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Enhancing replicability of in vivo and in vitro electrostimulation experiments with impedance spectroscopy

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Introduction

Electrical stimulation experiments with electrodes in direct contact with the sample are susceptible to electrochemical interface effects and non-linear electrochemical reactions such as corrosion. Moreover, manufacturing uncertainties can alter electrical properties. Consequentially, experiments are not replicable or even repeatable.
We investigated three electrode setups used in recent *in vivo* and *in vitro* research: SNEX-100 from Microprobes, Gaithersburg (USA), the ECIS culture plate 8W20idf from Applied BioPhysics, Troy (USA) and custom-made electrodes for 6-well plates consisting of titanium rods.

Methods

We used electrochemical impedance spectroscopy to record the electrical impedance of the electrodes from 1 Hz to 10 MHz in a two-electrode setup, i.e. no reference electrode was utilised. The electrodes were immersed in conductivity standards in a thermally stable environment to ensure replicability.
The impedance spectra were validated with the LinKK test utilising the open-source software ImpedanceFitter. Fitting the spectra with ImpedanceFitter yielded the system's electrochemical properties. The electrochemical properties were used in numerical simulations to provide information about observables that cannot be measured directly and thus predict the outcome of the experiments.
Monitoring the input current and estimating the DC equivalent with Ohm's law identified impedance changes during stimulation.

Results

The custom-made titanium electrodes serve as an example of corrosion. Energy Dispersive X-Ray analysis revealed a build-up of a calcium phosphate layer on the electrode surface.
Unusual impedance spectra of the SNEX-100 electrodes indicate changed geometries due to manufacturing tolerances.
The ECIS culture plates showed varying impedances in each well due to the non-negligible impedance of thin gold traces. That makes the culture plates unsuitable for electrical stimulation experiments.
All impedance spectra showed the expected double layer at low frequencies, characteristic of the electrode-electrolyte interface.

Conclusion

Impedance spectroscopy provides access to the electrode state before, during, and after stimulation. Knowing the specific shortcomings of each system allows improved experimental setups and thus increases replicability.

Acknowledgement

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Concept for a novel manufacturing technique of high-density feed-throughs for neuromodulation

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Introduction

Transverse Intrafascicular Multichannel Electrodes (TIME) is a penetrating electrode array used to stimulate multiple axon bundles within the peripheral nerve. This provides higher coverage and local selectivity, which translates into finer motor control, when used in neurorehabilitation. However, the high number of electrodes accompanies the need for a high-density feedthrough to fit into the limited space of an implant.

Traditional feedthrough fabrication techniques pose a limit to miniaturization while maintaining the hermetic structure and electrical isolation between channels. This restricts the density of the feedthrough, limiting either the quantity of connected electrodes or the degree of miniaturization.

Methods

A positive photo-resist mold of a matrix of dense electrical tracks is fabricated using ultra-high resolution, two-photon 3D printing. The mold is then embedded within a ceramic slurry comprised of Hydroxyapatite nanoparticles (nHA). The assembly is heated to remove the 3D printed structure through thermal decomposition, leaving an intricate array of channels within the partially sintered ceramic. The channels are backfilled with a metal paste, and fully sintered to achieve a hermetic ceramic filled with electrically isolated and conductive channels. All materials have strong evidence of biocompatibility in implantable devices.

Results

Co-firing the nHA ceramic slurry and photo-resist mold forms a corresponding network of channels embedded within the ceramic, with the photoresist completely removed via thermal decomposition. Shrinkage of 50% allows the ceramic to contract around the injected metal paste, removing any leakage pathways. Current work aims to optimize the sintering characteristics, to ensure the resultant structure is electrically conductive and hermetic, to achieve a functional and reliable feedthrough.

Conclusion

As two of the major drivers of implantable technology development are to reduce invasiveness through miniaturization, and increase impact by increasing number of electrical interfaces, this optimization exploits emerging technologies to achieve these goals through the improvement of high-density feedthroughs.

Ultrasonic-based communication for deeply-seated implants

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Introduction

Deeply-seated implants provide the opportunity to monitor patients' health parameters over an extended period of time. This feature allows implants to assist the patients' medical treatment in the course of a disease. Yet, this demands an exchange of information between the implant and medical professionals, enabling the making of informed decisions or adjusting the treatment. While most traditional approaches are based on inductive links, they show limitations on penetration depth for safe exposure levels. Ultrasound, in contrast, enables higher penetration depth in human tissue within safety limits, overcoming current distance-related constraints.

Methods

This contribution presents a proof-of-concept for ultrasonic-based communication using binary frequency shift keying (BFSK). For this setup, two ultrasonic transducers are placed 75 mm oppositely apart with a tissue-mimicking phantom in between, and are operated by two TI-MSP430 microcontrollers configured as sender and receiver, respectively. The mark (binary 1) corresponds to 8 pulses with f_m = 2 MHz each, the space (binary 0) to 8 pulses with f_s = 1 MHz each. The sender first transmits 20 preambles on which the receiver synchronizes before receiving and decoding the actual payload. Additionally, we monitor the energy demand for decoding messages, determine the bit error rate (*BER*) and evaluate the maximum data rate (D_r).

Results

The minimum energy demand per bit yields 10.5 µJ, increasing to 40.4 µJ by considering further peripherals. The *BER* was determined as 10^{-3}, the D_r amounts up to 747 bits/s. This D_r enables either a real-time reading out of the implant or transmitting a moderate number of data packages at a later time.

Conclusion

The distance of 75 mm exceeds most reported distances with inductive-based links, whereas the low power demand enables its integration in future implants. Potential applications include the monitoring of the body's internal temperature, health conditions of organs, or blood-flow measurements.

Tuning Mechanical Properties of Gelatin Methacryloyl (GelMA) Hydrogels for Biofabrication: Key Parameters and Interactions

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Introduction

Gelatin methacryloyl (GelMA) is a photocrosslinkable biomaterial that has gained significant attention in biomedical applications, particularly within the field of tissue engineering and biofabrication. In recent years, numerous efforts have been directed towards meeting the specific requirements of diverse tissues and mimicking the physical and biochemical characteristics of native extracellular matrix (ECM) with the main goal of improving biocompatibility, promoting favorable cellular responses, facilitating functional tissue regeneration, and ultimately enabling generation of personalized printable scaffolds. To tailor hydrogel's properties for specific applications, it is essential to investigate the key parameters and their combined interactions affecting photocrosslinking reactions. Understanding these dynamics is crucial for unraveling photocrosslinking kinetics and effectively controlling the mechanical characteristics of GelMA hydrogels.

Methods

This study employed a systematic approach to evaluate the mechanical characteristics and to shed light on the interplay between key parameters influencing photocrosslinking reactions. The mechanical properties of GelMA hydrogels were systematically examined using a Design of Experiment (DOE) methodology. Key parameters including GelMA concentration, degree of GelMA modification, photoinitiator concentration, and photocrosslinking time were tuned within a controlled range. Additionally, a sequential crosslinking strategy involving both physical and chemical crosslinking was implemented. Mechanical properties were subsequently determined through unconfined compression testing. Furthermore, the printability of the selected compositions was tested using an extrusion-based 3D printer.

Results

This comprehensive approach facilitated a thorough understanding of how photocrosslinking parameters collectively influence the mechanical characteristics of GelMA hydrogels. Considering the studied ranges of the parameters, GelMA concentration, degree of GelMA modification, and sequential crosslinking are found to be key parameters that improve certain mechanical properties through synergistic effects. Their combined effect leads to a more substantial enhancement in mechanical properties which enables e.g., the attainment of an elastic modulus spanning from around 10 kilopascals up to around 1.5 megapascals. The assessment of printability demonstrated constructs with high shape fidelity, underlining the importance of fine-tuning printing temperature for the precision of biofabrication.

Conclusion

This presentation focuses on optimizing GelMA hydrogel properties by gaining insights into the influence of key photocrosslinking parameters. The synergistic effects highlight the potential of GelMA hydrogel properties in designing customized materials for regenerative medicine, which holds promise for advancing personalized scaffold designs and improving clinical outcomes.

Growing Aortic Valve: Development of a Biohybrid Heart Valve with Growth Capability for the Treatment of Paediatric Patients

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Introduction

Heart valve replacement in children is a major challenge. In addition to other problems, current heart valves do not adapt to the growing size of the child's heart, leading to frequent reinterventions to adjust the size of the valve. The aim of this study is to develop a scaffold structure for a biohybrid implant that can adapt to the growing size of paediatric hearts.

Methods

In order to create a textile scaffold structure that can adapt to the growing diameter and orifice area of the valve in a time-controlled manner, a warp-knitted structure made of non-degradable yarns (polyethylene-terephthalate) was specifically reinforced with biodegradable fibres (polylactide, polylactide-co-glycolide, polycaprolactone). For the integration of degradable fibres, direct incorporation into the warp knitting process by means of combined lappings and tailored integration of reinforcing fibres into the structure were investigated at physiological load conditions. Samples were stored in phosphate-buffered saline solution at 37 °C to simulate degradation in vivo.

Results

The geometry and mechanics of the scaffold were evaluated as it degraded, including diameter, surface area, strength, elongation and compliance. By combining fibres with different degradation rates and geometric structures, valve diameter increased by up to 50% and orifice area by up to 60%. After fibre degradation, radial elongation varied from 5% to 50% for different tailored reinforcement structures. Integrating degradable fibres directly into a warp knit structure resulted in diameter increases of 10 - 22% for different stitch densities. This growth capacity is equivalent to the growth of a paediatric heart valve over ten years if implanted within the first year of life.

Conclusion

By combining a non-degradable textile base structure with a controlled degradable reinforcement structure, it was possible to realise a textile scaffold structure that can grow with the valve. These results are a decisive step on the way to a growth-capable heart valve implant for the treatment of small children and enable the next phase of in-vivo evaluation in the near future.

Investigating Corrosion-Triggered Delamination in AIMD

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Introduction

The ingress of bodily fluids into active implantable medical devices (AIMDs) poses a significant risk of failure. Delamination progresses along metal-polymer junctions of electrodes and conductive pathways leading to leakage currents and insulation faults, potentially causing device failure. However, understanding these delamination mechanisms is difficult due to the complex electrochemical-diffusive processes involved. To address this challenge a standardized test method and specimen were developed to investigate diffusion-based delamination processes of the polymer-metal interface. Medical grade materials were chosen for better transferability to real AIMD.

Method

As it is common in AIMD, such as cochlear implants, a medical grade silicone and platinum were chosen. Since the test uses a chemical reaction of the metallic surface to visualize diffusion in the silicone-platinum-interface, an indicator structure was added onto the platinum using PVD. For this study copper was chosen as it yields an intense color change in the chemical reaction and allows the corrosion process to be visualized without the use of hazardous chemicals simply by color-change. The test-specimens were immersed in a potassium sulfide solution serving as corroding agent. This way the corrosion time of the metallic layer was reduced to a few seconds, allowing an isolated investigation on delamination and diffusion phenomena. During the experiment, images were taken with a time-lapse camera, on which the progress of the diffusion front in the interface was observed. The images were analyzed in an automated Matlab script.

Results

The indicator structure was suitable to visualize and investigate the diffusion processes in the silicone-platinum interface. The experiments showed a high permeability and diffusion rate for ionic molecules that penetrate from the water into the interface.

Conclusion

The developed test has the potential to provide a better understanding of the degradation processes in the metal-polymer interface of AIMD. Furthermore, the test can be adapted for other substances by a suitable choice of indicator structures to investigate the diffusion rates in the interface for different substances.

Development of a dynamic bioreactor for the endothelialization of gelatin hydrogel tubular scaffolds: preliminary results on endothelialization parameters

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Introduction

Endothelialized synthetic vessel models represent a promising biomimetic environment for in vitro investigations on cardiovascular implants. Our study introduces a customized bioreactor for endothelializing gelatin hydrogel tubular models with a rotating cell seeding method. Initial findings on endothelial cell distribution and the impact of flow rate on cell morphology are presented.

Methods

The bioreactor consists of a chamber containing up to 5 rotating models as well as a peristaltic pump to provide culture medium through the system. Enzymatically crosslinked gelatin hydrogel models (length=50mm, ID=4mm) were prepared by molding method. A cell suspension of human umbilical vein endothelial cells was seeded on the model lumen with the cell density of 10^5 cells/cm^2 and subsequently inserted into the bioreactor within an incubator. After 4 days, homogeneity of cell distribution, elongation of cells in response to flow rates of 10, 20 and 100 mL/min, and proliferation rate were assessed via DAPI and F-actin fluorescence imaging.

Results

No cytotoxic effects on the growing cells were noticed. Endothelial cells adhered more homogeneously on the luminal surface when the vessels were rotated with 6 rph while some free-cell zones were observed in the vessels without rotation. Detecting more than 16×10^5 growing cells on the endothelialized vessels after 4 days proved a significant increase in cell number on the prepared scaffolds. The influence of flow rate endothelial attachment and elongation was proved, with high flow rates leading to a detachment of endothelial cells.

Conclusion

In this study, we present a tailor-made dynamic bioreactor suitable for parallel endothelialization of up to 5 vessel models. The introduced bioreactor can be controlled automatically to conduct study parameters on different scaffolds. We showed that the rotation of vessel models during cell seeding is an important factor in achieving a confluent monolayer of endothelial cells on the vessel lumen.

Woven Textile Scaffold for In-Situ Tissue Engineered Heart Valves

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Introduction

We present the investigation of a leaflet scaffold for heart valve replacement based on a load-oriented woven textile. The aim is to replace the current bioprostheses with leaflets made from decellularized animal tissue which are prone to calcification and structural degeneration. Our leaflet scaffold is designed to provide structural integrity and can be combined with a hemocompatible and bioactive coating for in situ tissue engineering.

Methods

Mechanical testing (tensile strength, elongation to break) was used to preselect the fabric configuration. The woven scaffolds (polyethylene terephthalate - PET and ultra-high-molecular-weight polyethylene - PE-UHMW) were mounted in a balloon expandable TAVI stent. Accelerated wear tests were performed under simulated physiological load in a LinA testing device (AME-HIA and ac.biomed GmbH) according to the ISO 5840 standard (sinusoidal load at 37° C, transvalvular pressure difference 100 mmHg, test frequency 700 bpm). The function of the leaflets and signs of wear were assessed by high-speed camera recordings, photography, and microscopic examination. Favorable textile scaffold-stent designs were tested with a higher number of load cycles. In addition, finite element analysis (FEA) was performed to investigate the stresses in the leaflet material and individual warp threads at the leaflet-stent interface during valve closure

Results

First versions revealed critical failure zones, especially near the commissures. The FEA confirmed areas of high stresses in the failure zones and quantified the influence of stent flexibility on the load dynamics. In subsequent versions thread damage and breaks were avoided by adapting the weave pattern and the way the weave is attached to the stent. After design optimization, current lab samples withstand more than 200 million load cycles (further testing in progress). The latest R&D results are presented.

Conclusion

Current results show the potential of a heart valve composed of woven leaflet scaffolds. It is planned to provide a durability of 400 – 600 million load cycles by further adaption of the weave structure. In addition to durability, hemocompatibility, cell colonization, and calcification testing are required to confirm suitability as an in situ heart valve replacement.

Fabrication of complex in vitro vascular models made of polyvinyl alcohol hydrogel

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Introduction

Polyvinyl alcohol hydrogel (PVA-H) vascular models have emerged as valuable tools in medical training and the development of vascular implants due to their unique features such as low surface friction, tunable mechanical properties, and transparency, offering advantages over in vivo studies. However, creating complex anatomical models, such as tortuous vessels and large-sac aneurysms, requires sacrificial materials which are compatible with PVA-H and can dissolve without changing the stability of PVA-H to form the vessel lumen.

Methods

This study explors various sacrificial materials, including carbohydrate glass and different wax mixtures, for fabricating vascular lumens. Preliminary characterizations assess stability of sacrificial materials in contact with PVA-H during its crosslinking and their solubility in suitable solvents. Moreover, the physical and mechanical properties of PVA-H, including elastic modulus and compliance, after the dissolution of sacrificial lumen were determined. Following optimization of physical and mechanical properties of the selected sacrificial material, a negative mold was 3D printed for fabrication of vessel lumen made of natural and synthetic wax mixture and followed by PVA-H casting to produce big-sac peripheral and intracranial aneurysms.

Results

Fabrication of complex aneurysm lumens using carbohydrate glass and different wax mixtures was achievable. However, carbohydrate glass exhibited premature dissolution upon contact with PVA-H. Different wax types showed varying melting temperatures, ranging between 53°C and 60°C, with melting times of up to 30 minutes. Dissolution times for the wax lumens from anatomical big-sac and standardized aneurysms were less than 30 minutes, differing among wax types. The compliance of PVA-H aneurysms closely resembled that of natural vessels, falling within the range of 0.4% to 0.5 % per mmHg. The fabricated aneurysm models were used to investigate the fluid dynamics and implant mechanics in a mock circulatory loop.

Conclusion

This study demonstrates the feasibility of fabricating complex vascular models using PVA-H and sacrificial materials. Compared to carbohydrate glass, mixture of natural and synthetic wax emerged as the optimal sacrificial material due to its stability and dissolution properties. These findings offer promising results for fabrication of accurate complex anatomical vascular models based of hydrogel with a potential of advancing medical training and testing of vascular implants.

Innovative Therapies with New Technologies – Self Expandable 3D-Patch Electrode as Bioelectronic Implant

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Introduction

Technological advances in micro- and nanotechnology have led to the development of new implantable medical devices. Active implantable medical devices are increasingly important in treating and curing many diseases that would otherwise be incurable, such as chronic heart failure. Here, we report the results of a BMBF research project aimed at developing core components for a minimally invasive (MIV) implantable patch electrode system. This effort has resulted in a self-expandable, highly flexible 3D electrode platform with micro technical and functional components made from thin TPU material, utilizing microsystem technology (MST) processes.

Methods

A micro-current MIV patch (5 cm^2) platform with a single Pt electrode on a polymer carrier was differentiated into individual system-level components. The foldable multi-layer patch system (<300 µm thickness) was manufactured via magnetron sputtering (PVD) and lamination. It was characterized through bench and animal testing within application scenarios. The patch electrode was scientifically examined for functionality, robustness, reliability, safety, reproducibility, and design complexity through tensile/mechanical, adhesion, visual, and electrical evaluations.

Results

MST platforms demonstrate reliable capabilities for flexible micro designs of bioelectronic long-term implants. The project's endpoint—a functional demonstrator for a micro-current MIV implant—will be presented and discussed. Data from bench and animal tests, including mechanical, electrical, physico-chemical, and functional evaluations shows technical window and feasibility of this multi-layer platform.

Conclusion

The researched design concept met the micro-current requirements in terms of electrode area, biocompatibility, corrosion resistance, handleability, flexibility, and robustness for a MIV chronic heart failure patch electrode. Advanced manufacturing processes from MST, combined with sputter deposition, can be used for future bioelectronic devices and implants. To fully realize the therapeutic and engineering potentials of MST technologies, dedicated design concepts are essential. Multilayer thin film bioelectronic platforms can be employed in various modern bioelectronic therapies, such as ablation, EP mapping, neuro-technologies, and electroporation.

Towards the development of the biohybrid lung: Analysis of the endothelial cells residing on gas exchange membranes under clinically relevant workload conditions

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Introduction

The development of an implantable biohybrid lung (BHL) is intended to provide an alternative to lung transplantation, which is currently the only treatment option for end-stage lung disease patients. The operating principle is based on the gas exchange hollow fiber membrane (HFM) technology used in clinically applied extracorporeal membrane oxygenation (ECMO), but to allow long-term use, the poly-4-methyl-1-pentene(PMP) HFM and all blood-contacting surfaces of the BHL are covered with an endothelial cells(EC) monolayer that prevents contact-activated thrombus formation and device occlusion. Therefore, ECs must endure the oxygen gradient between the oxygen-rich gas inside the HFMs and the hypercapnic/hypoxic patient blood. Thus, we investigated the influence of this clinically relevant oxygen tension on EC viability and function, under static and flow conditions.

Methods

PMP membranes (film and HFM) were coated with fibronectin and seeded with ECs. Upon reaching confluence, ECs were pre-cultivated under blood gas levels existing during respiratory insufficiency (50 mmHg pO_2, 80 mmHg pCO_2) for 24h followed by exposure to hyperoxia (>95% pO_2) for 24h. Using a customized miniature oxygenator, endothelialized HFMs were additionally challenged with 15 ml/min medium flow. Remaining ECs were stained with calcein vital dye and immunostaining agents for Collagen-IV and VE-Cadherin detection via confocal microscopy. Expression level change of oxidative stress (HMOX1, GCLM)- or inflammation (ELAM, VCAM, ICAM) related genes were measured via qRT-PCR. Apoptosis (AnnexinV/PJ) and reactive oxygen species(ROS) accumulation (CellRox) were investigated using flow cytometry.

Results

Confocal microscopy imaging confirmed confluent and viable EC-monolayers with intercellular junctions and *de novo* synthesized Collagen-IV under pre-cultivation or hyperoxia. Also, no change in prothrombotic/proinflammatory gene regulation was detected. Under dynamic and hyperoxic conditions, oxidative- and flow stress-associated genes were appropriately upregulated to keep apoptosis and ROS levels at bay.

Conclusion

The results of this study underline the feasibility of biohybrid lung application under clinical conditions.

Track:

Imaging Technologies and Analysis

Optimization of beamforming with a spiral 2D array

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Introduction

Volumetric ultrasound imaging requires either mechanical motion of 1D arrays or 2D matrix arrays. With 2D arrays, respecting the $\lambda/2$ criterion easily leads to thousands of elements per transducer, with the corresponding challenges with respect to transducer manufacturing, cabling and electronics. In clinical systems, channel reduction schemes such as multiplexing or the use of sub-beamformer ASICs are mostly implemented to find viable solutions for volumetric ultrasound imaging. The use of sparse arrays, where the element distribution deviates from a regular cartesian grid, is another approach to perform 3D ultrasound imaging. In our work, we investigated the potential of a 2D spiral array for volumetric imaging and focused on beamforming approaches adapted to this particular geometry.

Methods

Our spiral array consisting of 256 circular elements with a diameter of 1.6 mm and a centre frequency of 3.5 MHz in a sunflower spiral pattern was built in-house. A defocusing micro-lens is applied onto each element to achieve a larger field of view. Preliminary studies had shown that no ideal plane wave is generated as a result of the special geometry. Rather, significant trailing waves lead to artefacts in the reconstructed images. For identification of an ideal beamforming scheme, we implemented a simulation model and acquired data from a wire phantom. Channel data were reconstructed with diverging wave (compounding), plane wave (compounding) and focus transmit. Different metrics (FWHM in x and z, SLL) were used for the assessment of the different approaches.

Results

With all proposed reconstruction schemes, point reflectors could be reconstructed in depths between 5 and 13 cm. The lateral relsolution was depth dependent between 0.9 and 2 mm, with the most narrow PSF for the focus transmit followed by diverging wave compounding. Focus transmit showed the best contrast and the lowest level of artefacts with a SLL between 11 and 25 dB. On the other hand, focus transmit was based on the largest number of transmit events, leading to the lowest image frame rate.

Conclusion

Ultrasound imaging with our 2D spiral array was demonstrated and different approaches were quantiatively compared. For the given array geometry, focus transmit is the most promising approach since it allows reducing artefacts resulting from trailing waves. Future work will aim at a GPU-implementation of the algorithms for allowing real-time imaging and an in-vivo validation.

Comparison of a new fluorescence lifetime imaging ophthalmoscope to the gold standard

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Introduction

Fluorescence lifetime imaging ophthalmoscopy (FLIO) allows in vivo measurement of autofluorescence intensity decays of endogenous fluorophores. So far, only devices from Heidelberg Engineering (gold standard) have been used in FLIO research. The aim of this study was to compare the new FLIO system (based on RETImap, Roland Consult) with the gold standard using cuvette measurements.

Methods

We performed FLIO measurements using four fluorescent dyes filled in cuvettes: A (25µM eosin Y solution mixed with 5M potassium iodide solution), B (20µM erythrosine B with water), C (15µM eosin Y with 0.5M potassium iodide), and D (3.3µM eosin Y with water). For the two devices and all measurements, the laser power was 101µW. With the liquid column in focus, alternating between the devices, 20 measurements (approx. 1–3min each) were performed for each dye. Monoexponential fluorescence lifetime approximation was performed using the FLIMX software (www.flimx.de). A rectangular ROI (1000px) was defined for each. The mean fluorescence lifetimes of the ROIs were compared for the four dyes in the two spectral channels, short (498–560nm, SSC) and long (560–720nm, LSC). Statistical analysis was performed using Shapiro-Wilk, Mann-Whitney U, F, and t-tests. Bonferroni correction was used to correct for multiple comparisons.

Results

We obtained for the gold standard (mean fluorescence lifetime ± standard deviation) in the SSC: A|13.1±0.7ps, B|75.4±0.9ps, C|393.4±2.3ps, and D|1282.1±7.0ps. In the LSC: A|42.3±1.0ps, B|86.5±0.9ps, C|397.1±2.5ps, and D|1258.0±7.3ps. For the new device in the SSC: A|14.4±1.1ps, B|75.5±1.0ps, C|381.5±2.3ps, and D|1313.5±7.5ps. In LSC we found A|18.3±1.0ps, B|74.1±1.1ps, C|368.5±2.6ps, and D|1237.8±10.2ps. Mann-Whitney and t-tests revealed statistically significant differences in mean lifetimes between the two FLIO devices in SSC for dye D and in LSC for all fluorescent dyes. There were no statistically significant differences in mean lifetimes in SSC for dyes A, B, and C.

Conclusion

Results show that the devices differ significantly in the LSC and slightly in the SSC. Obtaining compatible results in less than half of the cases tested does not allow the conclusion that the results provided by the new device are compatible with those obtained from the gold standard. It is necessary to perform such a comparison on a larger number of measurements.

Wearable ultrasound device as biofeedback system for physiotherapy

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Introduction

Chronic back pain is a major health project in western countries leading to significant societal costs. Physiotherapy, in particular segmental stabilization exercise (SSE) is a typical therapy to enhance core stability. Unfortunately, such an exercise requires the selective contraction of deep abdominal and back muscles, which is challenging. Biofeedback systems have shown that they can support in performing physiotherapy training correctly and accordingly lead to faster and better therapy results. However, no such tools dedicated for optimizing SSE are available up to now. We therefore aimed at using ultrasound as biofeedback where an image of deep muscles allows assessing if exercises are executed correctly. We developed a customized portable ultrasound system and a wearable ultrasound transducer allowing monitoring of SSE.

Methods

The ultrasound biofeedback system consist of a portable 32 channel ultrasound electronics and a 256 element linear array transducer with a center frequency of 5 MHz and a pitch of 200 µm. The transducer has 128 TX (addressed in groups of four) and 128 RX elements and includes four 1:4 multiplexers used in receive mode. The electronics allow data transfer by USB or Wi-Fi to a tablet, where they can be processed in order to provide the feedback on the correct execution of SSE. For evaluation of image metrics, a multipurpose ultrasound phantom (040GSE, CIRS) was used. In-vivo evaluation was made by placing the transducer on the back to the side of the spine or on the lower abdomen using a special holder, allowing continuous data acquisition during SSE. Data were acquired on 10 probands (6m/4w, age 22-63 year).

Results

The system was characterized on phantoms and in first proband tests. Up to ~15 and > 500 frames/s could be obtained in Wi-Fi data transfer (1.7 Gbit/s) and USB mode respectively. Phantom data were analyzed by (automated) assessment of standard metrics (FWHM, SNR) after beamforming. A lateral resolution of 0.87 mm (at a depth of 22.5 mm) was obtained using a PWC (plane wave compounding) scheme adapted to the MUX-based array. In-vivo, an image depth of 70 mm was obtained with sufficient contrast to clearly identify deep abdominal muscles (DAM). Real-time data were acquired during typical SSE, where a change of the DAM thickness could be observed.

Conclusion

An ultrasound biofeedback allowing monitoring of DAM during SSE was developed and successfully validated on phantoms and in-vivo. The portable electronics and the transducer equipped with a dedicated holder allow data acquisition and real time processing during exercise. Ongoing work aims at AI-based segmentation and feature extraction with respect to the DAM in order to provide a simplified user feedback beyond B-mode images.

Track:

Additive Manufacturing and Bioprinting

On-chip isothermal detection of *Clostridioides difficile* toxin genes in a 3D-printed micro reaction chamber for POCT applications

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Introduction

Point-of-care testing (POCT) is becoming increasingly important in clinical settings to directly diagnose pathogens. *Clostridioides difficile (C. difficile)* is the most common cause of diarrhoea and an important nosocomial problem in hospital hygiene. The emergence of hypervirulent strains and the ability to form endospores makes rapid detection essential, as an early targeted antibiotic therapy prevent severe cases and spread.

Methods

In an additive process with a biocompatible photopolymer resin using digital light processing a monolithic micro reaction chamber was developed. The overall dimensions of the device are 38 mm × 10 mm × 1.7 mm with a reaction chamber volume of about 12 µL. The system was tested for biocompatibility, microfluidic effects and other optical factors (e.g. transparency, autofluorescence). Isothermal real-time recombinase polymerase amplification (RPA) assays, for the detection of *C. difficile* toxin genes *tcdA* and *tcdB,* were implemented in the 3D-printed micro reaction chamber and tested for sensitivity and specificity.

Results

The 3D-printed chamber showed no RPA inhibition and was analysed and optimised for fluorescence readout and microfluidic mixing structures. A duplex assay has been developed that allows simultaneous toxin gene detection at 39 °C in the 3D-printed micro reaction chamber. Qualitative results are possible within 15 minutes. The RPA systems are highly sensitive (LODs ≤ 688 DNA target copies) and specific.

Conclusion

The development of rapid and robust test systems for pathogen detection is of great importance to improve medical decisions. The established duplex RPA assay showed excellent amplification performance in the 3D-printed chamber even in a volume reduced to a quarter of the initial reaction volume.
For potential point-of-care applications, combining rapid prototyping with rapid pathogen detection has the potential to reduce the development and production costs of POC systems. This study has shown that the microfluidic reaction chamber can be expanded into a lab-on-a-chip system.

Fiber-based femtosecond 3D printing of polymer photoresists

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Introduction

Ultrashort laser pulses are often used in medical applications, for instance for soft-tissue surgeries or biomedical imaging. However, the progress on using such laser pulses for tissue structuring is rather marginal so far. Therefore, we aim to realize an endoscopic fiber-based femtosecond 3D printer to minimally invasively surgically repair organ damage on a micrometer scale. For this, high-power femtosecond laser pulses are required, in order to 3D print desired geometries with conventional polymer photoresists using two-photon-lithography. We aim at printing cell scaffolds inside the body by endoscopic 3D printing directly, which should allow for example bone tissue or cartilage tissue inside the body directly.

Methods

We utilize a grating compressor consisting of ruled reflective diffraction gratings to pre-chirp laser pulses by introducing anomalous dispersion, compensating the normal dispersion in optical fibers broadening these femtosecond laser pulses. We analyze our measurements of the output pulse autocorrelation and spectrum of single mode fibers as well as multicore fibers as a function of pulse duration, spectrum, compression, and nonlinear effects.

Results

By optimizing the grating position, peak powers are achieved that enable two-photon polymerization to 3D print arbitrary structures using photosensitive resins. We report on a multitude of arbitrary 3D printed microstructures up to several tens of microns based on conventional photoresists (IP-S and IP-Dip, Nanoscribe GmbH) using an optical single-mode fiber and a 3D printed immersion doublet on the fiber tip.

Conclusion

We report on dose tests as well as on extensive investigations on optimization of printing speed, laser power, pulse compression ratio and pulse duration, as well as slicing and hatching variation. We demonstrate solid cubes as well as connected lines, leading to 3D woodpile structures that represent scaffolds which ultimatively could be colonized by living cells. This direct printing of cell scaffolds inside the body by endoscopic 3D printing should allow in the future for example printing of bone tissue or cartilage tissue inside the body.

Replicating native muscle biomechanics in a synthetic muscle fiber

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Introduction

Synthetic muscles that recapitulate native skeletal muscle contraction and force generation are highly sought after for various applications such as actuators or for regenerative therapeutic interventions, as for instances muscle replacement.

Methods

We utilize two-photon stereolithography to 3D print synthetic muscles from bovine serum albumin to form a contractile hydrogel structure with tailored mechanical properties. Using a custom microscale tensile strength device, we quantify force-length relations and elastic properties in these 3D printed fibers.

Results

We observe that the pH-dependent contraction of these synthetic fibers results in active forces comparable to those occurring in native muscle fibers. Manipulating the length of the synthetic fiber affects force production, following a parabolic force-length relationship similar to native muscle fibers, characterized by an ascending limb, a plateau, and a descending limb as the length increases.

Conclusion

Hence, our two-photon crosslinked synthetic fiber can replicate the contractile dynamics of skeletal muscle tissue. This opens new avenues to further explore contractile synthetic materials, as well as their future refinement by integrating myocytes for a more realistic synthetic muscle fiber.

Fabrication of flexible, vascular models for surgical training by a new hollow lost core casting technique

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Introduction

Synthetic models of vessels may be used for numerous applications, including the training of surgical interventions. Conventional manufacturing with polymers (e.g. molding) allows to use various materials to mimick the mechanical properties of a blood-vessel. However, this restricts the possible vessel geometries. Additive manufacturing allows for greater geometric freedom and the fabrication of complex structures, but the material choice is limited. In particular, materials that are both flexible and transparent are not very common. A combination of different fabrication methods allows to combine the individual advantages and to overcome the drawbacks.

Methods

A hollow sacrificial core of water-soluble polyvinyl alcohol (PVA) is printed using an Ultimaker 3 3D-printer (Ultimaker, Utrecht, Netherlands). The outer form is printed of a stiff material (for example, Clear to make the form transparent and better control the molding process) using a Form 3B 3D-printer (Formlabs, Somerville, USA). The resulting mold is then filled with a two-component transparent silicone, or alternatively the silicone can be dyed to the specific need of the application. After the polymerisation, the core can be dissolved in water. Normally, this process is time-consuming due to a small contact surface between the water and the PVA, which is a disadvantage of the method especially for complex vessels. However, our method using a hollow core allows a dissolution of the core within 8 hours (depending on the thickness of the hollow core), which significantly improves the hybrid manufacturing of complex vessels.

Results

Arterial models, which are especially relevant for neurosurgical interventions, were printed using this method, including an aortic arch, subclavian arteries and carotid arteries. The transparent silicone we used for the production allows for the visual observation of the position of a catheter inside the vessel, and thus provides an excellent basis for highly accurate and cost-efficient surgical training. As the vessels are waterproof, perfusion can be simulated with a blood-mimicking fluid, while in addition, the haptic feedback is much closer to human vessels than in most other training phantoms, which greatly increases the realism of the training.

Conclusion

The novel method allows for the efficient production of blood vessels, which is not necessarily limited to arteries. Further development of the method can address the modelling of other pathologies as well, which would widen the range of training scenarios to other surgical procedures.

A three-layer head phantom for verification of the source localization models and algorithms

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Introduction

Accuracy assessment of electromagnetic source imaging techniques requires physical or simulated head models. A physical head phantom can provide a ground truth verification of the source localization. However, it remains challenging to construct a head phantom with realistic geometric shapes and structures from mechanically stable synthetic materials exhibiting electrical conductivity values similar to the standard values of human head tissues found in the literature. Here, we present the construction of a novel realistically shaped physical three-layer head phantom with embedded electric current dipoles.

Methods

The head phantom is based on the ICBM-NY model, which represents the average head anatomy of adult subjects. The scalp, the skull, and the intracranial volume of this model form the three compartments of the phantom. Casting molds for the three compartments were printed with production-oriented geometric adaptations for additive manufacturing. Electric current dipoles are designed to fit through the neck, be positioned inside the intracranial volume, and are activated e.g. with sinusoidal waveforms from constant current sources.

Results

The scalp layer is made of 2 wt% agar hydrogel with a measured conductivity value of 0.314 S/m. As for the skull layer, it is cast with gypsum and shows a measured conductivity value of 0.0017 S/m. To ensure mechanical stability, thin areas of the temporal bone of the skull are thickened outwards to reach 5 mm thickness. The intracranial volume is filled with 0.17% sodium chloride solution with a measured conductivity of 0.332 S/m. The head phantom is anatomically realistic and includes simplified features such as neck, ears, nose, eyes, and facial bones.

Conclusion

Our results show the applicability of the selected materials and construction techniques for a three-layer head phantom. These materials can mimic human head tissues with the required conductivity values. Verification studies of the functional suitability of the phantom is planned.

Towards endoscopic biofabrication on the micro-scale

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Introduction

Conventional surgery typically inflicts considerable tissue damage. Endoscopy based keyhole interventions helped to reduce side effects, however, surgical tools continue to operate in primarily subtractive fashion and our ability to directly regenerate tissue *in situ* remains limited. To overcome this, we propose a highly miniaturized bio-3D-printer at the tip of an endoscope to additively fabricate tissue scaffolds on site.

Methods

To facilitate two-photon 3D printing of organotypic bio-inks with sub-cellular resolution at the tip of an optical fibre, we use a 780 nm femtosecond laser combined with an anomalous dispersive pulse compression to compensate propagation through a 2.5 m long singlemode optical fibre. A custom high-NA immersion objective lens at the tip of the fibre tightly focuses the delivered femtosecond laser pulses to pattern commercial photoresist as well as custom protein based bio-ink recipes. Printed scaffolds are analysed using electron microscopy, in biocompatibility assays and for their micro-mechanical profiles.

Results

At the tip of the fibre, we reach up to 40-fold pulse length compression leading to pulse lengths down to 110 fs or peak powers up to 1900 W. We successfully seal our 3D-printed endoscopic writing objective against photoresist intrusion and demonstrate diffraction limited focal spots at an NA of 0.625. In our experimental setup we show endoscopic 3D printing of microstructures with lateral dimensions of ~ 1 µm and axial dimensions of ~ 5 µm with commercial plastic resin as well as custom hydrogel photoresists which demonstrates a plausible path towards endoscopic 3D printing of tissue scaffolds.

Conclusion

We propose endoscopic biofabrication as a novel approach to minimal invasive micro-surgery by building a two-photon bio-3D-printer at the tip of an endoscope. In a first proof of concept, femtosecond 3D printing through a singlemode fibre is successfully demonstrated by combination of pulse compression, a 3D-printed high NA immersion objective, and bio-ink engineering. These results could be the seed for an edoscopic biofabrication platform addressing a broad interdisciplinary spectrum of topics from physics, optical engineering, bio-/chemical engineering, microfluidics, and medical engineering.

Track:

Biosignal Analysis and Data Aggregation: Signal analysis and informative value

Recognition of sitting posture patterns from a pressure sensor mat analysis with machine learning algorithms: need for individual calibration

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Introduction

Extended sitting can lead to health issues. To alleviate tension, it's recommended to change positions every 30 minutes. In this study, we monitor the pressure pattern on a pressure sensor mat (PSM) and classify sitting postures comparing 3 machine learning (ML) algorithms: kNN, SVM and Random Forest (RF) with feature extraction vs raw data.

Methods

Two datasets were collected with the PSM: 1) ten participants (22 - 60 years old, 60 - 107 kg, 175 - 185 cm, 7 males, 3 female) taking five sitting positions with one image per measurement; 2) five participants (23 - 24 years old, 61 – 95 kg, 173 - 184 cm, 5 males) assuming eight postures on 7-second videos with 10 images per second. Dataset 1 underwent 10-fold cross-validation with a) random train-test-split; b) training on data from nine participants and testing on the remaining participant. For Dataset 2 images were divided into 4 quadrants, and white pixel distribution and distances from quadrant centres of mass (COM) and absolute COM were extracted, employing also a random 10-fold cross-validation strategy. Finally, the model was trained on Dataset 2 and tested on Dataset 1, with postures reduced to the identical five obtained in both studies.

Results

Accuracies in Dataset 1 decreased from maximum 93.3 % (SVM) for method a) to 72.0 % (SVM) for method b). In Dataset 2 all classifiers delivered 99.9 % accuracy for raw data and RF the best accuracy (99.6 %) for the extracted data. When training the model with the data from Dataset 2 and testing with Dataset 1, best accuracies decreased to 52.3 % (kNN) for raw data and 56.0 % (RF) for the extracted data.

Conclusion

Different evaluation scenarios yield varying accuracies for posture classification using ML algorithms. Results decreased for unknown participants in both datasets. Indeed, pressure distribution images on the PSM are influenced by individual characteristics such as gender, age, body structure, and habits. Moreover, the solution approach presented in this study is specific to our case and cannot be easily adapted to other problems. Thus, a calibration process for new users is essential for accurate posture estimation, requiring further research to determine the minimum calibration data needed for each individual.

Real-time PPG signal quality assessment: a fair comparison of deep learning-based algorithms on public data

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Introduction

Wearable devices integrating photoplethysmography (PPG) sensors enable noninvasive monitoring of vital parameters such as heart rate and blood oxygen saturation. However, the reliability of the measurements is compromised by motion artifacts. Deep learning approaches, particularly Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs), have shown potential in detecting corrupted segments and recognizing elusive patterns but are often evaluated on different non-public datasets, leading to incomparable results. This study assesses the fair comparative performance of these algorithms on the same public dataset for real-time signal quality classification.

Methods

We employed the PPG-DaLiA dataset, comprising 36 hours of data from 15 subjects performing various activities. Five algorithms were adapted from the literature and implemented for real-time operation: two one-dimensional CNNs (custom by Zargari et al. and InceptionNet) and two two-dimensional CNNs (custom by Roh and Shin, and VGG-19), as well as a Long Short-Term Memory (LSTM) RNN. The models were trained using a binary cross entropy loss function with the Adam optimizer, oversampling for class-balancing, an 80/20 dataset split for training and testing, and Optuna for hyperparameter tuning targeting accuracy.

Results

The accuracy and sensitivity values obtained for all algorithms on the public dataset were significantly lower than those presented by their authors for their own data. Besides, the biggest models (VGG-19 and InceptionNet) failed to converge. Nevertheless, the RNN LSTM model demonstrated the highest accuracy at 89.28%, followed by the 2D CNN at 87.5%. The RNN also showed the highest sensitivity (92.5%) and the fastest classification time of 0.0039 seconds, making it feasible for real-time applications.

Conclusion

In conclusion, the performance of deep learning algorithms for motion artifact detection in PPG varies across datasets. Still, the RNN LSTM showed the highest accuracy and fastest classification on the PPG-DaLiA dataset, making it a promising option for real-time signal quality classification.

Investigation of oxygen enrichment in rescue helicopters due to mechanical ventilation

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Introduction

Recently, especially during the COVID-19 pandemic, the number of medical air transports with mechanical ventilation has continued to increase. During mechanical ventilation, some forms of therapy (e.g. high-flow) require an increased oxygen level (or flow rate). It is therefore possible that the oxygen level in the cabin will increase significantly. Higher oxygen levels are associated with an increased rate of combustion, lower ignition temperature and can lead to spontaneous ignition. This risk must be examined to ensure flight and operational safety, as no standardized threshold values exist to date. In this study, the impact of varying oxygen flow rates in combination with air conditioning settings on the oxygen concentration in the cabin of two rescue helicopters were investigated. The research hypothesis is that an increasing flow rate leads to an increase in oxygen concentration and that certain air conditioning settings and flight phases favor oxygen enrichment.

Methods

The test setup comprised two rescue helicopters (Airbus EC135 and H145) with a ventilation circuit integrated into the cabin (EC135 vs. H145; cabin volume: 4.9 m³ vs. 6.03 m³). The circuit consisted of a gas supply, a mechanical ventilator (Hamilton T1) with respiratory mask, four oxygen sensors (PreSens OXYBase WR Blue) and a patient mock-up. The oxygen sensors (measuring interval: 1 s; resolution: ± (0.02 to 0.10) % oxygen) were placed in four locations: *cockpit*, *emergency physician*, *patient interface* (ventilator outlet), and the *rear* end of the cabin. For all measurements, the Hamilton T1 was set to PCV+ mode with a constant oxygen concentration of 100 %. The oxygen flow rates (*5 l/min*, *10 l/min*, *15 l/min*) and the four air conditioning settings (*summer*, *winter*, *recirculated air*, *off*) were systematically varied during the main flight phases (*ground run*, *forward flight*). Based on previous research, the measuring time per setting was set at 2 min. A total of n=24 measurement series per helicopter were recorded as part of these setting variations. In addition, a complete single setting (15 l/min, summer) verification flight was carried out (total measuring time: 21.5 min). The mean oxygen saturation ± standard deviation was calculated to assess the main points of interest.

Results

An increase in oxygen flow rate led to a slight increase in the concentration values in both helicopters (EC135 vs. H145; 5 l/min: (20.81±0.58) % vs. (20.53±0.62) %, 10 l/min: (20.86±0.60) % vs. (20.71±0.80) %, 15 l/min: (20.94±0.64) % vs. (20.97±1.31) %). The worst setting for air conditioning was the *off* mode (EC135 vs. H145: (21.36±0.77) % vs. (21.00±1.17) %). In addition, *ground run* was the flight phase with the highest oxygen concentration (EC135 vs. H145: 21.24±0.47% vs. 20.95±0.76%), which was also confirmed by the verification flight. Regarding sensor position, the highest mean values were observed at the *patient interface* (EC135 vs. H145; (21.08±0.79) % vs. (21.64±1.36) %).

Conclusion

The hypothesis that an increasing flow rate leads to an increase in oxygen concentration can be confirmed. The data show that higher oxygen flow rates led to slightly increased oxygen concentrations in both helicopters. However, this increase can still be considered safe. Differences between the helicopter types can be attributed to the cabin volume. Furthermore, the hypothesis that certain air conditioning settings and flight phases favor oxygen enrichment is confirmed. As expected, the oxygen concentration was highest at the sensor on the patient where the ventilator outlet was located. Conclusively, these results suggest that further research into the potential risk of oxygen enrichment in medical air transport is required to ensure patient and operational safety. Future research will focus on examining the feasibility of high-flow therapy.

Generating Training Data for Bioimpedance and Elastography Sensor Fusion in Bladder Tissue Differentiation

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Introduction

To improve the decision-making process during bladder cancer surgery, additional sensor measurements give valueable information about the tissue's mechanical, optical and electrical properties. Through fusing the different sensor domains, a meaningful assessment of the pathological state of the examined tissue can be made. Promising unimodal results have been obtained in the electrical and mechanical domains, which are intrinsically linked by the tissue's cellular structure. Given the limited availability of human tissue sensor data, a transfer learning strategy is employed. This includes the generation of measurement data crucial for pre-training an neural network (NN) architecture for sensor fusion.

Methods

As the aim for bladder surgery is to predict the percentage of tumor cells underneath the sensors, a regression network architecture is developed. Hence, a suitable pre-training dataset needs a continuous number as label. In order to achieve the domain fusion, the first step is to fuse the two most promising sensors: an electrical impedance sensor operating in the kHz frequency range and Water-Flow Elastography, which quantifies tissue stiffness through applying a predefined fluid pressure. Therefore, a test setup is developed to apply different pulling forces to porcine bladder tissue, enabling real sensor measurements under varying strain conditions.

Results

The aquired data demonstrate a direct correlation between pulling force, tissue stiffness, and bioimpedance. Elevated pulling force results in increased stiffness and bioimpedance and mimics the effect of higher tumor cell percentage on sensor data, serving as a surrogate label for tumor cell percentage estimation. This dataset enables the pre-training of the NN architecture, which is essential due to the high dimensionality of the sensor data.

Conclusion

We have established a method for generating porcine tissue measurements under varying strains. Utilizing this data, we pre-trained a regression NN, which is subsequently fine-tuned to estimate the percentage of cancerous tissue, thereby addressing the data limitation challenge.

Implementation of running denoising autoencoder (RunDAE) on Arduino for real-time denoising of ECG

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Introduction

The electrocardiogram (ECG) measures the electrical activity of the heart, often with interference from noise such as baseline wandering or movement artifacts. Therefore, it is important to denoise ECG signals for better clinical insights. Current DAE models have shown optimistic denoising performance. However, due to long input segments and several convolutional layers their implementation is challenging on limited hardware. This work describes the implementation of single-hidden-layer running DAE model for real-time denoising.

Methods

The proposed RunDAE uses L_1 weight regularization for the hidden layer, which is similar in size to the input layer, and a linear neuron as the output layer. The ReLU activation function had been selected for the hidden layer. The regularization parameter λ was heuristically set to 10^{-6}. Einthoven I recordings of 3 minutes duration each were recorded from eleven subjects using an Olimex ECG Shield in connection with an Ardunio GIGA R1 with a sampling rate of 250 Hz and an ADC resolution of 12 bits. Two minutes of each recording were used for training and the last minute for testing. All the signals were filtered using discrete wavelet transform, and then corrupted with different noises (level: 0.3 stdev[signal]). Finally, signals were segmented by a sliding-window into overlapped segments, each with length N=200 samples (approximately 0.8 s). The trained model was implemented in C++ on Arduino GIGA R1. Denoising performance was evaluated using root mean square error (RMSE) and signal-to-noise ratio improvement (SNR_{imp}).

Results

The program used 450 KB (23% of available flash), variables and parameters used 51 KB (10% of available RAM). Calculating one output sample from a 200 sample long input took 1.7 ms, which is less than the available 4 ms sample period. The achieved denoising performance is: RMSE=7.0×10^{-3} V, SNR_{imp}=4.6 dB for Gaussian white noise, and for mixed physical noise we got RMSE=6.0×10^{-3} V and SNR_{imp}=5.3 dB.

Conclusion

The results show that the proposed model requires only limited hardware while providing adequate denoising performance. Potential applications are the denoising of ecg signals with mobile measuring devices and the detection of artifacts on the basis of the deviation between RunDAE's input and output signal.

Concept for an EEG-based Gaming-Controller with Embedded Machine Learning Support

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Introduction

Modern brain-computer interfaces (BCI) allow precise and reproducible user-environment interactions using electroencephalography (EEG) recordings. In gaming applications, Perri Karyal uses the EMOTIV EPOC X EEG-headset (14-channel, wireless) to control game avatars. The online data stream processing takes place on computer. Our research is concerned with achieving a high level of user comfort with real-time processing on a mobile solution. This requires local signal processing and machine learning on an embedded platform.

Methods

Our objective is to achieve an end-to-end signal processing for controlling games with EEG recordings using comfortable dry Flower electrodes. Data acquisition is conducted using MentaLab Explore+ (12 channels, 1 kHz, wireless). The online data processing includes digital filtering and action recognition using AI accelerators on a Field Programmable Gate Array (FPGA) within the ElasticAI ecosystem. Therefore, AI models are trained using PyTorch, and transferred to the FPGA. To improve the robustness of our algorithm in gaming scenarios, we provide an extended dataset by combining EEG recordings and 9-axis acceleration data for artifact detection.

Results

We successfully acquired our first datasets using EEG recordings with dry Flower electrodes and MentaLab device. This dataset includes eight recording sessions for each of the six candidates to imagine the movement of the left or right hand. We assessed data quality by employing EEG-Net to classify the two classes, which achieves an accuracy of 97%. It is worth noting that the impact of pre-processing (digital filtering, pruning channels, reducing sampling rate) has been explored and shown to maintain the same level of accuracy.

Conclusion

Our first approach of building an EEG-based gaming controller allows to generate first datasets and to perform online data processing and ML inference on a workstation. In future, the dataset is extended to enable motion detection for gaming scenarios like 'Pac-Man'. Moreover, the AI models used are trained and transferred to the local hardware for controlling more complex video games.

Modeling and localisation of electrical signal sources using an L1-regularised multi-monopole approach

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Introduction

Electrical source localisation is important in biomedical engineering. It is about determining positions and charges of electrical sources in a given space, e.g., a body region. Accurate localisation of these sources can be important for diagnosing and treating various medical conditions, such as cardiac arrhythmias and epilepsy.

Methods

Three electrical monopoles and 50 measuring points for electrical potentials were randomly set in a defined area. The potentials of these true monopoles at the measuring points were calculated once at the beginning, for checking estimation properties 5% Gaussian white noise (GWN) was added. The starting model consisted of five monopoles with random positions and charges. Position and charge of the assumed monopoles were calculated iteratively by using the Rprop method to solve the inverse problem. The sum of the squared differences of these potentials was used as loss function in combination with L1 regularisation of the charges only.

Results

In five experiments each for noisy and non-noisy data, different starting values and electrode positions were used, while the positions and charges of the true monopoles remained unchanged. We found that the correct number of monopoles required for modelling the measured electric potential was correctly determined for various monopole and electrode configurations. It should be noted that the results are strongly influenced by noise. The relative errors achieved with noise-free potential measurements were in the percentage range, while the values for potentials that were noisy with 5% GWN in relation to their absolute values were in the ten percent range. We found that the L1 regularization significantly reduces or eliminates the charge of redundant monopoles (pruning).

Conclusion

The results indicate that L1 regularization aids in solving the inverse problem, which involves determining the number and characteristics of monopoles necessary to represent the electric potential of an unknown configuration of electrical monopoles. Nevertheless, the precision of the estimation is significantly influenced by the quality of the measured potentials. This approach could be extended to efficiently and sparsely estimate the properties of different electrical signal sources.

Robot-based contactless assessment of emotions and vital-signs in nursings homes

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Introduction

Based on current demographic developments it is predicted that in the near future (in the year 2035 and beyond) more than 500,000 positions in the inpatient, outpatient and intensive care cannot be filled in Germany. Similar developments are known in other European countries.

In the past decades autonomous robots and mobile platforms to compensate the lack of manpower have been developed and established, specifically for use in safe scenarios as e.g. within assembly lines or production, but also for the autonomous transportation of materials. Simple versions of such systems can already be found in domestic environments, as e.g., in the form of vacuum or lawn-mowing robots, industrial cleaning robots or – in simpler forms –CNC milling machines, 3D printers or programmable kitchen machines.
Even though "care robots" have been the focus of various national and international R&D projects in recent years, there has not yet been an urgent need to integrate them more closely into care processes. Reasons for this have been (a) the lack of investment and business models due to the fact that nursing staff are still available at short notice, (b) a lack of infrastructure such as comprehensive WLAN coverage, flat floors or closed doors in care facilities, day clinics or home environment for zje self-localization and navigation of the robots, and (c) fixed processes and less flexible workflows in the affected (care) facilities (intensive, inpatient, outpatient), which make it difficult to integrate mobile systems.

Methods

In the past years (also driven by the Covid19 pandemic) many of these challenges have been tackled and the prerequisites for the integration of service and cleaning robots in retirement and nursing homes have been created. So-called "social robots" such as the Paro-Robbe (an interactive cuddly toy) or the Pepper robot (for communication and animation) were also able to establish themselves in retirement and nursing homes, hence relieving specialists and nursing staff as well as unavailable relatives. Also various systems currently under investigatin for other person-near activities, such as the mobilization or transport of nursing home residents or patients.

Results

The next logical aspects for mobile platforms and robots in the care environment are their improved social capabilities as e.g. the recognition of emotions (happy, sad, surprised, pain, neutral) as well as the recognition of people in order to to act better, more empathetically or even situationally with human counterparts. Better human-like interaction possibilities also increase the chances of greater acceptance of technical solutions and help to reduce any existing reservations against them. Also, new capabilities are needed for such robotic systems to enable them to contact-less assess essential vital parameters (e.g. temperature, pulse, respiration, blood oxygen saturation, blood pressure) of patients, residents, relatives, visitors as well as of the nursing staff. This data can either be used for diagnostic purposes, but also so identitfy the state of mind of the human counterpart, and hence allow the robots to react adequately.

Conclusion

These developments are facilitated by rapid progress in the field of artificial intelligence. This enables the realization of interaction patterns that are essential -- not only in the care sector -- but also too complex for previous robots. All of this opens up completely new possibilities and represents real progress for autonomous care robots.

Track:

Devices and Systems for Surgical Interventions

Toward Context-Awareness in the Operating Room based on a Service-oriented Device Connectivity Interface for Intraoperative Checklists

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Introduction

The operating room (OR) is a cognitively demanding environment due to the high information density from various sources. To optimally support the surgical team, devices in the OR should behave context-aware, providing the right assistance at the right time. Information should be displayed only during the appropriate surgical phase and medical devices adapt to the current context. The current context in the OR can either be detected automatically or manually. To ensure manufacturer-independent interoperability, the context information must be administered by a dedicated system and the current situation communicated via a standardized network interface.

Methods

The emerging IEEE 11073 Service-oriented Device Connectivity (SDC) standards facilitate interoperability between medical devices. An intraoperative checklist application, that guides the surgical team through interventions, was extended with an SDC interface. The current surgical phase and additional procedure-related information are provided as metrics, depending on the user input. SDC-capable devices, such as the *OR-Pad* for the situation-dependent provision of medical information, can subscribe to metric changes to behave context-aware. The standardized provision via the interface and context-aware behavior of the *OR-Pad* was evaluated in the research OR at Reutlingen University for eight simulated interventions.

Results

The intraoperative checklists communicate status changes, i.e. the current surgical phase, via the OR network. The *OR-Pad* adapts its visualization depending on the phase to visualize preoperative information, such as images or laboratory values. Thus, context-awareness was achieved. Thereby, all systems must adhere to use the same phase definitions and encodings to ensure the correct interpretation of the provided information.

Conclusion

The developed SDC interface for an intraoperative checklist facilitates interoperable context-aware behavior of devices in the OR network. Reliability of context changes is ensured through situation interpretation by a member of the surgical team. In the future, an automatic situation recognition system is to be integrated to gradually reduce manual checklist ticking.

Increasing the efficiency of cryoablation by active thawing

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Introduction

Cryoablations are employed to eradicate tumor tissue by subjecting the target tissue to extreme cold. While the ablation center reaches very low temperatures, cells in the peripheral area of the frozen tissue may survive the treatment and lead to tumor recurrence. We hypothesized that active thawing using microwaves enhances cell destruction through osmotic injuries, particularly in the peripheral area of the frozen tissue, thereby making the treatment more efficient. The objective of this study was to evaluate the effect of active thawing after cryoablation on cell destruction.

Methods

In this study, cryoablations were conducted on 20 ex-vivo porcine kidneys, followed by active thawing of the frozen tissue using a microwave ablation system operating at 40 W. An offset arrangement of the ablation probes of 15 mm with partial overlap of the active zones enabled a comparison between actively and passively thawed areas. The precise positioning of the applicators was guided and monitored using CT imaging. Temperature measurements were conducted using three fiber-optic sensors and heating was halted upon reaching 0 °C between the probes to prevent coagulation by the microwave applicator. For evaluation, the kidneys were immersed in a contrast medium solution and examined using MRI imaging. Finally, intensity values were determined using regions of interest (ROI) in actively and passively thawed areas as well as untreated tissue from T1 sequences (SE, FLASH, T1-Map). In addition, the extracellular volume (ECV) was calculated. Based on the signal-to-noise ratio (SNR), the three areas were compared. Statistical analysis was performed with a sample size of $n = 20$ and a significance level of $\alpha = 0.05$ using a sign test.

Results

In the T1 sequences and ECV values, the examined kidneys showed a significantly ($p = 9.54e{-}7$) increased SNR in the actively thawed areas compared to the passively thawed areas and the untreated tissue.

Conclusion

In comparison, MRI imaging shows an increased SNR in the actively thawed area, which indicates increased tissue destruction. The presented method could be a novel approach to improve the efficiency of cryoablation, especially for the critical peripheral area of frozen tissue.

Proof of concept of a novel tracking system with a monocular camera for image-guided surgery navigation

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Introduction

Although commercial tracking systems, such as optical and electromagnetic solutions, enhance surgical precision, they have notable drawbacks. High costs and large marker sizes in optical systems make them less ergonomic for interventions like biopsies. To address these issues, a novel tracking system using a monocular camera and a zoom lens was developed. This system tracks smaller markers, potentially can reduce costs, and allows closer proximity to the target.

Methods

The system uses a 5.1MP monochrome monocular camera and a zoom lens with electronic control of zoom, iris, and focus. It employs a plastic dodecahedron-shaped marker with 5mm edges and ArUco markers on each face. The OpenCV ArUco library detects these markers, and the lens's zoom and focus adjust dynamically to maintain a constant Field of View (FOV) based on the marker's depth. The system was tested under various lighting conditions and camera and lens settings.

Results

Accuracy was measured using an NDI Polaris optical tracker, achieving a translational accuracy of 3mm and 2° rotational accuracy for a horizontal FOV of 25cm in a depth workspace from 10cm to 90cm. The zoom adjustment time between minimum and maximum points is about 2 seconds. Precision is significantly affected by lighting conditions.

Conclusion

The monocular camera-based tracking system achieves millimeter-level accuracy with a small marker, showing potential for use in image-guided interventions due to its ergonomics, image compatibility and range. The optical hardware, tracking algorithm, and marker have been adapted and evaluated for clinical suitability. However, some areas still need to be improved. Current zoom setup time limits real-time tracking applications and requires labor-intensive calibration. Future research will explore alternative lens technologies like liquid lenses and different marker materials and lighting sources to ensure consistent illumination across the workspace. Likewise, it will be evaluated in different clinical cases.

Erythropoietin and Thrombopoietin levels in Patients After Coronary Artery Bypass Grafting

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Introduction: The haematopoietic growth factors erythropoietin (EPO) and thrombopoietin (TPO) are main regulators of erythro- and thrombopoiesis. Cell loss caused by operative procedures may alter serum levels of the hormones, resulting in well known phenomenons like reactive thrombocytosis.

Material and Methods: Blood samples from 12 patients (mean age 62 ± 8 years) were obtained before and on days 1, 5 and 10 after CABG. sEPO and sTPO levels were determined by commercially available ELISA-Kits (R&D Systems, Germany). In addition, platelet count (PC) and hemoglobin concentration (Hb) were determined.

Results: Prior to CABG, sEPO (14.6 ± 9.1 mU/ml), sTPO (172.3 ± 67.0 pg/ml), PC (248.0 ± 119.5/nl) and Hb (9.4 ± 1 mmol/l) were within a normal range. At day 1 after surgery, Hb and PC were significantly decreased to 6.9 ± 0.8 mmol/l and 143.8 ± 95.6/nl. In contrast, sEPO and sTPO were significantly elevated to 36.0 ± 25.6 mU/ml and 378.9 ± 112.6 pg/ml, respectively, in spite of hemodilution. In particular, sTPO elevation was followed by a significant increase in PC (357 ± 178.6/nl) at day 10 after surgery compared to preoperative values.

Conclusions: Appropriate to the decrease in hemoglobin concentration and platelet count, clear alterations of serum erythropoietin and thrombopoietin levels could postoperatively be observed. Whereas hemoglobin concentration returned nearly in a normal range at day 10 after surgery, the alterations of the hormones resulted in the phenomenon of reactive thrombocytosis.

Track:

Hygiene / Hospital Engineering

Parenteral medium compounds distinguished by microwave spectroscopy

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Introduction

In numerous medical and pharmaceutical applications, such as parental nutrition, very different compositions of mediums are used. Automated systems for mixing and packaging are used in hospitals and other health facilities. In addition to the correct dosage, a critical thing is to prevent mix-ups, for example, 1 M KCl or 1 M NaCl. Using microwave spectroscopy, all substances are identified and the process will be stopped if an incorrect substance is detected. Therefore, automated quality assurance is to be extended by an online medium analyzer.

Methods

After connecting different reservoirs within one mixing unit, the different substances run through one single tube set. This inheres the risk of incorrect connection. All components are passed through a tube where a microwave based substance analyzer is applied. This device is arranged laterally and records the reflection and transmission spectrum in the frequency range 1 GHz - 6 GHz. From the combination of the spectral components, conclusions are drawn about the respective substance and its concentration using machine learning.

Results

Substances such as amino acid mixtures, glucose, and electrolytes of different concentrations can be safely distinguished from one another. However, currently, it is difficult to distinguish between electrolytes of the same concentration, such as NaCl and KCl. Recently, the overall selectivity will be significantly improved by optimizing critical parameters of the antenna, such as frequency response and coupling factor.

Conclusion

In principle, the measurement method can differentiate between essential groups of substances. The reliable detection of Cl- and Na-ions remains critical at least in the frequency range above 1 GHz. If a suitable contrast based on the ionic mobility or the water structure around the ions is not possible, supplementary or alternative measurement methods are considered.

Track:

Education and Training

Modelling the heart's magnetic behaviour using simulated transponder coils

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Introduction

The cardiac magnetic field ranges from 20 to 80 pT, which is several orders of magnitude smaller than the Earth's magnetic field or the magnetic fields found in urban environments. Because of the weak signals, the cardiac magnetic field can only be measured using highly sensitive sensors such as superconducting quantum interference devices (SQUIDs), which have been used since the 1970s. The need to cool the sensors to around -269 $°C$ to achieve the superconducting properties and the additional use of a magnetic shielding chamber have been barriers to the widespread use of SQUID-based magnetocardiograms. Today, other quantum sensors, such as nitrogen vacancy centre-based sensors, do not require cooling and a magnetic shielding chamber, but are not widely used due to insufficient knowledge about quantum sensors in the industrial sector.

Methods

In order to improve the understanding of quantum sensors and their potential, functional and macro models are to be created that support the visualisation of their use in the respective field of application. In addition to numerous industrial applications, there are use cases in the medical field, such as magnetocardiography (MCG). Using a suitable constellation of 3D field coils, a field distribution is to be generated in the plane of the MCG sensor array that corresponds to that of a human heart. This creates an artificial heart that simulates the magnetic stray filed of the human heart in spatial and time progression. The simulation is carried out on the basis of a field analysis using the Biot-Savart law using the BSMag Toolbox in Matlab. The toolbox offers an effective solution for calculating the magnetic flux density in magneto-static approximation, which is generated by a current carrier.

Results

Initial simulations with only the in the z-direction coil active show a good reconstruction of the z-component of the magnetic field in the coil plane. Above this plane at a distance of 50 mm, equivalent to the distance from heart to MCG, the strength of the magnetic field decreases significantly. In addition, the grid-like arrangement of the coils produces a more discrete distribution of the magnetic field compared to the real heart.

Conclusion

The presented model for the simulation of the magnetic field of the heart shows a promising approach but has to be extended. In addition to the three-dimensional excitation of the 3D field coils, other arrangements of the coils should be taken into consideration. The aim ist to improve the quality of approximation of the desired field distribution by adjusting the 3D field coil placement in the heart model. Since the Biot-Savart law is only valid in the magnetostatic approximation, the Jefimenko equations could be added to the analysis to include the time-dependency of the hearts magnetic field.

Implementing a method for design and manufacturing of neurovascular implants in teaching

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Introduction

At the Institute of Biomedical Engineering, a course focusing on implant manufacturing and testing was developed within the research field of implant technologies. In this course students focus on implant design by performing a theoretical parameter study according to a mathematical model based on trigonometry and spring theory, manually braid implants, finally test them and present their acquired knowledge. Over four years, continuous optimizations allowed to improve implant quality and reproducibility. We retrospectively compare manufacturing alternatives with regard to their applicability in educational perspective.

Methods

A microstructured mandrel was designed for manual braiding, whereas support rings ensure accurate shaping of implant loops. Braiding times of different students were measured and implant geometry was characterized. Different wire connection methods were mechanically evaluated and rated regarding simplicity and reproducibility. The influence of heat treatment parameters on implant mechanics was examined. Finally, the reproducibility of the manufacturing process and the calculations of the mathematical model concerning implant mechanics were validated via mechanical tests.

Results

Braiding times to manufacture a functional implant varied under the unexperienced students and decreased within two days braiding to approximately two hours. Three connection methods were associated with considerably different mechanical stability and behavior within a catheter. As expected, variation of heat treatment parameters led to differences in implant mechanics. Accordingly, a suitable parameter set was selected. The reproducibility of the manufacturing process was rated satisfactory with low variance in radial force. Delivery in an hydrogel aneurysm model using a 4 Fr catheter was feasible.

Conclusion

In the novel master course, students without previous expierence learned how to design and manufacture a braided implant in a time frame of six weeks. Next development steps are aimed at implant miniaturization, further improvements in implant manufacturing and fluid dynamics evaluation.

Key words: vascular implants; braiding; mechanical tests; in vitro models; teaching

Track:

Methods of Artificial Intelligence

Denoising of low dose CT scans by means of Denoising Autoencoder

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Introduction

In Computed Tomography (CT) imaging, higher radiation doses are typically required. If doses are lowered, the image quality can suffer due to increased noise. Therefore, techniques for noise reduction are constantly being improved to enable lower radiation doses in CT without compromising image quality. One effective method for denoising is through machine learning, particularly using de-noising autoencoders (DAEs). We have developed and tested a variety of network structures and optimization procedures, such as learning rules, to remove noise from CT images and improve image quality. We present a promising approach for this task.

Methods

A variety of Multiple Parallel Hidden Layers Denoising Autoencoder (MPHL-DEAE) structures and optimization procedures, such as the L2 loss function, were used to assess their denoising performance on clinical CT scans. The training was conducted on a dataset containing seven individual CT scans from different patients, while two separate CT scans were used to evaluate the performance. Siemens' software (CTRecon) was employed to reconstruct low-dose simulations of these scans to provide noisy samples. This facilitates the training and testing of various MPHL-DAEs' denoising performances using different measures.

Results

All MPHL-DAE models showed decent denoising performance. A significant gap in efficiency and denoising quality was observed between different network structures and training/network parameters. Additionally, we found that denoising capabilities also depend on the optimization procedure. However, the classical L2 loss function often led to blurred images, which could be avoided by using the Structural Similarity Index as a loss function (SSIM loss). By optimizing the learning rule, the average Structural Similarity Index Measurement (SSIM) of an image captured at 10% dose could be improved from 0.8408 to 0.9049, achieving an improvement of 5-10%.

Conclusion

Given the limited number of data samples used for training and testing, the quality of the results ranges from acceptable to good. In the field of machine learning or deep learning, optimizing not only the network design but also the training data, such as having a larger dataset available, would be necessary for more effective denoising of CT images acquired at low doses.

Simultaneous Feature Detection and Definition for Deformable Intraoperative Environments

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Introduction

Accurate orientation within the urinary bladder is crucial for locating biopsies and mapping tumors, despite the limited field of view in endoscopic setups. This necessitates defining and describing landmarks in monocular videos for reliable localization. However , intraoperative challenges such as varying brightness, reflections, and continuous deformations complicate feature extraction.

Methods

Due to intraoperative challenges, common adjacent pixel-based landmark descriptions are insufficient. Consequently, neural network approaches have been adopted in literature: detection and definition are performed in a single forward pass using a VGG16 convolutional neural network (CNN) on input images $I \in \mathbb{R}^{h \times w \times 3}$, yielding 3D tensors $F \in \mathbb{R}^{h \times w \times 512}$ as feature maps with 512 channels. Descriptors are then derived as all channels of a position and scored by an algorithm that quantifies their significance for detection. For registration, descriptors are compared using cosine similarity. However, this concept for feature extraction must be refined for deformable environments. The primary contribution of this work is the adaptation of the pretrained CNN through transfer learning to address the unique challenges of the bladder's dynamic environment. Training data is generated to simulate deformation by applying random transformations to endoscopic monocular images, accurately mimicking the bladder's deformable environment and defining ground truth assignments between images. New loss functions tailored to this dataset are defined and used to train the last two layers of the pretrained CNN.

Results

Simultaneous detection and description surpass pixel-based methods in intraoperative feature detection, improving the distance between predicted and actual positions by 80%. It extracts fewer but more accurate landmarks from cystoscopy data, focusing on areas with blood vessels.

Conclusions

The proposed feature description method could enhance bladder cancer diagnosis and treatment planning, laying the groundwork for generating digital bladder representations from monocular endoscopic videos. Future work will optimize the dataset, improve the matching process, and develop a system for continuous bladder representation updates.

How to comply with transparency requirements for AI-based medical devices

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Introduction

In addition to sector-specific regulations, e.g. Medical Devices Regulation (MDR), the new European Artificial Intelligence Act (AIA) is applicable for medical devices based on Artificial Intelligence (AI-based MD). One of the most challenging AIA requirements is the transparency of AI systems that "relates to making the data, features, algorithms, training methods and quality assurance processes available to external inspection by a stakeholder" [1]. Essentially the following provisions concerning transparency are laid down in the AIA:

- Technical documentation of AI systems shall contain a "detailed description of the elements of the AI system and of the process for its development" as well as "detailed information about the monitoring, functioning and control of the AI system" (Art. 11 and Annex IV)
- AI systems must be designed and developed to ensure that their operation is sufficiently transparent to allow users to interpret the output of the system and to use it appropriately (Art. 13 (1))
- AI systems shall be accompanied by "concise, complete, correct and clear" IFU being "relevant, accessible and comprehensible to users" (Art. 13 (2))
- Natural persons interacting directly with AI systems shall be aware of this interaction (Art. 52)

In the following paragraphs a practical approach is presented for meeting transparency requirements for both MDR and AIA.

Methods

First, relevant stakeholders in the healthcare sector were identified who have a legitimate interest in the transparency of AI-based MD. Second, regulatory documents dealing with transparency of AI systems, such as guidelines and standards, were identified and analysed. Third, a series of documents were developed specifically tailored to the needs of potential stakeholders, considering their level of education and knowledge.

Results

In the healthcare sector the following relevant stakeholders having an interest in the transparency of AI-based MD were identified: [2], [3], [4]

- users (e.g., physician),
- patients,
- (national) competent authorities,
- notified bodies, and
- healthcare providers (e.g., clinic).

Regulatory documents and guidelines containing transparency requirements were identified and analysed. Among these are:

- ITU FG-AI4H DEL2.2, [5]
- "Transparency for Machine Learning-Enabled Medical Devices: Guiding Principles" [6],
- Reporting guidelines (e.g., TRIPOD +AI, FUTURE-AI, DECIDE-AI, or CONSORT-AI) and
- ISO/IEC TR 24028.

However, all these documents are lacking a proposal of respective documents with an expected concrete structure and content.

To solve this problem, documents on the transparency of AI-based MD are proposed below. To ensure the necessary transparency towards competent authorities and notified bodies being involved in the market surveillance and the conformity assessment of AI-based MD the documents listed in table 1 shall be prepared by the manufacturer:

Tab. 1: AI- specific part of the manufacturer's technical documentation

Documents	Description	Content
AI model development plan and report	Technical details regarding the development of the AI model	Plan: responsibilities, procedure, deliverables, data objectives, planning/acquisition/preparation, and AI model quality objectives/planning Report: general information, characterization, training, tuning, testing, release, and maintenance
Data management report	Characterization of used training and testing data	General information, characterization, collection, (pre)processing and labeling, and maintenance
AI model evaluation plan and report	Description of technical evaluation (testing) of the AI model	Plan: specifications, tester, test environment, test data, justification of the selection of test procedures, and planning of functional and non-functional tests Report: specifications, tester, test environment, test data, performance and results of the functional tests and non-functional tests, and overall result of the evaluation

In addition, the documents in table 2 are needed to ensure the necessary transparency towards users, patients, and healthcare providers:

Tab. 2: AI transparency documents

Documents	Description	Content
AI model technical description	As part of the instructions for use (IFU) offering a summary of the most important technical details of the AI model	Technical characteristics, clinical benefits, and residual risks
AI model transparency information	As part of the instructions for use (IFU) offering description of the applied AI technology in clear language	General purpose and functioning, rational for using AI technology, safety and performance, currentness, general risks, official product certifications, and limitations

Conclusion

In this work, concrete documents for achieving transparency of AI-based MD in healthcare for different stakeholders were proposed for the first time. Moreover, this approach is also suitable for markets outside the EU, since regulators world-wide apply common principles, and it is promoting the use of innovative and trustworthy AI in clinical practice.

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Using signals generated by ECG denoising autoencoder during its learning results in a denoising performance collapse

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Introduction

If an electrocardiogram (ECG) is affected by interference, e.g. noise, signal processing methods can improve the signal quality. For this purpose, so-called denoising autoencoders (DAE) were proposed. However, the denoising quality depends on DAE's properties and on the training data. Using ECG, we show that the performance of the DAE collapses when data denoised by the DAE is used to generate new training data during continued learning.

Methods

Two DAE were designed, each with three layers. The input and output layer sizes were 80 data points each. The hidden layer comprised 40 neurons with a RELU activation function, while the output neurons were linear. Loss functions were either mean absolute and mean squared error. For basic learning 1,000 ECG segments for training and 250 for validation were randomly selected without replacement from a dataset. The duration of each QRS-aligned segment was 0.8 s and included P- and T-wave. The basic learning phase was to get the mapping $s+n \rightarrow s$, signal s and Gaussian white noise (GWN) n, by back propagation batch learning. After learning converged, k times a randomly selected segment of the training dataset was superimposed with GWN and then denoised by the DAE to replace the selected segment. A single batch learning step was then executed. This continued learning sequence was executed repeatedly, but the validation segments remained unchanged. The loss function used in each case was applied to estimate the errors.

Results

The monitoring of training and validation errors showed a significant decrease in training error combined with a significant increase in validation error during the continued learning phase for both models. The reason is the dimensionality reduction of the training data. The more signals are replaced per iteration, the faster the collapse. With a high number of iterations, all ECG segments used for continued learning became identical, resulting in a complete data collapse. Interestingly, the decrease in denoising performance, i.e., the increase in validation error, correlated positively with the increase in noise level.

Conclusion

This introduced process efficiently mimics the extension of DAE training data with DAE generated segments. The results show that recursive DAE processing of data must be avoided to prevent a collapse in denoising performance.

Track:

Magnetic Methods

Towards unshielded magnetorelaxometry imaging with optically pumped magnetometers

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Introduction

Magnetic nanoparticles (MNP) offer promising biomedical applications like magnetic hyperthermia and magnetic drug targeting. In magnetic hyperthermia, MNP are injected into the tumor and are heated by applying an RF magnetic field (e.g. 100 kHz, 20 kA/m). The knowledge about the spatial distribution of MNP in the tissue is a key for safe and efficient treatments. However, currently available clinical tools are not able to provide this information due to the high iron concentration used. Research grade magnetorelaxometry imaging (MRXI) is especially suited for these applications. In MRXI, the magnetic relaxation signals of previously magnetized MNP are recorded with high sensitive magnetometers and the spatial MNP distribution is reconstructed by solving an ill-posed inverse problem. Currently, the need for excessive shielding is preventing the broad applicability of MRXI, which we aim to address here.

Methods

The imaging setup is composed of 32 excitation coils, two synchronized dual channel optically pumped magnetometers (OMG, Twinleaf), and triaxial homogeneous field and field gradient coils. The imaging volume is 36x36x36 mm^3. Our 3D printed rat phantom is loaded with immobilized RCL-MNP with a clinically relevant iron amount. The environmental field is compensated. The excitation coils used for magnetizing the MNP are switched on for 200 ms and the relaxation is measured for 400 ms. Each coil is pulsed individually and sequentially. We apply extensive noise removal techniques like time-synchronized averaging, feed forward techniques, software gradiometry and correlation based data analysis before extracting the relaxation parameters from the measurement data.

Results

Point-like MNP sources in our rat phantom could be successfully reconstructed both in terms of location and quantification. Imaging parameters like the resolution and the iron detection limit are currently under investigation.

Conclusion

We demonstrated proof-of-principle quantitative imaging of MNP in an unshielded environment using magnetorelaxometry and optically pumped magnetometers.

OPM Setup for Investigating Temperature-Induced Changes in Relaxation Behavior of Magnetic Nanoparticles

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Introduction

One promising technique for monitoring magnetic hyperthermia is magnetorelaxometry (MRX), where magnetic moments of magnetic nanoparticles (MNPs) are aligned by an external magnetic field and the relaxation of their net magnetic moment is measured after the excitation field is switched off. In contrast to previously employed SQUID sensors, optically pumped magnetometers (OPMs) do not require cryogenic cooling, hence they are predestined for measuring relaxation signals in clinical applications. Based on relaxation signal parameters, the spatial MNP distribution is reconstructed. However, in hyperthermia applications relaxation signals are acquired at different temperatures. In this work, we present an OPM-based MRX setup for investigating temperature effects on relaxation signals.

Methods

Two commercially available, immobilized MNP samples (Perimag®, micromod and RCL-01, Resonant Circuits Limited) were placed between an excitation coil and an optical magnetic gradiometer (OMG, Twinleaf). Measurements were performed inside a shielded room and with a background magnetic field applied for operating the sensor. Two orientations of the background field and several magnetic flux densities of the excitation field were applied. During the measurement, the sample was continouosly heated to different temperatures using hot air and relaxation amplitude and time were evaluated.

Results

Our results show decreasing relaxation amplitudes and times for increasing MNP temperatures for both particles systems, all excitation field strengths and both background field orientations. After recooling, both relaxation parameters return to their initial values, indicating that the temperature effect is reversible. Preliminary results also showed a dependence of the temperature effect on the iron amount of the MNP sample. Investigations on that are currently ongoing.

Conclusion

Measurements with our OPM-based MRX setup revealed that the relaxation behavior of immobilized MNPs changes in dependence on the MNP temperature. That is why these temperature effects should be considered for reconstructions of the spatial MNP distribution, particularly for hyperthermia monitoring.

Development of a testing system to multimodally load fiber-based magnetic scaffolds for magnetic hyperthermia-controlled drug release

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Introduction

Magnetic nanoparticles embedded in fiber-based, drug-loaded scaffolds, hereafter called magnetic scaffolds, enable controlled drug release by on-demand magnetic hyperthermia induced degradation of the magnetic scaffold. To control the drug release, models that predict the degradation under specific hyperthermia applications are necessary. Here, the development of a testing system capable of multimodally loading the magnetic scaffolds to accelerate degradation and measure the resulting changes in the material properties is presented. The data gathered by the developed testing system will be used to develop the degradation prediction model.

Methods

An experimental setup was designed to simultaneously load the magnetic scaffolds with a thermal, mechanical, and a hydrodynamic load. The mechanical load, in the form of a cyclic uniaxial tensile strain on the fiber, and the hydrodynamic load, in the form of phosphate-buffered saline flowing at physiological conditions, were applied continuously. The thermal load was applied every three days for one hour analogous to the NanoTherm® treatment plan. Changes in the mechanical properties after multimodal loading were measured by performing tensile tests using a universal testing machine.

Results

No bulk temperature increase was observed at the applied magnetic field strength and frequency. A roughening of the magnetic scaffold's surface was observed. This, however, did not have an impact on the measured mechanical properties. Thus, the impact of the thermal and hydrodynamic load was limited. The results of the tensile tests show that the changes in the mechanical properties of the fiber-based magnetic scaffold after the long-term multimodal load are consistent with the standard linear solid model.

Conclusion

With the developed testing setup, we can measure changes in the mechanical properties due to the multimodal loading of the fiber-based magnetic scaffolds. Thus, the groundwork for the development of a model to predict the degradation of the fiber-based, drug-loaded scaffolds due to magnetic hyperthermia applications was laid.

Global Sensitivity of MEG Source Analysis to Tissue Conductivity Uncertainties

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Introduction

To perform magnetoencephalography (MEG) or electroencephalography (EEG) source analysis, the conductivities of the conductive head tissues must be known. The influence of inter-individual variations of tissue conductivities has been investigated in detail for EEG source analysis. Since MEG source analysis is assumed to be much less affected by these variations, this sensitivity has been investigated only in few studies, even though it might be important especially for a combined analysis of EEG and MEG.

Methods

MEG forward solutions of dipole sources regularly distributed in the gray matter compartment were simulated in a detailed five-compartment head model for three realistic sensor configurations using the FEM multipole approach. Subsequently, a generalized polynomial chaos approach (gPC) was employed to rapidly calculate MEG leadfields for varying tissue conductivities. Based on these gPC expansions, the sensitivity of MEG forward solutions towards tissue conductivity uncertainties and the influence on MEG source analysis was investigated for the three sensor configurations.

Results

A strong influence of tissue conductivity uncertainties on the MEG forward solutions is found especially for quasi-radial sources, e.g., on top of gyri. However, as such sources only have a very weak MEG signal and can therefore usually not be properly reconstructed, this has little practical implications. For quasi-tangential sources, a strong influence of the gray matter conductivity on the signal magnitude is found. The sensitivity of the signal topography towards tissue conductivity uncertainties strongly depends on the source location. Generally, the influence of tissue conductivity uncertainties on MEG forward solutions and source analysis is clearly weaker than for the EEG.

Conclusion

Even though the sensitivity of MEG source analysis towards tissue conductivity uncertainties is clearly weaker than for the EEG, it should not be completely neglected, especially in a combined analysis of EEG and MEG.

Multimodal magnetic microspheres for hyperthermia and drug delivery as well as immunomagnetic labeling and separation

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Introduction

Polymeric magnetic microspheres (MMS) can be used for multiple applications in medicine and biotechnology, including drug delivery, hyperthermia or immunomagnetic separation. Depending on the application, the MMS need to match specific requirements regarding their size, magnetic properties and antigen binding capacity. Therefore, we are developing size-controlled PLGA and PLA-MS with oleic acid coated magnetic nanoparticles (OA-MNP) and surface-conjugated antibodies.

Methods

Microspheres were produced by an emulsion-evaporation method. Polymer, MNP and drug within an oil phase are homogenized with an aqueous PVA phase. The solvent evaporates out of the droplets and solid MMS are formed. Synthesis parameters were varied to study the tunability of MS size utilizing static light scattering. For incorporating hydrophobic MNP into the MMS, we established an oleic acid coating. Distribution of OA-MNP in MMS was investigated with SEM on focused ion beam cross-sections of MMS. Vibrating sample magnetometry was used tu study the magnetic properties of MMS. Heating and drug release behaviour of Camptothecin was investigated. Last, antibody conjugation was evaluated using protein A and the biotin-avidin adsorption mechanism.

Results

We found the MS size to depend mainly on homogenization speed and PVA concentration, leading to diameters between 0.5 and 6 µm. Oleic acid coating enables monodisperse suspension of MNP in organic solvents and a homogenous distribution of MNP in the MMS for MNP concentrations up to 33 wt%. MMS can be heated to 43 °C in 100 to 540 sec, depending on MNP content. Drug release showed a burst type kinetic for 37 and 43 °C, whereby Camptothecin was released in its active lactone form, shown by HPLC analysis. Antibodies were im-mobilized on PLA microspheres and confirmed by optical measurements (ELISA).

Conclusion

We developed a toolbox of MMS that can be adapted to several applications by tuning their size, incorporating magnetic nanoparticles and conjugating antibodies to their surface.

Track:

Digital Health and Care

Evaluation of training in Point-of-Care Ultrasound: A Randomized, Controlled, Single-Blind Simulation Study

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Introduction

Point-of-care-ultrasound (POCUS) has been increasingly used in emergency departments and has shown to improve patient care [1,2]. Its use in prehospital emergency medicine is still uncommon and has only been used in isolated cases. However early detection of right heart strain can provide important information on the patient's condition [3].

Methods

A randomized, controlled, single-blind simulation study was conducted. It was approved by the Ethics-Committee of the Baden-Württemberg-Medical-Association (reference: F-2023-111). The primary endpoint was quality of the ultrasound examination and assessability of images. Subjects were 22 paramedics, randomized into two groups. The intervention group received basic training (4 hours) and an additional course by a DEGUM instructor (2 hours). The control group only got basic training. Both groups performed an eFAST-examination with telemedical support. The maximum time was limited to 10 minutes. Data were documented using a questionnaire. Theoretical knowledge was assessed on basis of a pre-/post-tests.

Results

The ultrasounds of the intervention group were rated as good (79.31%), the control group as satisfactory (71.03%). The average time to complete the test was 6:35 minutes in the intervention and 7:30 minutes in the control group. Post-tests from both groups were also rated as good, with the intervention group answering 82.67% and the control group 76.33% of the questions correctly. Both groups were able to improve their knowledge (intervention + 24.33%, control + 17.0%).

Conclusion

Both groups delivered sufficient results to argue the use of mobile ultrasound devices in practice. The differences in quality between the two groups were small and do not justify the additional expense of a further training. However, neither group was able to provide a reasonable time span to perform the ultrasound examination. More studies with more participants are needed to find ways to reduce the length of the examination and thus make it safe to use on real patients.

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Multisensor platform for measurement of physiological parameters with synchronized real-time analysis

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Introduction

The combination of physiological parameters in medical practice enables a more comprehensive understanding of the state of health and contributes to early diagnosis.[1, 2] Advances in microelectronics are leading to the development of new sensors that allow the creation of new sensor combinations.

For this reason, a measuring platform has been set up to test various sensors, and to perform series of physiological measurements. The focus is on the time-synchronous recording, real-time analysis, and visualization of acquired multisensor data. Simultaneously, another goal is to create a versatile platform for versatile sensor technologies, enabling the integration of different sensors to address diverse medical concerns. By utilizing specialized algorithms, we aim to analyse the data for individual health patterns and uncover novel findings in psychological medicine.

Methods

As a first iteration of the measuring platform, an available plug-in system with various boards for capturing different biometric signals like electrocardiogram (ECG), an electrooculogram (EOG) and the respiratory activity is used (supplier: MicroE). A special firmware that was written to perform the real-time recording of up to 6 sensors, the filtering of interference signals and the transmittance of the data to a server. The server enables interactive real-time visualization and calculates relevant metrics such as heart rate, respiratory rate, number of saccades and blinks caused by eye movements online. After recording, further statistical analysis and visualization are available, such as heart rate variability with its frequency spectrum and Poincaré plot. All recordings are organized in a customized database.

Results

Series of measurements for ECG, EOG, and the respiratory curve were conducted. The determined medical metrics and the visual analysis of the recorded data show a typical characteristic as described in the literature. To confirm the saccades and blinks captured with the EOG accompanying videos were recorded. Additionally, the integration of a skin conductance sensor including the corresponding algorithms is aimed as well as the development of a shielded housing.

Conclusion

As the results showed, our measuring platform enables the time-synchronized recording, real-time analysis, and visualization of multiple sensors. Based on that, we would like to point out the high potential of multi-sensor technology in the field of Mental Health. In the future, we plan to develop machine learning algorithms for sensor data fusion. Although, we aim to further miniaturize and modularize the measuring platform as well as de-wiring and wireless sensor modules to ensure greater convenience for the patient.

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Proposal of a Method to Identify Early Onset of Sepsis using Cardiovascular Vital signs

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Introduction

Sepsis is a life-threatening medical condition, characterized by organ dysfunction, resulting from an uncontrolled immune response to an infection. As it is the leading cause of mortality in intensive care units, rapid and early identification of sepsis is crucial. Vital signs are strong indicators of sepsis which are obtained non-invasively with minimal human intervention. Although studies have employed vital signs in sepsis detection, the independent potential of cardiovascular parameters is relatively unexplored in the current literature.

Methods

In this study, an attempt is carried out to identify sepsis using cardiovascular vital signs and regression model. The parameters namely heart rate, oxygen saturation, systolic, diastolic and mean arterial blood pressures of 295 sepsis and 305 non-sepsis patients are obtained from Physionet Computing in Cardiology 2019 challenge dataset. These vital signs are considered from the 7^{th} and the 9^{th} hour as these time points are reported to be within the early sepsis stage. Further, these parameters are fed into a least absolute shrinkage and selection operator (lasso) regression model to identify sepsis and parameter importance scores. Lasso fits the model 100 times by using a sequence of values for λ. The optimal lambda value is selected such that the model variance is minimum. The dataset is randomly split at a ratio of 70:30 for training and testing, and model performance is evaluated using standard metrics.

Results

Results demonstrate that the mean value of heart rate and blood pressure measurements are higher in the sepsis patients compared to non-sepsis at the considered time points. Also, the oxygen saturation level decreases in sepsis. The adopted model achieves an accuracy of 53% and 59% in identifying sepsis condition using cardiovascular vital signs obtained at the 7^{th} and 9^{th} hour respectively. Among the cardiovascular vital signs, it is found that the oxygen saturation level has the highest importance in classifying sepsis and non-sepsis patients in both the considered time points.

Conclusion

This pilot study focuses on cardiovascular vital signs for early sepsis detection, with changes in oxygen saturation showing a strong ability to differentiate sepsis conditions. However, extensive analysis utilizing advanced machine learning algorithms with large and diverse datasets could improve the performance of the model for clinical utility.

Zero-shot clinical entity linking in German clinical reports to SNOMED-CT

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Introduction

Large amounts of healthcare data reside in clinical reports and require standardization through medical terminologies such as SNOMED-CT to resolve ambiguity and enable clinical applications, such as heart failure prediction or symptom clustering. However, linking clinical entities in clinical reports, such as mentions of diseases or procedures to clinical concepts is complex: First, it requires clinical domain expertise to understand clinical reports alongside numerous abbreviations and synonyms; Second, knowledge about SNOMED-CT with over 360,000 concepts is needed to accurately link entities. However, the expertise needed for entity linking is expensive and hard to reach. This is even more pronounced for German clinical reports, due to a lack of a comprehensive German SNOMED-CT version and familiarity with the terminology.

Methods

We developed and tested a novel entity linking pipeline for German clinical reports. The pipeline steps entail context-dependent abbreviation disambiguation, German clinical report translation to English through biomedical translation models, and entity linking to SNOMED-CT using a zero-shot semantic-similarity-based approach. An implemented automated check regarding the patient's demographic and laboratory data determines the plausibility of linked concepts and reduces manual effort when evaluating the results. In a survey, physicians rated the accuracy of 120 linked concepts with stratified random samples on a three-point LIKERT scale.

Results

Our pipeline was successfully tested on clinical reports of over 800 heart failure patients from the University Hospital Aachen. Survey results indicate an up to 81.25% accuracy for correctly linked concepts. The results provide valuable knowledge on adapting the pipeline, for instance by leveraging grammatical structures of clinical reports through dependency parsing, to increase the accuracy.

Conclusion

The results demonstrate the applicability of automatically linking clinical entities in clinical reports to SNOMED-CT and open pathways for future applications, such as heart failure symptom clustering and heart failure prediction in patients.

Track:

Model-based and Automated Medical Systems

Impact of Finite Element Model Resolution on Current Density Distributions in Ocular Electrical Stimulation

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Introduction

Ocular electrical stimulation (oES) holds great potential for vision restoration applications. Individualized oES therapy, which targets the retina, requires current flow simulation. This work compares forward simulations of oES using finite element (FE) models with different mesh resolutions to find optimal model setups.

Methods

High- and low-density head models are constructed using an MNI template comprising 35.2 million and 13.6 million FEs, respectively. Tetrahedra with average side lengths of 0.4 mm and 0.2 mm represent the retina. A current of 1 mA, distributed at eight electrodes (ø 1 cm) positioned around the eye and one occipital return electrode (5×5 cm²) is impressed. Mesh generation and simulations are conducted with SimNIBS 4. The file size of the two models is 2.4 GB and 6.6 GB and simulations required 40 min and 2 hours, respectively, utilizing 16 cores of an AMD_Epyc7601 processor at 2.2 GHz with 240 GB RAM. Relative magnitude (MAGrel) and relative distance measure (RDM) compare the current densities (CDs) between the models' posterior poles of the retina, as region of interest (ROI). Differences in the 95th percentiles of CDs within the ROI are evaluated by area, center of mass (COM), and orientation of eigenvectors from a principal component analysis (PCA).

Results and Discussion

The average and standard deviation of CD magnitude in the ROI is 0.173 ± 0.049 A/m^2 for both models with an average difference of 0.0003 A/m^2 between the CD magnitude distributions and 95% confidence interval of [-0.0001, 0.0006] A/m^2. MAGrel is 0.001 and RDM is 0.037, 0.012, 0.047 in x, y and z directions. The 95th percentiles of the models show great overlap with a COM distance of 0.38 mm and an area difference of 2.78 mm^2. The three PCA eigenvectors of the percentiles show a small orientational deviation with a cosine similarity > 0.99.

Conclusion

Although the models differ considerably in the number and size of elements, their influence on the resulting, clinically relevant CD distributions in the target ROI is marginal. The lower-density model provides a reasonable choice for future oES simulations to decrease model size and computational effort

Development and analysis of a novel semi passive approach for controlled rate freezing in the field of cryopreservation

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Introduction

Cryopreservation plays a crucial role in various fields, including regenerative medicine and cellular therapies. The selection of an appropriate cooling rate in the freezing process is crucial for minimizing cell loss and optimizing therapy efficacy. In commercial cryopreservation, two primary cooling methods are applied: Passive cooling devices regulate the cooling rate by utilizing insulated alcohol baths or thermal insulation material within a -80°C freezer, while active cooling devices usually pump vaporized liquid nitrogen into the sample chamber for gradual cooling. We aim in this work to study different designs of a hybrid method through assuring a cold environment using a mechanical freezer and controlling heat extraction using thermoelectric elements. The designs should offer different cooling rates in the range of slow freezing ideally between 0.5 and 5 K/min.

Methods

The main blocks of the planned prototypes are the power supply and the control unit, which function outside of the cold environment, and the sample chamber consisting among other components of sample holders, a filling medium, insulation and Peltier-elements. Computer simulations are used to analyse and optimize the effects of various design parameters (e.g., geometry, materials of components, heat transfer by Peltier-elements) on temperature fields with respect to efficient heat transfer within the devices and controlled temperature profiles in the stored samples. Different heat sink types are studied for dissipating the heat of the thermoelectric elements. Prototypes are used to verify performed optimization steps and in-silico models.

Results

First simulations show realistic temperature distributions and provide valuable insights for the design of prototypes for effective and efficient temperature control. Simulated/Recorded temperature profiles in and close to the targeted samples serve as useful indicators for optimizing setups and protocols.

Conclusion

This study will be the corner stone in establishing a new generation of cooling devices, offering more flexible and reliable protocols whilst avoiding the high cost of the LN2 infrastructure.

Improved Chronic Wound Management with Smart Sensor Systems

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Introduction

Diabetes mellitus, a chronic condition impacting more than 422 million individuals globally, poses a significant public health concern due to its severe complications. Among these, diabetic foot syndrome (DFS) stands out as a prevalent and serious secondary condition, arising from diminished foot sensation and potentially culminating in irreversible consequences such as amputations. Presently, the treatment approach for DFS focuses on wound immobilization and offloading, yet it faces limitations in assessing crucial medical indicators between appointments and impeding further deterioration.

Methods

To overcome this constraint, a smart wearable monitoring and feedback system has been developed to complement conventional DFS care. This system comprises a miniaturized flat PCB sensor component connected via a flexible bridge to a communication unit, seamlessly incorporated into the DFS foot dressing. Continuously measuring temperature, humidity, and pressure in the wound area, the sensor promptly delivers active feedback to the patient's smartwatch in instances of wound overstressing or significant alterations within the wound area. Utilizing flexible and stretchable soft materials is essential to seamlessly integrate the sensor system onto the skin, thereby improving user-friendliness and ensuring precise data collection. To handle these enhancements a pressure sensor has been developed based on thin, flexible, and stretchable substrates.

Results

A randomised trial with twenty DFS participants (12 intervention, 8 control) evaluated the system. The participants were shown the pressure, temperature, and humidity values on their smartwatches. Furthermore, when participants in the intervention group exceeded the predefined pressure threshold, they received audio-visual alerts on their smartwatches. This biofeedback compensated for their reduced foot sensation. Consequently, participants in the intervention group adjusted their behaviours, reducing incorrect pressure on their feet and potentially enhancing wound healing.

Conclusion

The case-by-case analysis in this pilot study reveals the suitability of the sensor system for sensor-based DFS treatment but highlights areas for improvement in usability and sensor accuracy. While the current technology functions, integrating flexible sensors could improve overall effectiveness.

Development of a stochastic finite element model for use in the diagnosis of middle-ear pathologies.

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Introduction

For over four decades, finite element models of the middle ear have been essential for better understanding hearing mechanics, aiding implant and hearing aid development, as well as diagnosing middle-ear diseases. However, existing models are mostly deterministic and neglect individual variations in middle-ear parameters. While material parameterization is straightforward, geometry parameterization like ossicle and ligament arrangement pose challenges in finite element models. This study introduces a stochastic model that adresses these challenges and comprehensively parameterizes middle-ear geometry and material properties.

Methods

The stochastic model, based on an existing finite element model, simplifies ossicles as rigid bodies and ligaments as beam elements. Only the tympanic membrane, tympanic cavity, and ear canal are meshed with finite elements. This approach allows straightforward parameterization of ossicular mass and moments of inertia, joint and ligament attachment points and orientations, and tympanic membrane shape using publicly available or published computed tomography data and material properties. Stochastic variables are defined based on this data and linked in an anatomically plausible parameter chain using principal component analyses and copulas. The model is calibrated using standard data, and global sensitivities of parameters are assessed using Sobol indices. A neural network for differentiating between normal ears and those with otosclerosis and disarticulation is trained using simulated data from the stochastic model and tested on existing literature data.

Results

The calibrated model accurately reproduces the mean and variance of middle-ear measurements like impedance, reflectance, stapes and umbo transfer function. Ligament and joint material parameters have a significant effect on the variance of these measurements, while variations in center of mass positions, for example, have less effect. The neural network trained on the simulated data shows promise for diagnostics, achieving 86-100% sensitivity and 85-93% specificity for detecting otosclerosis and disarticulation, which is similar to the performance of classifiers trained on measured immittance data.

Conclusion

The stochastic model combines finite element modeling benefits with straightforward geometry parameterization. Calibrating the model significantly reduces uncertainties of difficult-to-measure material properties compared to literatur values. This facilitates future model validation for further middle-ear pathologies and makes the model valuable for diagnosing rare pathologies with limited validation and training data.

Track:

Micro- and Nanosystems

Spray-dried Microparticulate Drug-Delivery-System for Controlled Nose-to-Brain Transport Based on Functionalized Chitosan

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Introduction

Nose-to-brain drug delivery provides an alternative administration route for drugs to the central nervous system, bypassing the blood-brain barrier. Microparticle formulations based on chitosan have been explored in literature due to chitosan mucoadhesive properties, swelling behavior, and ability to open tight junctions. Thiolation of chitosan enhances its mucoadhesive properties, making it an attractive excipient for nose-to-brain drug delivery. A synthesis strategy for L-cysteine chitosan was developed and the resulting material served as a matrix for microparticles produced by the spray-drying.

Methods

Chitosan was chemically modified with L-cysteine through carbodiimide chemistry and the product was purified in an acidic medium and freeze-dried. The resulting material was physically-chemically characterized and used to prepare a 1% w/v solution in water or acetic acid. The solutions were spray-dried using a two-fluid nozzle and the resulting microparticles are characterized for size, morphology, swelling, and free thiols.

Results

Chitosan microparticles successfully encapsulated active biopharmaceuticals, allowing controlled release. To improve chitosan characteristics, the thiolation of chitosan was successfully achieved with a high amount of thiols per gram of polymer, which is connected to improved mucoadhesion. The resulting polymer showed high solubility in a wide range of pH, allowing for spray-drying in different conditions. The spray-drying yield was consistently above 60% in all conditions. The material proved suitable for spray drying and the free thiol content can be tuned easily by adjusting the pH of the feeding solution, resulting in a controlled crosslinking degree.

Conclusion

Chitosan microparticles proved a good platform for nose-to-brain drug delivery. Chitosan was successfully modified to achieve a water-soluble material with a high amount of free thiols per gram of polymer. The material proved suitable for spray drying and the free thiol content can be tuned easily by adjusting the pH of the feeding solution, resulting in a controlled crosslinking degree.

Acoustic MEMS Sensor System to emulate properties of the human hearing

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Introduction

The human hearing is one of the most astonishing senses, allowing us to receive and recognize sounds in various conditions, including noisy environments and multiple sound sources. A system which emulates the frequency decomposition in the basilar membrane, transduction of the sound wave and nonlinear amplification as well as the encoding in the hair cells provides an environment to study improvements for nowadays technological systems. The results can be used to improve systems like hearing aids and natural language processing systems, such as Alexa, Cortana, and Siri.

Methods

The acoustic sensor is a MEMS beam consisting of a piezo-resistive readout bridge to detect the bending and an aluminium heater for actuation. An additional circuit takes the signal from the piezo-resistive readout bridge and tunes the actuation signal depending on sound intensity and sound intensity changes. The completely in hardware realised setup allows further optimization for power consumption and scaling.

Results

The build setup with sensor and circuit implements adaption to constant sounds and therefore enhances sound changes like sound on- and offsets and encodes features like sound frequency and intensity. The sound can be encoded with an envelope signal and/or in spikes. Furthermore, the spike generation is based on a signal integration and therefore sound intensity dependent spike encoding, like time to first spike, rate coding, and rate coding with offset, is achieved. The different coding regimes and the ability to change the minimal input signal for spiking as well as the time constants in the circuit, leads to an encoding of various sound ranges for different acoustic sensors.

Conclusion

The implemented system with a tuneable acoustic MEMS sensor and a control circuit can be used to emulate properties of the human hearing like adaptation, feature extraction and encoding of sound. Different encoding techniques and adjustable circuit parameters allow a broad range of applications. Furthermore, sensing and encoding dependent on the environment can enhance important sounds, which can yield a better sound perception and analysis especially in hard-to-hear situations, and reduces data streaming and power consumption.

Step forwards in-vivo inflammation sensing in active implantable medical device with biodegradable conductive moleculary imprinted polymers

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Introduction

The cochlear implant (CI) is a widely used hearing aid in which a microelectrode array is surgically inserted directly into the cochlea where it remains ideally for life. However, statistically, 40% of CI devices fail after implantation and therefore require re-implantation. A potential complication accompanying CI implantation are inflammation reactions. Therefore, the information about inflammation is crucial for timely admistration of anti-inflammatory medication. Moleculary imprinted polymer (MIP) sensors on a CI electrode are promising candidates for this inflammation detection. For in-vivo applications, the MIPs must meet the requirements of biocompatibility, biodegradability and electrical conductivity. In the presented study, conductive MIPs electrodeposited on a platinum electrode and specific for biotin, used as a surrogate template for interleukin-6, are investigated. MIPs are first analyzed and subsequently degraded in a controlled manner using impedance measurements at varying electrical potentials.

Methods

PEDOT was selected as the conductive polymer and deposited by cyclic voltammetry. For the biotin sensing, MIPs were washed in acid-base solution and then impedance measurements were conducted in PBS with and witout biotin. Paracetamol and ibuprofen were also used to determine cross-sensitivity. Since PEDOT is not biodegradable, the polymer was electrochemical degraded in PBS by additional impedance measurements, where the applied voltage was varied to modulate degradation. Finally, to investigate the polymer biocompatibility according to ISO guidlines, the solution containing the degraded monomer molecules was analysed by FTIR.

Results

When impedance measurements were performed, the change in MIPs-impedance demonstrated a successful incorporation of biotin. With decreasing potential, fewer dissolved polymers and more degraded monomer molecules were detected. Below 205 mV, only dissolved monomer molecules were obtained, which enables renal clearance. Biocompatibility testing revealed a high biocompatibility for both the polymer and the solution with dissolved monomer molecules.

Conclusion

Based on these findings, we have developed conductive, biocompatible and controllably degradable MIPs capable of detecting biotin.

Capsule Endoscope for Liquid Biopsy

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Introduction

Liquid biopsy out of the small intestine provides information about the microbiome that can help in the diagnosis and treatment monitoring of health issues such as obesity, inflammatory bowel disease (IBD), diabetes, ulceration, and cancer. Currently, liquid sampling is conducted using traditional long tethered endoscopes with integrated pipes. Still, it is a big challenge to reach deeper regions in the small intestine. In this work, a capsule endoscope will be developed to locally sample a liquid biopsy at deeper and more complex regions in the small intestine.

Methods

A 3D multilayer integrated system with opening and closing elements, channels, a printed resistive microheater, a filter membrane, and a vacuum chamber has been built of laser-structured PMMA layers bonded together using pressure-sensitive adhesive. The opening element is made of wax, which melts when the microheater is turned on, allowing the liquid to flow through the filter membrane and to be aspirated into the vacuum chamber. Afterwards, the closing element made of a swellable material (cellulose) swells and blocks the liquid path into the chamber.

Results

The microheater is operated and controlled by a power supply applying 1 V and 0,18 A for 3-5 seconds, heated at 100 °C from a start temperature of 37° C, which leads to an instant melting of wax and opening of the opening element. Within 5 seconds, the vacuum chamber (100 mbar) aspirates the liquid and a sample of 150 µL is collected. The closing element sucks up the liquid and swells, closing the fluidic path into the sampling chamber within 20 min. The filter membrane of a pore size of 180 µm is integrated to sort out the stool particles.

Conclusion

The sampling mechanism showed full *in-vitro* functionality. Next steps will be to integrate it in a capsule set-up and test the operation *in-vivo*.

New Bioelectronic Platform and Tools from Microsystem Technology for Next Generation InEar Micro-Electrodes

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Introduction

Electroencephalography (EEG) is a critical tool in modern medicine, used to measure and record the brain's electrical activity. Prolonged EEG monitoring could significantly enhance patient care, especially for those with epilepsy, by enabling more precise diagnoses and personalized therapies. EEG also has potential applications in consumer and industrial technologies, such as monitoring attention in driver assistance systems. However, current adhesive and dry electrode systems have limitations that make them unsuitable for long-term use.

Methods

Modular tools using micro system technology (MST) through processes like PVD sputtering, electroplating, lamination, micro printing and laser fabrication were developed to create thin (<100um) versatile bioelectronic stacks. Stack feasibility for stable transcutaneous InEar-EEG recording were evaluated for bare gold (Au) and PEDOT:PSS gold microelectrodes (OD:2mm). Scientific characterizations by surface examinations, IES, tensile/mechanical and adhesion testing demonstrates functionality, biocompatibility, signal quality, signal-to-noise ratio (SNR), interface impedance and design flexibility. Finally, data for such bioelectronic stack were compared against industry-standard Ag/AgCl electrodes.

Results

The research highlights the capabilities of advanced MST platforms and tools in creating muti-layered high-fidelity, flexible, micro bioelectronics with contact impedances below 2kOhm. The technical end point - a functional bioelectronic platform designed for integration into an otoplastic carrier for InEar EEG recording – is feasible and will be presented. The data from extensive bench tests, assessing mechanical, electrical, physico-chemical, and functional performance reveals the possibility for long-term transcutaneous use.

Conclusion

MST platforms exhibit significant versatility for biomedical engineering, making them suitable for next-generation long-term micro electrodes. The signal quality of these MST-based electrodes is comparable to today's gold standard surface electrodes. However, to fully realize the potential of these advanced technologies, innovative micro designs are essential.

Track:

Neural Implants and Engineering

Behavior of an polyimide-based electrical circuit under mechanical load conditions integrated into a stent

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Introduction

Active stents consist of an electrically active component integrated into a stent and are intended to be used for monitoring physiological values such as blood pressure. Currently, there is no wireless, miniaturized, and functionalized system which is integrated into a stent, incorporating all requirements. Relevant are mechanical aspects during implantation procedure and body movement, plus long-term stability of all functionalities within the body.
The Chip-in-Foil technology represents a new approach for integrating an electrical circuit into a stent. Polyimide (PI) is used to apply and simultaneously encapsulate platinum conductors. This enables the manufacturing of a conformable circuit adaptable to the geometry of an existing stent.

Methods

Finite Element Analysis is utilized to understand the interaction and mechanical load conditions of a PI-based substrate braided into a Nitinol stent. Investigating the mechanical load, simplified models were generated in COMSOL™ in form of a cutout of the repetitive braiding pattern, specifically the PI-sample and stent strut. Conducted load represents the force generated by physiological blood pressure.

Results

The material behavior of the metal traces encapsulated in PI under load of up to 120 mmHg shows maximum stresses at the edges. Crossing points of the PI-sample and the Nitinol strut result due to braiding. The load onto the PI-sample was investigated by three cases: over, under and in-between two stent struts. The modelled case of the PI "in-between" the stent struts shows maximum stresses of approximately $2.2 \cdot 10^{-4}$ MPa. All cases show stresses at the interface between PI and Nitinol.

Conclusion

First insights of possible predetemined breaking points at the crossing points of a simplified integrated electrical circuit braided into a stent were investigated by computational modelling. Next steps of technological developments include stress-optimized geometries for maximized mechanical decoupling. Investigated sites with minimum stress behaviour can be used for the placement and integration of chips.

Bridging the Gap: From Neuromodulation Research to Real-Life Applications

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Introduction

Despite some groundbreaking research papers, much of the neuromodulation knowledge is stagnate, failing to transition into patient care applications. With the neuro-technology market estimated at $13 billion in 2022, and growing at 11.5% CAGR between 2023 and 2032, there exists a clinical need for such applications.

Why are research technologies failing to reach real-life applications?

Generally, challenges in safety, cost, and adoption hinder real-life applications of neuro-technologies. These challenges include long-term stability, biocompatibility, ease of surgical handling, power efficiency, level of miniaturization, regulatory compliancy, as well as ethical considerations. To overcome such challenges, strategic planning and risk-reduction measures are vital.

In this presentation, we describe how a systematic and structured development strategy can facilitate the transition of ambitious medical devices from the early technology stage to the medical market.

Methods

To illustrate this strategy, we use a fictional neuromodulation product, “CEPHALFUSE”. Each development stage is discussed using real-world examples that are representative of the technical challenges that must be addressed.

We will follow the story of “CEPHALFUSE”, a revolutionary health-monitoring brain implant, from early conception up to a functional-demonstration device. First, we carefully plan the itinerary of our innovation journey and gather the necessary technical requirements. Next, we will embark on the conceptual phase, within which creative solutions are proposed for every function of the device. We will then navigate through the design phase, where we build purposeful prototypes and iterate towards integration, miniaturization, and reduction of risks. Lastly, we verify and validate the neuromodulation device for the obtention of market approval. We will showcase how usability engineering can serve as a helpful travelling companion in such development.

Conclusion

With this example, we show that a solid process for innovation, testing, and regulatory compliance provides a useful structure to successfully complete the long, yet exciting journey from laboratory discovery to transformative neuro-technology applications.

Area-Selective Etching of Parylene-C on Platinum Surfaces

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Introduction

In the case of miniaturized neural interfaces, the surfaces are protected with biocompatible insulating polymers except for the microelectrodes. Here, area-selective etching offers the potential to replace error-prone and cost-intensive lithography steps, as the opening above the electrodes can be achieved by catalytic etching. Oxygen diffuses through Parylene-C to dissociate atomically on the platinum electrode surface. The resulting reaction partner can etch the Parylene-C above it. Parylene-C can be deposited from the gas phase and thus offers an excellent basis for the production of 3D electrodes and geometries.

Methods

Silicon wafers were coated with titanium/platinum and then coated with approximately 250 nm Parylene-C. The wafers were placed in a recipient in which the table temperature could be adjusted and in-situ ellipsometry was possible. The wafers were tested for etching under different conditions (oxygen flow, temperature, pressure). Tests were carried out in a vacuum and at atmospheric pressure.

Results

Under a process pressure of up to 250 mTorr and gas flow of up to 100 sccm of oxygen and at temperatures of up to 300 °C, no catalytic etching could be detected using ellipsometry. Catalytic etching only occurred at temperatures above 230 °C and under atmospheric pressure (approx. 750 Torr). Thus, in addition to the temperature, the pressure was crucial for catalytic etching. An etching rate of approx. 11 nm/min could be calculated for the Parylene-C on the platinum sample. No etching took place on the silicon sample under the same conditions.

Conclusion

The experiments have shown that selective etching of Parylene-C on platinum is possible. This opens up new possibilities for the production and encapsulation of 3D electrodes. Not only can the electrode surfaces of platinum be selectively opened, but they can also be subsequently selectively coated using the atomic layer deposition process.

Long-term stability and investigations of potential failure modes of flexible thin-film electrodes

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Introduction

Thin-film electrodes on polymer substrates have become standard in flexible neural interfaces. Longevity is a major challenge in translational research to use these approaches in chronic applications in preclinical and clinical studies. Understanding of all potential failure modes is mandatory for risk mitigation and development of concepts that last for a lifetime but at least 5 to 10 years.

Methods

We have investigated electrode arrays after chronic implantation to find out potential failure modes. Results have been obtained from animal studies (ferrets, ECoG arrays) in the central nervous system as well as from human implantations in the peripheral nervous system. Moreover, digital holographic microscopy allows for in vitro imaging and quantification of the mechanical displacement. It has been complemented by scanning electron microscopy to get insights into potential changes in the grain structure and material composition during stimulation.

Results

Experiments have been performed to quantify oscillation processes, model stress, size and adhesion. Analysis of thin-film arrays after 6 months of stimulation (humans) and about one year of recording (ferrets) have shown stability of devices and cases of adhesion loss as well as structural changes of platinum metallization.

Conclusion

We believe that methods of explantation and preparation of chronically implanted probes strongly influence further analysis steps and need to be identified. In addition, our in vitro studies indicate that oscillations in platinum thin-film electrodes can occur during electrical stimulation with progressive adhesion loss over the stimulation period. Understanding and mitigation of failure modes help to further enhance our thin-film electrodes for long-term applications.

A Computational Model of a Silicone Coated Ultrasonic Transducer Membrane for Miniaturized Biomedical Implants

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Introduction

Bioelectronic medicine aims to miniaturize and implant devices deeper into the body. This requires alternative forms of energy transmission rather than inductive coupling. Ultrasound offers an alternative approach to power deep-seated implants. Novel membrane-based ultrasound transducers allow implants to be miniaturized and thus be supplied with energy at almost any point in the body. Since encapsulation of ultrasonic transducers with hermetic packaging severely attenuates the power of ultrasonic waves, the aim is to encapsulate the implants with non-hermetic materials, in this case, PDMS. In this contribution, one-component silicone is used, in which by-products evaporate during curing, leading to shrinkage in the silicone and inner stresses.

Methods

A computational model of the physical properties of a micromachined ultrasonic transducer membrane and the silicone coating was created in COMSOL. Maximum deflections of the membranes under forced excitation and the inner stresses in cured silicone as a result of the shrinkage were calculated. These values were applied to simulate the stress at the membrane's interface, the eigenmodes of the membrane, and a possible shift in the resonance frequency.

Results

The inner stresses (σ = 4 kPa) inside the silicone coating result in stress at the interface between the membrane and the silicone, with a maximum at the center of the membrane. This stress also leads to an additional damped deflection (Δd = 7 nm) when the membrane is excited. To achieve an equally strong deflection, the membrane must now be excited with a higher voltage or an adjusted resonance frequency.

Conclusion

A computational model was developed and simulated in COMSOL to compute the effect of a one-component silicone adhesive on a micromachined ultrasonic membrane. The stress at the interface changed the membrane's oscillation characteristics, and the maximum deflection was damped. The simulation of a single membrane can be extrapolated and used for micromachined ultrasonic transducers for further suitable coating materials.

Track:

Optical Systems and Biomedical Optics

Optical Emission Spectroscopy for the Real-Time Identification of Malignant Breast Tissue

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Introduction

Breast conserving resection with free margins using electrosurgery is the gold standard treatment of early breast cancer. It requires a reliable discrimination between benign and malignant tissue at the resection margins. The margin status is commonly determined by histopathology after the surgery. In this study, both normal and tumor tissue samples from breast cancer patients were characterized ex vivo by optical emission spectroscopy (OES) from the sparks generally appearing during electrosurgical manipulation. The aim of the study was to determine spectroscopic features which allow future real-time tissue differentiation for margin assessment during breast cancer surgery.

Methods

Optical emission spectra were recorded during electrosurgical treatment of *ex vivo* tissue samples from breast cancer surgery of patients with ≥15mm invasive breast tumors of all histologic subtypes, but without neoadjuvant therapy. After histologic assignment of the tissue samples to either benign or malignant tissue and its correlation with the corresponding spectra, the classification performance for the differentiation of normal vs. tumor breast tissue by machine learning algorithms was evaluated. A data set of 972 spectra, comprising 480 from normal and 492 from abnormal tissues, was used for analysis. Spectroscopic features were detected and identified by a custom-designed analysis algorithm, and selected according to their occurrence rate in all spectra.

Results

Using all selected spectroscopic features a support vector classifier for tissue discrimination was trained. The classification of normal and tumor tissue exhibited high accuracies for each individual patient, resulting in an average accuracy, sensitivity and specificity of 96.9%, 94.8% and 99.0%, respectively. The study results have been reproduced in further studies while gradually developing the analytical set-up to a system suitable for clinical application.

Conclusion

Our study demonstrates the potential of OES in combination with electrosurgery as a promising tool for intraoperative discrimination between benign and malignant breast tissue with high sensitivity, specificity, PPV and NPV due to specific spectroscopic features. First steps towards clincal feasibility have been initiated. However, further research is required for the clinical transfer of OES as a unique fully integrated and real-time margin detection method for breast cancer surgery.

Monte Carlo Analysis of Near Infrared Wavelengths Towards an Optical NIR Blood Analyte Sensor

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Introduction

A Monte Carlo (MC) light-tissue interaction simulation was conducted for 7 near-infrared (NIR) wavelengths, 1050, 1200, 1300, 1450, 1460, 1550, and 1650 nm, to assess the penetration depth, pathlength, and detected power to develop non-invasive sensing methods. The wavelengths selected are commercially available as narrow-band miniature light-emitting diodes in the absorption band of analytes such as glucose, lactate, and creatinine, and are used on a novel non-invasive blood analyte concentration monitor. MC simulation was also run for 660 nm, a wavelength that is well documented in the literature, to assess the accuracy of the model. Results from the NIR simulations were also compared to experimental testing carried out on porcine tissue.

Methods

The MC simulations were performed using an adapted version of “MCmatlab: an open-source, user-friendly, MATLAB-integrated three-dimensional Monte Carlo light transport solver with heat diffusion and tissue damage”. A 7-layer tissue model was constructed with 'Stratum corneum', 'Epidermis', 'Papillary-dermis',' Upper-dermis', 'Reticular-dermis', 'Hypodermis', and 'Subcutaneous' layers. The absorption coefficient for each layer was defined with the equations based off Jacques "Optical properties of biological tissues: a review" absorption data found in the literature, and data obtained by experimentally by the authors. The emitter-detector spacing was set at 2 mm in reflectance mode. Each simulation was set for 12 hours. MATLAB was used to interpret and compare results.

Results

A MC simulation for the 660 nm wavelength launched 10e9 photon packets. The mean pathlength was 2.22 mm, the mean penetration depth was 0.855 mm. The maximum penetration depth was 5.706 mm. The percentage of photons collected by the detector was 0.0902 %. The maximum normalised fluence rate (NFR) was 129.379 W/m^2/W-incident located in the stratum corneum, and the maximum normalised absorption (NA) was 234.562 W/m^2/W-incident, located in the upper dermis layer. These values are comparitable to results found in the literature, concluding the tissue model is approprite.

Seven NIR MC simulations launching between 9e9-10e9 photon packets. All results are presented in order of wavelength: 1050, 1200, 1300, 1450, 1460, 1550, and 1650 nm. The mean photon pathlength was 2.330, 2.346, 2.432, 2.435, 2.439, 2.477, and 2.548 mm. The mean maximum photon depth was 0.986, 1.012, 1.057, 1.076, 1.080, 1.107, 1.141 mm. The maximum photon depth was 5.682, 4.699, 5.303, 5.348, 5.147, 6.366, and 5.819 mm. These depths are comparitable in to those seen through porcine tissue during experimental testing perfomrmed by the authors. Thus, the penetration depths seen in these simulations are likely to align with real tissues.

The percentage of photons collected by the detector were 0.054, 0.048, 0.044, 0.039, 0.039, 0.037, and 0.035%. The NFR was 87.86, 77.09, 71.43, 60.35, 60.05, 58.95, 56.10 W/m^2/W-incident located in the stratum corneum layer for all wavelengths. The NA was 16.3838, 12.99, 10.14, 37.03, 36.57, 19.42, 13.5243 W/m^2/W-incident located in the upper dermis.

Conclusion

The 660 nm pathlength and penetration depth was slightly smaller than the NIR wavelengths, and the NFR, NA, and percent of photons collected by the detector was larger as photons at lower wavelengths carry more energy. The penetration depth increases with wavelength as suggested by the increase in penetration depth from visible to SWIR. The percentage of photons detected is less than 0.1%, highlighting the importance for highly sensitive photodetectors with these wavelengths. MC simulations were carried out on NIR wavelengths to better understand the light-tissue interaction. The pathlength and penetration depths found will be used to develop sensor emitter-detector separation and device selection, and post processing algorithms for a non-invasive blood analyte concentration sensor.

Lab-On-Chip – Micro-Spectrometer System for Near-Infrared Analytics

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Introduction

Optical spectroscopy is an analytical technique in the biomedical field which often relies on expensive and inflexible solutions with a high level of equipment complexity. Especially due to the increased need for real-time, on-site data acquisition in biomedical research and diagnostics, miniaturization of such systems (lab-on-chip) would enable cost-effective real-time sensor technology. This motivates the development and construction of a novel micro-spectrometer system for the near-infrared (NIR) range. NIR spectroscopy is an analytical technique that is particularly suitable for organic components that require less sample preparation and thus becoming increasingly important in biomedicial analysis and diagnostics. A limiting factor for the broad application of NIR spectroscopy are available detectors for wavelengths above 1000 nm on the market: indium gallium arsenide (InGaAs) detectors are mainly used due to their performance, but at high fabrication costs. Instead we use germanium-on-silicon (Ge-on-Si) detectors which are fabricated by standard semiconductor processes. They can be monolithically integrated and scaled to larger wafer sizes, which makes it significantly more cost-effective than InGaAs-detectors.

Methods

The core of the micro system consists of an innovative spectral sensitive photonic chip that was developed by Institut für Mikrolektronik Stuttgart (IMS CHIPS) and Institute of Semiconductor Engineering of the University Stuttgart (IHT). It is equipped with a monolithic germanium-on-silicon (Ge-on-Si) 64 pixel sensor line and a backside diffraction grating which enables spectral resolution in the range of 1000 nm to 1600 nm on a single chip. The monolithic approach enables an ultra-compact and simple system design. The Chip Spectrometer is integrated into a miniaturized spectroscopy setup for quantitative analysis of a biomedical sample. The focus of the research task is on the interdisciplinary realization of a cost-effective system integration with all necessary system components that stands out from the high-priced, inflexible solutions currently on the market, which rarly offer complete systems.

Results

For the development of the micro system all spectroscopy components such as photonics chip, a broadband NIR light source, optical paths, sample adaption and electronics were realized under the aspects of cost efficiency, miniaturization and the aim of a high information content. All components where integrated in the spectroscopy system that is able to spectrally analyse a sample in parallel over the entire spectral sensitivity range (1000 nm to 1600 nm). As proof-of-concept a first table-top system on the scale of 100 mm x 80 mm x 100 mm was realized with the potential to become significantly smaller. A NIR spectroscopy based quantitative analysis of first liquid samples, different mixtures of water and isopropanol in a reflectance and a transmission setup was demonstrated.

Conclusion

A first setup of the micro-spectrometer system based on the cost-effective Ge-on-Si detectors was fabricated and successfully tested. This proof-of-concept shows that affordable micro NIR spectrometers can be achieved for a broad field of applications with a high need of miniaturization such as biomedicine. The next steps in the development would be to further miniaturize the setup in the direction of a chip-scale spectrometer with the potential to integrate it in, for example, a surgical instrument and to address a specific medical application, such as the on-site analysis of tissue and body fluid based on NIR spectroscopy.

Potential and Challenges of Coded Aperture Collimation for Intraoperative Gamma Cameras

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Introduction

In the field of Intraoperative Gamma Cameras (IGCs), coded aperture collimators promise excellent imaging properties but are not used in practice and require image reconstruction. Coded Aperture Imaging (CAI) uses a multi-pinhole collimator to combine the high sensitivity of parallel-hole collimators with the excellent resolution and magnification properties of pinhole collimators. The goal of this presentation is to demonstrate and discuss the potential and challenges of CAI.

Methods

After developing "ConvSim", a fast simulation framework for CAI with emphasis on near-field effects, a Convolutional Neural Network (CNN) was trained and compared to analytical reconstruction methods. Furthermore, 3D imaging with analytical reconstruction methods was investigated by generating 3D reconstructions from a sequence of planar reconstructions where the in-focus plane was incrementally shifted from 20mm to 100mm. The 3D reconstructions were used to determine the axial resolution and the localization accuracy for point-like sources that we captured with our experimental IGC.

Results

For planar reconstruction, the CNN approach produced images of superior quality compared to the analytical methods. The study of analytical methods for 3D imaging showed a decreasing axial resolution from 7.5mm to 34.8mm over the range of 20-100mm. The localization accuracy for point-like sources was found to be comparable to stereo cameras with an average accuracy of 2.64mm. However, we have shown that there is currently no reconstruction method that is fast, accurate, and precise. Further investigation are needed to determine the influence of the source size and the number of photons collected on the reconstruction quality and consequently on the localization accuracy. The datasets are publicly available at https://github.com/tomeiss.

Conclusion

Before IGCs can fully benefit from the high sensitivity and superior spatial resolution of coded aperture collimators and in order to exploit the full potential of 3D imaging, the challenges described above need to be addressed and possible solutions and limitations investigated.

Keywords: gamma imaging, coded aperture, image reconstruction, machine learning

Special Session:

Exzellenzcluster Hearing4all

Mechanical-dynamic properties of 3D-printed human middle-ear ligaments

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Introduction

Nowadays, human temporal bone preparations are commonly used as models in hearing research for testing implants and validating numerical results, as their properties are close to those of living humans. Measurements on cadaveric preparations are affected by large measurement uncertainties, which is why the use of technical models as reproducible test environments has significant advantages. Various research groups have pursued this goal, but so far, no adequate model of the middle ear has been achieved because the mechanical-dynamic properties of the ligaments cannot be realised with conventional 3D-printing materials. This is because those materials with a sufficiently low Young's modulus exhibit excessively damped material behaviour, and sufficiently damped material behaviour is associated with an excessively high Young's modulus. The aim of the present work is to develop a multi-material system using additive manufacturing, consisting of different proportions of photopolymer materials and whose dynamic-mechanical property profile corresponds realistically to that of human ligaments.

Methods

Homogeneously distributed multi-material substrates are produced using 3D-Inkjet technology. The mechanical-dynamic properties of these test substrates are analysed by vibration measurements and tensile tests. By a voxel-based definition of systematically varied separate photopolymers, whose individual property profiles range from almost ideal elastic to highly viscous behaviour, is intended to achieve a dynamic-mechanical property profile analogous to that of human middle ear ligaments.

Results

It was found that the material properties of the multi-material substrates can be specifically influenced by the systematic addition of three photopolymers (Tissue Matrix, Vero, Agilus). Mechanical-dynamic properties very close to those of the biological system can be achieved. Densities of 1100 to 1180 kg/m³, Young's modulus of 0.1 to 25 MPa and Poisson's ratio of around 0.3 have been achived. Target values for human ligaments reported in the literature vary, with densities ranging from 1100 to 1200 kg/m³, Young's modulus from 0.05 to 21 MPa, damping ratio from 0.003 to 0.05, and Poisson's ratio of around 0.3.

Conclusion

The use of the 3D-Inkjet method to produce human ligaments enables a realistic representation of the linear, dynamic-mechanical properties. Multi-material printing allows up to eight materials to be processed simultaneously, opening up further possibilities in terms of non-linear properties. The technology offers the potential for further development of technical models of the middle-ear.

Special Session:

Ultrasound – Therapy

Design and implementation of 2D theranostic ultrasound transducers for combined therapy and 3D cavitation monitoring

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Introduction

With the evolving potential of therapeutic ultrasound as a treatment method for various medical conditions, the need for the reliable monitoring of therapy accompanying effects such as cavitation is growing simultaneously. While the use of separate transducers is a simple approach for the implementation of the cavitation monitoring of ultrasound therapy, the structural integration of receiving elements in the therapy probe offers several advantages (compactness, fixed co-registration). In our study, we present two in-house built therapy transducers with different geometries operating at different frequencies (1 MHz preclinical /480 kHz clinical), which are both combined with 32 receiving elements for the simultaneous 3D cavitation monitoring (passive acoustic mapping, PAM) using different design approaches.

Methods

The geometry of both PAM arrays was defined based on a simulation model (numerical Vokurka model), which was used to simulate cavitation signals for different element configurations. For a quantitative comparison of the different geometries, the full width at half maximum values (FWHM) and the localization error are extracted after reconstruction to 3D cavitation maps with the delay, multiply, sum and integrate algorithm. The PAM transducers were set-up according to the optimal geometries identified in our numerical simulation study.
For the preclinical therapy transducer at 1 MHz, we designed and built a 32-receiving element frame surrounding the transmit aperture (Rx at 4 MHz centre frequency, 1 mm element size). In case of the clinical transducer at 480 kHz, the integration into the existing aperture was realized through the substitution of transmitting elements by receiving ones (Rx at 1 MHz centre frequency, 2 mm element size).

Results

For the preclinical setup, the reconstructions yielded axial and lateral FWHM values of 9.98 and 0.30 mm, respectively (localization error 2.5 mm). The clinical setup with randomly distributed elements showed values of 11.50 mm for the axial and 1.58 mm for the lateral FWHM (localization error 0.9 mm). The larger point spread function size for the clinical setup results from the larger distance to the cavitation source in combination with the lower receiving centre frequency.

Conclusion

Both the integration of receiving elements in the transmitting aperture itself and the design of a receiving frame as add-on to existing therapy transducers were numerically validated for 3D passive acoustic mapping. The two setups described have been built in-house, with the experimental validation of 3D PAM still ongoing. While the manufacturing process for the integration of the receiving elements in the transmitting aperture is more challenging, the simulation results show that this approach potentially allows a more accurate localization of the cavitation source. The add-on frame on the other hand can be adapted for already existing therapy transducers, highlighting that both design approaches are valid options for 3D cavitation monitoring.

Cross beam focusing using matrix array transducers for improved neurostimulation

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Introduction

Ultrasound neurostimulation is a promising new technique for treatment of conditions such as Parkinsons or Essential Tremor, which can be a non-invasive alternative to established approaches such as deep brain stimulation. For achieving isotropic resolution, up to now only very complex systems involving conformal transducer arrays ("helmet-like") are used. Matrix-array transducers can typically provide high x- and y- resolution but have a significantly larger focus size in z-direction (along the acoustic axis of the array). Using different matrix arrays in a cross-beam setup allows overcoming theses challenges. In such a setup, the x/y- focus size is defined by the focusing capabilities of the matrix and the z-focus results from the overlap of both sound fields. However, using several fully populated matrix arrays will increase the number of required channels in the transducer driving electronics. Using sparse arrays, where similar focusing properties can be reached with a reduced channel count, therefore is a promising alternative for cross-beam approaches.

Methods

We recently presented a 256 channel system (MR-Instruments Inc, licensed by Fraunhofer IBMT) for ultrasound neurostimulation allowing 3D beam steering based on the usage of a circular shaped 256 element matrix array (500 kHz, 3 mm pitch). This system allows -3 dB focus sizes of 2.9 to 5.4 mm in lateral dimension and 15 to 58 mm in axial dimension (for on axis focusing distances between 40 and 100 mm). We modified this system for being able to drive two apertures (of 128 elements each) of two different matrix array transducers in a 90° cross beam configuration. For optimized focusing properties with a limited amount of channels/elements, we chose a random sparse array configuration based on a 3 mm cartesian grid.

Results

Our 128 element sparse array showed a lateral -3dB focus size of 4.8 mm, which is very close to that of the fully populated 256 element matrix having 4.2 mm of lateral focus size (focus depth 70 mm). First cross beam experiments were performed as well in a water tank, in which the ability of reducing the overall -3 dB focus area to approximately the size of the lateral focus of a single matrix is demonstrated (-3 dB focus of 9 mm in z, ~5 mm in x/y). These experimental results were supported by a simulation model of the cross-beam setup.

Conclusion

Sparse array transducers for neurostimulation were developed and showed comparable steering properties as fully populated arrays. First crossbeam measurements were successfully conducted and showed a reduction of the axial -3 dB focus size by a factor of 4 (focus depth 70 mm), therefore achieving almost isotropic focus dimensions. Our work shows how that an almost isotropic focus in an ultrasound neurostimulation setup can be achieved while maintaining a constant total channel (and element) count of 256 by using 2x 128 sparse array cross beam configuration instead of a fully populated 256 element matrix array.

Well plate sonication device for the ultrasound induced blood-brain barrier opening in vitro

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Introduction

The blood-brain barrier serves as a natural protection mechanism against harmful substances. When it comes to the effective treatment of brain related diseases however, this barrier poses a significant obstacle. Multiple approaches to overcome the blood-brain barrier have been evaluated in recent years. Ultrasound as a non-invasive treatment method allows the transient opening of the blood-brain barrier, as shown in multiple animal trials and first human trials.
To minimize animal experiments, efforts to bridge the gap between in vitro cell models and in vivo experiments are necessary. While several studies have shown the transient opening of blood-brain barrier cell models using single transducers, the influence of different acoustic parameters on the outcome is still not fully understood. In our study, we acoustically simulated and built a well plate sonication device allowing the parallel ultrasound-treatment of 12 in vitro blood-brain barrier cell models, providing a platform for extended parameter studies with high throughput.

Methods

To sonicate each well of the 12-well plate, 12 single element transducers were integrated into a customized housing. All transducers are driven simultaneously at a frequency of 268 kHz. To assess the pressure being applied on the in vitro model, the pressure distribution field within the 12-well plate was measured using a three-axis motion stage and a needle hydrophone. For a first proof of concept, we sonicated a human induced pluripotent stem cell (hiPS) based in-vitro blood-brain barrier model with a peak negative pressure of approximately 0.88 MPa (± 20%), which is within the pressure range applied in clinical studies (0.48 to 1.15 MPa). The integrity / opening of the barrier was assessed via the transendothelial electrical resistance (TEER) value, with 300 Ohm cm^2 being the threshold value for a tight barrier.

Results

While the values in the control group (no treatment and microbubbles only) remained well above the threshold, the TEER values of the ultrasound-treated barriers dropped below the 300 Ohm cm^2 threshold. Permeability measurements (with sodium fluorescein) confirmed the opening of the barrier. After the initial drop, the TEER values rose again above the threshold, suggesting a reversible opening effect.

Conclusion

Using our in-house developed well plate sonication device, we could show the successful opening of the blood-brain barrier model. Further experiments are planned to confirm the first proof of concept and to assess the influence of acoustic parameters (pressure, PRF, pulse length, …) on the outcome of the blood-brain barrier opening.

Special Session:

Medical and Industrial Exoskeletons

Exoworkathlon – a systematic study approach to understanding effectiveness of exoskeletons

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Introduction

Industrial exoskeletons have recently gained importance as ergonomic interventions for physically demanding work activities. The growing demand for exoskeletons is leading to a need for new knowledge on the effectiveness of these systems. The Exoworkathlon, as a prospective study approach, aims to assess exoskeletons in realistic use cases and evaluate them neutrally.

Methods

Different test scenarios (Parcours) were developed with experts from the corresponding industries for the standardized and realistic evaluation of industrial exoskeletons. The Parcours represent a real work-scenario abstractly. Till now, Parcours from Logistics, Automotive, Construction Work, and Welding have been developed. The subjects are young experts from the corresponding area. A working time of 1 hr is chosen to ensure that the Parcours are realistic and feasible. Each participant runs the corresponding Parcour twice - 1 hr with and 1 hr without an exoskeleton, with a break of at least 2 hrs to recover. The order of exoskeleton conditions is randomized, and the exoskeletons are randomly assigned to the subjects. The recommended assessment parameters are muscle activity, metabolics, subjective user feedback, and quality aspects.

Results

So far, 125 subjects have been tested on six Parcours with different assessments. While the questionnaire was always included, the other assessments could not always be carried out. The effort of the task during the activity is reduced both Parcour-specifically and across all Parcours. Muscle activity was recorded in 21 test subjects, and a reduction can also be seen here. The usability (SUS scale) is rated as “good” across all exoskeletons. The welding quality (n=41) can be significantly improved, and a trend towards quality improvement can also be seen in the drywall Parcour (n=9).

Conclusion

The data from the 125 test subjects show potential relief and quality improvement in certain use cases. In future, musculoskeletal modelling can be used for detailed biomechanical analysis and to detect possible side effects.

Advancements in Tendon-Driven Exosuits for Upper Limb Assistance

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Introduction

Exosuits represent a promising technology for upper limb assistance, offering innovative solutions to enhance motor function in individuals with neuromuscular impairments. These lightweight, ergonomic devices transmit forces via artificial tendons to assist or augment human limb movements, ensuring user comfort and compliance during daily living activities support. However, challenges persist in synchronizing exosuits with human motion and controlling interactions with the environment. Integration of computer vision, particularly object recognition algorithms, can aid in understanding surroundings and adjusting behavior in terms of assistance level promoting a symbiotic interaction between user and suit. We developed an algorithm utilizing computer vision to optimize the assistance level of an elbow exosuit, thereby reducing joint stress during interactions with objects.

Methods

Our control approach is based on a Convolutional Neural Network (CNN), trained on a dataset of 1500 images over 80 epochs, selecting the model with the lowest loss. Three objects—hammer, drill, cable spool—were chosen based on weight distribution (LW 0.1 Kg, MW 0.9 Kg, HW 1.8Kg), their weights and confidence levels streamed to an Arduino board for real-time control. The control structure, based on the "Dynamic Arm Module," provides electromechanical assistance tailored to the user's anthropometrics to counteract gravitational forces, while computer vision estimates object weights, adjusting assistance levels accordingly. A low-level admittance control adjusts motor velocity based on torque error obtained by comparing the force that the suit applies to the user and the reference torque of the model.

Results

Testing the algorithm on six participants under conditions "Exo Off" (motor disabled), "Vision Off" (exosuit active without taking in account external loads) and "Vision On" demonstrated accurate recognition of LW, MW, and HW objects, each achieving over 93.5% accuracy. Our approach offers symbiotic control, providing proportional assistance based on lifted weight. During "Vision Off," interaction torque remains constant, contrasting with "Vision On" where LW increases by 7%, MW by 60%, and HW by 120%. This variance directly impacts biceps muscle activity, showing a 32% EMG reduction for MW and HW in "Vision Off" versus 45% and 54% in "Vision On" compared to "Exo Off."

Conclusions

These promising results suggest potential applications, though further studies are needed to assess real-world variability and user motion strategies. In conclusion, tendon-driven exosuits hold significant potential in upper limb daily living assistance, offering innovative solutions for individuals with neuromuscular impairments. Integration of computer vision for adjusting assistance levels based on lifted weights enhances user comfort and reduces joint stress during object interactions, representing a promising step towards enhancing human-robot symbiosis in assistive technologies.

An Autonomous Assistive Device for Detecting and Correcting Pathological Movements in Daily Activities

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Introduction

Neurodegenerative diseases such as Ataxia or Parkinson's can significantly affect daily activities such as eating and drinking due to motor control impairments, including tremors or overshooting arm movements. Wearable assistive devices offer a promising solution to overcome these challenges. However, real-time estimation of corrective forces requires the detection and prediction of the intended and dysfunctional movement components. The research project aims to develop such a lightweight assistive device attached to the forearm capable of actively applying corrective forces to only suppress dysfunctional movement enabling the intended movement.

Methods

To achieve this goal, the arm trajectories during activities of daily living need to be predicted and divided into intended and dysfunctional movements with their corresponding forces. Our approach uses inertial sensors and video recordings with bandlimited multiple Fourier linear combiners to detect the intentional and pathological movement in real-time. On the other hand, we use a computationally efficient neuro-musculoskeletal arm model to quantify the human upper limb stiffness responses in different postures. Furthermore, we employ reinforcement learning (RL) to simulate realistic arm movements, accounting for noise, optimality principles, and various task requirements.

Results

Preliminary results show that we can reliably detect the frequency and amplitude of tremorous movement components. Our numerical arm model accurately predicts human upper limb impedance characteristics, closely matching experimental data. Furthermore, our initial results indicate that combining RL with a neuro-musculoskeletal arm model can replicate highly stereotypical arm-reaching movements, including straight hand trajectories, bell-shaped tangential velocity profiles, and triphasic muscle activation patterns.

Conclusion

In conclusion, we have shown the feasibility of detecting dysfunctional movement and predicting both voluntary actions and necessary corrective forces using our approach. In our future work, these predictions will be integrated into real-time estimation for assistive devices, with the ongoing development of an intelligent controller pipeline to integrate all components effectively.

Special Session:

Improvements in Patient Safety

A modified, miniaturized perfusion system allows rodent studies on ex-situ machine perfusion of donor hearts according to the clinical procedure

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Introduction

Ex situ machine perfusion (ESMP) is an emerging technology for cardiac allograft maintenance. However, ESMP of donor hearts is still under development and requires optimization for specific donor subpopulations, such as donors with circulatory death, donors with advanced age, and donations with distant procurement. Thus, respective research projects in basic science are needed. Nevertheless, large animal models are expensive, require more personnel and fewer genetically modified strains are available. Thus, we modified a commercially available non-miniaturized experimental rodent heart perfusion apparatus into a clinically comparable and relevant miniaturized ex-situ heart perfusion system.

Methods

A commercially available rodent heart perfusion apparatus was used as a basis. The apparatus was modified with commercially available (micro-centrifugal pump) and self-constructed components (minimized glas reservoir, addition of a second reservoir), and short small diameter tubing (tygon) recerculation lines according to the human ESMP system. The hearts were procured from male and female Lewis rats (N=40). Equivalently to the clinical procedure, the system was primed with the heparinized blood of the organ donor animal instead of physiologic buffer solutions. After cannulation of the ascending aorta, the hearts were perfused in an anterograde fashion and in a pressure-controlled mode. The investigations were reviewed and approved the appropriate institutional Ethical Committee for Animal Experimentation.

Results

Our ESMP system consisted of a micro-centrifugal pump, a heat exchanger, a hollow fiber membrane micro-oxygenator, and a myocardial microcirculation monitoring system. The total priming volume of the system was 14 ml. No additional blood from another animal was needed. All hearts were maintained for one hour. Pacing was performed when required. After maintenance perfusion, we evaluated the ventricular contractility of the hearts in an ejecting-working mode.

Conclusion

Clinically relevant research questions can be investigated and answered in a rodent model of ex-situ donor heart perfusion while exactly mimicking the clinical procedure.

The new extracorporeal membrane oxygenation system Colibrì: Case series

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Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly used for circulatory or pulmonary support not only in-hospital but also out-of-hospital. Small dimensions and a lightweight design are important, especially for out-of-hospital use but also for intra-hospital transportation of patients who require ECMO support. We share our first experience with the new Colibrì ECMO system.

Methods

From December 2022 to January 2023, we used the new Colibrì ECC system in six patients with cardiac or pulmonary failure.

Results

The Colibrì system was used in-hospital in six patients with post-cardiac surgery low output syndrome, respiratory failure due to influenza or acute respiratory distress syndrome, cardiogenic shock, pulmonary embolism, and failed weaning from cardiopulmonary bypass. The system was implanted in venovenous (VV) and venoarterial (VA) fashion in 3 patients, respectively. One patient received left-ventricular unloading. The ECMO run time was up to 13 days. We did not notice any complications according to the extracorporeal circulation system. No ECMO system changes were required.

Conclusion

We conclude from this first case series that the new Colibrì system is safe and effective for in-hospital ECMO indications. The small dimensions and lightweight design are very beneficial for the transportation of patients. A use in out-of-hospital situations should be considered.

Special Session:

Biosignal analysis in the control of medical robotic systems

AI-based detection of medical instruments as basis to control intra-operative robotics and ensure OR quality management

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Introduction

In times of labor and qualification shortage, increasing the efficiency in the operating room (OR) for patient safety plays a crucial role [1]. As part of the "NeXD-OR" program at HFU, investigating the rapid provision of medical instruments is essential for the success of critical surgical interventions. To manage this situation the assistance of systems based on artificial intelligence (AI) and robotics is envisioned. A first attempt shows a YOLO-based camera (You Only Look Once) system, whereas further development of an own neural network will be presented.

Methods

AI is utilized in image recognition to determine geometry, type, number, orientation, and position of medical instruments and consumables. An innovative application of AI is presented, particularly using the YOLO algorithm in combination with a camera system, to enable precise identification and distinguishing of surgical instruments.

Results

To this end a YOLO-based camera system allows real-time detection and classification of instruments, capturing not only the type of instrument but also its number, orientation, and position. Overall, the model shows a high accuracy (0.89) and robustness (.95) and is further trained against confusion in certain classes of identification (e.g. scissors / clamp). As a result, a voice-activated robotic system can provide the required instruments to the surgeon upon request, thereby optimizing the surgical workflow. Furthermore, the camera observation system serves as an intra- and post-operational quality assurance tool by documenting the location/whereabouts and usage of instruments. All results are presented with respect to a medical workflow and usability.

Conclusion

The presented AI approach provides significant contribution towards a prospective OR robotic assistance system controlled by an AI-based camera system, thus enabling efficient instrument provision to the surgeon. This technology may counteract OR labor shortage and enhances safety and efficiency in the OR. This contributes to transparency and traceability, augmenting compliance with necessary OR standards.

Literature:

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Joint Session

Joint Session mit GMDS: Synthetic and augmented image and biosignal data enhancing and enhanced by AI research

Mechanistic Modeling and Simulation of the ECG as an Enabling Technology for Machine Learning: Concepts, Datasets, and Real-World Performance

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Machine learning in medicine is often hindered by limited availability of large, high-quality datasets. Recently, synthetic ECGs were used to enrich sparse clinical data or even replace them completely during training of machine learning approaches leading to improved performance on real-world clinical test data.
We introduce the concept of computational modeling & simulation of organ systems in the human body using the example of cardiac electrophysiology and highlight how simulation spaces can be augmented in a biologically consistent way. This scalable and well controlled research environment allows for the generation of almost arbitrary large, high-fidelity, well-labeled datasets such as the publicly available MedalCare-XL dataset.
Applications comprise the enrichment of clinical data in so-called hybrid datasets that were used with ECG data for identifying subtypes of atrial flutter and for diagnosing left atrial enlargement. Going further, such synthetic datasets can also be used as the sole resource during training and then evaluated on clinical data eventually. We will show examples for the prediction of the acute success of pulmonary vein isolation to treat atrial fibrillation and for localizing the origin of ventricular extrasystoles from body surface recordings to inform clinical procedure planning.
In conclusion, we present how mechanistic and data-driven modeling can synergistically complement each other and how simulation-based approaches can help to overcome current challenges in machine learning for medicine.

Creating Synthetic Long Term Coherent ECGs with Latent Diffusion Models

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Introduction

Following the introduction of products like DALLE and ChatGPT, generative AI models have demonstrated considerable capabilities in the areas of Natural Language and Image Processing. As access to high quality and specific biosignal data remains one of the limiting factors for the development of new methods, especially in the context of datasets for machine learning approaches, we investigated whether generative AI architectures could be employed to generate or augment such datasets.

Methods

We designed and implemented a state of the art latent diffusion model. The autoencoder was implemented as a VQ-VAE. The diffusion model was implemented as a Denoising Diffusion Implicit Model. We tested the generative capabilities of the latent diffusion model for generating segments of up to 320 seconds of ECG data. We quantitavely investigated whether individual generated biosignals followed similar long term dynamics than the training samples. Additionally, we compared a generated dataset to the training set to reveal how the distribution of parameters might differ between those sets. The comparison between training and generated set was done to better understand how generative models learn and reproduce the underlying data distributions. The ECG data was taken from the Charité Datawarehouse, an inhouse database of Charité patients.

Results

The diffusion model exhibits a high propensity for generating coherent, plausible looking biosignals. We explored long term behaviour via Heart-Rate-Variability (HRV). HRV values of individual, generated ECGs generally fell within the values encountered during the training process. However, the distribution of HRV parameters of the whole training set did not match the distribution of HRV parameters of a generated set of the same size, hinting at a fundamental flaw of diffusion models capability to capture the underlying data distribution.
The removal of noise and artefacts from real ECGs is possible via inpainting for short segments of a few seconds. Longer segments often displayed a different heart rate compared to the rest of the ECG.

Conclusion

Dataset augmentation via (conditional) biosignal generation is possible with the Latent Diffusion Model designed in this research. Individual generated Biosignals were generally plausible and coherent. However, since the distribution of HRV parameters differed between the generated set and the training set, the model should not be used as a surrogate sampler to augment a training set. Inpainting could be used as a way to clean datasets containing artefacts, but further research is necessary to ensure coherency of the inpainted sections.

Generative models for medical EEG time series data - applications, challenges, and opportunities

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Introduction

Electroencephalography (EEG) offers the opportunity to derive robust biomarkers for diagnosis and prediction of treatment response for psychiatric diseases such as major depressive disorder (MDD) or attention deficit disorder (ADD) [1]. Generative adversarial networks (GAN) form a class of generative machine learning models capable of producing data with desired characteristics by comparison with data processing said characteristics [2].

Methods

GANs can be utilized to create EEG time-series data from random noise to boost the training data set e.g. for a diagnostic MDD classifier [3]. Beyond this direct usage, synthetic EEG data also offers the opportunity to create public datasets for developing clinical applications without privacy concerns. Instead of creating synthetic data from scratch, GANs can also be used for pre-processing tasks such as artefact removal [4] from noisy EEG data.

Results

Some characteristics of the EEG signal can be faithfully reproduced by GANs, some cannot yet, which becomes especially apparent in the frequency domain [3].

Conclusion

In order to further the development of models for synthetic EEG data, however, suitable evaluation metrics are still needed. This work demonstrates the current state of what GANs can achieve with EEG signals exemplarily on selected use cases. It furthermore pinpoints their shortcomings when it comes to EEG data. I conclude with a discussion of the next steps to further this field.

Joint Session

Tissue Discrimination/Cancer Detection via Optical Sensors

Fiber-based optical coherence tomography in pituitary gland and adenoma tissue: preliminary results of an in vitro study in paraffin-embedded tissue samples

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Introduction

Fiber-based common path optical coherence tomography (CP-OCT) may find its application as a tissue sensitive guidance tool in pituitary adenoma resection. In the envisioned application, the pituitary adenoma is aspirated and characterized in real-time within the suction tool using (one dimensional) CP-OCT A-scans. To obtain a robust and reliable machine learning (ML) model for tissue discrimination, we recorded CP-OCT data on healthy pituitary gland as well as adenoma tissue embedded in paraffin. In this report, we present the results of thirty paraffin-embedded tissue samples.

Methods

To obtain enough training material for the data model, a two-dimensional matrix of equidistant 100 x 100 OCT A-scans was recorded for each paraffin-embedded tissue sample. Care was taken to set the minimum spacing between A-scans significantly higher than the spatial resolution of the applied CP-OCT device, to record different sample positions. For every A-scan, the following parameters were calculated: attenuation coefficient, residuum, intensity distribution of the backscattered light, and spectral properties. After preprocessing and scaling steps, various clustering methods were applied on these parameters to categorize the A-scans on different sample spots.

Results

En-face images based on different extracted A-scan parameters qualitatively show the varying ability of the parameters to discriminate between sample regions. The clustering methods detect multiple categories of sample areas. Blood within the tissue samples may lead to masking of tissue differences.

Conclusion

The data of thirty paraffin-embedded tissue samples show promising results in discriminating adenoma from healthy pituitary gland tissue by using in vivo OCT A-scans. The availability of haematoxylin-eosin-stained histological thin sections of the same samples later in the study will allow the creation of more accurate supervised machine learning models for the targeted application of guided pituitary adenoma resection.

Focus Session

Focus Session Sleep

Diffusion-based conditional ECG generation with structured state space models

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Introduction

Generating synthetic data is a promising solution for addressing privacy concerns associated with the distribution of sensitive health data. Recently, diffusion models have become the new standard for generating various types of data, while structured state space models have emerged as a powerful approach for capturing long-term dependencies in time series data.

Methods

Our proposed solution, the Structured State-Space Diffusion ECG Model (SSSD-ECG), combines these two technologies to generate synthetic 12-lead electrocardiograms (ECGs) based on over 70 ECG statements. In the absence of reliable class-conditional baselines, we also introduce conditional variants of two state-of-the-art unconditional generative models: WaveGAN* and Pulse2Pulse. We conducted a comprehensive evaluation of the generated samples by assessing pre-trained classifiers on the synthetic data and measuring the performance of a classifier trained solely on synthetic data.

Results

SSSD-ECG outperformed its GAN-based competitors in classification performance improvement when training exclusively on synthetic data, achieving an AUROC of 0.84 compared to 0.58 for WaveGAN* and 0.59 for Pulse2Pulse. The effectiveness of our approach was further validated through conditional class interpolation and a clinical Turing test. In the Turing test, SSSD-ECG synthetic samples improved diagnostic accuracy compared to real data (68% vs. 45%), while still maintaining the credibility of real samples across a wide range of conditions (77% of synthetic samples were believed to be real).

Conclusion

Through rigorous evaluation, SSSD-ECG demonstrated superior performance compared to existing GAN-based approaches, effectively producing high-quality ECG samples across various conditions. This approach shows significant promise in addressing privacy concerns in health data distribution while preserving data utility

Measuring of the sleep profile in the home environment - clinical opportunities and challenges of ambulatory EEG, smart devices, apps and more

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Introduction

According to German medical guidelines ("S3-Leitlinie") for treating slep disorders, measuring of sleep pattern is conducted either in a hospital by polysomnography (PSG) or in the home environment by sleep logs and actigraphy. PSG is considered to be gold standard however, it requires high resources and the capacities to perform are limited which result in long waiting lists. In contrast to PSG, the other mentioned ambulatory techniques are not able to record sleep profiles in a objective way. These issues drive motivation for developing, clinically testing, and validating new ambulatory methods of measuring sleep profiles objectively in an outpatient setting.

Methods

Recent developments such as self-applicable EEG based medical proved devices can objectively measure sleep profiles similar to those obtained by traditional PSG. Current studies in sleep labs use such devices to investigate different aspects of sleep. For example, differences in accuracy between home and lab measurement, variability of sleep pattern across several days, and capability of phenotyping of sleep disorders. Furthermore, much research is focusing on the use of surrogate parameters of sleep.

Results

Wearables such as rings, smartwatches, mattress sensors, bedside radar devices, and even smartphone applications using built-in sensors are more recent examples of new technology that can estimate sleep profiles. Such devices are initially sold as consumer products and later, in collaborations with scientists and clinicians, many try to transition to a clinically validated diagnostic device via validation research, subsequently resulting in a medically certified product. Typically, these validation studies have a specific target population like insomnia, sleep-wake-rhythm disorders, and sleep apnoea depending on the device capability. This will lead to faster and more tailored specific treatment for patients with sleep disorders, to long-term monitor clinical outcomes, but also to identify limitations and pitfalls when it should come to clinical practice. For instance, a trade-off has to be made by the potential of capturing data in a realistic setting at home and over longer periods, e.g. 24/7 on one hand and the risk of lowered quality of data by reduced sensor sets and non-standardised measurement environments on the other hand.

Conclusion

New developments of the measurement in the home environment have the capability to retrieve sleep profiles in a less-obtrusive way, to produce more realistic results, and to reduce the number of undiagnosed individuals. Therefore, they could become a remarkable step for enhancing the clinical management of people suffering from sleep disorders.

Characterization of cardiocerebral effects during sleep arousals by means of graph analysis

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Introduction

Arousals are a crucial aspect of human sleep and are linked to sleep-related disorders. Although it is known that arousal is associated with an interaction between the cardiovascular and the cerebral system, the exact underlying functions are not fully understood. Current research indicates a functional coupling between the autonomic and the central nervous system. We investigated this behavior by means of graph analysis to enhance the understanding of the underlying regulatory mechanisms of cardio-cerebral effects influenced by arousals.

Methods

We analyzed polysomnography recordings from 2,651 participants in the Sleep Heart Health Study by extracting electroencephalography band power as measure of activity in the central nervous system, and heart rate variability and QT interval variability as measures of activity in the autonomic nervous system. Transfer entropy (TE) was used to characterize the coupling behavior between central and autonomic nervous system measures represented as graph edges. We introduced the influence factor ρ as the fraction of TE after to before an arousal to quantify the bidirectional change in TE. To visualize the effects of arousal and sleep stages, we utilized graph analysis.

Results

Our results show a significant increase in TE from the central to the autonomic nervous system by 1.23% ($p < 0.05$) due to arousals. At the same time, TE from the autonomic to the central nervous system decreased by 1.16% ($p < 0.05$). Observable changes in graphs were found across all sleep stages, with deep sleep showing the largest difference of ρ between both directions by 15.6%. Consequently, we conclude that arousal from sleep provokes a cardiovascular response primarily through the central, instead of vice versa.

Conclusion

In conclusion, arousals can influence cardiocerebral regulation as a central nervous activation. Further investigations will examine the effects of sex, age, and disease on cardiocerebral effects using graph theory methods for improved quantitative interpretation.

Classification of apnoea events with artificial intelligence based on a segmentation technique

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Introduction

A considerable corpus of scientific literature exists on the subject of the recognition of automatic sleep apnoea. However, most such scientific works do not have a method for calculating the exact duration of apnoea events or the Apnoea-Hypopnoea Index (AHI). This work presents the development and validation of an artificial intelligence (AI) model (concretely a convolutional network architecture known as U-Net) using a segmentation technique through an engineering approach for calculating sleep apnoea events and AHI.

Methods

For calculating apnoea events, we used data from a well-known study that collected polysomnographic data: Sleep Heart Health Study (SHHS). 641 patients were used for the development and evaluation of the model. During the development of the AI model, as little preprocessing as possible was applied to the data (removing large artifacts and standardization). After this stage, the model was fed with such data. The study employed a set of three signals, comprising oxygen saturation (SpO2), heart rate (HR), and respiratory abdominal effort (AbdoRes) for each patient. The data collection frequency was 1 Hz, and the recordings were 10 hours long. Therefore, we used 36000 datapoints as an input. The data for the training was split into 3 subsets (60% for training, 30% for validation, and 10% for testing). For the AHI calculation, the duration of the apnoea events is first calculated, verified to be longer than 10 seconds and counted. The final sum is divided by the total sleep time or in this case, the total recording time.

Results

Following the training and evaluation of the AI model, the model demonstrated 85% accuracy, 84% sensitivity, and 84% precision on the test set. It is important to remember that this is a binary classification (the labels are 0s for no-apnea events and 1s for apnea events) and that there were more examples of non-apnoea than apnoea events. However, this fact is somewhat difficult to counter as we need the signal as a whole to be able to study the different apnoea events and the subsequent AHI calculation. The classification is done on a second-by-second basis.

Conclusion

From the point of view of accuracy, sensitivity or specificity, a overall result of approximately 85% was achieved, making the use of this method promising. As a future step, an artificial intelligence model will be developed fo rmulticlassification task to distinguish different types of apnoea.