterization of a high precision MEMS tilt sensor for surgical robot navigation

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V. INTRODUCTION & AIM

Surgical robots firmly established to support surgeons during minimally invasive interventions. In 2013, about 85 % of radical laparoscopic prostatectomies have been carried out robot-assisted in the USA and it is foreseeable the rate will still increase [1]. Fields of application beside the biopsy and resection of tumors are the locally limited high-dose irradiation, brain and abdominal surgery as well as cardiac surgery. Major advantages of these systems are the possibility to scale down the hand movement of the surgeon to high-accuracy fine pitched motions of the surgical instruments, the precise locking mechanism and tremor cancellation of the surgeon's steering movements [2]. Consequently, healthy tissue, blood vessels or nerves can be prevented from unintentional injury. High-precision motion tracking systems are essential for measuring the actual tilt of an endoscope and achieving very accurate instrument positioning. The placing of orientation detection sensors close to the endoscope is possible due to miniaturization of *microelectromechanical systems* (MEMS). Furthermore, the integration of *MEMS tilt sensors* into the surgical instrument near the mounting can facilitate the measurement of vibrations and their compensation. The developed high-precision capacitive MEMS tilt sensor can improve precise orientation measurements.

VI. FABRICATION TECHNOLOGY

The fabrication technology silicon high aspect ratio micromachining (HARM) was used to manufacture the sensor and 75 μm thick structures with about 4.5 μm trench size were achieved. The sensitivity of capacitive inertial sensors is strongly improved by the capacitance gradient due to an electrode movement. To magnify the capacitance gradient, the aspect ratio of the vertical comb electrodes can be increased. However, fabrication restrictions limit the minimum distance between the electrodes. The fabrication of sub-micron trenches [3] or structures with very high aspect ratios up to 100 [4] is advantageous for many applications. To increase the aspect ratio of the sensing electrode gap, different technologies for reduction of trench width of capacitive microstructures below the

technological limitations have been proposed and demonstrated in recent years [3].

VII. RESULTS & CONCLUSION

In this work, a high-resolution tilt sensor was developed using the innovative approach of laser-micro-welding [4]. High aspect ratios from initially 15 up to 100 for trench sizes down to 800 nm are fabricated. After all critical process steps the two initially separated sides of the differential capacitor were connected using the electrostatic force of the sense comb electrodes. The fixation was achieved by adhesive bonding of overhanging metal layers in the bonding zone and partly welding due to a briefly high current. Long time stability and reliability after the first fixation step was ensured by laser-micro-welding on the metal layers. Electrical and physical test of the sensor with customized ASIC shows an increased sensitivity from 7.2 $\text{fF}/^\circ$ up to 60 $\text{fF}/^\circ$ for the sensor with reduced electrode gap. By means of electrical and vibration measurements at 1g the working range was determined with several Hz up to 2 kHz. In conclusion, the developed sensor is able to precisely measure tilt angle and vibration. Due to its small size, it can be integrated in surgical instruments for orientation measurements.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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421 - Translational Journey of a Novel Bioactive Suture

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I. INTRODUCTION & AIM

Rotator cuff tears are a common and increasing problem, with post-operative re-rupture rates around 40%, despite technical improvements in surgery procedures. There is a clear need for materials that are both mechanically strong and also stimulate the endogenous repair process of tendon. A multifilament suture made of sub-micron electrospun fibers has been developed to fulfil this need. Preliminary testing has shown a good safety profile and improved cellular responses both *in vitro* and *in vivo* [1]. Following extensive research and development this biodegradable, bioactive suture is now in preparation for a safety and feasibility study commencing in 2018.

This paper aims to describe the transition from manufacturing the bioactive suture in a research laboratory to a cleanroom, along with the development of a quality management system (QMS) and work towards the first in-human trial.

II. METHODS

Adoption of ISO 13485:2016 Quality Management Systems: Requirements for Medical Devices, provides a practical foundation from which to address the regulations and responsibilities involved in medical device manufacture.

III. RESULTS & DISCUSSION

Given the characteristics and intended use, the bioactive suture will be classified as a class III medical device, and as such carries an increased regulatory burden. Prior to notifying the UK medicines and healthcare regulatory agency (MHRA) with the intention to perform a clinical trial, a number of challenges must be overcome to ensure the safety and effectiveness of the

device, these include but are not limited to: Regulatory compliance, biological safety, risk management, sterilization compatibility, device traceability, design control and continual development of technical documentation.

Implementation of quality control checkpoints and standardized operating procedures, along with personnel training to good manufacturing practice (GMP) also demonstrates a commitment to quality throughout the development process.

IV. CONCLUSIONS

With recent surges in development of novel therapies within academia, we believe that dissemination of this process will encourage others to further develop their research projects, with translation in mind from the early stages of design.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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422 - EEG Anesthetic Reactivity Test – A novel approach to assess hypoxic brain injury

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I. INTRODUCTION

Early detection of hypoxic brain injury after cardiac arrest is a substantial diagnostic challenge. While electroencephalogram (EEG) provides valuable prognostic information regarding the injury, administration of anesthetic agents often disturbs its interpretation during intensive care. Consequently, we have developed a novel method to assess hypoxic brain injury by measuring the EEG response to the anesthetic drug propofol. The method is based on measuring the slow wave (< 1 Hz) activity, which is the most important EEG signature of non-rapid eye movement sleep and can be induced with most general anesthetics such as propofol. Having a substantial importance in, for example, providing conditions for single-cell rest and preventing long-term neural damage, a disturbance in this neurophysiological phenomenon is a potential indicator of brain dysfunction.

II. MATERIALS AND METHODS

To validate our approach, we carried out an experimental pilot study with ten comatose post-cardiac arrest intensive care patients potentially suffering from hypoxic brain injury. We determined the slow wave activity by calculating the low-frequency (< 1 Hz) power of the EEGs recorded during a controlled propofol exposure approximately 48 h after the cardiac arrest. We then followed the patients' neurological recovery for six months to define the association between the propofol-induced slow wave activity and the hypoxic brain injury. The Regional Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland, approved the experimental protocol.

III. RESULTS

In patients without hypoxic brain injury (N = 6), propofol substantially increased the low-frequency power of EEG representing the slow wave activity. By contrast, the patients with hypoxic brain injury (N = 4) were unable to produce such activity. Furthermore, determining the slow wave activity only from the four forehead electrodes (Fp1, Fp2, F7, and F8) instead of using all 19 electrodes of the full EEG cap did not affect the results.

IV. CONCLUSIONS

The results of our experimental pilot data suggest that the comatose post-cardiac arrest patients with hypoxic brain injury are unable to generate normal propofol-induced EEG slow wave activity 48 h after cardiac arrest. The forehead electrodes seem to be as capable as the full EEG cap in capturing this effect. The findings offer potential for a novel, clinically practical technology for the assessment of hypoxic brain injury.

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CONFLICT OF INTEREST

J. Kortelainen, E. Väyrynen and T. Seppänen have filed a patent application on an apparatus and method for electroencephalographic examination. All other authors declare no competing interests.

426 - Characterization of hydrophobic and anti-reflective surface processed by laser lithography

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Hydrophobicity and anti-reflectivity are important features for functional surfaces. Researchers in different institutions have created various surfaces and foils with hydrophobicity and anti-reflectivity. However, the characterization of functional surfaces is a long-standing problem. Functional surfaces are commonly observed under SEM, which can only present images of the surface. The height of structures on functional surfaces are rarely measured. Additionally, parameters commonly used in surface metrology cannot characterize the specific structures on functional surfaces. Structures on functional surfaces can be processed by laser interference lithography. Mathematic simulation of the interferometry of the laser beams was performed. The pattern and structure on the machined surface were predicted. The laser beam generated by a nanosecond laser source was split into four beams and interfered at a point on a monocrystalline silicon wafer. The interfered laser beams created arrays of pore structures, which may trap air to make the surface hydrophobic and absorb light to make the surface anti-reflective. The topography and surface properties of the machined surface were measured. The surface was observed under

optical profiler and AFM, respectively. The result of optical profiler showed the distribution and general size of structures on the surface, including period and density, and provide guidance for further AFM measurement. But data missing existed in optical measurement because of the anti-reflectivity of the surface. A solution to this problem is to add a coating on the surface, to increase the reflectivity. AFM is another choice, which measures the surface more effectively without coating. The result of AFM showed the profile of each structure. The height and depth, as well as the distribution of the structures are considered together and a comprehensive geometrical report of the surface is given. Wettability of the surface was tested by contact angle measuring instrument. Reflectivity was measured by reflectivity measuring instrument. The result of the experiment showed that array structure can be machined on smooth surfaces by laser beam interference lithography to create hydrophobic and anti-reflective surfaces, and the topography of anti-reflective surfaces can be measured by optical profiler, combined with AFM.

428 - Experimental threshold for magnetophosphene perception triggered by retinal magnetic induction

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I. INTRODUCTION

Living in our modern environment implies that we are constantly subjected to various types of electromagnetic exposures coming from different artificial sources, such power-lines or electrical appliances. As a consequence, the question of possible biological effects from this type of exposure arises, and international organizations such as ICNIRP (International Commission on Non-Ionizing Radiation Protection) and IEEE-ICES (Institute of Electrical and Electronics Engineers - International Committee on Electromagnetic Safety) are responsible for issuing limits and recommendations to ensure public health and worker safety [1], [2]. In the context of the so-called Extremely Low Frequencies (ELF, <300 Hz), the time-varying magnetic field (MF) from the exposure induces electric fields and currents within biological structures, possibly leading to biological effects including on neuronal functions. In this frequency range, limits and recommendations are based on the exposure threshold at which acute effects are observed on synaptic communication in humans, hence resulting in modulated functional outcomes.

II. METHODS AND RESULTS

81 volunteers were tested in 4 frequency conditions (20, 50, 60 and 100 Hz), each delivered at flux densities up to 50 mT. Participants were sitting eyes closed in a dark room, and were asked to report magnetophosphene perception by button-press, while occipital EEG activity (O2, O1 and OZ electrodes)

was continuously recorded. The experiment was conducted according to the Helsinki Declaration of 1975, as revised in 2000 and 2008, and was approved by an ethics committee (HSREB #18882).

Results showed a frequency-dependent threshold: 2.51 T/s at 20 Hz, 6.28 T/s at 50 Hz, 7.54 T/s at 60 Hz, and 12.57 T/s at 100 Hz. Choosing dB/dt as the proper metric to analyze the data allowed to properly apprehend the in-situ electric field value. Results also showed greater magnetophosphene sensitivity at lower frequencies for a similar in-situ induced electric field level.

III. CONCLUSIONS

The induced electric fields interacting with the retinal rod membrane potential, translating in cascade into a visual perception is likely at the origin of magnetophosphene perception. Rods are graded potential neurones very sensitive to small membrane potential modulations, and this effect cannot be extrapolated to action potential neurones or to the entire central nervous system. This has critical implications from a guideline perspective. Also, since the induced electric fields and current densities are comparable to those produced by tDCS and tACS, possible translational applications can be envisioned.

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430 - Co-degradation and controlled release of ions from PLA/Bioactive Glass Composite

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I. INTRODUCTION

In one hand, polylactic acid (PLA) is one of the most well-known biodegradable polyester. It is used extensively in tissue engineering and drug delivery [1]. Typically, PLA is combined with growth factors to enhance the osteoconductivity of the polymer. In another hand, the use of bioactive glasses gained much interest in the past years with the development of new glass composition finding space not only in orthopaedics but also in dental applications [2]. However, despite their osteoinductivity, typical bioactive glasses have crystallization kinetics disabling their shaping as scaffolds, necessary in bone tissue engineering [3]. Therefore, PLA composite containing bioactive glasses able to release therapeutic ions are of utmost interest. In this presentation, we will discuss the processing of changes in mechanical properties of PLA rods containing 0, 10, 30 and 50 wt% of silicate or phosphate bioactive glass as a function of immersion time in TRIS buffer solution. Ion release are quantified by ICP-OES.

II. METHODS

A silicate (13-93) and a phosphate (Sr50) bioactive glass were prepared by the melt-quench method. The glass cullets were crushed into 125-250 μm particles. Medical grade PLA was extruded using a twin-screw extruder. The glass particles were introduced using a secondary feeder. The feeding rate of the polymer and the glass was set to obtain composites with 10, 30 and 50 wt% of glass in the PLA matrix. The composites were hydrolyzed for up to 40 weeks in TRIS buffer solution, refreshed every two weeks. At various immersion times the pH of the immersing solution was measured. The wet and dry mass of the composites were assessed. Mechanical properties were evaluated using shear and 3-point bending. The immersing solution was studied using ICP-OES to quantify the release of ions from the glass to the solution.

III. RESULTS AND DISCUSSION

A silicate and phosphate bioactive glass were crushed and co-extruded with PLA into rods ($\varnothing=3\text{mm}$). During the hydrolysis, the PLA alone did not induce any change in the pH, whereas addition of a silica-based bioactive glass led to an increase in pH due to leaching of Ca^{2+} and Na^{+} from the glass. Phosphate bioactive glass addition, led to a slight decrease in pH, due to the high phosphate release in solution. Regardless of the glass composition, an increase in glass content led to a decrease in both the stress at maximum load in three-point bending and shear. With immersion time, the shear stress remained constant. However, the bending stress first decreased and then increased at long immersion. ICP-OES measurement revealed that throughout the all dissolution study the bioactive glass leaches out into the solution releasing Ca, P, Si, K, Mg.

A. Conflict of Interest

The authors declare that they have no conflict of interest

IV. CONCLUSIONS

We report on the processing of PLA/bioactive glass composites. We demonstrate that the choice of the bioactive glass can lead to tailored release of therapeutic ions. The change in the mechanical properties with increasing glass content and immersion time is discussed in light of the co-degradation of the polymer and the bioactive glass

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433 - Refractoriness in human atria: Time and voltage dependence of sodium channel availability

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I. ABSTRACT

Refractoriness of cardiac cells limits maximum frequency of electrical activity and protects the heart from tonic contractions. Short refractory periods support major arrhythmogenic substrates and augmentation of refractoriness is therefore seen as a main mechanism of antiarrhythmic drugs [1]. Cardiomyocyte excitability depends on availability of sodium channels, which involves both time- and voltage-dependent recovery from inactivation [2,3]. This study therefore aims to characterize how sodium channel inactivation affects refractoriness in human atria.

Steady-state activation and inactivation parameters of sodium channels measured *ex-vivo* in isolated human atrial cardiomyocytes were used to reparameterise a mathematical human atrial cell model [4]. Action potential data were acquired from human atrial trabeculae of patients in either sinus rhythm or chronic atrial fibrillation. The *ex-vivo* measurements of action potential duration, effective refractory period and resting membrane potential were well-replicated in simulations using this new *in-silico* model. Notably, the voltage threshold potential at which refractoriness was observed was not different between sinus rhythm and chronic atrial fibrillation tissues and was neither affected by changes in frequency (1 vs. 3 Hz).

Our results suggest a preferentially voltage-dependent, rather than time-dependent, effect with respect to refractoriness at physiologically relevant rates in human atria. However, as the resting membrane potential is hyperpolarized in chronic atrial fibrillation, the voltage-dependence of excitability dominates, profoundly increasing the risk for arrhythmia re-initiation and maintenance in fibrillating atria. Our results thereby highlight resting membrane potential as a potential target in pharmacological management of chronic atrial fibrillation.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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435 - Prediction of knee osteoarthritis

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I. INTRODUCTION AND AIM

Excessive and cumulative joint loads, e.g. due to overweight, have been suggested to cause a high risk for the onset and progression of osteoarthritis (OA) [1]. The most cost-efficient and helpful treatment for the disease would be prevention. However, this would necessitate prediction of the disease progression that is currently problematic.

We develop a computational method and apply it to predict the progression of OA for overweight subjects.

II. METHODS

Knee joint models were generated from MR images and knee loading was applied similarly as before [2]. In the degeneration model, cartilages were modeled as fibril reinforced poroviscoelastic materials. The cartilage degeneration algorithm was based on excessive and cumulatively accumulated collagen fibril stresses in the knee joint [2], and it was implemented into the medial compartment of the knee. The threshold level for the onset and progression of cartilage degeneration was set to 7 MPa [2,3], *i.e.*, the collagen network stiffness was reduced when maximum principal stresses exceeded this threshold. This reduced stiffness simulated collagen fibrillation/reduced content, which are important signs of OA. Cartilage degeneration was simulated as a function of time for each subject. Results were compared with the follow-up data of 21 subjects (normal weight, KL0, and overweight, KL2 and 3). Mann Whitney U-test was used for statistical comparison between the groups.

III. RESULTS AND DISCUSSION

Volumes of degenerated elements in the medial tibial and femoral cartilage were significantly ($p < 0.05$) larger in the overweight groups (KL2 and 3) compared to the normal weight group (KL0). Also degenerated cartilage volumes were greater for the KL3 than KL2 group but this difference was statistically insignificant ($p > 0.05$).

The proposed algorithm was able to predict cartilage degeneration level in OA and, thus, may be clinically applicable to guide patients towards suitable intervention, such as weight loss and/or physical exercise, to prevent or delay the progression of OA.

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CONFLICT OF INTEREST

The author declares that I have no conflicts of interest.

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436 - Atrial Fibrillation in a Dish: Understanding Reentrant Mechanisms

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I. INTRODUCTION & AIM

The objective of this article is to clarify the mechanisms of reentry by using an in vitro model of fibrillating atrial cardiac tissue that resembles the process of remodeling during atrial fibrillation (AF).

II. METHODS

HL-1 atrial cells were studied at two different time stages: (A) early stage, 3 days after the initiation of stable fibrillation and (B) late stage, 9 days after the initiation of fibrillation [1]. We analyze the modification on rotor dynamics and gene expression following tissue remodeling and pharmacological treatments. Specifically, bright field images together with optical calcium mapping (Rhod-2AM staining) were obtained for evaluating remodeling and electrophysiological characteristics of cell cultures during basal conditions and after the administration of verapamil or flecainide. Tissue remodeling was analyzed by measuring the expression of main genes associated to ion currents. Experiments were performed in cell lines without the need of perform research in animals or human samples.

III. RESULTS

In all cell cultures, independently of the time of fibrillation and the degree of remodeling, rotors were the mechanisms of perpetuation of the arrhythmia. Interestingly, cell cultures fibrillating during more days showed a differential ion channel gene expression associated with higher atrial tissue remodeling (i.e., decreased SCN5A, CACN1C, KCND3, and GJA1 and increased KCNJ2).

This change in the expression of ion currents was associated with a higher number of singularity points per square centimeter in the late versus the early stage group (i.e., 1.12 ± 0.14 vs. 0.43 ± 0.19 phase singularities per square centimeter, $p < 0.01$) demonstrating how the complexity increased with the remodeling. Effectivity of sodium and calcium blockers to terminate the arrhythmia (i.e. flecainide and verapamil) was inversely correlated with the degree of remodeling ($p < 0.01$).

IV. CONCLUSIONS

Early and late stage HL-1 cell cultures present different degrees of electrophysiological complexity and tissue remodeling. Dynamics of functional reentries and response to anti-arrhythmic drugs showed a direct relation with the degree of remodeling.

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437 - Neurovascular coupling studied by means of functional near infrared spectroscopy and electroencephalography

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I. INTRODUCTION & AIM

Functional near infrared spectroscopy is gaining increasing attention in clinical engineering as a noninvasive, portable and inexpensive technique. There is little evidence on neurovascular coupling in the context of fNIRS, especially concerning the role of electrical brain rhythms. The aim of this work was to investigate the relation between rhythmical EEG activity and oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentration changes during a motor task.

II. METHODS

Five subjects took part in the experiment (mean age 26 years). The subjects were treated in strict compliance with the Declaration of Helsinki. They were informed about the experimental procedures and gave a written consent. The experiment was approved by the Ethical Commission of the Warsaw Medical University.

Subjects performed 30 sessions of right hand index finger tapping. Each session consisted of 20s of finger movement and 30s of rest. EEG activity was recorded by 32 active Ag/AgCl electrodes. A time-resolved NIRS system operating at wavelengths 690nm and 832nm was used to evaluate the hemodynamic changes. Two optical sources and eight detectors were placed symmetrically on both hemispheres over the sensorimotor cortex. Distributions of times of flights of photons were obtained. Changes in concentrations of HbO and HbR were calculated according to the modified Beer-Lambert law, where the mean path lengths were derived from the DTOF curves. Pearson correlations were computed between time dependent changes of power in α (7-13Hz) and β (15-25 Hz) EEG bands and concentration changes of HbO and HbR.

III. RESULTS

In the left hemisphere, specifically at locations overlying the primary motor cortex (PMC) of the right finger, after the stimulus, decreases of amplitude (desynchronization) in α and β

bands were observed. During the desynchronization an increase of concentration of HbO and decrease of HbR in the PMC were observed. The average, statistically significant ($p < 0,01$) correlation between the α band amplitude and hemoglobin changes was -0.63 for HbO and 0.55 for HbR; for the β band the values were -0.58 and 0.36 for changes in HbO and HbR respectively.

IV. CONCLUSIONS

Usually brain activation during a particular tasks is connected with an increase of HbO. The negative correlations between HbO and EEG amplitudes in the α and β bands may be explained by the fact that during motor action the decrease of α and β rhythms is accompanied by an increase of high frequency gamma rhythm (with a spectrum extending to 200Hz), which is difficult to observe in scalp recordings, yet is prominent in cortical measurements [1]. We have observed gamma activity around 40 Hz during a motor task involving single voluntary movements. EEG reflects synchronized neural activity, gamma rhythm is less synchronized than α and β rhythms and is strongly damped by extracerebral structures. fNIRS detects brain activity regardless of its synchronization. High frequency brain activity hardly detected in EEG is reflected in fNIRS as an increase of blood oxygenation level.

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CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest.

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438 - Minimum Spanning Tree based Hierarchical Super-pixels

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I. INTRODUCTION & AIM

Image segmentation is defined as the process of partitioning an image into interpretable regions of interest. It is a challenge, to get to the quality and the speed of any biological visual system. As a 'perfect' segmentation is very hard to achieve, the results of image segmentation algorithms are usually over/under-segmentation. Over-segmentation is a problem that is easily dealt with than under-segmentation [1]. Many classical image segmentation algorithms have been adopted to deliver super-pixels. Super-pixels are introduced in [4], by adopting the normalized cut algorithm [3]. The super-pixels are a pre-processing step for further image analysis. A super-pixel is defined as a region of pixels with similar properties (like color, texture, form etc.). Ideally, boundaries of super-pixel correlate with object contours (like cells, nuclei, organs etc.). Many current algorithms are not very well scalable to a large number of ROI. In medical image analysis, it is usually necessary to achieve efficient and effective image segmentation on the whole images, each of which might contain millions of ROI (like cells, nuclei etc.). Manual segmentation is tedious, time consuming and prone to errors. Inter variation between the results of different annotators, usually highly skilled physicians, makes the challenge even more tedious. Reliable results and the time of computation becomes a very important issue, when working with large medical images containing millions of regions of interest. As the number of super-pixels is lower than that of the original pixels, it is possible to use complex operations on the super-pixels in less time.

II. METHOD

The image is transformed into a graph with the vertices representing the pixels and the edge representing the neighborhoods, this is the base of the (irregular) graph pyramid. Vertices as well as the edges have attributes, e.g. edge weights could be the similarity between vertices. A new level of the pyramid (i.e. a new and reduced graph) is created by a merging procedure, thus vertices that show similar properties are merged by contracting edges that connect them based on the MST principle.

The merging procedure is iterative, and uses different merging criteria. Thus stacking the graphs one builds a hierarchy called graph pyramid. Note that each graph toward the top of the pyramid has a smaller size, i.e. graphs are stacked from the finest to the coarsest resolution. The relations between vertices in two subsequent graphs are represented in a tree like representation (the dendogram). This pyramid is used to deliver a segmentation results in [2].

III. RESULTS & DISCUSSION

The hierarchical algorithm in [2] is evaluated w.r.t the quality of super-pixels produced. Quality is defined by boundary recall and under-segmentation error. We compare the output of the hierarchical algorithm to other super-pixel methods. Many published algorithms focus on the super-pixels' adhesion to boundaries and rely on a ground truth (usually a human-made annotation). The Berkeley Image Dataset is used by many evaluation methods, [4]. Some evaluation methods focus on other qualities as well, e.g. the stability of the super-pixels for affine, etc. We report only the boundary recall and the under-segmentation error, and show the appropriateness of the hierarchical segmentation algorithm for super-pixels. The preliminary results show that the graph-based hierarchical (graph pyramid) approach is comparable with other state-of-the-art methods. In addition, the super-pixels are organized in a tree form (the dendogram), thus one can choose the coarseness of the superpixels, based on the requirements. Furthermore, the algorithm is parallel and suitable for very large medical images of tissues (for e.g. whole slice megapixel images of cells/nuclei in digital pathology).

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443 - Multivariate methods for brain functional connectivity from EEG/MEG data

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I. INTRODUCTION & AIM

In the last years, it has become evident that cooperation among brain regions across a wide range of spatio-temporal scales is crucial for brain functioning during task or rest [1]. Neuroimaging techniques with different spatio-temporal features, e.g. fMRI, MEG and EEG are used to disclose cooperating structures, with large efforts made in the development of new methods. To date, the majority of the approaches relies on the assumption that the measured signals are scalar quantities. While this is valid for fMRI or MEG/EEG sensor level data, it is a clear oversimplification for brain level data estimated through an MEG/EEG inverse problem, which are of multidimensional nature. Based on our experience on multivariate undirected functional connectivity methods [2], we here introduce an approach for directed connectivity explicitly designed to release the scalar assumption and to take advantage from the multidimensional nature of MEG/EEG brain signals. We focus on the frequency domain approach, ideally suited for the study of MEG/EEG oscillatory coupling in the 1-100 Hz range and with the property of robustness to spurious connectivity by source leakage [3].

II. METHODS

Given two data spaces A and B of dimension N and M, e.g. N=M=3 for dipole moments, the cross-spectrum between A and B has a block form with terms C_{AA} , C_{AB} , C_{BA} , C_{BB} of size $N \times N$, $N \times M$, $M \times N$ and $M \times M$, respectively. Connectivity between A and B can be evaluated by Multivariate Interaction Measure [2], while directed connectivity can be assessed by Multivariate Phase Slope Index, MPSI, (1), which we here introduce:

$$MPSI = 4 \cdot tr \left(\Sigma_f (C_{AA}^R(f) + C_{AA}^R(f'))^{-1} C_{AB}^I(f') (C_{BB}^R(f) + C_{BB}^R(f'))^{-1} C_{BA}^I(f) \right. \\ \left. + (C_{AA}^R(f) + C_{AA}^R(f'))^{-1} C_{AB}^R(f') (C_{BB}^R(f) + C_{BB}^R(f'))^{-1} C_{BA}^R(f) \right)$$

where f is frequency, $f' = f + df$ with df being an incremental step in frequency, tr matrix trace, C^R cross-spectrum real and C^I imaginary part. Simulations based on a multivariate autoregressive model with 6 terms representing two 3 dimensional spaces

and ten levels of superimposed Gaussian noise are here used to assess the performance of MPSI in detecting true connectivity. For each noise level, twenty sets, comprised by one hundred 3-dimensional pairs each, were simulated.

III. RESULTS & DISCUSSION

Simulations show that for a signal-to-noise-ratio of at least 0.5, MPSI accuracy is around 95%. For higher SNRs, it approaches 100%, while for SNRs between 0.3 and 0.5 it remains close to 90% and drops to chance only for very low SNR values (SNR = 0.2). Moreover, the proposed method is robust to source leakage by construction and is thus suitable for estimating directed connectivity in MEG/EEG data.

IV. CONCLUSIONS

The MPSI approach shows high performance in estimating directed connectivity in simulated multidimensional data, opening the possibility for expanding connectivity knowledge in real data.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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447 - Development of molecularly imprinted polymers for detection of folic acid via solid phase extraction

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I. INTRODUCTION & AIM

Folic acid (FA) is a water soluble molecule belonging to group B vitamins and is essential for normal cell growth and proliferation [1]. FA is a hematopoietic growth factor essential for amino acid synthesis and its shortage has been reported to cause megaloblastic anemia, cancer, Alzheimer disease, cardiovascular complications and even neural tube defects in new-borns.

The aim of the presented research is to develop a highly selective, Molecular imprinted polymer for Folic acid (FA MIP) with strong adsorption capabilities that can be later utilized as a solid phase for extractions (SPE), sample purification and concentration as well as for biosensing.

II. METHODS

Combinations of monomers (methacrylic acid (MAA), 4-vinylpyridine (4VPy) and vinylbenzyl trimethylammonium chloride (VBTMAC)) and crosslinkers (ethylene glycol dimethacrylate (EGDMA) and divinyl benzene (DVB)) have been synthesized in bulk (1:25:250 template:monomer:crosslinker ratio, 24 h incubation at 50°C followed by mechanical pulverization, sieving and microwave assisted cleaning) followed by FA binding characteristics analysis. Non-imprinted polymers (NIPs) have been synthesized in absence of FA and used for characterization and negative control. Adsorption capability and selectivity were assessed based on the amount of FA that can be bound to a MIP (B-value) and imprinting factor – MIP/NIP ratio, respectively.

III. RESULTS & DISCUSSION

In order for molecular imprinting process to be successful, the imprinting factor has to be greater than one – which was found in the case of MAA-EGDMA, 4VPy-DVB, VBTMAC-EGDMA and VBTMAC-DVB combinations. The best combi-

nation of monomer and crosslinker was found to be VBTMAC and EGDMA with its imprinting factor reaching values of up to 37 and adsorption capabilities of up to 3 mmol/g, plateauing in 3 h at 22°C.

IV. CONCLUSION

Characteristics of the synthesized FA MIP greatly exceed previously reported FA imprinting attempts and many other MIP characteristics in general and can be therefore be used in the future as a microfluidic biosensor for clinical FA monitoring.

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CONFLICT OF INTEREST

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448 - Design and formation of acoustic radiation force field to bend thin catheter using 2-dimensional array transducer

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I. ABSTRACT

Because the diameter of a guide wire is at least 500 μm , conventional catheter therapy is difficult to apply to blood vessels smaller than 1 mm. To develop new possibilities of more precise therapies using a thin catheter, we have proposed to utilize acoustic radiation force. Since an object in an acoustic field is propelled in the direction of acoustic propagation, we have confirmed the displacement of the tip of the catheter in proportion to sound pressure using a single transducer [1]. However, it is not enough for clinical application because installation position of ultrasound transducers on body surface is limited to adopt to various shape of *in vivo* blood vessel. Therefore, it is necessary to develop a method to bend a catheter to an arbitrary direction, which is independent of the direction of acoustic propagation. Because we have already developed 2-dimensional (matrix) array transducers to control the behavior of microbubbles [2,3], not only to design the shape of acoustic radiation force field but also to steer the position by changing delay time in sound elements. In this study, we compared the performance bending the thin catheter with the design of acoustic radiation force field using a 2D array transducer.

We prepared a concave 2D-array transducer with maximum 256 elements (central frequency of 1 MHz, radius of curvature of 120 mm). The thin catheter, which was made of perfluoroalkoxy (PFA) copolymer with outer and inner diameters of 0.2 mm and 0.05 mm, respectively, was set to be perpendicular to the surface of the transducer. Then, we produced several types of acoustic field including single focal point, two focal points

to pinch the catheter, and ring shape to trap the catheter. We have recorded the reaction of the tip of the catheter to measure displacement using an optical microscope

We could have our experiences through the various types of acoustic fields. We have succeeded to pinch the tip of the catheter to distract the axis of the catheter in any direction, which was impossible using a single focal point. In contrast, there was a limitation of displacement using the ring shape because of the dispersion of acoustic energy density. We will apply this technique to *in vivo* experiments.

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450 - Methodology for Assessing Innovative Aesthetic Devices Based on the Collaboration Among the Government, the Academy and the Industry

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II. MODEL FOR ASSESSING AESTHETIC DEVICES

Aesthetic medicine is a term used for specialties that focus on improving cosmetic appearance through the treatment of conditions. This area of medicine includes both surgical and non-surgical procedures [1]. These procedures can significantly improve quality of life, psychological wellbeing and social function. According to American Society for Laser Medicine & Surgery there were reported 20 million aesthetic procedures performed from 2014 to 2015 and the countries that performed the most aesthetic procedures in 2014 were: United States, Brazil, Japan, South Korea and Mexico. Americans spent approximately \$12.4 billion on cosmetic procedures in the same year [2].

Due to the increasing demand for aesthetic procedures the technological and medical advances whereby new cosmetics and devices have been established to treat cosmetic disorders with minimal downtime and complications. Numerous aesthetic devices and surgical procedures have been introduced by dermatologists and plastic surgeons and subsequently, by diverse medical specialties. Nonmedical practitioners, e.g. beauticians and spa operators, have jumped onto the bandwagon to provide such services [2]. "Many of these aesthetic treatments claim to rejuvenate the skin but are not supported by good scientific evidence". Concerns have been raised regarding safety issues as well as the quality of such services by the medical profession and the governments. Some patients even sustain injuries and complications from these procedures. In several countries, there is no proper accreditation process to regulate the safety assessment of medical devices used at aesthetic medicine to protect the public from unproven and unsafe treatments. In addition, leaving the aesthetic medicine industry to regulate itself is not a feasible solution as professional and ethical standards in an unregulated industry might take a hit in this lucrative business [3]. FDA has identified the risks to health generally associated with the use of the focused medical devices for aesthetic use; however there is a need to implement a proper guidance for industry and requirements for basic safety, all design specification and performance [4].

The aim of this research is to implement a simple methodology to be used by inspectors of the regulatory agencies supported by an innovative application for smart phone and a digital guide supporting the inspector during the assessment of aesthetic devices in order to establish the conditions for safety of the emergent technologies at the marketing and the evaluation of medical devices for use in aesthetic procedures. This paper presents the model for assessing aesthetic devices based on interdisciplinary work among the government, academy and medical devices industry in defining the best practices and conditions for safety of commercial aesthetic devices and the technical assessment of medical devices for use in aesthetics procedures. The research project was supported by the Colombian government, the Pan American Health Organization PAHO and the regulating agency INVIMA. The devices producers were visited by an interdisciplinary research team in order to establish the main needs and give them support by the development of the smart application and guidance of requirements for basic safety, design specification and performance based on the international standards of medical devices from the regulatory agencies by using the government expectancies and the ICT technologies developed by academia.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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462 - Can false rotors be recorded by catheters when mapping complex atrial propagation?

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I. OBJECTIVE

Basket catheters are currently being used to localize rotors in humans during atrial fibrillation (AF). However, they have not been yet systematically analyzed for accuracy and it is unknown how far field sources could affect rotor detection. Our objective is to analyze the effect of the far field on rotor mapping with basket catheter electrograms (EGMs) using computer simulations.

II. METHODS

We simulated reentrant electrical propagation in a 3D human atrial model by pacing the coronary sinus, and its recording using an intracardiac 64-unipolar-EGM basket located in contact with the crista terminalis and >0.5 cm away from the contralateral endocardium. Then we calculated the basket EGMs after reducing progressively the extension of atrial tissue considered in the computations to evaluate the effect of the far field sources: (1) whole atrial tissue; (2) tissue encompassing the CT rotor and the RWE; (3) tissue encompassing only the CT rotor. Hilbert transform on the interpolated basket EGMs enabled detection of phase singularities (PS) and instantaneous location of rotors.

III. RESULTS

Our simulation in the 3D human atrial model showed a rotor on the crista terminalis (CT rotor) maintaining complex propagation in the atria, with a distal wave extension (RWE) circulating around the inferior vena cava. However, basket phase maps showed some differences with respect to the electrical propagation in the atria when electrodes were at distances

greater than 0.5 cm from the endocardium. When considering the whole atrial tissue (1), the basket detected the CT rotor and the RWE rotating at the basket's south pole. Additionally, an imaginary rotor (IMPS) was detected, paired with other IMPS that was undetected because of lack of coverage at the basket's north pole. When only the tissue encompassing the CT rotor and RWE was considered in the computations (2), we still could observe the paired false rotors (IMPSs). However, after reducing the tissue considered in the computations to only the tissue encompassing the CT rotor (3), the false rotors disappeared. Therefore far-field sources interfered with the basket recordings and contributed in the generation of false rotors (IMPSs) when electrodes were at distances greater than 0.5 cm from the endocardium (1 and 2), but if the distance of the sources increased and their strength reduced, their influence was insufficient to generate IMPSs (3).

IV. CONCLUSIONS

Far field sources might generate false rotors when mapping the atria using a basket catheter. These data call for extreme caution in attempting to identify AF sources for ablation.

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469 - System for Dynamic Body Balance Measurement

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I. INTRODUCTION & AIM

Falls and their associated injuries profoundly impact health outcomes and health care expenses, particularly for the ever-increasing elderly population. Falls are both an intensively researched and an under prevented public health problem. Up to now, force platforms are the most commonly used tools in balance assessment. However, they are expensive and bulky, which makes them impractical. Employment of Inertial Measurement Units (IMU) in balance assessment although explored, has not yet become a laboratory standard [1]. Additionally, it was reported that dynamic balance measurement is a better indicator of functional balance performance than the static one [2]. Therefore, new techniques that allow objective measurement of the dynamic body balance and reliable methods to evaluate different aspects of stability are necessary. An effort is made to address these needs by developing an IMU based measurement system that can track in real time both the subject's sway and the surface inclination while the subject is trying to sustain balance on a balance platform.

II. METHODS

The system consists of two Bluetooth Low Energy (BLE) enabled sensors featuring a 3D digital accelerometer and a 3D digital gyroscope, a smartphone, as well as Android and iOS Apps. One of the sensors is attached to the subject's sternum and the other to the center of the balance platform. The sensors are time-synced and the raw data is transmitted in real time to a paired smartphone for diagram plotting, storage and further processing. The sensors feature dedicated firmware with dual role: to control the data sampling and transmission to the smartphone, and to support over-the-air updates to allow for future application program updates. The IMU are sampled at 100Hz, while the battery level is sampled at 0.1Hz. Dedicated Android and iOS Apps are developed to establish communication between the sensors and the smartphone allowing the user to receive, store, analyze and view the data through friendly interface. The Android App is written in Java with Android Studio v2.2 using Android SDK 23 and Object Oriented Methodology, where the iOS app is written in Swift 3.0 using XCode

8. The iOS app uses a reactive functional programming framework called ReactiveSwift, which facilitates the observation and manipulation of data without having to resort to callbacks. The data is stored locally using another iOS framework called Core Data and can be synced with a cloud for further analysis.

III. RESULTS & DISCUSSION

Preliminary measurements were performed with the proposed system using Vew-Do Balance Board (Balance Designs Inc.) and BOSU Ball (Ball Bounce & Sport, Inc.) where the sensors were attached by double-sided adhesive tape to the balance platform and with elastic chest strap to the subject's sternum. The acceleration data was used to calculate and plot in real time the projected paths of the trunk acceleration (sway diagram) and that of the balance platform.

The purpose of this work was to design and develop an IMU based, low cost and easy to transport dynamic body balance monitoring system that will allow further comparative studies in laboratory or clinical environments in order to evaluate the accuracy of the method as compared to force platforms in the assessment of postural stability. Typical applications may include balance rehabilitation, quantification of the severity of balance disorders, postural stability in neurological disorders, and effects of alcohol on balance, age and spontaneous sway.

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471 - Method for Automatic 3D Bone Segmentation in CBCT Data

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I. INTRODUCTION & AIM

Cone beam CT (CBCT) technique is widely used by orthodontics and maxillofacial surgeons. 3D models derived from CBCT are used in initial diagnosis, helps to plan treatment, assess changes in postoperative period [1, 2]. In daily practice, the segmentation process is mostly performed by selecting a global threshold value (manual thresholding). This factor has the most influence on the segmentation quality and repeatability [3].

The aim of the present research was to investigate the efficiency of the automatic segmentation method for the cortical bone segmentation from CBCT data sets. The automatic segmentation method is using locally based statistical information.

II. METHODS

In this study, 10 CBCT data sets of adult patients were selected from the database of the Simonas Grybauskas Orthognathic Surgery Clinic, Vilnius, Lithuania. 3D mandible models were segmented using manual and automatic thresholding methods. An experienced maxillofacial surgeon performed the manual thresholding. The automatic thresholding method was performed determining local threshold values combining Otsu thresholding method and volumetric sliding window technique. The filter is involved into the preprocessing of the data, which checks and ensures that CBCT volumetric histogram is bimodal. The filter is used also for the removal of irrelevant for the segmentation data set fields (air, metal artefacts). The efficiency of the method was tuned by created 3D digital model, which voxels intensities, size, distribution and resolution were modeled to be close to the real CBCT data sets. The surface reconstruction for extracted 3D voxels areas was performed by volumetric reconstruction algorithm using MeshLab software (Visual Computing Lab of ISTI – CNR, University of Pisa). The efficiency of the proposed segmentation method has been

validated by comparing automatic segmentation result with the manual segmentation method result using the iterative closest point (ICP) alignment algorithm.

III. RESULTS & DISCUSSION

The optimal parameters controlling the method were determined by using 3D digital model data. The main findings: the optimal volumetric area (800 mm³) is needed to obtain reliable local threshold; to reduce the time of segmentation the shift of volumetric field should be increased (from 0.3 mm (voxel size) to 4.5 mm) in analyzed area. Pilot study with real clinical CBCT data sets showed that proposed method could be used for segmentation of bone fields in CBCT data sets. The mean (SD) distance error of all surfaces between the manual segmentations and automatic segmentations was -0,414 (0,194) mm. The automatic method is more efficient, more reliable and simpler to use comparing with the manual thresholding method. It provides a possibility to use the locally adapted thresholding for bone segmentation and increase results repeatability.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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472 - Outdoor management of patients with Ventricular Assist Devices: Benefits of A standardized computer-supported Telephone Intervention

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I. PURPOSE

Ventricular assist devices (VADs) are an established therapeutic option for patients with chronic heart failure. Continuous monitoring of VAD parameters and adherence to management guidelines are crucial to detect problems in an early stage to optimize outcomes. A telephone intervention algorithm for constant communication with VAD outpatients was developed, clinically implemented and evaluated.

II. METHODS

An analysis of VAD outpatient outcomes with bi-weekly telephone interviews in their routine care (n=25) was conducted and compared to a propensity scored control group without telephone intervention (n=71). During the calls a structured inquiry about pump parameters, alarms, blood pressure, INR, body weight and temperature, driveline exit-site status and dyspnea/edema symptoms was performed. Answers were electronically categorized using a self-developed algorithm in 5 levels of severity: no problems, recall next day, refer to physician, follow-up visit next week and readmission. To minimize confounding, outcomes were analyzed using proportional hazard Cox regression, with risk adjustment based on telephone intervention-use propensity score model computed from demographics, risk factors and operative covariates. For quality assurance, an electronic recording of the calls was done after written agreements of the patients.

III. RESULTS

From February 2015 through May 2016, 25 patients (n=3 St. Jude Medical HeartMate II and n=4 HeartMate III, n=18 HeartWare HVAD) underwent 320 telephone interventions. Within

the first year of support, 50% of the calls determined no problems and patients adhered to institutional guidelines of blood pressure (85.4±9.4mmHg) and INR (2.4±0.4). In 4% of the cases, patients were recalled on the next day because of alarms. In 33% (n=106) the VAD coordinator had to refer to the physician due to elevated blood pressure (n=91, >85mmHg), INR <2.0 or >4.0 (n=20) or edema (n=2). 13% of the calls resulted in a follow-up visit because of equipment or driveline exit-site problems and could be solved by early intervention. Freedom from any readmission (59% vs. 36%, p=0.23) as well the average days of rehospitalization in the hospital (31.8±46.1 days vs. 18.6±21.8 days, p=0.42) within one-year post discharge were non-significantly higher in the control group vs. telephone group. Propensity-adjusted one year survival (95% vs. 67%, p=0.03) was significantly superior for the telephone intervention group. Overall, the patients highly welcomed the frequent tele-checkups. Only a single patient opted out of the two-weekly-calls, but asked to be included again after two months.

IV. CONCLUSIONS

Continuous, standardized communication with VAD outpatients has been demonstrated to be important for early detection of upcoming problems and leads to significantly improved survival and reduction of overall hospital readmission days. The procedure was highly welcomed by the patients. The investment of (moderate and mainly personnel) resources pays back in a remarkably improved outcome.

477 - In vitro dissolution of partly crystalline bioactive glass S53P4 scaffolds

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I. INTRODUCTION & AIM

Bioactive glasses (BG) are biomaterials used for e.g. healing bone defects [1]. Although bulk glass and granules are clinically more used, there has recently been a lot of research on BG scaffolds for more diverse spectrum of applications [1]. The aim of this study was to measure the long-term *in vitro* dissolution behavior of scaffolds sintered of bioactive glass S53P4. One additional goal was to quantitatively determine the effect of partial crystallization of the glass on the dissolution of the scaffolds.

II. METHODS

The scaffolds were sintered of S53P4 bioactive glass particles (300-500 μm) at 720 °C for 1,5 h in a nitrogen atmosphere furnace. The *in vitro* dissolution was studied using a set-up in which the solution (simulated body fluid and Tris) was continuously fed through the scaffolds at a controlled rate (0.2 mL/min). The solutions were collected to vials at certain time intervals throughout the tests up to 21 days. The concentrations of the ions dissolved from the scaffolds were analyzed using ICP-OES. The changes in the scaffold morphology after various dissolution times in both solutions were studied from the sample cross-sections using SEM-EDXA.

III. RESULTS AND DISCUSSION

In the as-prepared scaffolds, thin necks connected the softened and partly crystallized particles. The thickness of the crystallized layer at the particle surfaces was 60-80 μm . The crystals consisted of Na_2O , CaO , and SiO_2 . The dissolution of the scaffolds in Tris buffer could be divided into three different stages: 1) dissolution of the residual amorphous phase, 2) dissolution of the amorphous phase beneath the crystallized layer to give a hollow structure, and 3) selective dissolution of Na and Ca from the crystalline layer. The ion release data suggested that the residual Si-rich layer dissolved at a much slower rate than the other phases.

The preliminary *in vivo* results suggest that the partly crystalline layer does not inhibit bone formation within the scaffold structure. The layered structure of the scaffolds may be of interest in tissue engineering applications: the crystalline layer provides structural strength while supporting dissolution of the non-crystalline bioactive glass core during the first weeks of implantation but then gradually degrades.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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479 - Biomimetic Stimulation Platforms for Cell Culture Applications

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I. INTRODUCTION & AIM

To mimic physiological conditions *in vitro* cell and tissues cultures different stimulation techniques must be applied. In practice, majority of *in vitro* studies apply only a biochemical stimulation by supplying different chemical compounds within a culture medium. However, also other biochemical, mechanical, electrical, thermal and photonic stimulations affect to *in vitro* cultures [1-5]. For example, cells cultured inside an incubator with 5% CO₂ and atmospheric O₂ concentration (~20%) are not in physiologically relevant environment. Exposing cells to alternative biochemical stimulation by reducing culture environment O₂ near their natural environment *in vivo* (0-10% O₂), the behavior of cells is drastically different [6]. Similarly, different mechanical stimulation platforms can mimic the natural environment of the cells, and furthermore, affect cell fate, morphology, orientation, and differentiation [5]. In this paper, we present different biochemical and mechanical stimulation platforms that are serving biologists in different fields, from stem cells to cancer studies.

II. METHODS

We have developed and demonstrated variety of controlled cell culture environments and stimulation platforms that provides, for example, normoxia/hypoxia studies outside a standard incubator [1,2], equi- and uniaxial cell substrate stretching for mechanobiological studies [3], and efficient neuronal network formation [4]. Common for all these platforms is a soft silicone elastomer material, polydimethylsiloxane (PDMS), which provides advantageous properties for fabrication and prototyping of above mentioned systems.

III. RESULTS & DISCUSSIONS

Utilizing gas permeability properties of PDMS we have shown that we can maintain the human pluripotent stem cell derived neuronal networks on long-term (3 days) electrophysiological studies outside an incubator [1]. With the same technology, physiologically more relevant hypoxic culture conditions were demonstrated with different cancer cell lines [2].

Hypoxic conditions were maintained similarly in our mini-incubator than in a commercial hypoxia station. However, our mini-incubator enables for example long-term imaging while maintaining hypoxic conditions that is difficult to perform in hypoxic station.

Mechanical loading and stimulation is present in many biological processes. We have developed innovative cell substrate stretching device that provides excellent platform for high resolution imaging during the substrate stretching [3]. Equi- and uniaxial stretching platforms are available and demonstrated. For example, equiaxial stretching of cell substrate enhance osteogenic differentiation of adipose stem cells. Furthermore, uniaxial strain align cardiac cells that further mimics their natural presence *in vivo*.

However, the ultimate goal for these single stimulation applications shown above and those that are currently under development is to integrate them into a versatile biomimetic stimulation platform for laboratory use and research purposes especially for novel protocols of cell and tissue based studies.

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481 - From molecular interactions of pharmaceuticals to living cell studies for tissue engineering and diagnostics using Multi-Parametric Surface Plasmon Resonance

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Traditionally, Surface Plasmon Resonance (SPR) is used predominantly in drug discovery. It is a real-time technique that requires no labels and thus provides information on affinity and kinetic constants of biomolecular binding without the burden of fluorescent or radiolabeling. The traditional technique is limited to layers of 150 nm thick measured in liquid and thus is not suitable for material studies or studies of living cells. Recently, we have developed a new configuration of SPR, which overcomes these limits using angular scanning at multiple wavelengths.

Multi-Parametric Surface Plasmon Resonance (MP-SPR) provides the affinity and kinetic constant measurements as traditional SPR, but can measure on layers from 3.7 Ångströms (graphene monolayer [1]) up to tens of microns thick (transparent) materials in liquid or in air. Importantly, it also allows quantification of thickness and refractive index without knowing either.

The applicability of MP-SPR to tissue engineering is shown on several cases briefly described here.

On contact with biological fluids, implants or drug nanocarriers are covered with protein corona. Here the dynamics of soft and hard corona formation on surface-bound lipids in contact with 100% serum is measured. The soft and hard corona is quantified in terms of the corona thickness, refractive index and surface mass density [2].

Biocompatibility of implants is crucial to be understood and verified in static and dynamic flow conditions. Here 24 µm thick (thickness confirmed by scanning electron microscopy measurement) hydroxyapatite (HA) coating is plasma sprayed onto SPR sensor with ready TiO₂ coating. The adsorption of lysozyme and mesenchymal stem cells derived from human adipose tissue (AD-MS) was monitored using MP-SPR [3]. A separate study investigates the influence of the degree of sulfation of glycosaminoglycans (GAGs) on the adhesion of human adipose derived stem cells (ACS). This is shown on the interactions with an adlayer – fibronectin in this case [4].

Clinical diagnostics of cancer is still not fully solved. Here MP-SPR is shown to distinguish breast cancer cells (MCF7) from non-cancerous cells (MCF-10A) using a surface bound targeting peptide (18-4) [5].

Testing of novel pharmaceuticals and their nanocarriers can be performed label-free on living cells that are incubated directly on the SPR sensors. In [5], the uptake kinetics of several types of nanoparticles (silica nanoparticles, polyethylenimine–plasmid DNA polyplexes and extracellular vesicles) into HeLa cells is determined and confirmed by confocal microscopy.

MP-SPR has been shown on several examples as a platform for surface optimization in tissue engineering studies including biofouling, cell adsorption as well as diagnostics including cell detection.

ACKNOWLEDGMENT AND CONFLICT OF INTEREST

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482 - Drug releasing poly (lactide-co-glycolide) – polyvinyl alcohol microparticles

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I. INTRODUCTION & AIM

Progress in polymeric carriers for therapeutic and biological molecules open new possibilities to treat diseases. In this way, controlled drug delivery system (DDS) improve efficacy, reduce toxicity and enhance patient compliance. Controlled drug delivery takes place when a pharmaceutical agent is released from a carrier material in a predictable way. Controlled DDS increases the bioavailability, for example by protecting drug from too short life span in the body. Even more beneficial is to implant DDS straight into the defect site. In addition to the pharmaceutical applications, controlled drug delivery can be used in cell culture when bioactive agents, for example drugs or growth factors, are needed for extended period of time.

The aim of this study is to improve drug release profile of biodegradable drug release system based on poly (lactide-co-glycolide) (PLGA) – polyvinyl alcohol (PVA) microparticles. In addition, microparticle - hydrogel composite was designed by incorporating microparticles within/inside/in the hydrazone-crosslinked hyaluronan (HA)-PVA hydrogel. These DDSs were developed to encapsulate dexamethasone (DEX) which is serving as model drug.

II. METHODS

In this study, drug loaded, biodegradable, poly (lactide-co-glycolide) (PLGA) – polyvinyl alcohol (PVA) microparticles were produced using combination technique of oil-in-water solvent evaporation method and spray drying. Surface morphology and size distribution of the microparticles were studied using SEM and thermal properties using DSC. In vitro drug release studies of the microparticles were performed. Drug concentrations of the release samples were analyzed using HPLC. Gamma irradiation as sterilization method for the microparticles was also evaluated. Microparticle – hydrogel composite

was characterized using SEM and its mechanical properties were evaluated. Swelling ratio and preliminary in vitro drug release were studied.

III. RESULTS & DISCUSSION

Spherical microparticles in nano and micro scale were obtained. In vitro studies showed that when using microparticles dispersed in the hydrogel instead of microparticles alone, time period over which drug is released can be extended to double. Gamma irradiation had adverse effect to microparticle morphology and drug release profile. Incorporation of the drug does not affect to the glass transition temperature (T_g) of the polymer.

IV. CONCLUSIONS

By combining double emulsion process and spray drying techniques, it is possible to obtain microparticles with improved properties. They have potential to function as DDS as such or when embedded into the hydrogel matrix. Microparticle – hydrogel composite impress as promising drug delivery structure since the synergy between the different structures. Future studies are needed to understand the effect of composite structures, especially when modified drug release is concerned.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

492 - Two-Photon Polymerization of Microcylinder-Based Cell Culture Platform

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I. INTRODUCTION & AIM

One of the major strategies in the field of *in vitro* neuroscience is to develop 3D neuronal culture models to study, e.g., traumatic injury in the central nervous system (CNS). Furthermore, especially axons benefit from growth guidance to reconnect more efficiently after injury. Therefore, research groups worldwide are trying to discover the effective guidance cues for neuronal cells [1, 2]. In this study, physical guidance cues in the form of microcylinders were fabricated by two-photon polymerization (2PP), and subsequently tested for their ability to orient and support the growth of human neuronal cells.

II. METHODS

Microcylinders with a height of 150 μm and having an outer diameter of 77 μm and inner diameter of 75 μm were designed. The microcylinder arrays were fabricated from a polymer-ceramic hybrid materialOrmocomp[®] with a custom-built 2PP setup based on a femtosecond fiber laser. A constant scanning speed of 550 $\mu\text{m}/\text{s}$ together with an average laser power of 4 mW was used for the polymerization. Fabricated microstructures were characterized by SEM and AFM imaging. Neuronal cells for cell culture experiment were derived from human embryonic stem cell (hESC) line, Regea 08/023. Viability of the human pluripotent stem cell (hPSC)-derived neuronal cells was studied using fluorescent LIVE/DEAD Viability/Cytotoxicity Kit for mammalian cells. Cell phenotype was analyzed using immunocytochemical analysis against neuron specific proteins.

III. RESULTS AND DISCUSSION

According to SEM image analysis, the height of the microcylinders shrunk on average 21% and the inner diameter 4% on average. AFM imaging revealed that the cylinders had a smooth surface morphology with surface roughness of $R_a = 11$ nm. The cell culture experiment showed that the total cell number in the microcylinders stayed quite constant during the 4-week follow up. Cells grew along the inner and outer surfaces of the microcylinders and formed 3D networks. Similar micro-

cylinders ($h = 250$ μm , $\varnothing = 200$ μm) embedded in hydrogel matrix have been previously shown to support the formation of 3D neural networks around and across microstructures [3]. Our study showed remarkably similar results without the support of any hydrogel matrix. Relatively even distribution of the neuronal cells throughout the height of the tower was observed during the experiment. Cells had neuronal phenotype and showed maturation by expression of MAP-2 and β -Tubulin III proteins. According to the automated CytoSpectre [4] analysis of the neurite orientation, majority of the measured mean orientation angles of the neurites inside the microcylinders represented $\pm 10^\circ$ deviation from the longitudinal axis throughout the experiment indicating the presence of longitudinally oriented neurites. Overall, the fabricated microcylinder-based platform provided suitable environment for the growth of hPSC-derived neuronal cells thus supporting the orientation of neurites and formation of 3D cell-biomaterial complexes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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493 - PPG measurement and analysis based on pulse decomposition, Fourier transformation, and probability density functions

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Abstract— The biosignal processing methods are increasing for uncovering diseases states, however, diseases such as arteri-oscrosis (AS) is becoming a more common cardiovascular disorder among elderly people, especially in females. The negative impacts of AS on young people can be greater than on the elderly people in the long term. Arterial elasticity measurement (AEM) would provide a direct indicator for cardiovascular healthiness and would forecast AS. Analysis of AEM can be challenging in the cases of very elderly persons because of the challenging morphology of pulse waves. Accurate measurements and analysis of the blood vessel properties would be in any case important for better characterization of both arterial diseases and the development of reliable techniques. Photoplethysmography (PPG), especially pulse wave decomposition, envelope analysis, Fourier transform, and probability density function (PDF) could open the new health information on clinics. However, the exact mathematical solution for the pulse wave is replaced by numerical methods.

I. INTRODUCTION

The elasticity of arteries decreased in coronary disease patients. This suggests that age-related changes in arterial elasticity can occur in peripheral small arteries in addition to large arteries, which is a normal ageing process. Accurate measurements and analysis of the finger and toe arterial tissue properties can be important for better characterization of early artery diseases, also other than atherosclerosis. Development of reliable computational models is also necessary. Various non-invasive measurements methods for direct and indirect arterial characteristics are developed, such as the use of ultrasonic transducers (arterial wall thickness and flow pulse wave (PW)), optical photoplethysmograms (PPG) volume PW and different kind of force or pressure sensors (pressure PW). PPG waveform represents peripheral blood volume pulse and pulse flow and especially its variability. These methods can give new insights into the physiology and pathophysiology of the central and peripheral circulatory systems also other diseased states than arterial disorders. The wave reflects both peripheral and central hemodynamics tell the arterial elasticity on these locations. PPG uses infrared and red light emitting diodes, which

transmit light through the skin to be able to measure noninvasively hemodynamic parameters such as pulse wave velocity, and is thus a useful measure of vascular dysfunction and heart rate variability (HRV). By means of HRV in subjects at rest, we can acquire the fingertip PPG, which is as accurate as ECG for determining the HRV. In PPG technology, the main difficulty is its quantitative analysis, namely calibration, and comparison of PPG wave measurement obtained from different patients and skin areas. In measurements, the light intensities and wavelengths (640nm&920nm) are fixed. In the heart, the left ventricle causes the PPG waveforms as the propagating pulse waves. They travel through the arterial circulatory system and arrive the multiple peripheral, parallel capillary arteries. The propagation velocity depends on the force of the heart generated pulse and arterial wall elasticity, which is not well known. The whole PPG wave is the summation of forward and backward waves. The more elastic the arterial wall is, the slower the PPG pulse wave velocity is. Elasticity of the arterial wall changes as a function of aging, wall structure properties, and blood pressure. The raw PPG signal reflects peripheral circulation. Early detection of arterial elasticity loss can help us detect the development of atherosclerosis earlier to prevent peripheral neuropathy, or polyneuropathies in diabetes mellitus patients. So called “normal vascular aging” is causing the change of large artery elasticity. Clear change in wave morphology can be considered in this presentation.

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495 - Improving image quality and novel methods in ultra-low-field MRI

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I. INTRODUCTION

While conventional MRI has evolved towards increasingly high magnetic fields of several teslas, another approach has emerged, where the signal is detected in an ultra-low field (ULF) on the order of 100 μ T or less [1]. Despite many similarities, ULF-MRI differs from high-field MRI in several interesting ways. Using such low fields, the pulsed magnetic fields can be applied silently and with an open-geometry coil system. The detected kHz-range signal can be modeled from theory with high accuracy. The unique possibilities of ULF-MRI also include the combination of MRI and magnetoencephalography (MEG), the measurement of the weak magnetic fields generated by the electrical activity of the brain. ULF-MRI and associated methods such as current-density imaging (CDI) can significantly improve the localization of brain activity.

II. AIM

To make ULF-MRI ready for commercial devices for research and clinical applications, the image quality needs to be improved. Furthermore, the spatial calibration of the system is of high importance for localizing brain activity with high accuracy in hybrid MEG–MRI. Our aim is to, one by one, solve the problems that limit the quality of ULF-MRI and to implement new techniques such as CDI in practice. The long-term goal is to bring imaging of electrophysiology to the next level.

III. METHODS

Superconducting quantum-interference devices (SQUIDs) configured as pulse-tolerant magnetic-field sensors for ULF-MRI can also be used for MEG. Compared to our first hybrid prototype [2], our current-generation system uses more robust techniques and a new software platform.

With dedicated ultra-low-noise amplifiers [3], it is possible to switch off even B_0 during an imaging sequence. This enables encoding three-dimensional information for current-density imaging (CDI) using novel techniques [4]. We also describe

Dynamical Coupling for Additional dimensionNs in the design of techniques (DynaCAN) [5–6], a method using designed pulse waveforms to solve various problems in improving signal quality.

IV. RESULTS AND CONCLUSIONS

DynaCAN-based methods can allow increasing the signal amplitude by orders of magnitude by reducing unwanted effects of MRI pulses. The method also allows improving the accuracy and shortening the duration of spin flipping pulses. DynaCAN is not limited to ULF MRI.

We describe other results on improving signal quality in our new ULF MRI and MEG–MRI system with significant improvements compared to Ref. [2]. We also show recent results on CDI.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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497 - Management of patients with atrial fibrillation

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I. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia. Worldwide several million people suffer from AF. It has been estimated that in the Western countries every fourth middle-aged adults will develop AF. The main reasons for the AF epidemic are aging of the population and increases in the incidence of hypertension, obesity and diabetes.

All-cause mortality in AF patients is 1.5-2.0 higher than in sex- and age-matched population without AF. Death is mainly due to stroke, but AF is also associated with increased morbidity, such as heart failure and stroke. About 20–30% of strokes are due to AF, and many patients with stroke are diagnosed with ‘silent’ AF.

II. DIAGNOSIS

The diagnosis of AF requires ECG recording showing the typical arrhythmia pattern (irregular RR intervals and no discernible, distinct P waves). The most common symptom is palpitation. In addition, rapid and irregular heart rate often causes lethargy, dyspnoea, chest tightness, sleeping difficulties, psychosocial distress and dizziness. The symptoms of AF can be classified using the EHRA symptom score.

III. TREATMENT

Treatment of AF can be divided into five domains. 1) Acute rate and rhythm control aiming to hemodynamic stability in patients with acute AF, 2) Management of precipitating factors and underlying cardiovascular conditions, 3) Assessment of stroke risk and prevention of stroke 4) Assessment of heart rate and initiation of rate control therapy, and 5) Assessment of symptoms decision for rhythm control.

Many cardiovascular diseases and concomitant conditions increase the risk of AF and AF-associated complications. Hence, identification and treatment of such conditions (e.g. hypertension, diabetes, congestive heart failure, obesity, valvular disease, sleep apnoea) is important for optimal management of AF. It is crucial that the patients change their lifestyles and adhere to chronic therapy.

Oral anticoagulation: The cornerstone of AF therapy is oral anticoagulation (OAC). In clinical practice the need for oral anticoagulation is estimated using the CHA₂DS₂VASc score. OAC is indicated in patient with AF and CHA₂DS₂VASc

score ≥ 2 in men and ≥ 3 in women. Direct oral anticoagulant therapy is recommended in preference to a vitamin K antagonist except in patients with moderate-to-severe mitral stenosis or mechanical heart valves. ASA alone has no role in prevention of stroke in patients with AF. Left atrial appendage occlusion can be considered for stroke prevention in patients who are not eligible for long-term anticoagulant treatment.

Rate control: AF may cause tachycardia myopathy if the heart rate is too high for a long time. Therefore, it is important to assure that the target heart rate is achieved. The choice of rate regulating medication is made on an individual basis. Beta blocker monotherapy is usually the first-line rate-controlling agent. Beta blockers are safe also in patients with structural heart disease. Other drugs (e.g. digoxin or diltiazem and verapamil) or combination therapy can be used if beta blocker therapy is contra-indicated or not sufficient to improve AF-related symptoms or due to patient preference. Ablation of the atrioventricular node and implantation of permanent pacemaker should be considered if medications fail to control heart rate and symptoms.

Rhythm control: Many clinicians and patients believe that restoring and maintaining sinus rhythm improves outcomes in AF patients. However, to date no trials that have compared rhythm control to rate control have resulted in positive outcomes. Nevertheless, rhythm control therapy should always be considered if the patient remains symptomatic on adequate rate control therapy. Rhythm control should be initiated as early as possible because “AF begets AF”. Catheter ablation is usually used as a second-line treatment in patients with paroxysmal or persistent AF after failure of or intolerance to antiarrhythmic drug therapy. In such patients, catheter ablation is more effective than antiarrhythmic drug therapy.

IV. FUTURE DIRECTIONS

The key aspects in the prevention of AF are identification and treatment of factors and diseases (e.g., hypertension, diabetes, obesity and sleep apnoea) which are known to increase the risk of AF. In addition, we should work in close collaboration with basic scientists to better characterize the mechanism of AF. This might allow us to tailor the therapy of a given patient. More research is also needed on how much AF constitutes a risk for thromboembolic complications and to improve diagnostic of silent AF.

500 - A self-reporting tool to reduce the occurrence of postoperative adverse events after total hip arthroplasty

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I. INTRODUCTION & AIM

The occurrence of adverse events in health care creates a lot of unwanted costs and distress for society. In Norway, from 2011 to 2015, 16838 compensation claims were filed. 5308 people got compensated, which lead to 3,4 billion NOK in compensation costs. In addition to these costs comes patient suffering and absence from work, as well as diminished life quality. The leading field regarding adverse events in Norway was orthopedics, with 37% complaints nationwide [1].

Therefore, a self-reporting mobile application prototype for Android has been developed to help reduce these severe outcomes, more specifically regarding postoperative adverse events after total hip arthroplasty. The application is a segment of a safety reporting platform.

The aim of this study was to assess the feasibility of the prototype in the aforementioned setting, as well as evaluating the design.

II. METHOD

A user-centered design approach was utilized in order to develop the prototype [2]. Thereafter, an individual expert review was conducted with two experts in Interaction Design to evaluate it [3]. The review consisted of prototype testing, followed by a discussion.

Furthermore, an interview was carried out with a physiotherapist assessing the questions regarding self-reporting and the prototype

III. RESULTS AND DISCUSSION

The application enables the patient to report pain, anxiety, quality of recovery, mobility, and to take a picture of the surgical area which is expected to reduce the occurrence of adverse events. In addition to that, recommendations for the patient on how to reduce risk factors are also included.

The HCI experts stated that it was a useful application and very suitable for mobiles. Expert number one suggested to let some features directed towards self-reporting be optional, e.g. a picture of the surgical area. Expert two highlighted the importance of adding feedback from the application to the patient, such as *'the report has been read by your physician'*.

The physiotherapist was pleased with the self-reporting questions, as well as with the prototype itself. He has also suggested to add a question concerning if the patient had trouble getting in and out of bed.

The findings indicate that the prototype is very feasible in terms of postoperative self-reporting after total hip arthroplasty. Using the application to gather more data will contribute to a long-term improvement of patient self-reporting. In addition, patient data will help to complete the clinical picture during the postoperative recovery.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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503 - Improving Mechanical Strength of Bioactive Glass Scaffolds with Stereocomplex Poly lactide Coating

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I. INTRODUCTION & AIM

By controlling the stereoisomeric ratio of lactide monomers it is possible to synthesize polylactide (PLA) with different crystallization properties. PLA with significant amounts of both L- and D-forms, i.e. poly(D,L-lactide) (PDLLA) is amorphous, whereas chains rich in either L- or D-form may crystallize. By blending poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) so called stereocomplex crystallites can be formed. Stereocomplex PLA has been reported to have longer degradation time and higher mechanical properties, especially higher tensile strength, than homocrystalline PLLA or amorphous PDLLA [1].

The aim of this work was to study the compressive strength and in vitro degradation properties of bioactive glass scaffolds for bone regeneration with either amorphous, homocrystalline or stereocomplex PLA coating. Uncoated scaffolds were used as reference.

II. METHODS

Amorphous, three-dimensional, highly porous scaffolds of bioactive glass 13-93 were manufactured with the foam replication method. The scaffolds were dip-coated to produce either amorphous coating with PDLLA, homocrystalline coating with PLLA, or stereocomplex coating with a blend of PLLA and PDLA. Eight parallel scaffolds from each coating group were immersed in simulated body fluid (SBF) for 0, 2, 4, 6 or 10 weeks. The immersion solution was changed weekly to fresh SBF. In vitro degradation properties and compressive strength were measured. Morphological characterization was performed with SEM and μ CT to evaluate scaffold porosity, coating thickness and bioactive glass reactions.

III. RESULTS & DISCUSSION

The compressive strength of porous bioactive glass scaffolds increased several-fold by coating them with 3 wt.% PLA. Stereocomplex coatings showed on average the highest strengths, followed by homocrystalline and amorphous coatings. The compressive strength of coated scaffolds decreased markedly from the dry state at 0 weeks to the wet state at 2 weeks, and stayed thereafter on similar levels throughout the immersion time. The compressive strength of uncoated scaffolds was similar for all time points. Differences in other degradation parameters, such as pH of the immersion solution, were generally small. However, the water uptake of scaffolds with stereocomplex coating was markedly higher than that of scaffolds with either amorphous or homocrystalline coating.

The main conclusion of this work is that stereocomplexation of PLA can be a useful method to increase the mechanical strength of biomedical scaffolds.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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506 - Investigating the Interaction between Ballistocardiogram and Cardiac Age

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I. INTRODUCTION & AIM

Variations in the morphology of the PPG waveform have been studied previously and were correlated to atherosclerotic disorder and arterial stiffness, and cardiac health in general. In this paper, we explore variation of the features extracted from the Ballistocardiogram (BCG), with respect to an existing cardiac health index which is based on the changes in morphology of the PPG waveform. We used a dataset collected from 50 volunteers of different ages and health conditions, with a bed sensor positioned under the mattress. Results show considerable and congruent variations in multiple BCG features between different cardiac health groups (i.e., cardiac age).

The bed sensor used in this study is part of an in-home monitoring system that was developed to unobtrusively track health [1, 2]. Cardiac age is estimated using the index proposed by Hong et al. [3], which is based on the acceleration photoplethysmogram (APG) waveform; this index has previously been shown to correlate with disorders such as atherosclerotic and arterial stiffness. In this paper, by relating BCG waveform features to the cardiac health index, we explore how the morphology of the BCG waveform might be useful in recognizing and tracking cardiac health changes.

II. METHODS:

In total, 50 subjects aged from 19 to 95 years old (with mean \pm SD age of 67 ± 20 years), with different cardiac health conditions were recruited. Ten-minute synchronous ECG, PPG, and BCG were collected from each subject in the supine posture. APG was computed as the second derivative of the PPG. Then for every subject, an average waveform was created for their BCG and APG signals. We manually compared the shape of the APG averages to the templates provided by [3], and assigned a "Cardiac Age" to each subject: Young, Middle Age, Old, and Very old. We also counted the number of "Prominent BCG peaks" (peaks above the average) and extracted two J-peak features from the BCG averages: the difference and the

ratio of the two sides of the J-peak (JK-IJ and JK/IJ). Signal to noise ratio (SNR) of each channel was also computed by the ratio of the summed squared magnitude of the band-pass filtered component (signal), to that of the high-pass filtered component (noise).

III. RESULTS:

Our results show that, in addition to the variation in the APG waveform, older subjects tend to have noisier BCG waveforms. Signal to Noise Ratio for young to very old cardiac age groups are 30.5, 24.9, 18.9, and 25.6, respectively. This mirrors the differences in the number of prominent peaks across groups, where the values for young to very old are 3.6, 4.4, 5, and 4 prominent peaks, respectively. Also, both J-peak related features share a similar pattern across these groups, where the middle-aged group is the highest, and is followed by a decreasing trend for the older cardiac age groups. The JK-IJ feature has values of 56.7, 65.6, 62.1, and 52.6, respectively. The JK/IJ feature, has values of 4.5, 5.1, 4.5, and 3.7, respectively. In conclusion, we show that the BCG related features, including the morphological features and the SNR, change for different cardiac age groups. Similarity in variation of these features from younger to very old cardiac age groups has also been reported in this paper. These results show support for tracking cardiac health using BCG features extracted from an unobtrusive bed sensor. In the future, we plan to incorporate these features into our in-home monitoring system for use in longitudinal studies.

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508 - Vasovagal Syncope is Associated with Relative Autonomic Hypersensitivity and Lower Stroke Volume during Active Standing

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I. INTRODUCTION

The etiology of vasovagal syncope (VVS) is poorly understood [1]. The active stand (AS) provides a convenient assessment of autonomic and cardiovascular function [2], however no studies have examined its response in older adults with VVS.

II. AIM

To assess differences in the hemodynamic response to AS in older adults with VVS compared to age-matched controls (CON).

III. METHODS

Four groups of adults (Young-VVS N=64 Age=25.0 ±8.4; Young-CON N=37 Age=24±4.6; Older-VVS N=46 Age=66.9±10.3; Older-CON N=86 Age=65.3±9.5) completed an AS stand test for 3 minutes. Continuous beat-to-beat BP (Finometer™) measurement and pulse wave analysis (Model-flow™) was performed to measure transient hemodynamic changes after standing. All testing was approved by local ethics committee. Custom software (MATLAB®) was used for signal processing, while group comparisons of features were performed using Mann-Whitney U tests. P<0.05 was assumed significant.

IV. RESULTS

Compared to age-matched controls, older subjects with VVS demonstrated a higher resting heart rate (69.8±13.1 bpm vs 63.3±12.1 bpm; P=0.007), a smaller initial systolic blood pressure drop (-20.2±20.1% vs -27.3±17.5%; P=0.005), larger drops in stroke volume (-14.7±24.0% vs -2.7±23.3%; P=0.010) and a larger increase in total peripheral resistance (8.1±30.4% vs -6.03±22.8%; P=0.002) compared to CON. A similar pattern was noted for Young-VVS versus Young-CON.

V. CONCLUSION

While ageing is associated with poorer cardiovascular and autonomic function, VVS is characterized by relative autonomic hypersensitivity and larger drops in stroke volume when compared to age-matched controls. This information may inform future models of VVS etiology and its clinical management.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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509 - Different approaches to formulate gelatin - gellan gum hydrogels influence the cell behavior

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I. INTRODUCTION & AIM

Hydrogels are used as biomaterials in a variety of medical applications such as tissue engineering and drug delivery. However, hydrogels for current clinical applications in regenerative medicine are limited to 2D thin tissues. It remains challenging to engineer 3D thick tissues to be used in regenerative medicine. Gelatin is a protein derived from collagen that can form soft hydrogels and it is routinely used as coating material in cell culture applications. By thermal gelation, it is possible to form gelatin hydrogels, however, the gelation temperature is often below physiological requirements, thus, their use with cells or in vivo is limited. In addition, gelatin is weak in mechanical strength. On the other hand, gellan gum, a bacterial polysaccharide, is able to form hydrogels with excellent, tunable mechanical properties, nonetheless, the bioinert nature of gellan gum hamper the cell attachment. Here we aim to develop hydrogels based on the mentioned materials, in the way that they crosslink in situ under physiological conditions favoring the engineering of 3D tissues and organs.

II. METHODS

Here, we prepared in situ gelatin – gellan gum (GG) hydrogels using two different approaches. On the one hand, hydrogels were produced by the creation of an interpenetrating network (IPN) and on the other hand, hydrazone crosslinking reaction was used as gelation method. To obtain IPN gels, GG where oxidized producing GG-CHO and gelatin was modified by amination. Both polymers interact forming a base of Schiff and the gelation was complemented by the incorporation of the cationic polyamine spermidine. Hydrazide gelatin (gelatin-ADH) was also synthesized to react with GG-CHO in order to produce hydrogels based on the generation of the covalent hydrazone linkages.

III. RESULTS & DISCUSSION

According the production method, IPN or hydrazone crosslinking, the amount of gelatin possible to incorporate into the hydrogels differs, the hydrazone crosslinking being the method

that allow the incorporation of larger amount of gelatin (50%). The hydrogels obtained showed gelation times between 5 and 10 min. According the mechanical analysis, gelatin-ADH /GG-CHO showed a dramatic shift from brittle to elastic mechanical behavior, compared to the hydrogels obtained by IPN method. This elastic behavior is similar to real soft tissue during compression, as reported by us (1). The estimated elastic region also shifts to higher strain when increased the gelatin content. Hydrogels obtained by IPN have elastic region between 10-20% strain, while gelatin-ADH/CHO at 15-30% strain. The compressive modulus values are 13.3 kPa and 37.7 kPa respectively. In order to verify that modified gelatin maintain the cell response of native gelatin, human fibroblasts were exposed with the different gellatins for 24h. All the modifications showed good response. Hydrogels demonstrated cell attachment and high viability of encapsulated cells, indicating that the hydrogels and their crosslinking reactions were cyto-compatible, providing a suitable microenvironment. Fibroblasts elongation was observed in 2D and 3D experiments when de amount of gelatin was 50% in the composition, so hydrogels produced by hydrazone crosslinking were more promising for future studies.

IV. CONCLUSION

The developed of in situ crosslinkable hydrogels based on gelatin and gellan gum, may be useful for the fabrication of scaffolds to engineer 3D tissues and organs.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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512 - Economic Assessment of Medical Devices for Procurement Decisions

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I. INTRODUCTION & AIM

Growing health care costs and the limitations of available resources have led to the need of an assessment of effectiveness and appropriateness of expenses incurred on health care. Medical devices (MD) are a major component of health care processes. “Small” medical devices like stents play an important role in treatment of cardiac diseases; “large” medical devices like CT scanners are widely used for diagnostic purposes throughout almost all departments in a hospital. Therefore, a rational and appropriate selection of MDs for specific purposes is crucial for achieving the required level of cost-effectiveness in health care. These activities are supported by the World Health Assembly through a resolution with recommendations to formulate strategies and plans for an implementation of systems for medical devices assessment, planning, procurement and management [1]. This study is focused on searching an appropriate procedure for optimizing the selection of medical devices when deciding about procurement.

II. METHODS

The multiple-criteria decision analysis (MCDA) is currently one of the most commonly used analytic techniques in many areas, incl. science, economy and engineering. This approach is also known in health care, where it is used particularly for the choice of the appropriate drug or the proper treatment. There are some differences in the assessment of MDs in comparison with other health technologies [2], incl. short life cycle, frequent inability of application of QALY, wider economic implications, etc. Due to these differences, the MCDA is widely used also for evaluation of MDs [3-5].

III. RESULTS AND DISCUSSION

The point method, Fuller’s method and Saaty’s method were used for the criteria weight assignment. The following MCDA methods were studied: weighted sum method, TOPSIS method, analytic hierarchy process, and concordance discordance analysis. Altogether, twelve possible combinations were applied to the selection of lung ventilators and monitors of extracorporeal circulation. The main goal was to analyse the possibilities of clinical data utilization as well as technical and cost data integration into the MCDA process for a selection of MDs during a procurement process. The basic model for the selection of

MDs was designed based on the general structure of the procurement process. To evaluate the future effectiveness of the purchase, two variants were chosen with respect to relative costs. One option is to use the results of MCDA as the outcomes in the cost-effectiveness analysis. The other option is to use the cost data as additional criteria in the MCDA.

Different MCDA approaches were used for the selection of MDs with applications to lung ventilators and monitors of extracorporeal circulation. These studies covered an evaluation relevant for the particular requirements, a determination of real parameters of the instruments, as well as the proper calculations and evaluation of the effects. The calculations in these studies were further compared using the sensitivity analysis. This analysis shows the solution stability based on a selection of entry parameters for individual combinations of calculation methods. Two ways of cost data utilization in the MCDA process for MDs were compared. Based on the achieved results, the possibility of cost data utilization in MCDA studies for selection of MDs for procurement decisions were shown.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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513 - Online assessment and feedback of human motion in rehabilitation and strength exercises

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I. INTRODUCTION & AIM

Rapid developing of technology in the recent decade makes human motion tracking possible in many different ways. Any of these technologies presents a possible solution in development of intelligent supporting devices or systems for replacing (or additional helping) private, human trainers on daily basis. There is a number of parameters that influences capturing human motion, depending on intended use of the recorded data. Considering the equipment and technology needed for recording, it can be roughly divided in vision based Motion Capture System (MCS) and non-vision based MCS. In this abstract, aiming to low cost and sufficiently accurate measurements, we describe a non-vision MCS based on inertial and magnetic sensors for human motion tracking and evaluation.

II. MOTION CAPTURE SYSTEM WITH ECG MODULE

Our custom developed system for online assessment and feedback of human motion in rehabilitation and strength exercising is composed of one or several sensor nodes, located on different body segments and an application which can be installed on mobile phones or personal computers [1]. The sensor node which was used only for human movement monitoring had two main parts, a microprocessor Nordic Semiconductor nRF51822 with Bluetooth low energy and a nine axis (accelerometer, gyroscope and magnetometer, three axis each) MotionTracking sensor chip InvenSense MPU-9150. In order to use the sensor node during exercising also for recording an ECG signal, the Texas Instruments sensor chip ADS1192 was integrated. The custom-made system enables transmission and recording of raw signals which are stored and used for further optimisation of signal processing algorithms for recognition and evaluation of single movements in each particular exercise [2].

The particular problem is defining the margins of error in movements in different populations and for individuals in each phase of rehabilitation or sportsmen training. The margins of error have to be adjusted also to comply with the success rate

of individuals, in order to support the progress both physically and physiologically.

In our system, we provide on line information of the successfulness of each prescribed movement in any exercise of the training in two ways: 1) the person exercising is presented a virtual trainer who displays the right way to exercise, and on the same screen there is the avatar representing the movements of the person exercising so that a visual feedback is generated; 2) the numerical result of the exercise cycle is presented on the screen and saved in the platform.

III. CONCLUSIONS AND FUTURE WORK

Such a system with upgraded self-developed sensor nodes and virtual visualization on mobile or desktop app ensures a controlled and guided exercising procedure in either rehabilitation or in sports, with real time assessment and visualization of the movements. Due to the additional ECG module, the system can also be applied for various applications such as heart function monitoring, abnormal rhythm detection, atrial fibrillation etc. In future work we will compare and evaluate accuracy and usability of development sensor nodes with commercial system Shimmer. Available Shimmer unit contains accelerometer, gyroscope, magnetometer, altimeter and ECG module.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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520 - Propagation of the primary pacemaker activity in the human heart: a computational approach

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I. INTRODUCTION & AIM

The sinoatrial node (SAN) is the specialized tissue responsible for the heart rate in physiological conditions.

Early investigations on SAN tissue [1,2] in animal models date back to the 1980s. Based on the collected data, computational models able to describe the propagation of SAN activity were developed [3].

Recently, computational models that characterize histology and conduction pathways in the human heart have been proposed [4,5]. However a computational model of the electrical activity propagation in human tissue is still lacking.

Aim of the present preliminary work is the computational characterization of the propagation of the SAN action potential (AP) towards the atrial tissue in 1-D geometry, employing the recently developed Fabbri *et al.* human SAN action potential model [6].

II. METHODS

A 1D strand was built employing the Fabbri *et al.* [6] and Courtemanche *et al.* [7] models for the human SAN and atrial cells, respectively.

The investigation of the AP propagation was led through the identification of the minimal conductivity ($\sigma_{\text{coupling,min}}$) in a homogenous ($\sigma_{\text{SAN}} = \sigma_{\text{ATRIAL}}$) strand composed by 100 SAN and 100 atrial cells. Next, we tested the capability of the SAN to pace and drive a large atrial tissue varying the number of SAN and atrial cells (10 SAN vs. 100 or 200 atrial cells). In such simulations σ_{coupling} was set ten times larger than the identified minimal conductance. Finally, we simulated a 5 SAN and 200 atrial cell strand with a homogeneous conductance of 10 S/m.

The strand geometry, the coupling and the partial derivative equations describing the AP propagation were numerically implemented using the acCELLerate framework [8].

III. RESULTS & DISCUSSION

Manual tuning of intercellular coupling showed that $\sigma_{\text{coupling,min}} = 0.014$ S/m was the lower boundary that allowed 100 SAN cells to drive the atrial tissue. AP propagated through 100 atrial cells with a velocity of 0.55 cm/s. The last SAN cell (#100) showed a delay of 78 ms with respect to the previous one, due to the coupling with the atrial

cells. The first atrial cell (#101) lost the typical atrial waveform due to the influence of SAN cells. The characteristic spike-notch-dome waveform recovered in the next few following cells. Simulations with a lower number of SAN cells showed that 10 SAN cells were able to drive 100 atrial cells with $\sigma_{\text{coupling}} = 0.14$ S/m. AP propagation from SAN cell #1 to #10 took 117 ms. The AP spread out through the atrial tissue with a constant velocity of 7.14 cm/s. The velocity slightly decreased (6.75 cm/s) with a higher number of atrial cells. Five SAN cells, strongly coupled with the atrial tissue, were not able to reach threshold, showing a non-pace behavior. Simulations showed that the SAN to atrial cell ratio and the intercellular coupling play a crucial role for a successful pace and drive behavior. Different conductivity configurations, including spatial gradients, can provide further insight into the spread of the SAN AP towards and into the surrounding atrial tissue.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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523 - Impedance-based characterization of proliferating and differentiating neural stem cells on interdigitated microelectrode arrays

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I. INTRODUCTION & AIM

Since Giaever and Keese introduced bipolar impedance measurements using voltage excitation for monitoring the behavior of adherent cells on electrode surfaces [1], the methodology has been widely applied in cell-based investigations of, e.g., cytotoxicity [2] and characterization of stem cell differentiation [3]. The measured impedance comprises both the electrode interface impedance and contribution of the adhering cells.

Characterization of neurotransmitter release from neural stem cells on microelectrode arrays requires evaluation of the achieved cell coverage on the electrodes and the degree of cell differentiation. To eliminate the need for continuous microscopic monitoring, impedance analysis could be a means to distinguish between proliferating and differentiating cells. Here, we present the feasibility of impedance-based characterization using immortalized human mesencephalic stem cell lines LUHMES [4] and hVM1 [5], which have been developed as dopaminergic models of Parkinson's disease (PD) and candidates for PD cell therapies.

II. METHODS

LUHMES and hVM1 cells, seeded at different densities on Geltrex[®] coated microchips having 12 interdigitated microelectrode arrays (IDA) [2,3], were cultured in DMEM/F12 medium containing N2, 2 mM L-glutamine, 1% penicillin/streptomycin, and bFGF. Differentiation was initiated by 1 mM cAMP, 1 µg/ml tetracyclin (for LUHMES), and 2 ng/ml GDNF. Bipolar impedance measurements (100 Hz to 100 kHz; V_{rms} of 200 µV to minimize the invasiveness of voltage excitation) were performed every hour using a tailor-made 12-channel bipotentiostat [2,3]. Correlation of impedance measurements with cell morphology was done through microscopic imaging.

III. RESULTS & DISCUSSION

LUHMES cells generated a monotonous increase in impedance magnitude ($|Z|$) during proliferation, whereas during differentiation, reaching a maximum after 48 h followed by $|Z|$ decrease (up to 80% during 5-day differentiation) due to changes in cell morphology (smaller cell bodies, formation of non-adherent neurites). On the other hand, both proliferating and differentiating hVM1 cells showed a $|Z|$ maximum at 48 h followed by almost the same degree of $|Z|$ decrease (45-50%) for proliferating and differentiating cells, obscuring distinction between them if only applying the conventional $|Z|$ analysis. We have demonstrated that instead of only $|Z|$ analysis usage of an equivalent circuit model, comprising a resistor for cell substrate interactions in series with a parallel capacitor and resistor for cell membrane and cytosol, respectively, allowed detailed evaluation of cell adhesion as well as distinction between proliferating and differentiating cells. Especially in the case of hVM1 cells, the equivalent circuit modelling is the only feasible means of distinguishing between proliferation and onset/progress of differentiation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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525 - How clinical engineer involve in risk management in health services

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I. INTRODUCTION & AIM

The clinical engineer (CE) should support and enhance patient care with the application of engineering principles. It is a vital component of the health service system supporting the safe and effective application of medical technology. The CI. Engineers can contribute significantly to the financial health of the hospital by increasing productivity and improving resource utilization in clinical departments [3].

Highlighting the role of clinical engineering in addition to management of medical equipment during use, actively contribute to quality improvement activities and risk management (RM) events from the equipment.

II. METHODS

Risk management techniques (Risk Management) require specific guidelines and the establishment of a management team that will complete a report. Data can be collected from[4]:

- Interview the patient, relatives or the attendants,
- Contact the manufacturer
- Information policy legal plaintiff
- External independent consultants will inspect the device

In each survey, the team reviews the policies and procedures, noting any discrepancies and report on improvements.

III. RESULTS & DISCUSSION

Clinical engineers involved necessarily as members of interdisciplinary teams in the hospital for investigation and risk management and incident in which a medical device may have contributed to injury or death [5]. The clinical engineering can help to identify the main causes of failure. Understanding the operation of equipment and maintenance requirements contribute to the analysis of adverse incidents [1]. An understanding of systems theory and human factors engineering can shed light on the interaction between machines and humans.

The risk management associated with the device or procedure is implemented through three stages in identifying shortcomings: 1) the concentration of clinical and engineering data about an incident, 2) analyzing the data to determine the device points which contributed to the occurrence, or where there has

been operator error, 3) linking the clinical effects of operator conceptually with human errors.

IV. CONCLUSION

Participation of clinical engineers in risk management teams is a cornerstone in the health sector operation. The strategies that can be adopted and contribute to this are:

- To follow new strategies and methodologies in risk management,
- Develop partnerships networks within the health sector,
- To seek partnerships at national and international level to pursue common goals to enhance patient safety,
- Develop educational programs that improve the skills of professionals in the health sector and their ability to participate in risk management teams,
- To strengthen the certification of clinical engineering to analyze the root cause and in areas related to patient safety.

Finally has a management team requires the respect of each member to the other, good communication within the team, careful and thorough research, and reasonable proposals. The aim of any research must be the improvement of risk management processes and updating[2]. The risk management framework should ensure the maximum safety of patients and minimum exposure and liability for the provider of health services.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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526 - Numerical analysis of saline irrigable electrode for radiofrequency cardiac ablation

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I. INTRODUCTION & AIM

Radiofrequency catheter ablation is the interventional therapy that be employed to eliminate cardiac tissue caused by arrhythmias. During radiofrequency catheter ablation, the formation of thrombus can occur at electrode tip if the temperature of interface between electrode tip and cardiac tissue reaches around 80 °C, lead to the adherence of blood and make difficult to eliminate cardiac tissue. To prevent this phenomenon, the electrodes which can inject saline into blood-tissue interface through holes of electrode tip have been developed. There are numerous computational modeling about radiofrequency catheter ablation. The previous model[1] did not solve the fluid problem associated with the blood circulation in cardiac chamber and the saline irrigation flow, and substituted the convective heat transfer for the heat flux condition at the tissue-blood interface. The saline irrigation flow was substituted by fixing the temperature of electrode tip and simplified by the zone of the electrode surface corresponded the irrigation holes location without modeling individually the irrigation holes to reduce computational cost. The purpose of study is set up the numerical modeling of saline irrigable electrode including the flow problem about the blood circulation and the saline irrigation flow.

II. MODELING

The numerical model is based on coupled electric-thermal-flow problem and solved by COMSOL Multiphysics software. The governing equations are Energy equation, Navier-Stokes equation and Maxwell equation. We consider a temperature-control ablation on the electrode tip. To control electric potential in electrical boundary condition, the model implemented PI control system by setting the probe of temperature at electrode tip.

III. RESULTS

The results of numerical model show that the temperature distribution is affected according to the saline irrigation. The temperature of electrode tip with the saline irrigation is reduced by cooling effect for several seconds, increased by joule heating, controlled by PI system if the temperature of probe reaches the setting temperature. Since the time reached the setting temperature of the saline irrigable electrode is higher than the saline non-irrigable electrode, the saline irrigable electrode can obtain larger lesion volume than the saline non-irrigable electrode. But the temperature of tissue is exceeded 100 °C if the setting temperature at electrode tip is too high due to cooling effect. Consequently, the setting temperature which is determined to control the electric potential of electrode tip is key parameter in this numerical modeling.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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527 - Medical Device Vulnerability Discovery and Information Sharing

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I. INTRODUCTION: MEDICAL DEVICE CYBER SECURITY

Medical device cyber security risk represents a significant public health challenge. There is insufficient data today to effectively security assure medical device networks. Conservative estimates predict that there will be more than 200,000 billion exposures between patients and connected regulated medical devices in the EU and the USA over the next 10 years.

Three sessions will be delivered to address the critical aspects of medical cyber security including: (1) Cyber Surveillance and Threat Intelligence Sharing, (2) Medical Device Risk Management and Assessment, and (3) Medical Device Vulnerability Discovery and Information Sharing. Case studies will be presented to amplify this applied learning opportunity.

These sessions are designed to provide the necessary background on medical device cyber security, cover current state, identify key challenges and risks, review applied approaches for optimizing transparency and information sharing, and provide recommendations for stakeholder collaborations to mitigate cyber risk and deliver more robust digital health infrastructures.

Public health best practices provide the most effective approach to this complex, large, scale exposure and the sessions will clarify specific public health strategies and tactics that can support a successful response to this ill-defined risk associated with this very large scale exposure. The promotion of patient safety (clinical care) and population safety (emergency preparedness and response) will be emphasized while addressing the privacy risk; importantly, both safety and privacy risk share common root cause. This session will focus on Medical Device Vulnerability Discovery and Information Sharing.

II. AIM: MEDICAL DEVICE VULNERABILITY DISCOVERY AND INFORMATION SHARING

Medical device vulnerability detection, assessment, information sharing and response is a complex decision and operational process. Inappropriate management – too much too early or too little too late - can increase risk to patients. Presenters will review applied lessons from the past 7 years of stakeholder collaboration facilitated by MDISS and NHISAC; the emergence of MD-VIPER vulnerability reporting program in collaboration with the Food and Drug Administration (FDA), the medical device bill of materials and the process of coordinated vulnerability disclosure will be explained with emphasis on international standards and local regulatory approaches.

III. COMPLIANCE WITH ETHICAL REQUIREMENTS

A. Conflict of Interest

Michael McNeil is the Global Product Security & Services Officer at Philips Healthcare, a medical device manufacturer. Steve Abrahamson is the Senior Director for Product Cyber Security at GE Healthcare, a medical device manufacturer. Dale Nordenberg services as the Executive Director for the Medical Device Innovation, Safety and Security Consortium, a non-profit membership-based organization with paying members that include medical device manufacturers..

B. Statement of Informed Consent and Human and Animal Rights are not applicable.

528 - Medical Device Cyber Surveillance and Threat Intelligence Sharing

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I. INTRODUCTION: MEDICAL DEVICE CYBER SECURITY

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These sessions are designed to provide the necessary background on medical device cyber security, cover current state, identify key challenges and risks, review applied approaches for optimizing transparency and information sharing, and provide recommendations for stakeholder collaborations to mitigate cyber risk and deliver more robust digital health infrastructures.

Public health best practices provide the most effective approach to this complex, large, scale exposure and the sessions will clarify specific public health strategies and tactics that can support a successful response to this ill-defined risk associated with this very large scale exposure. The promotion of patient safety (clinical care) and population safety (emergency preparedness and response) will be emphasized while addressing the privacy risk; importantly, both safety and privacy risk share common root cause. This session will focus on Cyber Surveillance and Threat Intelligence Sharing.

II. AIM: CYBER SURVEILLANCE AND THREAT INTELLIGENCE SHARING

The paucity of data and information on threat intelligence (TI) related to medical devices compromises the building of robust medical device networks. The challenges with collecting and sharing TI for medical devices are complex and difficult to address. The session will explore current best practices, summarize currently available TI data, explain the criticality of addressing these gaps to provide robust device associated TI, explain impact of TI on risk assessment.

III. COMPLIANCE WITH ETHICAL REQUIREMENTS

A. *Conflict of Interest*

Michael McNeil is the Global Product Security & Services Officer at Philips Healthcare, a medical device manufacturer. Steve Abrahamson is the Senior Director for Product Cyber Security at GE Healthcare, a medical device manufacturer. Dale Nordenberg services as the Executive Director for the Medical Device Innovation, Safety and Security Consortium, a non-profit membership-based organization with paying members that include medical device manufacturers.

B. *Statement of Informed Consent and Human and Animal Rights are not applicable*

529 - Medical Device Risk Management and Assessment Methods

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I. INTRODUCTION: MEDICAL DEVICE CYBER SECURITY

Medical device cyber security risk represents a significant public health challenge. There is insufficient data today to effectively security assure medical device networks. Conservative estimates predict that there will be more than 200,000 billion exposures between patients and connected regulated medical devices in the EU and the USA over the next 10 years.

Three sessions will be delivered to address the critical aspects of medical cyber security including: (1) Cyber Surveillance and Threat Intelligence Sharing, (2) Medical Device Risk Management and Assessment, and (3) Medical Device Vulnerability Discovery and Information Sharing. Case studies will be presented to amplify this applied learning opportunity.

These sessions are designed to provide the necessary background on medical device cyber security, cover current state, identify key challenges and risks, review applied approaches for optimizing transparency and information sharing, and provide recommendations for stakeholder collaborations to mitigate cyber risk and deliver more robust digital health infrastructures.

Public health best practices provide an effective approach to this complex exposure. This session will clarify specific public health strategies and tactics that can support a successful response to this ill-defined risk associated with this very large scale exposure. The promotion of patient safety (clinical care) and population safety (emergency preparedness and response) will be emphasized while addressing the privacy risk; importantly, both safety and privacy risk share common root cause. This session will focus on *Medical Device Risk Management and Assessment* across the life cycle of medical devices..

II. AIMS: MEDICAL DEVICE RISK MANAGEMENT AND ASSESSMENT BEST PRACTICES AND FUTURE DIRECTIONS

There remains an enormous amount of work that must be completed to achieve a satisfactory level of assessments to

support safer medical device design, implementation and operations. This session will explain methods for medical device risk management and assessment across the device life cycle; review most relevant international standards; and share experiences to highlight successes and challenges for large scale assessment activities in health systems.

It will explain how the Medical Device Risk Assessment Platform (MDRAP) can support collaborative work and crowdsourcing of assessments to improve efficiencies and quality of the assessments; train biomedical and security professions, and support the development of safer devices and associated networks.

III. COMPLIANCE WITH ETHICAL REQUIREMENTS

A. Conflict of Interest

Michael McNeil is the Global Product Security & Services Officer at Philips Healthcare, a medical device manufacturer. Steve Abrahamson is the Senior Director for Product Cyber Security at GE Healthcare, a medical device manufacturer. Dale Nordenberg services as the Executive Director for the Medical Device Innovation, Safety and Security Consortium, a non-profit membership-based organization with paying members that include medical device manufacturers.

B. Statement of Informed Consent and Human and Animal Rights are not applicable

532 - Real time imaging of mechanical and biochemical actions of single cells under oxygen deprivation

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I. INTRODUCTION & AIM

Efficient transport of oxygen through the lungs into our blood flow is important. Acute oxygen shortage in the alveoli of the lung leads to hypoxic pulmonary vasoconstriction (HPV) with pulmonary arterial smooth muscle cells (PASMCs) as the effector cells. The cells immediately start to constrict upon hypoxia, which redirects the blood flow in pulmonary arteries to areas of higher oxygen content to optimize the oxygen uptake [1]. But, HPV supplemented by pneumonia, sepsis, during anesthesia or liver failure can become life threatening. A chronic narrowing of the pulmonary arteries causes the right side of the heart to work harder. Heart failure is often the consequence. One suggested triggering factor of HPV are reactive oxygen species (ROS), produced by NADPH oxidases (NOXs) or by the mitochondria. Resonance Raman spectroscopy has shown to be a valuable tool for investigations of mitochondrial biomarkers [2, 3]. Here, we present a gas tight lab-on-a-chip (LOC) that enables Raman spectroscopic-, and patch clamp experiments with control over the oxygen content. The system was tested, with focus on mitochondrial biomarkers, on cultured murine PASMCs during oxygen deprivation. Additionally, holographic stimulated Raman imaging (SRI) was developed. SRI has prospect of recording HPV induced by the PASMCs in real time and can be combined with the LOC.

II. METHODS AND RESULTS

The LOC was designed in a CAD program. Computational Fluid Dynamics (CFD) simulations of the LOC were performed in the commercial software Ansys CFX 16 investigating different outlet geometries. The channel system was thereafter CNC milled in polycarbonat. Freshly isolated PASMCs from C57BL/6J mice were grown on glass bottom dishes for 7 to 10 days prior to experiments. During recordings, PASMCs were continuously perfused (0.5 ml/min) with Tyrode's solution, bubbled with either 21 % O₂ (normoxia) or 1 % O₂ (hypoxia), 5.3 % CO₂, rest N₂. A green 532 nm excitation laser line was used for resonance Raman spectroscopy during normoxia and

hypoxia. The LOC provided a fast change of the oxygen content and a stable low oxygen level of 2%. Details of the holographic SRI can be found in ref. [4].

III. CONCLUSIONS

It was possible to follow redox states of the mitochondrial biomarkers by resonance Raman spectroscopy. Time resolved phase images were registered by the holographic stimulated Raman system. The SRS system has high prospects for many investigations where movement, mechanical strength and biomolecular changes have to be imaged simultaneously without alteration or manipulation of the sample.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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533 - Modeling of deep brain stimulation

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I. INTRODUCTION & AIM

Deep brain stimulation (DBS) is an effective method for treating patients suffering from refractory neurological disorders. In DBS surgery, the stimulation electrodes are implanted into deep brain structures. To produce the desired effect and avoid side effects it is necessary to locate the electrodes with accuracy in the order of millimeters. This prevails also for the knowledge of the electrical stimulation field in a very complicated geometry and varying tissue conductivity.

The aim of this work was to provide understanding of the neuronal activation by stimulation and how the different properties of tissue and implantation affect the results.

II. METHODS

In this study, we created a finite element model to observe the results of electrical stimulation on the brain. Stimulation response was measured with the concept of the volume of tissue activated (VTA) [1]. Uniform 3D model and an atlas based 2D model were created to study the effects of stimulation parameters, encapsulation, inhomogeneous tissue types and anisotropy on the VTA. Encapsulation thicknesses ranged from 100 μm to 1000 μm , which covers most of the values found in previous studies. Encapsulation also included acute and chronic states [2].

III. RESULTS & DISCUSSION

Results show that the encapsulation had a significant impact on the VTA. As an example, 300 μm chronic encapsulation reduced the VTA by roughly 45% at -5 V amplitude compared to

non-encapsulated state. Relative VTA decrease was larger the thicker the encapsulation and the smaller the stimulation amplitude. Encapsulation growth within the first months after the implantation had an impact of requiring the stimulation amplitude to be increased by over 100%, to maintain constant VTA.

Modeling a misplaced electrode indicated that the monopolar stimulation is the most suitable option if the anatomical target is perpendicularly aligned with the active electrode. Suitability was defined by requiring the smallest stimulation amplitude and generating the smallest VTA. Small-scale target movement in the vertical direction with respect to lead increased the amplitude requirements and VTA drastically in monopolar stimulation and thus favoring the bipolar stimulation.

VTA quantification is a complex task and this study gives an insight into the effects of encapsulation, electrode misplacements and different electrode configurations affecting the efficiency of the treatment

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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548 - Predicting the Effect of Cell Morphology on Intracellular Strain and Stress

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I. INTRODUCTION & AIM

Cells respond physiologically to external physical stimuli, where cell morphology and focal adhesion density were reported to modulate the effect of substrate stiffness on internal cell tension [1]. Cell mechanics including cell-environment and cell-cell interactions play important roles in aetiology of diseases. Exploring these interactions experimentally is often challenging, and computational modelling offers a complementary approach of inquiry. Most earlier work did not explicitly consider the effect of inhomogeneity and morphology of the cell. This has led to inaccurate results for computational modelling of single cells. To overcome this limitation, a constitutive model capable of accounting for the inhomogeneity of the cytoplasm is considered here.

In this study, we propose a micromechanical and hierarchical approach to capture the contribution of the stress fibres (SF) to cell morphology and mechanical properties of the cytoplasm for 2D cell-substrate interactions.

II. METHODS

The 3D geometries of cytoplasm and nucleus of two fibroblasts with morphologies (elongated and spread) were reconstructed (ScanIP, Synopsis Inc, USA) from confocal micrographs of a cells cultured in 2D and stain for actin fibres (Phalloidon) and nucleus (Hoechst). Cell geometries were imported into ABAQUS 6.14 (Dassault Systèmes, Providence, USA) and combined with a planar substrate. Cell morphology and cytosol anisotropy were linked by micromechanical formulation using the Mori-Tanaka homogenization scheme [2], considered a cytosol with randomly distributed stress fibres for spread and elongated cell respectively, satisfying a continuum hypothesis [3], and cells were subjected to stretch ($\lambda = 1.1$) of the substrate ($E_{\text{Sub}} = 2$ and 20 MPa).

III. RESULTS

For the elongated and spread cell, respectively, stretched on the softer substrate ($E_{\text{Sub}} = 2$ MPa), the highest maximum principal strain was 0.070 and 0.085 in the cortex, 0.090 and 0.085

in the cytosol, and 0.040 and 0.045 in the nucleus, whereas the highest von Mises stress was 0.18 and 0.2 kPa in the cortex, 0.09 and 0.08 kPa in the cytosol, and 0.20 and 0.29 kPa in the nucleus. For the stiffer substrate ($E_{\text{Sub}} = 20$ MPa), the largest maximum principal strain was 0.07 and 0.085 (in cortex), 0.089 and 0.096 (in cytosol), and 0.040 and 0.051 (in nucleus), whereas the largest von Mises stress was 0.18 and 0.20 kPa (cortex), 0.090 and 0.092 kPa (cytosol), and 0.20 and 0.30 kPa (nucleus) for elongated and spread cell morphology, respectively.

IV. CONCLUSIONS

In the spread cell, peak strain and stress were higher in cortex and nucleus but either the same or lower in the cytosol when compared to elongated cell shape. The largest effect of cell morphology was predicted for the nucleus stress. Substrate stiffness had no effect on intracellular mechanics for the elongated cell, whereas some changes were observed for the spread cell.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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549 - Assessment of cerebral perfusion by monitoring of time-resolved diffuse reflectance and fluorescence during optical contrast agent passage

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I. INTRODUCTION

Early detection of secondary events which develop after traumatic brain injury (TBI) is a major target of neuromonitoring in patients treated in intensive care units. Typically, intracranial pressure is monitored in such patients and biomedical imaging techniques like CT, MRI and transcranial USG are applied. However, these methods are rather expensive and need transportation of the patients to imaging facility. Consequently, it is impossible to monitor the patient. Considering these limitations the optical methods based on near infrared spectroscopy (NIRS) were intensively tested as tools which allow potentially for assessment of changes in brain oxygenation and perfusion in critically ill patients [1]. These methods are based on illumination of the head with the use of near infrared light and detection of the light remitted from the tissue in a spot located typically 3-4 cm apart from the source position.

In last 20 years a methodology based on monitoring of diffuse reflectance during injection of an optical contrast agent was proposed and validated. The method allows to assess passage of the dye through the brain tissues. Indocyanine green (ICG) was used in these studies which is a relatively non-toxic contrast agent accepted in medical diagnostic purposes. Experiments on animals and clinical tests on humans showed that the analysis of the inflow and washout of the ICG leads to assessment of cerebral blood flow and cerebral blood volume.

The NIRS technique suffers from influence of the extracerebral tissues on signals measured on the surface of the head. Time-resolved spectroscopy is used in order to overcome this limitation. The technique is based on emission of picoseconds light pulses into the tissue and analysis of the distributions of times of flight of diffusely reflected photons during travel through the tissue under investigation. Analysis of the photons arriving at long times allows to obtain parameters related selectively to the changes in oxygenation of the brain tissue [2]. Monitoring of diffuse reflectance at single wavelength (related to the maximum of the absorption of the dye) and application of the time-resolved technique allows to obtain selective parameters related to the brain perfusion.

In the last 10 years we analyzed usefulness of the signals of the fluorescence light excited in the dye circulating in the brain tissue for assessment of the brain perfusion parameters. We extensively studied methodology of such measurements: the optimal dose of the ICG, the interoptode distance and positioning of the optodes [3]. In series of experiments on healthy volunteers we presented feasibility of the brain perfusion assessment with the use of ICG-passage based technique [4]. Furthermore, we carried out clinical studies in which the ICG inflow and washout parameters were related with the clinical condition of the patients with TBI [5]. Currently, we verify usefulness of multi-wavelength time-resolved monitoring of inflow and washout of the ICG in clinical application.

ACKNOWLEDGMENT

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550 - Educating a biomedical engineer to become a generalist or a specialist?

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II. INTRODUCTION

The master of science in biomedical engineering in KU Leuven builds upon more than 40 years of relevant research in various research departments in the Faculty of Engineering Science and in the Faculty of Medicine. This master resulted from the combination of two study options on biomedical engineering that existed originally in the master of science in mechanical engineering and in the master of science in electrical engineering. Courses from these two options were combined and integrated to create the master of science in biomedical engineering that started as an independent master in 2006. The master program aims to deliver interdisciplinary-trained biomedical engineers that can act as an integrator between medical specialists and technological specialists by understanding the medical needs and by translating them into engineering requirements..

III. IMPLEMENTATION

The program is designed such that a general and broad education in state of the art biomedical engineering can be combined with specialization in one specific area if the student wishes so. A common core of 48 credits offers a combination of basic medical courses (12 credits) and medical technology courses (36 credits) covering all major areas of biomedical engineering. These courses focus on the engineering aspects and link with the medical applications where relevant. Students can take up elective courses for a maximum of 33 credits and general interest courses (covering e.g. management, communication or logistics) are obligatory for 9 credits. Project based learning consists of a design course and the master thesis and both add up to 30 credits.

The elective courses have been grouped in four clusters: Biomechanics and tissue engineering, Medical devices, Information acquisition systems, Information processing software. This was done upon request from the students to create coherent packages of courses that allow for a deeper specialization

in one or another area. Furthermore, by selecting the topic of the design course and the master thesis students can complete a specialization, complementary to the general education that is offered by the common core and the general interest courses.

IV. OUTCOME AND APPRECIATION

This master of science in biomedical engineering enjoys a steady increase in students, both national and international since the master program is entirely offered in English, in the international city of Leuven. Combined with the ranking of KU Leuven (e.g. ranked 40 in Times Higher Education 2017 worldwide) highlighting the link between excellent research, this master program is considered by many international students as an attractive alternative to more conventional choices for a master e.g. in the UK. The number of students enrolled in the master program increased from 29 in 2007-2008 to 119 in 2015-2016. 70% of the students finish their study in the scheduled two years.

The alumni are satisfied with the master program [1]. They appreciate the professional approach of the professors, the variety of courses and the balance between theory and practice. A majority of 62% of the graduates found a job in the biomedical industry. The student evaluation indicated that the students highly appreciate the social relevance of their study. The Industrial Advisory Board, linked to this program, confirms the vision and goals [1]. They would like to see a stronger focus on entrepreneurship, which is being implemented as a general strategy of the Faculty of Engineering Science at KU Leuven. This biomedical engineering program shows that a combination of generalism and specialism can be obtained.

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551 - Heart kinetic deconditioning after the 60-days ESA-RSL head-down bed-rest assessed by wearable monitoring based on Ballisto- and Seismocardiography

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I. INTRODUCTION & AIM

Head-down (-6°) bed-rest (HDBR) generates cardiac deconditioning that simulates some aspects of a long duration space flight. The effects of 60-days HDBR were assessed by a non-invasive wearable heart kinetic (HK) monitoring method. The Kino-Cardiogram by Heart-Kinetics [1], is a novel technique based on calibrated and combined multi-dimensional Ballistocardiography (BCG) and Seismocardiography (SCG). HK was compared to phase-contrast (PC) MRI-derived stroke volume (SV). We hypothesised that HDBR would result in lower SV and lower HK.

II. METHODS

24 healthy males (mean age 28 ± 6) were enrolled in the ESA-RSL-BR study. Protocols were approved by the local ethical review boards and informed consents were obtained. A controlled breathing (CB) protocol (breathing at 7.5 breath per minute) was imposed while acquiring HK before (PRE) and after 58-days (HDT58) of BR, on the same day as a PC-MRI protocol to acquire golden standard measures. A miniature accelerometer was placed on the skin in the lumbar region to record the 6-degrees of freedom (6-DOF) accelerations. BCG, SCG, ECG, ICG and respiration signals were recorded using CARDIOVECTOR, a portable digital system for human space physiology research [2]. Accelerations components were calibrated, integrated, squared and combined with the Newtonian equations of kinematics to provide total heart kinetic energy (HKtot), the sum of HKrot and HKlin. PC-MRI aortic images (Siemens mMobigraph 3T) were obtained, and velocities integrated over the aortic lumen area to allow computation of SV.

III. RESULTS

After 58-days HDBR, compared to baseline values a significant ($p < .05$, paired t-test) decrease in SV (22%), was accompanied by a similar decrease in HKtot (27%) and HKrot (30%) but not in HKlin (See table).

	PRE	HDT58	Δ %
SV MRI (ml)	115 \pm 18	90 \pm 9*	-22
HKlin (m J)	4.1 \pm 0.1	3.2 \pm 0.1	N.S.
HKrot (m J)	9.6 \pm 0.6	6.8 \pm 0.6*	-30
HKtot (m J)	13.7 \pm 0.9	10.0 \pm 0.7*	-27

IV. CONCLUSIONS

This is the first study assessing HK as a marker of cardiac contractility together with PC-MRI during HDBR deconditioning. HKtot decrease was mostly due to a decrease in HKrot and associated with a similar decrease in SV. As this could not be seen with the linear BCG, this suggests the great advantage of HK over past BCG techniques [3]. The Heart-Kinetics technology utilized in this study for simulated space research has a great potential for its use in clinical trials.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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552 - Metabolic coupling between the endothelium and neurons in the neurovascular unit revealed using human organs-on-a-chips

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I. INTRODUCTION AND AIM

The neurovascular unit (NVU) is a gatekeeper for function and health of the central nervous system (CNS). The NVU is the interface between systemic blood circulation and the central nervous system CNS. The NVU lines the 400 miles of capillaries that course through the brain and spinal cord and is formed by a complex network of endothelial cells, astrocytes, pericytes, neurons and a basal lamina. A tightly regulated interplay of transport events and metabolic conversions in-between the microvascular endothelium, the perivascular and brain parenchymal cells is critical for brain homeostasis as well as pharmacodynamics within the CNS. The aim of this study was to gain a deeper understanding of the metabolic and proteomic coupling of the different compartments of the NVU under steady-state and under acute methamphetamine stimuli.

II. METHODS

To model the human NVU, we constructed and connected three microfluidic Organ Chips – two blood-brain-barrier (BBB) Chips on each side of a brain neuronal chip (Brain Chip) to model compound influx and efflux, respectively. The BBB Chip is a polydimethylsiloxane (PDMS) device with two compartments containing primary human brain microvascular cells and perivascular cells. The chip was made with standard processing conditions and incorporated a permeable PET membrane. The Brain Chips is a polycarbonate

chip containing primary human neural cells. We carried out a full proteomic and metabolic assessment (untargeted and targeted mass spectroscopy) of each compartment of the NVU.

III. RESULTS

This system revealed a metabolic contribution of the brain vasculature to neural metabolism and neurotransmitter synthesis. Additionally, methamphetamine was identified to reversibly alter barrier function and *in vivo* correlated metabolites of drug effect were identified in the constituting organ units.

IV. CONCLUSIONS

This NVU platform illustrates how cellular interactions can be revealed by decoupling an organ function into connected compartments using microengineering. The method offers a new avenue to identify metabolic pathways in-between the constituting cells. Furthermore, it may be used to carry out efficacy and transport studies of CNS drugs.

CONFLICT OF INTEREST

D.E.I. holds equity in Emulate, Inc. and chairs its scientific advisory board.

553 - Optical-fiber based tissue identification for surgical guidance

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I. INTRODUCTION

Deep brain stimulation surgery is now widely accepted as a therapeutic avenue for late-stage Parkinson's disease patients who do not respond anymore to standard medication (L-Dopa)[1,2]. The surgery is time-consuming and relies on precise positioning of the stimulating electrode with the help of stereotactic frames and microelectrode electrophysiological measurements. However, the pre-operative MRI, unless it is a 3T or more, does not show all the relevant details with high precision and the data is affected by the displacement of the brain when the skull is opened for surgery (brain shift). Considering the 5-7 millimetre size of the target (subthalamic nucleus, STN), any millimetre inaccuracy translates into poor outcome of the surgery (since it limits the stimulation power to avoid side effects). Here, we demonstrate the development and the validation of a new fibre optic tool that inserts into the stimulating electrode to accurately indicate in real-time the position of the leads in the brain during the surgery based on local tissue measurements. This has been validated *ex vivo* as well as *in vivo* in non-human primates.

II. METHODOLOGY AND RESULTS

A complete optical system including laser injection and the detector for collection has been constructed. We illuminate the tissue with white light and collect the backscattered light to spectroscopically identify the tissue using a strategy based on principal component analysis. Two optical contrast methods are used and validated: spectral reflectance but also coherent Raman, which permit very refined tissue identification thanks to vibrational contrast[3]. The optical system has been tested *ex vivo* on cortical matter, myelin, and different structures in monkey brain slices for their rapid and simple availability, but also on human brain tissue from the Brain bank at CRIUSMQ. Following this validation, algorithms to identify the tissue from

their optical signatures are used to trace the most likely insertion tract in the brain based on optical data. Tissue identification during surgeries on adult cynomolgus monkey (*Macaca fascicularis*) is shown to demonstrate the feasibility of the strategy *in vivo*.

III. CONCLUSION

This optical fiber-based system can identify tissue from within the DBS electrode during a surgery. This information is used to estimate the most likely insertion tract and should help the neurosurgeon position the electrode for better DBS surgery outcome.

COMPLIANCE WITH ETHICAL REQUIREMENTS

All experimental procedures were approved by the *Comité de Protection des Animaux de l'Université Laval* (#2013-128), in accordance with the Canadian Council on Animal Care's Guide to the Care and Use of Experimental Animals (Ed2).

All human tissue used was obtained according to the ethical standards of the institution.

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554 - Dynamic changes in the cardio and cerebrovascular measures due to random step-wise thigh-cuffs pressure

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I. INTRODUCTION & AIM

Although assessing cerebral blood flow regulation ('auto-regulation') following spontaneous changes in blood pressure has been widely used, repeatability of such measurements is often poor and is associated with the relatively low variability of blood pressure [1]. One way to provoke a moderate increase in pressure variability, without inducing much discomfort, is to use random inflations of cuffs around the thighs [2-4]. The aim of this study was to examine the effect of the step-wise changes in thigh-cuff pressure (TCP) on blood pressure, heart rate (HR) and cerebral blood flow.

II. METHODS

The 5 minutes long recordings of arterial blood pressure (ABP), cerebral blood flow velocity (CBFV), end-tidal CO₂ (etCO₂) and ECG were acquired during three separate occasions (12±10 days apart), from 20 young adult healthy subjects (aged 25.5±3.5 years, height 168.3±12.3 cm, weight 64.5±16.4 kg, BMI 22.6±4.5, SP 119.6±15.4 mmHg, DP 70.5±8.3 mmHg) in supine rest. ABP was recorded non-invasively with a servo-controlled finger cuff (Finometer), CBFV with transcranial Doppler ultrasound in the middle cerebral artery, etCO₂ from a capnograph. ECG was also recorded and used for detection of heart beats and computing beat average (mean) values of the recorded signals. TCP of 80 and 150 mmHg were applied at 20 pseudo-random intervals of 5, 10 and 20 s on two groups of 10 subjects (5 females each). The signals were sampled at 125 Hz (with an exception of the ECG signal which was sampled at 250 Hz) and stored for offline analysis. Transient changes of mean ABP and CBFV, along with HR and etCO₂, were observed at the onsets and offsets of the TCP signal.

III. RESULTS AND DISCUSSION

There is a clear evidence of autoregulation for both TCPs. Significant difference between 80 and 150 mmHg in the amplitudes of the signal responses to the onsets and offsets in mean

ABP and CBFV ($p < 10^{-5}$, Wilcoxon) and HR ($p < 10^{-3}$, Wilcoxon) were noted. Moreover, there is a notable asymmetry in the responses to onset and offset. There is a greater percentage increase in power of CBFV than for ABP at 150 mmHg but not at 80 mmHg. The former contradicts our expectation of auto-regulation, but reflects sharp and presumably passive increase at the onsets and offsets of TCP before autoregulation becomes active.

IV. CONCLUSIONS

TCP transients induce a regulatory response in heart rate and blood flow. Due to the complex passive and active physiological responses, inferences regarding autoregulatory responses require some caution.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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556 - Brain-state dependent brain-stimulation with real-time EEG-triggered TMS

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I. INTRODUCTION

The brain functions as a large scale network, which requires a balance of integration and of differentiation, and a balance of stability and reactivity. When there is a dysfunction in part of the network, for example following an ischemic stroke, the entire system is affected, leading to disproportionate disability. Neurorehabilitation is a slow and difficult process and recovery is often incomplete despite intensive personalised care from specialised therapists. The promise of EEG-controlled non-invasive brain stimulation is that it enables a coupling with brain dynamics and a therapeutic modulation of brain networks using a closed-loop approach tailored to the individual brain.

II. METHODS

Here, a real-time EEG-triggered TMS neuromodulation method is presented, comprising of (1) a commercially available TMS compatible EEG amplifier system that streams the EEG signal to a dedicated processing system through a digital link with a latency < 3 ms; (2) spatial and temporal filters of the distributed EEG signal in order to isolate the signal of interest using anatomical and functional localisation; (3) a custom-built millisecond accuracy digital signal processing system based on Mathworks Simulink Real-Time that can detect instantaneous brain state based on oscillatory phase and power using an autoregressive forward prediction method in order to trigger a TMS pulse whenever a pre-defined brain-state occurs..

III. RESULTS

We present methodological data that validates the efficacy of the phase targeting of the method as well as neurophysiological results from mu-rhythm triggered single and repetitive TMS experiments that show, firstly, that different oscillatory phase states correspond to different local corticospinal excitability states and, secondly, that high-frequency stimulation targeted to such differential excitability states induces specific long-term plasticity effects. These results suggest that a temporal targeting of non-invasive brain stimulation using a real-time closed-loop method may enable new therapeutic approaches with the expectation of more reliable and specifically targeted modulation of pathological brain networks. Clinical trials are currently under way with patients suffering from major depression where the TMS pulses are triggered by the individual brain-state in an analogous fashion to the results from the motor system.

IV. CONCLUSIONS

In order to make such an approach widely available, a system is proposed whereby a EEG-analysis and TMS-triggering system is connected between existing EEG amplifiers and neurostimulation systems. Such a system can eventually be miniaturised and the EEG recording and real-time processing integrated to a standard TMS coil as an upgrade path for clinical TMS systems.

557 - Accreditation of Biomedical Engineering Programs in Hungary

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I. INTRODUCTION

In Hungary there is one biomedical engineering program. It is a master program (MSc) offered by Budapest University of Technology and Economics together with Semmelweis University of Medicine. Higher education institutions and programs are accredited by the Hungarian Accreditation Committee (HAC) established in the country's first higher education law in 1993. During program accreditation a given program is assessed at all institutions. HAC asks for a detailed self-evaluation then forms Visiting Committees that perform on site investigation. On average, institutions are evaluated once in eight years.

II. ACCREDITATION AT NATIONAL LEVEL

Programs are first evaluated by HAC at the phase of *establishment*. Establishment means creating the frame of the program (aim, basic knowledge and competencies students will acquire, etc.) The establishment of a program ends up in a *Training and Output Requirement*, issued by the Ministry of Education. When an institution wants *to start* an established program it has to ask for the evaluation of HAC again. This time the document contains the subjects taught and the name of the lecturers as well as all rules of study. It must also be shown that the planned study program matches the related Training and Output Requirements.

III. ACCREDITATION AT INSTITUTIONAL LEVEL

Quality management of study programs is implemented according to the *Codex of Education* of Budapest University of Technology and Economics. Both professional and administrative control belongs to each study program. When the university decides to start a new program first a professional committee responsible for it has to be formed.

Professional control means the approval of subjects and their program as well as the biannual review of BSc and MSc programs by the relevant professional committee. This committee

is also responsible for quality management of the program. The committee regularly checks the harmonization of subjects, the progress of students, the experiences of exams, theses and final exams. The committee integrates the opinion of external experts (representatives of employers and professional organisations), professors, lecturers and students.

Administrative control means the perpetual monitoring of the resources needed for the study program: progress of students, administration of studies, availability of lecture rooms and installation of laboratories, teaching load of staff members.

The Faculty assures the professional control of study programs. For joint study programs the university assigns a gestor faculty.

The request for establishing or starting a study program submitted to the University Senate contains the data according to the instructions of HAC as well as the following extra items:

- demonstration that the necessary human resources are available,
- summary of all professional duties of professors and staff playing important role in the study program (two third of the teachers can be responsible for maximum 25 ECTS credit worth subjects, for one third the maximum allowed is 35 ECTS credits),
- demonstration of the availability of the necessary infrastructure,
- the financial details,
- demonstration that textbooks are available for the subjects.

The quality improvement concerns the program of subjects, the textbooks, laboratory experiments and harmonisation of subjects.

The department is responsible for the subjects. The head of department appoints the person in charge of the subject. This person must have a PhD and must be a full-time employee. The professional committee reviews the subject file that is approved by the Faculty Council.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

558 - The Value and Process of Accrediting Undergraduate Clinical Engineering Programs

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I. PRELIMINARY REMARK

Now is the time to promote discussion regarding the value and process of creating accredited undergraduate programs in clinical engineering (CE). A pathway to realization of such programs eventually offered globally and accredited by the Accreditation Board for Engineering and Technology, Inc. (ABET, Inc.) is proposed. The two groups interested in having this discussion and perhaps in the eventual successful launching of such programs are 1) the IFMBE Clinical Engineering Division (CED) and 2) the IFMBE Education & Accreditation Committee headed by Ernesto IADANZA (Italy, 2015-2018) and Siew-Lok TOH, (Singapore, 2015-2018) respectively. Of course, it is possible that by the end of this discussion we will decide that the current system of providing engineers to work in clinical settings although haphazard, may be working just fine and that there is no reason to create or promote undergraduate clinical engineering programs. I suggest that IFMBE decide to go forward or not, no later than the 2018 IUPESM World Congress on Medical Physics and Biomedical Engineering.

II. INTRODUCTION

Currently, over 250,000 people in the USA die in hospitals due to medical errors each year [1,2]. How many deaths in World are due to Medical Error? Could Clinical Engineers play a role in reducing hospital deaths due to Medical Errors? The maturation of biomedical engineering programs in the United States is advancing rapidly, producing practitioners working in academia, industry and in the health care professions as academics, engineers, physicians and other professionals devoted to knowledge creation, medical device design, and delivery of healthcare. Very few graduates of undergraduate biomedical engineering programs work in industry immediately after obtaining their degrees unless they have had some internship or Co-Op experience. Industry, for some time, has been insisting on the Master of Science degree in biomedical engineering as the entry-level degree, unless the applicant has had a significant industrial internship or Co-Op experience. A few biomedical engineering undergraduates, upon receiving their B.S. degree, work in hospitals or shared-service organizations, but they often lack experience in critical clinical environments to be effective immediately. They need additional training to become effective. According to the most recent definition of a clinical engineer by the American College of Clinical Engineering (ACCE) used at the recent Global Clinical Engineering Summit in Hangzhou, China on 23 October 2015, "*A Clinical Engineer is a professional who supports and advances patient care by applying engineering, economics, communication and managerial skills to healthcare technology.*" - modified ACCE definition, 1992 [3].

III. STATUS OF CLINICAL ENGINEERING IN THE UNITED STATES TODAY

Although there are 97 accredited Bioengineering or Biomedical Engineering undergraduate programs in the United States today [6], there are no undergraduate programs offering clinical engineering degrees. In fact, there is only one Master of Science degree program and only eight (8) accredited biomedical engineering technology programs in the United States [6]. In addition, the Biomedical Equipment Maintenance Technician Training Program (BMET) of

the Defense Health Agency provides training for U.S. Service men and women, but these individuals face difficulties when trying to transition to bachelor degree programs.

IV. WAY FORWARD

According to the American Hospital Association, there are 5,724 hospitals in the U.S. [4] and 914,513 total staffed beds in U.S. Registered Hospitals [5]. Traditionally, Clinical Engineers (CEs) have played a critical and expanding role in health technology management and assessment. More recently, CEs are ideally positioned to be involved in integrating medical devices into electronic health records. CEs can also "help drive changes in clinical workflows at health organizations: planning, policies, acquisition, management, strategies, investments, risk, design of clinical environments and others. This is accomplished through the interoperability of devices and EHRs so that care everywhere (in-patient, clinic-based and mobile health) profoundly allows redesign of care delivery." [7] Sloane et al. [8] suggests that the profession needs practitioners with new skillsets - both for emerging graduates and people at all stages of their careers.

Now is the appropriate time to consider a) the realm of knowledge required for CEs to be successful in clinical environments and b) more formal educational vehicles needed for achieving these outcomes, possibly through accredited undergraduate and graduate educational programs [9]. Accrediting these programs will provide an independent structure for overseeing the development and evolution of the CE curriculum and in conjunction with academic institutions offering the CE programs and the relevant professional societies, e.g., American College of Clinical Engineers.

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559 - Training Contents of Continued Education for Accredited Clinical/Biomedical Engineering in Taiwan

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In order to implement the national professional accreditation system, the Taiwanese Society of Biomedical Engineering (TSBME) has offered professional accreditation related to medical fields for engineering technicians in Taiwan. Based on working environments, the accreditation is classified as three types: Clinical Engineer, Medical Equipment Technician and Biomedical Engineer, which is valid for three years and can be extended when he/she is qualified for an extension. In order to keep the profession of clinical/biomedical engineers and to encourage their advancement, 60 continued education credits, including more than 10 credits every year, are required within 3 years to maintain the accreditation. The TSBME provides many different continued education advancement workshop or education training courses, including “Health Technology Hazards”, “Medical Device Reporting Events Sharing”, “Medical Device Adverse Events Investigation & Management”, “Evidence-Based Maintenance (EBM)”, “Healthcare Risk & Patient Safety”, “Risk Management & Incident Investigations

(ADR)”, “Clinical Engineering (CE) Benchmarking”, “The Patient Safety Role of Clinical Engineering at Medical Center”, “Enhancement of Medical Device Post-market Surveillance”, “Empirical Basis Medical Device Management and Repair Analysis Operation in Hospital”, “The Configuration and Management of Nurse Call and Patient Monitoring System Integration”, “Adverse Events in Multiple Medical Systems Integration”, and “Patients Safety and Medical Device Evaluation Management”. After after-class questionnaire review, 92% of participant showed more understanding of medical device/instrumentation handling procedure; 88% of which agreed the importance to proactively provide experience sharing to medical device/instrumentation maintenance and management to the clinical engineers and specially the medical equipment technicians; 94% of which were satisfied to the conference topics, and 94% of which were satisfied to the conference content.

560 - Accreditation and Certification in Biomedical Engineering in the Czech Republic

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The aim of the paper is to inform about the system of undergraduate, postgraduate, and lifelong education in the fields of Biomedical Technology and Biomedical Engineering in the connection with the Act No.96/2004 Coll. on non-medical health service occupations and related regulations. The Act and related regulations define position of technical personnel in the health service system. This legal regulation distinguishes the following categories of technical personnel: another professional, health service professional with technical competence (biomedical technician (BMT) – B.Sc., biomedical engineer (BME) – M.Sc.), and health service professional with specialized competence (clinical technician – B.Sc., clinical engineer – M.Sc.). There exists a system of accredited medical institutions that can perform defined types of postgraduate and lifelong education. As part of lifelong education, credit system was introduced that specifies activities for which credit points can be awarded. The Act No. 96/2004 Coll. specifies the following types of educations: undergraduate education, i.e. bachelor and master study (minimum requirements are given by the official regulations No. 39/2005 Coll.); accredited qualification course; specialized education; lifelong education (this education is obligatory for all health service professionals and also for those working in the category another professional in health service).

Basic rules and requirements concerning undergraduate (Bc. and M.Sc.) and postgraduate (Ph.D.) study in general are defined by the Higher Education Act No. 111/98 Coll. and its amendment No. 137/2016 Coll. In this context, it is necessary to stress that in addition to standard accreditation of a study programme or field of undergraduate education performed by the Accreditation Board of the Ministry of Education, Youth and Sports of the Czech Republic (MEYS), the biomedical study programmes or fields must get the accreditation of the Ministry of Health Care of the Czech Republic (MHC) in the sense of the Act No. 96/2004 Coll. and related regulations. The graduates of these accredited fields get the certificate of qualification to perform health service occupations according to the Act No. 96/2004. The BME (BMT) qualification can be obtained by graduation in the Biomedical Engineering field of study (BME) or the Biomedical Technology field of study (BMT). Graduates of another bachelor or master study programme in electrical engineering can obtain the qualification for health service professionals with technical competence if they pass the accredited course in Biomedical Engineering (for M.Sc./Eng.) or Biomedical Technology (for B.Sc.) The accreditation for these courses

is delivered by the MHC. The conditions for this accreditation are defined in the official regulation No. 424/2004 Coll.

The minimum requirements on study programs to acquisition of technical competence for non-physician health care professions (including biomedical engineering) are defined by legal regulations (decree No. 39/2005). It was prepared by the MHC in agreement with the MEYS. This decree incorporates corresponding regulations of European Community and modifies minimum requirements on study programs leading to acquisition of technical competence for non-physician health care professions. It is necessary to stress that the MHC accredits only those study programmes satisfying the requirements. Then the graduates are allowed to certain defined positions in the hospitals and health care institutions. Graduates of other study programmes must attend specialized postgraduate courses in biomedical engineering. The specialized technical competence for clinical technicians and clinical engineers can be obtained by passing the specialized education and training finished by official examination. The examination board is appointed by the MHC. This specialized education and training can be provided only by those institutions that have the accreditation from the MHC. The Clinical Engineering is the specialized education and training for BMEs and the Clinical Technology for the BMTs.

The duty of lifelong education in the health care professions is defined by the Act No. 96/2004 Coll. The regulations No. 423/2004 Coll. and No. 321/2008 Coll. describe in detail the forms of lifelong education and also the credit system. It is possible to acquire credit points for participation in the following activities: innovation course; seminar; workshop; placement at specialized institution; congress; conference (international activities are awarded by higher number of credit points). Active participation is awarded by more credit points – these activities include: paper or poster presentation at a congress, conference, seminar or workshop; writing a journal article, educational activity (lecturing), research, development of a methodology. Each activity must be recorded in the personal certificate of specialization. This information serves as a basis for application of registration or registration renewal.

561 - Accreditation of Biomedical Engineering programs in Singapore and South East Asia

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An increasing number of Biomedical Engineering (BME) programs worldwide are obtaining accreditation under the Washington Accord. Singapore and Malaysia are the only two signatories with full rights of participation in the South East Asia region, while the Philippines appear in the list of provisional signatories. The approach used by the Washington Accord is an outcome-based one. Programme seeking accreditation must provide compelling and quantitative evidence of achievement of a predetermined set of program educational objectives (PEOs) and student learning outcomes (SLOs). SLOs are broad statements about what a student will know or be able to do as a result of a given educational experience.

In this talk, a brief overview of the accredited BME program in the South East Asia region will be followed by an in-depth analysis of the accreditation process of the undergraduate BME program at the National University of Singapore (NUS). The outcome-based nature of the accreditation process imposed the establishment of a series of educational and administrative practices that have far reaching effects on the quality of the NUS BME program. For example, one of the key

and most difficult aspects that need to be addressed is how to measure the achievement of the SLOs. The adopted solution involves measuring the achievements of the module learning outcomes (MLOs) of each of the modules offered within the program and argue that, collectively, all the MLOs contributed to the achievement of all the SLOs. To do so, every lecturer in the department has to reevaluate the module learning outcomes (MLOs) of his/her own module and to identify, within the assessment process of the course, a quantitative measure of achievement.

The reevaluation of the MLO described above is just one of several practices that is introduced to meet the stringent accreditation criteria. In general, these practices force a positive and constructive reflection of nearly all the educational activities within the program.

562 - The Relevance and Challenges for the Accreditation Process of the Clinical Engineering programs in Latin America

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According to the Australian Engineering Society, “Clinical engineering is a specialty within Biomedical engineering responsible primarily for the application and implementation of medical technology to optimize health care delivery”. In other words, they defined the main roles of clinical engineers to include training and supervising biomedical equipment technicians, working with governmental regulators on hospital inspections and serving as technological consultants for other hospital staff [1], [3]. The globalization and the emergent technologies implemented at the National Health Services in Latin America changed this time-horizon over which clinical engineers can influence the trajectory of bio medical innovation and they can establish a link between product originators and end-users. The new generation of clinical engineers is able to advise medical device producers regarding innovations and design new medical devices and improvements based on clinical experiences, as well as monitor the progression of state-of-the-art devices in order to redirect hospital decisions. According to the last publication in 2015: “Designing a Career in Biomedical Engineering” by Engineering of IEEE/EMBS Society, a biomedical engineering degree “typically requires a minimum of four years of university education”. The program must have both tangible and intangible components. “The tangible components mentioned include the science as well as engineering design and the intangible components, include the “soft skills,” such as: teamwork, practical experience, leadership, entrepreneurship, speaking, and writing—essentially a well-rounded education preparing the student for a wide variety of opportunities and challenges in life and career. Following this, the biomedical engineer may assume an entry level engineering position in a medical device or pharmaceutical company, a clinical engineering position in a hospital, or a sales position for a bio-materials or biotechnology company” [4]. The BME job market

is still small in LA, however the Clinical Engineering field is growing regarding the emerging technologies at the clinical environment and the promotion of the used of IoT for developing innovative medical devices and the regional governments are promoting the integration of new technologies at the national health services. Opportunities are greatest for clinical engineers with industry or clinical if the biomedical component in their education is of high quality [1], [2].

In order to save job opportunities, it is essential to establish solid and high quality Clinical Engineering programs that can be accredited by international agencies in Latin American region. In this paper the relevance and the challenges for the accreditation process of clinical engineering programs will be presented. In a competitive healthcare environment, the accreditation process is relevant for the academia and for the future Clinical Engineering; programs can have a marketing benefit for promoting new job opportunities [2].

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563 - Continuous Quality Improvement through Accreditation: Biomedical Engineering Program at The Hong Kong Polytechnic University

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Hong Kong's undergraduate education underwent a major change from 3-year to 4-year curriculum in 2012. Despite our 3-year Biomedical Engineering program being accredited since 2005, we had to seek new accreditation of our 4-year program (same for many other engineering programs in Hong Kong) from the Hong Kong Institution of Engineers (a signatory of the Washington Accord) [1–3]. In fact, the University's overall 4-year curriculum structure [4] and the accreditation criteria [5] had great impact on our curriculum design. An important consideration of the accreditation is the quality of our graduates as defined by the program outcomes (which are consistent with the graduate attributes stipulated by the Hong Kong Institution of Engineers) [5]. In addition to the outcomes measurement, another important consideration is the process of continuous quality improvement through feedback from various stakeholders (e.g., students, alumni, employers, academic advisors, and accreditation body). In this presentation, I will share our experience in outcomes measurement and feedback process. For

outcomes measurement, both direct (course-embedded assessment) and indirect (survey) measures have been used. For feedback process, formal channels have been established to engage the stakeholders. I will give specific examples of major changes in our curriculum over the past five years.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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564 - Unevenness metrics for carotid artery characterization

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I. INTRODUCTION & AIM

Strokes are the leading cause of mortality and morbidity in the western world. An early diagnose of this cardiovascular disease is crucial to minimize the short and long time effects of the disease both in individuals and in the population.

Currently, the preferred pre-surgery diagnostic method is computed tomography angiography (CTA). Manual measurement of the lumen minimum and average diameter is measured and the stenosis percentage calculated. This manual procedure is prone to intra and inter-operator errors and its' repeatability is hard to achieve. Therefore, there is the need not only of new methods for the artery automatic segmentation but also of new metrics describing the gravity of the atherosclerotic lesion.

II. METHODS

The patient database was composed of 23 patients that underwent CTA for the carotid arteries assessment. They represent a cohort that encompasses different CTA machines, imaging methods, contrast agents and various stenosis degrees and atherosclerotic morphologies. Using the algorithms previously developed in our group, the artery trees were extracted. Taking the lumen area in each slice, three different metrics were calculated: (i) Root-mean-square level (RMS), (ii) standard deviation (STD) and (iii) unevenness (UNEV, a metric based on the study of the railway tracks wear and tear). UNEVs' formulation

is: $\sqrt{(\sum((Area')^2))/n}$ (*Area'*: derivative of the lumen area with respect to the slice; n: number of samples per patient). These metrics were then plotted against the hand-calculated stenosis level and the R^2 value obtained from their linear fitting.

III. RESULTS & DISCUSSION

The final R^2 results for the aforementioned metrics are: for RMS 0.081, for STD 0.0223 ,and for UNEV 0.0195. Out of the 46 carotid arteries (belonging to the 23 patients) only for 21 the radiologist hand-calculated the stenosis percentage. The remaining 25 arteries were healthy or their stenosis level did not represent a danger for the patients.

The three metrics here studied do not represent correctly the atherosclerotic burden. This can be attributed to multiple reasons, such as the stenosis is more associated with the morphology of the plaque (components and their distribution) than we assumed, the metrics are not able to distinguish between the common carotid and the internal carotid, overestimating the stenosis, or a simple occlusion leads to the wrong segmentation of the artery.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

565 - Implantable microelectrodes - actual and foreseeable limits for refinement of stimulation selectivity

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I. ABSTRACT

Neural implants are technical systems that interface with neural target structures to restore lost functions or overwrite electrical patterns in neuronal diseases. Success stories include cochlear implants to restore hearing, spinal cord stimulators to alleviate chronic pain and deep brain stimulators that treat symptoms of Parkinson's disease. Even though applications deserve tailored electrode arrays to selectively interface with neuronal networks in the target tissue, they share target specifications like biocompatibility of materials and longevity of components and systems.

High-density electrode arrays have been widely used in in-vitro applications to study and alter cellular activity down to sub-cellular level. This allows a highly selective and specific targeting on single neurons in close proximity. However, in neuro-prosthetic brain-computer-interface applications further

constraints lead to a tradeoff between selectivity, efficiency and reliability. For instance, targeting deep neural layers, inflammatory tissue reactions, displacements of the device or corrosion of the electrodes become more important factors than temporal and spatial resolution.

Therefore, micromachined neural probes based on flexible polymer materials can become an alternative to commercially available silicon based microsystems for precision mechanics based probes in clinical applications. The use of clinically established materials and laser-structuring as relatively new technology in the context of neural interfaces will be introduced on the example of epicortical electrode arrays for epilepsy diagnosis and brain machine interfaces. Micromachined polyimide-based electrode arrays for peripheral nerve interfaces to treat phantom limb pain and to provide sensory feedback in hand prosthesis control are presented as an example for optimized devices matching the essential requirements of certain scenarios.

566 - Requirements to commercialize continuous non-invasive blood pressure technologies

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I. BACKGROUND

Several companies have recently focused on improving cuff based non-invasive blood pressure measurement technologies. They provide additional trend information between determinations using other physiological signals.

There also has been research to completely abolish the use of cuff based measurements, and provide calibration by different means.

A total of 16 different methodologies have been reviewed to measure blood pressure continuously without the need of invasive measurements.

Most of these technologies do not yet have the required accuracy for use during hospital care. They do not allow use for direct intervention by means of drugs or other therapy.

In addition, most of these technologies are not robust enough to avoid false readings, and be specific to changes in blood pressure only.

II. REQUIREMENTS

The clinical area where continuous measurements are most valuable are those places in the hospital where blood pressure measurements are done with a large interval in between relative to the hemodynamic stability of the patient.

In post-surgical conscious patients, there is especially a challenge in assessing at short intervals the blood pressure due to inconvenience to the patient.

Customer feedback indicates that additional technologies that are integrated in already existing components attached to the body will be easiest accepted.

When claiming a non-invasive blood pressure parameter accuracy, it must be validated according to a very strict well defined protocol. Some of the new technologies might not fall within the scope of these standards when only claiming them to be a trending index related to hemodynamic state changes. However, in practice a high commercial value of a continuous noninvasive parameter is only guaranteed when complying to these regulatory standards.

For cuff based measurements this requires relative to a lot of other physiological parameters a very extensive set of clinical tests with large variability in patients, patient state and cuff size.

III. METHODS

A clinical test protocol for validation of a traditional NIBP measurement system (E-PSM module, GE Healthcare) was made in accordance with the guidelines provided by the most recent International Organization for Standardization (ISO) 81060-2:2013 [1].

IV. RESULTS

38 Infant and neonatal subjects (a total of 328 determinations) were measured with SYS/DIA/MAP difference to invasive pressure reference of resp 0.8, 0, -0.2 mmHg with a std of resp 5.3, 2.4, 2.4.

V. CONCLUSIONS

The NIBP performance evaluation conforms to the ISO 81060-2 standard for the patient groups neonate and infant.

The mean and standard deviation of the errors were calculated separately for both subject populations. The device has passed the test per the standards when the mean error was within +5 mmHg and the standard deviation is <8 mmHg.

CONFLICT OF INTEREST

The author is an employee of GE Healthcare. This company is also the designer of the system described.

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568 - A subject-specific sEMG model of the first dorsal interosseous incorporating muscle fiber direction assessed through diffusion tensor imaging

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I. INTRODUCTION & AIM

Electromyography (EMG) is a fundamental tool in the investigation of processes underlying muscle activation and its alterations under different conditions, including pathological states. One of the most frequent targets for investigation is the first dorsal interosseous (FDI) muscle of the hand, given its important role in the precise movements of the hand, participating in both index finger flexion and abduction.

In this context, a realistic EMG mathematical model of the FDI can shed light on the influence of different structural and constitutive factors on the signal recorded at the skin surface, allowing for a more precise and thorough interpretation of these signals.

Here, we propose an anatomically-based finite element model to simulate motor unit action potentials detected at the skin surface (sEMG) during activation of the FDI. This model takes into account hand geometry and detailed FDI architecture including muscle fiber direction.

II. MATERIALS AND METHODS

Conventional magnetic resonance imaging (MRI) was used to assess general anatomical characteristics of the hand. Subjects were positioned lying, face down, in a Philips 3T Achieva scanner. Their dominant hands were positioned prone on a purpose-built rig in a 16-element transmit/receive radiofrequency knee coil. The MRI compatible rig was engineered to reduce involuntary hand motion during scanning. The acquired MRI data for the hand at rest were segmented into distinct tissues (bone, muscle, fat, skin) and a three-dimensional computational model of the hand was constructed. A finite element model was then elaborated with different dielectric properties associated with each tissue [1].

Diffusion tensor imaging (DTI) was used to assess specific FDI architectural details. Immediately after the anatomical MRI and using the same experimental arrangement, DTI data were acquired for the hand at rest. A deterministic fiber tracking approach, after motion and eddy current correction [2], was employed to estimate FDI muscle fiber direction. In the finite element model, the estimated fiber tracts were then used to account for muscle anisotropy, through the attribution of an anisotropic electrical conductivity to the FDI, and to determine the

propagation direction of muscle fiber action potentials. EMG detected at an array of electrodes located on the skin surface directly above the FDI were then simulated [3]. Motor unit action potentials (MUAPs) were simulated as the summation of single fiber action potentials detected during propagation of intracellular action potentials. Muscle fiber start-up and end-effects were incorporated at the fiber end-plate and neuromuscular junction respectively. Action potentials simulated using the subject-specific model were then compared with MUAPs experimentally recorded from the same subject. Surface EMG data were recorded and decomposed into constituent MUAPs using the precision decomposition EMG system (Delsys, Inc.)

III. RESULTS AND DISCUSSION

The approach proposed provides a basis for realistic subject-specific surface EMG models incorporating details of the hand anatomy and FDI muscle architecture. In particular, use of fiber tracking from the DTI data allowed fiber direction to be incorporated to enable accurate simulation of the direction of action potential propagation and tissue anisotropy. Simulation results for a specific subject displayed a variability in MUAP morphology that compares well to the experimental results recorded for the same subject. Indeed, signals simulated with our model incorporated alterations in shape which are not captured in simple analytical models, demonstrating its potential in providing insight into muscle activation under normal and pathological conditions, and the specific contributions of muscle architecture and fiber direction to the surface EMG signal.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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569 - Mid-IR spectroscopy as a diagnostic tool for real time in-vitro tumor classification: A preliminary study

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I. INTRODUCTION & AIM

Women with suspected early-stage Gynecologic cancer undergo surgical procedure that excises tumor samples from suspected areas to help in the clinical decision-making process. A common strategy is to perform a 'frozen section' histological analysis, which is a crude but rapid test.

The sensitivity of the 'frozen section' test is in the range of 75% to 100% and the specificity is in the range of 80% to 100% [1]. To increase the accuracy of this rapid test, additional measures of malignancy need to be available during the clinical decision-making process without an increase of the testing time.

The mid-IR ATR FTIR spectroscopy is a simple, rapid and sensitive technique that provides information about changes in the fundamental molecular structure. Hence it has the potential to differentiate between malignant and benign tumors.

The objective of the current study was to explore the potential of mid-IR ATR-FTIR technique in improving the accuracy of pathology evaluation during surgical procedure, while enhancing the sensitivity of conventional 'frozen section'.

II. METHODS

The study was approved by relevant ethics committees and was conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent.

18 samples extracted from suspected tumors were tested using an ATR-FTIR system (Arcoptix Rocket 2-12 μ m and PIKE HATR model). Mid-IR absorption spectra were measured and analyzed. In parallel, 'frozen section' and histopathological results of these samples were used to develop a discriminant model using multivariate classification methods.

III. RESULTS & DISCUSSION

Preliminary results of our study suggest that measured spectra of malignant and benign tumors differ from each other.

Our model demonstrated that the ATR-FTIR technique was able to correctly differentiate between malignant and benign tumors with 100% sensitivity and 93% specificity.

IV. CONCLUSIONS

The mid-IR ATR-FTIR technique was able to discriminate between malignant and benign tumors. Thus, it has the potential to be used as an additional or alternative technique to the 'frozen section' test during the clinical decision-making process. Further study is needed to support this finding.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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570 - Free water elimination and mapping from diffusion tensor imaging (DTI) in chronic schizophrenia

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I. INTRODUCTION & AIM

Diffusion tensor imaging (DTI) acquisitions allows the comparison of diffusion characteristics in vivo and gives a unique insight into tissue structure and pathology. However, a limitation of DTI post-processing is the assumption of a Gaussian distribution of diffusion in neural architecture. Free water modelling aims to address this issue, and we present the second application of FA of tissue and free water mapping.

II. METHODS

Diffusion weighted data (64 directions, $b=1300$ s/mm², Siemens 1.5T) was acquired for 19 participants (14M,5F, Mean-Age=37±10) with chronic schizophrenia and 19 controls (14M,5F, Mean-Age=39±11). Tract Based Spatial Statistics (TBSS) using threshold-free cluster enhancement (TFCE) was performed on fraction anisotropy (FA) from standard DTI data and freewater fractional anisotropy in tissue (FA_T). The freewater maps were generated using a bi-tensor model implemented in house using Matlab software (v7.11.0). Median FA and FA_T were extracted from regions of interests (namely the splenium, body and genu of the corpus callosum) and examined their relationship (Pearson's coefficient) to illness severity (GAF, SANS, SAPS), duration and the number of psychotic episodes.

III. RESULTS

The schizophrenia group showed widespread increased cerebral free water compared to healthy controls, overlapping with previously reported areas of decreased FA ($P<0.05$).

Focal areas (including the genu and splenium of the corpus callosum) demonstrated decreased FA in the presence of normal free water. Median tissue-FA in the splenium showed a proportional relationship with positive symptoms

(SAPS)($r=0.55$, $p=0.037$), unlike standard FA which did not correlate with any clinical assessment tools.

IV. CONCLUSIONS

Our findings are broadly in agreement with larger N Number studies demonstrating reductions in FA_T, with significant reductions in the body of the corpus callosum when compared with healthy controls [1]. However, we did not demonstrate significant changes in the posterior thalamic radiation bilaterally, the anterior limb of the internal capsule bilaterally and genu[1]. Free water increases are associated with neuroinflammation, atrophy, low dendritic quantity, low cell density, or a breakdown in the cellular membrane and any combination of these will skew a standard DTI assessment, which may explain the inconsistencies in DTI studies in schizophrenia to date[2]. By compartmentalizing freewater we can derive a more precise map of white matter degradation using FA_T. Our correlation with positive symptoms suggests that FA_T may be more specific to active pathophysiological processes generating symptoms in schizophrenia.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS

Ethical approval was obtained from the National University of Ireland Galway and University College Hospital Galway research ethics committees

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571 - Mid IR water spectrum estimation in biopsies: significance for in-vitro tumor classification during surgery

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I. INTRODUCTION & AIM

Currently, rapid clinical classification during surgical procedure relies on 'frozen section' histological analysis, which is a crude but rapid test.

Attenuated total reflection Fourier-transform infrared (ATR-FTIR) spectroscopy allows the objective classification of biological material on a molecular level. Previous studies have shown its potential in categorizing cancer and benign tumor in different tissues [1].

Infrared spectroscopy of wet tissue is challenging as prominent IR absorbance bands of water mask the absorption bands of other molecules in the measured sample. The accuracy of water spectrum subtraction has significant implications for accuracy of tumor classification algorithm.

The objective of the current study was to establish an ATR-FTIR data analysis protocol as a basis for high accuracy classification algorithm.

II. METHODS

The study was approved by relevant ethics committees and was conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent.

Samples from biopsies of suspected tumors sites were measured by the ATR-FTIR system (within 30 minutes of excision) while other samples from those biopsies underwent 'frozen section' histological analysis. Absorption spectra were calculated using measured spectra of the biopsies and the measured baseline spectrum of the system. Both spectra were measured within less than one minute.

Water content in each absorption spectrum was estimated using the height of a distinct water absorption band $\sim 3300 \text{ cm}^{-1}$. Water spectra of each sample were estimated using linear regression and partial linear regression analyses (PLSR) between the estimated water content and the measured spectra.

III. RESULTS & DISCUSSION

The estimated water content of the measured tissue varied over time (the tissue dried out in the open air) and upon application of pressure to the measured tissue that increased the water content at the measurement interface.

The estimated water spectrum in the samples, using either estimation method, was significantly different from known or measured spectra of saline solution. We used it to calculate "dry tissue" spectra and to develop a discriminant model for sample classification into benign/cancer classes.

Preliminary results show that the ATR-FTIR technique correctly differentiated between malignant and benign tumors with 96% accuracy.

IV. CONCLUSIONS

High accuracy tumor classification, during surgical procedure, was achieved using mid-IR spectrum of biopsies following water spectrum subtraction. A reliable water spectrum was estimated using either linear or PLS regression techniques.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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572 - A Preliminary Study of Biometric Identity Authentication Using Acoustic Impedance of Fingers[†]

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I. INTRODUCTION

Biometric authentication is an automated method of recognizing identity of individuals based on physiological (e.g., fingerprint, face, iris) or behavioral characteristics (e.g., signature, gait, voice) [1]. Fingerprint authentication techniques are the most successful example now everywhere in our life from smartphone to immigration identity authentication. However, the current state-of-art technologies could not reach the balance between false negatives and anti-falsification, risk against ways which bypass the system by copying the characteristic features. Therefore, researchers have been seeking new alternatives to meet those threats including ear contour [2], finger-knuckleprint [3], bio-impedance spectrum [4], and multimodal approaches. Here, we propose an approach of biometric authentication using acoustic impedance of fingers. Acoustic characteristics of our bodies and tissues have been used in biomedical diagnosis, emerged from ultrasound imaging to elastography and photoacoustic tomography. The acoustic characteristics of our bodies and tissues account for not only anatomical information but their biomechanical properties. Our preliminary results suggest that the acoustic impedance of fingers holds an immense potential for a promising option of biometrics modalities.

II. SYSTEM CONFIGURATION & EXPERIMENT

Our system was designed to measure the acoustic impedance spectrum across one or two fingers from audible frequency of 1 kHz to ultrasound frequency of 25 kHz. Sinusoidal input signal to a speaker (Samarium speaker, 8 Ω , Devicemart, South Korea) was generated by a programmable waveform generator (AD9833, Analog Devices, MA, USA). The acoustic signal passed through a finger was obtained by a microphone (SPU0410LR5H, Knowles, IL, USA) and amplified before moving onto a phase sensitive lock-in amplifier configured with a demodulator (AD630, Analog Devices). The output signal of the lock-in amplifier was acquired by ADC of a microcontroller board (Arduino Nano, Italy). A preliminary experiment for the newly designed finger acoustic impedance

measurement system was performed for each finger of index, middle, ring, and little fingers or two adjacent fingers. The acquired acoustic spectrum data were transmitted from the microcontroller to a computer through serial communication.

III. RESULTS & DISCUSSION

Acoustic impedance across fingers was measured and analyzed using Matlab (Mathworks, MA, USA). The acoustic impedance data was normalized by the reference data obtained in the free space spectrum without a finger inserted between the transmitter and the receiver. Here, the reference signal is the combinatorial characteristics of the transmitter and the receiver. We speculate that the difference of acoustic impedance spectrum measured across fingers is due to the response of anatomical features and biomechanical characteristics of the finger tissues, which vary in the modulating sound frequency. Overall, we demonstrate that the acoustic impedance of fingers can be a candidate of the biometric authentication modality. We are currently working on additional experiments on the different ways of contacting fingers to the device.

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573 - New approach of Biometric Authentication Using Bioelectric Finger Impedance Analysis[†]

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I. INTRODUCTION

Biometric authentication is a security process that relies on the individual unique biological characteristics. Of the variety types of biometric traits, fingerprint is becoming the widest choice in our life because of its convenience. Although fingerprint technology has many benefits, it has a fatal drawback. It is possible to trick the fingerprint scanner by using a printed gelatin mold over a real finger because this technology can't recognize an artificial fingerprint [1].

Here, we suggest a new method of biometric authentication using BI (bioelectric impedance) difference of fingers in each person. In terms of electrical and biological parameters, BI of fingers could considerably vary from person to person thanks to the intrinsic variability of biological tissues and cells or the movement of ions within muscles and bones in fingers [2], and also it can't be easily changed in one person's life. Therefore, this BI modality of fingers can be used to uniquely identify each person, and our results suggest that the BI of fingers represents an immense potential for a promising option of identity authentication.

II. SYSTEM CONFIGURATION & EXPERIMENT

The BI of cellular tissue can be modeled as a resistor in parallel with a resistor and capacitor in series. This results in a change in impedance may vary with the modulation frequency. Therefore, in this study, bio-impedance measurement system based on a multi-frequency constant current source was designed. It included a MCU (Arduino Nano, Italy), a programmable waveform generator (AD9833, Analog Device), and a voltage controlled current source (VCCS). The MCU was used to program the AD9833 to produce the multi-frequency sinusoidal signal via serial peripheral interface. Then, this signal was converted to constant current of 100uA using a VCCS-based enhanced Howland current pump [3]. An experiment for the developed system was performed for different four combinations of two adjacent fingers: (a) Thumb – Index, (b) Index – Middle, (c) Middle – Ring, (d) Ring – Pinky, for each person. The current was applied to the fingers from two electrodes

mounted on the PCB. Each experiment was conducted five times for 10 subjects. We scanned the impedances for the frequency range from 1 kHz to 100 kHz with an increment of 1 kHz. Each measurement was conducted once again after taking 10-minute break. All the measured data were transmitted to PC through RS232 communication.

III. RESULTS & DISCUSSION

The measurements and analysis were conducted using MATLAB (R2017a, Mathworks, USA), and the results showed that the proposed method could provide good performance to correctly identify each person with good reproducibility. It was observed that BI decreased gradually with increasing frequency, and the gradient patterns and values of each data were clearly different not only depending on the subject but also depending on the combination of fingers.

It is shown that the proposed multi-frequency bioelectric finger impedance measuring system could provide a new method for biometric authentication applications. We are currently working on the additional tests including contact impedance effect of fingers. We will further consider support vector machine (SVM) and the multi-modality of impedance and the phase difference of the output current at higher frequencies to improve the system.

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574 - Carbon nanotube-based scaffolds designed for tissue engineering

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I. INTRODUCTION & AIM

Carbon nanotubes (CNTs) bring exceptional properties to scaffolds, forming versatile composites that can be optimized for the intended interaction with cells and tissues [1, 2]. Already commercialized in other fields, CNTs have been considered to be applied in tissue engineering just lately with limited amount of data and publications (820 according to Web of Science). According to literature [1,2], the unique features of CNTs includes: (1) Extraordinary mechanical properties to withstand in vivo stress and deformation; (2) Ability to quickly adsorb significant amount of protein, enhancing cell adhesion; (3) Synthesis flexibility to create hierarchical structure by means of scale, (4) Freedom of shape (physical) and functional (chemical functionalization) design; (5) Electrical properties which could be used to promote healing by electrophysiological stimulation.

This work aims to develop CNT-based scaffolds with enhanced functional properties to promote cell adhesion and proliferation. One main goal is to explore the outstanding electrical properties of CNTs, which could facilitate electrophysiological signal transfer and be used to promote tissue healing via electrical stimulation. Here, we present three different approaches to fabricate CNT-based scaffolds.

II. METHODS

A. Vertically aligned patterned CNT

CNT structures are synthesized directly by catalytic chemical vapor-phase deposition method on 3D growth templates. The method enables to generate patterned vertically aligned CNTs with micrometer resolution.

B. 3D CNT-hydrogel scaffolds

CNT were functionalized with COOH-groups and dispersed in water solution via sonication and centrifugation. Gelatin gum hydrogel was used to create a 3D matrix.

C. Poly (*L,D-lactic*) acid (PLDLA)/CNT membranes

CNTs were chemically modified by creating PLDLA-CNT membranes via breath figure method [3].

III. RESULTS & DISCUSSION

The vertically aligned patterned CNT was evaluated via viability and attachment assessment of mesenchymal stem cells (MSC). MTT assay clearly shows that CNT does not have any effect on the MSC viability and the cells grow and proliferate as well as in the control sample (polystyrene). Scanning electron microscopy assessment images indicate that the spacing between the CNT pillars can induce the cell morphology to change.

3D CNT-hydrogel scaffolds were successfully synthesized with different CNTs concentrations (0.01 – 0.1mg/mL). Although homogenous CNT-hydrogels are known to be difficult to obtain, in this work CNT was well-dispersed into the hydrogel matrix for all the tested concentrations.

The developed protocol to fabricate PLDLA-CNT membranes resulted in honeycomb-like thin films. The obtained films are currently under physicochemical characterization with special emphasis to electrical properties, which will be used to promote cell growth via electrical stimulation.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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575 - A Wearable Outdoor Mobility Aid for Subject with Parkinson's Disease

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I. INTRODUCTION & AIM

Parkinson's disease (PD) is a chronic neuro degradation disease which affects the motor and ambulation abilities including shaking, rigidity, slowness of walking, difficulty with walking and shuffling gait. These motor disabilities greatly influence the daily life and cause inconvenience and high risk of falling. Researchers have shown that gait performance can be improved with visual and auditory cues. Our previously developed assistive device can provide visual cues with virtual tile for assisting the initiation and optical information for improving turning of PD subjects in a laboratory environment. There is strong clinical need that the PD gait assistive device should be available for outdoor application. The aim of this project is to design a wearable shoes mountable device with optical flow and inertia-embedded sensor for outdoor PD gait training.

II. METHOD

A. Movement Acquisition

To get precisely visual cues projection, a motion sensory unit is necessary. Gait detection using inertial motion sensor is very common approach. Our previous study using five sensors each on waist, both knees and both ankles, which showed good result for gait analysis. Signal of sensors could be applied to do the real-time control of visual aids and also transmit real-time data to specific device such as laptop or mobile phones.

B. Visual Aids Projection

A special design of projection unit contains light projector and micro motor unit to control the projection direction depends on the motion sensors. The whole device could be implemented inside the outer shoes with light weight and convenient to don/doff.

C. Walking with the Shoes

Our device is a wearable design that fit to most of people, users only need to wear the device on, turn on the power, do some simple adjustment and then walk with the projection visual aid.

III. RESULTS AND DISCUSSION

We have developed simple algorithm which is able to identify the swing phase and stance phase in gait cycles. Also, the rotation angle during turning movement can be measured. The control unit can synchronize the movement of shoes and the projection direction of light to guide the next step of PD subject.

This novel medical device responds well to the clinical unmet need for outdoor training of PD gait in a wearable device. It is believed that our system can assist PD subjects in outdoor gait performance and impacts on the neural rehabilitation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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576 - Predicting very rare events in big EEG datasets: The particular case of epileptic seizure prediction

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I. INTRODUCTION & AIM

About 30% of epileptic patients suffer from medically intractable (refractory) epilepsy that limits their social integration and increases the possibility of severe injuries. Epileptic seizure prediction is of extreme importance for these patients, who have no viable treatment and need a solution for the improvement of their quality of life. Information derived from electroencephalogram (EEG) has long been used to develop methods for seizure prediction. Despite some promising results were claimed, the fact is that the existent methodologies do not generalize in real-world situations. A recurrent problem is related to the usage of short-term and discontinuous datasets that not reproduce the situation of a real world-operating scenario. Improving seizure prediction is likely to be achieved using large and continuous datasets, which allows the attainment of representative training examples and robust estimation of the algorithms performance.

This abstract describe results obtained form the analysis of the EPILEPSIAE database [1] that contains simultaneous long-term (165 h on average per patient), and continuous EEG (>10 and <125 electrodes) and ECG recordings, sampled at rates that range from 256Hz until 2048Hz. Given the recording durations, number of simultaneous recording electrodes and sampling frequencies considered, this analysis involved the processing of terabytes of data and seizure prediction in this conditions is really a BigData problem.

II. METHODS

We developed a patient-specific methodology consisting of feature extraction, classification by machine learning techniques, post-classification alarm generation, and performance evaluation using long-term recordings in a quasi-prospective way. For six selected electrodes, multiple quantitative features were extracted from successive five seconds sliding windows

of electroencephalogram recordings. The classifiers were trained to discriminate preictal and non-preictal states. We applied three machine-learning techniques: support vector machines, and two artificial neural networks. The first part of the feature time series was considered for training, a second part for selection of the “optimal” predictors of each patient, while the remaining data was used for prospective out-of-sample validation. The performance was assessed based on sensitivity and false prediction rate. The prediction performance was statistically evaluated using an analytical random predictor.

III. RESULTS & DISCUSSION

We have tested our seizure prediction algorithms on long-term electroencephalogram recordings of 109 patients collected in three different clinical centres with a total of 20,319 hours of recording time including 1405 seizures. The validation data consisted of 5876 hours of interictal data and 579 seizures. We found that 75 seizures were correctly predicted ($\approx 13\%$) with an average false prediction rate of $0.28h^{-1}$. The observed performances were considered statistically significant for $\approx 10\%$ of the patients. The EPILEPSIAE database enabled the evaluation of the seizure prediction performance on continuous out-of-sample validation data of several days duration. The obtained results provide a “proof-of-principle” that at least for some patients there is possible to achieve prediction above chance.

CONFLICT OF INTERESTS

None to declare.

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577 - Long-term analysis of cardiovascular manifestations in epilepsy

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I. INTRODUCTION & AIM

Epileptic seizure prediction is of extreme importance for refractory epileptic patients, who have no viable treatment and need a solution for the improvement of their quality of life.

Information derived from electroencephalogram (EEG) has long been used to develop methods for seizure prediction. However, EEG-based approaches fail to attain real-world applicability either by analyzing short-term discontinuous EEG data or by making use of highly selected and low numbered databases. Furthermore, the brain state alterations depicted by the EEG are often associated with simultaneous extracerebral manifestations which raises the hypothesis that new sources of information are can be very useful in the epilepsy context. As matter of fact, epileptic seizures have implicit manifestations on other body functions, such as alterations in the normal autonomic function activity. Parameters such as heart and respiration rates, and blood pressure, are controlled by the autonomic nervous system [1]. Heart rate (HR) was reported to increase during seizures, being typically associated with high variability. This observations prompted new search lines addressing the differences in HR across the periods before, during and after the seizures [1].

This abstract aims at assessing how well known electrocardiogram (ECG) derived features behave before seizures and ultimately contribute to the improvement of seizure prediction. Results were obtained from the analysis of long-term ECG time series contained in the EPILEPSIAE database [2]. The ECG recordings last in average 165 h and were sampled at rates that range from 256Hz until 2048Hz.

II. METHODS

Time-domain features were computed from the ECG signals using a 300-s window and a 98% overlap. The feature set comprises: the minimum, maximum, mean and variance of the RR intervals (RRMin, RRMax, RRMean and RRVar); the minimum, maximum, mean and variance of the number of beats per

minute (BPM) (BPMin, BPMax, BPMMean and BPMVar); approximate entropy (AppEn). Another four features were obtained by the frequency spectrum analysis of the ECG data: The power in the very-low-frequency (VLF); the power in the low-frequency (LF) range; the power in the high-frequency (HF) range; the ratio LF/HF. In order to inspect the behavior of the ECG features four hours before the seizure happens, the correlation between the ECG feature and the corresponding regression line during that period was obtained using the Pearson correlation coefficient and named CorrCoef. According to this procedure, a value of correlation is obtained for each seizure and the idea was to analyze those correlation values in light of the metadata characterizing each seizure (vigilance state, seizure type and occurrence hour).

III. RESULTS & DISCUSSION

We analyzed 1275 seizures from 164 patients. The results allowed us to conclude that, even though a high correlation has been obtained for some seizures, that variation was not associated with a particular vigilance state, seizure onset hour or seizure type. It was possible to observe that, in general, higher values of correlation were obtained for features such as RRMax, RRMean, BPMMean and BPMin, indicating that these features have more potential to exhibit a consistent pattern of transition from normal to seizure state.

CONFLICT OF INTERESTS

None to declare.

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578 - Electrophysiological assessment of retinal explant cultures in therapy development

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I. INTRODUCTION & AIM

Retinal degenerative diseases decrease the life quality and independence of affected patients. Currently, new treatments for these diseases are urgently needed requiring novel methods for therapy development. Here, we tested electrophysiological assessment of retinal explant cultures as a tool for investigating the effects of drugs on the functionality of the retina. Most of the existing research on retinal explant cultures has focused on morphological assessment. Insight into the functionality of the retinal explant during culture is thus well warranted.

II. METHODS

Mouse retinae were cultured for several days on culture membranes under *ex vivo* conditions, as described previously [1]. Electrophysiological methods were used to follow the effects of a test drug (rapamycin) on the functionality of the retinal tissue at 2DIV (days *in vitro*) and at 7DIV. Multielectrode array (MEA) technique was used to record neuronal activity of retinal ganglion cells (RGCs) from fresh retinae and from retinae after drug treatment.

We used perforated MEAs (60pMEA200/30iR by Multi Channel Systems MCS GmbH). Signals were acquired by the MC_Rack software (Multi Channel Systems MCS GmbH). The data was further analyzed with NeuroExplorer (Plexon Inc.) and MATLAB (MathWorks Inc.) software. Spike sorting was conducted by publicly available spike sorting algorithm Wave_clus [2] to separate the waveforms from single cells.

III. RESULTS & DISCUSSION

MEA recordings revealed rapamycin induced changes in spontaneous and light-evoked activity of RGCs. Overall, electrical activity diminished and its frequency-content changed after rapamycin treatment. By 2DIV, the amount of recorded cells per retina decreased by 49% (spont. activity) and by 29% (light-evoked activity) after rapamycin treatment, and by 0% (spont. activity) and by 14% (light-evoked activity) in control retinae. By 7DIV, rapamycin treatment diminished the amount of rec-

orded cells near to zero. On control retinae, the amount of recorded cells decreased by 60% (spont. activity) and by 53% (light-evoked activity).

Rapamycin did not induce clear changes on the mean firing rates of RGC activity. However, there was a difference in the high frequency firing between rapamycin-treated and control retinae. In freshly isolated retinae, light stimulation induced changes in the firing of RGCs by increasing their maximum mean firing rates and shifting the frequency distributions towards higher frequencies. Similar light-induced changes were observed at 2DIV in rapamycin treated retinae, but not in control retinae. Instead, in control retinae at 2DIV, a higher frequency firing appeared in the spontaneous activity of RGCs.

IV. CONCLUSIONS

Electrophysiological assessment utilizing MEA technique allows investigating the functional integrity of retinal tissue during culture. In this study, we followed retinal functionality for 7DIV and observed clear drug-induced changes in RGC activity. The method thus represents a valuable tool for testing long-term effects of pharmaceutical compounds to retinal tissue.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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579 - Finite element method based evaluation of geometry for action potential propagation measurements

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I. INTRODUCTION & AIM

Neuronal cell culturing in different microfluidic platforms has lately significantly increased [1-4]. In these papers, one can see at least two kind of waveforms for a single action potential because of used geometry and ground placement.

In this work, Hodgkin-Huxley (HH) model [5] is implemented in a finite element method model. The aim of the study is to model how the propagation of the action potential is to be measured inside a microfluidic system and to understand how microscale channels surrounding an axon affect the measured signal.

II. METHODS

Comsol Multiphysics 5.2a software is used to model and simulate action potential propagation in a microfluidic structure. The microfluidic structure contains two large chambers for cell feeding. Six channels with restriction channels in both ends are placed between the chambers. The aim is to let only axons to grow from one chamber to other and restrict the somas to grow in the chambers.

6x8 matrix of MEA electrodes are placed beneath the structure. The spacing and size of electrodes are as in multichannel systems 60MEA200/30 MEAs [6]. The HH model is implemented in geometry similarly as in Joucla et al.[7].

III. RESULTS AND DISCUSSION

The propagation of the action potential inside six channel system indicate that the signal amplitude significantly enhances in the electrodes of the small cross-section restriction channels compared to the electrodes beneath wider channels or the chambers.

The role of the ground electrode is very significant regarding single electrode measurements. Shape of the signal is significantly changed depending on the ground electrode selection. When using differential measurement between two electrodes next to each other, the position of the ground does not affect as much as the most sensitive detection area will be located between the selected electrodes.

A single action potential passing a restriction channel anywhere in the structure is measured by all electrodes. Part of the transmembrane current flow back to the axon through the neighboring channels. This causes small potential difference in electrodes and can be seen as an extra peak in the simulated signal.

As a conclusion, modelling and simulation of even a single action potential will provide valuable insights what to expect from the measurement. In the coming studies, six channel geometry will be experimentally tested in cell recordings. Also, work for building a more complex model will be continued.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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580 - Cell-Type Specific Modulation Of Motor Plasticity Using Optogenetic Telemetry

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I. INTRODUCTION & AIM

Cortical theta burst stimulation (TBS) can modulate corticostriatal plasticity, which makes TBS a potential therapy for motor disorders [1, 2]. To investigate the functional roles of excitatory neuron in TBS-induced motor plasticity, we applied optogenetic stimulation specifically on glutamatergic neurons using implantable optogenetic telemetry. Cortical excitabilities were examined by motor evoked potentials to reveal long-term potentiation/depression (LTP/LTD) effects induced by optogenetic TBS. In this study, an implantable fiber optics-based telemetric stimulator was applied. With RF transmission, the stimulating scheme was programmed and uploaded to telemetry to achieve chronic cell-type specific neural modulation.

II. METHODS

All animal experiments were approved by National Cheng Kung University Medical College Animal Use Committee. CaMKIIa promoter driven channelrhodopsin-2-eYFP (CaMKIIa::hChR2H134R-eYFP) was packed and delivered by lentivirus transduction. Expression of hChR2-eYFP in glutamatergic neuron in primary motor cortex (M1) was monitored by intrinsic eYFP fluorescence. Optogenetic telemetry was implanted into abdominal cavity while light-guiding optical fiber was stretched to brain through subcutaneous space. Blue light stimulation was achieved by wireless RF controlled telemetry. Neural responses excited by optogenetic stimuli were collected by cortical electrode. Motor plasticity was evaluated by measuring changes in MEPs before and after optogenetic TBS treatment.

III. RESULTS & DISCUSSION

MEP amplitude was significantly increased after optical intermittent TBS (iTBS) treatment, while no remarkable changes in

MEP was found after continuous TBS (cTBS). Our results indicate that by specifically stimulating glutamatergic neurons in M1, iTBS can induce LTP as expected while cTBS failed to induce LTD. These observations suggest a critical role that glutamatergic neurons may play in determining the direction of neuroplasticity modulated by TBS. We also demonstrated the modulation of motor plasticity using cell type-specific TBS scheme in M1. This finding may contribute to develop high efficient therapies for neural disorders via targeting specific neural circuit.

IV. CONCLUSIONS

An implantable optogenetic telemetry with RF-controlled optical stimulation was developed for application of neural modulation. Instead of depression, cell-type specific (glutamatergic neuron) optogenetic cTBS could enhance MEP activity while conventional cTBS down-regulate MEP activity. This study indicated a cell-type specific effect beneath LTP/LTD like motor plasticity.

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CONFLICT OF INTEREST

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581 - Development Of Wireless Optogenetic Neural Interface

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I. INTRODUCTION & AIM

Optogenetics is an emerging technique that involves using precisely controlled light to regulate the activities of genetically modified neurons in a tissue-type specific way [1]. Typical hardware for optogenetics requires fiber optics and tethered electrophysiological recording [2]. However, there are many restraints when applying tethered optogenetics in the studies involving motor performance and social behavior. Therefore, a wearable or implantable optogenetic device for freely moving animal is desirable.

II. METHODS

In this study, a wireless neural interface coupled with micro light-emitting diode (μ LED) stimulator has been developed. The optogenetic stimulation scheme is generated and transmitted to from a remote infrared (IR) emitter to head-stage. Head-stage contains an IR receiver and amplifier to convert IR signal into blue μ LED driven current. Head-stage is attached and connected to and implantable optrode, which is composed of blue μ LED, light-guiding structure and $50\mu\text{m}$ platinum-iridium electrode. Multi-unit activities are picked up by electrode and transmitted by radio-frequency (RF) transmitter attached on head-stage, when the head-stage was connected to the optrode. A RF receiver was used to receive and filter electrophysiological signal before sampling. Stimulation scheme, data acquisition, signal processing and analysis were achieved by programmable Lab-view environment (National Instruments). Channelrhodopsin-2 expressed SD rat was established for device testing. All animal experiments were approved by the National Cheng Kung University Medical College Animal Use Committee. Adult male SD rats, weight 300-350gw, were obtained from the Animal Center of National Cheng Kung University Medical College.

III. RESULTS & DISCUSSION

The optrode was implanted right after lentivirus transduction. With the identification of intrinsic fluorescence, expression of CaMKII α promoter driven ChR2-eYFP was confirmed

in M1 area targeted to forelimb.). To activate ChR2, various optical intensities of blue laser were emitted into cortex. Optogenetics activated action potentials were quantified as numbers of spikes from the recording trace pre-filtered with 0.5~1 kHz filter. Local field potential (LFP) were extracted from 10~300Hz trace after coherent averaging. Representative LFP traces during various intensities of single-pulse optical stimulation are shown to demonstrate a light-induced artifact caused by photoelectric effect in the traces from both ChR2-negative (ChR2-) and ChR2-positive (ChR2+) rats. Representative LFP waveforms induced by laser light of various optical intensities are plotted after coherent averaging. A linear dependency is observed ($R^2 = 0.91$) between peak-to-peak amplitudes of evoked potential and progressively increased optical intensity in logarithmic scale.

IV. CONCLUSIONS

An implantable optogenetic neural interface with wireless optical stimulation and neural recording was developed for freely moving small animals. The device is easily fabricated, durable and low cost, which can achieve real-time neural recording with synchronized optical neural stimulation and behavioral performance.

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582 - MiniHypoxy – Mobile alterable oxygen environment for cell biology research

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I. INTRODUCTION & AIM

Standard cell culture experiments are carried out in ambient laboratory air with 21 % level of oxygen. This value is considerably different from values found in human body which are well below and shifting in the range of 2–9 %. [1] For mimicking human body conditions, cells should be cultured in physiologically relevant environment for achieving better *in vivo* comparable results. Temperature, pH and oxygen concentration should be regulated and maintained stable during experiments, but normal incubators are only capable of controlling temperature and pH parameters. For controlling oxygen concentration, there are heavy stationary equipment specially designed for hypoxia (low oxygen) studies. These stations require huge investment and running costs and their fixed position in laboratory limit experiment possibilities. For example, possibilities for radiation treatment and microscopy of cells are limited. We have developed a cost efficient and portable mini-incubator where we can reliably create different oxygen levels and culture cells in controlled environment.

II. METHODS

Miniaturized and modular cell culture platform was developed, where oxygen concentration can be controlled in addition to maintain constant pH and temperature. This independent device uses supply of low rate (1 ml/min – 5 ml/min) non-humidified (dry) gas to maintain the gas concentration environment. With an integrated heating element and CO₂ containing gas mixture, other parameters are kept constant in the culture. In this study, gas mixtures with different oxygen levels (0 %, 1 %, 5 % and 10 %) were used and oxygen conditions in the device were measured by using non-invasive optical oxygen sensor method [2]. Furthermore, hypoxic conditions have been demonstrated with HeLa carcinoma cells and MCF7 breast cancer cells [3].

III. RESULTS & DISCUSSION

Temperature, pH and varying oxygen concentrations can be maintained in this device in prolonged experiments. Measured data also shows dynamical behavior of the system with different oxygen levels.

Cell culture experiments and oxygen sensor measurements demonstrates that our device is capable of creating hypoxic conditions equal to commercial hypoxia stations, but with more versatile analysis possibilities provided by its portability. With this device, laboratories can control oxygen concentration in their cell cultivation studies without heavy monetary investments and limitations caused by stationary equipment.

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583 - New covalent coating methods of polydimethylsiloxane substrates for cell stretching applications

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I. INTRODUCTION & AIM

Polydimethylsiloxane (PDMS) elastomers are widely used in various biomedical applications, and perhaps most notably as substrates for cell culture. However, pristine PDMS does not provide any support for cell adhesion, thus some kind of surface treatment is essential for successful cell culture experiments. Nowadays, PDMS surface treatment methods are plentiful. Still, most researchers rely on simple physisorption or the widest referenced covalent crosslinking methods to bind extra cellular matrix (ECM) proteins onto their cell culture devices. All of these come with problems. Physisorbed ECM proteins can detach in dynamic culture conditions, and the used crosslinker chemicals are usually either cytotoxic or too expensive for wider use. The demanding dynamic culture systems and complex stem cell culturing and differentiation experiments demanded more suitable surface treatment methods; here we aim to solve these issues.

We provide a novel L-ascorbic acid (AA) crosslinker based surface treatment method for PDMS, especially for the needs of long-term cell stretching applications. Also known as the essential vitamin C, AA is often used as a supplement in cell culture mediums to aid in growth, proliferation, and ECM production of the cells. Here we exploit the chemistry of AA to act as a crosslinker between primary amine functionalized PDMS and collagen Type I ECM protein, and characterize how this affects the substrate with fluorescent imaging and dynamic adipose stem cell culture experiments.

II. METHODS

Three, namely AA1, AA2, and AA3, novel AA crosslinked collagen Type I coating methods for cell culture purposes were created based on the enzyme binding experiments conducted by Tiller *et al.* [1].

Various static and dynamic experiments with and without cells were conducted to characterize the novel ascorbic acid based surface treatment methods. In these experiments, the AA crosslinked collagen coatings were compared to physisorbed collagen coating (PHY) and glutaraldehyde crosslinked collagen coating (GLA).

The durability of the bound collagen was characterized without cells with sonication and stretching experiments. The collagen was visualized in these tests with collagen specific fluorescent labelling. Finally, the surface treatment methods were tested with human adipose stem cell culture in static and 5 % stretched conditions.

III. RESULTS & DISCUSSION

The durability experiments with sonication and stretching show a clear implication of covalent immobilization of collagen. PHY samples lost most of their collagen during these experiments, while GLA and AA1-3 showed a similar smooth collagen layer as the static controls. Furthermore, the occasional aggregates of collagen, also visible in GLA and AA1-3 coatings, were removed by sonication and stretching, giving another sign of the frailness of physisorbed collagen.

The adipose stem cell culture experiments showed clear differences between the coating methods. In the static test, PHY provided almost no support for the cells. GLA and AA3 initially promoted cell attachment, but provided poor support for proliferation and showed problems with cell death, which could be a sign of cytotoxicity problems. AA1 and AA2 showed superior results by promoting cell attachment well and reaching confluence in 14 days. In the dynamic cell culture test, GLA, again, showed poor proliferation after 3 days of static and 10 days of stretched culture, while AA1 and AA2 both supported the stretched cell culture by reaching confluence after 3 days of static and 10 days of stretched culture.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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584 - Metastasis detection using feature engineering and machine learning

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I. INTRODUCTION & AIM

We present a machine learning approach for detecting cancerous tissue from scanned whole slide images. This method [1] is based on feature engineering and supervised learning with a random forest model. The features extracted from the whole slide images include several local descriptors related to image texture, spatial structure, and distribution of nuclei. The method was evaluated in breast cancer metastasis detection from lymph node samples.

II. METHODS

The dataset used in this study contains altogether 270 (160 normal and 110 cancerous) whole slide images (WSI) obtained with two different scanner devices. The dataset was provided for Camelyon16 challenge [2].

Each image was processed blockwise in 200x200 pixel blocks. The properties of each tissue sample block were described with 104 texture features extracted from the hematoxylin channel, same 104 features extracted from the eosin channel, and additional six nuclei density features. Texture features included gray level co-occurrence matrix (GLCM) properties, such as, contrast, correlation and energy. Properties of the tissue sample were also extracted using scale-invariant feature transform (SIFT) [3], local binary pattern (LBP) [4], histogram of oriented gradients (HOG) descriptors [5] and maximally stable extremal regions (MSER) [6]. Nuclei density descriptors, such as, mean inter-nuclei distance and number of nuclei were extracted from binary image of segmented nuclei.

The feature representations of tissue samples were then used to train multiple random forest models. Each model was an ensemble of 50 classification trees. Bootstrap aggregation was used to improve the stability and accuracy of the models. Leave-one-out cross-validation (LOOCV) was used to assess the performance of our random forest classification approach. Each sample block from one WSI not used in training was scored with confidence for being either a normal tissue block or a tumor tissue block using a random forest model trained with all other WSIs.

III. RESULTS & DISCUSSION

The implemented method provides detection of hot-spot regions from histological images. The results show that the method detects metastatic areas with high accuracy (AUC = 0.97–0.98 for tumor detection within whole image area, AUC = 0.84–0.91 for tumor vs. normal tissue detection) and that the method generalizes well for images obtained with different scanners. Further, the method outputs an interpretable classification model, enabling the linking of individual features to differences between tissue types.

The feature classification approach presented here is generic in nature and therefore it can be applied to a variety of segmentation and detection tasks. Additionally, the method is easy to interpret and can be extended with new features or deep learning methods. The combination of engineered features and convolutional neural networks would provide a method with the benefits of deep learning methods while preserving also the interpretable features.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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585 - Disrupting acute healthcare

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I. INTRODUCTION & AIM

Acute public health systems are struggling to meet increasing demand arising from an ageing population and improving survival rates. Topol [1] focuses on the democratization of healthcare, and shifting the balance of control of the patient's health away from the system and towards the patient. O'Riordan & Elton [2] discuss similar themes, acknowledging a fast-changing healthcare environment. Many publications promote lean healthcare delivery in hospitals, eg Graban [3], and artificial intelligence in healthcare has begun to challenge the medical hierarchy in areas such as dermatology, pathology and radiology [4].

Clinical Engineers are ideally positioned as architects of this new environment and we propose a road-map based on preliminary research towards a disrupted healthcare environment offering faster, better management of patients in the acute hospital sector and a set of metrics to evaluate the impact of disruptive technology on the patient journey.

II. METHODS

Patient flow metrics in the acute hospital were reviewed to identify those which are potential indicators of improved patient journey performance. Patient pathways were selected, reviewed, pivotal moments in the patient journey where technology can play a role in faster decision-making, diagnosis or treatment were identified. A protocol for identification of opportunities for implementation of "disruptive" technology and new approaches to results formatting was proposed.

III. RESULTS

Metrics reflecting an improved patient journey are:

- Emergency Department (ED) metrics
- Length of Stay (LOS), Patient Experience Survey
- Out-Patient Dept: waiting time, new:return ratio

Pivotal moments in the patient journey are:

- GP or ambulance, ED triage, admission, GP follow-up, OPD

Relevant data:

- Heart rate, ECG, Falls history, images (dermatology), activity levels & weight changes
- Glucose, Troponin, medication and implant history

Data source and presentation:

- Smart watch, smart apps & camera
- Point of care testing
- Data on patient device, presented as infographic.

IV. CONCLUSIONS

Our preliminary investigations provide a roadmap for improving healthcare delivery by disrupting the medical technology status quo through the compilation of a new health technology platform. This is based on off-the shelf, "cheap", devices and apps to support faster, better management of patients in the acute hospital sector. Upcoming challenges are implementation of "destructive" devices, clinician buy-in, provision of intelligent readers of data especially for remote review, and integration of data with the patient record.

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The advice and guidance of Richard Reilly is greatly appreciated.

CONFLICT OF INTEREST

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586 - Three-dimensional evaluation of static magnetic field exposure near MRI scanners

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I. INTRODUCTION AND AIM

A variety of physiological effects observed during exposure to an inhomogeneous static magnetic field (SMF) in the work environment (such as: phosphenes, vertigo, loss of balance) may disturb the work performance, or even cause fall down accidents [1-3]. A variety of parameters characterising the static and dynamic influence of SMF, such as B-field level and spatial distribution, spatial gradients (e.g. dB/dx), as well as dynamic changes of exposure caused by body movements (dB/dt) are used to evaluate patterns of exposure to the SMF – with respect to the module of the B-field vector or to its 3-dimensional components (xyz). The use of such complex, and partly unmeasurable, exposure parameters creates huge challenge for the routine practice of the occupational safety engineers (officers).

The main aim was to apply a three-dimensional (3D) and dynamic evaluation of SMF exposure during the regular activities of magnetic resonance imaging (MRI) workers, with respect to analysing how the exposure of the head and torso complies with the exposure limitations set out in international guidelines [1-3].

The second aim was to apply the conclusions from the environmental studies in the drafted labour legislation (which transposed European directive 2013/35/EU to Poland) and in occupational safety practice.

II. METHODS

The 3-axis Hall probe connected to a pocket data logger was used when 3D mapping the SMF exposure parameters near various MRI scanners of 0.1-7T, as well as when monitoring the dynamic changes in the level of workers' exposure to SMF.

The measurement results were analysed with respect to the exposure parameters characterising the exposure of the head and torso, while performing various kinds of workers' activities. The dynamic parameters of exposure were analysed also in the function of the maximum SMF at the workers' position.

III. RESULTS AND DISCUSSION

The performed assessment of SMF exposure of MRI workers showed that complex set of tools applied in occupational safety practice is needed to sufficiently cover various hazards caused by the static and dynamic influence of SMF on workers: the enlarged set of SMF action levels (200 and 400 mT; 1, 2 and 8T), together with 3D mapping of the SMF distribution in the workspace near the MRI magnet. Such an approach also helps workers to develop a work practice, which reduces both components of daily exposure to SMF. Labour law in Poland, which transposed the provisions of EU Directive 2013/35/EU in 2016, applied this approach. It is under the process of implementing in practice in MRI centres.

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CONFLICT OF INTEREST

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587 - Citizen involvement in health technology assessment: challenges and opportunities.

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The European Economic and Social Committee (EESC) is a consultative body of the European Union. The EESC contributes to strengthening the democratic legitimacy and effectiveness of the European Union by enabling civil society organizations from the Member States to express their views at European level. The EESC has three main goals: helping to ensure that European policies and legislation tie in better with economic, social and civic circumstances on the ground; promoting the development of a more participatory European Union; promoting the values on which European integration is founded and advancing, in Europe and across the world, the cause of democracy and participatory democracy, as well as the role of civil society organizations.

The EESC assists the European Parliament, Council and European Commission, making use of EESC members' experience and representativeness, dialogue and efforts to secure consensus serving the general interest.

In 2014, the EESC instructed Dirk Jarré and me to draft an opinion on biomedical engineering and assistance. A theme never before addressed. This was the start of an unexpected journey, conducted with the support of a world leading fellowship, bringing together the International Federation of Medical and Biomedical Engineering (IFMBE), European Alliance for Medical and Biological Engineering & Science (EAMBES), the World Health Organization (WHO) and the European Parliament. This journey terminated with a report, titled "Opinion of the European Economic and Social Committee on Promoting the European single market combining biomedical engineering with the medical and care services industry", which was published the 4th of September 2015 in the Official Journal of the European Union (4/09/2015/C 291/07). The report stated for the first time that: *2biomedical Engineering is not simply a subset of modern medicine. Modern medicine predominantly secures important advances through the use of the products of biomedical engineering.*"

It also highlighted the strategic importance of biomedical engineering industry, which represents a major step forward for Europe, also in terms of healthcare and of quality of life. Biomedical engineering represents also an opportunity to face the rising demand for quality, affordable, safe and permanently reliable health services at a time when public spending is under pressure. For a healthy and well cared for population, there is a huge need for systems engineering approaches that redesign care practices in line with changing needs and integrate local, regional, national, and global health IT networks.

Nonetheless, this conclusions and recommendations require some help and continuous attention, in order to be listened by European and National Institutions. Moreover, since access to health and care services is a fundamental right in Europe, the EESC underlined the importance of closely involving potential users of biomedical engineering products in decision-making processes, in order to determine, together with biomedical engineering experts, the direction of biomedical engineering research and the subsequent design of products and services.

In this light, the rule of citizens is fundamental. What does a citizen do, in order to be sure that elementary rights must try to make our loved country and our dear Europe more civilized? Rediscover the values of citizenship. Do not delegate. Take responsibility for the common good. Citizen in the highest sense. A title to be taken with pride, like *cives romanus sum*, (Cicero), or *Ich bin and berliner* (J.F.Kennedy).

Health Technology Assessment (HTA) is the natural bridge among research, policy makers and end users.

This presentation will highlight the importance of the rule of the citizens in this process, but also the challenges that European organizations have to face in order to empower the citizen making their contribution proactive and effective. Ongoing National initiatives will be presented to highlight how the rule of citizens is fundamental to catalyze attention around emerging challenges.

588 - Introductory remarks on interaction of FES technology with physiological interface conditions

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Functional Electrical Stimulation (FES) can provide many supportive options for movement rehabilitation. On one hand, it is underrepresented in clinical practice, though its value for assessment, therapy and health economy have been clearly demonstrated, on the other hand it is too often overrated in scientific and popular publications, which can lead to false hope, disappointment and skepticism among patients and healthcare professionals, and impedes adequate consideration in rehabilitation protocols.

This special session aims in sketching the actual possibilities and limitations as well as an outline on realistic developments towards the foreseeable future. Continuous progress in technical developments tends to refine specificity of interaction with nerve and muscle structures, nevertheless control of selective functions down to atraumatic single fiber activation seems not in sight with current possibilities. But in close synergy of engineering, physiology and clinical expertise a lot can already be accomplished and recognition of individualized physiological conditions in patients with movement disorders has become a key for significant progress in therapeutic outcome.

The session address basic conditions for interaction of technology and physiology as well as representative examples for restoration of paralyzed movement functions in the upper and lower extremity with strong emphasis to what is presently realistic and adequately beneficial for clinical application. Also, an outlook on foreseeable innovations and long-term visions will be included.

The special session addresses how FES currently can support movement rehabilitation with focus on interaction of advanced technology with physiological conditions, and contains the following contributions:

Introductory remarks on interaction of FES technology with physiological interface conditions. Winfried Mayr, Vienna, Austria

Implantable microelectrodes - actual and foreseeable limits for refinement of stimulation selectivity. Max Eickenscheidt, Freiburg, Germany

Influences of control mode and stimulus shape variation on motor unit recruitment in non-invasive neuromuscular stimulation. Jose Luis Vargas-Luna, Monterrey, Mexico

MoreGrasp – BCI-controlled sensory and motor grasp neuroprosthesis for individuals with high spinal cord injury. Ruediger Rupp, Heidelberg, Germany

Assistive and therapeutic effects of non-invasive neuroprostheses for gait correction. Thierry Keller, San Sebastian, Spain

Spinal cord stimulation, a versatile tool for assessment and monitoring, modification of spasticity and augmentation of movement. Matthias Krenn, Vienna, Austria

ACKNOWLEDGMENT

The author thanks the Austrian Society for Organization of EMBEC and the EMBEC organizers for supporting the special session "How can Functional Electrical Stimulation currently support Movement Rehabilitation: advanced technology meets physiological reality"

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

589 - Influences of control mode and stimulus shape variation on motor unit recruitment in non-invasive neuromuscular stimulation

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I. INTRODUCTION & AIM

Transcutaneous Functional Electrical Stimulation (FES) has been proven a useful tool for diagnostic, rehabilitation and research because of its non-invasive characteristics, reversibility and low cost. Due to the multidisciplinary scope in which FES is applied, many technical and physiological principles are often overseen or not considered during therapy or device design. Two of these important aspects are the control mode of the stimulation—either current-controlled (CC) or voltage-controlled (VC)—[1] and the stimulation pulse shape [2]. In this work, we show that both of them can strongly modify the recruitment of the motor units in non-invasive neuromuscular stimulation.

II. METHODS

The experimental protocol was approved by the Ethics in Research Committee the School of Medicine of the Tecnológico de Monterrey (Mexico) and conducted according to the principles of Helsinki Declaration.

A. Current-Controlled Vs. Voltage Controlled

In five healthy subjects (4 Female), we studied the differences in the activation of the quadriceps muscles when current and voltage pulses of different pulse widths (from 50 μ s to 1000 μ s) and intensities—from the sensory threshold until ± 115 mA in steps of 5 mA and until ± 55 V in steps of 5 V for CC and VC, respectively—were applied. For both stimulation types, we used a symmetrical charge-balanced biphasic (BP) pulses. The motor unit recruitment was estimated with the use of the knee torque and the M-waves evoked in the rectus femoris.

B. Pulse Shape effect

In eight healthy volunteers (4 Female), we studied the differences of the pulse configuration by comparing the evoked

responses on the soleus muscle when electrical stimulation is applied to the tibial nerve at the popliteal fossa level. For this part of the study we used monopolar (MP), biphasic and biphasic with different interphase interval (IPI) at a fixed intensity and pulse width.

III. RESULTS AND DISCUSSION

The results show that in CC stimulation the intensity and the pulse width can effectively modify the number of motor units depolarized during the stimulation, whereas on VC stimulation the recruitment is only depending on amplitude variations for pulse widths longer than 150 μ s—which means pulses longer than this do not produce stronger contractions.

On the other hand, we found that MP pulses produce stronger contractions than BP. This difference is because the second phase might restrict the propagation of the action potentials evoked during the first phase, producing a smaller compound action potential at the muscle. This effect can be avoided by introducing an IPI between the phases, which allow all the action potentials to flee the hyperpolarization area that the second phase produce. For our application the minimum IPI to avoid this effect was 250 μ s, but it can change depending on the electrode configuration.

These results also show the importance of a proper understanding of the FES methods, which can importantly reduce the intensities required to achieve the desired contraction and, therefore, reduce the risk and discomfort for the patients.

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590 - MoreGrasp – BCI-controlled sensory and motor grasp neuroprosthesis for individuals with high spinal cord injury

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I. INTRODUCTION & AIM

Motor neuroprostheses based on functional electrical stimulation (FES) can restore permanently lost functions in people with high spinal cord injury (SCI), in particular of grasping. An EEG-based Brain-Computer Interface (BCI) [1] may serve as a neuroprosthetic user interface to control grasping by imagination of movements [2, 3]. While the basic feasibility of the combination of BCI with FES was already shown in single case studies, intuitive EEG-based BCI-control of a noninvasive grasp neuroprosthesis is still missing. Due to the limited capabilities of noninvasive BCI systems for real-time control autonomous closed-loop grasp pattern control is needed, but remains still a challenging task. The EU-project MoreGrasp aims at the realization of both.

II. METHODS

In two high-resolution EEG studies with 15 able-bodied subjects each, we investigated the decoding classification accuracy of 6 single joint movements of the same arm and of 3 different grasp types of the same hand, respectively. In both studies, the motor-related cortical potentials (MRCPs) in a narrow 0.3 to 3 Hz band were investigated.

Following the protocol of these 2 studies, we investigated the classification of 2 subsets of movements with 5 participants with high cervical SCI (Neurological level: C3 - C5).

Two sets of multi-pad electrodes were developed:

1) a stackable screening electrode matrix consisting of 15 (5 x 3, HxW, 6.3 x 3.8 cm) electrodes (diameter 7mm, inter electrode distance of 2.5 cm) made of conductive silicone, and 2) a personalized forearm silicone sleeve with 64 electrodes and two inertial measurement units (IMUs) for wrist rotation angle measurement. For automatic selection of the appropriate electrode pads, a depth camera recording the finger kinematics was used.

III. RESULTS & DISCUSSION

The 1st study revealed a classification accuracy of 37% (chance level 16.7%), with classifier sources mainly in premotor and primary motor areas. The 2nd study showed that grasps can be decoded from MRCP features (binary classification of 74% grasp vs. grasp). Experiments with SCI showed a classification accuracy of 53 % (subset 1) and 57 % (subset 2).

Multi-pad test results of 3 able-bodied subjects and 1 end user with SCI reveal that not only quantification of the degree of denervation is possible, but also robust electrode positions for palmar or lateral grasps and electrode switching strategies during wrist rotations can be defined.

The studies show that it is possible to detect single movements of the same arm from the EEG, either single joints or different grasps. The multi-pad concept of the MoreGrasp grasp neuroprosthesis helps to overcome major challenges of noninvasive grasp neuroprostheses for everyday use.

ACKNOWLEDGMENT

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The authors thank the Austrian Society for Organisation of EMBEC and organizers for supporting this special session on Neuroprostheses in Movement rehabilitation.

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591 - Assistive and Therapeutic Effects of Non-Invasive Neuroprostheses for Gait Correction

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I. INTRODUCTION & AIM

Non-invasive, transcutaneous neuroprostheses (NP) for gait correction have shown to be as effective in improving gait parameters as ankle-foot orthoses, but allowing active and more natural movement of the ankle joint [1].

We conducted a pilot study to investigate assistive and therapeutic effects of a multi-channel dropfoot system that allows gait correction by stimulation of eversion/inversion balanced ankle dorsi- and plantar-flexion. With such a NP we expect superior improvements of gait functions than could be shown so far by one channel FES dropfoot NP.

II. METHODS

In 20 FES sessions a multi-channel dropfoot NP was applied to four sub-acute stroke subjects (at least three months post stroke). The system consisted of an electrical stimulation system with integrated demultiplexer that distributed the stimulation pulses to up to 16 channels, a knee garment including an array of two times eight 1.5cm² big electrode pads, and an IMU sensor attached on the forefoot.

The study was carried out at the clinic for rehabilitation "Dr Miroslav Zotović", Belgrade, Serbia. Each subject received 30 min FES therapy, five times a week during four weeks, supervised by a physiotherapist. Each session included a NP setup and stimulation optimization phase (calibration phase), and approximately 20 minutes of FES assisted walking (training phase). In the calibration phase the passive and active ankle ROM were measured.

Prior the first session a baseline assessment was carried out and repeated after 10 sessions and again after concluding the study after 20 sessions. The assessment included: The Fugl-Meyer Test, The Berg Balance Scale, The Modified Ashworth Scale, and The Mini Mental State Examination. Gait specific the foot trajectories and kinematic data were recorded with inertial sensors placed on the insets of both legs and the 10m walking test was performed with and without FES.

Ethical approval for this study was obtained from local ethic committee.

III. RESULTS & DISCUSSION

Both observed gait parameters (ROM and gait velocity) showed assistive and therapeutic effects of the FES system.

The stimulated (assistive) ROM increased, possibly due to increase in the muscle strength and reduction of spasticity, from 28° in the first session to 42° after 20 sessions.

The assistive effect was present with the first use of the system (28° with stimulation compared to 19° without stimulation), but reduced in later sessions of therapy due to the therapeutic effect. During the training the difference between active and passive ROM decreased from 14° to 4°. This shows a clear therapeutic effect of FES.

The piloted group, after 20 sessions clinically meaningful [2] increased walking speed for more than 0.1 m/s, even when the stimulation was turned off, emphasizing a therapeutic effect of the FES training. Without FES, an increase of 38% in walking speed after 20 training sessions could be measured. With FES at baseline the gait velocity could be increased by 17% (assistive gain) and remained 17.5% at the end of the training. We could also quantitatively measure improved gait symmetry towards normal values.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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592 - Spinal cord stimulation, a versatile tool for assessment and monitoring, modification of spasticity and augmentation of movement

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I. INTRODUCTION

Severe spinal cord injury (SCI) is associated with disability and a drastic decrease in quality of life for affected individuals. Ongoing research is developing strategies that could be introduced into the clinical treatment of SCI in the short term. One approach is to move the attention away from the pathology at the injury site and from the attempt to reconstruct spinal descending and ascending pathways but to emphasize the remaining motor function of the spinal cord structures below the SCI zone [1, 2]. Here, we address the spinal network below the injury using electrical stimulation.

Spinal cord stimulation (SCS) provides afferent input to posterior root neurons and showed to improve volitional movements [3], posture [4], and control spasticity [5] in the lower limbs.

II. METHODOLOGY

Transcutaneous SCS (tSCS) depolarizes the posterior root afferents and may elicits spinal reflex responses and is able to modify the related spinal networks. The stimulation configuration is utilized by para-spinal stimulating electrodes at a predefined position at the vertebral level T11 to L1, with indifferent electrodes placed over the abdomen or iliac crest.

For assessment of the lumbosacral spinal cord properties, we activate the lumbosacral spinal network using sustained electrical stimulation having repetition rates from 1 to 80 pps and intensities from sub- to supra-motoric thresholds.

III. RESULTS AND DISCUSSION

Preliminary results show that the motor neuron pool can be activated with repetitive external input. The total motor output

is increasing up to a stimulation rate of 15 pps and then declines progressively for higher frequencies. In general, it can be observed that the responses profile is constant for low (2 to 10 pps) stimulation rates, fluctuating for medium (10 to 50 pps) rates, and suppressive for high (50 to 80 pps) rates.

tSCS a non-invasive assessment tool for identifying functional control profiles of sub-lesional neuronal networks and residual supraspinal control after physiological alterations following the injury. Especially, clinical accomplishments are strongly depending on each individual's physiological state and specific methodical adaptation to that physiological state which can be monitored using sustained stimulation of the posterior roots.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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593 - Does the Human Body Alter Measurement Uncertainty of A Multi-Band Wearable Distributed Radio Frequency Exposure Meter?

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I. INTRODUCTION & AIM

Human exposure to radio frequency (RF) radiation is usually measured by personal exposimeters (PEMs). The main issue of PEMs is that the presence of the human body results in large uncertainties up to 35 dB [1].

For the first time, a multi-band multi-node wearable distributed RF exposure meter (MBWE) is designed and calibrated on body. The goal is to reduce the influence of human body on measurements of the MBWE. This is achieved in terms of on-body calibrations. Moreover, the MBWE is calibrated on five human subjects to assess the influence of human body on its measurement uncertainty.

II. METHODS

The MBWE is designed to measure the actual incident power densities (S_{inc}) for 11 frequency bands and consists of 22 nodes distributed in an optimal way on the front and back of the body torso. Each node is a textile antenna equipped with a receiver circuit. The nodes are integrated into an outdoor garment and a master node controlling the whole system.

The locations of the nodes are optimized by calibrating the MBWE on a 28-year old male subject.

The calibrations are performed in an anechoic chamber; The subject is rotated 360° around his axis perpendicular to the ground floor of the anechoic chamber in the far field of a transmitting horn antenna. The free space S_{inc} values were also measured in absence of the subject. From these measurements, an effective on-body AA is determined per frequency band and location. These AA values will be used to calculate S_{inc} during the measurements in a real environment. A similar procedure is repeated for four male and female subjects with an age range of 28 to 61.

III. RESULTS AND DISCUSSION

Using the MBWE, we obtain a reduction of 22 dB in uncertainty (defined as 68% confidence interval of AA, CI_{68}) over the considered frequency bands, compared to classical single exposimeters. Moreover these results are much lower (4-12 dB) than CI_{68} of a PEM calibrated on body. The results are consistent over all subjects. The MBWE also showed CI_{68} of 0.1-3.2 dB for five different people in all frequency bands which is one fourth of the similar value for a PEM.

IV. CONCLUSIONS

A MBWE is designed and calibrated on body for five human subjects. The MBWE showed a reduction to 22 dB for the measurement uncertainty in presence of human body and to one fourth for five different body morphologies.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Abstracts of 4 page papers

010 - Novel adaptive approach for correcting baseline wander from ECG signals

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Abstract— The purpose of this study is to create effective algorithm for eliminating baseline wander from ECG signals and compare performance of different approaches for baseline wander correction. A new adaptive method for baseline wander elimination, based on reference signal composition of adaptive filter by using multiresolutional wavelet transform of noisy ECG signal, was proposed. Efficiency of different baseline wander correction methods for processing model ECG signals contaminated by baseline wander was researched. The accuracy of determining the ST-segment deviation for real ECG signals by using proposed approach in comparison with established baseline wander filtering techniques was studied. The proposed method of adaptive filtering with reference signal obtained by wavelet decomposition is distinguished from existing baseline wander correction methods by relatively high processing efficiency and small distortions of the ECG signals after filtering.

011 - Motion artifacts reduction in wearable respiratory monitoring device

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Abstract— The aim of this study is to create a wearable device for long-term real life respiratory monitoring as well as to investigate the possibility of using adaptive noise cancellation approach for reducing motion artifacts occurred during respiratory signal recording. In our study wearable respiratory monitoring device have acquired respiration by using bioelectrical impedance plethysmography and human movement with triaxial accelerometer. To achieve effective and robust motion artifacts reduction we create the respiratory signal processing method based on band-pass filtering and adaptive noise cancellation. Performance of proposed processing technique was evaluated for the group of people that were asked to control their breathing frequency using an auditory signal from an electronic metronome during the rest and intensive physical exercises.

013 - Development of radiofrequency ultrasound based method for elasticity characterization using low frequency endogenous motion: phantom study

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Abstract— This paper presents developed radiofrequency (RF) ultrasound based strain elastography imaging method, which operates and could be adjusted in frequency domain. The method was verified by using agar-based tissue mimicking substitute. The phantom had 7 kPa stiffness background material and two inclusions of different stiffness 15 and 30 kPa. The displacements in the phantom material were induced by hand. The obtained strain contrast-to-noise ratio between the background material and two inclusions is 1.32 and 1.50 respectively. These results confirm the differentiation power of the method characterizing relative elasticity in vitro.

014 - A simple approach to detect alcoholics using electroencephalographic signals

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Abstract—In this paper, we have analyzed electroencephalogram (EEG) acquired from alcoholics and controls. Raw EEG signal has been filtered with an 8-30 Hz bandpass filter. Normalization of EEG trials to a range [-1, 1] was performed to filtered EEG signal. We employed relative entropy and mutual information to select the optimal channel configuration which maximize classification of alcoholics and controls. From standard 10-20 electrode system (19 channels), five channels which are more active in classification of alcoholic and control were chosen. Feature vectors of training and test data were obtained by concatenating variances of these five channels. When relative entropy was used for channel selection, 80.33% accuracy was obtained with k-nearest neighbors classifier accompanied with Mahalanobis distance metric. And mutual information for channel selection process provided 82.33% accuracy with k-nearest neighbors classifier accompanied with Euclidean distance metric. The results of the experimental analysis are satisfactory for alcoholic detection and may be useful in studying genetic predisposition to alcoholism.

015 - Automatic Segmentation of Computed Tomography Images of Liver Using Watershed and Thresholding Algorithms

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Abstract— Computed tomography (CT) imaging is widely used for control and diagnosis of diseases nowadays. Segmentation of medical images is quite important, especially for diagnosis and treatment of cancer. In this study, similar and different tissues in CT images of liver are determined by using two different methods; watershed and histogram thresholding. The images have been preprocessed before segmentation. First, images are converted to grayscale. Next, they are smoothed with a bilateral filter. To apply the watershed technique, edges are extracted with a Gradient operator. The over segmentation of the watershed method is overcome by merging the closest segments in terms of their features. The merging is obtained via vector quantization of the features; fuzzy c-means clustering and k-means clustering algorithms by grouping mean and standard deviation of segments. The images are divided into five segments corresponding to liver, vertebra, tumor, lining and others. In the histogram thresholding method, multi thresholds are obtained with Otsu method from the smoothed image and segmentation has been performed. The results of two approaches have been compared. Pixel value, directional derivatives (DD), local binary patterns (LBP), difference of pixel with its neighborhood (DP) are employed as features to determine the segment class. Classifications of the regions were obtained from a single pixel and segment separately by dividing 44 liver images to two training (22 images) and test sets (22 images). The best accuracy for classification from a pixel was obtained 95.64 % with difference of pixel with its neighborhood feature whereas 98.88 % was obtained for categorization from the whole segment with directional derivatives feature by using histogram thresholding algorithm. This application may help physicians to distinguish and determine the similar or different tissues in the medical images.

018 - Ultraviolet Ray Strength for Pre-irradiation in Gafchromic EBT2

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Abstract— Ultraviolet (UV) rays strength and density change of Gafchromic EBT2 were investigated. It has previously been suggested that UV rays can be used as a substitute for the X-ray double-irradiation technique to correct non-uniformity errors when using Gafchromic EBT2. Here, the appropriate strength of the UV-A rays for irradiating the active layer of Gafchromic EBT2 was investigated.

Ultra violet-A rays having a wavelength of 375 nm was used to irradiate Gafchromic EBT2 for various durations, and the resulting density change was investigated. Pre-irradiation with the UV-A lamp was conducted at a distance of 72 cm for 30 min. A UV light-emitting diode (LED) that generates UV-A of 375 nm was used to irradiate the Gafchromic EBT2 film with varying durations of 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 min. From these results, the most appropriate irradiation time could be determined. A circular region of interest of 0.5 inches diameter was set by the irradiation area, and a histogram of pixel values was created. The choice of conditions was decided based on two important requirements: first, there is no zero values mode and seconds, the 1/10 level intersects both sleeves of the histograms.

The above requirements having been satisfied in pixel value which performed subtraction of data. In the case of Gafchromic EBT2, the irradiation was 170.86 mJ/cm² for 2 min, with a pixel value of mean 573.47 ± 251.43.

When a UV ray of 375-nm wavelength was used to irradiate Gafchromic EBT2 as a substitute for X-ray irradiation, it was demonstrated that irradiation of approximately 5 minutes (427.17 mJ/cm²) was sufficient at a distance of 7.5 cm.

019 - Clinical Engineering and the Changing Face of Patient Safety

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Abstract— Patient safety has always been an important responsibility for Clinical Engineering Departments (CEDs), but the breadth of safety issues changed dramatically over the years, from electrical-focused safety and electromagnetic interference in the latter half of the twentieth century, to a concern with adverse events and medical errors in the twenty-first century. With the advent of several new technologies such as Electronic Medical Records (EMRs) and Clinical Decision-Support Systems (CDSSs), a new role emerged for clinical engineers. These professionals need to work closely with developers and vendors of such systems to integrate Information Technology (IT) solutions into patient care, helping to reduce or even eliminate adverse events and medical errors.

021 - Enhanced Patient Queue Management: Development of Slot-Back Model Equation Using University of Maiduguri Medical Centre as Experimental Site

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Abstract – The review of existing queue management systems shows that the systems, though vary in concept, sophistication, and area of application, but all without exception lack the ability to consider an absent queue. Therefore, the work presented in this paper is basically designed to handle cases of absence on queue due to pressing needs. This is to be achieved by slotting back absentees into the queue using our model equation. The research work reported here uses experimental data obtain through field work and survey at the University of Maiduguri medical centre to arrive at terms such as longest average time of absence (LATA), average consultation time (ACT) and number of doctors on duty (NDD) resulting into a Slot-back model equation thus: $SbP = LATA(1/(\frac{ACT}{NDD}) + c$.

026 - The Influence of Pharmacological Autonomic Blockades on Multi-Scale Measures of Heart Rate Variability

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Abstract—Multi-scale measures have been used extensively to characterize non-linear dynamics of heart beats. However a physiological interpretation of the exponents associated with various scales of these measures and the role of the sympathetic and parasympathetic activities have not been attempted. In this study three multi-scale measures were compared at different scales in a pharmacological autonomic blockade experiment, starting with a control phase. It was then followed by injection of propranolol causing sympathetic blockade and injection of atropine resulting in the blockade of both sympathetic and parasympathetic pathways.

Multiscale Entropy (MSE), Multi Fractal Detrended Fluctuation Analysis (MFDFA) and Renyi Entropy (RE) were compared using a paired test statistics. The measures performed differently depending on the scale factors and RE showed the best results indicating a good discrimination particularly at higher scale exponents. This study provides a basis for understanding the effect of autonomic activity on multiscale measures with respect to changes in parasympathetic and sympathetic activity.

027 - Impact of High-Frequency Electromagnetic Fields on Secretion and Structure of Pancreas in Rats

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Abstract- We studied the impact of high-frequency electromagnetic field (HF EMF) on pancreas tissue, of sexually mature rats Wistar strain. Experimental animals were exposed to HF EMF, characteristics: frequency of 1,9 GHz, electric field strength: 4,79 V/m, magnetic field strength: 0,24 A/m and Specific absorption rate (SAR) value: 2,0 W/m², 7 hours per day and 5 days per week, for thirty days. These are the same fields which are emitted by antennas for mobile communications and mobile phones. The experiment was conducted on total of 30 male rats divided into two groups: one group with 15 animals who were exposed to aforementioned fields and the other group with 15 individuals who weren't exposed. Hematological analysis established a change of glucose and insulin concentration in blood, of exposed and control rats. Histological and stereological analysis established a change in volumetric density of exocrine and endocrine component of the pancreas and change in absolute surface of exocrine and endocrine cells in both groups were determined by unbiased design-based stereology. There was statistically a significant difference between the parameters in pancreas tissue exposed and control groups animals (ANOVA, F=7,15, p<0,05). Results of this research reached to significant statistical change in concentration gradient of insulin and glucose at animals who were exposed to HF EMF comparing to control group. Furthermore, histological measurements of stereological parameters show significant change at animals who were exposed to electromagnetic fields in contrary to control group. In conclusion our analysis shows pancreas' sensitivity on impact of high-frequency electromagnetic fields.

029 - Wearable multi-antenna multi-band measurement system for personal radio-frequency exposure assessment

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Abstract—Rising concern about the potential harmfulness of human radio-frequency exposure causes scientists to be highly interested in measuring these exposure levels. The set of measured signal levels on a map of locations is then used for epidemiological research, looking for correlation to the incidence of certain illnesses. Currently available hand-held exposimeters have the disadvantage that the measured signal levels are often significantly different from the exposure to which the human body is actually subjected. Therefore, a personal distributed exposimeter was developed and documented in this paper. Multiple on-body antennas are employed in order to measure the electromagnetic field strengths directly on the body. In this design, 11 commonly used frequency bands are measured, with front and back textile antennas for each of those bands. These 22 antennas are implemented in substrate-integrated-waveguide technology, thereby combining a compact size with a large bandwidth. The measurement system operates autonomously, through measurement, control and data-logging circuitry directly integrated onto the antennas. The textile-antenna based nodes are unobtrusively integrated into a garment, resulting in maximum comfort for the user. A measurement campaign using the system is currently underway in a number of European countries, yielding a large amount of valuable and unique data for epidemiological analyses.

034 - Three-dimensional Magnetic Camera for the Characterization of Magnetic Manipulation Instrumentation Systems for Electrophysiology Procedures

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Abstract—We present a three-dimensional magnetic camera consisting in an array of 64 CMOS integrated monolithic three-dimensional Hall-Effect sensors. The camera covers a 40x40x40 mm³ volume and performs a synchronous sampling at 100 samples per second of each of the 64 three-dimensional magnetic flux density signals. Recent results in the design of magnetic manipulation instrumentation systems for e.g. electrophysiology procedures or magnetic particle imaging have shown that an extensive use of calculations and

finite element method simulations is done during the development. In practice, there is a lack of suitable configurable magnetic camera to perform experimental magnetic field mapping and verify simulation results. Magnetic field and field gradients determine respectively the force and torques applied to the manipulated object and shall therefore be precisely known for an accurate steering of the object. The new magnetic camera described in this paper has to our knowledge no commercial equivalent. It answers to the need of experimental characterization of magnetic manipulation systems and offers the designers some new experimental performance assessment capabilities. The camera is both suited for small object manipulation where the steering field reaches a magnitude of about 1 mT and for electrophysiology applications where the magnetic steering of catheters requires a magnetic flux density that typically can reach up to 150 mT. Based on Hall-Effect, the magnetic camera could be easily adapted to reach even larger dynamic ranges and could fulfill the requirements of magnetic manipulation of objects using a MRI magnetic field.

037 - The Effects of Different Material Properties on the Hemodynamics of Human Fetal Umbilical Vein/Ductus

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Abstract— There are various types of diseases which lead to abortion of the fetus in different stages of pregnancy. Any abnormality of hemodynamics in ductus venosus (DV) or umbilical vein (UV) could accelerate the process of abortion. The present study has focused on the hemodynamics in the human fetal UV/DV based on four different mechanical properties of UV including elastic (uniaxial test method), elastic (circumferential), viscoelastic, and rigid. The studied hemodynamic parameters consist of velocity, shear stresses, and maximum pressures of Isthmus and UV areas. The obtained results show that the maximum pressure did not vary much along UV or Isthmus. However, the maximum shear stress occurred in hyper elastic model. The velocity of Isthmus is also maximum for hyper elastic model

040 - A Case Study of Focal Bayesian EEG Inversion for Whitney Element Source Spaces: Mesh-Based vs. Cartesian Orientations

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Abstract—This paper concentrates on the Bayesian detection of the neuronal current distributions in the electroencephalography (EEG) imaging of the brain activity. In particular, we focus on a hierarchical *maximum a posteriori* inversion technique applicable when the lead field

matrix is constructed via the finite element method. We utilize the linear Whitney (Raviart-Thomas) basis functions as source currents. In the numerical experiments, the accuracy was investigated using two spherical head models. The results obtained suggest that the interpolation of the dipolar source space does not necessarily bring any advantage for FEM based inverse computations. Furthermore, the divergence conforming Whitney-type sources were found to be sufficient for precise and highly focal Bayesian modeling of dipole-like currents.

041 - Multiresolution MAPEM Method for 3D Reconstruction of Symmetrical Particles with Electron Microscopy

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Abstract— The resolution and accuracy of the 3D images obtained with single particle reconstruction (SPR) highly depend on the number and signal to noise ratio of the particle images. The maximum a posteriori probability expectation maximization (MAPEM) reconstruction methods have been successful in suppressing noise and compensating for the limited angular sampling. This paper presents a multiresolution MAPEM (mMAPEM) method to improve the resolution and accuracy of the 3D images of the symmetrical particles reconstructed using SPR. The method utilizes the median root prior and the symmetry information about the reconstructed structure in the image domain. The method was compared with the conventional Fourier Reconstruction (FR) method using phantom and experimental datasets for different noise levels and projection angle sampling conditions. The numerical and visual assessment of the reconstruction results demonstrate that the mMAPEM method provides more accurate results than FR.

042 - Effect of sinus attenuation in MR-based attenuation correction in ¹⁸F-FDG brain PET/MR

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Abstract—Attenuation correction is essential for image quantification in PET. At minimum, bone, soft tissue and air need to be included in MR-based attenuation correction

(MRAC) of the head. Additional tissue classes might be beneficial to improve the accuracy of MRAC further. We studied the attenuation effect of nasal sinuses in MRAC by four attenuation maps and by assessment of regional PET quantification.

MR-based attenuation maps using 0.151 cm⁻¹, CT template-based, 0.100 cm⁻¹, 0.060 cm⁻¹ for sinus attenuation coefficients were created. A volume of interest (VOI) analysis of MRAC reconstructed PET data was conducted. Relative difference against PET data reconstructed with CT-based attenuation correction (CTAC) was calculated. Bias ratio images across the subject group were studied.

The mean relative difference in the whole brain to CTAC reconstructed PET for each of the methods were as follows: -2.88 %, -3.16 %, -3.17 % and -3.42 %. The difference to CTAC reconstructed PET was not statistically significant ($p > 0.05$) with any of the methods. The bias ratio images showed the largest differences in sinus region while gray matter activity remained largely unchanged. The maximum differences between the methods were 1.46 % and 2.35 % in the Cerebellum and in Gyrus Rectus.

Therefore, when investigating only the changes in the gray matter radioactivity in neurodegenerative diseases, there is no critical need to account for sinus attenuation for MRAC of the head in ¹⁸F-FDG brain PET/MR.

043 - DataBrain: a web-accessible database for three-dimensional reconstructions and quantitative morphometrics of neurons

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Abstract— Thanks to the new advanced tools and the innovative methods to image deep in the brain at cell resolution, neuroanatomy is quickly redefining its protocols for quantitatively studying neurons in their own three-dimensional arrangement. The huge amount of data generated has to be managed and shared among labs: this need has led us to develop DataBrain, an on-line archive of three-dimensional single neuron reconstructions and their associated morphometrics. DataBrain interface allows users to upload and download data, to easily search neuron using filters and to on-line view both three-dimensional reconstructions and morphological parameters. Here we describe DataBrain's main features and show an example of how it can be used to store morphological quantitative datasets of Purkinje cells from murine clarified cerebellum slices acquired using a confocal microscope.

044 - Influence of scattered radiation on Gafchromic EBT3

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Abstract—Gafchromic EBT3 (EBT3) is used as a radiochromic film in half-value layer (HVL) measurement methods, which are used to calculate the effective energy for QA and QC. HVL measurements using EBT3 display a precision of less than 5 % compared with the results of standard method with an ionization chamber (IC) dosimeter, and offer a simple procedure for determining the HVL consistently and quickly without the need for an IC. However, it is difficult to apply this technique because of the scattered radiation caused by the geometric layout of the X-ray computed tomography (CT) apparatus. In this study, the effect of scattered radiation on EBT3 is investigated. It was found that the EBT3 is not affected by scattered radiation at positions beyond 50 mm from the scattering substance. Therefore, the results suggest that EBT3 is suitable for use in X-ray CT HVL measurements. On the other hand, when the distance from the scattering substance was 10 mm or less, EBT3 showed very high absorption compared to a semiconductor detector. Therefore, EBT3 is more sensitive than the semiconductor detector at a close range and can be used to measure scattered radiation when the distance from the scattering substance is 10 mm or less.

045 - Basic research on countermeasures against barium sulfate aggregation using a gastric phantom

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Abstract— The principal aim of this study was to conduct basic experiments to examine countermeasures against barium sulfate aggregation caused by denture adhesive in gastric cancer screening test. Experiment 1 ; barium sulfate aggregation was reconstructed in petri dishes and the degree of reducing aggregation by seven types of commercial drink and tap water was assessed visually. The most effective one was tap water. Experiment 2 ; two types of aggregation (severe and mild aggregation) were reconstructed using gastric phantom BMU-1, tap water of 30-150ml was added and the degree of reducing aggregation was assessed with the images. In the case of severe aggregation, the most effective quantity of tap water was 120 ml and the next was 150 ml with the following of 90, 60 and 30 ml ($P < 0.05$). In the case of mild aggregation, the order of effective quantity was 90, 60, 120, 30 and 150 ml ($P < 0.05$). The results of this study suggested that tap water drinking of the subject was effective for the reduction of barium sulfate aggregation in gastric cancer screening and the most effective quantity of tap water was 120 ml in the case of severe aggregation and 90 ml in the case of mild aggregation.

049 - Fabrication and characterization of nanocellulose aerogel structures

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Abstract— Nanocellulose is a promising new renewable and low-cost nanomaterial which has potential applications in many different fields from biomedical to electronic applications. Here, we report the fabricated aerogels from aqueous CNF and CNC dispersions using freeze-drying technique and analysis of their structural analysis using different microscopic techniques. Also, we report the development of dispenser for aqueous nanocellulose solutions to be installed into 3D-printer system.

053 - A Developed Magnetic Force Microscope

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Abstract— In this paper, a magnetic force microscope (MFM) was developed for applications in liquid environment. The 3D structure of the developed MFM system was designed first and then the components of every part were machined and assembled. The laser beam horizontally reached the mirror and reflected vertically to the cantilever of the probe to reduce the effect of air, glass and liquid refraction. This research focuses on the design of a specific MFM system to obtain the magnetic force images in liquids.

055 - Laser Interference Lithography for Applications in Biomedicine

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Abstract—This paper presents a new maskless laser nanoscale manufacturing technology to fabricate micro and nano structured surfaces with specific functionalities. Cross-scale fabrication of micro and nano structures on biomaterials (such as metal, alloy and polyethylene) with wear resistant properties. Investigation of conditions and process parameters for cross-scale fabrication of micro and nano structures with specific functionalities (wear resistant properties) for the target applications in biomedicine.

056 - Development of a pneumo-tactile vibrissae stimulator for freely behaving rodents

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Abstract—Studying rodent behavior within virtual worlds and their interaction with them is a fairly new field of research. While virtual reality is able to visually present an unlimited variety of worlds to the animal with ease, physical stimulation often remains unsatisfactory and is usually difficult to achieve. Rodents such as rats mainly experience their environment using their whiskers. Though, electrical stimulation using subcortical electrode implants have been successfully used for sensory stimulation, the underlying principles are still poorly understood. One possible and less invasive alternative method is physical stimulation of the whiskers using puffs of air with the added benefit of avoiding

the overall risks of brain surgery for intracranial microstimulation.

057 - Nonlinear Dynamics of Heart Rate Variability in Children with Asthmatic Symptoms

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Abstract—Asthma is a chronic lung disease that is prone to start during childhood. Although symptoms can be usually controlled with medication, early diagnosis is crucial to reduce the risk of permanent airway obstruction. Despite the fact that origin of asthma is still uncertain, abnormal parasympathetic nervous system (PNS) activity has been pointed out to play a major role in its pathogenesis. In this work the use of nonlinear heart rate variability (HRV) indexes is proposed in order to look for differences between children classified as high- or low-risk of suffering from asthma in the future. PNS activity is assessed through a filtered HRV signal. Correlation dimension analysis showed statistically significant differences distinguishing high- and low-risk. Decreased complexity observed in high-risk group suggests that abnormal PNS activity might be related with increased risk of developing asthma.

061 - A Novel Composite and Suspended Nanofibrous Scaffold for Skin Tissue Engineering

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Abstract—Electrospinning is a technique for creating continuous nanofibrous networks that can architecturally be similar to the structure of extracellular matrix (ECM). In this

work, a kind of PLGA/silk fibroin composite electrospinning nanofibrous scaffolds is proposed for the growth of skin cells in combination with the good mechanical properties with not easy to deformation of silk fibroin and the self-floating of PLGA. The SEM experiment of the silk fibroin/PLGA composite nanofibers indicated that the prepared nanofibers are smooth, uniform in size and have good porosity. The floating experiment is shown that this scaffold is able to suspend in water and is also able to suspend in cell culture medium, hence, the skin cells seeded on the scaffold are exposed to air as required in skin tissue engineering. The wrinkled contrast experiment and the degradation experiment are verified the usefulness of this scaffold.

064 - The Role of Simulation for Preoperative Planning in Patients Requiring Mechanical Circulatory Support

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Abstract – Mathematical modelling and simulation have the potential to become clinically applicable tools for detailed evaluation of the cardiovascular system and clinical decision-making to guide therapeutic intervention. This approach has a great potential for application in heart failure where the impact of left ventricular assist devices (LVADs) has played a significant role as a bridge to transplant and more recently as a long-term solution for non eligible candidates. We sought to investigate the value of simulation in the context of a heart failure patient with a view to predict or guide further management. CARDIOSIM[®] software was used to find out the most appropriate course of action to apply in this clinical setting. The outcome of the simulation was compared with the decision previously made in the clinical environment. Although there was an encouraging agreement, other factors play a role in the clinical decision process. Patient-specific modelling may add a more quantitative approach but requires willingness to accept a different way of thinking.

065 - Sensitivity Distribution of Electrical Impedance Epithelial Measurement Systems

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Abstract—Epithelia are essential tissues that separate body compartments from each other and are affected by a

plethora of diseases and conditions. Electrical properties are a convenient method to study the state of these tissues. There are various measurement setups for studying these properties. However, there has been no studies on how the setup of the electrodes affects the sensitivity distribution of the measurement system. We created a computational model of 4-electrode electrical impedance measurement system to study how the placement of the electrode as well as defects in the epithelium affect the sensitivity distribution. Our results show that the sensitivity is highly dependent on the frequency as well as on the distance between the electrodes and the epithelium. The sensitivity become more concentrated to areas between the electrodes when they were moved closer to the epithelium. The sensitivity should be taken into account when developing measurement systems to study localized phenomena with the electrodes placed close to the epithelium.

067 - Development and Testing of a XYZ Scanner for Atomic Force Microscope

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Abstract—Atomic force microscopy (AFM) is a widely used tool in nano measurement and manipulation techniques. However, a traditional AFM system suffers from the limitation of slow scanning rate, due to the low dynamic performance of piezoelectric positioners. As an important part of AFM system, scanner will have a significant impact the result of the scanning imaging and operation. It is well know that high-speed operation of an AFM are increasingly required, and it is also a challenge for the researchers. In this paper, we proposed a parallel kinematic high-speed piezoelectric actuator (PZT) XYZ scanner. The design is aimed at achieving high resonance frequencies and low cross-coupling. The developed stage consists of a parallel kinematic XY stage and a Z stage. The Z stage is mounted on the central moving platform of the XY stage. To achieve the design objective, several parallel leaf flexure hinge mechanisms, arranging symmetrically around the central moving platform of the XY stage, are utilized to provide large stiffness and reduce cross-coupling. For the Z stage, a symmetrical leaf flexure parallelogram mechanism is adopted to achieve high resonance frequencies and decoupling. Then, finite element analysis (FEA) is utilized to validate the characteristics of the XYZ scanner. Finally, extensive experiments are conducted, demonstrating feasibility of the proposed scanner.

069 - Picking the winner: How HTA of medical devices can help identify routes to a sustainable healthcare system

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Abstract—Healthcare systems face huge challenges: how do we meet this increased demand for improvements in healthcare whilst at the same time delivering improved efficiencies so we can manage within our resources. We know that the future will bring more fantastic advances in healthcare technology that have the potential to revolutionise how we deliver health and wellbeing. But which technologies will bring increases to both patient benefit and healthcare systems efficiencies; which will promise patient benefits but turn out to be unaffordable and which will simply be expensive white elephants.

Can Healthcare Technology Assessment (HTA) for medical devices help us separate the wheat from the chaff and provide a robust system to support decision makers?

071 - Day-to-day variation in sleep quality and static balance: results from an exploratory study.

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Abstract—Sleep plays a critical role in promoting health and wellbeing. Variations in sleep quality and pattern may effect human balance. This study investigated whether day-to-day variations in sleep quality result in balance deteriorations during quiet standing. Ten healthy volunteers underwent sleep and balance assessment over two consecutive days. Sleep quality was assessed using sleep diaries, whereas balance was assessed in a gait laboratory to measure Center of Pressure (CoP) and Center of Mass (CoM) displacement. Results demonstrated an association among worsening in sleep quality and CoP displacement measures, both with eyes open and closed. The correlation coefficients between CoP and CoM also showed significant differences in subjects reporting a sleep worsening over the two days. These results suggest that short-term worsening in sleep quality may affect our balance and its associated mechanisms of control.

072 - Electric field of EEG during anesthesia

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Abstract—Electroencephalogram (EEG) has been clinically used to estimate the level of consciousness during anesthesia, but its physiology and biophysics are poorly understood in anesthesiological literature. The electrical sources of EEG are in cortical structures. EEG currents create closed-loops, which flow from the surface of the cortex and then return to the inside of the hemispheres. In the case of widespread synchronous activity like physiological sleep or anesthesia, the currents return through the base of brain and skull. Here we show with a typical EEG pattern of anesthesia, burst-suppression, that due to those currents EEG is recordable outside of scalp area. We also present the sensitivity field of electrodes located submentally, as well as the electrodes used for anesthesia monitoring, calculated from a realistic head model of the potential distribution and currents of EEG.

Our results show that anesthesia EEG can be recorded with a pair of electrodes anywhere on the surface of head, as well as inside of head and brain, because the EEG current loops produce recordable voltage gradients in the whole head. A pair of electrodes submentally is most sensitive to basal parts of the brain. The typical electrodes used in anesthesia monitoring are most sensitive to basal surface of frontal lobes as well as frontal and mesial parts of temporal lobes.

073 - 2D-EEG Topography and fMRI Brain Images for Relaxation and Letter Writing

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Abstract—Electroencephalography (EEG) can localize neural electrical activity and track in vivo brain functions in milliseconds with high temporal resolution. Even though EEG is said to be time accurate and spatial inaccurate, the approximate spatial information is still useful. In view of the shortcomings of imaging modalities, the purpose of our work is to propose EEG as a potential neurofeedback protocol since it can provide concurrent feedback and progressive states of neuronal activation. The preliminary work here intends to study the correspondence between the 2D EEG topography and brain images from fMRI for the normal adults during relaxation state and letter writing, being the first attempt ever reported. With OpenViBE as the platform, the EEG signal acquired was segmented, filtered and extracted

for significant features, before the EEG topography is generated. Despite difficulty in finding the corresponding brain images, it is found that the EEG topography along the reading-writing pathway is a close match to images from fMRI studies and neurological theories.

074 - UV Intensity of Pre-irradiation in Gafchromic XR-RV3 and XR-SP2

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Abstract—UV-A irradiation of Gafchromic XR-RV3 and XR-SP2 are considered to be a substitute for X-ray irradiation in the double irradiation of Gafchromic XR-RV3 and XR-SP2. It makes it possible to compensate for heterogeneity errors in the active layers of Gafchromic XR-RV3 and XR-SP2. UV-A with a wavelength of 395-nm was irradiated to Gafchromic XR-RV3 and XR-SP2, and irradiation time and color density change were investigated. At first, Gafchromic XR-RV3 and XR-SP2 were pre-irradiated for 2 and 4 hours, respectively, by UV-A with a wavelength of 365-nm, with UV-A fluorescent lamp as the radiation source, located at a distance of 72 cm. Secondly, a UV-A light emitting diode (LED) capable of generating 395-nm UV-A was used. The irradiation times of UV-A for Gafchromic XR-RV3 and XR-SP2 were from 5 to 120 minutes and from 30 to 300 minutes at a distance of 5.0 cm, respectively. From these results, appropriate irradiation time was considered. A 0.5 inches diameter region of interest was set for each irradiation area, and a histogram of pixel values was obtained. The selected condition was two items "There is not 0 in a mode", "A 1/10 level intersects both sleeves of graph".

When Gafchromic XR-RV3 and XR-SP2 were irradiated with ultraviolet rays of wavelength 395 nm as an X-ray substitute for double irradiation technology, it was proved that 60 minutes (5511.00 mJ/cm²) and 270 minutes (24799.50 mJ/cm²) were sufficient for irradiation time respectively. And both distance was 5cm.

076 - Detection and Assessment of Sleep-Disordered Breathing with Emfit Mattress

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Abstract— Measuring respiratory effort during sleep is a demanding job. It needs intrathoracic pressure monitoring via nostril inserted catheter in the esophagus. Though the size and material of catheter are nowadays more comfortable than earlier, it is still quite invasive and cumbersome technique, and it does not suit for clinical use. It is known that mattress-type contactless sensors can be used to detect respiratory movements and overall cross-body movements. Beating heart produces mechanical activity called ballistocardiography (BCG), which can be assessed with Emfit (Electromechanical film transducer) mattress sensor too. These heart-related movements with increased breathing effort cause patterns called spiking in the mattress signal. We have studied esophageal pressure changes during this spiking and showed that this phenomenon appears when intrathoracic pressure decreases under -8 cmH₂O. These increased breathing efforts quite often appeared together with loud snoring. That is why we have also studied the spectral content of Emfit signal using the power spectral density (PSD). Snoring epochs displayed a power increase in all frequency bands. This increase was best quantified using the power ratio between 60–100 Hz (BW3) and 16–30 Hz (BW2). We have shown that this type of contactless sensors suits well for the screening of snoring, and the increased respiratory effort was visualized too. Mattress-type movement sensors are inexpensive and unobtrusive, and thus provide an interesting tool for sleep research.

077 - Center of Pressure based Assessment of Balance Responses to Repeated Perturbations of Upright Stance

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Abstract— In this study a description of balance response to sudden external perturbations of the upright posture was performed. To this aim, subjects underwent to a series of translational perturbations at fixed speed in backward and forward direction. Center of pressure (CoP) displacement was analyzed in terms of temporal and spatial characteristics,

showing a repeatable waveform which allowed the identification of two main response periods: the destabilizing and the counterbalancing phase. Different control features of balance response have been observed in both phases, with a temporal-based control of CoP displacement in the first phase and an amplitude-based control in the second one. Moreover, the analysis of CoP could be useful to identify the presence of the first trial effect and the habituation rate, two well-known features of perturbed posturography. These findings could contribute to the understanding of balance control in perturbed conditions and suggest CoP as a valuable measure in studying not only the quiet but also the perturbed stance.

078 - Split Ring Resonator Inspired Passive UHF RFID Antenna System For Wireless Intra-Abdominal Pressure Sensor

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Abstract— We present a passive UHF RFID tag based on a spatially distributed split ring resonator antenna system. The physically separated parts of the tag form a remotely detectable platform, which can be partly implantable and partly wearable. This is the first stage in our research toward a RFID-inspired wireless intra-abdominal pressure sensor. The tag consists of a wearable split ring and a small implanted split ring resonator carrying the RFID microsystem. In our experiments, the tag is detectable at a distance of 1 m with a 10 mm implant depth and 0.3 m with a 30 mm implant depth. Our results also show that the tag tolerates a rotational misalignment up to 45° between the implanted and wearable parts without severe performance deterioration.

082 - Integrating human factors and health economics to inform the design of medical device: a conceptual framework

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Abstract—The reliability and clinical utility of a medical device are required to demonstrate its impact and to enhance its success in the market. To fully establish these attributes it is necessary to investigate the context of use and the needs of the users. In healthcare, there is a growing use of human factors and health economics methods to generate evidence of the potential success of a new device. This requires investigating not only the device itself but also the elements surrounding the technology - e.g., end-users, environment of use, other operators and technologies, etc. Acquiring this in-

formation in the early stages of device development is essential. This enables designers to appreciate the operational challenges and barriers that the device will face in real life settings and may enable improved design to better fit with the environment in terms of ease of use, safety and cost effectiveness. Human factors and health economics experts have not traditionally worked together to achieve this. However, both health economists and human factors experts need to understand and map the context of use to develop realistic scenarios for the cost-effectiveness analysis and for usability testing of a new device. This paper presents a new conceptual framework for the integration of human factors and health economics to evaluate new diagnostics devices. The framework is currently under test, and its full implementation represents an ongoing aim of the National Institute for Health Research Diagnostic Evidence Co-operative of London.

086 - Computational modeling of radiofrequency ablation with an internally cooled wet electrode

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Abstract—A finite element model of radiofrequency tumor ablation with an internally cooled wet electrode was built and its computer results were compared to those reported in a clinical study involving 17 patients with hepatocellular carcinoma. The model whose results best matched the clinical results was based on three compartments and assumed a hydrated tumor: computed transversal diameter of 39.2 mm vs. reported diameter of 33.7 ± 7.1 mm. The impedances of the model (47.9 Ω) and the clinical trials ($46 \pm 6 \Omega$) were also similar, both at 140 W. The results showed the advantage of a three-compartment over a two-compartment model when simulating the real effects of treatment on cancerous tissue.

089 - Quantitative pigment extraction analysis for human pluripotent stem cell derived retinal pigment epithelial cells

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Abstract—Pigmentation is a typical feature for retinal pigment epithelial cells (RPE), and each RPE cell represents individual characteristics. Although, type and intensity of pigmentation may vary, still most cells are pigmented to some extent.

In this study, we set-up a standardized quantitative melanin content analysis for human embryonic stem cell (hESC) derived RPEs (hESC-RPE) and compared this method to an image based pigment quantification technique. The optical quantification of pigmentation was done from micrographs of hESC-RPE. The extracted pigment was quantitated with spectral analysis, with UV-Vis spectroscopy, and the size-distribution with dynamic light scattering.

The results revealed that the measured particle sizes of extracted melanin corresponded to known sizes extracted melanosomes. In addition, the optical pigmentation and absolute melanin concentration were clearly correlating.

Our data suggests that image analysis and quantitative melanin content analysis can be interchangeably utilized in pigmentation quantitation: if the relative pigmentation of hESC-RPE cells is desired to be estimated with a non-invasive method then image analysis is the choice of method, but if the exact amount of melanin needs to be evaluated, then the new melanin extraction method presented here, should be chosen.

091 - Bayesian Modelling of Skull Conductivity Uncertainties in EEG Source Imaging

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Abstract—Knowing the correct skull conductivity is crucial for the accuracy of EEG source imaging, but unfortunately, its true value, which is inter- and intra-individually varying, is difficult to determine. In this paper, we propose a statistical method based on the Bayesian approximation error approach to compensate for source imaging errors related to erroneous skull conductivity. We demonstrate the potential of the approach by simulating EEG data of focal source activity and using the dipole scan algorithm and a sparsity promoting prior to reconstruct the underlying sources. The results suggest that the greatest improvements with the proposed method can be achieved when the focal sources are close to the skull.

092 - Predicting Optimal Stopping Criteria for Automatic Detection Using Magnitude-Squared Coherence: Application to EEG During Auditory Stimulation

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Abstract—Detection of Auditory Steady-State Responses (ASSR) has been used in the estimation of a comprehensive physiological audiometric profiles, benefiting patients with cognitive problems. The presence or absence of response can be inferred by using techniques of Objective Response Detection (ORD). In clinical tests, where the minimum test time is required, ORDs can be applied while collecting signals. However, the repetitive use of ORDs can lead to increased false positive rates. An alternative to solve this problem is to define the presence of an ASSR, when the ORD detects the presence of response for number of consecutive tests (NCT). The objective of this study was to determine the value of NCT, with a significance level of 5% as function of the parameters of the detection protocol. The detection technique used was the so-called Magnitude-Squared Coherence (MSC). To estimate the results the Monte Carlo Method (30,000 interactions) was used. The results showed that NCT can be estimated by a linear equation with adjusted coefficient of determination (R^2 adjusted) of 0.9651. The equation was used in EEG signals for different protocols and false alarm rates lower than 5% were obtained. Used the estimated NCT on EEG signals for different protocols and obtained false alarm rates of less than 5%.

093 - Syncope Prediction using Photoplethysmography

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Abstract—The development of a reliable and robust algorithm for prediction of syncope events is still a major challenge, especially when it is based on the analysis of the photoplethysmogram (PPG) alone. Several algorithms have been proposed in the literature based on the joint analysis of the electrocardiogram, the blood pressure and also the PPG [1]. However, when considering the analysis of the PPG alone, the ability to predict syncope events is still unsatisfactory. The aim of this work is to provide a more reliable PPG-

based algorithm with higher prediction ability, using a dataset with 43 patients. Parameters related to the chronotropic, inotropic, blood pressure, vascular tone and autonomous nervous system responses have been extracted and evaluated. Several features were computed and the most relevant were selected and ranked with a proper score system. Additionally, different algorithm setups were also tested. The best setup achieved the following results: $F_m=86\%$, $SE=100\%$, $SP=85\%$, $FPR_h=1.9h-1$ and $PT= 242.3 \pm 226.9$ sec.

094 - Determination of Stimulation Timing Pattern based on EMG Signals for FES Cycling with Pedaling Wheelchair

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Abstract— A simple functional electrical stimulation (FES) cycling control with the pedaling wheelchair was developed in our previous study. However, it needed measurement of muscle response time of each stimulated muscle before cycling. In addition, cycling speed varied between subjects and between trials. In this study, stimulation timing pattern was determined based on EMG signals and tested in FES cycling for the pedaling wheelchair with healthy subjects. The EMG-based stimulation timing, in which stimulation start timing for the rectus femoris was modified to be the same as the vastus lateralis, was shown to be effective improving cycling speed and stability of FES cycling. The timing pattern could be practical because it does not require measurements of muscle response times.

097 - A Neural Network Model of Peripersonal Space Representation Around Different Body Parts

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Abstract— The Peripersonal Space (PPS), the space immediately surrounding the body, is coded in a multisensory, body part-centered (e.g. hand-centered, trunk-centered), modular fashion. This coding is ascribed to multisensory neurons that integrate tactile stimuli on a specific body part (e.g. hand, trunk) with visual/auditory information occurring near the same body part. A recent behavioral study, using an audio-tactile psychophysical paradigm, evidenced that different body parts (hand and trunk) have distinct but not independent PPS representations. The hand-PPS exhibited properties different from the trunk-PPS when the hand was placed far from the trunk, while it assumed the same properties as the trunk-

PPS when the hand was placed near the trunk. Here, we propose a neural network model to help unveiling the underlying neurocomputational mechanisms. The model includes two subnetworks, devoted to PPS representations around the hand and around the trunk. Each subnetwork contains two areas of unisensory (tactile and auditory) neurons communicating, via feedforward and feedback synapses, with a pool of audiotactile multisensory neurons. The two subnetworks are characterized by different properties of the multisensory neurons. An interaction mechanism is postulated between the two subnetworks, controlled by proprioceptive neurons coding the hand position. Results show that the network is able to reproduce the behavioral data. Network mechanisms are commented and novel predictions provided.

099 - The Effects of Different Material Properties on the Hemodynamics of Human Fetal Umbilical Vein/Ductus

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Abstract— There are various types of diseases which lead to abortion of the fetus in different stages of pregnancy. Any abnormality of hemodynamics in ductus venosus (DV) or umbilical vein (UV) could accelerate the process of abortion. The present study has focused on the hemodynamics in the human fetal UV/DV based on four different mechanical properties of UV including elastic (uniaxial test method), elastic (circumferential), viscoelastic, and rigid. The studied hemodynamic parameters consist of velocity, shear stresses, and maximum pressures of Isthmus and UV areas. The obtained results show that the maximum pressure did not vary much along UV or Isthmus. However, the maximum shear stress occurred in hyper elastic model. The velocity of Isthmus is also maximum for hyper elastic model

100 - Contactless 3D detection of respiratory effort

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Abstract— Respiratory effort is a major feature for detection and classification of apneas in polysomnography. Presently, somnologists apply flow sensors and/or rip belts at the thorax and abdomen for this purpose, causing practical problems with the montage and re-adjustment during the

night and disturbing patients' sleep. Contactless measurements would be a desirable alternative. We utilized a 3D time-of-flight camera to monitor respiratory-related chest movements to decipher epochs of normal breathing and apnea. Time-synchronized comparisons of 3D measurements of chest movements due to respiration to signals from rip belts and nasal airflow proved that the 3D sensor provided equivalent results. This new technique could support the diagnosis of sleep apnea and Cheyne-Stokes breathing. It simplifies the procedure, saves personnel capacity, improves data quality and releases the burden to the patient by replacing body-mounted sensors and cabling.

101 - Functional connectivity of hand-arm muscles during a repetitive dynamic task

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Abstract— The aim of the study was to investigate the temporal changes in functional connectivity between pairs of selected hand-arm muscles. I recorded the surface bipolar electromyographic (EMG) activity of biceps brachii, triceps brachii, deltoideus anterior, serratus anterior, upper and lower trapezius during a repetitive dynamic task performed until participants' rating of perceived exertion reached eight on Borg's CR-10. The functional connectivity was assessed in terms of Wiener-Granger-causality (G-causality) between each pair of EMG time series revealing the contribution of one muscle (e.g. Y) to yield an improved prediction of EMG time series of another muscle (e.g. X) at each time point over and above the prediction which could be achieved from previous values of X itself ($Y \rightarrow X$). Only the G-causality from deltoid anterior to biceps brachii (deltoid anterior \rightarrow biceps brachii) increased with time, suggesting a possible co-contraction effect associated with fatigue development. However, the extent of functional connectivity was not associated with time to task termination suggesting the inability of the subjects in this study to adopt a load sharing pattern among the hand and arm muscles assisting them to prolong the time to task termination. Investigating the functional connectivity between the involved muscles in a task can provide some insights to the mechanics of the movement pattern.

102 - Application for pre-processing and visualization of electrodermal activity wearable data

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Abstract— Using sensors to gather physiological data about users can provide valuable insights that are not available merely using traditional measures. Electrodermal activity

(EDA) can act as an indicator for both physiological and psychological arousal. Measuring arousal has several application areas. For instance, prolonged and often recurring high arousal levels can indicate that a person is suffering from chronic stress. At the other extreme, for example, in elderly care constant low arousal levels can signal that the senior citizens are not getting enough activity and attention from the care personnel. In the context of events, measurement of arousal can indicate when the persons get excited and when they are more calm. This study presents a pilot study of EDA measurements conducted during a trade fair. Providing timely and meaningful information for a group of people being measured, however, requires pre-processing the data and creating visualizations that enable both individual and collective level sense-making of the results. The aim of this study was to develop a process and an open source application that can automatically pre-process large amounts of data from wearable sources, and create visualizations, to be used in events for immediate sense-making.

103 - Non-Thermal Effects of Electromagnetic Fields in Biology and Medicine

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Abstract— I discuss several aspects of non-thermal effects of electromagnetic fields while showing results of experiments demonstrating how EMFs influence growth of corn seedlings and growing of cress seeds. Not only EMFs of selected frequencies but also broadband electromagnetic noise affects living organisms. Hypersensitivity to EMFs should be a matter of special concern.

105 - Ultra-sensitive SQUID instrumentation for MEG and NCI by ULF MRI

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The requirements for the construction of ultra-sensitive SQUID instrumentation as used in biomagnetism are presented. Typically, SQUIDs are inductively coupled to pick-up coils and for this arrangement one can improve the noise performance by increasing the sensing coil area. To achieve optimum sensitivity one has to consider the signal-to-noise ratio (SNR), which is an intricate interplay between source characteristics and noise origin. It turns out that separate pick-up coil designs are needed for various noise characteristics even for an identical source. Hence, a hybrid system with differently sized pick-up coils presents the best option for multipurpose applications. A single channel system with close to SQUID intrinsic noise level is also described. This is possible by utilizing a special dewar design and thereby enabling a further increase in SNR. Such a system might be used for current density imaging and neuronal current imaging by

ultra-low-field magnetic resonance where it also must be able to be field-tolerant to up to 100-200 mT.

106 - Low Invasive Technology of Sclera Crosslinking: an Experimental Implementation

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Abstract – Purpose: an experimental implementation of scleral collagen crosslinking using a new device that enables low-invasive delivery of UVA radiation combined with riboflavin onto the equatorial and posterior pole areas of the eye. For UVA sclera crosslinking, a device was manufactured which contains a LED source of continuous UVA radiation (wavelength 370 nm, radiation intensity 3 mW/cm²), connected via a matching optics with multimode quartz optical fiber encased in a polymer shell. This fiber is located in one of the two channels of a dual removable metal ferrule; the second (hollow) channel is designed for simultaneous delivery of riboflavin solution onto the surface of the sclera. The device was used to perform scleral crosslinking on 8 eyes of Chinchilla rabbits. The intact fellow eyes served as controls. Prior to the procedure, as well as 2 days after it and 1 month after it, the acoustic density of the sclera (ADS) was measured in vivo using an ultrasound device, VOLUSON 730 Pro (Kretz). At the same time points, the elasticity modulus of scleral samples were determined on the testing machine (Autograph AGS-H, SHIMADZU, Japan) and the level of collagen crosslinking was measured using differential scanning calorimetry (calorimeter, Phoenix DSC 204, Netzsch, Germany). After UVA treatment, ADS grew from 86.7±5.1 to 98±4.9 dB, the elasticity modulus was found to be 1.5 times higher than the control, while denaturation temperature growth matched the 15–18% increase of cross linking of scleral collagen. The outcome of experimental implementation of low-invasive technology for scleral collagen crosslinking shows that it as a promising method of scleral strengthening treatment of progressive myopia which requires further clinical studies.

107 - Some Problems and Supports in the Colorectal Cancer Screening Behavior in Japan

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Abstract— The colorectal cancer screening test is effective for the early detection of the disease.

In order to increase the rate of having colorectal cancer screening test in Japan, this study was conducted to demonstrate the problems and supports in the colorectal cancer screening behavior. The subjects of the questionnaire survey were older than 40 years, namely in the risky age range of colorectal cancer.

The result of this study showed several important matters for encouraging colorectal cancer screening behavior. They were right understanding on colorectal cancer and the screening test, good environment to have the test including human support for parenting and care, and financial support for medical cost, corresponding on individual situation.

108 - Assessing representativeness of a rural Australian clinical database using a spatial modelling approach

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Abstract—It is generally recognized that people in rural Australia and world-wide do worse in terms of health outcomes compared to the urban population. Epidemiological studies rely on large datasets obtained through national surveys but efforts to survey rural populations usually result in small datasets. Hence small datasets are often disregarded even if they are the only source of health data available to study health outcomes at the local level. The main criticism is usually lack of representativeness of the general population. In this study, a spatial modelling approach was developed to assess the representativeness of a rural Australian clinical database. We compared two methods commonly used in health geography, namely Generalized Additive Models and the spatial scan statistic. Both methods were shown to have strengths that can be exploited to detect underrepresentation of a small health dataset. We concluded that our participant data are largely representative of the underlying population and highlight focus areas for further participant recruitment, allowing disease cluster mapping to with confidence, even on the small dataset.

109 - Automatic identification for surgical instruments using UHF band passive RFID

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Abstract—Post-operation vestigial remnant of surgical instruments is a very serious problem in the operating room. The current two-dimensional symbol system is being used to help manage this problem. However, the two-dimensional symbols of this system have to be identified one at a time, since the symbols are a sort of printed matter. An HF band passive RFID system was also proposed to help manage surgical instruments. This system also had problems in identifying the signals of a large number of surgical instruments in bulk, since the scope of its identification area as a detection area was relatively small. To improve the deficiencies of this system, a UHF band passive RFID system was developed to identify the signals of all the surgical instruments, since its identification efficiency was far better than that of the HF band RFID system. From the results of our experiment using 100 surgical instruments, all the instruments were identified in approx. 15 seconds with this new RFID system. The electrical field intensity was also kept at a low, safe level, maintaining the working integrity of any electronic device within the operating room. These results are very promising and indicate that the proposed RFID system will be an improvement to the surgical instrument management systems currently being used. This new system will also undoubtedly reduce the workload of surgical nurses, while reducing human error in the operating room.

111 - Inter-regional Dynamics in Hippocampal Sub-Networks Co-cultured on Micro-electrode Arrays and Connected via Micro-Tunnels

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Abstract— Different pairs of adjacent sub-regions of rat hippocampal neurons were co-cultured within two-well devices on micro-electrode arrays (MEAs). Micro-tunnels allowed passage of axons, strong structural connectivity, and information transmission between wells. Paired-pulse stimuli were delivered at each electrode to increase the probability of the excitation without overstimulation. Because of the micro-channel construction, the electrodes inside these tunnels

pick up more activity than those within each well. In particular, the strong axonal inputs from the sources of native feed-forward EC-DG and CA3-CA1 co-cultures evoked more target activity than the feed-back networks. In contrast, the evoked target activity in the native feed-forward DG-CA3 networks was lower than the reverse flow of information.

115 - Health Technology Assessment of Medical Devices in Low and Middle Income Countries: study design and preliminary results

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Abstract— Health Technology Assessment (HTA) of Medical Devices (MDs) remains an open challenge in particular for Low and Middle Income Countries (LMICs). Wide literature investigated how economical constrains may affect HTA in LMICs. Much less has been done in analyzing systematically how MDs safety and efficacy depend from environmental conditions (e.g., users, plants, and operational spaces) and how this affect HTA. After recalling the main differences among MDs and drugs, in order to highlight dependencies from environments that can diminish MD safety or efficacy, this paper explicates the main minimum requirements that are assumed as granted in Europe and that may affect MD safety and efficacy if not met in LMICs.

116 - Volumetric Assessment of Bone Microstructures by a 3D Local Binary Patterns –Based Method: Bone Changes with Osteoarthritis

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Abstract— Osteoarthritis (OA) causes progressive degeneration of articular cartilage and pathological changes in subchondral bone, conventionally assessed volumetrically using micro-computed tomography (μ CT) imaging *in vitro*. The local binary patterns (LBP) method has recently been suggested as a new alternative solution to perform analysis of local bone structures from μ CT scans. In this study, a novel 3D LBP-based method to provide a new lead in bone microstructural analysis is proposed. In addition to the detailed description of the method, this solution is tested using μ CT data of OA human trabecular bone samples, harvested from patients treated with total knee arthroplasty. The method was applied to correlate the distribution of orientations of local patterns with the severity of the disease. The local orientations of the bone fibers changed along the severity of OA,

suggesting an adaptation of the bone to the disease. The structural parameters derived from the process were able to provide a new approach for the assessment of the disease, supporting the potential of this volumetric LBP-based method to assess trabecular bone changes.

119 - Mechanism of Low-level Microwave Radiation Effect on Brain: Frequency Limits

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Abstract— This study aims to investigation of frequency limitations for the recently proposed new mechanism of low-level microwave radiation (MWR) effect on human brain bioelectrical oscillations. The frequency dependent properties for the main steps of the mechanism, the rotation of dipolar water molecules, the disturbance of hydrogen bonds and the enhancement of diffusion, were evaluated based on published theoretical and experimental data. The investigation of frequency dependence of the MWR effect on the modulation frequency was performed using 450 MHz MWR, SAR 0.3 W/kg. The relative changes in electroencephalographic (EEG) signal power between the EEG segments with and without MWR exposure were selected as a measure for detection of the effect. Additional experiment at modulation frequencies 217 and 1000 Hz was performed and the raw data from our EEG database at modulation frequencies 14, 21, 40 and 70 Hz were also employed. Experimental results showed enhancement of EEG power with MWR exposure at all modulation frequencies; the changes were statistically significant at 14, 21, 40, 70 and 217 Hz. The analysis of published data confirms that the low-level MWR effect is limited to carrier frequencies up to around 100 GHz. The experimental results suggest that the effect of modulated low-level MWR on brain bioelectrical oscillations is not limited to the modulation frequencies within the EEG spectrum.

120 - Analysis and optimization of clinical pathway of a cancer patient in a University Hospital

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Abstract— A clinical pathway can be defined as a macro process that includes the complete management of a health problem. It could be considered the equivalent of diagnostic and therapeutic pathway, but the word clinical includes also

the person assistance to self-care and the psychological and social support. Managing and organizing a clinical pathway in order to exploit as efficiently as possible all available resources could be the aim of all hospitals.

The simulation is a modern approach that allows understanding, with a logical sequence, the entire process, in order to identify, analyze and underline characteristics, advantages and problems of the specific context. Nevertheless, simulation is not effective if the process analysis and the mathematical model are overlooked.

The purpose of this work is to characterize clinical pathways, and try to understand and optimize weak points. The various phases of the work allowed conducting a precise, clear and detailed analysis, in order to develop a more efficient process. Finally, the simulation model is able to consider all possible variables that could modify the efficiency of the process and also confirms that the reorganization proposal could be effective and sustainable before a real implementation.

122 - Impact assessment and risk analysis in the redevelopment of a healthcare structure

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Abstract— Any upgrading process aims for improving and optimizing operational conditions of every work environment. It generally includes the development of a change focused on organizational, technological and structural advancements in the expected conditions of specific active fields of interest.

The upgrading process has to be always well planned and organized in order to be a source of growth for the structure considered and not becoming an obstacle for the daily routine of the structure itself. This aspect is much more relevant in case of health facilities since everyday activities must be constantly kept at a standard level and under an accurate control.

To meet the needs of technological and legislative progress, the change following the upgrading process must be a long-term one. However, it will represent a significant variable both for the employees working conditions and the quality of the health care given to the patients.

In this work an objective and complete procedure has been developed to quantify, in an impartial and univocal way, the impact that an upgrading process can have on health activities. In order to prevent and neutralize all the possible risks for patients, employees and health workers, it is of utmost importance the objectively evaluation of effects and hazards that these processes involve.

124 - Low-Field NMR Relaxation Times Distributions and Their Magnetic Field Dependence as a Possible Biomarker in Cartilage

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Abstract— The dependence of the proton NMR relaxation times on field strength and on location within the tissue has been determined for a number of bovine and human articular cartilage samples. While the strong variation of T_2 across the triple-layered cartilage structure as well as its orientation dependence are well known from clinical and laboratory high-field studies, T_1 shows similar behavior only in low magnetic fields. At 0.27 T, the ratio of longest to shortest T_1 has been found to cover a ratio of about 3-5 in healthy tissue. At the same time, the average T_1 was found to be strongly field dependent in the range down to 0.25 mT, but no spatially resolved data are available under these conditions. By correlating the spatially resolved T_1 distribution obtained at field strengths of 0.27 T with mathematical decompositions of the signal recovery function into multiexponential components, an attempt is made to quantify the width of $P(T_1)$ for variable field strengths, and to identify the field value where this distribution is widest, being optimally situated as a biomarker for laboratory studies or pre-clinical low-field investigations where spatial resolution is absent or insufficient to resolve the cartilage layer structure.

127 - Separation of Superimposed Electrocardiographic and Electromyographic Signals

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Abstract—Electrocardiography (ECG) and surface electromyography (SEMG) are two non-invasive tests to evaluate cardiac and muscular functionality, respectively. They are both acquired by placing electrodes on the body surface so they become one the interference of the other. Typically, linear filters are used for ECG and SEMG separation: high-pass filters with cutoff at 20 Hz to attenuate ECG interference in SEMG, and low-pass filters with cut-off at 50 Hz to attenuate SEMG interference in ECG. In spite of that, linear filtering is not adequate due to the presence of a 20-50 Hz frequency-band in which the two signal spectra overlap. The aim of the present study was to evaluate the ability of the Segmented-

Beat Modulation Method (SBMM) for ECG and SEMG separation and by accurately maintaining signals characteristics. SBMM is a template-based technique for ECG denoising: under the hypothesis of ECG and SEMG linearly superimposed, it first provides an ECG estimation, and then an SEMG estimation by subtraction. In order to test the method under several conditions, SBMM was applied to simulated as well as clinical recordings with superimposed ECG and SEMG. SBMM was able to accurately estimate both ECG and SEMG in all cases. Indeed, ECG and SEMG were estimated to maintain their features such as amplitude (estimation errors <6%), heart rate and heart-rate variability. Moreover, estimated ECG was always characterized by a spectrum mostly (76.4-100.0%) included in the 0-50 Hz frequency-band, whereas estimated SEMG was always characterized by a spectrum mostly (80.9-95.6%) included in the 20-450 Hz frequency-band. Such results confirm the existence of a 20-50 Hz frequency-band in which ECG and SEMG spectral components are overlapped. Thus, SBMM is a robust filtering procedure to separate superimposed ECG and SEMG.

130 - Association between Accelerations and Decelerations of Fetal Heart Rate

A. Agostinelli¹, G. Belgiovine¹, M.C. Fiorentino¹, G. Turri¹, A. Sbröllini¹, L. Burattini², M. Morettini¹, F. Di Nardo¹, S. Fioretti¹ and L. Burattini^{1*}

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Abstract—Cardiotocography (CTG) is the most popular test for establishing the fetal health status. Among its characterizing features there are the fetal heart rate (FHR) accelerations (ACC), usually considered a sign of fetal well-being; and decelerations (DEC), some of which may indicate the risk of fetal hypoxia. Thus, ACC and DEC are usually considered independent phenomena possibly providing opposite information on the fetus clinical status. CTG is typically analyzed by visual inspection; still a computerized analysis may provide a more objective CTG interpretation and precise ACC and DEC characterization. Aim of the present study is to propose an automatic procedure for ACC and DEC identification and characterization, and to investigate a potential relationship between their occurrence. The 552 tracings of the Physionet “CTU-CHB intra-partum CTG database” were analyzed according to a procedure that includes: FHR preprocessing; 20 min windowing; baseline estimation; and ACC and DEC identification and characterization. Specifically, ACC and DEC were defined as FHR deviations from baseline of at least 15 bpm for at least 15 s and then characterized in terms of length (s), amplitude (bpm) and area (length·amplitude; bpm·s). Only 383 (69.4%) CTG recordings showed sufficiently good FHR signal quality to be enrolled in the study. Number of DEC per window was significantly higher than ACC (4.0 vs 2.5; $P < 10^{-14}$). DEC were

characterized by a comparable length but higher amplitude and area than ACC (LNG: 56 s vs 61 s, $P=0.2573$; AMP: 12 bpm vs 10 bpm, $P<10^{-11}$; AREA: 688 s·bpm vs 618 s·bpm, $P=0.0032$). DEC total area in a 20-min window was higher than that of ACC (3074 s·bpm vs 2007 s·bpm, $P<10^{-9}$), but such areas were also strictly correlated ($\rho=0.72$; $P<10^{-62}$). Thus, in a CTG recording, ACC and DEC are not independent phenomena but their occurrence is strictly associated.

131 - Crosswalk – a time-ordered metric

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Abstract— We are concerned with glucose-dynamics modelling. When determining parameters of glucose-dynamics model, we use a metric to quantify fitness of calculated glucose levels to measured glucose levels. To the best of our knowledge, no glucose-dynamics study used nor devised a metric that calculated with time ordering of measured glucose levels. Therefore, we designed a new metric, Crosswalk, which calculates with the time ordering. We compared the proposed metric with other metrics, using empirical cumulative distribution function. Based on the results, we draw recommended metrics. The Crosswalk metric qualified as the best candidate for glucose-dynamics modelling.

132 - Wearable RFID perspiration sensor tags for well-being applications – from laboratory to field use

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Abstract— RFID technology has proven to have many possibilities in sensing applications. Smart sensor solutions would be especially helpful in the health and well-being sectors. There is already research on wearable RFID-based sensors, but most are only tested in controlled laboratory environments. The emphasis of this paper is 1) to analyze the performance of two moisture sensor textile tags in realistic field use and through this 2) to discuss their application possibilities. Based on the measurement results, different kinds of textile tags were differently affected by moisture. Especially with embroidered tags the presence of moisture could be detected, including in field conditions. Many applications were also found for the tags. The results indicate potential of

RFID-based sensing also in field use, but the actual use environment must be carefully taken into account when implementing the technology.

133 - No Changes in Glucose Effectiveness in Condition of Reduced Insulin Action but Preserved Glucose Tolerance as Assessed by Minimal Model Analysis

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Abstract— Glucose effectiveness (S_G) represents the ability of glucose *per se*, under basal insulin concentrations, to stimulate its own uptake and to suppress its own production. S_G and its two components BIE (Basal Insulin Effect) and GEZI (Glucose Effectiveness at Zero Insulin) are known to decline in subjects whose glycemic status worsens, but no study aimed to analyze whether changes may occur even before, when a normal glucose tolerance status is still preserved but insulin resistance has already arisen. To investigate this issue, S_G , BIE and GEZI were estimated from the minimal model interpretation of frequently sampled intravenous glucose tolerance (FSIGT) test data in two groups of subjects with normal glucose tolerance (basal glycemia < 5.6 mmol/l): a group of control participants (CNT, $n=50$) and a group of subjects with pathologies or conditions causing insulin resistance (IR, $n=50$). No difference in mean values of S_G was observed in the IR with respect to the CNT group (2.3 ± 0.9 vs. $2.5 \pm 0.9 \cdot 10^{-2} \text{ min}^{-1}$; $p = 0.17$). BIE was found to be the minor component of S_G in both CNT and IR group. The GEZI component provided a significantly higher proportional contribution to S_G in the IR with respect to CNT (89% vs. 81% of S_G , $p < 0.0001$). In proportion, a significantly lower contribution was provided by BIE in IR group (11 ± 1 vs. 18 ± 1 , $p < 0.0001$). These results indicate that, at the real starting phase of the process of glucose tolerance impairment (reduced insulin action but normal tolerance), no variation in S_G occurs with respect to normality. An increased proportional contribution of GEZI, when BIE declines, may allow the maintenance of normal glucose effectiveness.

134 - Identification of feasible pathway information for c-di-GMP binding proteins in cellulose production

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Abstract—In this paper, we utilize a machine learning approach to identify the significant pathways for c-di-GMP signaling proteins. The dataset involves gene counts from 12 pathways and 5 essential c-di-GMP binding domains for 1024 bacterial genomes. Two novel approaches, Least absolute shrinkage and selection operator (Lasso) and Random forests, have been applied for analyzing and modeling the dataset. Both approaches show that bacterial chemotaxis is the most essential pathway for c-di-GMP encoding domains. Though popular for feature selection, the strong regularization of Lasso method fails to associate any pathway to MshE domain. Results from the analysis may help to understand and emphasize to the supporting pathways involved in bacterial cellulose production. These findings demonstrate the need for a chassis to restrict the behavior or functionality by deactivating the selective pathways in cellulose production.

135 - Impacts of laminin and polyethyleneimine surface coatings on morphology of differentiating human SH-SY5Y cells and networks

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Abstract—The viability and morphological differentiation of the neuronal cells are often enhanced by attachment on surface coating proteins or polymers. Laminin is a basal membrane protein and one of the matrix components in the nervous system. Polyethyleneimine is a positively charged polymer widely used for improving attachment of cell cultures. The aim of this study was to find a favorable surface coating for cultures of differentiating human SH-SY5Y cells in order to promote homogenous cell adhesion, neurite sprouting and formation of the complete network structure. Two surface coatings were examined; laminin and polyethyleneimine alone or when used together. The impacts of the coatings on morphology of undifferentiated or retinoic-acid and cholesterol differentiated human SH-SY5Y cells and networks were then assessed. In addition, the influence of coatings on the number of cell nuclei at 10 days *in vitro* was quantified. The morphological analysis of the study shows that laminin enables homogenous attachment and oval cell nuclei formation, whereas polyethyleneimine induces clusters of cells in form of multicellular spheroids. Furthermore, laminin supports branching of long neurites and neuronal network formation, whereas polyethyleneimine induces straight neurite bundles between the spheroids of differentiated human cells.

138 - Heart Rate Variability Analysis and Performance during a Repeated Mental Workload Task

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Abstract— We designed and conducted an experiment using a repetitive task to investigate associations between mental workload, performance, and Heart Rate Variability (HRV) features across repetitions. According to the literature, we define mental workload as the interaction between a person and a task that causes task demands to exceed the person's capacity to deliver. Mental workload was triggered by the use of a highly-paced video game repeated over time. Before engaging with the task, each subject was assessed in controlled condition (i.e., relaxing period) for a short time. Short term HRV features variations between the baseline (i.e., control situation) and each repetitive gaming session (i.e., mental task) were explored. The results show that HRV dynamics diminish with repetitions, while performance increases. Importantly, this suggests that HRV features can be well correlated with performance. Overall, this study advances the use of HRV analysis in the behavioral sciences at large, allowing the design of flexible neurophysiological lab-based experiments. Thus, it also opens the way to future autonomic behavioral neuroscience research.

139 - An Evolution Equation of Blood Flow in a Dilated Artery

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Abstract—In this study we derive an evolution equation for propagation of nonlinear waves in a blood-filled artery with a local dilatation (an idealized aneurysm) in a long-wave approximation. The equation is a version of the perturbed Korteweg-deVries-Burgers equation with variable coefficients. Exact travelling-wave solution of this equation is obtained by the modified method of simplest equation where the differential equation of Riccati is used as simplest equation. A numerical example of the obtained exact solution is presented and discussed from the point of view of arterial disease mechanics.

143 - To What Extent Can We Shorten HRV Analysis in Wearable Sensing? A Case Study on Mental Stress Detection.

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Abstract— Mental stress is one of the first causes of cognitive dysfunctions, cardiovascular disorders and depression. In addition, it reduces performances, on the work place and in daily life. The diffusion of wearable sensors (embedded in smart-watches, phones, etc.) has opened up the potential to assess mental stress detection through ultra-short term Heart Rate Variability (HRV) analysis (i.e., less than 5 min). Although informative analyses of features coming from short HRV (i.e., 5 min) have already been performed, the reliability of ultra-short HRV remains unclear. This study aims to tackle this gap by departing from a systematic review of the existing literature and investigating, in healthy subjects, the associations between acute mental stress and short/ultra-short term HRV features in time, frequency, and non-linear domains. Building on these findings, three experiments were carried out to empirically assess the usefulness of HRV for mental stress detection using ultra-short term analysis and wearable devices. Experiment 1 detected mental stress in a real life situation by exploring to which extent HRV excerpts can be shortened without losing their ability to detect mental stress. This allowed us to advance a method to explore to what extent ultra-short HRV features can be considered as good surrogates of 5 min HRV features. Experiment 2 and 3 sought to develop automatic classifiers to detect mental stress through 2 min HRV excerpts, by using a Stroop Color Word Test (CWT) and a highly paced video game, which are two common laboratory-based stressors.

Results from experiment 1 demonstrated that 7 ultra-short HRV features can be considered as good surrogates of short HRV features in detecting mental stress in real life. By leveraging these 7 features, experiment 2 and 3 offered an automatic classifier detecting mental stress with ultra-short features (2min), achieving sensitivity, specificity and accuracy rate above 60%.

145 - Carbon on poly(ϵ -caprolactone) (PCL) Ink-jet Printed Sensor for Monitoring Cell Cultures of Myoblasts

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Abstract- Nowadays techniques for sensitive non-invasive, real-time monitoring of cell differentiation and maturation are highly demanded. In light of this, the development of electrochemical printed sensors impedance-based could represent a promising tool. In the present work, we developed 2D ink-jet printed sensors for myoblasts adhesion monitoring, using carbon-based ink on a substrate consisting in non-woven electrospun mats made in crosslinked poly(ϵ -caprolactone) (PCL). First of all, sensors printability was optimized and the biocompatibility tested. In order to determine the possibility to employ the prepared systems as scaffolds for dynamic cellular cultures, the mechanical response of the PCL scaffold was evaluated through the application of cyclic deformation tests. After that, electrical characterization of ink and substrate was performed, followed by electrochemical impedance-based measurements to evaluate myoblasts adhesion. Biocompatibility assessment showed good results for both carbon and PCL. Mechanical tests findings suggested that a training of 50 cycles and a proper value of strain should be applied before the cell seeding, in order to ensure a subsequent controlled strain amplitude. The sensorized scaffold allowed us to correlate cell adhesion with an increase of impedance module, in agreement with biocompatibility testing. Thus, this first preliminary testing suggested that this non-invasive impedance spectroscopy-based measurement system can be used for sensitive monitoring of cells adhesion, in static and moreover, as suggested from mechanical characterization, in dynamic conditions.

147 - Changes in network activity in a neuro-robotic environment

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Abstract— A hybrid neuro-robotic architecture was developed, where a biological neuronal network was able to communicate with a small wheeled robot. The robot had to perform an obstacle-avoidance task and every time the robot hits an obstacle, the biological network receives a tetanic stimulation, aimed at strengthening connectivity. Here, we investigated the impact of tetanic stimulation on network activity of hippocampal culture grown on grids of 60 substrate-embedded microelectrode arrays. We found that closed-loop tetanic stimulation produced an enhancement of activity in

terms of evoked response, not seen in control and sham (i.e. open-loop tetanic stimulation) experiments. The obtained results demonstrate that activity-dependent interaction with the environment is essential to significantly impact network behavior. Our study constitutes a further step towards the development of neuro-artificial interfaces.

148 - Time-frequency analysis of surface EMG signals for maximum energy localization during walking

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Abstract—The purpose of this work is to assess the maximum energy localization in time-frequency domain of the surface EMG signal of the main lower-limb muscles usually involved in able-bodied walking. The maximum energy localization in time-frequency domain has been identified by means of Continuous Wavelet Transform (CWT), a time-scale analysis method for multiresolution decomposition of continuous-time signals. WT coefficients allowed to reconstruct the scalogram function, providing an estimate of the local time-frequency energy density of a signal. Then, localization of maximum energy density has been identified as the interval in time-frequency where the scalogram is exceeding the 72% of the peak value of energy density in both time and frequency domain. Results showed that the localization of maximum signal energy in time coincided with the region of maximum muscle recruitment during walking. A common frequency band of maximum information content was identified for all muscles between 70 and 160 Hz. These findings could be suitable for both supporting the use of WT for sEMG analysis and providing clinical indications on muscle recruitment during walking.

149 - Enhanced Wiener Filter for Ultrasound image denoising

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Abstract—Speckle phenomenon strongly affects Ultrasound (US) images. Over the past last years, several efforts have been done in order to provide an effective denoising methodology. Although good results have been achieved in terms of noise reduction effectiveness, most of the proposed approaches are characterized by a high computational load and require the supervision of an external operator for tuning the input parameters. Within this manuscript, a novel approach for noise reduction is investigated, based on Wiener filter. With respect to classical Wiener filter, the proposed

Enhanced Wiener filter is able to locally adapt itself. By automatically tuning its kernel a good combination of edges and details preservation with effective noise reduction can be reached. This behavior is achieved by implementing a Local Gaussian Markov Random Field for modeling the image. Due to its intrinsic characteristics, the computational burden of the algorithm is sensibly low compared to other widely adopted filters and the parameter tuning effort is minimal. Results on a simulated dataset are reported, showing the interesting performances of the approach.

150 - Ultrasound despeckling based on Non Local Means

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Abstract—Ultrasound images are characterized by speckle, a multiplicative noise that degrades their quality. In the last decades, several efforts have been done for developing effective denoising filters able to provide effective signal regularization and noise preservation. Recently, the so-called Non Local Mean approaches have proven to be well suited for such kind of problems. Within this manuscript, a new despeckling filter for ultrasound data is presented, developed in the Non Local Mean framework that jointly exploits several acquired video frames for reducing speckle. The main novelty consists in the metric adopted for the evaluation of patches similarity, which is based on the statistical properties of the acquired data. More in detail, the Kolmogorov-Smirnov distance between the cumulative distribution functions of the involved pixels, computed on the available frames, is evaluated. The method has been tested on simulated data and compared to other state of art despeckling filters belonging to different families, showing interesting performances in combining good details preservation with effective noise reduction.

154 - Gait asymmetry in Winters' group I hemiplegic children

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Abstract—Hemiplegia is a neurological disorder that in children is a common consequence of cerebral palsy. Hemiplegia involves one-half of the body, while the other half is typically not affected. Aim of the study was to evaluate gait asymmetry in Winters' group I hemiplegic children (W1), by

identifying possible differences between hemiplegic and non-hemiplegic side in foot-floor contact and activation patterns of gastrocnemius lateralis (GL). To this aim, basographic and EMG data from 12 hemiplegic cerebral palsy children (Winters' group I) were analyzed. Gait data from 100 normal developing children were used as reference. Mean decrease ($p < 0.05$) of normal cycles (i.e. normal sequence of gait phases HFPS) and a concomitant increase ($p < 0.05$) of atypical cycles (PFPS) were detected in hemiplegic side of W1, with respect to both non-hemiplegic side and control group. No relevant variations of GL recruitment were observed between hemiplegic and non-hemiplegic side of W1, in terms of muscle activation patterns and occurrence frequency. In conclusion, the study suggested that gait asymmetries detected in W1 lie in foot-floor contact patterns, but not in GL recruitment.

156 - A Preliminary Study in Neonatal Cardiorespiratory Monitoring through Diaphragmatic Electromyography

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Abstract—Cardiorespiratory monitoring continues to be a challenge in the Neonatal Intensive Care Unit due to the sensitivity of current techniques to false alarms and artifacts. Surface diaphragmatic electromyography (EMGdi) can be used to measure directly the respiratory muscles activity and to reduce motion artifacts. We propose to acquire ECG and EMGdi with the electrodes placed on the diaphragm to measure heart and respiratory rate in neonates. Data from fourteen neonates was analyzed to compare the measurements of the signal acquired in the diaphragm with the ECG bipolar leads and a reference respiration signal from piezoelectric respiratory effort belt. Bland-Altman plots showed agreement between heart rate monitoring in the diaphragm with no significant differences. Detection of breaths showed similar results in the EMGdi derived wave compared with the reference signal. Thus, heart and respiration rate monitoring in neonates can be accomplished with ECG and EMG signals acquired from the diaphragm.

157 - Simple Assessment of Insulin Sensitivity in the Zucker Rat

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Abstract—The model-based assessment of insulin sensitivity in Zucker rat from Intravenous Glucose Tolerance Test (IVGTT) data is a common procedure. The minimal model methodology provides a very reliable assessment but requires specific competence for running the model. The aim of this study was presenting calculated S_I (CS_I), as a surrogate index for the simple assessment of insulin sensitivity in the Zucker Rat from IVGTT data. To this aim 25 Zucker Lean Rats (ZLR) and 25 Zucker Fatty Rats (ZFR) were considered. Reference insulin sensitivity (S_I) was estimated in each rat through the minimal model methodology. CS_I is defined as the ratio between the rate of glucose disappearance (K_G) and the mean supra-basal area under the insulin curve during the test (ΔAUC_{INS}), corrected by the proportionality term, α . Regression analysis between S_I and $K_G/\Delta AUC_{INS}$ was performed to identify the α coefficient. Results showed as the computed value of CS_I presented a high correlation ($r = 0.89$, $R\text{-square} = 0.80$ and $p < 0.0001$, slope ≈ 1) with S_I . Mean value of CS_I over the whole population was not significantly different from correspondent S_I value ($p = 0.17$). CS_I is able to detect the well-known reduction of insulin sensitivity in the ZFR group (1.0 ± 0.1 vs. $5.0 \pm 0.7 \text{ min}^{-1}/\mu\text{U}\cdot\text{ml}^{-1}$, $p < 0.001$), in accordance with the results provided by S_I . In conclusion, the present study proposes CS_I as a suitable empiric index for a simple and reliable assessment of insulin sensitivity in Zucker rat and able to provide the same quantitative information of model-based S_I .

159 - Non-Contact Estimation of Sleep Staging

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Abstract—Non-contact sensing technology can allow quantitative measurement of sleep beyond the hospital setting, in a user-friendly and cost-effective manner. Wrist actigraphy has been extensively validated as an alternative to polysomnography (PSG), the gold standard in sleep monitoring. Results reported in the literature indicate actigraphy-based devices to be highly sensitive but poorly specific to sleep, without providing a breakdown of sleep into different stages [1, 2]. In this study, the sleep staging performance of a novel non-contact sensing technology was compared to PSG on healthy subjects. Forty subjects were recruited for this study, and a single night of their sleep was monitored using PSG and the non-contact sensor. Three experts scored the PSG data, and a consensus scoring was derived using a voting mechanism across the three scorers. Data were split into training and testing sets and proprietary algorithms were developed using the training set. The analysis presented in this paper refers only to the independent testing set. Inter-scoring variability of each scorer was assessed against the consensus scoring and compared to values quoted in the literature. PSG scoring for this study compared favorably to the scientific literature. The non-contact device algorithm produced good performance compared to PSG. No statistically

significant difference in total time for each sleep stage, in sleep onset or sleep efficiency was observed. Furthermore, performance of the non-contact device in detecting Wake, REM and N3 sleep stage was superior to that reported in the literature for wrist actigraphy. The non-contact sensor technology presented can provide a viable alternative to PSG in the home environment, allowing reliable monitoring of long-term sleep trends.

160 - Enhanced Sensing of Interleukin 8 by Stripping Voltammetry: Carbon Nanotubes versus Fullerene

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Abstract— The ability to detect protein biomarkers at a sub-nanomolar level represents a pervasive challenge in order to bring a significant improvement in early diagnosis or progression of patho-physiological processes. To this aim, Screen Printed Electrochemical Sensors have been acquiring a predominant importance. The possibility to use them with different measurement techniques, and to customize their surface to improve the performance represent really attractive features. In this work, performances of two different carbon nanostructures in combination with Stripping Voltammetry were evaluated as tools to improve the detection of Interleukin 8, a cytokine that has pivotal roles in various inflammatory processes and considered as a universal biomarker. Commercially-available Carbon sensors were modified using Carbon Nanotubes and Spherical Fullerene through drop casting technique. Interleukin 8 was quantified using an indirect techniques based on silver stripping catalyzed using Alkaline Phosphatase. The nanostructured sensors showed better sensitivity with sub-nanomolar limit of detection: 0.39 ng/ml for carbon nanotubes and 0.61 ng/ml for fullerene compared to bare carbon electrodes. These modification method is promising for sensitive detection of protein biomarkers in several applications, including the monitoring of inflammatory processes.

161 - A strategy for dissecting the kinetics of transcription repression mechanisms

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Abstract— Promoters in *Escherichia coli* include an ‘OFF’ state, during which transcription is halted. Here, we propose a novel empirical method for assessing the time-length spent by promoters in this state. It relies on direct measurements of RNA production kinetics at the single molecule level at different induction levels, followed by an estimation of the RNA production rate under infinite induction, which is then compared to this rate under real, maximum induction. We apply it to the LacO3O1 promoter and infer that, under full induction, on average, 15% of the time between successful transcription events is spent in the OFF state. We verify this result by comparing the kinetics of a mutant strain lacking repressor molecules with that of the inferred rate under infinite induction. We expect this strategy of dissecting the kinetics of transcription repression to be applicable to a wide number of promoters in *E. coli*.

163 - Testing of infusion pumps in healthcare institutions in Bosnia and Herzegovina

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Abstract— This paper presents the results of safety and performance inspection conducted on 325 infusion pumps in the period from January 2015 to January 2016 in public and private healthcare institutions in Bosnia and Herzegovina. Electrical safety inspection was conducted according to IEC 60601 - Medical electrical equipment: General requirements for basic safety and essential performance of medical devices. Periodical performance inspections were conducted according to legal metrology framework, more specifically according to Rules on metrological and technical requirements for infusion pumps, published in Official Gazette of Bosnia and Herzegovina (BH) No. 75/14. Our results show that approximately 9% of all tested infusion pumps do not meet electrical safety requirements or have performance outside the specifications. The causes of such faulty performance are environmental conditions, long period of usage of devices, faulty motors and device casing, as well as lack of systematic maintenance and regular safety and performance inspections in previous period. This paper addresses the importance of periodical performance inspections of these medical devices.

164 - Testing of dialysis machines in healthcare institutions in Bosnia and Herzegovina

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Abstract— This paper presents the results of electrical safety and performance inspection of 500 dialysis machines conducted in public healthcare institutions in Bosnia and Herzegovina. All measurements were made by independent laboratory for inspection of medical devices appointed by National Metrology Institute of Bosnia and Herzegovina in accordance with national rules published in Official Gazette of Bosnia and Herzegovina No. 75/14.

The results show that 12.6% of inspected devices do not meet electrical safety requirements or have performance outside the specifications. Specifically, 2% of tested devices did not pass the safety inspection in accordance with IEC 60601. Additionally, 11.32% of devices from this group had performance that was not in accordance to device specifications although malfunction was not reported.

These results help to develop awareness among patients and medical personnel about safety and accuracy of devices used in treatment of disease as well as set the ground for planning the upgrade in dialysis departments in the healthcare institutions.

167 - Clinical Trial of Wireless Epidermal Temperature Sensors: preliminary results

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Abstract—Body temperature is one of the most effective biometric indicators revealing the health conditions of a person. Wireless wearable sensors may completely change the way the body temperature is collected, stored and hence processed. Very recently, the authors developed battery-less low cost wireless thermometers by using the paradigm of the emerging Epidermal Electronics technology. Such devices are suitable to placement over the skin like a plaster or a tattoo and are compatible with the UHF Radiofrequency Identification (RFID) standard. Their potential application in clinical usage is here discussed by the help of volunteers at the University Hospital of Roma Tor Vergata. The experimental study is aimed at understanding the robustness of the sensor output versus the measurement procedure, the positioning over different body parts and several patients. Early results of the on-going clinical trial revealed that the variance of

RFID sensors is comparable with that of tympanic thermometer. The required compensation offset resulted rather patient-specific and can even vary for a same user along different days. Nevertheless, the on-chest placement is likely to mitigate this uncertainty.

168 - Effects of small and rapid temperature oscillations on adherent cell cultures: Exposure system, experimental method and a pilot study on human cancer cells

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Abstract—We present an original and simple system to aseptically incubate multiple adherent cell cultures simultaneously in a static and/or rapid oscillating temperature environment while monitoring the cell culture surface temperature in real-time. Additionally, in a pilot study, we show how exposure with this system to small ($\text{Temp}_{\text{varying}} \leq 2.5^\circ\text{C}_{\text{peak-to-peak}}$) and rapid ($\text{Freq} = \frac{1}{7} - \frac{1}{25}$ Hz) oscillations about a static temperature ($\text{Temp}_{\text{static}} = 37.0^\circ\text{C}$) limits the growth rate of human fibrosarcoma cell cultures (HT1080), to the extent not seen by exposure to static temperatures in the same range and causing no apparent damage to cells. Additionally, the magnitude of the growth rate limitation depends on the thermal oscillation frequency, and its manifestation depends on specific experimental parameters such as culture seeding concentration and time point of observation. Although further scrutiny of the mechanism of action behind the effects here reported must be performed, we hypothesize that these effects may be due to the periodic stimuli affecting the functioning of cellular autonomous biochemical oscillators and processes. This experimental regime and initial findings may help expand on the current knowledge of the effects of small and rapid energy deposition regimes causing oscillatory thermal exposures on biological systems, with possible implications in therapeutic, cell culture and regulatory arenas.

169 - A Hybrid Machine Learning Method for Detecting Cardiac Ejection Murmurs

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Abstract— This paper presents a novel method for detecting cardiac ejection murmurs from other pathological and physiological heart murmurs in children. The proposed method combines a hybrid model and a time growing neural

network for an improved detection even in mild condition. Children with aortic stenosis and pulmonary stenosis comprised the patient category against the reference category containing mitral regurgitation, ventricular septal defect, innocent murmur and normal (no murmur) conditions. In total, 120 referrals to a children University hospital participated to the study after giving their informed consent. Confidence interval of the accuracy, sensitivity and specificity is estimated to be 87.2%–88.8%, 83.4%–86.9% and 88.3%–90.0%, respectively.

175 - Assessment of Health Risks of Intermediate Frequency Magnetic Fields

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Abstract— Health effects of electromagnetic fields have been studied mainly focusing on extremely low frequency magnetic fields and radio frequency fields. Less attention has been paid to intermediate frequency magnetic fields (IF MFs) even though number of applications is increasing and information on potential health effects is sparse. We are conducting a series of studies to assess the exposure to IF MFs and the consequences of exposure.

Based on our measurements near electronic article surveillance (EAS) devices, cashiers are a group with exceptional IF MF exposure. Reproductive health effects are studied among female cashiers in an epidemiological study.

Behavioural and cognitive effects in mice exposed to 7.5 kHz MF were assessed. Post-mortem histochemical analyses were also performed. Blood cell samples from animals exposed to IF MFs are being assayed for genotoxicity. Male fertility indicators were measured in exposed mice. A behavioural teratology study is being conducted: mice are exposed to IF MFs *in utero* and the pups are tested for cognitive effects.

In vitro studies were performed with rat primary astrocytes. Cells were exposed to a vertical 7.5 kHz MF. DNA damage and DNA repair, and micronucleus formation were analyzed. To assess joint effects, genetic damage was induced with two known genotoxic agents. Selected endpoints were measured immediately after exposure and 36 days after exposure to assess induced genomic instability.

No adverse effects of IF MFs were observed on fertility in male mice or genotoxicity in cell cultures. However, interesting findings indicating protective effects were observed, which need to be confirmed in further studies. The behavioural studies suggested impaired spatial learning and

memory. The behavioural teratology study, *in vivo* genotoxicity and the epidemiological study are still ongoing. Assessment of health risks will be done when all results are available.

177 - A comparison between the commercially available gamma criteria evolution software and new modified algorithm for field-in-field technique

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Abstract— new gamma evaluation algorithm was created to improve ability of gamma criterion to determine, whenever field – in field plan two dose distributions are acceptable for further therapy. New parameter, dose gradient, was introduced to differentiate high dose gradient regions from low and use only those with high dose gradient. The aim of this article is to determine whether the new gamma criterion algorithm evaluation principle is suitable for FIF plans verification. For this study a 17 x 12 cm rectangular 6MV photon beam was used. Rectangular fields, sized 5 x 12, 6 x 8,5 and 3 x 4,3 cm were added as segments for each 17 x 12 cm base field in center. Dose distribution was calculated using treatment-planning system (TPS) to be used as a starting point to make distorted plans with segments displaced in superior, inferior, lateral left and lateral right directions to simulate patient movement or positioning errors during irradiation. Dose distributions for the distorted plans were measured using pixel ionization chambers detector array. The resulting dose distributions were compared to the reference one provided by TPS using gamma criterion. For acceptance criteria $\Delta DM=3\%$ dose-difference, $\Delta dM=3$ mm distance-to-agreement (DTA) and dose gradient 5% were used and 95% of all pixels should be within this criterion. For all the plans, considered in the present paper, 95% threshold was exceeded before the displacement reached clinically significant values of 3 mm. New algorithm show steep decrease of “pass” pixels at 3 mm even for segments with 3 x 4, 3 cm size. One has to conclude, that created algorithm should be investigated at comparison of dose distribution plans of clinical field in field conformal radiotherapy.

181 - Entropy-based Axon-to-Axon Mutual Interaction Characterization via Iterative Learning Identification

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Abstract—This paper presents a novel strategy to characterize the mutual interaction between the neural axons. Based on the mutual coupling factor and assumptions about

the recording micro-electrode array, the estimated potential is affected by the coupling factor matrix. In other words, the axon-to-axon interaction can be described by the extended membrane potential model with some unknown coupling factors. To identify these factors, entropy analysis is applied with an iterative learning approach using the simulated data. The advantage of this approach is to avoid solving the non-linear dynamic membrane potential equation. Simulation results indicate the effectiveness and correctness of our interaction model.

182 - Portal and Hepatic Vein Segmentation with Leak Restriction: A Pilot Study

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Abstract—A safe liver resection requires an optimal resection line to be planned with good correlation between blood inflow and outflow, and to avoid bleeding through large vessels. The objective of our research is to conduct a pilot study on the development of a portal and hepatic blood vessel segmentation method that will help significantly in the planning and navigation of liver resections. The proposed method is divided into two parts: pre-processing and liver blood vessel segmentation with leak restriction. On evaluation of our results, 80% of blood vessels of radius 2.5mm and 100% vessels from 3.0mm were detected by the proposed method. The time taken for processing was shown to be less than 2 minutes. We have developed a clinically valuable, semi-automatic portal and hepatic vein segmentation method that can be used for planning and intra-operative organ update in liver resection surgery.

185 - Optimizing the detection of characteristic waves in ECG based on exploration of processing steps combinations

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Abstract—In this paper, algorithms for detection of characteristic waves in ECG are examined and modified. We distinguished four processing steps of detection algorithms: noise and artefacts reduction, transformations, fiducial marks selection of wave candidates, and decision rule. Several algorithms for detection of QRS, P, and T waves are explored through combinations of processing steps, in order to achieve accurate detection results. Algorithms are tested on public available ECG databases with both QRS and P and T waves annotations. We found that, depending on the database, the combination of Sun Yan's MMF or MMD methods with Elgendi's algorithm works best for QRS detection (Se = 99.77% +P = 99.72% for MMF on MIT-BIH Arrhythmia Database and Se = 99.90% +P = 99.89% for MMD on QT Database), while P and T waves were best detected using only Elgendi's algorithm (P waves: Se = 60.84% +P = 59.61%, T waves: Se = 88.79% +P = 93.55% on MIT-BIH Arrhythmia Database). Our work shows that combining the best proposed methods in literature may lead to improvements in ECG waves detection, although P and T waves detection is still less than satisfactory and warrants further research.

186 - Linearity of Simultaneously Recorded Impedance Pneumography and Direct Pneumotachography in Thoracic Surgery Patients

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Abstract—Current assessment of postoperative lung function of thoracic surgery patients based on spirometry requires patient's mechanical effort. Non-invasive impedance pneumography (IP) has the potential to evaluate postoperative patients while alleviating their effort. The objective of this study was to assess the agreement of IP and pneumotachography (PNT) of adult cardiac and pulmonary surgery patients before and after surgery. IP was measured simultaneously with the flow signal from the mouth for one minute. Pearson correlation coefficient and linearity test were used to evaluate the agreement. 324 measurements had $r \geq 0.7$ and 23 measurements had $r < 0.7$. Linearity studies revealed that the average deviation from the linearity and sample-by-sample difference were similar between the surgery groups. The visualization shows that there is more deviation from the linearity in the lung resection group than in the cardiac surgery group during inspiration. The linearity was similar perioperatively, thus the surgery did not affect the agreement of IP and PNT. The results indicate that IP is potential to be used

for evaluation of postoperative lung functions of cardiac and pulmonary patients.

189 - A Technique for Quantifying the Relative Angular Movement of the Head and Shoulders

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Abstract - The objective of this study was to develop a method for quantifying the relative angular movements of the head and shoulders. To analyze and quantify the movement of aforementioned body parts, a turns index (TI) and range of motion (ROM) methods were chosen and used. It should be noted that the TI method hasn't been used before in neurological practice. By using the TI, the physicians are directly informed about the intensity of patient movements. The measurements of both inclination and rotation were done to accuracy of 1° by MoCap system containing a combination of camera and gyroscope systems. Then, 2-D plot comparing the head and shoulder rotations and another 2-D plot comparing the head and shoulder inclinations were obtained. Combination of TI and ROM was then used to model the measured data distribution and evaluate the patient's stability of his body posture. The correlation between the TIs and ROMs is negative moderate to negative strong. It is possible to use the new method for rehabilitation and diagnosis purposes.

190 - An automatic deep learning approach for coronary artery calcium segmentation

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Abstract—Coronary artery calcium (CAC) is a significant marker of atherosclerosis and cardiovascular events. In this work we present a system for the automatic quantification of calcium score in ECG-triggered non-contrast enhanced cardiac computed tomography (CT) images. The proposed system uses a supervised deep learning algorithm, i.e. convolutional neural network (CNN) for the segmentation and classification of candidate lesions as coronary or not, previously extracted in the region of the heart using a cardiac atlas. We trained our network with 45 CT volumes; 18 vol-

umes were used to validate the model and 56 to test it. Individual lesions were detected with a sensitivity of 91.24%, a specificity of 95.37% and a positive predicted value (PPV) of 90.5%; comparing calcium score obtained by the system and calcium score manually evaluated by an expert operator, a Pearson coefficient of 0.983 was obtained. A high agreement (Cohen's $\kappa=0.879$) between manual and automatic risk prediction was also observed. These results demonstrated that convolutional neural networks can be effectively applied for the automatic segmentation and classification of coronary calcifications.

191 - Evaluation of a Deep Convolutional Neural Network method for the segmentation of breast microcalcifications in Mammography Imaging

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Abstract—Cluster of microcalcifications can be an early sign of breast cancer. In this paper we present a deep convolutional neural network for microcalcification detection and compare its results to a classical approach. In this work we used 238 mammograms to train and validate our neural network to recognize which pixels in a mammogram correspond to a calcification; we tested the results on 52 images and obtained an accuracy of 83.7% against only 58% of the classical approach. Our results show how deep learning could be an effective tool to use for microcalcification detection and segmentation, outdoing classical approaches.

195 - Importance of HTA in modern Clinical Engineering

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Abstract— Despite actual significant improvements on clinical engineering management, the risks incidence on patients and users is still considerable, such as equipment failures and associated adverse events. Today it is of the utmost importance to pay attention to new ways that could offer better results, such as the multidisciplinary concept involved in Health Technology Assessment (HTA), which analyzes the technology from different perspectives.

In this way, taking into consideration the current success of HTA, the new way to avoid the increasing incidence of adverse events in medical equipment, more attention should

be paid to some failures arising from the complexity, or the lack of compliance with manufacturing and maintenance standards, and also because they do not have adequately trained professionals to perform good preventive or corrective maintenance. This paper analyzes the increasing importance of ways similar to HTA or evaluation of biomedical technologies, in its clinical, technological and economic aspects, together with the analysis of factors that determine medical devices failure and how to achieve a technological surveillance and other measurement that allows reduce adverse events.

197 - Prostate cancer detection ex vivo combining Raman spectroscopy and tactile resonance technology

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Abstract— Prostate cancer is the most common cancer for men in the western world. The most prevalent curative treatment is radical prostatectomy. However, prostate surgery can give unwanted side effects and there is a need for an instrument that can provide decision support to the surgeon during surgery on the presence of cancer cells in the surgical margin. A dual-modality probe, combining Raman spectroscopy and tactile resonance technology, has been used for detecting cancer in fresh human prostate tissue. The tactile resonance modality measures the tissue stiffness and Raman spectroscopy depicts the molecular content in tissue, both related to cancer. After ethical approval, the study investigated the potential of the dual-modality probe by testing its ability to differentiate between normal and cancerous prostate tissue ex vivo. It also investigated the minimal amount of measurement points needed to securely detect cancer on the surface of prostate tissue. Measurements on three prostate tissue slices show that the tactile resonance modality measuring stiffness was able to detect differences between normal and cancerous tissue on a significant level of 90%, but the sample size was too low to draw any firm conclusions. It was also suggested from the study results that the high wavenumber region in the Raman spectrum can give valuable information about cancer in prostate tissue. A number of 24 measurement points were enough for detecting cancer in prostate slices in this study. It can be suggested from this study that combining these two sensor modalities is promising for accurate detection of prostate cancer that is needed during prostate surgery, but more measurements including more prostates must be

performed before the full value of the study result can be established.

198 - Managing heterogeneous data in the HEALS project

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Abstract— A database system to support researchers in the EU HEALS project was implemented, storing heterogeneous data such as medical data, questionnaire results, omics data, satellite images, and more. The system provides hybrid storage supporting SQL, NoSQL and file style data. A flexible access control subsystem regulates how each user can access each data resource.

199 - Classification of physical activities and sedentary behavior using raw data of 3D hip acceleration

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Abstract—The purpose of this study was to develop and validate an algorithm for classifying physical activity (PA) classes and sedentary behavior (SED) from raw acceleration signal measured from hip. Twenty-two adult volunteers completed a pre-defined set of controlled and supervised activities. The activities included nine daily PAs. The participants performed PA trials while wearing a hip-worn 3D accelerometer. Indirect calorimetry was used for measuring energy expenditure. The raw acceleration data were used for training and testing a prediction model in MATLAB environment. The prediction model was built using bagged trees classifier and the most suitable extracted features (mean, maximum, minimum, zero crossing rate, and mean amplitude deviation) were selected using a sequential forward selection method. Leave-one-out cross validation was used for validation. Activities were classified as lying, sitting, light PA (standing, table wiping, floor cleaning, slow walking), moderate PA (fast walking) and vigorous PA (soccer and jogging). The oxygen consumption data were used for estimating the intensity of measured PA. Total accuracy of the prediction model was 96.5%. Mean sensitivity of the model was 95.5% (SD 3.5) and mean specificity 99.1% (SD 0.5). Based on the results PA types can be classified from raw data of the hip-worn 3D accelerometer using supervised machine learning techniques

with a high sensitivity and specificity. The developed algorithm has a potential for objective evaluations of PA and SED.

200 - Embedded Sensor Systems for Health – collaboration between industry, academia and healthcare

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Abstract— Embedded Sensor Systems for Health (ESS-H) is a research profile at Mälardalen University (MDH) in Sweden, where researchers are working together with several industrial partners, and healthcare organizations. The aim of the research profile is to develop novel embedded sensor systems promoting health. The sensor systems are developed with the aim to monitor health conditions and follow health trends of elderly at home, and also for monitoring of drivers and machine operators in order to achieve a safer work environment. Several companies are involved in the work in various ways; providing specialist competence, providing equipment and access to advanced laboratory settings, and also working as adjunct professors and providing industrial PhD students to the environment. Healthcare providers are involved in the work, providing end-user perspective to the work. This includes to provide real user-driven challenges, and involvement in all development phases.

201 - Cohort Description for MADDEC – Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease

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Abstract— The risk for mortality and prevalence of comorbidities of patients treated for cardiovascular diseases are high. Several risk estimation algorithms based on traditionally obtainable clinical information have failed in recognition of patients at risk even when medical interventions would be available. Usually the poor performance of risk prediction algorithms is attributable to heterogeneity in risk factors related hazards between different populations, national health care systems and even hospitals.

MADDEC is an ongoing research project focusing on the use of mass data in the development of accurate hospital-level risk prediction algorithms among patients treated for

different cardiac conditions. The study population comprises all patients treated (and to be treated) in TAYS Heart Hospital (electronic health records of ~73.000 individuals from a ten-year period) with a special focus on high-risk patients such as patients admitted for myocardial infarction or undergoing major interventions such as cardiothoracic surgery (both ~700 patients annually). The goal is to combine all past, present and future clinical data between years 2007 and 2029.

Hospital electronic patient records are combined with a database (KARDIO) designed specifically for research and quality control purposes updated daily by physicians. Additional phenotype information is acquired from bio-signal data from systems monitoring patients in hospital and from portable or mobile devices after discharge. Background and endpoint data of all previous and future hospital admissions, drug reimbursements and disability allowances are collected from national registries. Finally, mortality data will be monitored from national causes of death registry allowing also adjudication of different causes of death for more accurate endpoint definition.

All data are integrated to a dedicated noSQL/SQL research database service. The technical aim is to develop and deploy beyond state-of-the-art signal analysis and machine learning methods for hospital-data driven risk analysis. The clinical aim is to develop easily applicable tools for patient-level risk estimation used in facilitation of clinical decision-making. These tools can be used for example in estimating risk of short term-mortality after myocardial infarction or before heavy invasive operations.

203 - Predicting Gene Expression Levels from Histone Modification Signals with Convolutional Recurrent Neural Networks

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Abstract— In this paper we study how a Convolutional Recurrent Neural Network performs for predicting the gene expression levels from histone modification signals. Moreover, we consider two simplified variants of the Convolutional Recurrent Neural Network: Convolutional Neural Network and Recurrent Neural Network. The performance of the methods is evaluated with histone modification signal and gene expression data derived from Roadmap Epigenomics Mapping Consortium database, and compared against the state of the art method: the DeepChrome. It is shown that the proposed models give a statistically significant improvement over the baseline.

204 - Evaluation of the accuracy and reliability for photoplethysmography based heart rate and beat-to-beat detection during daily activities

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Abstract— With the advances in sensor technology and the emergence of new sensor systems, it is important to assess the accuracy of these devices. In this paper, we describe an evaluation study for two wrist-worn devices, namely PulseOn (PO) and Empatica E4 (E4), measuring photoplethysmography –based heart rate (PPG HR) and inter-beat intervals (IBIs). The accuracy and reliability of PPG HR and beat-to-beat detection are evaluated with respect to electrocardiography (ECG) –based HR and IBIs during different daily activities, such as sitting, standing, household work and cycling. The evaluation study employed data from twenty male subjects. The absolute difference of PPG and ECG HR was less than 10 bpm for 90-99% and 81-97% of time for PO and E4, respectively. The accuracy and reliability of the devices were decreased during household work due to the excess hand movements. On average, the mean absolute error in HR was 2.5 bpm higher in PO and 3.7 bpm higher in E4 during household work than during sitting. The percentage of correctly detected heartbeats was 89% for PO and 68% for E4 during sitting but 76% for PO and only 9% for E4 during household work. PO showed better beat-to-beat detection accuracy than E4 in all activities. The errors in heart rate variability measure (HRV) of root mean square of successive inter-beat interval differences were 3.5 ± 3.9 ms for PO and 10.2 ± 6.7 ms for E4 during sitting, but 18.0 ± 10.9 ms for PO and 48.7 ± 21.8 ms for E4 during cycling. As a conclusion, PPG –based wrist-worn devices are accurate and reliable for HR and beat-to-beat detection when the amount of hand movements is not excess but HRV can be estimated from PPG IBI data reliably only during resting conditions. Moreover, there were significant differences in accuracy between different devices.

205 - Physical characteristics of collimators for dual-isotope imaging with ^{99m}Tc and ¹²³I

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Abstract—The purpose of this study was to compare the physical characteristics of Low Energy High Resolution (LEHR), Low Energy Ultra High Resolution (LEUHR) and Medium Energy Low Penetration (MELP) collimators for simultaneous ^{99m}Tc and ¹²³I imaging. MELP collimator performed well with ¹²³I high-energy gamma photons, but low resolution makes it unsuitable to use for acquisition of small structures such as parathyroid adenomas. LEUHR collimators optimized for ^{99m}Tc have highest resolution, but the differences in septal penetration and sensitivity in favor of LEHR collimator needs to be tested with specific parathyroid phantoms.

206 - Optimization of ^{99m}Tc-sestamibi/¹²³I subtraction SPECT/CT protocol for parathyroid scintigraphy

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Abstract—The purpose of this study was to optimize effective, but technically challenging ^{99m}Tc-sestamibi/¹²³I subtraction SPECT/CT protocol for parathyroid scintigraphy. An anthropomorphic parathyroid phantom was set up using a small sphere, a thyroid phantom and a thorax phantom with clinical range of activities of ¹²³I and ^{99m}Tc. SPECT/CT acquisitions were performed using three collimators (Low Energy High Resolution (LEHR), Low Energy Ultra High Resolution (LEUHR) and Medium Energy Low Penetration (MELP)) and two energy window settings. Images were reconstructed with a combination of four different numbers of iterations and with or without scatter correction. Images were subjected to visual and quantitative evaluation. The effect of collimator, energy window selection and reconstruction parameters had a significant effect on visual appearance and adenoma contrast in parathyroid ^{99m}Tc-sestamibi/¹²³I subtraction SPECT/CT. Symmetrical energy windows and ultra-high resolution collimator yielded best results with some improvement with scatter correction.

207 - Stochastic Modelling and Optimal Spectral Estimation of EEG signals

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Abstract—The study of a time-frequency image is often the method of choice to address key issues in cognitive electrophysiology. The quality of the time-frequency representation is crucial for the extraction of robust and relevant features, thus leading to the demand for highly performing spectral estimators. We consider a stochastic model, known as Locally Stationary Processes, based on the modulation in time of a stationary covariance function. The flexibility of the model makes it suitable for a wide range of time-varying signals, in particular EEG signals. Previous works provided the theoretical expression of the mean-square error optimal kernel for the computation of the Wigner-Ville spectrum. The introduction of a novel inference method for the model parameters permits the computation of the optimal kernel in real-world data cases. The obtained MSE optimal time-frequency estimator is compared with other commonly used methods in a simulation study, confirming the error reduction. Optimal spectral estimates are presented for the case study, consisting of EEG data collected within a research on memory retrieval.

208 - Semi-automatic hippocampus delineation algorithm using surface fairing

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Abstract— Background: Manual hippocampus segmentation on structural magnetic resonance images (MRI) is labor intensive and time consuming. This paper presents a semi-automatic hippocampus segmentation method that decreases segmentation time without compromising accuracy.

Methods: We present a method that reconstructs sparse delineations into full hippocampal surfaces meshes with a smooth surface reconstruction technique. From fully manual segmented hippocampi in ten subjects with about 20 slice contours, we simulated sparse delineations ranging from 4-10 contours to simulate decreased contouring time by at least half. We compared the original hippocampi with reconstructed hippocampi as well as automatic segmentations obtained from each subjects' T1 weighted MRI using FSL-FIRST and FreeSurfer. We computed Dice overlap indices, percentage volume differences (PVD) and intra-correlation coefficients (ICC) with manual hippocampus segmentations.

Results: For the hippocampi reconstructed from 4 to 10 contours, we obtained high mean dice overlaps, low mean

PVDs and high ICCs in the range of $81(\pm 0.03)$ - $91(\pm 0.01)\%$, $6.85(\pm 5.33)$ - $1.98(\pm 1.63)\%$ and 0.970 - 0.997 respectively. Reconstructed hippocampi agreed consistently better with manual segmentations than automatic segmentation methods, even when 5 contours were used.

Conclusions: We were able to reconstruct hippocampi from a minimum number of contours and maintained high accuracy results that were consistently better than automatic methods. We next need to test this method on a larger scale and validate reproducibility and robustness.

209 - Predictive Health Technology and Policy Assessment of Socioeconomic Impacts

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Abstract— Impact evaluation of new policies, practices, and technologies is imperative for the effective and efficient provision of high quality health care. Traditionally the approaches for health technology assessment have focused on data collected from controlled trials. This has given the approach scientific rigor and precision. On the other hand, impacts to health and health care systems have far-reaching ripple effects in the society. Many of such impacts are not directly measurable in practice. They can be physically unmeasurable, too costly to measure, or the time delays from cause to effect are too long for practical purposes. This can leave loosely related data and expert opinion as the only sources from which to assess the impacts. In particular, for a future oriented assessment to inform a decision prior to a costly trial, a predictive approach not dependent on data collected in a trial is needed. Also, there can be significant indirect impacts from reactions to the primary impacts. To inform the decision makers, a systemic approach will provide a coherent holistic perspective encompassing both short and long-term impacts. We propose an approach using system dynamics to present such systemic structures and forecast their behavior by simulation. System dynamics is a proven technique to model complex systems to improve understanding of their behavior and evaluate intervention and policy alternatives. As a case example, we present a model considering traumatic brain injury and its socioeconomic costs. The model contains several feedback loops from which outcomes and secondary effects have amplified impacts.

210 - Determination of Mass-Inertial Characteristics of the Human Body in Basic Body Positions: Computer and Mathematical Modelling

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Abstract— The aim of the current article is: 1) to determine the mass-inertial characteristics of the human body of

the Bulgarian male on the basis of 16-segmental biomechanical model generated within a SolidWorks medium. They are needed in order to design wearable or rehabilitation robots and devices properly; 2) to verify the model via analytical results from our previous investigation; 3) to predict the inertial properties of a human body in various body positions. The comparison performed between our model results and data reported in literature gives us confidence that this model could be used to calculate these characteristics at random postures of the body.

211 - Motor control strategies in gastrocnemius muscles are affected differently in younger than in older adults after 14-day bed rest

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Abstract — We recorded high-density surface electromyograms (hdEMG) of gastrocnemii muscles in young and older healthy subjects performing isometric plantar flexion at 30 % of maximum voluntary contractions pre and post 14-day bed rest. We decomposed the hdEMG signals by convolution kernel compensation technique into contributions of individual motor units and analyzed common and individual oscillations in motor unit discharge rates before and after the bed rest. We further compared the results to oscillations of measured plantar flexion force. Our results demonstrate that, after the bed rest, muscle control strategies in young volunteers change differently than in older. Specifically, after the bed rest, the young exhibit slower oscillations of common drive to gastrocnemii muscles than older adults, but faster individual motor unit discharge rate oscillations. They also exhibit higher frequency oscillations of force. These results demonstrate the potential of hdEMG decomposition in identifying and quantifying the changes in muscle control strategies after bed rest.

213 - K-Band Doppler Radar is feasible and accurate to record and assess overnight respiratory rate

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Abstract— Sleep-disordered breathing (SDB) occurs in 10% to 17% of the male and 3% to 9% of the female population, and is identified as one of the leading causes of hypertension and cardiovascular morbidity. Polysomnography as the current state-of-the-art monitoring and diagnosis technique is highly resource intensive and significantly obtrusive for long term overnight usage. In this study, we aimed to develop a contact-less respiratory measurement device to facilitate long-term home based SDB diagnosis and monitoring. We used a dual channel Doppler transceiver to transmit electromagnetic waves (K-band, 24 GHz) and a non-linear arc-tangent demodulation scheme to measure the resulting phase variations in the received waves, reflected from the thorax of the subject. A band-pass filter isolated the periodic respiratory chest wall movement from the received signal. A peak detection algorithm counted the inspiratory maxima during a given period of measurement (respiratory rate). We compared the respiratory rates from our prototype (RR-PTP) with the gold standard respiratory inductance plethysmography (RR-RIP) in overnight studies with two volunteers. Linear regression yielded: $RR-PTP = 1.06 * RR-RIP - 1.22$, $r^2 = 0.96$, $n=405$. Bland-Altman analysis showed a mean bias of -0.14, and upper and lower limit of agreement of 0.86, -1.1 respectively. The current prototype for contact-less estimation of overnight respiratory rate correlates and agrees very well with the gold standard respiratory inductance plethysmography.

214 - Magnetic fields and childhood leukemia; science and policy in the Netherlands

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Abstract Long-term health effects of extremely low frequency (ELF) magnetic fields are not very well understood. Scientific studies comparing groups of children living near and far from overhead power lines indicate a higher leukemia risk for children living close to the power line. The ELF magnetic field (50, 60 Hz) near the power line possibly plays a role, but there is no scientific consensus on a possible mechanism for ELF fields leading to childhood leukemia and animal studies fail to confirm an increased leukemia risk. Therefore, a causal relationship between exposure to magnetic fields and childhood leukemia remains unproven.

In the Netherlands public concern about the health of children living near overhead power lines, combined with the scientific uncertainty led to a national policy based on the precautionary principle. The Ministry of Housing, Spatial Planning and the Environment issued the policy in 2005 as an advice to municipalities and grid companies. The policy is restricted to new situations. Aim is to avoid, as much as reasonably possible, creating new situations involving the long-term presence of children in areas near overhead power lines

where the (annually averaged) magnetic field exceeds 0.4 microtesla.

The presentation focusses on the scientific evidence for a relationship between childhood leukemia and power line magnetic fields and some details of the Dutch power line policy, and concludes with a short hands-on evaluation.

215 - Prior Variances and Depth Un-Biased Estimators in EEG Focal Source Imaging

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Abstract—In electroencephalography (EEG) source imaging, the inverse source estimates are depth biased in such a way that their maxima are often close to the sensors. This depth bias can be quantified by inspecting the statistics (mean and covariance) of these estimates. In this paper, we find weighting factors within a Bayesian framework for the used ℓ_1/ℓ_2 sparsity prior that the resulting maximum a posteriori (MAP) estimates do not favour any particular source location. Due to the lack of an analytical expression for the MAP estimate when this sparsity prior is used, we solve the weights indirectly. First, we calculate the Gaussian prior variances that lead to depth un-biased maximum a posteriori (MAP) estimates. Subsequently, we approximate the corresponding weight factors in the sparsity prior based on the solved Gaussian prior variances. Finally, we reconstruct focal source configurations using the sparsity prior with the proposed weights and two other commonly used choices of weights that can be found in literature.

216 - Cuff-induced changes of pulse arrival time: models and experimental results

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Abstract— We present experimental evidence suggesting, contrary to previous models, that arm cuff induced pulse arrival time (PAT) changes are primarily created under the cuff, and that they increase with cuff length and decrease with arterial diameter. The observed PAT changes are consistent with a transmission line model for the cuff segment of the arm.

217 - Long-Range Antenna Systems for In-Body Biotelemetry: Design Methodology and Characterization Approach

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Abstract—Long-range in-body biomedical telemetry enables monitoring of physiological parameters while maintaining mobility and freedom of movement. This emerging technology creates new applications in medicine, clinical research, wellness, and defense. Current in-body biotelemetry devices operate within about a meter around a user that limits their applicability. Here we examine the variety of approaches that, combined, can significantly extend the operating range. The radiation efficiency is constrained by attenuation and reflection losses in tissues. First, choosing an optimal operating frequency can minimize the losses. A specific antenna design is then required to decouple the antenna from a body. Two successful antenna design approaches are reviewed: (1) using loop antennas and (2) dielectrically loaded microstrip antennas. On-body matching layers and repeaters can be used to further improve power transmission. Finally, we present the radiation characterization method for in-body antennas in spherical phantoms with a direct illumination technique using an analog fiber optic link.

218 - Correlation of Depth of Anesthesia Indexes with MAC in Volatile Anesthesia

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Abstract—The aim of this study is to investigate the effectiveness of the commercial EEG-based indexes (BIS, SE/RE, AEP) and the sample entropy measure in assessing the depth of anesthesia in case of different agents (isoflurane, desflurane and sevoflurane) and induction protocols (propofol, VIMA, VCRII). The relationships between the indexes and the anesthetic concentration were quantified in 82 orthopedic patients using the linear Pearson's correlation coefficient and the Spearman's rank correlation coefficient. The highest Spearman's rank correlation coefficient was observed for the SE in sevoflurane, and for RE in isoflurane and desflurane anesthesia. If the linear Pearson's correlation coefficient is considered, BIS gives better correlation in isoflurane and desflurane, and SE in sevoflurane anesthesia.

219 - Electrocardiographic QRS Onset and Offset Time Estimation Using Bandpass Filtered Hilbert Transform: A Simulation Result

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Abstract—Use of bandpass filter as a preprocessing for Hilbert transform in electrocardiographic QRS complex feature detection is discussed here, based on computer simulation results. The main topic is onset and offset estimation on QRS complex. The bandpass filter is configured for the frequency range of QRS complex. Hilbert transform is applied to the filter output in order to generate an envelope signal which most reflects the QRS complex. From such an envelope signal, the onset and offset of each QRS complex are estimated by means of the tangent line projection method. The simulation ECG waveforms were generated from a dipole source vector with the lead vectors of the standard limb leads as an application of the lead field theory and the single dipole source model. The simulation results demonstrated that the estimation was stable against changes in the ECG source-measurement relation, which depends on the ECG lead selection and the ECG lead vector.

221 - Multiregional Fuzzy Thresholding Segmentation Completed by Spatial Median Aggregation: Modeling and Segmentation of Early Pathological Findings of Articular Cartilage

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Abstract— In the field of the clinical orthopedics, articular cartilage is one of the essential object which is evaluated. From the clinical point of view, the early osteoarthritis changes are increasingly challenging especially due to their insufficient contrast against image background. Therefore, those findings are often only subjectively estimated from MR records. We have proposed a mathematical model based on the multiregional thresholding methodology, which is able to differentiate of physiological articular cartilage from osteoarthritic findings. Segmentation method is composed from two parts: brightness modeling via fuzzy triangular functions, and spatial median aggregation procedure taking into account the spatial pixel information which makes the model robust against noise and artifact which are often incorrectly classified. A method was tested on the sample of MR data from Proton Dense sequence and Fat Suppression sequence with satisfactory results.

222 - Actively Breathing Mechanical Lung Simulator Development and Preliminary Measurements

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Abstract— The active mechanical lung simulator iLung 2.1 provides the possibility of simulating physiological human breathing patterns. The simulator can be used for assessing the environmental impacts as well as the inhaled aerosols with respect to the used lung equivalents, like latex bags and primed porcine lungs, whose anatomical properties are similar to the human lung. The progress in development of the iLung 2.1 and a comparison of the simulator test measurements with preliminary spirometry measurements is presented. The simulator is controlled by a cRIO system. This setup allows to control the simulation settings in real-time. Data for iLung 2.1 test measurements were taken by using a certified medical spirometer. Measurements were conducted in two simulation modes using two different lung equivalents. The iLung 2.1 measurements were compared with human spirometry measurements. Results show similarity between breathing patterns simulated by iLung 2.1 and normal human breathing allowing further validation and possible research applications.

227 - Health Technology Assessment of Medical Devices: The Canadian Experience

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Abstract— In Canada, health care decision-making and priority setting are decentralized and occur at various levels in the health care system. Most reimbursement coverage decisions for market-approved medical devices in Canada are done in hospitals within constraints of their annual budget. Canadian HTA bodies exist at the national, provincial, and regional/hospital levels to reflect the decentralized decision making structure. HTAs are conducted for a small number of new medical devices entering the market. HTA organizations in Canada are faced with several limited number of new medical devices entering the market. The pan-Canadian Health Technology Assessment Collaborative was formed in 2011 to share best practices, mitigate the risk of duplication of effort through information sharing, and to identify and participate in joint initiatives in the HTAs of medical devices, procedures and diagnostics. HTA organizations in Canada are faced with numerous challenges. They include, but are not limited to, costly health technologies entering the market at a fast pace, while health care budgets experience pressures

given a number of factors, such as economic down turn, aging population, and increasing consumer demand.

229 - Electrode Comparison for Textile-Integrated Electrocardiogram and Impedance Pneumography Measurement

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Abstract—Wearable electronics is a quickly broadening category in sports, wellbeing and entertainment products. Also, fully textile-integrated electronics is used increasingly to improve user experience. Medical industry is interested in exploiting, especially the latter sub-category of wearable electronics in long-term home care. In this study, we report a textile-integrated electrocardiography (ECG) and impedance pneumography (IP) measurement system. The performance of the system is evaluated by comparing the measurement accuracy for heart rate and respiration rate obtained with different electrode types and different measurement methods. Three electrode types: disposable, textile, and printed electrodes, are investigated and both, bipolar and tetrapolar measurement methods are compared by using modified commercial evaluation board. Disposable electrodes provide the least noisy signal and most accurate results. most stable results. However, the skin irritation caused by these electrodes prevents their use in long-term monitoring. The textile and printed electrodes did not seem to cause similar skin irritation. From the two measuring techniques, tetrapolar measuring method had higher noise levels, but heart rate and breathing were estimated with better accuracy compared to bipolar measuring method.

230 - Simple and convenient remote photoplethysmography system for monitoring regional anesthesia effectiveness

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Abstract—Simple and inexpensive remote photoplethysmography system for monitoring the effectiveness of regional anesthesia was developed and tested. The system involves surgical lamp as light source, compact video camera and computer with custom developed software. Data from eight patients were processed and the effectiveness of regional anesthesia was calculated. The results showed that the standard surgical lamp can be used as a light source together

with camera for remote monitoring of regional anesthesia effectiveness.

231 - The Venous Occlusion Effect To Increase The Accuracy Of Electrical Impedance Peripheral Veins Detection

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Abstract—The peripheral veins of the forearm are widely used for medical conditions such as requiring blood draw, drug and fluid administration. Biological tissues of the forearm have different electro-physical properties. The electrical resistivity of venous blood is lower than the surrounding tissues, which makes it possible to detect veins using electrical impedance method. However, the influence of the inhomogeneity of electro-physical properties of the surrounding soft tissues to the measured impedance values is comparable with the change due to blood vessel depth location, which decreases the accuracy of electrical impedance method of peripheral veins detection. In this study, we proposed the use of venous occlusion simultaneously with electrical impedance measurement to achieve better accuracy of vein projection on skin surface.

236 - Functional Brain Connectivity analysis using Coherent Measures

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Abstract—Brain connectivity gives detailed anatomical connections between the different brain regions all through the nervous system. The functional communications are all over the brain networks depending on neuronal oscillations. To know brain practicality, it is important to understand the interaction among sources of current movement within the brain. In this paper, we applied the multivariate analysis to the detection and synchronization between large-scale brain sources. All methods discussed in this article mostly based on the idea of a longtime connectivity measure known as the coherency.

238 - Markerless Motion Analysis for Early Detection of Infantile Movement Disorders

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Abstract—The analysis of spontaneous movements provides valuable information for diagnosing infantile movement disorders. However, analysis is time-consuming and interpretation requires well-trained experts. We present an automated system that captures 3D joint positions and head rotation of infants without attached markers or sensors. We introduce motion parameters of head, trunk, upper and lower limbs of both body sides that are related to range, variability, and symmetry of motions and offer objective diagnostic information for assessment of motor behavior. We analyze 6 recordings of 5 infants who are at high-risk of impaired motor development, and show how the system highlights movement characteristics that hint at disorders.

240 - A piezoelectric organic surface to control bacterial adhesion and growth

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Abstract—All organisms respond to vibration and bacteria are no exception. Previous studies showed that bacteria cells respond to vibrational cues, but the precise mechanisms of adhesion and growth in such conditions are still poorly explored. This work aims to unravel the mechanisms underlying bacterial adhesion to surfaces by investigating how vibrational environments influence bacterial behavior. To answer such questions, substrates based on the piezoelectric polymer Polyvinylidene Fluoride (PVDF) are used.

Abstract—The device in object consists on a glass slide on top of which a flat PVDF layer sandwiched between two gold electrodes is fabricated. Experiments are conducted on *E. Coli* bacteria expressing mCherry as a fluorescent marker, in a specifically designed chamber that ensures to avoid external perturbations. Vibrational stimuli are applied to the surface via the gold electrodes for different durations using a frequency generator. The substrate is then rinsed and bacteria attached to the surface are observed and quantified using a confocal fluorescent microscope. This project has several applications ranging from the medical field at an industry level to a niche area such as laboratory work related to bacteria. Being able to inhibit bacterial adhesion to surfaces would help preventing infections in humans caused by bacterial bio-

film formation on medical instruments and implantable devices; monitoring bacteria growth at the desired speed by simply sweeping the voltage applied to the surface would represent an interesting technique to adopt in laboratories. A flipped approach would bring to think of bacteria as active elements in electro-mechanical sensors.

242 - Predicting Blood Glucose Levels for a Type I Diabetes Patient by Combination of Autoregressive with One Compartment Open Model

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Abstract—Preventing complications in diabetes as well as support physicians and patients to treat the disease optimally, prediction of blood glucose levels is essential. In the most common treatment of type I diabetes, the diabetic measures the blood glucose level daily, based on which a proper dosage can be determined. Additionally, there are several other factors that affect the blood glucose concentration, such as carbohydrate intake and level of exercise. One of the main challenges is to make accurate long term predictions. Autoregressive models in combination with compartment models for estimating the insulin concentration can be determined as the first approach to this purpose. This paper provides a snapshot of the state-of-the-art for the model predictor, testing the results and comparing them with results from short-term prediction.

243 - Determination of Drug Activity on Pulmonary Arterial Hypertension using Time Domain Parameters of ECG

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Abstract—Electrocardiography (ECG) signals and the information obtained from the analysis of these signals are the main source of information in determination of numerous cardiovascular system diseases. Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature which results failure in the right side of heart and finally death. In this study, experimentally measured ECG signals were analyzed in computer environment for determi-

nation of the effect of PAH disease and its possible treatments on ECG signal's main waves (P wave, QRS complex and T wave). Wavelet transform based computer algorithms were developed for both filtering the raw signals and feature extraction. Finally, determined main wave amplitudes and durations were statistically analyzed and obtained results were discussed.

245 - Artificial Eye Blink Pacemaker - A First Investigation into the Blink Production Using Constant-Interval Electrical Stimulation

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Abstract— Facial paralysis due to damage of the facial nerve affects the function of facial muscles, including the muscles responsible for eye blinking. The absence of the eye blink can lead to severe and permanent corneal damage as the protection and lubrication of the eye is decreased. Thus, it would be highly important to provide an aid to sustain the eye health. The present aim was to study the effects of long-term electrical eye blink stimulation using a facial stimulation prototype. Five healthy participants watched a movie for 78 minutes, while the eye blinks were produced to their left eye by pre-programmed, timer-triggered blink stimulation at fixed intervals. We analyzed the functionality of the stimulation prototype, potential changes in the quality of the produced blinks, and the ratings of experiences in terms of pain, discomfort, and naturalness. We also analyzed the acuity of vision before and after the stimulation. The results showed that the stimulated eye blink was rated as not painful, somewhat uncomfortable, and slightly unnatural. With three participants the stimulation evoked a full eye closure throughout the study, and with two participants, the stimulation evoked partial blink after some time. Further, on four of the cases, the vision of the stimulated eye was better after the movie than before it. The participants told that the stimulation did not disturb the movie watching. As the findings were promising, the next steps include more comprehensive tests both with intact participants and with persons having an acute facial paralysis.

246 - Heart Rate Variability During Cardiorespiratory Exercise Test in Type 1 Diabetes

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Abstract—Type 1 diabetes is a metabolic disorder, which has been associated with decreased heart rate variability (HRV) and increased risk for adverse cardiac events. The aim of this paper was to examine HRV dynamics during a cardiorespiratory exercise test. 13 male subjects with type 1 diabetes (age 33.0 ± 6.7 years) and 25 healthy male controls (age 33.7 ± 7.6 years) participated the study. HRV was analysed from pre-exercise rest, warm-up, light exercise (40 W cycling), peak exercise, and recovery time periods. The main finding of the study was that subjects with diabetes had higher HRV complexity (higher multiscale entropy) during peak exercise when compared to healthy controls. HRV during rest, warm-up and light exercise was similar between the groups.

247 - High Resolution E-Jet Printed Temperature Sensor on Artificial Skin

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Abstract—Skin-conformable electronics research field has grown rapidly during the recent years. Body monitoring systems are shrinking in size and integrating more seamlessly with the human skin. To make these monitoring systems feasible options, new suitable materials and manufacturing processes needs to be studied. This paper presents materials and a simple fabrication process for skin-conformable, E-jet printed silver temperature sensors. Utilizing printing processes and biodegradable substrate materials, the skin-conformable electronics may become attractive for disposable systems by decreasing the manufacturing costs and reducing the amount of waste materials. In this study, the temperature sensors are fabricated with E-jet printed silver nanoparticle ink and the printing is done on a bacterial nanocellulose substrate. During the characterization, the silver temperature sensors were able to reach more than 0.06 % resistance

change per degree Celsius sensitivity and they exhibited positive temperature dependence.

248 - Modeling of ocular and eyelid pulse blood filling in diagnosing using transpalpebral rheophthalmography

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Abstract— The paper presents mathematical modeling of eye blood filling based on the registration of rheographic signals received through the eyelid. We briefly discuss the method of transpalpebral rheophthalmography and propose a two-layer model for transpalpebral rheophthalmography, for which we choose optimal parameter options. Calculations made in analyzing signals obtained from myopic patients show that eyelid blood filling contribution to the total volume of the signal amounts to less than 16%. A rheophthalmography signal registered transpalpebrally is shown to allow the calculation of amplitude values of ocular blood flow.

249 - Photoplethysmographic authentication in long-term scenarios: a preliminary assessment

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Abstract—The photoplethysmogram (PPG) is a biomedical signal that estimates the skin blood flow by means of infrared light. It is normally used to measure the oxygen saturation and the heart rate. During the last few years, some studies have been published to assess the PPG potential for its use in biometric authentication systems, but results are inconclusive. In this paper we propose a new approach for PPG biometric identification based on the Karhunen - Loève transform for the feature extraction and on the Euclidean distance for the classification. Using a public PPG database and a small local database, we have evaluated the possibility of using the PPG for authentication in the long term run. The new method obtains an equal error rate (EER, value where the proportion of false acceptances is equal to the proportion of false rejections) value of 4.8% in the best case, degrading to 20% in the long-term run, which suggest a performance degradation with time.

251 - Cardio-respiratory phase locking in newborn and one month infants as a function of sleep state

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Abstract— Respiratory and cardiac rhythms of newborn infants have been extensively investigated, in order to highlight pathological conditions. Nonetheless, given their tight dependency, methods observing their interactions could provide further insight. This study investigates the phase synchronization of heart rate (HR) and respiration in a group of healthy newborn and one month infants. Synchronous epochs of different n:m orders are identified (n cardiac : m respiratory cycles). Synchrograms provide their graphical representation while λ is an index of circular variance. Differences between epochs of quiet and active sleep and between newborn and one month infants are observed. Results show that the percentage of time spent in synchronization and the average length of periods of synchronization significantly increase during quiet sleep, both for the newborn and the one month infants. In Sudden Infant Death Syndrome (SIDS) the occurrence of infant distress generated by uncoupled cardio-respiratory response has been hypothesized. This confirms the relevance of the proposed analysis and results.

253 - Bots in messaging platforms, a new paradigm in healthcare delivery: application to custom prescription in dermatology

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Abstract—Messaging platforms enhanced with bot users are called to be a new paradigm in healthcare delivery. From patients communities to healthcare professionals groups, bots can provide advice, help (e.g. medication reminders), guidance and follow up to these communities integrated into messaging platforms, thus aligning people's increasing use of these platforms with healthcare services delivery. In this paper, we discuss the use of bots and messaging platforms for ehealth services and present a prototype of a bot, aimed to provide guidance in the process of personalized medication design in dermatology integrated within Slack messaging platform.

254 - Rényi and permutation entropy analysis for assessment of cardiac autonomic neuropathy

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Abstract— Cardiac autonomic neuropathy (CAN) is a complication of diabetes with a long asymptomatic phase that is associated with high morbidity and mortality. Early identification of CAN in Type 1 diabetes mellitus (T1DM) may be possible using heart rate variability (HRV). However, the power of HRV analysis to identify CAN depends on the selection of suitable features that provide reliable information regarding cardiac autonomic regulation. Our aim was to compare the performance of Rényi entropy (RE) and permutation entropy (PE) for identification of T1DM patients with CAN. RE and PE measures from 235 data points and 5 min of cardiac interbeat interval (RR) sequences were analysed in 18 T1DM patients without CAN, 14 T1DM patients with CAN, and healthy controls matched for age and sex. RE was calculated for different orders α (-5, 5), pattern lengths λ (2, 4, 8), and tolerance σ . For PE analysis λ was set to (3-4) and time delays τ to (1-10). A forward stepwise discriminant analysis was carried out for estimating the classification functions. Accuracy was estimated following a K-fold cross-validation ($k = 14$). RE calculated for RR sequences of $\lambda = 2$, $\alpha > 0$ showed the best performance for differentiating T1DM patients with CAN ($p < 0.0001$). PE measures showed better performance with ordinal patterns and $\tau = 4, 5$ and 7 for differentiating patients with CAN. RE and PE provide complementary information achieving 100% classification accuracy ($p < 0.0001$ and $p < 0.001$, respectively). This approach might be promising as a sensitive and specific tool for CAN diagnosis in T1DM.

260 - Performance of Systolic Blood Pressure estimation from radial Pulse Arrival Time (PAT) in anesthetized patients

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Abstract— The performance of estimating Systolic Blood Pressure (SBP) in anesthetized patients via Pulse Arrival Time (PAT) techniques was studied with respect to the minimum required time in between two recalibration procedures.

Materials: a clinical trial [NCT02651558] involving 14 patients was conducted measuring PAT from an ECG and an arterial line inserted into the radial artery.

Methods: comparison of BP estimates from PAT measurements against invasive BP values was performed in terms

of mean error and standard deviation of the error (AAMI/ANSI/ISO 81060-2), cumulative percentage of readings falling within 5, 10 and 15 mmHg (BHS criteria), and MAD - Mean Absolute Difference (IEEE Std 1708). Two calibration strategies were explored, involving time between recalibration periods ranging from 10 seconds to 8 minutes.

Results: assuming an affine calibration function between PAT and SBP, different slope (Mean Slope: -1.45, CI: -1.64 to -1.27 mmHg/ms) and offset values (Mean Offset: 575, CI: 517 to 633 mmHg) were found in between patients. In addition, given a patient, affine calibration functions at different anesthesia phases also showed to be variable. When assessing agreement in terms of existing international standards it was found that PAT-based SBP estimates complied with requirements when time between two calibrations was smaller than 60 seconds.

261 - Contactless Respiration Monitoring in Real-Time via a Video Camera

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Abstract—Until today, vital signs monitoring in neonatal intensive care units (NICUs) is based on wired sensors, known to cause discomfort and false alarms. In view of overcoming such issues we investigate a contactless method for respiration monitoring by means of a simple video camera. Unlike many other solutions proposed in the literature, our approach makes use of a motion estimation with low computational complexity which facilitates a real-time implementation. To do so, the input image is split into blocks, for each of which motion is estimated. Thereafter, these block motions are classified according to their likelihood to contain true respiratory activity, enabling an automatic region of interest detection. Aside from the respiratory rate (RR) our algorithm also computes a quality index, representing the confidence of the given RR. The proposed approach was tested and evaluated on 16 healthy adults, both during illuminated and dark conditions, using a color or near-infrared camera, respectively. On more than 2 hours of recording, Bland-Altman analysis reveals an error of 0.2 ± 2.3 bpm (breaths-per-minute) when compared to the reference measure, a thoracic strain gauge belt. Our analysis further indicates that -- independent of light or dark conditions -- the near-infrared camera alone is sufficient to achieve satisfying results. These findings pave the way towards a simple, low-cost and contactless RR monitoring. While currently only tested on healthy adults, future work includes the evaluation of this approach in clinical scenarios, such as NICUs in particular.

262 - General Data Format Security Extensions for Biomedical Signals

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Abstract—Biosignals recorded using personal health devices and stored in General Data Format (GDF) are vulnerable when the data is transferred, processed and stored to the external servers. The aforementioned vulnerabilities influence data security and user's privacy. In this paper, we propose modifications of GDF format that enables the encryption both - personal data and biosignals. These modifications do not corrupt the intrinsic structure of the GDF format and allow to encrypt independently the header with personal data and the section of biosignals. The proposed modifications were implemented, embedded and tested in a personal health device – multiparametric scale. The header data and biosignals are encrypted directly in the scale, and saved in the micro-SD card using our modified GDF format. Finally, we present the required resources needed for encryption process.

263 - Incorporating spike correlations into an SVM-based neonatal seizure detector

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Abstract—In this paper, we have adapted a spike correlation (SC) method of neonatal EEG seizure detection, so that it can be directly incorporated into an SVM-based algorithm. To this end, we estimate several features based on the analysis of the smoothed non-linear energy operator (SNLEO). SNLEO features alone resulted in a median AUC of 0.963 (IQR 0.919-0.985). This AUC was significantly higher than with the original SVM-based method ($p=0.024$). The SNLEO method was significantly improved by incorporating a selected number of features from the SVM-based detector ($p=0.002$). Median AUC with this feature set was 0.981 (IQR 0.942-0.994). This study confirms, that incorporating SNLEO features adapted from the SC method significantly improve the performance of an SVM-based neonatal EEG seizure detector.

265 - Tensor Regularized Total Variation for Third Harmonic Generation Brain Images

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Abstract— Third harmonic generation (THG) microscopy is a label-free imaging technique that shows great potential to visualize brain tumor margins during surgery. However, the complexity of THG brain images makes image denoising challenging. Anisotropic diffusion filtering (ADF) has been recently applied to reconstruct the noise-free THG images, but the reconstructed edges are in fact smooth and the existing methods are time-consuming. In this work, we propose a robust and efficient scheme for ADF to overcome these drawbacks, by expressing an ADF model as a tensor regularized total variation (TRTV) model. First, the gradient magnitude of Gaussian at each point is used to estimate the first eigenvalue of the structure tensor, with which flat and non-flat areas can be distinguished. Second, tensor decomposition is performed only in non-flat areas. Third, the robust-to-outlier Huber norm is used for the data fidelity term to maintain image contrast. Finally, a recently developed primal-dual algorithm is applied to efficiently solve the resulting convex problem. Several experiments on THG brain images show promising results.

266 - Design and Implementation of a Web Portal for Non-Medical Prescribing

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Abstract— Non-medical prescribing is the process of connecting patients to non-medical, generally community-based resources to support health and wellness. Despite increasing interest in non-medical prescribing, there has been little discussion of the potential role of technology in supporting the practice, and little exposition of the current role of technology in the area. Here we define a number of components of non-medical prescribing, noting how they lend themselves to technical solutions. We present an implementation of a non-medical prescribing platform intended primarily for use in an acute hospital setting. The platform facilitates the role of clinical experts as prescribers, an important consideration in building prescribing platforms that can contribute to the evidence base for non-medical prescribing as an impactful intervention.

270 - Time characteristics of prolonged partial obstruction periods using an Emfit mattress

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Abstract—Prolonged partial obstruction (PPO) is a sleep disordered breathing (SDB) characterized by increased respiratory efforts for extended periods of time. In this research, we analyzed the time characteristics differences of the Emfit (Electromechanical film transducer) signal between PPO and normal breathing (NB) periods. An experienced neurophysiologist selected ten-minute periods of PPO and NB from a sample of 10 patients suffering from PPO using the esophageal pressure as a Gold reference. Time features were extracted to study the differences between the two types of breathing. Statistical differences of a set of time-related features were assessed with Mann-Whitney *U*-test. The individual diagnostic performance was determined using receiver operating characteristics (ROC) analysis. Additionally, the diagnostic performance of a subset of features was evaluated using a support vector machine (SVM) classifier. In the evaluation, average results over ten-fold Monte Carlo cross-validation with 80% training and 20% testing splits were reported. Sixteen features reached statistical significance. The classifier achieved sensitivity and specificity of 85±12%, 87±14%, respectively.

272 - Characterization of Chloride Channels in Human Embryonic Stem Cell Derived Retinal Pigment Epithelium

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Abstract—Retinal pigment epithelium (RPE) is vital for vision. Its ion channels play important roles in the various functions of RPE that are critical for retinal welfare. These functions are often disrupted in degenerative eye diseases leading to visual impairment and even blindness. New treatments are currently being developed and transplantation of human embryonic stem cell (hESC)-derived RPE is showing great promise. For the success of these therapies, functionality of the transplantable cells needs to be verified. Presence of ion channels in hESC-derived RPE remains poorly known, particularly regarding the various chloride (Cl⁻) channels. We addressed this issue by investigating the Cl⁻ conductivity of hESC-derived RPE by whole-cell patch clamp recordings followed by immunolabeling of the Cl⁻ channels typical to RPE. Our recordings showed a diverse pattern of slowly inactivating currents characteristic to voltage-dependent Cl⁻ channels (ClC) previously reported for RPE. Some of the

identified currents were modulated by changes in intracellular calcium concentration. This data, together with the immunolabeling, demonstrated the presence of bestrophin-1, cystic fibrosis transmembrane regulator (CFTR) and ClC-2 channels in hESC-derived RPE thus indicating their capability to mimic native Cl⁻ physiology.

273 - Graphene electrodes for long-term impedance pneumography - a feasibility study

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Abstract—Typical disposable Ag/AgCl electrodes have potential drawbacks from a long-term measurement perspective. Particularly, they can cause an allergic reaction of the skin and can detach in case of sweating during physical activity or sleep. As they are disposable, the electrodes cannot be removed for cleaning. They must be connected to a device with separate cables, which adds to the wearer's discomfort and increases the possibility of motion artifacts. Therefore, graphene electrodes of different shapes and sizes were prepared to assess their electrode-skin contact properties compared to standard electrodes, and to evaluate the quality of obtained impedance pneumography signals and calculated tidal volumes. The results showed higher electrode-skin impedance, which did not prevent the registration of respiratory activity, after several minutes of stabilization. The accuracies of tidal volumes were comparable to the those of standard Ag/AgCl electrodes. This highlights the potential use of graphene-based, clothing-printed electrodes in cardiorespiratory and physiological healthcare, athletics, or even sleep applications.

274 - Motion artifact detection in respiratory signals based on Teager energy operator and accelerometer signals

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Abstract—Growing number of applications in which respiratory activity could be measured during natural functioning of patients amplifies the need for replacement of spirometric or pneumotachometric testing with other, indirect methods. One of them, impedance pneumography, thanks to

the use of electrodes mounted on the chest, can produce signals distorted by motion artifacts. Since the subject of detection and removal of artifacts from impedance pneumography signals had not been properly studied yet, we proposed a real-time method based on the Kaiser-Teager energy operator and 3-axis accelerometer signals. 24 participants were asked to follow a breathing protocol involving imitating sleep-time changes in body position and sleeping normally. Compared to manual marking, we obtained 81.3% accuracy (80.9% sensitivity and 81.6% specificity) for the optimal combination of coefficients used to estimate the threshold level based on the operator and accelerometer signals.

275 - Connectivity Analysis of Full Montage EEG in Traumatic Brain Injury Patients in the ICU

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Abstract—Long-term full montage (19 channels) electroencephalographic (EEG) recordings of 6 patients, treated in the Intensive Care Unit (ICU) for severe Traumatic Brain Injury (TBI), were analyzed using the methodology of connectivity analysis. Two connectivity measures, Coherence and Cross Frequency Coupling (CFC) were calculated for each pair of channels in two frequency bands, 8-13 Hz and 13-35 Hz. In the case of CFC, frequencies below 2 Hz were considered as the modulating rhythm. The ability of the measures to indicate the outcome of treatment was evaluated using the Mann-Whitney U-test. The results indicate that CFC values tend to be higher in good outcome patients for (modulating) frontal EEG channels. For the Coherence measure, U-statistic values close to 0.9 were obtained for some channel pairs, however, no clear pattern could be observed.

277 - Coronary artery disease diagnosis by means of heart rate variability analysis using respiratory information

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Abstract—Heart rate variability (HRV) analysis during exercise has been used to evaluate cardiovascular response to the stress of exercise, which may offer additional value than in rest condition. To properly analyze HRV during exercise, several challenges need to be addressed, such as including respiratory information and removing the dependence with the mean heart rate (HR) level. The objective of this work is to extract parameters from HRV analysis and respiratory information during exercise to evaluate their capability of diagnose coronary artery disease (CAD). Significant differences in mean HR were found due to medication effect in patients with CAD. By correcting the HRV parameters by mean HR, this effect is minimized. Power related to high frequency, when guided by respiration, results to have the best diagnosis capability (AUC > 0.7).

278 - Heartbeat Detection Using Multidimensional Cardiac Motion Signals and Dynamic Balancing

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Abstract—Ballistocardiography (BCG) is seeing a new renaissance mainly due to access of new miniaturized and sensitive MEMS accelerometers and gyroscopes that provides us a new tool for unobstrusive measurement of cardiac signals. These signals, however, suffer from high signal morphology variability and commonly signals are at least partly of low quality. A characteristic of a BCG signal is commonly a brief oscillation associated with each heartbeat which caused by the hearts mechanical movement. We developed an algorithm to detect these wavelets using an envelope enhancement filtering and subsequent dynamic balancing to alleviate the problem of high peak amplitude variability. The beat detection resulted in 0.87% missed beats and 0.31% false beats using the gyroY axis of the mobile phone's integrated motion sensors. Also it is shown, that if the used axis could be chosen optimally for each measurement accuracy of 0.22% missed beats and 0.21% false beats could be reached within the used measurements. A photoplethysmography

(PPG) signal was used as a verification reference. The data set consisted 2 min recordings from 66 healthy subjects and in total 8870 beats.

279 - Automated Pipeline for Brain ROI Analysis with Results Comparable to Previous Freehand Measures in Clinical Settings

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Abstract—Diffusion tensor imaging (DTI) has become a relatively common MR imaging technique in only 10 years. DTI can provide important information of brain microstructure *in vivo*. Many quantitative DTI analysis methods utilize either region of interest (ROI) or voxel-wise whole-brain methods. ROI methods do not require potentially bias-inducing image data altering, e.g., resampling and smoothing, and are the preferred method in clinical settings. We present an automated pipeline for quantitative ROI analysis of brain DTI data. The pipeline includes pre-processing, registrations, and calculation of mean (and SD) DTI scalar values from the automated ROIs. In addition to atlas regions, the pipeline accepts freehand ROIs, as long as the frame of reference is also provided. By the uniquely designed pipeline, we ensure that the results can be retrospectively compared to previously conducted manual freehand ROI measurement results, if desired. We validated the feasibility of the pipeline by comparing manual freehand ROI measurement results from 40 subjects against the results obtained from automated ROIs. A single set of freehand ROIs (drawn similarly to the original freehand manual ROIs in the population) was input to the pipeline, and the resulting scalar values from the automated ROIs were compared to the manual freehand ROIs' data. Adopting a limit for goodness of fit of $z = \pm 1.6$ resulted in 94 % success rate for the pipeline's automated ROI registrations in the whole population. The pipeline can reduce the time taken in clinical ROI measurements.

280 - Fast skull conductivity estimation using Boundary Element Method

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Abstract—Inter subject variability of skull conductivity highly constraints the possibility to use EEG (Electro Encephalography) amplitude parameters as a biomarker to compare the amount neural activity between different patients. The same inter subject variability limits the accuracy by which it is possible to localize the current sources underlying EEG using forward models with standardized parameters for the conductivity of brain, skull and skin. To solve this problem, it has been proposed to estimate conductivity parameters *in vivo* by analyzing the potentials generated by precisely known electric currents, injected into different pairs of EEG electrodes.

Here the efficiency of this conductivity parameter estimation problem is analyzed in the context of boundary element method (BEM). The geometries of brain, skull and skin compartments are fixed and given by triangular meshes, whereas the conductivity parameters are varied in order to predict the observed potentials. Using the Woodbury update formula, a method is here proposed to quickly update the BEM matrix, for new combinations of conductivity parameters.

In a simulation study, using a BEM model it is shown that that the gain in speed amounts to factor of 20, compared to the direct computations. This gain in speed is achieved without compromising the numerical accuracy. Therefore, we foresee that the proposed algorithm will play an important role in future EEG systems where patient specific head models are constructed in the EEG preparation phase, to enable calibrated EEG and accurate source localization.

281 - Investigation of photoplethysmographic signal augmentation index estimation differences between fingers

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Abstract— Photoplethysmographic signal augmentation index (PPGAI), proposed in our previous study, correlates strongly with aortic augmentation index and it is possible to discriminate patients with increased arterial stiffness from healthy subjects. This pilot study was aimed to investigate the PPGAI estimation differences between fingers in healthy subjects. The 8 channel analog front-end was built for the synchronous registration of PPG signals from left and right hand fingers. The PPG signals were recorded from 10 healthy subjects. The PPGAI was estimated for each period of the recorded PPG signals. It was found that the average PPGAI values of left hand fingers are higher compared to the right hand. T-test revealed that the differences are statistically significant ($P < 0.05$). In addition, there were found statistically significant differences in PPGAI values between the fingers of left hand. As a conclusion the PPG signal should be regis-

tered from right hand for the PPGAI estimation. More detailed studies should be carried out about the bilateral PPG waveform differences using larger study group.

287 - Treatment planning of microbrachytherapy with 3D NSGA-II

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Abstract—An innovative form of radiotherapy, microbrachytherapy, is under development for solid, inoperable, radioresistant tumors. A method of treatment planning is proposed using a multi-objective algorithm, NSGA-II.

A suitable treatment plan was found that treated the tumor (a sphere of 10 mm radius) with 6 injections. Each injection had a volume of 5 μ L, containing ⁹⁰Y microspheres with an initial activity of 50 MBq.

The treatment plan respected both the constraint on the tumor (95% of the tumor to receive at least 95% of the target dose, 100 Gy) and the constraint on a nearby organ at risk (no more than 10% of the organ to receive over 10 Gy).

Optimization time was less than 7 minutes for a population of 800 treatment plans over 100 generations with a 2.5 GHz quad-core MacBook Pro.

291 - To improve patient care & safety of rural patients empowering the village doctors

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Abstract— In most developing countries, although the vast majority of the people are living in the rural areas, the qualified medical doctors are not available there. Health care workers and village doctors are largely responsible for the rural medical care. Mishaps due to wrong diagnosis and inappropriate medication have been causing serious suffering that is preventable. In order to improve rural health care facilities and achieve health equity and patient safety, together with the local partners in Bangladesh, we set up a model center for empowering the village doctors and female health workers through training them to use smart and affordable medical devices and appropriate ICT tools, to address some of the most serious health problems of the rural disadvantaged people, and offer Point-of-Care services for women and children in particular. Our earlier e-Health initiatives in rural settings in Bangladesh with some ICT based solutions and approaches to local needs have shown potentials for improving village doctors' performance. Taking advantages of the popularity, affordability, potentials and acceptance of smartphones and Internet access, this work provided a model for improving rural health environment. Our work first initiated in 2009, initiated included : i) identification of the problems and sustainable solutions, ii) created access to reliable,

robust and cost effective medical devices, iii) developed education and training packages for safe use the diagnostic devices and ICT tools, iv) provided robust and reliable connectivity to the medical experts for disease treatment and offering Point of Care services, v) developed appropriate e-Learning content on health education for disease prevention and treat health problems which routinely afflict the rural people. Further e-Health work, with the local needs and conditions in mind, will gain acceptability among rural people for illness management, disease detection and prevention, health awareness improvement, and all that can lead to poverty reduction, and sustainable socio-economic development.

292 - The Effect of Occlusion with the Cuff

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Abstract— The widely used non-invasive blood pressure measurement methods occlude the brachial artery with a cuff. The occlusion modifies the blood flow and affects the systolic and diastolic blood pressure. The paper presents the results of measurements taken from patients with cardiovascular diseases and from healthy senior and young persons. Changes in pulse wave transit time (PWTT) were found to be applicable to characterize the effect of occlusion. PWTT was cut into two parts: PWTHC from the heart to the cuff and PWTTFC from the cuff to the fingertip. The occlusion affected PWTHC and PWTTFC differently: increased the former and decreased the latter. Increased PWTHC reflects a less rigid arterial wall resulting in an underestimation of blood pressure using the cuff-based measurement method.

294 - Texture-property relations of bioamine crosslinked gellan gum hydrogels

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Abstract— Gellan gum is a hydrogel with potential for soft tissue engineering but a quick and thorough method is needed for screening of different possible compositions for more extensive studies. Here optical projection tomography in bright field mode was used to image nearly transparent hydrogels to record their optical texture in 3D. The gained Haralick's textural features were then analyzed with multiple discriminant analysis and combined with data from mechanical testing and neuronal cell culturing. We show the usefulness of optical texture analysis in screening of hydrogel compositions when aiming for tissue engineering applications.

295 - Electrodermal activity asymmetry in sleep - a case study for migraine detection

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Abstract—Migraine is a poorly understood disease and it is estimated that 15% of people in Europe alone are affected by it. In this study skin electrodermal activity (EDA) signals of left and right wrists were collected from a migraine patient to see if the asymmetry associated with EDA signals will affect to migraine detection based on wearable sensors. In the study, nighttime EDA storm epochs were detected and visual inspection on total time of EDA storm epochs and timing of EDA storms between wrists were done. Also filtered EDA signals of nights that preceded migraine attacks were visually checked. According to the results, EDA measurements from one wrist are enough to detect changes before a migraine attack because the EDA asymmetry measured between wrists might play not a significant role in migraine prediction.

296 - Optical Projection Tomography Imaging of Single Cells in 3D Gellan Gum Hydrogel

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Abstract—3D cell culturing has become attractive in biology and tissue engineering laboratories as it mimics the natural environment for the cells to grow, differentiate and interact in all directions. To study cells and cellular interactions within 3D, cell culture requires a non-invasive, non-toxic, and high resolution imaging technique. The existing imaging techniques face challenges to image cells in 3D macro-scale environment because of the sample size, photobleaching or resolution requirements. Optical projection tomography (OPT) is a non-invasive 3D imaging technique for samples in the range of 1-10 mm. It works in both emission and transmission modes for fluorescence and bright-field imaging, respectively. Here, we demonstrate the use of OPT for imaging of cells and cellular materials in 3D gellan gum hydrogel. Fluorescence projection images showed alive and dead human lung fibroblast cells encapsulated in hydrogel. The mineralized extracellular matrix secreted by the human adipose stem cells in the hydrogel was evenly distributed throughout the sample and analyzable in 3D volume.

297 - Sleep-wake detection and computation of sleep continuity from a wrist unit in children, adolescents and adults

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Abstract—This work first aims at demonstrating a new accelerometer-based sleep-wake detection algorithm. Results are shown against gold standard polysomnography (PSG), in adults. We also used subjective sleep quality measures to elaborate a sleep continuity index (SC). We hereby provide the evidences that this approach correlates with subjective appraisal of sleep quality. Finally, we show how this quality index is distributed amongst children, adolescents and adults.

300 - Early stage Health Technology

Assessment of Electrochemotherapy of skin-directed therapy for skin melanoma and Basal Cell Carcinoma

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Abstract—One of the most successful medical application exploiting electroporation is an antitumor therapy called electrochemotherapy (ECT). Clinical use of electroporation in medicine is in full swing and in need of Health Technology Assessment (HTA) analysis. The early stage HTA would enable easier equipment purchase and increase opportunities for including ECT in the list of treatments covered by health insurance and raise the general awareness of electrochemotherapy cost in comparison to benchmark treatments. Few cost efficacy analysis have already been performed [1] but they are lacking information on Quality of Life (QoL) increase. The cost effectiveness of electrochemotherapy will be evaluated for treatment of skin melanoma and Basal Cell Carcinoma (BCC). Because cancer is a recurrent disease, we choose Markov modeling strategy. The article is composed of a detailed model description and procedures defined for future data collection. With this article we would also like to emphasize the importance of EQ 5D questioners, a standardised instrument for use as a measure of health outcome and numerical reporting of QoL increase.

302 - Removal Estimation of Uremic CVD Marker Phosphate in Dialysis Using Spectrophoto-and Fluorimetric Signals

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Abstract— The high phosphate (P) level is considered a key player in the genesis and progression of vascular calcification in chronic kidney disease. Therefore, it is necessary to assure the sufficient removal of this uremic retention solute during dialysis. The aim of this study was to develop models on the basis of optical signals of a particular biofluid - the spent dialysate, a waste product of kidney replacement therapy, to estimate concentrations and removal of phosphate. Eleven uremic patients from Tallinn, Estonia, were studied during altogether 42 hemodialysis treatments. Dialysate samples were collected during each treatment and analyzed at a laboratory. Ultraviolet absorbance and fluorescence spectra of the spent dialysate samples were measured. The spectral values were transformed into phosphate concentration using multiple linear regression models. Three different models were created, one used UV- absorbance values, second fluorescence values and third combined both signals. Mean phosphate concentration (mmol/L) measured in the lab was 0.299 ± 0.141 , and 0.298 ± 0.114 , 0.296 ± 0.115 , and 0.296 ± 0.118 estimated by UV, fluorescence and combined model, respectively.

Total removed (TR) amounts of phosphate were calculated using phosphate concentration values from the lab and all three models. Achieved (TR) values (mmol) were 42.17 ± 11.42 , 43.23 ± 9.55 ; 41.80 ± 9.59 and 42.91 ± 8.69 measured in the lab and estimated by different models respectively. The results were compared regarding mean values and SD. The phosphate concentration and total removed amount values calculated using optical models did not differ from the phosphate levels and removal measured in the clinical laboratory ($p \leq 0.05$). This study indicates that it is possible to estimate phosphate level and removal during the dialysis procedure using only optical signals of the spent dialysate.

303 - Optimized Raman Setting of Objective Lens, Laser Power and Integration Time for High and Low Concentration of Nonstructural Protein 1

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Abstract—Surface Enhanced Raman Spectroscopy (SERS) is a powerful analysis technique for detection of biological molecules. The quality of Raman spectra is highly dependent on the concentration of the molecules and the setting of Raman equipment. This paper describes the optimization of Raman setting which are the microscope objective lens, the laser power and the integration time for detection of non-structural protein 1 (NS1). NS1 protein is a biomarker for diseases related to flavivirus infection such as Dengue Fever (DF), Murray Valley Encephalitis (MVE), Yellow Fever (YF), Tick-borne Encephalitis (TBE), West Nile Encephalitis (WNE) and Japanese Encephalitis (JE). Optimum Raman setting for high (10ppm) and low (0.1ppm) concentration of diluted NS1 are determined. From experiments, it shows that objective lens of 50X, laser power of 150mW and integration time of 30sec, produces Raman spectra with highest peak intensity, at high concentration of NS1. With the same objective lens and integration time, laser power of 300mW is observed to produce highest peak intensity, at low concentration of NS1.

304 - Temperature effect on the baseline noise in MEA measurements

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Abstract— It is a well known fact that increasing temperature increases noise in all kind of electronics, which applies also to cell and tissue measurements by microelectrode arrays (MEAs). We show that ambient temperature may have a surprisingly big role in the noise level of MEA measurements. To study that we measured the baseline noise when the MEA amplifier was subject to temperature variations, either in a temperature chamber or by preventing amplifier unit's normal heat exchange. Around room temperature ($+24^{\circ}\text{C}$) the RMS value of the baseline noise was found to increase approximately $0.14 \mu\text{V}/^{\circ}\text{C}$, which is a huge variation as the default RMS noise at that temperature with our setup was only around $5.5 \mu\text{V}$. Additional cooling of the MEA amplifier could thus be a clever way to decrease the noise level at very sensitive measurements and on the other hand, one should not interfere the amplifier's normal heat exchange to the ambient air in order to avoid additional warming and thus increasing the noise level.

306 - Nocturnal Use of Light Compression Garments and Recovery

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Abstract— The aim of the study was to investigate nocturnal effect of wearing whole-body light compression garments on post-exercise recovery. HRV analysis was used to evaluate the recovery. The study involved sixteen female Finnish baseball players for four three-day-periods. The participants wore light compression garments every other three-day period and kept record of daily events. The analyzed period was 4 hours starting from the moment subjects fell asleep. The HRV analysis was performed for the time domain, frequency domain and nonlinear measurements. There were no statistical differences in HRV parameters between nights when subjects used or did not use light compression garments. This indicates that whole-body light compression garments had no benefits on the post-exercise recovery during the night.

308 - Medical Devices – Importance of Safety and Performance Testing

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Abstract— Nowadays, more than 10,000 different types of medical devices can be found in hospitals. The medical devices used in medical centers and hospitals for monitoring and treatment of patients require periodic safety and performance checking in order to have confidence in their functioning and operation. Physicians need better accurate medical measurements in order to better diagnose diseases, monitor patients and deliver treatments, in this way failure to ensure appropriate measurements will certainly have diverse effects.

Safety and performance testing of medical devices in the medical sector is a one of the key factor in improving public health. Acquiring results of some investigations indicate a need for new and severe regulations on periodic performance verifications and medical equipment quality control program especially in high risks instruments. It is also necessary provide training courses on the fundamental of operation and performance parameters for medical staff in the field of metrology in medicine and how can get good accuracy results especially in high risk medical devices.

310 - Evaluation of the effective and functional connectivity estimators for microelectrode array recordings during *in vitro* neuronal network maturation

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Abstract—During maturation, neurons and neuronal ensembles interact and build connections. Changes in the network structure have effects on the overall electrophysiological activity, and consequently on the observable connectivity. In this paper, we assessed effective and functional connectivities during neuronal network development by means of directed connectivity and synchronization, respectively.

For that, we analyzed *in vitro* dissociated mouse cortical neuronal networks during four weeks using microelectrode arrays. Functional and effective connectivities were estimated with CorSE and transfer entropy (TE), respectively. Here, we describe the advantages of the methods relative to each other.

We observed that the functional connectivity analysis may provide networking information in earlier phases of network development than effective connectivity. On the other hand, effective connectivity analysis provides information on the sources and targets of information flows. By corroborative analysis using CorSE and TE, one can investigate possible effects of early synchronizations on information transfer during the later stages of network development.

In conclusion, using effective and functional connectivity assessments jointly provides for enhanced analysis of the development of information transfer during the structural development of a neuronal network.

311 - The importance of VERIFI ("Vasomotoric Elimination and Reconstructed Identification of the Initial set-point") for the performance of the CNAP technology

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Abstract— The mechanisms implemented in CNSystems' Continuous Non-invasive Arterial Pressure (CNAP) devices are a combination of the traditional Vascular Unloading Technique (VUT) and the VERIFI (Vasomotoric Elimination and Reconstructed Identification of the Initial set-point) mechanism. The hypothesis that the VERIFI mecha-

nism (which deals with slow physiological rhythms and vasomotor changes) is mainly responsible for the accuracy of CNAP was tested in laboratory measurements with 20 subjects. The adapted CNAP software (with VERIFI only) followed changes in mean arterial blood pressure (BP) during extensive BP-changing maneuvers and was able to provide accurate mean arterial BP values comparable to those of the standard CNAP software: correlation was $R=0.8873$; average bias was 0.30 ± 4.47 mmHg (limits of agreement -8.46 to 9.06 mmHg); percentage error was 10.60 %. Thus, the VERIFI mechanism can be considered as mainly responsible for CNAP's overall accuracy.

312 - Nonlinear Local Projection Filter for Impedance Pneumography

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Abstract—The ability of impedance pneumography (IP) for recording tidal flow during long periods of free breathing make it a promising tool for assessing temporal complexity of respiration. However, techniques quantifying complexity may be sensitive to the noise in the IP signal resulting from the current processing method. A nonlinear local projection filter (NLPF) is presented as the solution to the current linear processing method, failing to reduce noise without distorting the flow signal. Current and proposed NLPF methods were applied to an existing data set of raw IP recorded in 21 infants during a methacholine challenge test. Methods' performance was compared in a battery of test using mouth flow as a reference. NLPF achieved lower sample-by-sample error, and higher frequency attenuation, while linearity with mouth flow was maintained. Therefore, we concluded that NLPF superiorly reduces noise without distorting respiratory information.

317 - Comparison of linear and non-linear heart rate variability indices between preterm infants at their theoretical term age and full term newborns

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Abstract— Heart rate variability (HRV) enables non-invasive evaluation of cardiac autonomic activity. Preterm infants are known to have altered HRV characteristics that remain even when reaching their term age. Little is known about non-linear HRV measures between full term and preterm babies close to their theoretical full term. In this study, we calculated sample entropy, shape-describing parameters (skewness and kurtosis) and detrended fluctuation analysis coefficients α_1 and α_2 from RR time series of 16 very preterm babies (<32 weeks gestational age, "PT group") measured at their theoretical term age. The values were compared to the values of nine full-term (>37 weeks, "FT group") infants. Compared to the FT group, smaller values of sample entropy and lower values of α_1 were found in the PT group. No difference in α_2 , kurtosis, or skewness was found. This indicates decrease in overall complexity of HR dynamics in the PT group. When various HRV indices, that included also non-linear indices, were projected to the principal component analysis space obtained from the FT group, a good separation between the PT and FT groups was found. The study was limited by a small sample but the results were in line with literature. The combinations of several HRV parameters can be of interest for future studies on the degree of ANS maturity.

318 - A Framework for Technology Enhanced Education in Orthopaedics: Knee Surgery Case Study

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Abstract— The paper presents a framework for technology enhanced education (TEE) in orthopaedics aimed at employment of ubiquitous information and communication technology (ICT) and digital technologies in order to compensate for an unaffordable learning environment. On the other side, the concept involves both (bio)engineers, ICT specialists, and orthopaedic surgeons in an interprofessional collaboration, leveraging multidisciplinary approaches to improve the quality of clinical-oriented education. Preliminary results indicate increased motivation and satisfaction of both the learners and educators.

319 - Open source technology in biomedical engineering: fast track towards sustainable development

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Abstract—Recently the concept of Open Source Medical Devices (OSMD) has gained some attention, particularly with stunt-like displays of 3D printed prostheses capturing the imagination of the public. In this paper we argue that OSMD technology can be used to propel advancements in healthcare in developing countries in Africa, with equally beneficial consequences in more established economies, provided that the correct framework of training, sharing and safety and efficacy assessment is constructed. We demonstrate how such a framework can be created and show some examples of open-source engineering-based activities which we have conducted. The pros and cons of our approach are discussed in the context of biomedical engineering education, innovation and regulatory harmonization.

321 - Biophysical Evaluation of Microwave Radiation for Functional Research of the Human Brain

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Abstract—In paper discusses study spectral characteristics fluctuations of the brain microwave radiation for estimation changes the metabolic production in the brain tissues. Computer simulation of this problem showed that frequency band ranging from 650 to 850 MHz is optimal. The results based on the analysis phenomenological models of the brain tissues radiation and thermodynamic processes in it, and, also, on the experimental data obtained with the measuring system the Radiophysical complex. The fluctuation of the brain microwave radiation in the frequency band from 0.02 Hz to 0.013 Hz characterized mainly liquid circulation in the intercellular and intracellular spaces of the brain tissue. In the frequency band below 0.013 Hz, these fluctuations defined mainly by thermodynamic changes in the tissues.

323 - Peculiarities of Spectral and Multifractal Estimates of the Brain Microwave Radiation

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Abstract—The paper presents the results of dependency assessments of the spectral and multifractal analysis of the brain microwave radiation signals. Twenty neurology healthy volunteers participated in study. The biomedical signals formed by the dual-channel microwave radiometer. The research method used a machine-learning algorithm that allows predicting relation between the spectral power and the Hurst exponent. Compare the distribution of possible functions with data obtained from different channels were present. The results obtained allowed to demonstrate the absence interrelation between spectral and multifractal estimates of the brain microwave radiation signals.

324 - Altered synaptic signaling due to β - amyloid interference in astrocytes: A modeling study

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Abstract—Astrocytes are active participants in brain physiology and a known target of pathological processes of several diseases. Using a mathematical model of a tripartite synapse, we investigated the effects of astrocyte intracellular β -amyloid 1-42 fragments on astrocyte Ca^{2+} signaling and synaptic signal transmission. Our results show that with this model, β -amyloid interference of astrocyte Ca^{2+} signaling can considerably alter signal transmission at the synapse, and even silence postsynaptic firing. We conclude that when disturbing astrocyte Ca^{2+} signaling, β -amyloid fragments can potentially contribute to changes in synaptic signaling.

326 - Ankle Muscles Co-Activation Patterns During Normal Gait: An Amplitude Evaluation

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Abstract—The objective of this work was to quantify co-activations of ankle muscles during able-bodied walking, in terms of amplitude values of surface electromyographic signal (sEMG). Gastrocnemius lateralis (GL) was analyzed as representative muscles for plantar-flexion. Tibialis anterior (TA) was analyzed as representative muscles for dorsi-flexion. Rudolph's dynamic co-activation index was computed on the sEMG acquired from 182 strides, with the aim of quantifying the ankle-muscles co-contraction amplitude. Four different co-activations between GL and TA were observed during Heel strike (HS), Foot contact (FC), Push-off

(PO), and Swing (SW), respectively. No differences were detected in time-duration of co-contractions detected in the different phases ($p < 0.05$). TA/GL co-contraction activity is more intense in stance phase (especially during HS and FC), where a more intensive muscular control is needed for weight-support and Center of pressure (COP) progression. Co-contractions in swing phase are more frequent but milder. SW co-contraction in adults was pointed out only recently; to our knowledge, the present work is the first that quantifies it in terms of absolute and comparative amplitude. PO seems to be a transitory phase between high-level (HS and FC) and low-level (SW) co-contraction intensity regions. Present findings could be useful for deepening the physiological interpretation of ankle muscles co-activity during walking.

329 - Photoacoustic image reconstruction with uncertainty quantification

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Abstract—Photoacoustic tomography is a hybrid imaging technique that has various applications in biomedicine. In a photoacoustic image reconstruction problem (inverse problem), an initial pressure distribution is reconstructed from measured ultrasound waves which are generated by the photoacoustic effect induced by an optical excitation. In this work, the image reconstruction problem is approached in the framework of Bayesian inversion. The approach is tested with three dimensional numerical simulations. The initial pressure distribution is reconstructed in full-view and limited-view setups. In addition, the reliability of the obtained estimates is assessed. The numerical studies show that accurate estimates of the initial pressure distribution and uncertainty information can be obtained utilizing Bayesian approach.

333 - Low-latency EMG Onset and Termination Detection for Facial Pacing

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Abstract—An adaptive method for reliable and fast detection of muscle activity from surface electromyographic (sEMG) signals is introduced. The aim of this research was to minimize the delay of the onset and termination detection, while still retaining the reliability and simplicity of the detection algorithm. The proposed algorithm is based on a double-threshold detector. The algorithm applies the same principles as a constant false alarm rate (CFAR) processor that is often used to distinguish events from noisy environments with dynamic noise characteristics. The algorithm was tested with different noise conditions and frequencies. For each condition, a set of 1000 computer-simulated EMG signals were processed multiple times with different processing parameters in order to find the optimal settings for reliable muscle activity detection. The results for the detection delays were comparable to previously published results, and for low-noise conditions the detection worked without errors. The performance of the algorithm was verified using real sEMG signals. Performance in termination detection that has often been neglected in prior studies, is also reported. The results show that the method could be applied in the targeted real-time application: facial pacing.

335 - Optical wrist-worn device for sleep monitoring

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Abstract—This paper presents and clinically validates a new method to accurately classify sleep phases within a wrist-worn device (e.g., smartwatch, fitnessband). The method combines inertial and optical sensors to compute the wearer's motion, breathing rate, and pulse rate variability, and to estimate the different sleep stages (WAKE, REM and NREM). The presented method achieves a sensitivity and specificity for the REM of 89.2% and 77.9% respectively; for the NREM class 83.4% and 84.9% respectively; and a median accuracy of 81.4%. The assessment of the performance was obtained by comparing to the gold standard measure in sleep monitoring, polysomnography.

337 - Expectation--maximization algorithm with a nonlinear Kalman smoother for MEG/EEG connectivity estimation}

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Abstract—Current techniques to determine functional or effective connectivity from magnetoencephalography (MEG) and electroencephalography (EEG) signals typically involve two sequential steps: 1) estimation of the source current distribution from the sensor data, for example, by minimum-norm estimation or beamforming, and 2) fitting a multivariate autoregressive (MVAR) model to estimate the AR coefficients, which reflect the interaction between the sources. Here, we introduce a combination of the expectation-maximization (EM) algorithm and a nonlinear Kalman smoother to perform joint estimation of both source and connectivity (linear and nonlinear) parameters from MEG/EEG signals. Based on simulations, we show that the proposed approach estimates both the source signals and AR coefficients in linear models significantly better than the traditional two-step approach when the signal-to-noise ratio (SNR) is low (≤ 1) and gives comparable results at higher SNRs (> 1). Additionally, we show that nonlinear interaction parameters can be reliably estimated from MEG/EEG signals at low SNRs using the EM algorithm with sigma-point Kalman smoother.

339 - Magnetic Resonance Imaging Restoration based on Kolmogorov-Smirnov Non Local Mean

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Abstract—The random noise arising from the acquisition process of magnetic resonance images negatively influences the diagnostic process. Thus, a denoising step is commonly adopted in case of many image processing and analysis tasks. The main criticism of denoising filters is to preserve edges and details while reducing noise across the image. Within this manuscript the a novel denoising filter, namely the KS-NLM, is proposed, with the aim of improving the denoising quality. The approach belongs to the Non Local Means (NLM) family as it exploits groups of similar pixels. The novelty consists in the similarity measurement, that is based on the statistical distribution of data instead of the similarity between the local textures of the image. In particular, the Cumulative Distribution Function for each pixel is evaluated from the acquired data, and subsequently the Kolmogorov-Smirnov distance is computed as similarity metric. Similar pixels are subsequently fused. The method has been tested on a real dataset acquired via a 3T scanner, and its performances have been compared to other state-of-art filters.

341 - Stimulation Waveform Selection to Suppress Functional Electrical Stimulation Artifact from Surface EMG Signals

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Abstract—We present a simple method to suppress the artifact that functional electrical stimulation causes to surface electromyography signals. The method is based on selecting a high-frequency sinusoidal wavelet as the stimulation waveform to make the artifact frequencies easily removable from the measured signals, and combining it with simple filters in the hardware and as digital filters. Our theoretical computations demonstrate how the selected stimulus pulses attenuate significantly compared to commonly used square wave pulses already in a first-order low-pass filter used before the measurement amplifier. The experimental results with 8 participants show that the artifacts can be suppressed in our target application: facial pacing for unilateral facial paralysis. The method can be beneficial also for other neuroprosthetic applications that apply functional electrical stimulation in combination with electromyography measurements. More complex artifact suppression methods are unnecessary and the delays of the processing are caused only by the simple filters in the signal processing chain.

342 - EEG Spectral Asymmetry Index Detects Differences Between Leaders and Non-leaders

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Abstract—The aim of the study was to find an objective indicator for evaluation of occupational stress. For this purpose, the electroencephalographic (EEG) spectral asymmetry index (SASI) was applied to estimate the differences between leaders and non-leaders. The experiments were performed on a group of 82 healthy volunteers who were divided into two subgroups of leaders and non-leaders taking into account whether their position comprised the leadership role or not. The resting eyes closed EEG signal was recorded and the signal in channel Pz was selected for calculation of SASI. The results indicated higher SASI values for the subgroup of leaders when compared to non-leaders and the difference between the subgroups was statistically significant. Higher SASI values could indicate increased psychological stress in leaders group and SASI could be a promising method in occupational health analysis.

343 - Computational model for multifocal imaging in optical projection tomography and numerical analysis of all-in-focus fusion in tomographic image reconstruction

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Abstract—Optical projection tomography (OPT) is a non-invasive 3D imaging method that has been used to study small biological samples. In OPT samples can be mounted in hydrogel scaffold mimicking real life extracellular matrix, and hence grown in all natural dimensions. In optical imaging systems, focusing lenses are required for image acquisition. Due to these lenses, particles at a certain distance from objectives — in the focal plane of the lens — are captured accurately and the further a particle is from the focal plane the blurrier it is captured in the resulting image. To compensate this limitation, multifocal OPT is implemented, where images from each angle are taken with multiple focal planes at different distances. From these images, parts in focus are detected and combined into a single image using all-in-focus fusion algorithm. In this work we present computational way of modeling multifocal imaging and use the presented model to assess the performance of two different all-in-focus fusion methods.

346 - Investigation of LVAD Sputnik electrical parameters for modified geometry of the rotor

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Abstract— Electrical parameters and interaction of the left ventricular assist device (LVAD) Sputnik stator with different configurations of the rotor were investigated. Analysis of the rotor geometry and materials allows optimizing parameters of the system. Modified rotor with removed blades was used in the studies. Cylindrical tips were mounted onto the smooth surface of the rotor. This work addresses the effect of the tips material and outer diameter on the VAD parameters. Both ferromagnetic material (steel) and paramagnetic material (titan) were used for the tips. Tips of the following diameters were constructed: 11.95 mm, 13.05 mm, 14 mm, 15 mm, and 15.75 mm. The difference between the highest impedance (observed at $d=15.75$ mm) and the lowest impedance (observed at $d=11.95$) is about 13% for the tips made of titan and about 50% for the tips made of steel, respectively.

Impedance values can be used for analysis of energy losses in the system and energy transfer efficiency. Results of the research show significant effect of the cylinders diameter on the total impedance of the tips for the tips made of steel.

347 - Broadband dielectric characterization of zebrafish embryo suspensions using the impedance spectroscopy technique

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Abstract— This paper presents the electrical characterization of biological suspensions using the impedance spectroscopy technique combined with simulation methods based on finite elements. For this purpose, a modified coaxial line is used as a test fixture enclosing the biological suspension to be characterized in the frequency range from 100 kHz to 100 MHz. In the study we have used a suspension of Zebrafish (*Danio rerio*) embryos due to its potential applications to biomedical and toxicological research areas. The electrical parameters of the different suspensions under test are obtained by fitting the experimental impedance spectra to the spectra obtained from simulation of the model of the test fixture using finite elements (FE). The impedance spectra obtained for the suspensions allow the identification of different stages in blastula period of embryonic development of the zebrafish as well as of viable and non-viable embryos. The good results obtained with the combined experimental and simulation techniques may provide a basis for a non-invasive method to monitor the dielectric changes in any biological suspension.

348 - A wearable 12-lead ECG T-shirt with textile electrodes for unobtrusive long-term monitoring – Evaluation of an ongoing clinical trial

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Abstract—The recording of a long-term ECG is an important diagnostic method in the field of cardiology, e.g. in order to investigate occasional arrhythmia. Standard Holter ECGs using adhesive electrodes may cause skin irritations to the patients and can also detach. In order to increase patient comfort and ease of handling, we developed a wearable 12-lead ECG T-shirt with dry textile electrode patches connected

to a recording device by active circuitry. In this paper, we present the application and evaluation of our T-shirt in a clinical study, during which we obtained 422 hours of data from five subjects. We investigated the temporal coverage of our ECG T-shirt by identifying ECG signal segments with artefacts and those unaffected by artefacts using a three-stage artefact detection algorithm. Average coverage for individual leads ranged from 20.9% to 56.3%. After temporal fusion of all leads, coverage increased to up to 81.9%.

354 - Knowledge and Data Driven Approaches Applied to Clinical Assessment

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Abstract – The clinical assessment of a specific patient's condition can be a very difficult process as multiple variables/risk factors may be involved. Thus, clinical guidelines frequently recommend the use of models that were developed with the objective of aiding the clinical decision. However, these models still present some significant flaws that must be overcome. On the other hand, recent clinical datasets that result from patients' data gathered directly in the hospital or through telemonitoring systems are available.

The conjugation of this evidence, lead to different perspectives in the improvement of clinical decision: enhancement of the representation of clinical knowledge (current clinical models); extraction of new useful knowledge from recent clinical datasets; flexible combination of these two elements. This paper presents some achievements in relation to the improvement of current clinical models as well as to the extraction of knowledge from recent clinical datasets. In relation to the first issue an approach based on decision trees complemented with an optimization procedure to adjust the respective decision thresholds was applied while the latter is based on clustering theory in order to derive simple and interpretable rules.

This work is validated in the context of cardiovascular disease namely with coronary artery disease patients, assessing the risk of death 30 days after the admission. The largest Portuguese coronary artery disease patients dataset (13902 patients with acute coronary syndrome), provided by the Portuguese Society of Cardiology is used for validation purposes.

Some preliminary results were achieved, showing the potential of the proposed strategies to aid the clinical decision. This is an ongoing research with several possible research paths that are being pursued.

355 - Artifact detection in neonatal EEG using Gaussian mixture models

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Abstract—The neonatal electroencephalogram (EEG) is often contaminated by artifacts. These artifacts make visual inspection difficult and negatively influence the results of automated analysis. There is a significant lack of comprehensive artifact detection systems for the neonatal EEG. We present an automated artifact detection system based on a semi-supervised Gaussian mixture model (GMM). We examined the effects of feature set size, mixture number and the use of principal component analysis (PCA) as a pre-processor. Performance was assessed using the area under the receiver operating characteristic (AUC) and estimated using leave-one-patient-out cross-validation. The best performing system was obtained with 23 features, 30 mixtures and no PCA (median AUC=0.950, IQR: 0.831-0.993). EMG and movement artifacts were detected with the highest accuracy.

357 - Efficient techniques for gait-analysis: comparing marker-less and IMU-based tracking systems for monitoring rehabilitation processes

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Abstract— We compare the applicability of IMU- (inertial measurement unit) based and marker-less tracking systems used in the context of rehabilitation processes for the treatment of gait-impaired patients. With respect to the application domain we have to limit the number of employed sensors to keep the overall effort for setup and measuring within acceptable bounds. We then evaluate the fidelity of the sensor feeds delivered by the two employed technologies and discuss the impact on more advanced gait metrics like the displacement of the center of mass.

362 - Prediction of Bone Mineral Density in Menopausal Women by Using Bioimpedance Parameters

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Abstract—Body bioimpedance (BI) characteristics are function of body composition as well as bone mineral con-

tent. Regardless of the measurement axis, the specific capacitance of the trabecular bone (more susceptible to osteoporosis than cortical bone), shows a strong positive correlation to bone mineral density. In this study, measured Cole-Cole model characteristics of 54 post-menopausal women, together with their anthropometric measurements, are used in modelling their total lumbar spine and total hip bone mineral densities. The measurements are then replicated with a control group of 48 subjects to validate the proposed model. Bone mineral densities (BMD) are measured with Dual-energy X-ray absorptiometry (DEXA). Cole-Cole characteristic frequencies are statistically different for different DEXA BMD scores. Having body mass index as a regression parameter together with the characteristic frequency has improved the model for hip bone mineral density and helped to explain the variance better.

363 - Robust Assistance Control of Left Ventricular Assist Devices

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Abstract—Rotary blood pumps (RBPs) are increasingly used as left ventricular assist devices (LVADs) to treat patients with advanced heart failure. In clinical practice, RBPs are fixed speed controlled which causes an insufficient adaptation of the pump flow to the varying blood flow demand of the patient. This can lead to undesired or even dangerous operating conditions and impedes patients leading a normal life with an LVAD. This paper presents a robust nonpulsatile control strategy that amplifies the remaining native physiological control loops that affect the total cardiac output (CO). The setting option of this control strategy is called Assistance, which is defined as the time-averaged ratio of pump flow and total CO. By keeping the Assistance at a constant level, the cardiac workload is shared between the native heart and the LVAD, even when the blood flow demand is changing. The control strategy was implemented on a real-time computer operating a transvalvular LVAD. The Assistance is determined using estimations of the pump flow and the aortic flow rate. The latter is estimated with an extended Kalman filter based on pressure measurements provided by optical pressure sensors mounted on the pump inlet and outlet. Proof-of-concept was established in hybrid mock circulatory loop trials, in which stable Assistances ranging from 20% to 77.5% were achieved. In case the native CO control loops are still intact, the Assistance control strategy adequately maintains the systemic circulation and offers an intuitive setting option for the treating physician.

364 - The Study of Needle Electrode Characteristics for Venipuncture Electrical Impedance Controlling System

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Abstract—The electrical impedance method is a novel approach for detection of needle puncture to blood vessel. The method is based on sending a small current through needle electrode for measurement of electrical impedance in two-electrode setup. The design of appropriate electrode system, that can achieve the maximum sensitivity for puncture identification, is an actual task. In this study, we propose the use of special electrode system in a form of multilayer coaxial needle electrode. Experimental studies have been carried out on a constructed phantom, which simulate the soft tissues and blood vessel.

366 - Quantification of T-wave Morphological Variability Using Time-warping Methods

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Abstract—The aim of this study is to quantify the variation of the T-wave morphology during a 24-hour electrocardiogram (ECG) recording. Two ECG-derived markers are presented to quantify T-wave morphological variability in the temporal, d_w , and amplitude, d_a , domains. Two additional markers, d_w^{NL} and d_a^{NL} , that only capture the non-linear component of d_w and d_a are also proposed. The proposed markers are used to quantify T-wave time and amplitude variations in 500 24-hour ECG recordings from chronic heart failure patients. Additionally, two mean warped T-waves, used in the calculation of those markers, are proposed to compensate for the rate dependence of the T-wave morphology. Statistical analysis is used to evaluate the correlation between d_w , d_w^{NL} , d_a and d_a^{NL} and the maximum intra-subject RR range, ΔRR . Results show that the mean warped T-wave is able to compensate for the morphological differences due to RR dynamics. Moreover, the metrics d_w and d_w^{NL} are correlated with ΔRR , but d_a and d_a^{NL} are not. The proposed d_w and d_w^{NL} quantify variations in the temporal domain of the T-wave that are correlated with the RR range and, thus, could possibly reflect the variations of dispersion of repolarization due to changes in heart rate.

368 - The level of mental load during a functional task is reflected in oculometrics

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Abstract—Modern occupations have increasingly become mentally demanding. This underlines the needs for investigation of the interaction of mental and physical workload. This study assessed the effects of mental load on ocular metrics and their consistency across days. Eighteen participants performed a five minute simulated computer work with three different levels of mental load in two days at least seven days apart. Eye movements in response to the task mental load level were recorded. Along with eye movements, task performance, and national aeronautics and space administration task load index (NASA-TLX) scores were acquired. Peak saccade velocity decreased, and pupil dilation range increased with the task load level and the response remained consistent across experimental days. Increased NASA-TLX score and reduced performance were in association with mental load demand. The study shows the feasibility of quantifying the mental load demands by monitoring oculometrics during a functional task such as computer work.

369 - Inter-observer variation in segmenting glioma on MRI before and after resection

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Abstract—Longitudinal MR images obtained for treating glioma patients contain valuable diagnostic and prognostic information. One way to extract this information is to delineate tumor related entities and compare these in large cohorts. Reproducible and reliable measurement of volume and location is a necessary condition to obtain valid results. Manual segmentation of glioma by an expert is considered to be the gold standard, and is often provided by a single rater. In this study the agreement between different raters is recorded in both enhancing and non-enhancing glioma before and after surgical treatment, and at progression (pre-op, post-op and progression respectively). A total of 40 patients were

included, of which 20 have non-enhancing glioma, usually of WHO grade II or III, and 20 have enhancing glioma, usually glioblastoma. Inter-rater agreement is recorded with the generalized conformity index (CIgen). Three raters of the VUmc neurosurgery department have performed the segmentations.

Patients with non-enhancing glioma show no enhancing elements with the exception of three patients in the progression time point and one patient in pre-op. The segmented non-enhancing elements have a median CIgen of 0.64, 0.30, and 0.27 in the pre-op, post-op and progression respectively. For patients with enhancing glioma both enhancing and non-enhancing elements are observed. The segmented enhancing elements have median CIgen scores of 0.86, 0.24, and 0.69 in pre-op, post-op and progression respectively. Median CIgen for the non-enhancing elements is 0.47, 0.07 and 0.20 in pre-op, post-op and progression respectively.

A Jaccard-like score for object comparison of small objects is sensitive for small volumes, returning a low score for slight misalignment. When dilating small volume segmentations to 10 mL as compensation for small volume comparison with the CIgen the attained scores are not much improved indicating that different raters not only disagreed about object shape but also about location.

370 - Evidence-based approach to medical equipment maintenance monitoring

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Abstract—Maintenance is a crucial part of the life cycle of medical equipment. We applied a specific set of codes to classify the corrective and scheduled maintenance work orders at the University Hospital of Careggi (Florence, Italy). A set of Key Performance Indicators (KPI) (financial, technological and organizational) helps in evaluating the performance of the medical equipment maintenance. The analysis of KPIs (related to costs, age and SM completion rate) revealed some problems in maintenance strategy. The results show, starting from the evidences (i.e. the failures), that the combination of these two methods can give a periodical cross-analysis of the maintenance performance and indicate the most appropriate procedure.

372 - Clinical Decision Support Systems for COPD: a general overview

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Abstract—The purpose of the present paper is to provide a general overview of the current state of art in the field of the Clinical Decision Support Systems (CDSS) for the home telemonitoring of patients affected with Chronic Obstructive

Pulmonary Disease (COPD). The paper will highlight which are the main physiological parameters measured and collected by the CDSSs for the telemonitoring of the patient's health status, the main algorithms used by the CDSSs to make clinical decisions according to the gathered data, the performances in terms of Accuracy, Sensitivity and Specificity reached by the CDSSs and the main issues linked with CDSSs in this field.

373 - IBM Watson Analytics for Managing Congestive Heart Failure

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Abstract— The purpose of this study is the evaluation of the web cloud-based analytic service IBM Watson Analytics as a tool for the management of Congestive Heart Failure (CHF). In particular, we want to assess if this service is suitable for the identification of physiological parameters able to predict outputs of interest such as disease severity, among a set of various physiological parameters and the realization of a predictive model. Using IBM Watson Analytics, we analyzed a database consisting of 250 records containing physiological parameters from 250 patients suffering from Congestive Heart Failure. Among the physiological parameters, we identified the best predictors of 2 outputs of interest (Severity of Congestive Heart Failure and Exacerbation Frequency) and analyzed the relationship between outputs and predictors and between predictors and the other physiological parameters.

375 - Human Activity Recognition Using A Single Optical Heart Rate Monitoring Wristband Equipped with Triaxial Accelerometer

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Abstract—This paper investigates activity monitoring using a single wrist-worn optical heart rate monitoring sensor that is equipped with a triaxial accelerometer. Wearing accelerometers on the wrist provides more convenience and therefore improved wear-time compliance compared to other measurement sites. Reliability of wrist acceleration for activity monitoring has been addressed in former research. However, integration of wrist acceleration with physiological signals has not been comprehensively explored yet. We investigated a variety of home-specific activities (sitting, standing, household, and stationary cycling) performed by 20

male participants. Random Forest (RF) and Support Vector Machines (SVM) were applied for activity classification. Various features calculated from acceleration, heart rate (HR), and heart rate variability (HRV) were used as classified inputs. Results of leave-one-subject-out cross-validation showed 89.2% and 85.6% average recognition accuracies for RF and SVM, respectively. HR and HRV features improved the classification rates of high-intensity cycling by 8% for RF and 7% for SVM.

377 - Atrial Signals – Modeling Meets Biosignal Analysis

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Abstract— Today, patients suffering from atrial arrhythmias like atrial flutter (AFlut) or atrial fibrillation (AFib) are examined in the EP-lab (electrophysiology lab) in order to understand and treat the disease. Multichannel catheters are advanced into the atria in order to measure electric signals at many intracardiac positions simultaneously. Complementary to clinical learning, comprehension of the disease and therapeutic strategies can be improved with computer modeling of the heart. This way, hypotheses about initiation and perpetuation of the arrhythmia can be tested and ablation strategies can be assessed in-silico. Modeling and biosignal analysis can benefit from mutual fertilization. On the one hand, modeling can be improved and personalization can be achieved via high density mapping of the atria. On the other hand, new algorithms for the interpretation of multichannel electrograms can be developed and evaluated with synthetic signals from computer models of the atria. This article illustrates the synergetic potential by examples and highlights challenges to be addressed in the future.

378 - Reproducible preparation method of hydrogels for cell culture applications – case study with spermidine crosslinked gellan gum

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Abstract— Hydrogels are promising materials to culture cells in 3D environment. Their mechanical properties are decisive, as cells understand the stiffness of their surroundings. Herein, a method is presented to produce ionically cross-linked hydrogel matrices. A reproducible method is needed, because conventional methods cause inconsistent properties.

The investigated material is gellan gum, crosslinked with the bioamine spermidine. Samples were prepared with the more conventional ‘pipetting’ technique and with self-developed ‘uniform mixing’ technique. The two preparation techniques are described in detail and the obtained hydrogels are compared. The mechanical properties are analyzed with compression testing.

The obtained results show that samples by the so-called ‘uniform mixing’ method have more uniform dimensions and higher compression modulus. A preliminary stability test in cell culture medium was also carried out.

379 - Interpretation of the pinched point position in human skin memristor measurements

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Abstract— It is shown that human skin acts like a memristor but systematic studies on skin memristance are not published, yet. If e.g., a low frequency voltage is applied to human skin and the current is measured, a hysteresis loop can be seen in the voltage-current plot. In skin measurements, the pinched point of the hysteresis loop can be shifted from the coordinate origin. In this paper, possible reasons for this observation shall be investigated and interpreted by the use of simulation. Two example measurements on human skin are presented, as well.

382 - The use of the TLD-100 for quality assurance in Total Body Irradiation (TBI)

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Abstract—Total body irradiation (TBI) is a radiotherapy treatment of significant complexity. The planning of this type of treatment aims at ensuring the homogeneous distribution of the prescribed dose over the entire volume of the patient, which will inevitably present various thicknesses and densities. In order to verify the quality of a TBI during its accomplishment it is recommended to use thermoluminescent dosimeters (TLD) to measure the doses delivered to the patient. This work explored the use of TLD-100 in vivo dosimetry during a TBI by developing a calculation method to find the doses deposited on the medium of the DAP in various regions of a patient's body. The thermoluminescent dosimetry required a rigorous selection of the TLDs, followed by the calibration of the same ones in the same conditions practiced in the TBI. The results of the measurements showed a good agreement between the values planned to meet the medical prescription and the values measured in-vivo. In addition, the

variation between dose values overestimated for the various regions studied showed good dose homogeneity over the entire patient volume.

383 - MEDICIS-Promed: an Innovative Training Network for a new generation of professionals in nuclear medicine}

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Abstract—MEDICIS-Promed is an Innovative Training Network supported by the European Commission Marie Skłodowska-Curie program within Horizon2020. It directly supports 11 doctoral students, completed by 4 doctoral students from Swiss partner institutions, in all fields covering the production, handling, and use of radioisotopes for nuclear medicine and hadron therapy. Their research on novel medical radioisotopes is supported by a comprehensive training program covering all aspects of the research topics as well as providing them with an understanding of how to integrate and transfer their knowledge for entrepreneurship, institutional support, and widespread communication. The training is open to any participant interested in sharing the experience offered within the MEDICIS-Promed network.

385 - Effect of Nitrocellulose Membrane on the Electrochemical Behavior of Hydroquinone

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Abstract—Hydroquinone (HQ) is an electroactive product formed from hydroquinone diphosphate (HQDP) reaction with an alkaline phosphatase (ALP). Despite the advantages, this reaction is not very often used for the immunochemical assays and was not yet described for lateral flow assay. In the literature, only basic behavior of HQ formed in immunochemical assay can be found. In our work we studied deeply the effect of common lateral flow buffers and materials on the electrochemical behavior of HQ using different electrochemical methods in order to select conditions and the most convenient and sensitive method for the further application of HQDP in lateral flow immunoassay.

388 - Utilization of Discharge Singlet Oxygen Generator 6 in Biomedical Engineering

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Abstract— Discharge Singlet Oxygen Generator 6 (DSOG-6) is a device generating reactive oxygen and nitrogen species (including singlet oxygen, ozone, atomic oxygen, NO_x) by a hybrid RF/DC electric discharge. These reactive species are often used in biomedicine. In this work reactions of selected cell cultures (B16, HT29 and HaCat) with DSOG-6-generated particles were observed and analyzed.

Cell cultures were exposed to singlet oxygen or reactive oxygen species generated by a hybrid electric discharge for different time periods. After the exposure a microscopic analysis of the cytomorphology of cells was carried out. Furthermore, cell proliferation of B16 cell line was investigated by xCELLigence System. Finally, preliminary results of qPCR from B16 exposed to singlet oxygen are presented.

The main goal of this work was to evaluate if singlet oxygen/reactive oxygen species generated by DSOG-6 could be used in biomedical application (concretely in oncology and dermatology) and DSOG-6 could become a new biomedical device. The secondary aim was to observe the dependence of cell lines behavior on exposure parameters (time intervals, particles in discharge, etc.).

389 - Deep Learning for outcome prediction of postanoxic coma

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Abstract—Electroencephalography (EEG) is increasingly used to assist in outcome prediction for patients with a postanoxic coma after cardiac arrest. Current literature shows that neurological outcome is invariably poor if the EEG remains iso-electric or low-voltage at 24 h after cardiac arrest or if it shows burst-suppression with identical bursts; such patterns are observed in approximately 30-50% of patients. Return of continuous EEG rhythms within 12 h after cardiac arrest predicts good neurological outcome with sensitivities in the range of 30 to 50% at specificities near 100%. In previous work, we reported on the Cerebral Recovery Index to assist in the visual assessment of the EEG. In this paper, we explore a deep learning approach, using a convolutional neural network for outcome prediction in patients with a postanoxic encephalopathy. Using EEGs from 287 patients at 12 h after cardiac arrest and 399 patients at 24 h after cardiac arrest, we trained and validated a convolutional neural network with raw EEG data (18 channels, longitudinal bipolar montage). As the outcome measure, we used the Cerebral Performance Category scale (CPC), dichotomized between good

(CPC score 1-2) and poor outcome (CPC score 3-5). Using 5 minute artifact-free epochs from the continuous EEG recordings partitioned into 10 s snippets, we trained the convolutional neural network using 80% of the patients. Validation was performed with EEGs from the remaining 20% of patients. Outcome prediction was most accurate at 12 h after cardiac arrest, with a sensitivity of 58% at a specificity of 100% for the prediction of poor outcome. Good neurological outcome could be predicted at 12 h after cardiac arrest with a sensitivity of 58% at a specificity of 97%. In conclusion, we present a classifier for the prediction of neurological outcome after cardiac arrest, based on a convolutional neural network, providing reliable and objective prognostic information.

390 - Biomedical Engineering Education in Context of New Legislation in the Czech Republic

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Abstract— The aim of the paper is to present an overview of the development of biomedical engineering education in the Czech Republic in the context of recently adopted amendment to the Higher Education Act in the Czech Republic. The amendment introduces evaluation procedures similar to those existing in many other countries. In addition to existing procedure of accreditation of study programs, it introduces accreditation of the whole higher education institutions. Regular assessment of educational and research activities will be performed regularly. The results may serve for various purposes, however one of the most important issues is calculation of budget from state resources (in case the institution is fully or partially state financed). The amendment defines two types of study programs, both in Bachelor and Master level, namely academically focused and professionally focused. In the paper we discuss impact on education in biomedical engineering field.

392 - Research and development of methods and means, based on the analysis of processes of human brain activity, for creating the control systems of the anthropomorphic technical devices

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Abstract - This article is devoted to the researches in the field of biomechanics, specifically to the achievements in the development of the methods and means for control of the bionic prostheses of upper human limb. The article discusses the main advantages and disadvantages of existing bionic prostheses control systems. In connection with what the basic

requirements to the investigated control method had been stated. The developed control system implies a recording of electrical activity of the brain, which is produced by a non-invasive manner using methods of electroencephalography (EEG). The article details the principles of the system and further ways of the development of a control method.

393 - Bayesian multi-dipole localization and uncertainty quantification from simultaneous EEG and MEG recordings

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Abstract—We deal with estimation of multiple dipoles from combined MEG and EEG time-series. We use a sequential Monte Carlo algorithm to characterize the posterior distribution of the number of dipoles and their locations. By considering three test cases, we show that using the combined data the method can localize sources that are not easily (or not at all) visible with either of the two individual data alone. In addition, the posterior distribution from combined data exhibits a lower variance, i.e. lower uncertainty, than the posterior from single device.

394 - Controllable Limiter of Signal Amplitudes for Bioimpedance Measurements

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Abstract—In electrical bioimpedance (EBI) measurements, the amplitudes of excitation signals is strictly kept within certain limits by several circumstances. This is a reason, why also the signal-to-noise ratio (SNR) becomes low that increases the probability of saturation of measurement channels by noise, leading to nonlinearity and signal cutoffs this way. Moreover, larger disturbances may damage the circuitry intended for low-level signals. To avoid this, keeping the amplitude of a sum of signal-plus-noise within certain limits is required. However, due to the low level of signals and the sensitivity to stray impedances (mainly capacitances), the standard limiter circuits are not always applicable in EBI measurements. A typical case is an input of the current-to-voltage converter (transimpedance amplifier). Moreover, the required limiting levels should be low but accurate and adjustable, typically. The introduced novel limiter circuit efficiently protects the input of the transimpedance amplifier (TIA) from overloading and avoids saturation of its output stages. It allows adjustment of limiting levels of the output signal down to the voltage drop of a single diode (0.6 V typically) and has a minimal impact on the TIA properties above this level. However, limiting of the signal amplitude has still considerable impact on the accuracy of measurement channels. The caused errors are measured and calculated for different SNR values. The results described here could be useful

also in other implementations where limiting of low-level signals is required.

395 - A camera-based multispectral setup for remote vital signs assessment

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Abstract—Photoplethysmography Imaging and Infrared thermography are the two imaging modalities studied at the Philips Chair for Medical Information Technology which allow for remote assessment of vital signs such as heart rate, heart rate variability, breathing rate, oxygen saturation and temperature distribution. Both modalities use video cameras for recording different parts of the electromagnetic spectrum and deliver 2D images or videos. In this work, we will introduce the Philips-MedIT camera setup for multispectral measurements and set it into context with earlier developments at RWTH Aachen University.

399 - Evaluating Different Shapes of Cranial Fixation Mini-plates Using Finite Element Method

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Abstract—Medical grade 3D printing offers the possibility to manufacture patient-specific implants to treat cranial defects. The performance of the implant assembly depends on many factors, such as material, thickness, size and manufacturing accuracy. A significant factor in the stability and success of the assembly is the fixation method. Cranial implants are usually fixed to the skull by means of mini-plates. Biomechanical assessment of fixing the implant to the skull might be helpful not only for mini-plate design but might be beneficial also for the surgeons. In this study, four different mini-plate designs were analyzed and compared based on the stress-strain analysis of one cranial implant fixed at three locations by mini-plates. Computational simulations were done using Finite Element Method.

400 - Assessment of Instantaneous Heartbeat Dynamics in amnesic Mild Cognitive Impairment

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Abstract—In this study, we employ a time-varying, probabilistic model of linear and nonlinear heartbeat dynamics to investigate the possibility of detecting subtle autonomic alterations in subjects suffering from amnesic mild cognitive impairment (aMCI) by exploiting heartbeat information alone. aMCI is a frequent form of cognitive dysfunction which increases the risk of culminating in Alzheimer's disease (AD)-related dementia, and previous studies have demonstrated that AD is accompanied by alterations in autonomic function, which in turn have been linked to cognitive performance in non-demented subjects. We compare 13 MCI patients without overt dysautonomia to 13 age- and gender-matched healthy controls by feeding an autonomic nervous system-related linear and nonlinear feature set into a classification framework. Our results show a satisfactory classification performance (73% balanced accuracy), which dropped to 65% when excluding cardiovascular nonlinear/complex features. This outcome confirms the presence of subtle autonomic dysfunction in aMCI (a possible prodromal condition to AD), which can only be detected through the use of our comprehensive modeling strategy which comprises time-varying, nonlinear/complex estimates of heartbeat dynamics.

401 - Blood flow analysis for prediction of pressure ulcer development using diffuse correlation spectroscopy

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Abstract—Microcirculation is essential for supply of oxygen and nutrients to organ tissues as well as the removal of

waste products of metabolism. Consequently, microcirculatory blood flow is of substantial interest to clinicians for assessing tissue health, particularly in regards to pressure injuries and suspected deep tissue injury. We used optical methods of noninvasive diffuse correlation spectroscopy (DCS) and diffuse near infrared spectroscopy (DNIRS) to predict the development of pressure injuries by measuring dermal and subcutaneous red cell motion. We recruited 14 rehabilitation patients with non blanchable redness in the sacrococcygeal area and 20 healthy volunteers from Magee Rehabilitation Hospital in Philadelphia, PA. Among the rehabilitation patients, 3 developed open pressure injuries (PO) within four weeks of enrolling while 11 patients did not (PNO). Our measurement protocol consisted of three stages in order to collect blood flow changes during baseline, applied body weight pressure, and released pressure stages. The characteristic time of DCS temporal correlation function scattered light intensity, τ_{exp} , characterized the tissue blood flow and were compared for both patient groups. Results from baseline measurements showed τ_{exp} values approximately five times larger ($p=0.0002$) for POs compared with PNOs, suggesting POs have faster blood flow than PNOs in their respective areas of redness. Similar differences were obtained for two next monitoring stages. Preliminary results suggest the used method is able to accurately predict the progression of early stage pressure injuries in the sacrococcygeal area.

402 - Pre-processing to Enhance the Quantitative Analysis of Glucose from NIR and MIR Spectra

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Abstract— This paper introduces a novel pre-processing method based on optimizing the window size for the Savitzky-Golay smoothing coupled with bandpass filtering to further enhance the prediction performance of the of glucose concentration from both Near Infrared and Mid Infrared spectra. The proposed method is compared to the bandpass filtering with Savitzky-Golay using fixed window size and RReliefF pre-processing technique for further evaluation. The developed prediction models have been validated to predict the concentration of the glucose from both Near and Mid Infrared spectra of a mixture of glucose and human serum albumin in a phosphate buffer solution. The results confirm that the proposed technique enhance prediction performance of the linear calibration models the Principal Component Regression and the Partial Least Squares Regression models and

achieve better results than the bandpass filtering with Savitzky-Golay with fixed window size technique.

404 - Geometry-based Computational Modeling of Calcium Signaling in an Astrocyte

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Abstract—In the last two decades, astrocytes have gained more interest due to the realization that they are involved not only in information processing and memory formation but are also linked with several neurodegenerative disorders and brain diseases. Communicating indirectly with synapses via released gliotransmitters such as glutamate, astrocytes take part in the neuronal activity by propagating intracellular and intercellular waves of calcium (Ca^{2+}). However, it is not clear what effect does the astrocyte geometry have on these Ca^{2+} wave dynamics. In this study, we present a geometry-based computational model of an astrocyte that is used to simulate the stimulation and propagation of intracellular astrocytic Ca^{2+} waves. To our best knowledge, this is the first computational model to study the effect of the single astrocyte geometry on the Ca^{2+} wave propagation, while taking into account the intricate biological pathways that regulate internal Ca^{2+} dynamics. By simulating theoretical astrocyte geometries with a fixed glutamate stimulus, we found that narrower astrocyte processes lead to stronger Ca^{2+} wave dynamics, in comparison to wider processes. From this study, we concluded that the geometry does have a visible effect on the overall intracellular Ca^{2+} dynamics.

407 - The Thermodynamic Cost of Intelligence

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Abstract—The concept of *Information*, is probably one of the most difficult physical (or maybe not) quantities to be comprehended. This is true not only due to the definition and physical meaning of *Information*, but also due to the difficulty in quantifying *Information*. It has been an intense field of study, especially in the 20th century, due to the revolution of information technology, where the notion of *bit* dominated the information discipline. Further on, after the *bit* the next term introduced in information theory was the *qubit*, the quantum bit. The present work tries to answer the question

on the thermodynamic cost of intelligence. It attempts to build a connection between information and thermodynamics in terms of energy consumption and work production and in particular from a macroscopic point of view. From an initial observation we have reached the outcome that when introducing the concept of information into the thermodynamic equilibrium, it appears that it violates the law of energy conservation. Yet, we pose a hypothesis that *Information per se* carried energy and thus the conservation of energy is true.

409 - Augmented virtuality platform for usability evaluation of a novel endoscope concept

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Abstract—The endoscope is a key component of minimally invasive surgery, and several methods for improving the traditional rigid endoscope have been proposed. These generally increase the complexity of the endoscope, and thus the feasibility of operation of such devices should be ensured through user testing in an environment that closely resembles the real use scenario. We present an augmented virtuality endoscopy simulator that can be used for evaluating virtual endoscope concepts. We achieve this by having the operator of the endoscope hold a physical object resembling the prototype, and through operating the physical object, have a virtual version displayed through a head-mounted display behave accordingly. We evaluate the system through implementing a previously proposed novel articulated endoscope. The system allows for usability evaluation of endoscopes in a setting closely resembling that of the real surgical room without the need for constructing a working physical prototype, potentially saving costs and allowing for quicker prototyping of novel endoscope concepts.

410 - Extents, Locations and Geometrical Configurations of Calcification in Abdominal Aortic Aneurysm

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Abstract— Calcification (Ca) is one of the main characteristic of aortic wall degeneration, and often associates with

the risk of aneurysm rupture and the failure of endovascular repairs (EVAR). It is hypothesized that, not only the intrinsic properties of Ca, but also the location and the geometrical configuration of Ca may alter the global behavior of the aortic wall. In this study, a quantitative and qualitative analysis has been performed over 34 patients having abdominal aortic aneurysm (AAA), to analyze the potential morphological effects of Ca on AAA.

415 - Learned vs. Hand-Designed Features for ECG Beat Classification: A Comprehensive Study

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Abstract—In this study, in order to find out the best ECG classification performance we realized comparative evaluations among the state-of-the-art classifiers such as Convolutional Neural Networks (CNNs), multi-layer perceptrons (MLPs) and Support Vector Machines (SVMs). Furthermore, we compared the performance of the learned features from the last convolutional layer of trained 1-D CNN classifier against the hand-crafted features that are extracted by Principal Component Analysis, Hermite Transform and Dyadic Wavelet Transform. Experimental results over the MIT-BIH arrhythmia benchmark database demonstrate that the single channel (raw ECG data based) shallow 1D CNN classifier over the learned features in general achieves the highest classification accuracy and computational efficiency. Finally, it is observed that the use of the learned features on either SVM or MLP classifiers does not yield any performance improvement.

417 - Improvement in Quantitative Analysis of RBCs Velocity in Microcirculation Based on Block-matching Motion Estimation

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Abstract—This paper presents an improved method towards a semi-automated method for the quantification of red blood cells (RBCs) velocity in individual microvessel. Our aim is to use straightened vessel centerline in individual microvessel, which offers a main benefit to reduce computational time for quantitative analysis of blood flow velocity based on block-match motion estimation. The quantitative

method used the modified block-matching method based on straightened vessel centerline image to perform a wide range of changes in amount of search comparison, subsequently, to use the optical flow method for fine adjustment pixel by pixel and to complete the overall velocity estimation. In the evaluation experiment, the current method and the proposed one were applied to make tests on simulated vessel images for performance comparisons. The estimation results are quite rapid and accurate.

418 - Application of photocatalytic nanolayers SmartCoat in health care facility

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Abstract — To prevent the transmission of nosocomial infections is one of the key roles of each health care facility. Regular painting, usage of disinfectants and disposable material is now standard practice. This study describes another way in prevention of nosocomial infections. Using one of the commercial available photocatalytic nanolayers in health care facility can reduced the possibility of their transfer. Technology SmartCoat was chosen and applied in University Hospital Hradec Kralove. Technology is using the effect of photocatalyst TiO₂ which provides antimicrobial and superhydrophobic properties. The own methodology of testing was compiled together with experts to verify the effects of photocatalysis in practice. The primary method used to verify the effectiveness was ATP bioluminescence method. Testing was conducted over 25 days and based on more than 279 samples. The study also summarizes the main positive and negative benefits in the field of safety, economy and clinical implications.

419 - Numerical modeling of cardiovascular physiology Study of dynamic changes during autonomic reflexes

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Abstract—In this paper, we present a computational software to analyze simultaneous left ventricle (LV) pressure and volume measurements that takes full advantage of the single-beat method. LV pressure and volume data may be combined to construct pressure-volume (PV) loops, which enables the extraction of valuable parameters for LV and arterial physiologic function assessment, in particular LV systolic and diastolic performance, mechanical energies and efficiency. Using this software, we analyzed instantaneous and dynamic hemodynamic changes in vivo in rabbits during acute cardiovascu-

lar perturbations produced by 1) cardiac baroreflex, 2) arterial chemoreflex, and 3) von Bezold-Jarisch reflex. This paper reports results of this analysis.

420 - The evaluation of medical devices: are we getting closer to solve the puzzle? A review of recent trends

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Abstract— Over the last decades, the fast pace of innovation, high profile regulatory failures and updates in the medical devices directives, together with intrinsic or environmental characteristics of the products and industry, have turned the attention to the evaluation of medical devices. Medical devices are recognized to be different from drug technologies, however it is still not entirely clear whether these differences really matter with respect to their evaluation. In the title we ask the question of whether we are getting closer to solve the puzzle of the evaluation of medical devices. Thanks to years of research work, debates, discussion, experimentation and learning from errors, we have certainly made progress and developed a better understanding of what it is needed for a better evaluation of medical technologies. In this manuscript we present innovative approaches and promising trends, from *in silico* trials to early HTA, parallel submissions and, overall, adaptive pathways to evidence generation that could enable better, safer, and faster regulatory and patient access to devices. In the next future, it will be important to monitor the development and diffusion of these approaches and assess their impact. If the regulatory and HTA evaluation of medical devices is to continue to improve, establishing inter-disciplinary collaborations between clinicians and engineers, policy makers, patients and industry representatives will become key.

423 - PathValue: Pathways with Value

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Abstract—This work proposes a tool called PathValue, that aims to identify commercially interesting reaction routes for bioproduction. PathValue evaluates large sets of pathways using stoichiometric data, pathway properties such as compounds involved and estimates of market information. The public databases Rhea, ChEBI and IntEnz were utilized in this work for reaction, compound and enzyme data, respectively. Data were handled using Python whereas the PathValue tool was implemented as a JavaScript-based web

application. The tool generates, filters and evaluates biochemical pathways. The functioning of the framework was assessed by querying pathways for ethanol and isoprene production and measuring the similarity of the generated pathways to known reference pathways.

425 - Life Science innovation ecosystem in Poland – case study of BioTechMed Cluster Mazovia

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Abstract — developing successful innovation ecosystems is a strategic element for economic policy in Poland. EU structural funds are supporting this task in years 2007-2020 with planned amount total of 23 billion euro. Among defined priorities for innovative development is “healthy society”. Poland science base is providing significant scale and quality of basic research in life sciences, there is access to qualified R&D personnel, top infrastructure and financial support. Nearly 40% of all the potential in life sciences is located in Mazovia region. Since 2011 the region is developing cluster initiative BioTechMed Mazovia. Cluster is concentrating on providing professional technology transfer support based on developed Bridge2Market model.

427 - Dependence of the EEG Nonlinear Coupling on the Frequency Bands and the Segment Lengths

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Abstract— The aim of the current study is to compare the degree of electroencephalogram (EEG) nonlinear coupling in different frequency bands and segment lengths. EEG recordings from 37 healthy volunteers during eyes-closed resting state are analyzed in six different frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), gamma (30-45 Hz) and total (1-45 Hz) frequency band. Multi-variate surrogate data method is used to estimate the degree of EEG nonlinear coupling. The null hypothesis that time series were generated by a linear process was rejected by statistically comparing the nonlinear statistics calculated for original and

surrogate data sets. Synchronization likelihood is used as a nonlinear estimate of functional connectivity and three different

segment lengths are inspected: 5.12, 10.24 and 20.48 seconds. As a result of the study, the degree of nonlinear coupling increased as the length of the segment increased and was limited to 6% for shorter and 20% for longer segments. Nonlinear coupling was most dominant in total, alpha, beta and theta frequency bands.

431 - Prediction of meditation experience using fMRI functional connectivity and multivariate pattern analysis

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Abstract—Mindfulness meditation is a complex psychological process that involves emotional, attentional and awareness practices. In this work, we predict the years of meditation experience of Buddhist monks using Multivariate Pattern Regression and functional connectivity analysis. 12 Buddhist monks underwent a meditation session according to two meditation styles while BOLD fMRI at 1.5 T was recorded. Functional connectivity matrices were calculated between functionally subdivided ROIs. Correlations were used as features for a Support Vector Regression with target the monks' experience. Regression weights highlighted prominent connections and differentiated meditation styles.

432 - Automatic real time derivation of breathing rate from thermal video sequences

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Abstract — The breathing rate (BR) is one of most important physiological parameter used for cardiopulmonary arrest prevention and for evaluating respiratory problems as (sleep) apnea, congestive heart, hypo / hyper –ventilation, asthma etc. In this paper, we propose an efficient method for non-contact estimation of BR using thermal imaging. The system is based on computer vision algorithms and sequentially performs: face detection, interest points extraction and tracking, geometric transformation between successive frames and nostril position estimation. The performance of the proposed framework is evaluated against the BR measured using a wired thermistor. The thermistor is placed near the subject nostril and is connected to an acquisition system designed for medical applications. The experimental evaluation validates the proposed methodology, returning high accuracy scores. In terms of the computational complexity, the system performs the BR estimation in real time.

434 - Predictive Modeling of Exercise Response in CVD Patients under Rehabilitation

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Abstract—Exercise-based rehabilitation plays a key role for patients with cardiovascular disease (CVD) in improving their well-being and reducing their symptoms. Monitoring and assessing the exercise response at an individual level is critical toward achieving better health outcomes. 15 exercise sessions performed by 5 CVD patients and 9 sessions from 3 regularly active individuals were monitored, and heart rate (HR) data were acquired. A model based on the HR dynamics during exercising at different intensities was built, and simulations were performed to assess performance in different scenarios of exercise selection. Our results show that the application of simple rules in exercise selection, which consider both the HR and the beneficial HR zones of individuals, can lead to beneficial execution of exercise programs (%time spent in beneficial HR zones: 60.6±27.5 for CVD patients). Personalized guidance during exercise has the potential to significantly contribute in the beneficial execution of exercise-based cardiac rehabilitation programs.

439 - Insulin Bolus Calculator with Automatic Speech Recognition

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Abstract— There is a recommendation regarding diabetes treatment with insulin pens or pumps that elevated blood glucose concentration after meal should be compensated by insulin bolus. This requires effective estimation of food carbohydrates and performing arithmetic calculations, what may be challenging tasks for many persons with diabetes. Consequently, their glycemic control is poor with glycated hemoglobin level higher than recommended. When this state lasts too long, it directly leads to microvascular and macrovascular diabetes complications. Microvascular complications include

retinopathy leading to blindness, nephropathy leading to renal failure and neuropathy leading to diabetic foot disorders leading to amputation. Macrovascular complications include cardiovascular diseases, strokes and serious reduction in blood flow rate to legs. Good metabolic control in diabetes delays the onset and progression of diabetes complications. Some help may assure insulin bolus calculators. They must be safe, effective and easy to use. The developed VoiceDiab system helps users in estimation of insulin dose based on voice description of a meal. It consists of smartphone application and MS Windows servers working with developed linguistic database and nutrient database. The system calculates the insulin dosage for insulin pen or pump users. The system automatically suggests a dual-wave bolus, if there is significant amount of proteins and fats in a meal. The outpatient clinic study revealed that patients supported by the system or those unsupported had comparable means and variabilities of blood glucose concentration. The inpatient clinic trial showed that the VoiceDiab system was able to properly estimate insulin boluses compensating meals based on the voice description of these meals.

440 - Variation of Cardiac and Respiratory Waveform on Human Thorax in the Case of Inductive Coupling

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Abstract— The usage of magnetic induction monitoring on human thorax for detecting the cardiorespiratory activity is shown in this paper. The utilized device for measuring the changes in equivalent parallel resonant impedance of a single coil, caused by the breathing and heart beating, is represent. The waveforms of cardiac and respiratory activity together with the waveforms of reference monitoring of ECG and breathing are depicted. The measurements were done in twelve positions on the surface of the thorax of a single volunteer by using predetermined protocol. The respiratory activity was found to be available in all of the chosen positions. The cardiac activity was found to be recognizable in the positions on both sides and front side of the thorax. The influence of the concurrent movements was verified. The positions, suitable for monitoring the both processes of breathing and heart rate, are proposed.

441 - Optically Induced Semiconductor Gas Sensor: Acetone Detection Range using Continuous and Cyclic Optical Irradiation Types

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Abstract— In previous studies the possibility to use optically induced semiconductors to sense acetone vapors was demonstrated [1]. One of the studies demonstrated the possibility to sense and determine various solvent gases, where acetone vapor showed the highest signal increase [2]. In this study, two optical irradiation types (continuous and cyclic) are compared.

The study demonstrates that irradiation mode can affect the sensitivity of the system. Experimental results are in close accord with predictions [3] and demonstrate a non-linear response.

With continuous irradiation mode acetone sensing range of the system is between 18 to 818 ppm with measurement deviation from the regression curve of $\pm 0.96\%$ ($k=2$). Cyclic optical irradiation demonstrated sensing response of acetone in the range between 167 ppm to 2190 ppm with measurement deviation from the regression curve of $\pm 0.11\%$ ($k=2$).

By comparing results of both irradiation types possible influence of optical irradiation intensity on sensor response can be observed. This has potential for future work.

442 - Setup of a white light selective plane microscope to investigate microprobe insertion in a brain model

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Abstract— Little can be seen during the actual, dynamic implantation of microprobes into the bulk of brain tissue, mainly due to the high absorption and scattering properties of the neuropil. Fluorescent selective plane microscopy has revolutionized biology by producing optical 3D stacks of whole tissue, without slicing. The following describes a simple adaptation of white-light selective plane microscopy to visually monitor the insertion of tungsten rods with different velocities into micro-bead charged agarose gels, a good model for brain mechanics. We report on a surprising, speed dependent penetration mechanism resembling bow wave accumulation of gel.

444 - The Quality of Automatic Artifact Identification in Ambulatory Impedance Cardiography Monitoring

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Abstract— In Ambulatory Impedance Cardiography (AICG), a large number of motion artifacts might occur in recordings collected during exercises. The adequate identification of the artifacts is the most important task for automatic analysis of the AICG signals. The aim of this study was to manually assess the efficiency of the classification algorithm described in our earlier papers. We intended to identify which point detected on ECG and impedance cardiography (ICG) curves is more likely to provide false indications. It was found that in most cases the artifacts were created by false recognition of the point of closing of the aortic valve (97%, range 91-100%). Modifications of the appropriate part of the algorithm were suggested.

445 - Calling Homopolymer Stretches from Raw Nanopore Reads by Analyzing k-mer Dwell Times

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Abstract— Oxford Nanopore Technologies' (ONT) MinION device is capable of reading single molecule DNA strands tens of thousands of bases long, by passing a strand through a nanopore and recording the changes in electric current. The error rate of the platform is higher than most mature next-generation sequencing (NGS) platforms, with many of the deletions accumulating in stretches of identical bases (homopolymers). However, the mean time each 5-base long subsequence (k-mer) of the molecule spends inside of the pore (dwell time) can also be used to infer the length of the true sequence. We developed a method called NanoTimer, which estimates the homopolymer length from the dwell times. It relies on the redundancy of having multiple reads covering a reference sequence, and the depth of coverage determines its accuracy.

446 - HMM Based Cough Sound Analysis for Classifying Pneumonia and Asthma in Pediatric Population

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Abstract— Separating pediatric asthma from pediatric pneumonia is one of the major issues in remote areas. These diseases have overlapping symptoms, but require drastically different treatments. Existing guidelines for pneumonia classification in resource poor regions from The World Health

Organization call for the use of bronchodilator test to separate asthma from pneumonia. However, bronchodilator is an expensive test to conduct and not easily available in remote areas. In this study, we propose an innovative and novel technique using cough sound analysis to separate pneumonia cases from asthma. In the work of this paper we analyzed cough sound data from 20 subjects (10 pneumonia and 10 asthma patients). Using mathematical features of cough sounds, an HMM classifier was trained to identify pneumonic cough and asthmatic cough. Then by computing Pneumonic Cough Index each patient was classified as either into pneumonia or asthma. Proposed method achieved an accuracy of 90% (sensitivity = 100% and specificity = 80%) in classifying pneumonia and asthma patients. Our results indicate that cough sound carry critical information which can be used to separate asthma patients from pneumonia. Proposed technique in this paper shows potential to become an alternative for bronchodilator test in the resource poor areas of the world.

449 - Application of digital imaging for quantitative assessment of wheal formation

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Abstract— There is a lack of a simple mathematical formula that relates the wheal formation, commonly used diagnostic indicator for quantification of skin prick test result, to critical parameters applied to characterize the movement of interstitial fluid and proteins. The studies were performed to validate a new approach to solve this problem. The method is based on the application of digital imaging technique to determine the wheal volume. The time course of wheal formation is described by a mathematical model based on the pathophysiology of the process. The numerical solution of the model equations was verified by a comparison with the experimental data. Next a simplification was introduced to the model to assure the analytical solution. This simple analytical formula reproduces the data very well. The present work therefore gives a simple, quantitative description of the wheal formation process.

451 - Evidence-gathering across industry and academia on early Health Technology Assessment (HTA) of medical devices: survey design and piloting

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Abstract—The adoption and reimbursement of a new or novel medical device frequently occurs after an economic evaluation of the innovation. One important factor for reimbursement rejections by the English National Institute for Health and Care Excellence (NICE) Medical Technologies Evaluation Programme (MTEP) appears to be the scarce or no attention to early assessment.

This protocol describes a mixed methods research strategy employed to develop and test the quality, validity and consistency of two survey questionnaires aiming to explore the early Health Technology Assessment (HTA) level of adoption, and potential barriers to its adoption, across industry and academia. Qualitative interviews involved two types of key stakeholders: people working in the R&D or market access departments of small and medium enterprises, and academics working in the field of health economics, across England and Italy. We analysed the content of 25 informant interviews, constructed, and piloted two different academia and industry-tailored questionnaires. We then piloted the revised questionnaires with 15 professionals (5 developers and 10 academics) and re-piloted both a month later.

To our knowledge, this study is the first to develop and test a survey that investigates the views in academia and in private companies on how conducting early HTA might affect the introduction of new medical devices to the market. Due to few original research papers on early HTA in the published literature and limited application of the guidance for early HTA in reimbursement claims, the incorporation of a more robust analytical framework including a societal perspective is necessary to understand whether early assessment can be effectively embedded into all aspects of the development process.

453 - Clinical Engineering Revisited: the Grip of Leadership - Part 1

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Abstract—A survey on two fundamental questions - Q_A: What is Clinical Engineering (CE)?, and Q_B: How can International Federation for Medical and Biological Engineering (IFMBE) with its partners advance CE globally? - was emailed to the Clinical Engineering Division of the IFMBE (CED/IFMBE) members at large. The survey actually consists of ten sub-questions Q_{A1}-Q_{A5} and Q_{B1}-Q_{B5}. This work presents answers and discussion of the CED/IFMBE leadership related to question Q_A. The survey response rate was 35% (18/51). CE is not equal to biomedical engineering (BME), but a subset of BME for 16/18 (89%) responders, and a kind of new identity associated with BME in 2/18 (11%) cases. CE is not equal to health technology management (HTM) for 17/17 (100%) responders, but 11/17 (65%) stated that CE encompasses HTM, 5/17 (29%) stated that CE and HTM are two sets that intersect, and 1/17 (6%) stated that CE

is a subset of HTM. CE practitioners are health professionals for 94% (17/18) responders, and are not in 1/18 (6%) cases. CE is not for engineers only in 13/18 (72%) responses, and it is for engineers only in 5/18 (28%) responses. Corresponding white paper of the CED/IFMBE is expected to be published soon.

454 - Overview of Health Behavior Change Interventions to Promote Physical-activity-related Adherence in Patients with Heart Disease

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Abstract—The ongoing increase in the incidence of cardiovascular disease is often associated with unhealthy lifestyle choices, while healthy lifestyle is one of the most important medical recommendations for patients with heart disease. Despite the importance of making healthy decisions daily, patient adherence to such changes is typically poor with the lowest level reported on physical activity regimen. To facilitate patient health behavior change towards a healthy lifestyle, use of health behavior interventions seems to be the most preferred tool in cardiac care routine. However, the question about use and development of successful interventions is remaining of relevance due the increasing rates of patient dropouts in rehabilitation programs and hospital readmissions. Researchers from different domains, including eHealth, are working on enabling intervention optimization. Thus, to analyze the design components that can be further used in patient adherence intervention development from the Health behavior informatics perspective, this paper provides an overview of interventions' designs in the domain of physical-activity-related adherence in patients with heart disease. The analysis of the design approaches lead to the conclusion that the central elements for intervention design are the target patient population with its specific characteristics, and chosen type of physical-activity-related behavior. Additionally, we have found that study design and its quality should be considered when analyzing a specific intervention or intervention program effect.

455 - Short-term stability of combined finger and toe photoplethysmogram analysis

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Abstract—Arterial pulse waves (PWs) provide information on the vascular health and could be utilized in the early detection of atherosclerosis. The aim of the study is to characterize the short-term repeatability of combined finger and toe photoplethysmographic (PPG) signal analysis method which we call finger-toe plot (FT-plot) and compare it with other methods proposed for vascular characterization. PPG signals were recorded from 24 atherosclerotic and 47 control subjects from finger and toe. The repeatability of the method was analyzed by means of intra-class correlation coefficients (ICC) and free-marginal multirater κ agreement. The metrics were computed for individual PWs as well as for averages based on 10--100 PWs. The ICCs increased with number of PWs utilized — ICCs and κ agreements higher than ≥ 0.90 were widely achieved based on the averages of ≥ 20 PWs, depending on the parameter or study group. Based on the present results, the FT-plot based detection of atherosclerotic changes has at least equal repeatability compared with a current clinical standard, ankle-to-brachial pressure index. However, further studies should validate the findings before the method is ready for the screening of atherosclerotic changes.

456 - Clinical Engineering Revisited: the Grip of Leadership - Part 2

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Abstract—A survey on two fundamental questions - Q_A: What is Clinical Engineering (CE)?, and Q_B: How can International Federation for Medical and Biological Engineering (IFMBE) with its partners advance CE globally? - was e-mailed to the Clinical Engineering Division of the IFMBE (CED/IFMBE) members at large. The survey actually consists of ten sub-questions Q_{A1}-Q_{A5} and Q_{B1}-Q_{B5}. This work presents feedback of the CED/IFMBE leadership related to question Q_B. The survey response rate was 35% (18/51). The answer on question 'Q_{B1}: Do/can we legislate?' was 'Yes' in 9/17 (53%) cases, and 'No' in 8/17 (47%) cases. The answer

on question 'Q_{B2}: Do we register?' was 'Yes' in 11/16 (69%) cases, 'No' in 4/16 (25%) cases, and ambiguous in 1/16 (6%) case. The answer on question 'Q_{B3}: Do we certify?' was 'Yes' in 15/17 (88%) cases, and 'No' in 2/17 (12%) cases. The answers on question Q_{B4} were descriptive, and on question 'Q_{B5}: Do we support accredited CE undergraduate programs?' were 'Yes' in 9/12 (75%) cases, and 'No' in 3/12 (25%) cases. Corresponding white paper of the CED/IFMBE is to be published.

457 - Day-to-day repeatability of the results of the finger-toe-plot analysis

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Abstract—Non-invasive arterial pulse wave (PW) measurement provides valuable information on the vascular health. The aim of the study is to characterize the between-visit or day-to-day repeatability of combined finger and toe photoplethysmographic (PPG) signal analysis method called finger-toe plot (FT-plot) and compare it with the repeatability of other methods proposed for vascular characterization. Ten 22-36-year-old subjects were examined on 3 different days in order to find out the day-to-day repeatability of the results. The repeatability of the extracted parameters was analyzed by means of intra-class correlation coefficients (ICC) and free-marginal multirater κ agreement. ICCs varied widely from below 0.2 to almost 0.9, but κ coefficients higher than 0.7 were achieved for most of the results. Based on the presented results, the FT-plot analysis has at least sufficient day-to-day repeatability. However, further studies with real patients and different stages of cardiovascular diseases are required for confirming the findings.

463 - Artificial Astrocytic Modulation of Neuron's Output

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Abstract—Artificial Neuron-Glia Networks (ANGN) are feed-forward multilayer artificial networks that are composed of two types of information processing elements: one type that emulates neurons and another type that emulates astrocytes. These networks implement an astrocytic modulation that simulates the ability of astrocytes to modify the synaptic space, enhancing the weights of the connections. In this

work ANGN have been implemented with a new type of astrocytic modulation observed in the brain: artificial astrocytes act on the output value of artificial neurons increasing or reducing the amount of neurotransmitter released in the synaptic terminal. For three classification problems the results of the comparison of the new type and the previous type of modulation and Artificial Neural Networks without astrocytes are shown. It is observed that depending on the problem, one or another type of astrocytic modulation is better, but in all cases the performance of artificial networks with astrocytes is superior.

464 - Early Stage Health Technology Assessment of eHealth solution for Diabetes. Experience on the usage of the MAFEIP tool: data collection.

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Abstract— Evaluating eHealth solutions to improve the management of Diabetes requires a multidimensional perspective but, at the same time, there is need to converge the different dimensions in order to make decisions towards further stages of innovation. The work described in this paper informs on how the results of a European funded project have been re-elaborated in order to collect data for a cost-effectiveness analysis carried out through the MAFEIP tool that, since 2015, the European Commission has made available to assess innovations in health and social care for European regions.

465 - Does asthma-like increased breathing load influence impedance pneumography signal?

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Abstract— Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing. During an asthma attack, a bronchospasm occurs. In order to overcome increased resistance of airways forced breathing is necessary. It affects the intrapleural pressure, blood volume within the thoracic cavity and therefore it may affect also impedance pneumography signal. We tried to imitate asthma-like conditions by increasing breathing load in to find out, whether it influences impedance pneumography signal. Forced breathing was performed as a respiration through adjustable respiratory loads. The study subjects breathed through 4, 7 and 10 cmH₂O*s/liter breathing loads, at 6 and 12 breathes per minute rates. A calibration coefficient between tidal volume and impedance pneumography and the effect of breathing

load on cardiac component of impedance pneumography signal were determined. We found that forced respiration did not significantly affect the impedance pneumography signal, thus it seems unlikely that asthma-like bronchospasms will disturb calibration of the impedance pneumography signal. Thus it is likely, that this technique can reliably measure respiratory parameters during long-term ambulatory monitoring of patients with asthma.

466 - Co-creating with consumers and stakeholders to understand the benefit of Internet of Things in Smart Living Environments for Ageing Well: the approach adopted in the Madrid Deployment Site of the ACTIVAGE Large Scale Pilot

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Abstract— The ACTIVAGE project is a multi-center *Large Scale Pilot* that has as main objective the demonstration that the Internet of Things (IoT) paradigm plays a fundamental role in deploying cost-effective and sustainable solutions for ageing well and independent living of European senior citizens. In this work, we present the approach that is currently adopted in one of the centers of the pilot, the Madrid *Deployment Site* (DS), to derive, from the main objective, meaningful values for end-users and stakeholders of the solutions.

467 - Line Contrast Figure of Merit for Dual Energy X-ray Image Quality Assessment: Initial Results

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Abstract— Various Figures of Merits (FoMs) are used in order to evaluate the quality of x-ray images. A new Figure of Merit (FoM) is presented, which is based on analysis of data extracted from line profiles within the image. This FoM is referred as Line Contrast (LC). In order to evaluate its performance, the proposed FoM along with Contrast to Noise Ratio (CNR) and Contrast Michelson are applied in simulated Brain CT images and the resulting FoM values are compared. Brain CT images are created using the XRAYImagingSimulator, an in-house developed software platform for x-ray imaging simulation. A 3D brain phantom especially modified for x-ray imaging that contains volumes of gray, white, skull and cerebrospinal fluid was used. Presented Dual Energy CT images were produced with the low/high energy combination of 100/110 keV monochromatic beams. All images were evaluated using CNR, Contrast Michelson and LC FoM, both with and without the simulated presence of noise.

Initial results from the application of FoMs show that LC comes into full accordance with visual assessment and that it overpasses the traditionally used CNR and Contrast Michelson. Initial results are presented here, while further studies on the evaluation of the proposed FoM are in progress.

470 - Association of Drivers' sleepiness with heart rate variability: A Pilot Study with Drivers on Real Roads

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Abstract—Vehicle crashes lead to huge economic and social consequences, and one non-negligible cause of accident is driver sleepiness. Driver sleepiness analysis based on the monitoring of vehicle acceleration, steering and deviation from the road or physiological and behavioral monitoring of the driver, e.g., monitoring of yawning, head pose, eye blinks and eye closures, electroencephalogram, electrooculogram, electromyogram and electrocardiogram (ECG), have been used as a part of sleepiness alert systems. Heart rate variability (HRV) is a potential method for monitoring of driver sleepiness. Despite previous positive reports from the use of HRV for sleepiness detection, results are often inconsistent between studies. In this work, we have re-evaluated the feasibility of using HRV for detecting drivers' sleepiness during real road driving. A database consists of ECG measurements from 10 drivers, driving during morning, afternoon and night sessions on real road were used. Drivers have reported their average sleepiness level by using the Karolinska sleepiness scale once every five minutes. Statistical analysis was performed to evaluate the potential of HRV indexes to distinguish between alert, first signs of sleepiness and severe sleepiness states. The results suggest that individual subjects show different reactions to sleepiness, which produces an individual change in HRV indicators. The results motivate future work for more personalized approaches in sleepiness detection.

473 - Topics and Trends Analysis in eHealth Literature

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Abstract— eHealth is an interdisciplinary research area that fosters application of informatics and communication technologies for the improvement of healthcare delivery. In this paper, we present an overall analysis of eHealth topics and trends in published literature indexed in PubMed (all records till 31 Dec 2016, search on 25 Jan 2017), based on unsupervised topics modeling and trends analysis. Overall the analysis indicates a slightly declining (non significant) publication trend when compared to the overall PubMed corpus growth. Within the area of eHealth, a high negative trend is found for topics related to applications that support medical expert collaboration and consultation (e.g. teleradiology, image transmission, telesurgery, consultation between centres). On the contrary, a high positive trend is found for topics related to personalized eHealth applications, including mobile devices and patient empowerment.

474 - Evaluation of SAR induced by a Planar Inverted-F Antenna based on a Realistic Human Model

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Abstract—In this paper the absorption by the human body of electromagnetic (EM) radiation generated by a Planar Inverted-F Antenna (PIFA) from a modern mobile phone is investigated through the evaluation of the Specific Absorption Rate (SAR) in head, brain and hand regions using Sim4Life (S4L) and a realistic anatomical model. Several scenarios were evaluated, by varying the distance between the antenna and the head, the feeder position and the orientation of the antenna. The effect of the presence of the hand was also studied and, finally, different communication bands were considered. The main results show that the presence of the hand is determinant to reduce SAR on head and brain, while bottom orientations of the antenna reduce the SAR on the brain, but increase the SAR in other tissues..

475 - Conduction velocity effects due to ephaptic interactions between myelinated axons

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Abstract—Electrical ephaptic interactions between axons have the effect of modulating their conduction velocities and adjusting the frequency via synchronisation of action potentials. These interactions have been studied for unmyelinated axons, but have been generally disregarded for myelinated axons. However, the existence of this type of interactions in myelinated axons is expected to play a role in the transmission of signals along nerves. In this work, we run a simulation of propagation of action potentials using models of three parallel myelinated axons which interact with each

other via the extracellular electrical field, and show how modifications in the conduction velocity and synchronisation occur.

476 - The Precordial Electrical Impedance Methods Possibilities in the Evaluation of Local Heart Chambers Contractility

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Abstract — The paper considers the possibility of precordial electrical impedance measurements in the evaluation of the heart chambers mechanical activity. It is shown that the precordial electrode systems allow to analyze the heart wall movement in systole of the atria and ventricles. In particular, radial mapping method allows to estimate the ventricles walls local movements.

478 - Clinical Engineering Online Courses for Africa

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Abstract— In this paper is described one of the most interesting new projects of the Clinical Engineering Division of the International Federation for Medical and Biological Engineering (IFMBE/CED). This project is denominated “Electronic courses (E-courses) for developing countries”. The aim of this project is to train people living in developing countries on the activities involving medical equipment maintenance and management, using a virtual learning system for the lectures. The main outcome is the development of a strategy that can support training of Clinical Engineers as well as Biomedical Equipment Technicians. A system that can, at low price, develop training courses in several parts of the world, using distant and local expertise, not limited to language barriers. The E-Course project design began in late 2015. The initial focus has been put on three African countries: Gambia, Zambia and Mozambique. Today the project has designed two main streams for 2017 and 2018. The challenge is now keeping involving the target countries to be sure to fit and fulfil their needs. A desirable goal is the creation of a sort of “experts bank”, involving many of the IFMBE structures such as divisions and committees, to have a dynamic list of professionals that can be consulted or asked to travel to specific destinations. This will be an important outcome that will facilitate the passage from this pilot experience to a project addressed to other developing countries all over the world.

480 - IFMBE/Clinical Engineering Division projects for the advancement of the profession of Clinical Engineering

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Chairman, Clinical Engineering Division of IFMBE

Abstract— The IFMBE/CED has been conducting, in the past years, a project aimed to know and understand the current programs for registration and certification of clinical engineers in the whole world. A similar project has been designed and budgeted in the CED action plan for the triennium 2016-2018. One of the key issues for arriving to a worldwide guideline is having a common glossary of definitions. As a result of the first Global Clinical Engineering summit, a document has been outlined to define what are the main activities describing Biomedical Engineers and Clinical Engineers. The main purpose of this document is inserting the Biomedical Engineering and Clinical Engineering professions in the forthcoming ILO International Standard Classification of Occupations (ISCO-2018). This will be a milestone for every current and future programs of professional certification, since it will give a clear worldwide reference. One other important project is the International Forum of Clinical Engineering Societies, aimed to discuss regional but also common problems among the participants, identifying the possibility of exchange of experiences not only among the societies but also among experts worldwide. The other project that is closely connected to those above-mentioned is the definition of both a Body of Knowledge (BoK) and a Body of Practice (BoP) for Clinical Engineering. The results of this ongoing project, which at the moment involves taking online questionnaires to hundreds of clinical engineers worldwide, will form the basis for the definition of the forthcoming IFMBE/CED white paper for the assessment and design of certification and registration programs.

483 - Evaluation of WAMP protocol in real-time remote ECG monitoring

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Abstract—Feasibility of using Web Application Messaging Protocol (WAMP) to implement a real-time, distributed software component architecture for remote ECG monitoring was evaluated. A prototype distributed system consisting of software components organized into several real-time signal processing pipelines was constructed. WAMP and a Crossbar router were used to interconnect the components, and the signal processing and connection latencies were measured during real-time simulations of three different scenarios. In all the scenarios, the mean latency from a device to a remote interface was less than 40 ms in real-time streaming of two-lead ECG with compression; less than

50 ms in PVC event notification; less than 50 ms in real-time tachogram updates; and less than 400 ms in heart rate variability (HRV) statistics updates. According to the results, WAMP protocol can support real-time ECG streaming with a 250 Hz sampling rate, real-time HRV analyses, and real-time alarm notifications. Especially life critical alarm notification delays can be reduced into millisecond range. Although network congestion can increase the latencies, WAMP has potential to be used in developing scalable real-time remote ECG monitoring platforms.

484 - Data Flow and Collection for Remote Patients Monitoring: From Wireless Sensors through a Relational Database to a Web interface in Real Time

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Abstract—A reliable, secure, and real-time data collection from sensor devices to the end-user is an open research problem. Many research works have been focusing on the wireless communication level to obtain quality of service. This paper widens the problem, and provides a comprehensive system design, where it covers all the elements in a remote health monitoring application. The system collects measurements in a relational database, either through a C#.NET or a LabVIEW program. The end-user is able to observe either real-time data (i.e. with insignificant delay) or processed historical data on any web browser. We have shown that the inclusion of the relational database may impose a need for the data to be buffered before inserting into the database within a single transaction, but the buffering does not entail delays bigger than 50 ms.

485 - Chronic Disease Management via Mobile Apps: The Diabetes Case

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Abstract— Given the great potential of mHealth applications as far as chronic diseases management is concerned, we investigated the level of intervention provided by mobile applications for the case of diabetes. Online stores (Google Play Store, App Store, Windows Phone Store) and mHealth-related databases were used as our investigation field and applications were reviewed upon several criteria. Our results indicate that there is still enough room for improvement in order to approach a holistic management point-of-view from an mHealth perspective.

489 - Circadian blood pressure pattern in positive drug responsive hypertensives, hypertensives and normotensives, and gender influences.

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Abstract— Circadian rhythm is a characteristic behavior of human physiology and it is known that, in healthy subjects, blood pressure (BP) increases during the day and decreases during the night, as a result of sleep-wake changes. Some studies highlighted that female had lower office BP values than male and this should be considered for define the threshold of hypertension. With the introduction of the Holter Blood Pressure Measurement, it has been possible to record the blood pressure for 24 hours. This innovation allowed to analyze the circadian Blood pressure pattern (CBPP) and some studies identified the differences between normotensives and hypertensives subjects. In this study, we examined the circadian pattern in positive drug responsive hypertensive patients in respect of negative ones and of normotensive subjects and the differences due to gender. The results demonstrated that positive drug responsive hypertensive patients had the same circadian blood pressure pattern as normotensives. Moreover, the difference in circadian blood pressure values between male and female was about 2-4 mmHg.

491 - Designing a mobile system for safety reporting of arthroplasty adverse events

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Abstract— This paper presents a mobile software application development for safety reporting of adverse events within the field of arthroplasty. Proposed user interface enables entry of data specific for adverse events of the knee and hip implants. Besides the patient data, the system supports entry of the event, its classification (serious, non-serious), its follow up, as well as a connection to the database maintained within the Helse Bergen hospital information system. Safety reports can be initiated and retrieved on request and depending on the adjudication of the event; suspected severe events should be followed up until their resolution. Expert evaluation of the first design solution was performed using low fidelity prototype. It has shown that design was relevant, straightforward, done in a way that official reporting would commence. Some users were positive to the reporting, some

felt it would demand more work. A comprehensive evaluation with different potential user groups is planned to meet their needs and understand their views.

496 - Design and Development of a Low-Budget Infrasonic Detector

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Abstract— Infrasonic waves, or simply infrasound, are sound waves with frequencies lower than 20Hz, which are not audible to humans. Although there are many sources of infrasound in the environment, either natural or man-made, whose related research is ongoing for many years, a strong concern has emerged over the last decade about whether infrasound poses a threat to our health. The main cause of this concern is the frequent complaints of residents, living in areas where wind turbines are installed and operate. Residents claim that the operation of the turbines and specifically the infrasound generated by them, has a negative effect on their health. These facts justify the development of a low-cost device, able of detecting and suitably amplifying infrasonic waves so that the processing and study of infrasound waves can be measurable. Until now the equipment designed specifically for this purpose has been quite expensive and hardly available. Therefore, we propose a simple, functional and low cost device to address the infrasound detection thresholds.

498 - Estimation of kinematic parameters in a model of artificial aortic valve leaflets

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Abstract— Currently, one of the least invasive methods of replacing a dysfunctional aortic valve in humans is Transcatheter Aortic Valve Implantation (TAVI). The shapes of expandable stents have an influence on the geometry of the leaflets and differ from those mounted by open heart valve surgery. There are different types of balloon and self-expandable TAVI valves. For the purposes of analysis of the influence of constraints on the kinematic parameters of aortic valve leaflets, prototype leaflets were made of polyurethanes. Results from the numerical model and a machine for testing the durability of the heart valve are presented.

499 - Current trends in Electronic Family Resilience Tools: Implementing a tool for the cancer domain

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Abstract— It is well documented that the diagnosis of cancer affects the wellbeing of the whole family adding overwhelming stresses and uncertainties. As such, family education and enhancement of resilience is an important factor that should be promoted and facilitated in a holistic manner for addressing a severe and chronic condition such as cancer. In this paper, we review the notion of resilience in the literature identifying three tools that try to support it. Then we focus in the cancer domain and we describe a tool implemented to this direction. To our knowledge, this is the first time such a tool is used to complete patient profile with family resilience information, eventually leading to patient and family engagement and empowerment.

501 - Automatic Classification of Forum Posts: A Finnish Online Health Discussion Forum Case

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Abstract—Online health discussion forums play a key role in accessing, distributing and exchanging health information at an individual and societal level. Due to their free nature, using and regulating these forums require substantial amount of manual effort. In this study, we propose a computational approach, i.e., a machine learning framework, in order to categorize the messages from Finland's largest online health discussion forum into 16 categories. An accuracy of 70.8% was obtained with a Naïve Bayes classifier, applied on term frequency-inverse document frequency features.

502 - Performance Analysis of Novel Flexible Electrodes for Wearable ECG/Heart Rate Monitoring

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Abstract— The development of manufacturing methods has made it possible to add metal materials as flexible electrodes into wearables. This paper presents effective methods of manufacturing custom electrodes that give reliable ECG/HR signal and maintain textile comfort. Screen-printing, micro etching and electro plating have been used to make dry electrodes that are integrated into common types of heart rate straps. Each manufacturing method of dry electrodes is related to single electrode material. The effects of different materials on signal quality are investigated. Tested materials were platinum, silver ink and stainless steel. These heart rate straps were used during rest condition, cycling, walking and running. Ten users were included (7 male and 3 female) and were measured during physical activity. Electrode performance was measured and signals were compared simultaneously with silver/silver chloride gel electrodes. In this study, platinum has the smallest signal error; therefore, it is the most appropriate of the tested materials. Followed by Ag ink, disposable Ag/AgCl and lastly stainless steel. The results obtained during exercise indicate that, all of the tested materials worked reliably with these activities and there is no statistical difference between them. The HR error % in all materials was below 20%, which was considered the limit for reliability. It can be concluded that their signal measurement reliability is adequate for sportswear and health care applications. These electrodes did not rub or the edges scratched the skin. The additional result is that they are reasonably comfortable to wear during exercising.

504 - Pattern recognition techniques and classification sets supporting behavioural tagging when using a limited number of body sensors

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Abstract— Stress and physical activities are important aspects of life of people. Body reactions on stress and on physical activities can be very similar but long-term stress leads to diseases and damages the body [1]. Currently there is no method to differentiate easily and clearly between these two aspects in a time slot. We have confronted this problem while developing a mobile system for detection and analysis of stress. This paper presents an approach, which uses a long-term monitor with ECG/EKG capabilities and analysis of the heart rate data that is extracted from the device. The focus of the work is to find characteristics that are useful for differentiation between physical activity and stress.

505 - A scale with ECG measurements capability for home cardiac monitoring

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Abstract— Presented device -a scale developed for enabling extra measurements, in addition to body weight and composition, the electrical activity of the heart (electrocardiogram - ECG) and the level of oxygen saturation in the blood SaO₂. Electrical activity is recorded in the form of six leads, so-called. limb leads. The device allows measurement of all standard limb leads and without the need for additional procedures. ECG, although the measurement is performed in an unconventional standard, and the results should be treated as if they were made using a standard ECG monitor.

507 - Capacitively coupled ECG measurements - a CMRR circuit improvement

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Abstract—A typical galvanic-connected electrocardiogram (ECG) measurement system utilizes two signal's electrodes and a third one in driven-right-leg (DRL) circuit for improving a common-mode rejection ratio(CMRR) of the acquisition system. In capacitively-coupled ECG similar techniques are used, however it is expected, that the utilized DRL subsystem is formed using a capacitive coupling approach, too. An improvement of the acquisition system performance by improving DRL circuit is presented in the paper.

510 - Dry electrode sizes in recording ECG and heart rate in wearable applications

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Abstract— The rise of wearable electronics is paving the way for textile integrated sensor applications. ECG and heart rate monitoring are common in health care and consumer applications, respectively. In short term monitoring Ag/AgCl, conductive polymer or fabric electrodes can be used. In long term monitoring the electrolyte and adhesives may cause skin irritation, therefore textile integrated skin friendly dry electrodes may be a solution. The electrodes need to be cost-effective, easy to integrate, need no special care from the user and perform well. Conductive polymer and textile used in sports applications perform poorly when used without electrolyte. Stainless steel is common, affordable, easy to process, biocompatible (selected alloys), and provides adequate ECG quality. In this paper, we study different size stainless steel dry electrodes in ECG and heart rate monitoring and

compare those with commercial disposable Ag/AgCl electrodes. The results show that stainless steel dry electrodes performed well throughout the tested activities if the circular electrode diameter was 20 mm or larger.

511 - Intermediate frequency voltage transients in the electrical grid – which mechanisms can explain biological effects?

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Abstract—Epidemiological studies focusing on low-level magnetic fields health effects have provided limited evidence of harmful effects. Lately there has been interest in Intermediate Frequency (IF) area, pulsed electromagnetic fields and voltage transients. This paper looks at biological effects related to electroporation, and inspects whether voltage transients within the electrical grid have properties supporting possible harmful biological effects. It is suggested that in health studies there is much to learn from the EMC and EMI areas, where focus is on voltage transients and capacitor damage.

514 - Stroke volume assessment by impedance cardiography: Comparative analysis with transthoracic echocardiography

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Abstract— The aim of this study was to compare the accuracy and precision of measurements of stroke volume (SV) and stroke index (SI) by using a Hotman System in comparison with transthoracic echocardiography method. The ICG signals were registered by using Hotman System. The echocardiographic images were saved synchronously with the ICG signals. Measurements were taken in 10 healthy subjects. This research demonstrated that the average values of the SV and SI that are measured using Hotman System and echocardiography device differs from each other. Bland-Altman plot revealed that the differences between two modalities are statistically nearly 21% and Hotman System overestimates averagely the SV by 21ml. To make general conclusions, more studies should be carried out on a larger study group.

515 - Method for Evaluation of Surgical Wound Healing: A Case Study

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Abstract—We arranged a case study in order to examine whether tetrapolar bioimpedance measurement could be applied for evaluating the healing of a surgical wound. We measured the donor site surgical wound of a patient who had undergone a breast reconstruction surgery. The measurements were conducted three times in a nine days period, starting from the first postoperative day. As a reference, the impedance of an unaffected site was also measured. The electrodes were placed at equal distances, four centimetres apart in a parallel formation. The results show that, at low frequencies, the impedance of the wound increases with time. At higher frequencies, the situation is opposite; the impedance of the wound is initially higher than the reference and decreases with time. Both ends seem to approach the reference impedance as the healing proceeds. Our results are in accordance with the normal course of surgical wound healing and more specifically appear to be related to the diminishing swelling around the wound site. We conclude that the obtained results are interesting in a level that calls for further investigation.

517 - Using quantitative parameters of ocular blood filling with transpalpebral rheophthalmography

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Abstract—This paper presents a new parameter of eye blood filling based on the registration of rheographic signals and blood arterial pressure. The method of transpalpebral rheophthalmography is briefly discussed. The transpalpebral rheophthalmography technique which includes an electrodes system and a fixing system is presented. A two-parameters calculation method for transpalpebral rheophthalmography is proposed. Calculations made in analyzing signals obtained from myopic patients are presented. A rheophthalmography signal recorded transpalpebrally is shown to allow defining change dynamics of ocular blood flow during therapy.

518 - Simulation of the Vectorcardiogram using a simple Volume Conductor Model

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Abstract—In developed countries cardiac diseases are still the number one cause of death. For this reason, research aims to understand physiological and pathological processes of the heart. Proper functioning of the heart and therefore, the supply of organs with blood is triggered by electrical activity. For each contraction of ventricles an excitation of action potentials through the cardiac cells has preceded. Research to model the excitation of the heart is a relevant topic in order to understand ongoing coherences in the heart and be able to test cardiac devices in vitro. Therefore, in this model we demonstrate a physiological motivated abstracted simulation of the vectorcardiogram (VCG). In this model, we developed the conduction pathway of action potentials in the heart by applying a predefined propagation direction. The segmentation of heart was performed in order to distinguish between the different existing heart tissues. A tree structure was implemented, in which each node of the tree represents a cardiac cell and each edge of the tree structure the transition between cells. Therefore, the edges of the conduction tree are weighted with the conduction velocity in the considered heart area. Due to the predefined conduction orientation a reduction in complexity can be achieved. The choice of a simple volume conductor facilitates the transfer from the source signals to the chosen observing points on the volume conductor. The simulation of a lead system similar to the Frank lead system shows morphological reasonable results, so that for further investigation the simulation of pathological scenarios is conceivable. Typical characteristics of the VCG like P-Loop, QRS-Loop and the T-Loop are clearly identifiable. The reduction of complexity promises to reach real-time capability using this model for testing in ECG-triggered medical devices (Amacher et al. 2013).

519 - Determination of the Effect of SiO₂ Nanoparticles on Spontaneous Activity of Rat Uterus Smooth Muscles using Wavelet Scalogram Analysis

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Abstract— Today, nanomaterials are used in many industrial areas such as electronics, optics, textiles, as well as in medical devices, biosensors, etc. Among various types of nanoparticles (NPs), silica nanoparticles (SiO₂ NPs) are one

of the most used NPs, especially in nanostructuring, drug delivery, cosmetic and optical imaging agents. Although NPs have a great importance in nanotechnology, they also have a potential toxic effect, which cause health problems. Uterus is a hollow muscular organ situated deep within the female pelvic cavity. The uterine smooth muscle, which is situated in uterus, is able to produce regular spontaneous contractions without any hormonal or nervous input [17]. Uterine contractions are important in many reproductive functions including the transport of sperms and embryo, menstruation, pregnancy and parturition. In this study, the effect of SiO₂ NPs on uterine contractions are investigated. Experimentally recorded spontaneous activity of uterus are analyzed using wavelet transform. Obtained results show that, increasing doses of SiO₂ NPs decrease the contraction frequency significantly, while energy of contractions does not change considerably.

521 - Detection of sleep stages in neonatal EEG records

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Abstract—The aim of this study is the detection of changes in sleep stages in EEG recordings in full-term and preterm newborns. We use a k-NN algorithm as a method of classification. The novelty of our approach lies in semi-automatic etalon (prototype) selection with combination of temporal analysis for sleep stages detection. The semi-automated etalon extraction includes the k-means algorithm for etalons suggestion and an expert-in-the-loop for verification of these etalons. The semi-automated approach improves significantly the time spent on the etalon selection (extraction) by the expert. The whole procedure of EEG signal processing consists of adaptive segmentation, feature extraction, semi-automatic etalon selection using k-means and expert-in-the-loop, classification using k-NN algorithm and temporal profile analysis that is able to detect the neonatal sleep stages for the full-term and even for the preterm neonates, which makes it a unique detection method.

522 - High radio frequency biosensor for a nano-concentration detection of the label free Prostate Specific Antigen cancerous cells

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Abstract—This research presents an original and novel biosensor based on the transmission line geometry of a high radio frequency microstrip filter which aims to achieve rapid

diagnostics of cancer. The analytical design of the biosensor has been computationally verified. The biosensor was fabricated by patterning a 10 μm nickel/gold metal layer on a 1.6 mm FR-4 dielectric base with a continuous metal back plane. Subsequently, the microstrip was integrated with a microfluidic channel. Characterization of scattering parameters was performed by a vector network analyzer (VNA), with results showing good agreement with the modelling. To assess functionality, sensitivity to prostate specific antigens (PSA) was quantified. Initially, the biosensor was functionalized by coating it with antibody receptors (Ab) to capture PSA. Thereafter, sensitivity and repeatability towards the detection of captured PSA was assessed by immobilization of PSA onto the treated golden surface. Measurements were taken directly after each stage of coating and capturing. A nano-concentrations (2000-20ng/ml) of PSA were sensed. The characteristic dips in the reflection signal parameter (S_{11}) all showed both an amplitude and frequency shift, most notably at 0.6, 1.08 and 1.32 GHz respectively. This therefore revealed the ability of this biosensor to immobilize and detect nano-concentrations of PSA analyte by measuring the signal changes due to the presence of PSA, with variability in results being attributed to the surface quality of the biosensor. Mostly, electrical biosensor research is focusing on low frequency (<1MHz), on the other hand, the work reported here proves the achievability of this new high frequency approach.

524 - Auto-regression-driven, reallocation particle filtering approaches in PPG-based respiration rate estimation

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Abstract—Interest towards respiratory state assessment with non-obtrusive instrumentation has led to the design of novel algorithmic solutions. Notably, respiratory behavior has been observed to cause modulative changes in two discreetly measurable physiological signals, PPG and ECG. The potential to integrate respiratory rate measurements in widely used instrumentation with no additional cost has made the research of suitable signal processing methods attractive. We have studied and compared auto-regressive (AR) model order optimization and coefficient extraction methods combined with a reallocation particle filtering approach for respiration rate estimation from finger PPG signal. The evaluated coefficient extraction methods were Yule-Walker, Burg, and Least-square. Considered model order optimization methods were Akaike's information criteria (AIC) and Minimum description length. Methods were evaluated with a publicly available dataset comprised of approximately 10-minute measurements from 39 healthy subjects at rest. From the evaluated AR model parameter extraction methods, Burg's

method combined AIC performed the best. We obtained the mean absolute error of 2.7 and bias of -0.4 respirations per minute with this combination.

530 - Twelve Years Follow-up of Ballistocardiography

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Abstract—The purpose of this work is to study the effect of long term alterations of ballistocardiography during 12 years time recorded in sitting position by using EMFi (Electromechanical Film) sensors. ECG, BCG, ankle pulse signal and carotid pulse (CP) signal from the neck near the carotid artery were recorded from a single person and duration of the signal components according to R spike of the ECG and amplitudes of the signals were studied.

The time domain properties of BCG, CP and ankle pulse signals at different times (time interval around 1 year during 12 years time) remained rather stable within the same person. The BCG signal stability endured during 12 years time showing that no major changes happened in the condition of the heart-vasculature system.

534 - The Use of Multichannel Photoplethysmography for the Analysis of Heart Rate Variability

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Abstract—Heart rate variability (HRV) is a parameter of heart reactivity which is used to describe fluctuation of intervals between two consecutive heart beats. The paper focuses on the analysis of HRV from PPG and ECG signals derived from multichannel PPG. The suitable methods of preprocessing of signals are described in order to obtain the accurate result of HRV analysis and several effects causing changes in HRV are evaluated. Its object is to evaluate accuracy of the measurement from PPG beside ECG because this method is not used in common practise and analyse the changes of HRV during day.

537 - Biomedical Engineering Education: Need for Harmonisation

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Abstract— Medical technology has radically reshaped the way healthcare is delivered today and continues to improve it in an accelerated pace. Biomedical Engineering (BME) is a multidisciplinary field lying in the cross-section of medical/biological sciences and engineering. Healthcare today is technology-driven and delivered by teams rather than individuals. Biomedical Engineers (BMEs) as professionals are playing a vital role in these developments, being behind the recent advances and involved during the whole life cycle of Medical Devices (MDs), from the innovative idea to their final use. More than five hundred thousand MDs models are available in the world market today. As a result, the BME profession is expected to be the first in demand amongst all other engineering subspecialties in the years to come. However, this rapid evolution creates a constant pressure for new knowledge and skills for the BMEs and therefore for continuous curriculum updates in order to meet R&D and market demands, but also for harmonisation of studies worldwide that will facilitate staff and students' mobility and collaboration.

Educational programs for graduate and postgraduate studies in BME should be built upon the basis of evidence-based data from specific studies, surveys and reviews on existing educational programs in BME and the required knowledge, skills and attitudes emerging from recent advances in medical technology and the MDs industry perspectives. The wide acceptance of a consensus-based agreement on a generic core curriculum that would be part of a great number of BME programs, based on the Bologna process [1], will promote employability, competitiveness as well as staff and student mobility through the use of the European Credit Transfer System (ECTS) [2] and will facilitate a worldwide opening of the BME job market, through mutual recognition of the competencies acquired.

538 - Analysis of Instantaneous Cardiac EBI Signal Variability over the Heart Cycle(s): Non-Linear Time-Scale Approach

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Abstract— The paper presents a method similar to the dynamic time warping (DTW) that normalizes cardiac Electrical Bioimpedance (EBI) periods' waveforms in time domain by scaling period waveforms along the time axis. In opposite to DTW, where the matrix of local distance measures

is analyzed to find the best warping path, the proposed method uses adaptive Bézier curve fitting approach to find "warping path", minimizing the sum of squared error measures between the EBI periods waveforms. For the normalization, the vector of time instances of the cardiac period is approximated by the Bézier curve with 6 points (4 control points and 2 end points). Results are presented in time domain for 2 persons selected from the available patients population of 53 voluntary persons.

539 - An evaluation of the direct electromagnetic influence on the safety of users of wearable insulin pumps caused by low frequency magnetic field

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Abstract— Wearable insulin pumps are among the most efficient treatment methods in diabetes therapy. Their users devices may experience exposure to low frequency electromagnetic field, with a dominant magnetic component when stay near sources, such as: magneto therapeutic applicators, electric gastronomy devices and industrial electro thermic appliances – where local exposure may significantly exceed the typical level of public exposure. The electric field induced in tissues is a direct biophysical effect of exposure to low frequency electromagnetic field. According to international safety guidelines, this is an assessable parameter (by numerical simulations) due to the evaluation of the health and safety hazards from such exposure - with respect to limits provided to protect against nerve stimulation caused by exposure. In the case of electromagnetic exposure of an insulin pump user, the needle injected into the body influences the effects of exposure in the surrounding tissues. The results of performed numerical studies on tissues near the insulin pump needle show biophysical effects of exposure to magnetic field at frequencies from the range 10-1000 Hz that are up to approximately three-times higher than without injection. The level varies with the polarisation of the relevant magnetic field and the material of the needle. In addition to the discussed direct electromagnetic hazards, there is also the issue of the electromagnetic influence on the electronic structure of the medical device, which is worthy of attention, in accordance with the rules of electromagnetic compatibility tests.

541 - Shielding static magnetic fields from Magnetic Resonance Imaging units by ferromagnetic material

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Abstract— This study investigated the effectiveness of iron sheets in shielding static magnetic fields from MRI units. The neighbouring rooms of two 3T MRI units were measured, located in different healthcare facilities, one fully shielded and the other only partially shielded (only the ceiling was shielded) from static magnetic fields. In order to achieve a significant shielding effectiveness from the MRI static magnetic field, the examination room should be fully shielded, including the walls, ceiling and the floor. The MRI unit with only partially shielded room allowed ten times more static magnetic field to propagate into the premises one floor below. The average static magnetic field below partially shielded MRI unit was 1.178 mT, whereas below fully shielded MRI unit 0.176 mT.

542 - Quantization of the response signal differences for the electrical bioimpedance measurement

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Abstract—Solutions for practical implementation of the electrical bioimpedance acquisition typically need to be optimized and adapted for the task at hand. One of the most challenging measurement tasks is impedance plethysmography, the test that measures tiny changes in electrical conductivity, related to changes in biological volumes. These changes depend on the underlying biological processes, measurement locations, and added random artefacts. Changes in the acquired impedance due to the cardiac activity can easily be 0.1% and lower. In modern devices, the digitalization of the data acquisition results is almost mandatory, and it places heavy demand on the used analog-to-digital converters. Only few levels are left from 16-bit converter for the direct digitalization of the impedance plethysmography signal, given that the useful signal is only around thousandth of the full impedance scale, and that some margin must be left. Several solutions have been proposed, such as a direct compensation of the carrier of the response signal in order to emphasize tiny variations of it, or in the case of analog preprocessing capacitive coupling helps to separate static component of the impedance. A novel solution for the direct digitalization of the response signal is proposed. Differences between adjacent analog samples taken synchronously to the carrier are quantized instead of the full value. Essentially derivative of the response signal is digitized in this case. Number of the required quantizing levels is reduced significantly. Solution is easily embeddable and customizable.

543 - The possibilities of electrical impedance definition of damaged intervertebral discs

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Abstract — The paper considers the possibility of electrical impedance measurements in the localization of definition the spinal pathology. It is shown that the electrode systems allow to analyze the blood supply of back muscles in the damaged spinal area.

546 - Academia Industry Partnerships in the Biomedical Engineering Domain

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Abstract— The current complex socio-economic environments due to fiscal constraints pose severe challenges world-wide for making technological advances working alone by academia or by industry. Effective academia-industry collaborations can be meaningful avenues for technological advancements, productivity and revenue generation as well as for promoting professional growth and educating future engineers globally. The above explanations apply to all engineering domains including biomedical engineering. The objective of the paper is to explore multifaceted academia-industry partnerships, their benefits and challenges, and to make suggestions for successful outcomes. The results based on several case histories support the formation of carefully planned academia industry partnerships to yield significant benefits to all the constituent members.

555 - MRI imaging texture features in prostate lesions classification

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Abstract—Prostate cancer (PCa) is the most common diagnosed cancer and cause of cancer-related death among men. Computer Aided Diagnosis (CAD) systems are used to support radiologists in multiparametric Magnetic Resonance (mpMR) image-based analysis in order to avoid unnecessary biopsies and increase radiologist's specificity. CAD systems have been reported in many papers for the last decade. The reported results have been obtained on small, private data sets and are impossible to reproduce or verify concluded remarks. PROSTATEx challenge organizers provided database that

contains approximately 350 MRI cases, each from a distinct patient, allowing benchmarking of various CAD systems. This paper describes novel, deep learning based PCa CAD system that uses statistical central moments and Haralick features extracted from MR images, integrated with anamnestic data. Developed system has been trained on the dataset consisting of 330 lesions and evaluated on the challenge dataset using area under curve (AUC) related to estimated receiver operating characteristic (ROC). Two configurations of our method, based on statistical and Haralick features, scored 0.63 and 0.73 of AUC values. We draw conclusions from the challenge participation and discussed further improvements that could be made to the model to improve prostate classification.