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Special Session:
Roadmap DiGA DiPA and beyond -
A success story?
DiGA, DiPA, Telemedicine on the rise - What are potential hurdles for further digitalization of the German healthcare market

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The BMG’s digitization strategy for healthcare and nursing already includes numerous measures to change the regulatory framework and the prerequisites for successful strategy implementation. Is this sufficient? What is still missing with regard to the successful establishment of DiGA, DiPA and telemedicine in Germany? This question will be tackled by the talk.

In Germany, the digitization of healthcare continues to gain momentum. However, the level of digitization in the German healthcare sector is still very low, both in an international comparison and in a comparison of sectors within Germany. Despite major political efforts to further advance the digitization of medicine, certain hurdles appear to be severely hampering the digitization process. The fast-track procedure for digital health applications (DiGA) under Section 139e of the German Social Code, Book V (SGB V) has created access for digital therapies to the world’s largest interconnected healthcare market. But the acceptance for DiGA’s on both the practitioners and patients side is still rather low. And many hurdles to overcome. Discussions on that are ongoing since implementation of DiGA scheme.

The procedure for digital care applications (DiPA) according to § 78a SGB XI recently paved the way for the use of digital care support systems in Germany. There is no experience yet, but many discussions ongoing about the hurdles like the low reimbursed price or the need to provide full evidence to have a successful market implementation scheme for digital care applications.

Telemedicine, what was excluded from the DiGA reimbursement scheme, is also on the rise. Dedicated reimbursement programmes start.

So is all good and Germany is on its way to digital healthcare, especially in the outpatient sector? There are definitely still many hurdles that need to be overcome. The presentation provides an insight and sheds light on what still needs change for this to happen.
Special Session:
DiGA DiPA Development
Application Readiness: a new framework for digital therapeutics, based on the example of the German DiGA

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Introduction
One major goal during the development of health technology is to reach compliance with regulatory procedures such as the Medical Device Regulation (MDR). Thus, the Technology Readiness Level (TRL) framework has often been used to assess the development maturity. However, with the rise of DiGA, more patient-centred application readiness frameworks are required. Whereas the MDR defines technology aspects of readiness, DiGAs being integrated into healthcare procedures and reimbursement also must acknowledge other key aspects including social acceptance, clinical effectiveness, as well as costs/pricing related aspects. Here, existing regulatory procedures focusing mainly on TRL are not sufficient for DiGAs to successfully address patients’ needs and reach healthcare provider (HCP) acceptance. Consequently, a comprehensive assessment framework addressing all of these key aspects to assess application readiness of DiGAs is still missing.

Methods
Within a funded translational research project more than 20 DiGA innovators received guidance on how to comply with the German Digital Health Care Act to be approved as DiGA. First, based on application readiness workshops with single innovators a comprehensive requirement assessment was undertaken. The requirements were grouped into different readiness categories. In a second step, these categories were mapped against existing frameworks including the Model for Assessment of Telemedicine (MAST), the Health Technology Assessment (HTA) Core Model and the Guidance and Impact Tracking System (GAITS).

Results
We propose a novel comprehensive assessment framework for DiGA including six key categories of application readiness: Society, Technology, Integrated Healthcare, Evidence, Health Economy and Business. Distinct differences between focus on different key aspect categories were observed, especially addressing reimbursement and business readiness aspects.

Conclusion
In the future, this framework can be used as a guiding roadmap for DiGA innovators and accelerators, identifying barriers and optimizing DiGA implementation. Furthermore, it can increase patient and HCP acceptance by providing an ideal use case for digital transformation in medicine.
Special Session:
Cardiac Insufficiency
Impact of effective refractory period personalization on prediction of atrial fibrillation vulnerability

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Introduction
The effective refractory period (ERP) is one of the main electrophysiological properties governing arrhythmia maintenance. However, ERP personalization is rarely considered when creating patient-specific computer models of the atria. State-of-the-art personalized models usually assume heterogeneous ERP based on population-level data for different anatomical regions. We evaluated the impact of incorporating patient-specific clinical ERP measurements when creating in silico personalized models to predict vulnerability to atrial fibrillation (AF).

Methods
Clinical ERP measurements were obtained from three patients from multiple locations in the atria. The protocol for ERP identification consisted of trains of 7 S1 stimuli with a basic cycle length of 500 ms followed by an S2 stimulus with a coupling interval between 300 and 200 ms in decrements of 10 ms until loss of capture. The atrial geometries from the electroanatomical mapping system were used to generate personalized atrial models. To reproduce patient-specific ERP, the established Courtemanche cellular model was gradually reparameterized from control conditions to a setup representing AF-induced remodeling. Four different approaches were studied: (1) non-personalized homogeneous; (2) non-personalized heterogeneous; (3) personalized with discrete regions; and (4) personalized with continuous ERP distribution. Arrhythmia vulnerability was assessed by virtual S1S2 pacing from multiple locations. The number of inducing points was determined for each of the four approaches.

Results
The patient with the lowest mean ERP had the highest number of inducing points. Modeling regions of ERP was the most arrhythmogenic scenario due to abrupt ERP changes. The non-personalized approaches had lower inducibility when compared to the personalized ones, thus reflecting lower vulnerability for AF.

Conclusion
The incorporation of patient-specific ERP values has an impact on the assessment of AF vulnerability. The type of personalization affects the likelihood of AF inducibility. Larger cohorts need to follow to demonstrate the role of incorporating clinical patient-specific ERP values into personalized models for predicting AF vulnerability.
Conceptualizing a pipeline to map German clinical reports to SNOMED-CT to facilitate heart failure prediction via clinical decision support systems

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Introduction
Clinical decision support systems (CDSS) could assist physicians in streamlining and improving diagnostic processes of patients with particularly complex diseases, such as heart failure. But making knowledge usable from patient data, such as clinical reports with CDSS poses major challenges due to semantic ambiguity. While existing approaches address this problem by mapping English clinical reports to the Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT), similar approaches in other languages such as German are lacking. Therefore, in the scope of this study, we conceptualize a resource-efficient SNOMED-CT concept extraction and validation pipeline, which leverages natural language models for the translation and processing of German clinical reports.

Methods
We analyzed heart failure patient data in form of German clinical reports to identify challenges of developing a mapping pipeline. Problems were detected regarding medical abbreviations, synonyms, and the language barrier when mapping German text to English SNOMED-CT concepts due to the lack of a German SNOMED-CT version. As a solution, we explored abbreviation dictionaries, synonym mapping via the SNOMED-CT structure itself, and existing term-based approaches such as Medcat and MetaMap. Additionally, we investigated leveraging language models to translate the clinical reports into English and to capture semantics for the SNOMED-CT mapping via named entity recognition through zero-shot classification with similarity-based approaches.

Results
First German clinical reports are successfully mapped to SNOMED-CT concepts via a Bidirectional Encoder Representations from Transformers (BERT)-based cosine similarity approach. Leveraging pre-trained biomedical language models yields the potential to extract SNOMED-CT concepts without requiring annotated datasets for training purposes. Evaluating resulting mappings by clinicians poses a resource-efficient validation pipeline to continuously improve the mapping performance.

Conclusion
Automatic mapping of free-text clinical reports to validated SNOMED-CT concepts opens up opportunities for downstream analysis tasks. Zero-shot classification with biomedical language models seems to be a promising tool to improve patient health with clinical decision support systems.
Special Session:
Terahertz in Medicine
Terahertz passive wireless biosensors based on photonic crystals for environmental monitoring

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Introduction
Remote sensors for environmental monitoring can play an important role in pathogen detection in the future. The development of remote sensors is complicated by various requirements such as high sensitivity, long reading range, compactness, and low cost. Electromagnetic (EM) sensors have the advantage that they can use the same radiation for sensing, communication, and localization. Among various EM sensors, terahertz (THz) photonic crystals (PhC) can achieve high sensitivity and long communication range simultaneously.

Methods
The proposed remote sensor consists of a PhC resonator for sensing and a dielectric rod antenna (DRA) for efficient coupling from the free-space. Pathogens can be identified and quantified by a frequency shift of the resonance. The signal from the resonator is radiated from the DRA and can be extracted by a read-out device and post-processing steps. The PhC chip is fabricated with alumina using lithography-based ceramic manufacturing technique and characterized using a vector network analyzer connected to a horn antenna. The chip is placed in front of the horn antenna at a distance of 0.5 m. 1.5 µL of different concentrations of protein solution as a mock-up for the pathogen is pipetted onto the resonator.

Results
The resonance frequency can be wirelessly detected with a high signal-noise-ratio. The dried protein leads to a resonance shift. The resonance shift is linearly related to the protein concentration with a slope of 5.2 MHz µL µg⁻¹.

Conclusion
The proposed PhC chip can detect biomolecules with long range wirelessly. In addition, the proposed chip has the advantage of being non-electronic, having a long lifetime, and being suitable for harsh environments.
Body Motion detection using epidermal electronic graphene patches

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Introduction
Rehabilitation aiming at patient mobilization often requires mechanical guidance, using equipment such as motorized exoskeletons or prosthetics. The state of the art enables this using complicated setups, where sensors are a vital part of the human machine interface. Yet, as typically one sensor is attached to one cable, depending on the complexity of the system, this has strong limitations in terms of errors, interference and patient comfort. Epidermal electronics is a potential solution, conforming directly to the surface of the skin and capable of integrating a multitude of sensors without negatively impacting patient comfort. Yet, despite all its promise, real world applications have eluded epidermal electronics so far, due to Young’s modulus, silicon front end and substrate breathability challenges.

Methods
Here, we introduce a concept, which completely rethinks epidermal electronics to address above issues, and to enable passive, wireless exoskeleton or prosthetics control. Our approach makes use of the unique THz properties of Graphene, which are tuneable by electronic gating, such as by muscle induced skin surface potential variation, enabling the efficient control of THz reflection and absorption. This makes passive and wireless epidermal electronics possible, relying only on an external THz transceiver, e.g. exoskeleton or prosthetic integrated, which measures muscle movement in reflection from a graphene based passive and chipless epidermal electronic matrix.

Results
A proof of principle of this concept will be demonstrated, using a Reconfigurable Intelligent Surface (RIS) based on Al / AlOx / Graphene / Au stack, where the Au electrode features graphene windows, allowing THz reflection measurements in dependence of the potential difference between the two electrodes. This is evaluated in the 500GHz to 3THz range, using a TDS system with a spectral range \textgreater 6 THz and a single shot dynamic range of up to 60dB.

Conclusion
By controlling the skin surface potential dependent THz absorption and reflection of Graphene, a novel chipless and passive epidermal electronics concept becomes feasible, for which as a proof of principle is demonstrated here using a gateable RIS.
Towards muscle sensing by a non-contact optical system using photogrammetry

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The measurement and analysis of muscle activity has enormous significance for patients suffering from stroke or other neurological disease who run through rehabilitation. Although the control of assistance and rehabilitation systems like prostheses and exoskeletons depends on it. This is made possible primarily by body-worn measurement systems such as the electromyogram, which provides a precise output of the electrical activity of the measured muscle units. The problem with established systems is that the patient is impaired by the bulky, often wired systems.

Based on the assumption that muscle activity causes skin deformations, a non-contact camera-based method is developed that can capture multiple images of the skin surface of a preferred body part. By using a photogrammetry tool and computing a 3D model of the body part, time-varying deformations can be represented that can be attributed to muscle activity. To do this, a 3D printer and tripod were used to create a camera mount that can vary in height and also change orientation. For the camera system itself, the Raspberry Pi Camera Module 3 Wide with an image resolution of 12 megapixels was selected according to specially defined evaluation criteria.

The first images showed promising results in terms of simultaneous recording and transmission of images to a central computer.

The next step is to finalize the measurement system. Afterwards, the photogrammetric part can start to enable the measurement of muscle activity. In the future, this stand-alone system will serve as ground truth for a contactless THz-based system to be developed in the terahertz.NRW initiative. The envisioned THz-based approach for muscle sensing will enable reflectance measurements with a THz beam directly on the skin surface. Since skin deformation also plays a significant role here, it makes sense to include a reference system such as the camera system to properly evaluate the results.
Terahertz – based non-contact vital sign measurements

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Introduction
Vital signs are essential indicators of a person’s physiological status and overall health. Regular monitoring of vital signs enables early detection of health issues, guides treatment decisions, and aids in assessing the effectiveness of interventions. Conventional methods have the disadvantage of being contact-based, which leads to low comfort when worn especially for people with sensitive skin. In recent years, terahertz technology has emerged as a promising candidate for contactless vital sign measurement. We are presenting an overview of our latest research that investigates the feasibility and accuracy of using terahertz technology for assessing vital signs without contact.

Methods
Our approach to non-contact measurement uses terahertz-based reflection measurements at 230 - 320 GHz. Terahertz reflection measurements give the possibility of evaluating accurate distances. That can be used to determine heart rate and respiration rate, as the heart beats, the blood flow induces minute movements of the body, including the chest, and the skin. These movements can be measured by the system.

Similarly, during respiration, the expansion and contraction of the chest result in movements that can be detected by the measurement system. By analyzing the resulting signals, the respiratory rate can be calculated.

Results
We successfully determined and evaluated the heart rate and respiration rate in clinical and care environment. In particular, the use of neural networks allows to detect critical conditions and changes over time.

Conclusion
Our approach highlights the potential of terahertz technology for non-invasive and contactless measurement of vital signs. The results indicate that terahertz-based-systems can measure more accurately than classical radar-systems. They can detect and monitor changes in heart rate and respiratory rate. Furthermore it gives the opportunity to be miniaturized in future due to the higher frequency. By using artificial intelligence, critical conditions can be detected and changes over time can be analyzed.
Special Session:

Magnetoelectric Sensor Systems for Biomedical Applications
Surface acoustic wave magnetic field sensors

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Introduction
Surface acoustic wave (SAW) sensors are widely used in medical technology, e.g. for the analysis of microfluids. In recent years it has been shown that SAW sensors can also detect low magnetic fields [1]. They reach a limit of detection (LOD) below 100 pT/Hz for a frequency range between 1 Hz and 10 kHz. Therefore, they are promising for magnetic field assisted medical therapy such as deep brain stimulation.

Methods
The SAW sensor excites an acoustic wave at interdigital transducers (IDT) on a piezoelectric substrate. A wave guiding layer confines the wave to the surface. The IDTs are arranged in a delay line, with a magnetostrictive sensing element located in between. A magnetic field generates a phase change in the SAW via the $\Delta E$ effect - change of elastic properties as a function of magnetization - in the sensing layer. For sensor fabrication, a ST-cut quartz substrate is coated with gold IDTs and amorphous SiO\textsubscript{2} as a wave guiding layer. As a magnetic sensing layer amorphous FeCoSiB is sputtered by PVD on top. The sensitivity is determined by a Zurich Instruments UHFLI lock-in amplifier via a dynamic phase detection. Soft magnetic ribbons (Vitrovac 602SX) are used as flux concentrators, yielding a sensor size of 1.5 cm x 3.5 cm.

Results
The state-of-the-art magnetic film deposition yielding in a high sensitivity is discussed. The dominant noise sources are found to be magnetically induced 1/f noise at lower frequencies and a constant thermal noise at higher frequencies. We show that flux concentrators can be used to increase the sensitivity to 7500°/mT at the expense of spatial resolution. The limit of detection is 15 pT/Hz at 10 Hz.

Conclusion
The use of flux concentrators for magnetic sensing with SAW sensors results in 3 times greater sensitivity and 2 times smaller LOD.

Magnetomyography with Optically Pumped Magnetometers – Table-top Magnetic Shield versus Magnetically Shielded Room

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Introduction
In clinical neurophysiology the measurement of electrical potential differences with needle or surface electrodes is well established to assess functional processes in the musculature. Needle-electromyography (n-EMG) is the daily used gold-standard but is invasive and painful. Since the underlying processes are electrodynamic, recording the biomagnetic fields (magnetomyography, MMG) poses an alternative measurement option, which might be superior to surface electromyography (EMG) and potentially partially replace invasive n-EMG [1,2]. Here, optically pumped magnetometers (OPMs) enable a new level of noninvasive biomagnetic measurements in terms of flexibility, spatial sampling density and proximity to the respective field source. While biomagnetic measurements are typically performed in magnetically shielded rooms, the shield dimensions with miniaturized OPMs are determined by the object to be measured [3].

Methods
We have measured the magnetic activity of the muscle abductor digiti minimi (ADM) after electric stimulation of the ulnar nerve with commercial zero-field OPMs inside PTB’s heavily shielded room (BMSR-2) as well as inside a four-layer table-top cylindrical magnetic shield, open on both ends.

Results
We compare the results of both measurements and discuss the pros and cons of both measurement conditions. BMSR-2, with low residual field and gradients, provides unique conditions to record undisturbed signals. In contrast, the table-top shield provides an inner volume that is shielded well enough to operate zero-field OPMs but disturbances from external fields are present and need to be suppressed by filtering and can be reduced further by averaging.

Conclusion
Our results demonstrate that OPM-MMG does not necessarily require a magnetically shielded room, since e.g. limb muscles can be surrounded by a small, table-top magnetic shield. Therefore, compact mobile systems are favorable, in terms of both costs and space required, paving the way for biomagnetic measurements in future studies and finally in daily clinical routine. Limitations still arise from the bandwidth of the employed OPMs, which are sensitive up to 500 Hz, while to fully substitute EMG a bandwidth of at least a few kHz would be needed. Additionally, further medical validation of MMG is required.

[3] Iwata et al., Biomedical Engineering, 67, 333 (2022)
Quantitative Evaluation of Magnetic Nanoparticles for Bio-imaging by Magnetoelectric Thin-Film Sensor

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Introduction
Magnetic particle mapping (MPM) is a promising non-invasive bio-imaging method for medical applications. However, the practical challenges, such as the sensor's behavior in unshielded clinical environments, the limit-of-detection (LOD), and the sensitivity level, require attention. This study investigates the feasibility of using thin-film magnetoelectric (ME) sensors for detecting nanoparticles within a desired distance range.

Methods
The necessary conditions for nanoparticle detection and the behavior of the ME sensor were assessed via Magnetic Particle Spectroscopy (MPS) and numerical simulation, respectively. The third harmonic response of various nanoparticle types was studied within a magnetic field range. To evaluate the proposed method, a mini-lab MPM setup was developed. A special lowpass filter was designed and utilized to generate a mono-frequency signal. A low-noise embedded charge amplifier enhanced the ME sensor output and signal-to-noise ratio. The concentration detection limit was investigated by analyzing the nanoparticle response. The optimum applied field amplitude was chosen based on the total harmonic distortion for the third harmonic response of nanoparticles. The sensor's nonlinearity behavior was studied by numerical simulation.

Results
A linear relationship between the applied excitation field and harmonic response can be seen in the MPS experimental results. However, generating a higher magnetic field with a pure signal in practical measurements is found to be a challenging task. The minimum value for quantitatively assessing the MPN concentration is restricted by different parameters, such as the measured distance, LOD, and a linear Input-Output-Amplitude-Relation. According to the simulation results, the nonlinearity behavior of the sensor is observed near the magnetostriction saturation points, which is consistent with the experimental findings.

Conclusion
The capability of using ME sensors and the proposed approach for bio-imaging applications is demonstrated by the numerical/experimental evaluation. However, the pilot quantitative assessment highlights potential challenges, including nonlinearity issues that need to be addressed in further research.
Introduction

Biomagnetic sensing represents the next frontier in advanced diagnostics, as it offers contactless and rapid acquisition of medical signal information. However, the primary challenge for biomagnetic applications in medicine is the lack of a suitable sensor technology that can operate in clinical environments while maintaining ultra-low noise levels. The ongoing development of thin film magnetoelectric (ME) sensors positions ME technology as an increasingly promising candidate for biomagnetometry. This pilot study investigates the utilization of current state-of-the-art ME sensor for magnetocardiography (MCG) through an experiment involving a healthy volunteer inside a magnetically shielded room (MSR).

Methods

A converse ME sensor is employed for the first time for MCG and compared against competing optical magnetometry technology (QZFM, QuSpin) for evaluation. This specific ME sensor type ensures a noise amplitude spectral density below 20 pT/√Hz at 10 Hz. Due to the sensor's noise level, the signal-to-noise ratio of the sensor output must be optimized in a digital post-processing step using unweighted signal averaging. Signal
averaging is initiated by the R-peak, which is time-synchronously recorded from a one-channel electrocardiogram (ECG).

Results

After averaging across 60 heartbeats, an RMSE between the averaged ME and OPM signal of approximately 21 pT is obtained. The signal from the ME sensor is repeated three times to ensure reproducibility. In contrast, the optically pumped magnetometer displays a corresponding signal without averaging. The recorded ME signal demonstrates comparability to the unaveraged signals from both OPM and ECG, particularly in the R-wave region, although minor amplitude variations are observed in the R-peak.

Conclusion

This pilot study demonstrates the feasibility of recording an averaged cardiac magnetic field with a converse ME sensor, focusing on the R-wave within an MSR. The results presented here are expected to be a significant initial step toward the physiological application of ME sensor technology as a room-temperature sensor. Furthermore, additional MCG experiments involving SQUIDs for evaluation are currently being prepared.

Keywords: Magnetolectric (ME) sensors, Magnetocardiography (MCG), Biomagnetometry
Experimental Study of Artificial Tumor Assessment via Magnetic Susceptibility Particle Mapping

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Introduction
Magnetic Particle Imaging (MPI) is applicable to many medical procedures, such as disease detection, diagnosis, and treatment. Although MPI has high tissue penetration and almost no background signal from biological tissue, little is known about its application for cell imaging. An alternative and much less complex, though powerful, method is Magnetic Susceptibility Particle Mapping (MSPM). This study aims to investigate the MSPM method for experimental cell assessment using spheroids.

Method
MSPM employs a Magnetoelectric (ME) sensor and utilizes the delta-E effect for the readout scheme. The nanoparticle response is extracted from the motion modulation technique under rotational movement. Final reconstructed images are created using a Fast Iterative Shrinkage Thresholding (FISTA) algorithm. To demonstrate the capability of the MSPM as an imaging technique, microtumor-like spheroids of MCF-7 and MDA-MB-231 breast cancer cell lines were assessed in a non-shielded environment. The breast cancer cells were labeled with citric acid-coated MNPs. The cell viability is assessed before and after exposure to the operational conditions in the MSPM setup.

Result
Experimental evaluation indicates that the magnetic spheroid sizes range between 200–300 mm, and, their iron uptake was monitored for 6, 24, and 48 hrs., we found the highest uptake at 24 hrs. The final reconstructed image results are verified by performing confocal microscopy. Furthermore, the detection limit of MSPM was evaluated for magnetic particles in an aqueous solution, with a minimum detectable threshold of 20 mg.

Conclusion
This work demonstrates the feasibility of the MSPM method for detecting microtumors of breast cancer cells with a spatial resolution of a few millimeters. Compared with the complexity of MRI and MPI systems, the detection limit is made possible using a single ME sensor and simple/low-cost setup, which could be a good candidate for clinical investigation.
Novel Magnetic Field Sensor Based on a Magnetostrictive Polymer Composite – A Proof of Principle

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Introduction
The demand for magnetic field sensors has increased rapidly, driven not only by the need for systems with navigation, orientation, and motion tracking, but also by their growing use in the automotive sector and particularly in biomedical applications. The magnetosensitive material of the sensor presented here is a magnetostrictive polymer composite (MPC) composed of ferromagnetic particles embedded in a soft polymer matrix. The capacitive sensor includes an electret and is suited for biomedical applications due to its low resonance frequency of approximately 100 Hz.

Methods
The sensor was characterized through three measurements. The AC resonance frequency of the sensor was determined through a frequency sweep, followed by a DC magnetic bias field measurement to identify the optimal working point. For the final measurement the sensor was operated at resonance frequency with the optimal bias field. The amplitude of the resonance frequency was decreased with each measurement to determine the minimum field that the sensor can measure.

Results
The resonance frequency ranged from 50-150 Hz, which strongly depends on the geometry of the MPC. The sensor needs a bias field of several mT. This measurement also demonstrates that nothing within the sensor is remagnetized during the bias sweep. Even when not optimized, the sensor shows a linear behavior over 4 orders of magnitude and has a limit of detection of 9.6 nT.

Conclusion
The sensor characterization of this novel sensor concept showed that it works in principle and that its magnetic properties are not changed when exposed to magnetic fields. It may provide insight into the limiting factor of all magnetic field sensors, which is noise. The mechanical properties of the sensor arise from the polymer matrix, while the magnetic properties are dominated by the particles. Both components can be changed independently.
An Iterative Algorithm for Magnetic Motion Tracking

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Introduction
This contribution presents a new motion tracking algorithm. Motion analysis is of great interest in virtual reality projects and medical diagnostic applications. In this case, the motion tracking application is to be used as a control interface for robotic surgery. To do this, the hand movement needs to be tracked in real time. We assume the hand as a kinematic chain model with magnetic sensors on every chain element. The commonly used localization algorithms are often computationally very intensive and are not suitable for an application with 30 or more sensors. Thus, a new and cheap iterative algorithm has been developed.

Methods
This approach uses an iterative procedure to estimate the attitude of the hand. This is done by specifically designed magnetic excitation signals that allows to extract special features from the received sensor signals. These new features could be used to calculate the orientation for any position or the position for any orientation. These relations were combined with a priori knowledge of the human anatomy to form an iterative algorithm.

Results
The functionality of the algorithm was verified using a simulation. For this purpose, the algorithm was implemented in a real-time toolkit and individual movements were tested. A small prototype with a demo joint was built to test the algorithm in reality.

Conclusion
In summary, a method for estimating hand posture has been developed. This method is characterized by a very low computational complexity. In the future it will be necessary to refine the utilized anatomical model and to improve the performance using a Kalman filter or other post-processing algorithms.
Development of functionalized magnetic nanoparticles for early detection of anastomotic leakage in gastrointestinal anastomosis using magnetoelectric sensors

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Introduction
Anastomotic leakage (AL), which usually occurs after intestinal surgery, is considered a life-threatening complication for patients due to the resulting inflammation. It is of high importance to detect AL at very early stages after the surgery; however, the existing diagnostic tools are not specific or fast enough [1]. Molecularly imprinted polymer (MIP)-based synthetic receptors can be used in vivo to recognize and capture a target of interest [2]. Using MIP-functionalized magnetic nanoparticles, we aim to detect the biomarkers specific for AL with the help of magnetoelectric (ME) sensors [3]. The readout is based on phase behavior of the particles upon change in their hydrodynamic diameter and Brownian relaxation [4].

Methods
Interleukin-6 (IL-6) is a peritoneal cytokine that appears at the inflammation site of AL. In this study, magnetic MIPs specific for IL-6 were synthesized via core-shell epitope imprinting approach. IL-6 epitope as the template molecule was covalently immobilized on superparamagnetic iron oxide nanoparticles prior to synthesizing the MIP shell. The optimum shell thickness was determined by changing polymerization time. Finally, the template molecules were removed from the polymer network and the IL-6-specific cavities were obtained to be used as receptors in the ME sensor setup.

Results
Fourier-transform infrared spectroscopy (FTIR), dynamic light scattering (DLS) and transmission electron microscopy (TEM) images confirmed the fabrication of the MIP shell on the magnetic nanoparticles, while fluorescent spectrometer revealed the affinity and specificity of the MIPs towards the target analyte. Vibrating sample magnetometer (VSM) was employed to verify the magnetic behaviour of nanoparticles.

Conclusions
The results proved the successful design and synthesis of magnetic core-shell MIPs as well as the promise of the developed sensor approach for AL detection at very early stages without the need for highly sophisticated tools.

References
Gradiometer setup for magnetic ambient noise reduction using Magnetoimpedance Sensors

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Introduction
With the rising popularity of bio-magnetic field (MF) measurements, there is a need for miniaturized and highly sensitive magnetometers working under ambient noise conditions. A gradiometer consisting of a vector magnetometer such as a Nitrogen-Vacancy (NV) magnetometer and scalar magnetometers like Magnetoimpedance (MI) sensors could allow bio-magnetometry in unshielded environments. As a first step, we present a gradiometer using MI-sensors only.

Methods
A controlled reference MF was induced through a rectangular signal coil wire arrangement. Eight commercially available MI-sensors (MI-CB-1DH, Aichi Steel Corporation, Tokai, Japan) formed two linear sensor-arrays (four sensors each on one axis), 20 cm apart symmetrical to the signal coil wire in the z-direction. Two sensors of equal height and orientation (orthogonal towards the signal coil surface) represent a gradiometric sensor pair.

An input/output-device (USB-6009, National Instruments, Austin, USA) acquired the differential analogue signal between sensor pairs. To improve the Signal-to-Noise-Ratio (SNR), we applied a high-/lowpass-filter at 0.5 Hz/48 Hz and spatial averaging over the four resulting gradiometer signals. We additionally developed a Magnetic-Flux-Concentrator (MFC) made of nickel-zinc ferrite (Neosid Pemetzrieder GmbH & Co. KG, Halver, Germany).

Results
The noise level of a single non-gradiometric MI-sensor exhibits a root-mean-square (rms) amplitude of ≈100 nT after postprocessing. Our findings indicate a noise-reduction to ≈7 nT rms by utilizing pairwise gradiometers. Further spatial averaging leads to ≈700 pT rms without substantially diminishing the reference signal.

The use of MFCs on either side (aligned with the sensor’s sensitive axis) increases the signal amplitude by a factor of 1.9.

Conclusion
We have developed a first-order MI-gradiometer for ambient noise reduction in unshielded environments. The setup achieves a noise reduction by a factor of 100. Through further temporal averaging (~100 times) and the use of MFCs, sensitivities suitable for bio-magnetometry are reached.

We thank the BMBF-initiative QSENS: QSCALE for their support.
Special Session:
Nanomedicine and Theranostics
Monitoring RNA delivery via multimodal and multiscale optical imaging

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Introduction

RNA therapeutics are a highly promising and emerging class of drugs for the treatment of various diseases in oncology and beyond. Their success rely on the use of drug delivery systems (DDS). Improving DDS-based RNA delivery requires implementation of superior imaging strategies. We herein show a multimodal and multiscale approach for monitoring the transfection, efficacy, biodistribution, and target site accumulation of RNA nanotherapeutics.

Methods

RNA lipid nanoparticles (RNA-LNPs) with variable characteristics were manufactured using a T-junction or chaotic mixer microfluidic setup. The LNPs were assessed for their size, dispersity and zeta-potential via dynamic light scattering and electron microscopy. The particle uptake and transfection / knockdown efficacy were assessed via fluorescence microscopy and colorimetry. Therapeutic efficacy was assessed via life-cell imaging, visualizing changes in fluorescence life-times (FLIM) of NAD(P)H autofluorescence excited via two-photon microscopy. The biodistribution and target-site accumulation of a Cy7-labelled, firefly luciferase mRNA-loaded LNPs were assessed via hybrid µCT and fluorescence tomography (µCT-FLT).

Results
Systematic screening of LNPs showed tuneable particle properties depending on the lipid composition or microfluidic settings. Functional screening in 4T1 and Hepa1-6 cancer cells demonstrated consistent differences in transfection/knock-down efficacy. FLIM data demonstrated quantifiable changes in redox-states of L929 fibroblasts before and after stimulation, and further visualised the metabolic and cell death response of Hepa1-6 after gene silencing using RNA-LNPs. Finally, µCT-FLT of 4T1 tumor-bearing mice showed distinct biodistributions of Cy7-mFLuc-LNPs upon different routes of administration, including tumor accumulation at 24h after i.m. injection.

Conclusion

Using FLIM, we successfully evaluated cellular redox-state readouts for differentiating cell death pathways in treated cells. We further visualised and quantified particle uptake and RNA expression/knockdown in vitro and went on to track labelled particles with expressing mRNA in vivo.

Keywords: RNA delivery, lipid nanoparticles, Optical imaging, Microfluidics
Introduction
We developed a dextran-coated superparamagnetic iron oxide nanoparticle (SPION)-based MRI contrast agent (SPION$_{\text{Dex}}$), that shows a remarkable biocompatibility. The stability of such nanoparticles is a crucial parameter that determines their performance and shelf life, however, it is often not given as much attention as it deserves. In this study, we investigated the storage stability of iron oxide NPs at different temperatures.

Methods
SPION$_{\text{Dex}}$ were synthesized using a large scale co-precipitation method and purified via tangential flow filtration. The stability of NPs was evaluated by monitoring their size distribution, magnetic susceptibility, pH, FTIR and UV-Vis signal, after storage at 4, 25, and 37 °C for up to two years.

Results
Our results showed that the storage stability of iron oxide nanoparticles was strongly dependent on the storage temperature. At 4 °C, the nanoparticles showed minimal to no changes in properties during the complete storage period. At 25 °C, the nanoparticles exhibited a gradual increase in size over time. At 37 °C, they showed a fast and significant increase after a short period of storage.

Conclusion
In conclusion, the storage stability of iron oxide nanoparticles is highly dependent on the storage temperature. Our results suggest that our SPION$_{\text{Dex}}$ can be stored at 4 °C for an extended period without significant changes in their size distribution and magnetic properties. However, storage at higher temperatures, particularly at 37 °C, should be avoided to maintain the stability of SPIONs.
Carbon nanotubes as powerful platform for optical biosensing

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Introduction
Single-walled carbon nanotubes (SWCNTs) are an emerging material for chemical imaging, stand-off in-situ diagnostics, and process control. This is due to their near-infrared (NIR, 870 – 1700 nm) fluorescence emission, which offers extremely low background in biological samples. Chemical modification of the SWCNTs enables molecular recognition of target analytes with high sensitivity and selectivity by a fluorescence change upon analyte interaction. Powerful SWCNT-based sensors have been developed for bacterial motifs, signalling molecules like neurotransmitters or H2O2, lipids and proteins. However, so far, SWCNT sensors have mainly been processed from mixtures of different chiralities, because SWCNT growth cannot be adequately controlled during fabrication. Since the emission wavelength depends on the respective SWCNT chirality, this means a spectral overlap and congestion. At the same time, the emission in the NIR makes detection with typically used silicon-based cameras difficult due to decreasing sensitivity in the NIR (around 5% at 1000nm).

Methods
Therefore, we developed an efficient separation approach to obtain (6,4)-SWCNT species (emission at 880 nm) from commercial SWCNT mixtures and tailored them exemplarily as sensors for the important neurotransmitter dopamine using specific DNA sequences.

Results
It enabled us fast imaging (< 50 ms) with high-resolution standard cameras (> 50x more pixels compared to expensive InGaAs detectors actually designed for the NIR range and typically used). In addition, these sensors are 1.7-fold brighter and 7.5x more sensitive for dopamine. Furthermore, we show high-resolution imaging of dopamine release from cells.

Conclusion
In conclusion, this approach provides fluorescent sensors that enable NIR biosensing and imaging of these nanomaterials in any conventional microscope or camera. Thus, the assembly of biosensors from (6,4)-SWCNTs combines the advantages of nanosensors working in the NIR with the sensitivity and low cost of standard cameras. This advance will make these powerful molecular sensors available to a broad community.
Introduction: Nanomedicines and Theranostics

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Introduction: Cancer treatment options include surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy. The choice of therapy depends on tumor location, stage and histopathological type, as well as on the general state of the patient. Although anticancer drug therapy may be indicated in advanced stages, it is generally only moderately effective due to suboptimal in vivo performance, toxicity, and distribution.

Methods: Drug delivery systems (DDS) have been developed to improve biodistribution and therapeutic index.

Results: The number of new drug approvals and investigational applications based on DDS has steadily increased, but setbacks have triggered discussions about the future of anticancer DDS design and clinical translation.

Conclusion: In this session we will discuss strategies to overcome the current challenges in the field of anticancer DDS development and to explore therapeutic and theranostic scenarios that lead to improved patient outcomes. These include pharmacological or physical treatments that modulate tumor blood vessels and the microenvironment to improve drug delivery, strategies to boost the efficacy of immunotherapy and the use of companion diagnostics and nanotheranostics for patient stratification.
Predicting tumor accumulation of nanocarriers in murine and human tumors using immunohistological biomarkers

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Introduction

There is no clinically established prediction tool for the tumor accumulation of untargeted nanocarriers. While imaging of radioactively labeled nanocarriers is in principle an alternative, it is challenging to implement in daily clinical routine. As an applicable alternative, we here identified blood vessels and macrophages as histological biomarkers to differentiate between low- and high-accumulating tumors.

Methods

Tumor-bearing mice (A431, MLS or CT26) were injected with a fluorophore-labeled polymer (poly(HPMA), 10-20 nm) and the tumor accumulation was imaged via CT-FLT. Histological stainings of e.g. blood vessels, macrophages, smooth muscle actin, collagen or nuclei were used to screen for biomarkers correlating with the tumor accumulation of polymers. The whole set of biomarkers was further evaluated by gradient tree boosting identifying blood vessels and macrophages as predictive for tumor accumulation. In addition, resected patient tumors (head and neck, breast and lung) were histologically evaluated and compared with accumulation levels based on Harrington et al [PMID:11234875].

Results

Polymer accumulation varied between models (from 5 ID% for A431 up to 11 ID% for CT26) and several histological biomarkers correlated with tumor accumulation. Gradient tree boosting further confirmed the importance of blood vessels and macrophages (R² values of 0.5 for blood vessels and 0.8 for macrophages over all three models). Based on tumor accumulation values of doxorubicin-loaded liposomes in patients (head and neck, breast or lung, from Harrington et al.,) we could also show that it might be well possible to identify tumors that are highly unlikely to accumulate sufficient amounts of a nanocarrier using stainings of blood vessels and macrophages.

Conclusion

Using immunohistological stainings of blood vessels and macrophages, we were able to predict the nanocarrier accumulation of murine tumors. Our findings on human samples point towards a possible cost-efficient and broadly available measure to preselect patients in clinical trials.
ENGINEERING MESOSCOPIC 3D TUMOR MODELS WITH A SELF-ORGANIZING VASCULARIZED MATRIX

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Introduction

Despite the essential role of animal experimentation in biomedical research, ethical considerations motivate efforts to develop physiologically-relevant in vitro models that mimic the tissue-scale and organization of human solid malignancies. We present a novel 3D bio-printed artificial tumor model that self-organizes into functional and perfusable vascular structures.

Methods

We utilized extrusion-based bio-printing techniques and gelatin mixed with EC as vascular and fugitive bioink. The printing was conducted into a custom-designed PEEK bioreactor that is imaging-compatible. An ECM-mimicking collagen-fibrin hydrogel blend mixed with stromal cells was casted between the printed gelatin strands, where a multicellular tumor spheroid was positioned. After gelatin liquefaction, the bioreactors were cultivated for up to three weeks under physiological flow conditions in a recirculating fluid loop, and capillary network formation and functionality were assessed by the use of red blood cells and microbeads.

Results
We successfully bioprinted tumor feeding vessels that mimic natural vessel conformation, including anastomoses, curves, and variations in lumen size. Our PEEK bioreactor with optically transparent windows enabled real-time monitoring of cell growth, and its inner spaces of centimeter thickness could contain sufficient volumes of hydrogel for long-term durability while facilitating growth of biological material beyond the micrometer scale. Angiogenic tumor spheroids promoted the growth of the vascular network, and the supportive vascular network, in turn, promoted the growth of co-cultivated tumor spheroids. The self-evolved vascular structure infiltrated the tumor spheroids, forming functional connections with the bioprinted endothelium, and proved perfusability to erythrocytes and 10 μm polystyrene μbeads. Additionally, our bioengineering approach proved suitable for the cultivation of patient-derived material, reflecting the phenotypic heterogeneity of human malignancies, similar to engraftment of cancer cells in mice.

Conclusion

Our novel 3D platform has the potential to enhance the predictive power of in vitro experimentation in basic cancer research and drug development, reducing the reliance on animal use.

Keywords: Tissue Engineering
Prototyping 3D printing phantoms for diffuse optical imaging and fluorescent probe evaluation

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⁶RWTH Aachen University, Aachen

Introduction:
This study explores the use of 3D printing in the biomedical field, specifically for developing phantoms to be used in hybrid optical imaging systems for fluorescence detection. By using 3D-printed phantoms, researchers can improve the mimicry of models at optical and topographical levels, which provides better tools for demonstrating photon detection performance.

Materials and Methods:
The phantoms were manufactured using fusion deposition modeling (FDM) and filled with NIR-labelled nanomedicine formulations at various concentrations. The liposome-containing phantoms were imaged using fluorescence reflectance (FRI) and hybrid computed and molecular tomography (FLT/CT) to assess the detection limit, sensitivity, and linearity of the two imaging modalities. Mouse-shaped phantoms were also printed to mimic organ topology, volume, and optical properties.

Results:
Compared to the standard single-well model provided by the company, the ABS multi-well phantom displayed a higher photon count with less deviation, higher linearity, and sensitivity. Simple geometries and watertight enclosures allowed evaluations of different concentrations in the same acquisition. A multi-depth phantom provided insight into detection capacity at progressively intermediate penetration levels. A mouse-shaped phantom was developed by averaging topologies and organ volumes of a pre-existing dataset. By reverse engineering and computer-aided design (CAD), models were sliced and printed in-house allowing for fluorescence detection in a manner similar to the in vivo-scenario via FLT/CT.

Conclusion:
The results suggest that 3D-printed phantoms can improve model mimicry at optical and topographical levels, provide users with better tools for demonstrating photon detection performance, and enable faster and simpler sensitivity and linearity interrogations. The design freedom of CAD modeling and the optically relevant characterization of materials allowed evaluations of various solutions in a single acquisition, reducing acquisition times and related costs. Overall, this study highlights the potential of 3D printing in the development of advanced and personalized optical imaging phantoms.
In vitro sonoporation using hard shell microbubbles under various ultrasound intensities

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Introduction
Sonoporation describes the creation of pores in cells as a consequence of nearby microbubble (MB) oscillation observed under ultrasound (US) exposure. Hard shell MB respond differently to US than soft shell MB which have been extensively analyzed in the past decade. This study evaluates suitable US parameters for the application of hard shell poly(n-butyl cyanoacrylate) (PBCA) MB to open cell membranes and cell-cell contacts.

Methods
Epithelial cells were seeded on the bottom side of transwell inserts, brought into direct contact with the PBCA-MB which were treated with focused US at 1 MHz and five different acoustic pressures between 300-1500 kPa for 2 s. Cell membrane opening (n=9/ pressure) was investigated by propidium iodide (PI) uptake, the cytoplasm of intact cells was stained with fluorescein diacetate (FDA). Opening of cell-cell contacts (n=6/ pressure) was monitored by transepithelial electrical resistance (TEER) measurements using an EVOM2 device with a STX2 electrode before and after US application. Control groups were equally treated as the treatment groups, but without MB.

Results
US-MB treated groups showed higher uptake of PI in comparison to the control groups (US only). PI uptake increased with US intensity. Independent of the US intensity, the TEER values decreased after US-MB and only US treatment. However, TEER drop in the US-MB treated groups was significant larger than in US only groups pointing to an opening of cell-cell-contacts mediated by MB-US interaction.

Conclusion
Sonoporation with hard shell PBCA-MB induces pores in the cell membrane and disrupts intercellular contacts indicated by PI/ FDA uptake and change in TEER, respectively, already at low US intensities. As a next step, we will evaluate whether similar sonoporation effects can be induced by using soft shell MB with the same US settings.
Analysis of doxorubicin-telmisartan combination therapy using 2D co-cultures and 3D multicellular tumor spheroids

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Introduction

The tumor-microenvironment (TME) plays a key role in disease progression, thus emerging as a promising therapeutic target. For preclinical evaluation of TME-targeted therapies, we need models that (i) mimic the basic in vivo architectural features of solid malignancies (ii) are composed of distinct cell populations, and (iii) allow for longitudinal monitoring via imaging. Here, we utilized customized 2D co-cultures and 3D multicellular tumor spheroids to evaluate the efficacy of antifibrotics in combination with chemotherapeutics as a TME-targeted therapy.

Methods

Ovarian cancer cells were co-cultured with fibroblasts to obtain customized 2D and 3D in vitro models. Different therapies such as (i) free-telmisartan, (ii) free-doxorubicin, and (iii) telmisartan-doxorubicin electrostatic pair (TelmiDOX) were applied to both the systems. 2D co-cultures were analyzed 24h and 48h post treatment whereas 3D spheroids, 2- and 5-days post treatment. The therapy outcome was analyzed via brightfield (BF) microscopy, western blotting, immunofluorescence (IF) and XTT to assess the ECM deposition and profile drug toxicity.

Results

In 2D, quantification of IF images showed similar collagen deposition upon DOX and TelmiDOX treatment, suggesting the prevailing action of DOX over telmisartan. Spheroids showed reduction of diameter upon treatment with DOX and TelmiDOX. Similar cytotoxicity profiles for DOX and TelmiDOX indicated that electrostatic combination of doxorubicin with telmisartan did not alter the cytotoxic effect of DOX. The marginal
differences between DOX and TelmiDOX allude to the insignificant / slow action of telmisartan and consideration of sequential administration in vivo.

Conclusion

We demonstrated the use of 2D and 3D in vitro models for evaluating the effect of TME-targeted therapies. The multicellular spheroids displayed ECM deposition by stromal cells and were sensitive to drug treatment. The prevailing effect of DOX in the complex with Telmisartan, denotes that a sequential administration should be selected in an in vivo set-up, where a preceding administration of Telmisartan is selected.

Keywords: Combination therapy, Tumor microenvironment
Introduction

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Keywords: Combination therapy, Tumor microenvironment
Polymeric micelles as drug delivery system for combined chemo-radiotracer therapy against triple-negative breast cancer

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Introduction
Chemo-radiotherapy combinations are commonly employed in clinical oncology. However, external radiotherapy has inherent some limitations, including damage to surrounding tissues while still missing small tumor manifestations locally. Instead, radionuclide based internal radiotherapy (and its combination with chemotherapy) has demonstrated to decrease side-effects and potentiate therapeutic outcomes. We have previously established a new therapy approach against BRCA-mutated triple negative breast cancer (TNBC) by a two-hit strategy, which is based on combining the inhibitory effect of a poly (ADP-Ribose) polymerase inhibitor (PARPi) with the radiotherapeutic effect of ¹²⁵Iodine. Preliminary preclinical evaluation showed poor biodistribution and instability of the developed ¹²⁵I-tracer. We here aim to develop a polymeric micelle-based formulation of ¹²⁵I-PARPi to improve the tracer stability, biodistribution and tumor retention for efficient chemo-radiotracer therapy.

Methods
Co-loading of polymeric micelles with radioactive and non-radioactive I-PARPi was done via nanoprecipitation method. Physicochemical and pharmaceutical properties were analyzed by high-performance liquid chromatography (HPLC), dynamic light scattering and transmission electron microscopy. Drug encapsulation efficiency (EE) and retention inside the micelles, as well as in vitro tracer stability and cell uptake were quantified via HPLC. Gamma-counter measurements determined the cell uptake of radioactive I-PARPi.

Results
Micelles had sizes around 70 nm and polydispersity index (PDI) below 0.1. Radioactive and non-radioactive I-PARPi were efficiently co-encapsulated with EE values of about 80 %, and at least 50 % of drug was retained within the micelles after 72 hours. Furthermore, formulation in micelles improves tracer stability 10-fold by prevention of deiodination in vitro, and it enhances the cell uptake of radioactive I-PARPi in BRCA-mutated TNBC cell lines.

Conclusion
We have successfully developed a stable radioactive and non-radioactive I-PARPi co-loaded polymeric micelle formulation that holds potential for efficient chemo-radiotracer therapy combination in TNBC. Ongoing work involves in vivo investigation of the drug delivery system in terms of tracer blood stability, tumor uptake and clearance.
Enzyme-sensitive Self-immolative Prodrugs for Cancer Nanotherapy

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Introduction
Chemotherapeutics are widely employed in clinical oncology. Commonly used drugs encompass doxorubicin, cisplatin, paclitaxel and gemcitabine, among others. Despite their success, they often show poor biodistribution and low target selectivity, which can lead to significant side-effects and limit chemotherapy efficacy and broad application. Combining prodrug chemistry and drug delivery systems can help overcome some of these limitations. Our aim is to develop a modular prodrug strategy for (hydrophilic) drugs that (1) can be selectively activated by tumor-specific enzymes and (2) increases drug retention in π-π stabilized polymeric micelles (Fig 1).

Methods
Standard synthesis, micelle formulation and characterization techniques (nuclear magnetic resonance spectroscopy, high-performance liquid chromatography (HPLC), mass spectrometry and dynamic light scattering) were employed in prodrug preparation and micelle formulation. Prodrug activation and their retention in micelles was followed by HPLC. In vitro assays were performed in breast cancer cells and in vivo studies in EO771 triple-negative breast cancer mouse models.

Results
We synthesized several self-immolative prodrugs of gemcitabine and doxorubicin with different numbers of self-immolative linker copies in the structure. The prodrugs can be enzymatically converted into the parent drugs by the enzyme β-glucuronidase (typically overexpressed in the tumor microenvironment), with different activation kinetics based on the number of self-immolative linker copies. In vitro assays showed that prodrugs have reduced cytotoxicity in cancer cells. In vivo studies showed good tolerability based on mice body weight changes. Finally, the aromatic-based structure of prodrugs significantly contributes to enhance (pro)drug encapsulation efficiency and retention in the hydrophobic core of π-π stabilized micelles.

Conclusion
Overall, our work highlights the potential of such prodrug platform to increase drug tolerability while, at the same time, maintaining anticancer efficacy and promoting formulation in polymeric micelles for improved cancer nanotherapy.

![Prodrug Synthesis and Micelle Formulation](image)

*Figure 1. Enzyme-sensitive self-immolative gemcitabine and doxorubicin prodrugs. Schematic representation of the enzyme-sensitive glucuronide-capped self-immolative prodrug structure, synthesis and formulation in π-π stabilized polymeric micelles.*
MONITORING THE EFFECT OF THE FIBROTIC TUMOR MICROENVIRONMENT ON TUMOR-TARGETED DRUG DELIVERY IN ALLOGRAFT MODELS.

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Introduction

Biological barriers, coming from the tumor microenvironment (TME), play a crucial role in drug delivery.

Methods

To mimic these barriers, we developed two fibrotic tumor models. For the breast cancer model (BC) drug-resistant 4T1, and as comparison, drug-sensitive 4T1 cells were inoculated into mice and tumors harvested. To generate a Hepatocellular Carcinoma (HCC) model, mice were pretreated with CCl4. Dt81-Hepa1-6 cells were then injected and metastatic livers were collected. For control, another group of mice was left untreated. The TME of breast tumors, control livers, metastatic livers was analyzed using immunohistochemistry (IHC). In the BC model, the impact of the TME on drug delivery was investigated by monitoring the tumor accumulation and penetration of fluorophore-labeled nanocarriers with multimodal and multiscale imaging. The effect of the TME in resistant tumors on the treatment efficacy of liposomal chemotherapeutics was studied.

Results

The TME of resistant tumors is enriched in collagen and fibronectin. Additionally, vascular perfusion is increased. Treatment of livers with CCl4 triggers fibrosis and leads to overproduction of collagen and fibronectin in the surrounding tissue. Most importantly, the HCC lesions in the metastatic livers show a 7-fold oversecretion...
of ECM as compared to healthy liver. No differences can be seen for vascular density. At the whole tumor level, liposomes accumulate slightly more efficiently in resistant than in sensitive tumors. At the individual blood vessel level, liposomes are less able to extravasate out of the vasculature and penetrate the interstitium in resistant tumors. A final in vivo efficacy study of free vs. liposomal doxorubicin in resistant and sensitive tumors reveals a negative effect of the TME on the treatment efficacy.

Conclusion

Elevated fibrosis and consequently overproduction of ECM impacts accumulation and penetration of nanocarriers and thereby impedes success of nanomedicine.

Keywords: Drug delivery, Tumor microenvironment, Fibrosis
Paclitaxel and dexamethasone co-loaded polymeric micelles with sequential release

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Introduction
Paclitaxel (PTX), a commonly used chemotherapeutic, is present in several nanomedicine formulations with indications in fibrotic cancers. Fibrotic tumours are notorious for having abnormalities such as a dense extracellular matrix, which impede nanomedicine penetration and limit (nano-)therapeutic efficacy. To tackle these obstacles, strategies such as tailoring nanocarrier size and using tumour microenvironment (TME) remodelling agents have shown promise. Dexamethasone (DEX), a potent corticosteroid, has been demonstrated to attenuate fibrosis in the TME. Here, we aimed for a size-tuneable nano-formulation for combination therapy by co-delivery of a chemotherapeutic (PTX) and a TME-priming agent (DEX), using polymeric micelles based on amphiphilic HPMA-based copolymers.

Methods
We prepared block copolymers of three different sizes via free radical polymerization, and used them to formulate PTX and DEX coloaded micelles. The size and polydispersity index (PDI) of the resulting micelles were measured by DLS. Drug encapsulation and release were quantified using HPLC.

Results
Block copolymers of three different sizes were synthesized (namely, small, medium, and large). The size of the co-loaded micelles showed a positive trend as the Mn of the polymers increased, with values of 50, 70, and 150 nm for small, medium, and large polymers, respectively. Both drugs were efficiently loaded with EE values of at least 80 %. Furthermore, release studies showed higher drug retention in micelles from polymers of larger sizes and an overall faster release of DEX as compared to PTX in all the cases.

Conclusion
This polymeric micelle platform demonstrates promise for effective co-delivery of PTX and DEX with a sequential release profile in which DEX is released faster than PTX. Such a sequential release can be beneficial from a pharmacological point of view, where the earlier released DEX can already start priming the TME to further promote the penetration of the micelles.
Microfluidic Formulation and Long-Term Stabilisation of [(mPEG-b-p(HPMAm-Bz)]-Based Polymeric Micelles

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Introduction

Manufacturing is a key challenge in nanomedicine clinical translation. Measures to control batch-to-batch reproducibility and to ensure long-term stability are crucial during pharmaceutical development. Continuous-flow manufacturing technologies have proven valuable in controlling nanomedicine production, as seen during the recent upsurge of mRNA-containing lipid nanoparticles. Here, we employed microfluidics to control the production of paclitaxel (PTX)-loaded [(mPEG-b-p(HPMAm-Bz)]-based polymeric micelles, which have shown promising preclinical anticancer performance. In addition, we systematically explored strategies to enhance long-term stability by using cryoprotective excipients.

Methods

PTX-loaded micelles were prepared using 3D-printed microfluidics chips and compared with the corresponding bench-scale formulations. Size, polydispersity index, transmission electron microscopy, and drug encapsulation efficiency (EE) and retention were used to characterize the formulations. Different cryoprotectants were explored, and their effect was evaluated by subjecting the PTX-loaded micelles to a freeze-thaw cycle. Long-term stability of the formulations was evaluated via either cold chain supply or freeze-drying technology.

Results

3D-printed microfluidic chips can tune the physicochemical properties of the micelles, and enable high drug-loading (EE ≥ 80%, comparable to the bench-scale method). Among the different cryoprotectants assayed, sucrose showed superiority in preserving the properties of the PTX-loaded polymeric micelles after freeze-thawing. Finally, PTX-loaded micelles formulated via microfluidic and in the presence of sucrose were stable up to 6 months at – 20°C, which allows cold chain supply at an easily achievable temperature.

Conclusion

Our results demonstrate that microfluidics allows to produce PTX-loaded micelles with better control over critical formulation properties. Cryoprotectant choice is crucial for optimal preservation of micelles upon freezing. By using microfluidics, we formulated cryoprotected PTX-loaded micelles with good long-term stability, thereby paving the way towards industrial development and translation.
Special Session:
Medical Communication Systems
5G FORUM – wireless low-latency connectivity for the operating room

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Introduction
5G FORUM is a Franco-german joint research project including academic and industrial partners from both countries, among them RWTH Aachen University, eCential Robotics and SurgiTAIX AG. The project aims to reduce cable connections in the operating room (OR) by employing 5G as a secure, performant and scalable alternative to WiFi and other shared-spectrum options. The project focus is operating room Point-of-care connectivity for critical devices with strict latency requirements. Wireless connectivity could provide a substantial ergonomic advantage and increased mobility in crowded ORs, where spatial constraints and tripping hazards directly translate to prolonged operative time, subpar patient safety and higher costs.

Methods
The technical foundation is achieved by combining innovative networking technologies such as Time-sensitive networking (IEEE 802.1 Qbv), 5G small-cell campus networks and Service-oriented device connectivity (ISO IEEE 11073 SDC). The technologies apply to different layers in the OSI networking model, complementing each other to automate previously manual setup and configuration steps. The necessary network Quality of Service (QoS) can be set up automatically for plug-and-play usability during all surgery steps.

Results
Practical applications include timely execution and synchronization of device functionalities (e.g. signals from user input devices) and real-time robot control with 5G in-the-loop. Since wireless devices tend to have a higher uptime than wired devices, more medical data can be generated and saved along with surgery documentation. There are also foreseeable benefits for hospital management: Continuous system monitoring opens the door for indoor localization, usage analysis and predictive maintenance.

Conclusion
The innovative combination of networking technologies could drastically reduce the amount of cable connections in the OR while simultaneously making it feasible for more devices to remain persistently connected. In this way, 5G, TSN and SDC pave the way for a more user-friendly, safe and ergonomic working environment in modern clinics and other medical facilities.
Concept for Video Transmission in Non-reliable Medical Networks

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Introduction
The MOMENTUM project aims to improve emergency care by implementing a data transmission system over mobile networks. Part of this data is a bi-directional, real-time audio and video connection, consisting of IP-camera video and streaming of various medical devices. To improve telemedical treatment, uninterrupted, low-latency transmission via the available network is necessary. Hence, the streaming quality has to be adaptable.

Methods
WebRTC is a technology for transmission of audio and video data in real-time. It is supported by most web browsers without the requirement for additional extensions. Therefore, it provides a flexible, OS-independent solution. Implementing a performant self-developed solution of WebRTC has proven to be very resource expensive. Another way would be the integration of an already working system, such as Jitsi, Microsoft Teams or Zoom. The last two require their own servers for data-transmission, thus implying the inability to keep the data in our own network.

Results
The open-source platform Jitsi has been chosen as solution for our use-case. A custom server is used to set up video and audio connections between clients in our network. We alter the quality of these connections on available network capacity using the Jitsi-iFrame-API. First tests reached latencies less than 100ms in a local environment. For WebRTC to work properly, https is required. Our own Certificate Authority enables secure connections in our local network without being linked to the internet.

Conclusion
By using Jitsi we were able to integrate a bidirectional audio and video connection in our local network. The Jitsi-API is used to change stream quality to adapt by available network capacity. But these changes still depend on the parameters the API allows us to modify. A more customizable WebRTC-implementation is desirable. The MOMENTUM project will strive to improve the presented solution.
Special Session:
Model-based control of biohybrid implant maturation
Fibrin-polysaccharide based hydrogels for design of heart valve implants

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Introduction
Because of the increase of human population, heart valve diseases have become one of the main causes for mortality rates worldwide. Current treatment using mechanical and biological heart valves are limited by their ability to grow, therefore tissue-engineered heart valve implants (TEHVIs) are strived for. For the design of TEHVIs, a biomaterial is required that functions as a scaffold for cells and is able to enhance cell proliferation and differentiation. For this, fibrin hydrogels are a promising biomaterial due to their abundance in the body, excellent cell compatibility and nonlinear elastic properties. However, non-modified fibrin hydrogels have low mechanical properties and degrade fast. To combat these problems, additives e.g. polysaccharides are introduced. Polysaccharides have the advantage of being biocompatible, biodegradable and abundant.

Methods
Here, we introduce fibrin-polysaccharide based hydrogels for the design of TEHVI. These hydrogels are synthesized through the simultaneous gelation of fibrinogen to fibrin and functionalised polysaccharide with cross-linkers. By varying type of polysaccharides (e.g. dextran, pectin) and the concentration of fibrinogen, polysaccharides and cross-linker, mechanical properties, degradation rate and pore sizes can be tuned.

Results
Rheology is used to determine the gelation properties and stiffness of the fibrin-polysaccharide hydrogels. These hydrogels exhibit an increase in the storage modulus compared to pure fibrin hydrogels. The structure of the fibrin-polysaccharide hydrogels was visualised with scanning electron microscopy, which showed changes in pore sizes dependent on the concentration of the used polysaccharide. Confocal microscopy is used to observe the fibrin structure of the hydrogels. Degradation tests of the hydrogels indicate a decrease in degradation rate for the fibrin-polysaccharide blends. Viability tests of cells seeded on the hydrogels confirm the absence of cytotoxic effects.

Conclusion
In conclusion, fibrin-polysaccharide hydrogels with adaptive mechanical properties and morphologies as well as a tuneable degradation were successfully developed for the design of TEHVI.
In Situ Tissue Engineered Heart Valve based on Woven Textile Scaffold

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Introduction:
Bioprostheses with leaflets made from animal pericardium represent the current state of the art in the treatment of valvular heart disease. These valves are prone to calcification and structural degeneration, which limits their lifespan and requires repeated surgical interventions. The goal of this project is to investigate a leaflet scaffold based on a load-oriented woven textile. It is designed to provide structural integrity and can be further processed with a hemocompatible and bioactive coating for in situ tissue engineering.

Methods:
Mechanical testing (tensile strength, bending stiffness, thread shift) was used to preselect the fabric configuration, followed by porosity testing. The woven scaffolds were coated with TPU chloroform (Carbothane PC-3585A, Lubrizol) and mounted in a valve ring. Accelerated wear tests were performed under simulated physiological load in a LinA testing device (AME-HIA and ac.biomed GmbH). The function of the leaflets and signs of wear were assessed by slow motion movie, photography and microscopic examination. Favorable textile scaffold-valve ring designs were tested with a higher number of load cycles.

Results:
After design optimization, current lab samples withstand more than 90 million load cycles (testing is ongoing). Critical defect zones occur near the commissures. They could be addressed by adapting the weave pattern and the way the weave is attached to the valve ring. The latest R&D results on both aspects will be presented.

Conclusion:
Preliminary results promise to achieve reasonable durability of a valve composed of woven leaflet scaffolds. Further hemocompatibility, cell colonization, and calcification testing are required to confirm suitability as an in situ heart valve replacement.
Development of a testing system for the calcification potential of cellularized biomaterials in vitro

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Introduction
Biohybrid implants are a promising advancement for treating many diseases, but remain difficult and expensive to develop, test, and validate. Structural degeneration is one of the most significant problems associated with bioprosthetic heart valves. While novel anti-calcification treatments are improving the longevity of these heart valves, the mechanisms of structural valve degeneration (SVD) are poorly understood. One major contributor to SVD is the formation of calcium deposits on and in the leaflets. Novel biohybrid prosthetic heart valves may reduce the risk of SVD through self-renewability, but their calcification potential remains to be fully explored.

Methods
A bioprosthetic heart valve testing device driven by a linear actuator and a real-time control system was used to generate physiological pressure waveforms while samples were exposed to calcification medium containing elevated levels of calcium and phosphate. Bovine pericardium and polycarbonate patches were tested in the device for two weeks in calcification medium and standard medium. Polyurethane (PU) serves as the negative control for calcification. Cytotoxicity assays were performed to confirm the cell compatibility of the device materials. Sterility was tested throughout the trial and at the endpoint. Calcifications in the material were assessed using von Kossa staining and fluorescence-labeled fetuin-A protein. Total calcium content of material samples was also analyzed.

Results
Cytotoxicity assays showed that no materials in contact with the medium affect cell compatibility. Sterility tests showed no signs of contamination after two weeks of continuous operation. Bovine pericardium showed measurable calcification in all trials, while PU showed none. Calcification in pericardium was visualized using von Kossa and fetuin-A staining.

Conclusion
This testing platform will allow for critical insight into calcification mechanisms and thorough validation of biohybrid implants without animal models. Additionally, this platform is compatible with sterile cell culture, facilitating the investigation of native heart valves and novel systemic anti-calcification treatments.
Novel bio mimetic heart valve scaffold: a comparison of two different approaches

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Introduction
Application of tissue-engineered heart valves in the high-pressure circulatory system is still challenging. One approach to overcome these constraints is the development of bio hybrid scaffolds, in which textiles are used as reinforcement to achieve improved mechanical properties. We present a manufacturing process of bio-inspired fiber-reinforcements for an aortic valve scaffold.

Methods
To produce the scaffolds we designed two unique cylindrical e-spinning collectors:
1. Multiple fibers are used (A)
2. A single continuous fiber is used as reinforcement (B)

The production process starts by covering the collector with an e-spun layer. Then the reinforcement fiber is deposited, fixed and then covered by another e-spun layer. The produced scaffolds are tested mechanically and hemodynamically.

Results
Both designs result in an usable scaffold functioning as a heart valve under aortic conditions. Scaffold A possesses superior mechanical properties in radial and circumferential direction compared to B (328.25±20.36 N/m membrane tension compared to 286.1 ± 15.2 N/m in radial direction and 461.64±58.87 N/m to 73,8±6.0 N/m in circumferential direction). The burst pressure for A is also significantly higher with 1402±324 mmHg compared to 255.7±51.3 mmHg. When tested hemodynamically according to ISO 5840 scaffold A is within the limits concerning all values whereas B fails in every test.

Conclusion
A seems to be the obvious candidate for further studies, the design has some shortcomings, which were eliminated by design B. Hence, a third design with a combination of both approaches could be considered.
Non-invasive imaging properties for textile reinforced tissue-engineered heart valves and vascular grafts

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Introduction
Heart diseases becoming more and more prominent in the last decades and clinically solutions in the form of artificial heart valve/vascular graft prostheses have considerable limitations. Biohybrid tissue-engineered heart valves (TEHV) and vascular grafts (TEVG) pose a promising alternative regarding their remodeling and regenerative capacity. Biohybrid tissue-engineered constructs have to be matured in bioreactors in vitro to gain their mechanical and physiological properties before implantation. Neither the textile reinforcement structures nor the grown cells provide sufficient imaging modalities for non-invasive monitoring to precisely control the placement of TEHV and/or TEVG in vivo. These key aspects have increasingly motivated the application and investigation of 19F-MRI providing high image contrast due to the almost complete lack of fluorine background in living organisms. Therefore, this study aims to add imaging visability for in vitro/vivo monitoring of our biohybrid TEHVs and TEVGs via innovative textile materials.

Methods
Highly fluorinated thermoplastic polyurethane (19F-TPU) was spun into fibers to be used as the detectable textile component in our TEHV and TEVG. The 19F-TPU was incorporated into clinically used Poly(ethylen therephtalat) (PET) or biobased Poly(L-lactid acid) (PLA) in various ratios to improve the poor spinning processability and simultaneously determine the amount of 19F-TPU needed to generate a high signal-to-noise ratio. The imaging modality of the produced compounds and fibers were tested in 1H/19F 7T MRI.

Results
Neat 19F-TPU compound and fibers provide a high signal and clear visability. Incorporating the 19F-TPU into PET or PLA, the crystal morphology and the orientation of the polymerchains in the fibers hinder the 19F-TPU to be stimulated by 19F-MRI. Hence, no signal can be detected from the compound-fibers. Variations in fiber production are conducted.

Conclusion
Here, we present the current research progress for the production of novel textiles with non-invasive monitoring ability via 19F-MRI for reinforced TEHV and TEVG.
Towards multiphoton endoscopy of the maturation process of tissue-engineered heart valves

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Introduction
The use of tissue-engineered heart valves (TEHV) is a promising approach for treatment of cardiovascular valve diseases. With the main idea of maturing heart valves from patients' native cells extra-corporeally, this approach solves intrinsic problems of implants of mechanical or xenogeneic origin. However, the maturation process of TEHV is complex, especially because of case-to-case differences due to the patient-specificity of cells. Thus, the maturation process not only needs to be well-defined and controlled, but also requires reliable analysis of current state of the cells, enabling feedback mechanisms for case-tailored control. Here we present multiphoton laser scanning endoscopy (MPLSE) as a potential tool for integration into the TEHV maturation process, being able to non-destructively detect the current state of intra- and extra-cellular matrices.

Methods
TEHV constructs were matured for up to 21 days and stained with immunohistochemistry. Imaging was carried out in two different conditions: using standard bench-top multiphoton laser scanning microscope (MPLSM) and custom made MPLSE system. The images were post-processed using super-resolution radial fluctuations (SRRF) temporal analysis, and analyzed for protein quantification.

Results
We show the successful imaging of the TEHV constructs in 3D using both MPLSM and MPLSE, proving that they can be used for intracellular and extracellular protein quantification in 3D without physically slicing the samples. Furthermore, we demonstrated that the MPLSE system, although employing a minimized probe that can be integrated into bioreactors, can achieve sufficient resolution for protein quantification, which is further enhanced by post-processing tools.

Conclusion
Our results pave the path for further integration of a MPLSE probe into TEHV maturation process. With some further adjustments we are currently working on (e.g. replacement of immunohistochemistry with life-compatible probes or label-free imaging), we may be able to monitor maturation “on-the-fly”, providing current-state data, which can be used as a feedback for the control of maturation process.
Special Session:
Modern Sleep Monitoring -
Signal Acquisition and Analysis
Contactless recording of vital parameters to evaluate the quality of sleep in the nursing environment

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Chronic Fatigue Syndrome (CFS) is a nervous system disorder that causes severe physical weakness in patients worldwide. The number of people affected in Europe is currently estimated at two million, including around 300,000 in Germany. Due to the COVID-19 pandemic, a sharp increase in the number of affected people can be expected. The post-viral symptoms such as fatigue, muscle pain, and neurocognitive symptoms that occur after a corona infection are known as long-COVID. It is assumed that around 30% of those infected with COVID-19 suffer from these symptoms.

The goal of this work is to develop contactless monitoring of body parameters of CFS patients, quantify the level of activity and thus avoid overexertion of patients. Measurable parameters include vital and sleep parameters. The measurement hardware consists of a multispectral 3D sensor system with an RGB camera and two near-infrared cameras, as well as dedicated narrow-band infrared LEDs. Sleep parameters are estimated through the estimation of the pose of the person lying in the bed although a blanket obscures the person. Vital parameters are determined by measuring and analyzing the time course of color, spectral, and temperature values of human skin. Using ensemble learning approaches, the body parameters are bundled into a sleep protocol and quantified to a sleep score. A connection to a database and the design of a visualization system allows for two-way feedback, for both the patient and the physician. The measurements are carried out with reference to polysomnography, the gold standard in sleep diagnostics. The visualized results are evaluated by sleep physicians.

The proposed solution for contactless sleep quality monitoring of CFS patients has the potential of improving the assessment of available energy during the day and therefore reduce overexertion events. This hypothesis shall be validated and quantified with respect to polysomnography in the continuation of this study.
Model adaptability for sleep staging from different cardiorespiratory signals

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Introduction: The most common approach for sleep staging from cardiorespiratory signals is based on previously calculated features, e. g. heart rate variability features. When adapting such a feature-based model to use a different input signal, this results in implementing new features or manually adapting established features. However, when using a signal-based model, the adaption process is part of training the model. The only manual adaption step is simple signal preprocessing to transform the new signal into the expected input shape. The following examples of sleep staging from cardiorespiratory signals demonstrate the simplicity and robustness of this approach.

Methods: In previous investigations, we optimized a model architecture to classify sleep stages based on RR (beat to beat) intervals and BB (breath to breath) intervals from electrocardiogram and respiratory inductance plethysmography. We then (i) applied different variations and noise to these inputs, (ii) changed the input to different signals, e. g. oxygen saturation, and (iii) used varying preprocessing approaches on the signals. Afterwards, we trained models with the same model architecture on these different input options. We compared model performance by Cohen’s Kappa while distinguishing five sleep stages.

Results: Generally, models trained on different inputs yielded similar model performance by Cohen’s Kappa. Especially using the lowpass filtered respiratory inductance plethysmography rather than BB intervals improved classification performance. Classification from heart rate signal and oxygen saturation (as commonly recorded by pulse oximeters) turned out to perform as good as classification from RR intervals.

Conclusion: The previously optimized signal-based model architecture is very robust to input variations. Change of input signals and optimization of signal processing may further improve model performance in signal-based models, even after the model architecture was optimized to another input.
Heart rate and heart rate variability during wake as a predictor for sleep apnea severity

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Introduction
Heart rate and heart rate variability during sleep show characteristic changes with sleep stages and with sleep disorders, such as sleep apnea. This had been exploited to estimate sleep stages and estimate sleep apnea. Heart rate is modulated by sympathetic and parasympathetic tone. An open question is in how far these characteristic changes carry over to daytime effects on heart rate and hear rate variability.

Methods
We used 1622 sleep recordings which were systematically collected in the international sleep apnea global interdisciplinary consortium (SAGIC) study group. We selected 5 minutes of ECG during the wake period before sleep onset with quiet breathing to calculate heart rate variability with standard time domain, frequency domain, and non-linear parameters. The parameters were compared to sleep apnea severity.

Results
We could use 1247 recordings with parallel recording of breathing and proven wakefulness. With ANOVA analysis it was possible to detect statistically significant parameters in heart rate variability for sleep apnea severity. Time domain parameters (SDNN, RMSSD) and Shannon entropy showed best effects. Frequency domain parameters did not show significant differences.

Conclusion
It is possible to estimate severity of sleep from a 5-minute ECG recording using heart rate variability analysis, when recorded with quiet breathing before sleep onset. Now, it should be investigated, whether a morning test of 5-minute ECG recording would give the same results. It reamins to be checked whether the results are specific for sleep apnea or may be confounded by other disorders such as hypertension.
Sleep Arousal Detection with Head Movements

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Introduction
Sleep arousal (SA) is defined as a temporary elevation of the vigilance level. SA manifests brief frequency shifts in the electroencephalogram (EEG) during sleep and could be detected using wearable EEG devices in real-time at home. However, EEG-based detection is not always available. In this work, we propose an alternative approach based on the detection of head movements and compare it to an EEG-based approach.

Methods
We designed an algorithm to detect SA based on the amplitude and duration of head accelerations obtained from a head-mounted 3-axis accelerometer. For comparison, we adapted an algorithm based on power-spectral analysis of single-channel EEG [1]. We validated and compared both algorithms on 6 recordings from 3 female subjects wearing the MHSL-SleepBand v3 [2] at home. An expert labeled sleep stages and SA using the EEG according to the AASM rules [3]. We calculated sensitivity, precision, and real-time detection delays of both algorithms. In addition, we put these results in the context of 4 other EEG-based algorithms that included post-processing and were validated on different data sets [1].

Results
The head movement-based algorithm achieved a sensitivity of 81.4% and a precision of 62.8%, the EEG-based algorithm 85.2% and 53.3%, respectively. This was within the range of other existing algorithms (sensitivity [65%-86%], precision [42%-86%]). The mean real-time delay was 2.54 s for head movement and 4.93 s for the EEG-based algorithm.

Conclusion
Both algorithms showed similar performance, but due to time-domain based calculations, the head movement-based algorithm showed earlier real-time response. Therefore, a head-mounted accelerometer could be a valid alternative to detect arousals during sleep.

Acknowledgements
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References
Special Session:
Medical robotics
Automatic Glasgow Coma Score Determination for Mobile Robots

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Introduction
In rescue scenarios, it is of great importance to assess the health condition of a victim as quickly as possible. This is hard in environments too dangerous for humans, for example in areas with toxic chemicals, or in situations with a large number of potential victims. Therefore, we develop a method to assess a victim's degree of consciousness in such a scenario. We use the procedure described in the Glasgow Coma Score (GCS) as a template and deploy a demonstrator on a robotic platform.

Methods
For assessing the victim's state of consciousness using the GCS, we develop a software that combines skeleton tracking with an AI-based language interaction model. Therefore, we assess the victim's response to certain stimuli, which can be verbal instructions or physical interactions. The response is processed either using the natural language processing or visual interpretation. Visual interpretation is based on a commercially available skeleton tracking software, measuring the victim's pose and analyzing their movement over time. Based on these measurements, socially appropriate verbal instructions are given to the victim and reactions are processed either using robust speech recognition and language understanding techniques or visual analysis.

Results
Preliminary results show that a person can reliably be detected by the skeleton tracker and the positions of the joints are being stored correctly and consistently. A first version of the verbal interaction system has been implemented. The demonstrator shows the general feasibility of the algorithm.

Conclusion
Concluding, our implementation of the GCS is a promising way of assessing the urgency of a victim's need for assistance without human interaction. The GCS is used as a guideline for information flow. The next steps are to fully automate and optimize the procedure.
Joint-Session:

DGBMT & DGfK
Laser-Doppler-Flowmetry allows monitoring of myocardial microvascular circulation during machine perfusion of donor hearts in a resting state

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Introduction
Normothermic ex-vivo machine perfusion (EVMP) of donor hearts with blood in a beating state is a novel method for donor heart maintenance. However, we have shown in porcine hearts that hypothermic EVMP with a crystalloid preservation solution in a resting state is superior to blood perfusion in maintaining contractility of the left ventricle. Lactate release and visual inspection of cardiac contractility are common options for heart monitoring during blood perfusion. Nevertheless, neither allow evaluation of the heart and the perfusion during hypothermic, cardioplegic perfusion. Thus, we investigated if laser-doppler-flowmetry allows monitoring of myocardial microvascular circulation during hypothermic, crystalloid EVMP of hearts.

Methods
In a pig model, hearts were harvested and maintained by EVMP with a hypothermic, oxygenated preservation solution for a transportation time of 4 h. During EVMP, we measured myocardial microvascular circulation by laser-doppler-flowmetry in the left-ventricular wall. After EVMP, hearts were reperfused with blood, and left ventricular contractility was measured with a balloon catheter. The laser-doppler-flow (LDF) during EVMP was correlated with contractile parameters during reperfusion.

Results
LDF showed an individual course during EVMP in each heart. The highest $r^2$ for end-systolic pressure was 0.77 (p=0.027), the maximal slope of pressure increment was 0.73 (p= 0.037), and for the maximal slope of pressure decrement was 0.75 (p=0.032).

Conclusion
Monitoring of myocardial microvascular circulation by laser-doppler-flowmetry is possible during crystalloid, hypothermic EVMP of hearts. Myocardial LDF during cardioplegic EVMP correlates with contractility after EVMP.
Joint Session:
Model-based Personalized
Medical Technology
The role of graded bone modelling in finite element simulations of dental implants

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Introduction
In finite element analysis, bone is often treated as two-layered material that has a discontinuity between the cortical and cancellous bone, which leads to a singularity and incorrect stresses. The goal of this study was to eliminate this singularity and to create a more realistic representation of bone.

Methods
Finite element analyses with dental implants placed in bone were conducted. In the new approach, bone was modelled as a graded material by inserting node-specific values for Young’s modulus in the finite element simulation, whereas the transition zone thickness was derived from a CT scan. The distance of each node to the surface was calculated to determine its location in the model (cortical zone, cancellous zone, transition zone) and to assign the corresponding Young’s modulus. In this way, a transition zone with a linearly changing Young’s modulus is obtained. The modelling was performed semi-automatically, and the maximum principal stresses of the new approach were compared to those of a conventional approach.

Results
The highest maximum principal stresses can be found at the edge of the cortical bone near the implant and the cancellous bone. In the conventional approach, the stresses change abruptly between the two bone tissues. In the graded approach, the peak stresses were overall lower and stress transitions more smoothly. A mesh convergence study showed stress convergence in the graded approach and stress divergence in the conventional approach.

Conclusion
The new approach was found to effectively avoid singularities and provides more accurate predictions of stress in areas of the bone transition zone. A graded bone model leads to a smoother stress distribution for threaded and non-threaded dental implants compared to the conventional modelling approach. As the approach is automatable and causes rather small overhead, it is recommended for use in future work.
Semi-automated generation of bone loss defects around dental implants and its application in finite element analysis

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Introduction
The finite element method is well established in the field of (dental) biomechanics. Unfortunately, building CAD-Models used for FE-Analyses is often time-consuming due to complex geometries and a low automation level. In this work, an approach for automated modelling of bone defects around dental implants for patient-individual mandibular geometries is presented. The approach aims at reducing the model building cost for predicting the biomechanical consequences of peri-implant bone loss.

Methods
The graphical algorithm editor Grasshopper, which is integrated in the CAD-software Rhino 3D, was used to program a tool that is capable of generating bone loss for a given mandibular geometry, with a user defined depth, width and place. Several types of bone loss were programmed, based on geometries that were clinically observed. The developed algorithm was used to generate mandibular bone models with different types and depths of bone loss around the implant body of an implant supported crown (right first molar). FE-Analyses based on these CAD models were conducted and the resulting principal stresses were compared.

Results
The FE results show that different types of bone loss defects applied in this work do not have a significant impact on the observed stresses. The stress distribution in the peri-implant bone was found to depend mainly on the depth of bone loss.

Conclusion
The developed automated approach for bone loss modelling was successfully applied and seems suitable for future work. As the type of defect had a negligible influence on the stresses, it seems plausible to use only one defect type when generating bone loss models for prognosis in order to save time.
Investigation of different grading approaches for additively manufactured dental implants

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Introduction
Additive manufacturing enables local grading of the stiffness of dental implants through targeted adjustment of the manufacturing parameters. The extent to which such a manufacturing approach affects the interaction between the implant body and the surrounding bone, and what grading is optimal, is currently insufficiently investigated.

Methods
In this study, graded implant bodies were examined using the finite element method. For the simulation, a section of the mandibular jawbone with an implant was used. A force of 100 N parallel to the implant axis and 20 N in distal direction was applied onto the crown. First, for a non-graded implant, it was determined which parts of the implant could potentially be responsible for problematic loading. Based on those results, five different graded material approaches were created for the implant and then examined, to see if they would lead to reduced stresses in the peri-implant bone.

Results
The results show that both the maximum and minimum principal stresses (tensile and compressive) in the surrounding bone of a loaded implant can be reduced by targeted local adjustment of stiffness. The reduced loads might minimize the probability of implant failure due to reducing bone loss caused by overloading.

Conclusion
Based on the results, a graded stiffness in dental implants appears to be suitable for developing advanced, patient-specific implant solutions. However, the effect of the gradations studied on the expected failure loads under static or cyclic loading has not yet been investigated.
Aortic valve tissue in pulsatile dynamic culture in a microphysiological system: Simulation of calcification potential and tissue deflection

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Introduction
Tissue culturing microfluidic devices in aortic valve research have to fulfill particular requirements regarding flow rate, shear forces and pressure to closely reflect in situ conditions. Current experimental models in calcific aortic valve disease (CAVD) research lack certain physiological, anatomical or biomechanical features. Therefore a tissue incubation chamber (TIC) associated to a microphysiological system (MPS) was designed, initially implementing rectangular porcine AV subsections. This study aims to accomplish this model concerning biomechanics, pulsatile tissue deflection and calcifying potential by application of circular AV tissue subsections.

Methods
MPS design was edited to a 4mm TIC diameter to enhance shear strain. Porcine aortic valve (pAV) tissue viability was evaluated using resazurin reduction assay every 2nd day and finally visualized by LDH activity in cryosections after 14d. Calcification potential of pAV was induced by ADGMedium and histologically visualized by alizarin red and von Kossa staining. To implement circular excised AV tissues vertical to medium flow, tissue adhesive was used for edge fixation on TPU-ring and impact on viability was preevaluated.

Results
After 14d of incubation resazurin reduction rate decreased significantly to 59.5 ± 10.7% in static controls, but only to 72.4 ± 6.4% within the 4mm TIC. LDH stain revealed missing LDH activity in central regions of static controls but only minor areas of dynamically incubated samples. Application of ADGM induced microcalcifications in AV tissues and resulted in a further decrease of viability (42.3 ± 6.6%). Tissue adhesive application prior to TIC implementation did not result in a minimisation of resazurin reduction rate. Merely a thin contact zone showed decreased LDH activity.

Conclusion
MPS system in CAVD research allows modelling of in vivo conditions with the potential to simulate tissue calcification using induction media. Native tissue preservation can profit from established deflection movement, side-specific biomechanical impact and is focus of ongoing research.

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In silico modeling of gas washout methods for the assessment of pathological changes of the small airways

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Guideline-based spirometry is the standard method for the diagnosis of obstructive pulmonary diseases. However, this method lacks the necessary sensitivity for the early diagnosis of those diseases, since pathological changes in the small airways that occur in the early stage cannot be detected. For this purpose inert gas washout methods can potentially be used. The complexity of lung anatomy, physiology and pathology makes it difficult to interpret washout data such as the phase 3 slope ($s_3$), which is a measure of gas distribution in the alveolar regions. Existing numerical lung models have supported the analysis of washout methods, but either do not adequately represent the complex interactions between physiological and pathological processes or are computationally intensive.

We present a new numerical lung model based on finite difference method in which the branched airway structure is reduced by a compartmental approach leading to reduced computational effort. The airway geometry, convection and diffusion are modelled using electrotechnical quantities. A multi-breath washout study with 50 breaths ($1 \leq n \leq 50$) with the tracer gases sulfur hexafluoride (SF$_6$), oxygen (O$_2$) and helium (He) was performed to investigate the influence of asymmetric volume ratios of 1.25/0.75, 1.50/0.50 and 1.75/0.25 between parallel lung units in the airway generations 15-18 on $s_3(n)$. The total volume flow is 500ml/s.

Our results show that the maximum value of $s_3(n)$ shifts from $n=1$ to higher $n$ when asymmetries occur in generations 15-17 and 16-18 for He and O$_2$ respectively, representing the transitions between convection- and diffusion-dominated zones for these two gases. The maximum values of $s_3(n)$ for SF$_6$ are at $n=1$. The values for $s_3(n)$ correlate with the degree of asymmetry.

With our new numerical model, we are able to simulate the washout methods. We conclude that $s_3(n)$ of different gases can provide information about the generations in which the asymmetries occur.
Complex musculoskeletal model of the human shoulder after total joint replacement

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Introduction
Anatomical total shoulder replacement (ATSR) is an established treatment for osteoarthritis of the glenohumeral (GH) joint, whereas reverse total shoulder replacement (RTSR) is commonly performed for irreparable rotator cuff tears and in case of revision. Current simulation models of the shoulder joint after total shoulder replacement usually do not include translation of the GH joint and are often limited to inverse dynamic analyses. Therefore, this study aimed to implement a complex musculoskeletal model of the shoulder after ATSR and RTSR.

Methods
The GH joint was modeled with three rotational and three translational degrees of freedom using a polygon contact model for the articulating implant surfaces after ATSR and RTSR. The forward dynamics model is driven by 67 muscle elements for the ATSR and 37 for the RTSR using a computed muscle control algorithm to calculate the muscle forces from a simplified inverse dynamics model with a spherical GH joint to generate the abduction movement.

Results
The model was validated with results from own robot-based tests (hardware-in-the-loop simulations) with the same implants and data from an experimental study. Muscle forces, GH joint forces and translational movements were evaluated, showing good overall agreement. The prescribed in vitro abduction movement was reproduced with a root-mean-square error below 0.59° for the ATSR and below 1.51° for the RTSR. Translations were below 0.3 mm for the RTSR and highest in the inferior-superior direction of the ATSR with 1.41 mm. GH joint forces during the abduction movement with a maximum absolute force of 82% bodyweight for the ATSR and 45% bodyweight for the RTSR were calculated.

Conclusion
The presented musculoskeletal model of the shoulder provides muscle and joint forces as well as translations during an active abduction movement. It will be employed for further biomechanical analyses regarding complex joint movements, loading conditions and muscular deficiency.
Joint Session:
Multimodal Signal Analysis for Cardiovascular Assessment
Keynote: Advances in biomedical time series data acquisition and analysis systems

S Herberger

Introduction
The recording and analysis of biomedical data are subject to constant change through technological advances and evolution of clinical applications. Technological progress from recent years offer hope for underserved patient populations and risk groups that result from demographic change and the lack of resources in the healthcare system, yet significant hurdles stand before the realization of these potentials.

Methods
Advances in electronics and sensor technology have opened up unprecedented possibilities for data acquisition, which can now be performed on the patient's body, independent of their location. The rapid evolution of machine-learning-based data analysis methods offers prospects for improving established analysis methods and for the generation of novel insights that go beyond our current understanding. The potential for technological progress stands against established processes and structures of the healthcare system, and tradition and habits in provision of health services.

Results
Using concrete examples from medical practice, advances and possibilities of new technologies are discussed in the context of their technical requirements and their application space, wherein examples from cardiology and sleep medicine will be used: Firstly, advances in microelectronics and sensors are discussed, which form the basis of biomedical measuring systems. In this context, the evolution of ECG technology is highlighted, with a multitude of different systems is already available, and more to come. In a second part, advances in automated data analysis methods are examined using recent examples from cardiology and sleep medicine.

Conclusion
Societal change requires better and more efficient systems for diagnosis and treatment. The prospect of improved systems for recording and analyzing biomedical time series arising from rapid technological progress is past years offers such opportunities. Meanwhile, large hurdles remain to be solved for their implementation into clinically applicable solutions, including regulatory, but also requirements in the clinical context and the particular healthcare system.
Home sleep monitoring with electrode patch and contactless recording of breathing and pulse

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Sleep disorders are a major contributor to an increased risk factor of cardiovascular disease. Sleep apnea affects 425 million of the world's 30- to 69-year-olds. Insomnia has been identified as a predictor of recurrent cardiovascular events. Early detection of sleep disorders may help to mitigate subsequent diseases via targeted therapies. This motivates the development of a modular home sleep monitoring system.

The focus of the development is on a novel electrode patch for recording electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG), the contactless recording of breathing, pulse and body movement with radar and the algorithms for the automated evaluation of this data. In a study with 12 subjects, the selected electrode positions of the electrode patch were evaluated using hypnograms of a mobile polysomnography. The evaluation was performed by annotation of an experienced scorer and by automatic classification. The recording of respiration and heartbeat by radar was tested in a study with 21 subjects in comparison to the recording of breathing and an electrocardiogram (ECG) via a chest belt. The evaluation was based on frequency analysis and a rule-based approach to account for expert knowledge.

Averaged over all sleep phases, an F1 score of 0.74 (W:0.77, N1:0.51, N2:0.78, N3:0.85, REM:0.80) is obtained based on the annotations of the scorer in comparison of electrode patch to PSG. The automated analysis scores a mean F1 of 0.75 (W:0.75, N1:0.58, N2:0.77, N3:0.81, REM:0.86) when comparing electrode patch versus manual annotation based on PSG. When analyzing breathing based on radar data, there is a deviation of less than 3 breaths per minute for a duration of 7.4 hours over the combined measurement period for all subjects of 10.5h.

Prototypes and analyses represent a promising opportunity for home sleep monitoring and thus a relevant support to detect sleep disorders for their mitigation by appropriate interventions and therapies.
Morphological ECG Analysis – Revealing Valuable Features for Medical Diagnosis

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Introduction
Cardiovascular disease (CVD) is the most common cause of death worldwide. Changes in biosignals can provide early indications of CVD. Current research shows that the analysis of QT variability (QTV) in the electrocardiogram (ECG) can contribute to diagnosis and risk stratification of various CVDs. Today's methods for QTV analysis can reflect complex morphological changes only to a limited degree. However, the analysis of these changes opens new approaches to the diagnosis and therapy of CVD.

Methods
To overcome current limitations and to provide the basis for a clinical application, a novel method for analyzing the morphology of biosignals has been developed. The method is based on an iterative two-dimensional deformation of a one-dimensional template (2DSW, Two-Dimensional Signal Warping). The adaptation of the template is made with a two-dimensional warping grid to analyze complex changes, especially the QT interval morphology. Focusing on robust detection of subtle quasiperiodic changes as well as a generalized implementation, the method is feasible in various applications.

Results
The evaluation of 2DSW showed a higher robustness for common artefacts compared to current methods. At the same time, 2DSW shows an improved sensitivity to subtle beat-to-beat changes in different simulated and clinical data sets. Amongst others, we could demonstrate for the first time a significant influence of sleep stages on QTV. Based on 2DSW, new QTV parameters have been developed that have improved risk stratification in various clinical trials. For example, in assessing acute mental stress that is associated with higher CVD risk in the long-term, the parameters developed were shown to provide substantial additional value.

Conclusion
The improvements in the detection of complex morphological changes in ECG by 2DSW result in more accurate QTV analyses and provide the possibility to extend existing clinical monitoring procedures to QTV analysis, thus contributing to better diagnosis of CVD and potential therapeutic approaches.
Wearable chest patch as a source of multi-modal data for seizure detection in epilepsy.

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Introduction

Wearable electrocardiography (ECG) patches allow comfortable long-term monitoring of heart activity. In our interdisciplinary working group, we investigate how they can be used to detect focal unaware seizures in epilepsy. The long-term goal is to develop transparent detection algorithms robust to data quality fluctuations. The objective of the presented work is to develop a data-analysis pipeline that allows sensor synchronization and automatic quality assessment necessary for making informed decisions on the robustness of candidate model features. This pipeline also enables the extraction of an additional relevant data modality, namely breathing rate.

Methods

ECG and activity (accelerometer) data are collected with a custom-made chest patch from patients at the video-EEG monitoring unit. In parallel, data from routinely used ECG and EEG (electroencephalography) monitors are recorded. The seizures are labeled, and several patients are additionally monitored with breathing belts.

Three algorithms for ECG data synchronization are modified from works [1], to support further robustness analysis. The quality metrics are adapted from [2]. The breathing rate is obtained by fusing accelerometer data and respiratory sinus arrythmia available from ECG (similarly to [3]).

Results

In this work, we show the preliminary results from 10 patients. Synchronization algorithms are compared for execution speed and robustness towards noise. Signal quality is compared for both ECG sensors before, during and after the seizures. Extracted breathing rate is compared against the breathing belt data, similarly, in different peri-ictal time intervals.

Conclusion

The presented pipeline aligns two sources of ECG data, derived breathing rate and quality assessment. Seizures are found commonly linked to the drop in the data quality for both ECG sensors. Therefore, in further work, a strong focus will be put on continuous quality assessment, robustness of the extracted features and quantification of the trust level assigned to the algorithm outputs.
Potential of multi-site pulse recordings for a refined cardiovascular assessment

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Introduction: Multi-site pulse measurements can reveal valuable information with relevance for a refined cardiovascular assessment. The aim of this contribution is to (1) overview existing research in the field, (2) present own results from experiments featuring multi-site and multimodal photoplethysmography (PPG) and (3) discuss ideas on the usage of multi-site photoplethysmographic data for cardiovascular assessment in face of the existing literature.

Methods: Our analysis bases on experimental data from 39 healthy volunteers (13 female, mean age 30.5 years) during a cold pressure test (CPT). The multimodal recordings featured PPG measurements under varying recording setups, namely contact acquisition from finger and earlobe and non-contact facial acquisition by cameras. Employing the different recording setups, we analyzed four common PPG features (amplitude, slope, area, pulse width at half amplitude (PWHA)) from three epochs (30 seconds before, 20 seconds after and 40 seconds after immersion).

Results: As expected, the CPT led to a pronounced physiological effect including a persistent blood pressure increase. With respect to PPG recordings, all recording setups yielded significant changes between epochs. However, effect size varied between recording setups with finger PPG typically showing the most pronounced effect. In case of PWHA, we even found inverse effects between finger and head recordings.

Conclusion: Our results indicate substantial differences between recording setups hinting at different dominating factors in the formation of PPG signals. Considering the literature and with respect to the future use of multi-site measurements, our findings imply three main conclusions: first, joint analyses of multi-site PPG signals, e.g. using signals’ timing, should consider potential morphological changes. Second, analyzing the interaction of PPG signals from different recording setups has the potential to refine cardiovascular assessment. Third, models should be developed that reflect differences between recording setups and relate existing differences to health and disease to make purposeful use of them.
Track:
Digital Health and Care
Change of ST-level during and after physical activity in young men

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Introduction
Longterm ECG - for example provided by wearables - can monitor short-term changes due to different physiological states. ST-elevation, typically associated with severe cardiovascular diseases such as myocardial ischemia, is frequently observed in young healthy men. Therefore clinical guidelines recommend general higher thresholds for young men. However, automated ECG analysis without age and gender consideration may trigger false alarms. Therefore, we aim to quantify the incidence of physiological ST-elevation in healthy subjects during and after physical activity.

Methods
Serial ECGs of 24 male subjects (23-29 years), provided by the EPHNOGRAM database, were analyzed. Data was acquired with a prototype ECG device and 30 s recordings before and after 30 min physical activity were analyzed. R-peaks were detected using the open-source library ‘Neurokit2’ (detector: ‘kalidas 2017’) for each subject in both physiological states. Subsequently, fiducial points (P/QRS/T peak, on-/offset) were detected and typical ECG parameters were derived.

Results
While resting, the majority of subjects showed ST-elevations and the virtual heart beat showed an average of 0.2 mV elevation. 66.6% of subjects were above the age-adjusted threshold of 0.25 mV defined by the American Heart Association guideline. We observed decrease of ST-elevation in all subjects after exercise, with only 20.8% being above the threshold.

Conclusion
Age- and gender-related changes pose a challenge for automatic ECG interpretation based on clinical guidelines. We demonstrated that even gender- and age-adjusted thresholds are surpassed by the majority of the analyzed cohort. However, decrease of ST-elevation during exercise is observed - in contrast to cardiovascular patients, where stress typically increases ST-elevation. Therefore, we propose to consider the stress-induced trend of the ST-level in the clinical interpretation of ST-elevation. As the presented work comprises a limited number of subjects a and non-medical grade ECG device, we plan to test our hypothesis in a large-scale clinical study.
Extracting digital biomarkers for classifying Parkinson’s disease with voice recordings from mobile phones

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Introduction

Due to varying symptoms, early diagnosis of Parkinson’s disease (PD) and objective measurement of medication effect is challenging. We investigated which features of mobile phone voice recordings can differentiate between participants with and without PD (PDCLASS) and identify pre- and post-medication conditions (PRE/POST).

Methods

We formed 4 classes ‘With PD’(3758), ‘Without PD’(4001), ‘BeforeMedication’(1324) and ‘AfterMedication’(1602) from 10-second recordings of /a/-vowel phonation from the mPower dataset (https://doi.org/10.1038/sdata.2016.11). We extracted 60 features and grouped them into jitter, shimmer, non-linear dysphonia, mel-cepstral-coefficients, amplitude, frequency-power, temporal, wavelet, pitch, and tremor. To identify the most salient features, we performed a cyclical analysis using a multilayer perceptron classifier for each classification.

Groups were added one-by-one during a 5-fold cross-validation, updating the feature vector if accuracy increased. The most informative groups were those that the most often increased accuracy. Features were then removed one-by-one and, if the average accuracy remained unchanged or increased, removed definitively. Then all remaining unused features were randomly added one-by-one and, if the average accuracy increased, included. Finally, we build two classifiers with the selected features and demographics (age,sex).

Results

The number of features reduced from 60 to 7 (PDCLASS) from 3 groups (amplitude, temporal and pitch) and to
9 (PRE/POST) from 4 groups (tremor, mel-cepstral-coefficients, frequency-power and pitch). The AUC of PDCLASS was 95.1%, which was slightly higher than the 82.6% achieved with 5 features plus demographics. The AUC for PRE/POST was 59.1%. This may be explained by the fact that extracted features don't include a sufficient number of useful information.

Conclusion

PDCLASS requires different voice features than PRE/POST medication detection.

Keywords: Parkinson's disease, Voice Recordings, Mobile Data, Feature Extraction, Classification
A smartphone-based approach to continuous monitoring of Parkinson’s disease patients

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Introduction
Idiopathic Parkinson’s disease (PD) is a prevalent neurodegenerative diseases. The motor- and non-motor symptoms which undergo fluctuations multiple times a day, presents challenges in assessing disease progression. Annual assessments are inadequate in capturing deteriorations and addressing the burden faced by patients and caregivers. An early, home-based assessment is a crucial of needs-oriented-care of PD-patients. This mobile application aims to bridge the gap between annual appointments and assist healthcare professionals in monitoring patients and responding to changes in their condition.

Methods
In accordance with the medical device regulation, motor-tests such as the finger-tapping-test as well as a collection of standardized questionnaires will be possible. Besides the proof of a positive care effect, the validation of the smartphone-based monitoring includes a corresponding proof of completeness, functionality, usability, safety and performance of the application. Meeting these requirements is a prerequisite for approval as a digital health application (DiGA) which we are targeting. The application is designed to benefit patients, doctors, and caregivers alike, facilitating communication and information sharing between all stakeholders.

Results
By our multi-professional team of developers, movement disorder specialists and patients, a prototype was developed, which has already been tested on various patients. The patients’ evaluation of their user experience was positive. Within the scope of our ongoing studies, each individual test module will be subjected to clinical testing. As a long-term goal, we expect to measure a positive care effect through more frequent, more accurate and unbiased data collection. Development is accompanied by preparation of documents for the approval of the medical device, as well as data protection measures.

Conclusion
The digital health application developed here will put patient-centered-care at the heart of therapy for people with Parkinson’s disease. Parkinson’s sufferers will thus benefit from better therapy and an increased self-awareness of their symptoms and needs arising from the disease.
Track:

Devices and Systems for Surgical Interventions
Nitinol catheterization cannula for MRI-guided vascular interventions

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Introduction
Using MRI-guidance for vascular interventions is a promising technique to reduce X-ray exposure for patients and clinicians. Yet, the sheer lack of suitable instruments to perform interventions inside the MR environment is a hurdle that could only be taken by innovative redesigning conventional devices. For the first link in the procedural chain during a catheter intervention, we present preliminary data of an MR Conditional cannula for vascular access.

Methods
Since nitinol is a reliable material for interventional devices, the new 18G cannula was designed on an 80 mm nitinol tube glued to a clear plastic hub with a female Luer connector. A bevelled tip was chosen similar to conventionally available cannulas for femoral arterial access with facet grinding applied by electrochemical machining. The manufactured models were examined regarding the force to penetrate foil at a 45° angle. SEM images of the nitinol cannula and a conventional model were acquired before and after penetration tests. Further, the cannula was used on a silicone patient phantom to perform MRI-guided stenting.

Results
Force-Path diagrams of the nitinol cannula and the stainless steel are similar, with the Nitinol model showing a higher maximum force needed (4,3 N ± 0,2 N vs 3,3 N ± 1,2 N). Optical and scanning electron microscope images revealed no visible abrasion at the bevel after multiple PU foil penetration for either the nitinol or the conventional cannula. In hands-on tests with silicone tubes, no noticeable difference was recognized regarding handling, penetration force and bending properties in comparison with a conventional catheterization cannula.

Conclusion
The nitinol 18G cannula presented no drawbacks compared to a conventional stainless steel cannula. In addition, usability and applicability for femoral access when used in combination with a nitinol 0,035" introduction guidewire were successfully validated during silicone phantom studies by clinicians with affirmation in animal trials pending.
IMU-based displacement detection of spinal vertebrae during image-based surgeries

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Introduction
Modern spinal cord surgeries employ image-based navigation systems to enable precise interventions. During the procedure, preoperative scans and a motion-tracking system are used to guide the surgeons. However, space constraints and a permanently required line of sight forbid using marker targets on the treated vertebrae. Therefore, displacements of the treated vertebrae relative to the tracked vertebra cannot be detected, which can lead to severe injury of blood vessels or nerves. To address this issue, we propose to attach inertial measurement units (IMU) to the spinous processes of the treated vertebrae. The sensors are small, do not interfere with the procedure, and do not require a line of sight like motion-tracking systems.

Methods
A unit consisting of a consumer-grade IMU (Adafruit LSM6DSOX + LIS3MDL), motion-tracking markers, and a microcontroller was attached to the C3 vertebra of a phantom spine. As ground truth reference, motion-tracking targets were placed on the C2 and C3 vertebrae. The IMU and motion-tracking system were integrated into the hardware-agnostic robot operating system, and data was recorded as rosbag. An error-state Kalman filter was implemented in Matlab because of its low linearization error. The measurement covariance matrix was tuned using a static measurement. The process noise was tuned by minimizing the error of the estimate compared to the ground truth.

Results
Preliminary results show that the error-state Kalman filter can robustly track the roll and pitch angles using the IMU’s accelerometer and gyroscope. Due to unreliable magnetometer measurements, the yaw angle cannot be estimated robustly. The translational estimates drift without additional sensors.

Conclusion
When applying realistic forces to the vertebrae, most of the displacement is expected in the roll angle, which can be tracked robustly. Thus, small IMU units attached to the treated vertebrae could be used to detect critical displacements during surgical interventions.
Track:

Rehabilitation Technology
A Hybrid FES-Exoskeleton with ILC Control for Gait Assistant

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Stroke and spinal cord injury (SCI) are leading causes of paralysis, necessitating the development of innovative solutions for gait assistance. This study introduces a novel hybrid functional electrical stimulation (FES) exoskeleton with iterative learning control (ILC) for individuals with impaired gait. The hybrid exoskeleton combines an FES system and a motorized exoskeleton to provide comprehensive assistance during walking.

The key contribution of this study lies in the utilization of the ILC algorithm, which enhances the exoskeleton's performance by dynamically adjusting the FES and exoskeleton control parameters to minimize tracking error. This cooperative control strategy improves the synchronization between the user's motion and the exoskeleton's assistance, leading to a more precise and natural gait pattern.

Experimental results demonstrate the effectiveness of the proposed hybrid FES exoskeleton with ILC control in assisting gait for individuals with lower limb impairments. The study reveals significant improvements in the gait pattern and a reduction in energy expenditure during walking. These findings highlight the innovation and superiority of the proposed ILC approach compared to existing methods for hybrid exoskeletons.

The implications of this research are promising, as the proposed hybrid FES exoskeleton with ILC control shows potential in enhancing the quality of life for individuals with gait impairments. By providing tailored assistance and optimizing gait performance, this technology has the capability to improve mobility and independence for individuals affected by stroke or SCI.
Track:
Medical Device Regulation and Innovation
Could artificial intelligence turn clinical need into a driver of innovation to bridge the valley of death in medical translation?

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Introduction
Extended time to market, late failure finally in clinical implementation, and declining innovation in healthcare – these are all symptoms of the translational crisis in biomedical engineering.
Far too often, innovative medical devices are lost in the valley of death due to complexity and the lack of connection to clinical demand, typical for the technology push approach. Although demand driven innovations are more likely to get marketed, hardly any procedures have been established to effectively find an optimized technological solution from a given clinical need with the greatest possible technology openness.
Therefore, we explored the potential of AI-based mining of published knowledge to find demand matching technological solutions for a real oncological use case.

Methods
Starting from a scoping review, two different seed-document-based and automated search procedures, bag-of-words (Bow) and a readily available semantic PubMedBERT model trained on sentence similarity task, are engaged on localized PubMed and PATSTAT databases. A final machine learning classifier is trained using scoping results to accelerate the relevance screening. A workshop of experts contributed to evaluate and embed the AI based steps into a process leading from clinical demand to substantial funding or investment.

Results
While the Bow approach revealed 91% work-saved-over-sampling and overall recall at 76% on publications, it performed weak on patents. Here the semantic BERT approach showed its strength.
The manual synthesis suggested three possible feasibility projects to be conducted simultaneously and finally guided by e.g. regulatory experts towards venture team building and pitching.

Conclusion
The results point the way to a comprehensively modified innovation path starting from unmet medical needs. But to shape such a disruptive demand driven innovation path, technology openness, parallelism in early innovation phases, and a reduced sector structure in public research funding must be instituted.
Track:
Hospital Engineering
Improved system for linearizing expiratory flow in ventilated patients

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Introduction

We have developed an enhanced version of the FLow-controlled EXpiration (FLEX) system for linearizing expiratory flow that is usable in conjunction with a conventional ventilator and with spontaneously breathing patients. Being demonstrated an important option for lung-protective ventilation already, we hope that linearization of the expiratory flow based on closed-loop control will further improve patient outcomes and provide a more effective impact of mechanical ventilation for studies in patients with lung diseases.

Methods

We have developed our improved FLEX system based on self-designed 3D-printed parts, as well as a flow sensor and up to three pressure sensors. These sensors enable comprehensive monitoring of respiratory parameters and fine-tuning of expiratory flow. The system employs a rotating disc within a tube to adjust the size of an aperture. This disc is magnetically connected to an external hollow-shaft stepper motor, enabling contactless flow adjustment. This design allows for precise linear step-wise flow control, and by serving as a media-separated flow control valve, it eliminates the need for electronic components in the breathing tubes. We tested the new FLEX system with various mechanical ventilators and different test lungs and in large animal experiments.

Results

The system effectively linearized expiratory flow, even at high expiratory flow rates up to 100 liters/min, and with various ventilation modes. In animal studies, our system was able to linearize the expiration in lung-healthy and lung-injured pigs, even with respiratory rates up to 50/min.

Conclusion

We have developed an improved FLEX system that provides a more accurate and reliable means of linearizing expiratory flow even at high flow rates and high respiratory rates, which makes it particularly effective in achieving lung-protective ventilation. Furthermore, due to the contactless control of the aperture the gas-carrying tube remains intact. This would allow a save use in patients without risk for leak.
Low-cost small animal ventilator developed from commercially available components

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Introduction

Small animals, especially mice and rats, are mostly used in pre-clinical studies. For all models where the respiratory system is depressed or subject of analysis, mechanical ventilation is indispensable. However, commercial small animal ventilators are both expensive and limited in their functionality, as they only provide limited ventilation patterns. The development of a low-cost small animal ventilator comprising exclusively of commercially available components that allows for more comprehensive ventilation options could greatly benefit the research community.

Methods

We have developed a small animal ventilator based on a cylinder pump system (Festo), which is driven by a linear motor with a lead screw (Nanotec). This system allows for precise and controlled delivery and removal of a defined volume of gas to and from the animal's lungs. Valves (Bavaria Fluid Systems) are used to enable fresh gas supply and a variable positive end-expiratory pressure (PEEP). The system is capable of generating respiratory rates up to 120/min with tidal volumes up to 4ml in ventilation mode, and also tidal volumes up to 15ml with lower respiratory rates, e.g. for recruitment maneuvers. The ventilation patterns can be customized by choosing different inspiration and expiration curves following any mathematically representable curves.

Results

The small animal ventilator was confirmed to deliver the desired tidal volumes and respiratory rates with an external flow and pressure measurement at various ventilation patterns including linear, exponential and sinusoidal flow patterns in inspiration and expiration. The results showed that the delivered tidal volumes, respiratory rates, PEEP and ventilation curves were in agreement with the set parameters and independent of the chosen ventilation pattern. Total component costs were about 650€.

Conclusion

In summary, this system allows labs to set up a small animal ventilator at a significantly lower price than commercially available models and to customize ventilation patterns with any mathematically representable curves.
Disinfection effectiveness of a UV-C robot in a clinical setting

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Introduction
The disinfecting effect of UV-C radiation on microorganisms has long been known [1]. The technology is already being used in some areas such as water treatment. Recently, another field has been developing, namely autonomously acting UV-C robot systems [2]. In this work the disinfecting potential of such an UV-C System (HERO21, ICA Traffic GmbH) was investigated for the possibility of disinfection in a clinical setting. Such systems could be an additional factor in infection prevention and patient safety.

Methods
The UV-C robot system was tested in the Research OR (OTH, Amberg-Weiden) for its effectiveness. For this purpose, standardized soiling with a solution of test bacteria (Staphylococcus aureus, ATCC 6538; 1*10⁶ CFU/ml) was applied and the residual contamination after UV-C disinfection was determined by contact plates. In a second test run, the implementation of the system in hospital setting was investigated. Therefore, surfaces were contaminated in a patient room following the routine measures anaolgous to the first test and the efficiveness of the UV-C robot system was evaluated in a real clinical environment.

Results
The evaluation showed effective germ reduction by the system. Due to the test concept and set-up, the maximum germ reduction of >3.7 log levels could be achieved at almost all test sites. The tests in the hospital under clinical conditions also showed similar results. Lower reduction rates were achieved at test sites difficult to clean and reach by UV-light (drawers, backs of surfaces, etc.).

Conclusion
The study could prove the effectiveness and feasibility of integrating such a system into clinical settings. However, in a realistic clinical environment, limitations of the application also become apparent. Further investigations are needed to clarify how the use of such a UV-C robot can support the clinical staff in infection prevention and control in the future.
Track:
Additive Manufacturing and Bioprinting
Active wound patch with electrical stimulation

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Introduction
Chronic wounds refer to wounds that show no healing tendencies after eight weeks or have not been healed[I]. This project aims to develop a therapy that leverages the electrical gradient to induce cells in regenerative tissue to migrate and polarize in a guided way for accelerated[II] and enhanced wound healing using an "intelligent electronic patch".

Methods
We benchmarked different conductive silver-based and carbon based inks as well as insulators to choose best materials for screen-printing. The selected materials were printed, analyzed for their morphology and adhesion tests were performed. The propagation of electric field strength in the human body was simulated to a depth of 5 mm and based on this a multi electrode design was conducted, electrodes were printed for cytotoxicity testing and durability tests (voltage-carrying electrodes in cell medium over different operating times). The electrodes were used in vitro to demonstrate biological effectivity in stimulating HaCat cells in a scratch assay test at a partner university.

Results
Our project defined the use of an anode for a maximum operating time of 120 minutes to prevent potentially harmful introduction of agglomerates or metal ions into the wound dressing. To ensure a therapy time of 4x120 minutes, we designed the final demonstrator with four electrically separately controllable anodes and a large-area cathode. This design layout extends the operating time of the patch to 96 hours vs. the addressed 76 hours.

Conclusion
Compared to the state of the art[III], we demonstrated printed electronics on medically approved substrates. To confirm the suitability of material combinations in challenging humid environments, we conducted extensive reliability testing. Furthermore, we demonstrated material combinations (silver/carbon) and the necessary process control for deposition on flexible substrates. In addition, a demonstrator with vias for complex signal routing was developed to show possibilities in assembly and connection technology.
Optimizing the fiber architecture via melt electrospinning for graded fiber scaffolds in musculoskeletal tissue engineering

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Introduction
Injuries to the bone/tendon junctions can lead to various pathologies in the musculoskeletal system, which can be caused by aging or metabolic diseases. Melt electrospinning (MES) has been increasingly used to produce graded polymeric fiber scaffolds that can aid in the reconstruction of tissue interfaces. One of the key advantages of MES is the ability to control the deposition of polymer fibers, allowing for the creation of scaffolds with a reproducible, three-dimensional structure. This study aims to fabricate and assess the mechanical behavior and cell compatibility of melt-electrospun fiber mats with varying fiber geometries.

Methods
Electrospun fiber scaffolds were manufactured from a polycaprolactone (PCL, MW=45kDa) melt, with different fiber geometries, including non-oriented (i), grid-patterned (mesh width 20µm) (ii), and graded scaffolds with fibers of different deposit densities (iii). For fabrication of the graded scaffold, the collector speed was changed during the process. To investigate the mechanical behaviour both unaxial and dynamic tensile tests were conducted. Additionally, cytocompatibility tests were conducted with hMSC. Cell viability was measured after 1, 3, and 7 days.

Results
The average diameter of the fiber scaffolds varied depending on the scaffold type, with values of 25µm, 22.2µm, and 28µm for types (i), (ii), and (iii), respectively. Uniaxial tensile tests showed a force at break of 15N for (i), 17.5N for (ii), and 20.2N for (iii). Cell viability significantly increased in short-term (1d) cell attachment for scaffold type (iii) compared to (i), and long-term viability and proliferation of hMSC was comparably high for scaffold types (i) and (iii), whereas lower survival rates were observed for type (ii).

Conclusion
This study demonstrates that MES can be used to produce graded fiber scaffolds with varying fiber geometries that exhibit improved mechanical stability and good cytocompatibility. These findings have important implications for the development of tissue engineering strategies to treat musculoskeletal injuries.
Towards an Hydraulically Actuated Extruder for Bioprinting

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Introduction
The interest in 3D bioprinting is rapidly growing since it enables manufacturing functional human tissue for individualised transplants and in-vitro testing. Extrusion-based bioprinting is the most commonly used bioprinting technique. The vast majority of existing extruders is pneumatically actuated, which reduces their precision when extruding fluids with time-dependent viscosity due to the changing flow resistance. More powerful mechanically actuated extruders do not suffer from this drawback but are often bulky and heavy. We combined advantages of pneumatically and mechanically actuated extruders by developing a novel compact and robot-mountable hydraulically actuated one.

Methods
A prototype of a hydraulically actuated syringe-pump extruder for high-viscosity fluids was built and evaluated. We used a low-cost high-precision membrane-based micro pump, an Arduino microcontroller, a standard glass syringe, a custom piston, and a custom cap to built the prototype. The actuation-fluid and the extrusion-fluid are only separated by the piston. To evaluate the performance of the extruder, we performed several timed extrusions onto a high-precision scale. The flow rate was calculated using the extruded mass-per-time-interval and the density of the extruded fluid.

Results
The prototype of the compact hydraulically actuated extruder was small, light, easy to set up, and able to extrude high-viscosity Xanthan-based hydrogels. By setting the amplitude and frequency for the membranes of the micro pump, we achieved flow rates from 1.1 to 7.0 ml/min. However, a large variability in trial-to-trial flow rates for constant pump settings was observed.

Conclusion
We demonstrated the feasibility of a hydraulically actuated extruder for bioprinting. Due to its compactness and light weight, it is especially interesting for systems with a low payload and/or restricted workspace. A current limitation is the imprecise flow rate control due to the inconsistencies in the performance of the micro-pump. Future work will address this issue through feedback control using flow or level sensors.
Track:

Biomaterials and Implants
First clinical application of spider silk for repair of long distance peripheral nerve defects

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Introduction
Repair of long distance peripheral nerve defects is still one of the major challenges of reconstructive surgery. Poor outcome is primarily caused by the lack of autologous donor nerves or artificial nerve grafts to treat defect sizes > 4 cm. In previous experiments performed in a sheep animal model, we were able to successfully regenerate 6 cm nerve gaps with spider silk nerve conduits, leading to restored functional outcomes. As a translational step we describe here the first application of spider silk for peripheral nerve repair in humans. For compassionate use, nerve injuries with a defect length >20 cm were treated with conduits composed of spider silk and autologous veins.

Methods
Extended nerve defects of four patients were reconstructed using spider silk conduits consisting of an autologous saphenous vein longitudinally filled with drag line silk from Trichonephila edulis. In three patients the conduit had to be combined with additional plastic reconstructive procedures. All patients were evaluated at least up to two years post reconstruction, clinically, and by neurography. Final follow-up in one patient was performed up to 10 years after the spider silk nerve conduit transplantation.

Results
In all patients, primary wound healing and no adverse reactions to the implanted material were observed. Surgical procedures as well as results are very diverse due to the individual circumstances. In summary all patients regained protective sensibility and in parts motoric function, depending of the defect side in fingers/hand/arm or toes/foot/leg. No neuroma formation nor neuropathic or chronic pain occurred in any of the patients.

Conclusion
For patients with extended peripheral nerve defects in the extremities, who have no alternatives for treatment, spider silk nerve reconstruction offers the possibility of restoring sensory function, as seen in three of four cases. Patients benefit from being spared of neuroma formation and chronic pain.
Release behaviour of model drugs from polydimethylsiloxane (PDMS)-thin films for cochlea implant electrode functionalization

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Introduction

A natural response to the implantation of a cochlear implant is the formation of connective tissue. Reduction of this growth can be achieved by incorporation and release of anti-inflammatory drugs from nanostructured silicone coatings. We compared the short-term release kinetics of two model substances to determine their suitability for further investigations.

Methods

Thin films were prepared by coating PDMS (Sylgard 184) drug mixtures (aspirin (300 mg/g, A), uranine (30 mg/g, U)) on glass plates, heat treating for 1 h at 100 °C and storing overnight at room temperature. Pure PDMS films were used as controls (C). Film thickness and contact angle were assessed using a microscope and drop shape analyser. 30 mg pieces were stored for 22 h at 37 °C in 1.5 ml artificial perilymph and analysed spectroscopically (excitation 488 nm, emission 511 nm) and photometrically (absorbance, 296 nm, 263 nm).

Results

Measured mean thicknesses were 182.79±8.63µm (A), 212.62±10.22µm (U) and 344.31±29.64µm (C). Contact angles were determined to be 111.5 ± 0.66° (A), 113.9 ± 0.01° (U) and 115.33 ± 1.244° (C). A showed limited growth release of aspirin (saturation after 20 hours, 3.43 mg/ml). U exhibited a burst release of uranine in the first 3 hours, followed by a plateau and an increasing rate of release after 20 hours. Control C had no release at all investigated wavelengths.

Conclusion

Photometric determination of A showed more consistent results compared to U, making it more suitable for assessing the release behaviour of PDMS thin films. The results and established methods are being used to determine the release behaviour of electrospun, nanostructured PDMS coatings of cochlear implant electrode arrays. Ongoing work is dedicated to adapting the kinetics by incorporating diffusion barriers using sandwich structures or coaxial fibre structures, as well as performing dynamic release experiments to better mimic physiological conditions.
Modeling interfacial diffusion-based corrosion in Active Implantable Medical Devices

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Introduction
Ingress of body fluids into active implantable medical devices (AIMD) is one of the major failure mechanisms. Progressive delamination along the metal-polymer junctions, where electrodes and conductive pathways enter the implant interior, leads to leakage currents and insulation faults in the worst case resulting in implant failure. Delamination mechanisms in these interfaces are lacking complex modeling and proper characterization due to complex electrochemical-diffusively processes occurring superimposed. A standard test and specimen of defined geometry were developed for modeling of the diffusion-based delamination processes at the three-phase-boundary interface (body fluids, polymer, metal).

Methods
As it is common in AIMD, such as cochlear implants, a medical grade silicone was chosen. The platinum(-alloy) conventionally used in implantable electrodes was replaced by copper, as it allows the corrosion process to be visualized without the use of hazardous chemicals simply by color-change. The specimen were immersed in a potassium sulfide solution serving as corroding agent. This way chemical reaction time of the metallic corrosion was reduced to a few seconds and becomes negligible, allowing an isolated investigation on delamination and diffusion phenomena resolving in a computational model. For following specimen a successive transition to more inert metals (i.e. Cu > Ag > Au > Pt(Ir)) is planned to ensure a better transferability to real implants.

Results
The first series of tests showed that diffusion and delamination processes in the interface could be visualized, so that a first modeling approach could be successfully carried out. A major challenge was bulk diffusion overlapping to the interface phenomena disturbing the measurement. Improved specimens were developed with a diffusive barrier blocking bulk diffusion in order to get an isolated, undisturbed view on interface diffusion.

Conclusion
The main diffusion based degradation mechanisms in the interfacial layer could be identified and described in a first suitable model.
Foreign Body Reaction: Establishment of an in vitro Model for Medical Device Testing

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1. Introduction
The foreign body reaction (FBR) can lead to serious impairment of medical devices and is defined as the adverse response of the host tissue towards implanted material. After implantation, proteins are absorbed to the material’s surface, followed by recruitment of immune cells. Attached macrophages undergo “frustrated fusion” to form foreign body giant cells (FBGC). Finally, a fibrotic encapsulation is established.

2. Objectives
FBR is currently not part of in vitro biocompatibility testing, according to ISO 10993 for accreditation of medical devices. Therefore, it is of interest to establish a protocol in assessing FBR induction to better ensure patient’s safety and to avoid unnecessary animal testing.

3. Materials & methods
Since macrophages are orchestrating FBR signalling, primary rat alveolar macrophages were chosen as the model system. Macrophages (2x10⁵/per well of 24-well plates) were plated onto implantable polyethylene materials to assess the FBR upon those materials. After 4, 12, and 72 h supernatants were collected for measuring membrane damage and different chemokines/cytokines. Furthermore, formation of FBGC was analysed after 72 h of incubation by confocal microscopy using DAPI staining and alpha-tubulin immunofluorescence.

4. Results
In line with its use as an implant material, ultra-high-molecular-weight polyethylene (UHMWPE) after 24 h of incubation did not induce cytotoxicity (0 ± 0.2 % cytotoxicity) or CINC-1 release (33 ± 3.7 pg/mL), as compared to 0 ± 2.5 % and 33 ± 13.5 pg/ml for untreated cells, respectively. CINC-1 functions as an inflammatory marker. However, there was formation of FBGC on the UHMWPE material as shown by confocal microscopy.

5. Conclusion
The results indicate that UHMWPE induced an FBR in the absence of cytotoxicity and inflammation. UHMWPE might, pass ISO 10993-5 testing, whilst FBR is still ongoing. Hence, the FBGC inspection might represent an add on for ISO 10993 in vitro biocompatibility testing and thus ensure better patient’s safety.
First in vivo Test of a Degradable Polymeric Stent for the Eustachian Tube in Sheep

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INTRODUCTION
Eustachian tube dysfunction (ETD) is one of the most common challenges in otorhinolaryngology. To date, there are several methods used, that have the potential to help the patient, but in most cases the long-term effect remains questionable. Therefore, stent implantation into the Eustachian tube (ET) could be an alternative. It was earlier reported on first in vivo tests in sheep using a permanent stent made from nitinol. As not all patients might need permanent support, also a degradable stent is under development.

METHODS
Stents (diameter: 3 mm; length: 15 mm) were made from PLLA and crimped on a balloon catheter. These were guided into the ET of nine female healthy black headed sheep under endoscopic control using the insertion tool of the nitinol stent and inflated at 10 bar for 2 minutes. Ventilation of the middle ear was controlled weekly by tympanometry for the entire observation periods of 3, 6, or 12 months (3 animals each). After the final exam, heads were scanned by cone beam computed tomography (CBCT) and prepared for histology.

RESULTS
All stents could be inserted and positioned as intended. Stent positions could be verified in all but one animal by incorporated x-ray markers at the end of the respective observation period. After three months the stents were still fully functional even though first fragments were found, whereas after 6 and 12 months the ET was collapsed close to its natural shape again with stent fragments of different sizes being distributed in the tissue beneath a fully epithelialized ET.

CONCLUSION
Results indicate that the stent in its current shape supports the ET for at least 3 months but less than 6 months.

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Production of submicrometer-sized active pharmaceutical ingredients by pulsed laser fragmentation in liquids in a flow-through reactor

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Introduction:
One challenge in formulation development of active pharmaceuticals is that most newly developed substances have low solubility in aqueous media, resulting in insufficient oral absorption. Size reduction is an established route to increase drug solubility, though established techniques like cryo-milling or high-pressure homogenization suffers from undesirably high portions of contaminants. [1] Laser fragmentation in liquids (LFL) of suspended microparticles (MP) is an alternative comminution method, however, low productivity and high chemical degradation in frequently used batch setups has to date omitted its usability [2].

Methods:
LFL was done in a liquid-jet flow-through reactor, using picosecond pulsed lasers. The model substances naproxen, prednisolone, megestrol acetate, and ketoconazole, and curcumin were used. Size reduction was monitored using SEM and centrifugal sedimentation while chemical degradation was tracked using ATR-FTIR, XRD, and HPLC. Solubility of the drug was determined by UV-Vis spectroscopy of drug particle supernatants.

Results:
We show a quantitative conversion of the model drug MP into sub-micrometer particles (SMP) by LFL with a conversion efficiency 100 times higher than in a batch setup and with minimal chemical degradation (<<<1%). This is attributed to the more efficient irradiation in the modern liquid-jet flow-through reactor. A 50% increase in solubility was documented in the laser-processed drug SMP.

Conclusions:
Flow-through reactors for LFL of drug MP were shown to work at high efficiency and with chemical degradation far lower than with established comminution techniques. As these setups can also operate in a continuous mode, these findings could help to establish LFL of drug particles in technical applications.

References:
In vivo applications of neuronal electrodes structured with laser-generated platinum nanoparticles by electrophoretic deposition

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Introduction:
Platinum-based neural electrodes are routinely used in clinical practice to modulate basal ganglia activity and aid in the treatment of movement disorders. However, stimulation efficiency is still restricted due to an increased impedance at the electrode-tissue interface. One way to overcome this drawback is to modify the electrodes with ligand-free platinum nanoparticles by electrophoretic deposition (EPD).

Methods:
Platinum nanoparticles were fabricated by laser processing in liquids. EPD of nanoparticles on 3D Pt electrodes was carried out in a self-designed deposition chamber using varying field types and solvent compositions. Electrodes were characterized in vitro using SEM, cyclic voltammetry, and electrochemical impedance spectroscopy. For in vivo experiments coated electrodes were implanted into the subthalamic nucleus (STN) of rats, which were stimulated for 4 weeks.

Results:
DC vs. pulsed-DC deposition techniques were compared and the solvent was varied using ethanol-water mixtures. The impedance of the electrodes was significantly reduced in the case pulsed-DC was used \cite{Ramesh et al., Langmuir 2021, 37, 9724} and ethanol-water mixtures with 30 vol% ethanol yielded the highest electrochemical performance \cite{Ramesh et al., Journal of the Electrochemical Society 2022, 169, 022504}. The in vivo impedance of the coated electrodes was more stable in comparison to uncoated controls and significantly reduced when coatings from pulsed-DC fields were used. Adverse effects on the tissue were comparable to uncoated controls \cite{Angelov et al., J. Nanobiotecnol. 2016, 14, 3}. Mechanical stability of the coatings in vitro and in vivo was high with minimal delamination, yielding Pt concentrations below systemically toxic levels \cite{Ramesh et al., Adv. Healthc. Mater 2022, 11, 23}.

Conclusions:
EPD nanostructuring of neural electrode surfaces could be established as a suitable method to improve their performance, which may pave the way towards their clinical applicability.

References:
Microstructures based on hot embossing of Parylene for self-sticking surfaces on medical wearables

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Introduction
Medical wearables, such as smart plasters for the continuous monitoring of patients’ individual vital signals require a direct, biocompatible and long-term stable attachment to the skin. However, currently used chemical adhesives tend to cause injuries, including irritant contact dermatitis, allergic reactions or even skin tearing. Inspired by geckos, adhesive-free attachment is possible by hierarchical microstructures, which enable strong contact forces. Continuing our previous work [1], the reproducibility of the hot embossing process for the biocompatible polymer Parylene C and the improvement of the sidewall quality are investigated in this study.

Methods
The hot embossing parameters were varied in a temperature range of 305 °C to 325 °C and forces between 15 kN to 25 kN. Demolding temperatures down to 40 °C and a demolding speed of 0.2 mm/min to 0.5 mm/min were tested. The process was performed in vacuum in order to avoid degeneration or oxidation. Profilometer and confocal measurements as well as SEM imaging were used for characterization. Additionally, an extensive material analysis was performed to characterize the impact of the hot embossing process on the properties of Parylene.

Results
Hot embossing of Parylene C was successfully demonstrated as a reproducible process with increased side wall quality of the pillar structures with heights of 10 μm, diameters of 20 μm and varying pitches of 20 μm, 40 μm and 80 μm. Optimal reproducibility was found at embossing temperatures of 305 °C and forces of 25 kN. Demolding the samples at 40 °C with 0.2 mm/min significantly reduced delamination and sidewall roughness.

Conclusion
Hot embossing enables the reproducible and, hence, reliable manufacturing of high quality Parylene C microstructures. By adding a metallization layer and encapsulation, structured Parylene C is a promising candidate for medical wearables and other applications, e.g. ultra-thin circuit boards as well as optical waveguides and microfluidic systems in medical sensors.

References
Histological Findings of Human Cadaveric Ear with Inserted Inner Ear Catheter

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Introduction
Various attempts are under investigation to prevent cochlear implant electrode array insertion trauma. Increasingly, trauma prevention by drug delivery via an inner ear catheter becomes the focus of research. However, it has not yet been examined what degree of trauma the inner ear catheter causes after insertion and liquid application into the cadaveric ear.

Material and Methods
In this study, a prototype of an inner ear catheter (MED-EL, Innsbruck, Austria), with an insertion length of 20 mm and a diameter between 0.5 and 1.3 mm, was manually inserted into the cochlea of a human cadaveric ear (N = 1). Catheter was filled with X-ray contrast medium. After catheter insertion, contrast medium was applied into the scala tympani and catheter was fixed with glue. Subsequently, CT images were obtained. The ear was histologically prepared, and the sections were analyzed for tissue integrity.

Results
According to CT imaging, the catheter insertion part was completely inserted into the cochlea along the basal turn. Moreover, histological sections showed that the inner ear catheter is freely placed in the scala tympani and touches hardly the lateral wall in the basal turn. Additionally, insertion and contrast medium application caused no detectable trauma to the endocochlear structures such as elevation or rupture of the basilar membrane.

Discussion
In this work, inner ear catheter insertion can be described with least intracochlear trauma. These results indicate that inner ear catheters can be used to prevent trauma without being traumatic itself. However, future studies with a larger number of samples need to be performed to confirm this finding.
Characterization of a mechanically strain-stiffening structure using different elastic materials for potential applications in soft tissue engineering and implants

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Introduction

During positive strain, soft biological tissues and single cells exhibit a characteristic known as strain-stiffening. In single cells, strain-stiffening occurs because actin filaments are crosslinked into stress-fibers as a response to such a strain. This crosslinking mechanism was the inspiration for a unique, minimalistic design that is based on parallel slats between several backbones in an elastic material: During elongation of this mechanical metamaterial, the flexible slats come into contact with each other, resulting in mechanical interactions and hence stiffening of the 3D-structure.

Methods

Single strain-stiffening units in the cm-range were cast from different materials to study the effect of cell-inspired strain-stiffening. Elastic materials, such as silicone, latex or PU were molded using 3D-printed molds. By uniaxial tensile testing, changes in geometry, total scale and the impact of various materials were examined for their effect on the mechanical behavior. Using stereolithography, elastic materials were 3D-printed directly and their mechanical behavior was compared to the molded samples. To examine the mechanical properties of 3D-configurations, combinations of in-series and in-parallel arranged strain-stiffening units were used.

Results

The analyzed structure has a highly nonlinear, adjustable, rate-independent, reversible strain-stiffening behavior that can be implemented into various elastic materials. Changes in geometry affect the point of
stiffening as well as the initial and final stiffness of the material. The strain-stiffening mechanics can be used in complex three-dimensional arrangements like sheets or tubes in addition to single strain-stiffening units.

Conclusion

Strain-stiffening units and complex strain-stiffening arrangements were created from different materials and mechanically examined, demonstrating their unique strain-stiffening behavior. These characteristic properties make our structure promising for implants that resemble the mechanical characteristics of soft tissues like blood vessel grafts or skin-integrated electronics. Hence, our strain-stiffening metamaterial has vast application potential in the medical field, where a non-linear, tunable, two-stage mechanical response is desired.

Keywords: Biomaterials, Tissue Engineering, Metamaterial, Strain-stiffening, 3D-printing
Surface Modification of Stimulation Electrodes by Electrospinning of Polydimethylsiloxane

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Introduction
In response to implantation of cochlear implants, connective tissue forms to surround and electrically insulate the implant. This is reflected in increased impedances and energy consumption, as well as unpredictable stimulus propagation. Connective tissue growth on electrodes can be reduced by microstructuring the electrode surface with hydrophobic materials. We evaluated methods for the deposition of polydimethylsiloxane (PDMS) fibers on cochlear implants using the electrospinning process.

Methods
Sylgard 184 resin was mixed with condensation agent. Acetone and tetrahydrofuran (THF) were used as solvents. A heated plate collector and infrared lamps were used to accelerate vulcanization of the fibers. Additionally, Sylgard 184 was electrospun in a coaxial approach. Polyvinylpyrrolidone (PVP) in dimethylformamide (DMF) was used as a supporting shell structure. Fiber morphology and chemical composition were evaluated.

Results
Electrospinning of PDMS resin in both acetone and THF yielded stable processes within a wide range of process parameters. Without further treatment, fibers did not solidify on the collector resulting in polymeric films. Heating of the collector up to 100 °C and the addition of infrared lamps improved the vulcanization of the fibers. Coaxial electrospinning of PDMS and PVP yielded fibers with diameters of about 10 µm. Absorption bands at 1260 cm⁻¹ (Si-CH₃ deformation) and 1018 cm⁻¹ to 1078 cm⁻¹ (Si-O-Si stretching) clearly indicated the presence of PDMS in coaxial electrospun fiber mats. Aforementioned peaks were also present in PDMS films and absent in fiber mats containing PVP only.

Conclusion
Our findings indicate that Sylgard 184 can be processed into fibers for the surface modification of cochlear implants using a coaxial electrospinning approach with PVP as a supporting shell structure. A stable electrospinning process was also obtained with pure PDMS. Ongoing work is necessary to ensure a sufficient vulcanization strategy for pure PDMS so that fibers maintain structure after being placed on the collector.
Dynamic in vitro calcification of bovine pericardium patches using compressed air

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Introduction
The durability of biological heart valve prostheses is strongly influenced by pathological calcification. Calcification refers to the formation of mineral deposits containing calcium phosphate on the surface (extrinsic) and inside (intrinsic) of the prostheses. Dynamic in vitro methods are crucial for a time- and cost-saving analysis of the calcification process. Therefore, we developed a compressed air-based method for the dynamic in vitro calcification of bovine pericardium patches. Furthermore, hyperspectral imaging was evaluated as a technology to visualize calcified areas.

Methods
Three glutaraldehyde crosslinked bovine pericardium patches were calcified in vitro under dynamic conditions. Patches were dynamically loaded using compressed air at a frequency of 1 s⁻¹ for nine weeks. The calcification solution was weekly replaced. The composition of crystalline phases was investigated by Raman spectroscopy. Hyperspectral imaging in the near infrared light region (NIR) and short wavelength infrared light region (SWIR) was performed to visualize deposits of calcium phosphate. Calcium content of the patches was measured using ethylenediaminetetraacetic acid titration.

Results
White crystalline phases could be observed on all patches after nine weeks of in vitro calcification. Crystalline phases exhibited peaks at wavenumbers of 959 cm⁻¹ to 962 cm⁻¹ in Raman spectroscopy, indicating the presence of hydroxyapatite. Those peaks could not be found in apparently non-calcified areas. Both extrinsic and intrinsic calcified areas of the patches could be detected and localized through SWIR hyperspectral imaging. Calcium content of the patches was 5.41 mg ± 1.89 mg according to titration.

Conclusion
The test bench developed was able to successfully reproduce the process of calcification in vitro, even by using relatively low loading frequencies of 1 s⁻¹. Our findings indicate that SWIR hyperspectral imaging is a promising approach for two-dimensional mapping of extrinsic and intrinsic calcified areas in biological heart valve prostheses or patches. Future work will address surface modification of patches to prevent calcification.
Assessment of in-ear soft dry electrodes for electrocardiography

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In-ear signal capture, such as ear electrocardiography (ECG) monitoring investigated in this paper, represents a promising addition to mobile health (mHealth) due to its non-invasive and user-friendly nature. By providing a convenient and comfortable means of physiological signals monitoring, in-ear signal capture could potentially increase patient compliance and engagement with mHealth applications. The development of reliable and comfortable soft dry in-ear electrode systems could therefore have significant implications for both mHealth and Human Machine Interface (HMI) applications.

This research evaluates the quality of the ECG signal obtained with soft dry electrodes inserted in the ear canal. An earplug with 6 soft dry electrodes distributed around its perimeter was designed for this study, allowing the analysis of the signal coming from each electrode independently with respect to a common reference placed at different positions on the body of the participants. An analysis of the signals correlation in comparison with a reference signal measured on the upper right chest (RA) and lower left chest (LL) was performed.

The high correlation with the reference signal suggest that the soft dry electrodes in the ear provide a high quality measurement of the ECG signal. 3 typical behaviors are observed. Some electrodes have high correlation with the reference signal directly after inserting the earplug, other electrodes need a settling time of typically 1-3 minutes, and finally others never have high correlation.

The soft dry electrodes used in this research have proven to be perfectly capable of measuring a physiological signal, paving the way for their use in mHealth or the HMI applications. The use of several electrodes distributed in the ear canal has the advantage of allowing a more reliable acquisition by intelligently selecting the signal acquisition locations or to allow a better spatial resolution for certain applications by processing these signals independently.
Miniaturized PCB with Wireless Power and Data Telemetry for Active Stents

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Catheter-based interventions enable a minimally invasive treatment of cardio- and neurovascular pathologies. Self-expandable implants, which are more commonly known as stents, are nowadays employed and allow for a great reduction of catheter dimensions. The implantation of stents is a worldwide established method. Due to the continuously increasing number of heart diseases around the globe, there is enormous need for advanced stents with observation functions. Such in-vivo measurements of, e.g., blood pressure and other physiological indicators have significant potential in the long-term monitoring of the cardiovascular system and in applications of preventive healthcare.

Prototyped systems to monitor biomarkers such as blood pressure and restenosis have been demonstrated in prior art, and addressed some of the challenges regarding ultra-low power consumption and wireless powering. Nevertheless, further advancements are necessary to improve feasibility in a clinical context, e.g., maximize the achievable implantation depth and improve the data rate.

For systematic tests and as inexpensive non-integrated circuit platform, we have utilized discrete, commercial components to craft a PCB-prototype for wireless power and data telemetry, which is supplied through an inductive link, where the connected stent is intended to act as secondary coil. It includes power management and a ultra-low power microcontroller; backscattering by load modulation is used to transmit digital data stream containing sensor data; a Zener diode protects the microcontroller from damage by over voltage, as the power link is susceptible to any changes in alignment. As the PCB should be as small as possible to potentially attach it to a large stent in a prototyped setup, the utilized components were un-packaged with the use of 70% nitric acid. As a result, the volumes are reduced by over 95% to allow for final volume of the electronic platform for an active stent of only 6.6mm x 1.5mm x 0.4mm.
Low Temperature ALD Processes for Cardiac Implant Encapsulation

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Hermetical sealing of implants is mandatory to provide patients' security and to guarantee a proper functionality of implants over their lifetime in the patient's body. Due to the demand of size reduction in implants' housings, Atomic Layer Deposition (ALD) is getting more and more an established method. ALD can realize compact and hermetic implant encapsulations with a significant lower space requirement compared to metal and silicon housings. For a cardiac implant with a requested operation time of a few weeks, we present a combined encapsulation method based on a stack of Parylene C and ALD layers grown at low temperature. Parylene C is an established biocompatible encapsulation material, which by itself has already good encapsulation properties for a certain period of time. To improve long-term stability, a low-temperature ALD process is being developed to provide the Parylene C with an additional ceramic barrier. For this purpose, Al2O3 and Ta2O5, which are both biocompatible materials, are chosen. To guarantee a compatibility with the temperature sensitive Parylene C layer underneath, ALD processes with deposition temperatures below 150 °C are being developed. It has been shown that Al2O3 and Ta2O5 provide sufficient barrier properties on solid surfaces, but tend to propagate cracks when deposited on soft Parylene C surfaces. Nevertheless, a sufficient barrier layer consisting of Parylene C in combination with Al2O3 and Ta2O5 could be developed for the targeted operating time. All in all, an alternating stacking of both Parylene C and ALD ceramic layers could be an option to achieve a further increase in the maximum operating time of the implant.
Towards the development of the biohybrid lung: Endothelialization of Blood Contacting Surfaces Inside a Miniaturized Oxygenator


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Introduction
For the treatment of end stage lung diseases, no other alternative option than lung transplantation is available yet. Annually increasing numbers of patients and scarcely available donor lungs, urgently call for an alternative treatment solution, which we aim to provide by the development of the biohybrid lung (BHL). Therefore, extracorporeal membrane oxygenation (ECMO), already applied clinically, provides a technology for achieving sufficient lung support. However, the direct contact of the heparinized blood with the ECMO device’s foreign synthetic surfaces usually entails thrombotic occlusion and device failure after days to weeks. To avoid clotting and enabling perpetual long-term application we aim to colonize all blood contacting surfaces with a blood vessel-like anti-thrombogenic endothelium. Following the successful proof-of-principle in vitro, the next milestone in development will be the endothelialization of whole oxygenators, for which we assessed specific key parameters affecting endothelial cell (EC) monolayer formation inside a lab scale miniature oxygenator.

Methods
Fibronectin-coated membrane samples were mounted in a miniaturized oxygenator. EC suspensions were injected at different concentrations, and adhesion was allowed under rotation vertically (axis1), or horizontally (axis2) around the parallel aligned fibers for either 6h or 24h. Endothelialization was assessed fluorescence-microscopically after calcein staining. During 24h seeding medium was sampled for glucose, lactate, pH and gas saturation. Gene expression was assessed via qRT-PCR. Apoptosis was determined using the Annexin-V/PJ assay after or without medium change during 24h.

Results
The formation of a viable near-to-confluent monolayer on membrane and housing parts was best when 15.2x10⁴/cm² ECs were applied for rotational seeding around axis2 and for 24h. Inflammatory/coagulation-associated genes (ICAM,VCAM,ELAM,TF,TM) were not upregulated, while medium change during seeding corrected pH and nutrient availability, and mitigated apoptosis sufficiently.

Conclusion
Key parameters enabling efficient endothelialization inside a pre-assembled oxygenator could be identified which will now be transferred for seeding original-sized oxygenators.
Towards the development of the biohybrid lung: Analysis of endothelial cells residing on gas exchange membranes under hyperoxic 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 patients with end-stage lung disease. The operating principle of the BHL is based on the gas exchange hollow fiber membrane (HFM) technology used in clinically applied extracorporeal membrane oxygenation (ECMO). The poly-4-methyl-1-pentene (PMP) HFM and all blood-contacting surfaces of the BHL are covered with endothelial cells (EC) to prevent thrombotic occlusion of the device to allow long-term use. Therefore, ECs must withstand the nonphysiological oxygen gradient between the oxygen-rich gas inside the HFMs and the hypercapnic/hypoxic patient blood. In this study, we investigated the influence of this hyperoxic environment on EC viability and function, under static and flow conditions.

Methods
PMP membrane films were coated with fibronectin and seeded with ECs. Upon reaching confluence, ECs were exposed to a hyperoxic atmosphere (95% pO₂) for 24h under static culture conditions. Using flow cytometry, alteration of EC viability, apoptosis (AnnexinV/PJ) and reactive oxygen species (ROS) accumulation (CellRox) was investigated. Expression level change of oxidative stress (HMOX1, GCLM)- or inflammatory (ELAM, VCAM, ICAM) related genes was measured via qRT-PCR. Using a customized miniature oxygenator endothelialized HFM were ventilated with 95% pO₂ and exposed for 24h to 15 ml/min flow with culture medium. Remaining viable ECs were stained with calcein and assessed fluorescence-microscopically.

Results
Flow cytometric analyses revealed that film-seeded ECs tolerated the hyperoxic conditions for 24h. EC populations remained viable (normoxia: 86.56% vs hyperoxia: 86.73% viability), while no elevated numbers of ECs accumulating ROS were detected (normoxia: 6.09% ROS⁺ vs hyperoxia: 1.53% ROS⁺). Also, upregulation of prothrombotic/proinflammatory genes was not detected. On ventilated HFM under flow conditions, EC remained confluent and viable.

Conclusion
The results of this study represent another milestone towards the feasibility of a clinically applicable biohybrid lung.
Enhancing Efficiency of Solution Electrospinning of Small Diameter Tubular Structures

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Introduction:
For many tissue-engineered constructs, small tubular structures with inner diameter < 1 mm are needed. These structures may be created using solution electrospinning. Due to the use of a small collector, process parameters significantly influence fibre yield on the collector and scaffold structure. The aim of this study is to optimise the electrospinning process to achieve a stable process of small tubular structures with an electrospinning solution containing the degradating polymer Poly(lactide-co-glycolide) (PLGA) in 1,1,1,3,3,3-Hexafluoro-2-propanol (HFP) while maximizing the fibre yield on the collector.

Methods:
During this study, influence factor analysis of electrospinning parameters was performed. To eliminate existing disturbance variables, a new setup for application of negative potential on the collector and for control of climatic conditions was designed. Control variables were optimized using statistical experimental design with the aim of achieving maximum fibre yield and process stability. Structural characterization was carried out to determine the mass, thickness, and fibre structure of the scaffold. SEM images were taken to characterize the scaffold properties. Statistical analysis of the results was performed and a regression model was implemented to determine the correlation between manufacturing parameters and the obtained fibre yield and the properties of the scaffold structure.

Results:
The application of negative potential has resulted in significant increase in fibre yield, from under 25% to over 90%. The established electrospinning process with PLGA in HFP is stable and reproducible. Furthermore, structure properties of the scaffold can be adjusted based on the investigated parameters.

Conclusion:
The results of this study have several helpful implications for further process establishment. Firstly, the new setup is cost-effective due to material savings in the production of the enclosure. Secondly, the study's methodology is transferable to other applications such as the production of nerve channels and of scaffolds guiding the growth of nerve fibres.
Biohybrid Aortic Valve with Growth Capability for the Treatment of Paediatric Patients

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Introduction

Heart valve replacement in paediatric patients imposes unique challenges in terms of material and design requirements. While mechanical heart valves require permanent anticoagulation, they are not commonly used in children due to the high risk of life-threatening haemorrhages. On the other hand, biological heart valves do not require anticoagulation but degenerate quickly in children. Furthermore, both types of heart valves lack adaptation to the growing size of the child's heart, leading to frequent reinterventions to adjust the valve size. The objective of this research study is to develop a scaffold structure for a biohybrid implant that can adapt to the growing size of children's hearts.

Methods

In order to create a textile scaffold structure that can adapt in a time-controlled manner to the increasing diameter and orifice-area of the valve, a warp knitted structure was developed using non-degradable yarns (polyethylene-terephthalate & polyvinylidene-difluoride) that was specifically reinforced with biodegradable fibres (polylactide, polylactide-co-glycolide, polycaprolactone, silk). For integrating degradable fibres, direct integration into the warp-knitting process by means of combined lappings as well as subsequent integration of reinforcing fibres into the warp-knitted structure were investigated. Samples were stored in phosphate-buffered-saline at 37 °C in order to simulate degradation in-vivo.

Results

Geometric and mechanical parameters of the scaffold structure were evaluated at different degradation points, including diameter, surface-area, strength, elongation and radial compliance. Selective combination of fibres degrading at different rates and different geometric structures of the reinforcement structures resulted in a stepwise controlled increase of the valve diameter by > 30 % and the valve orifice-area by > 40 %.

Conclusion

By combining a non-degradable basic textile structure with a controlled degrading reinforcement structure, it was possible to fabricate a textile scaffold structure capable of growing with the valve. These outcomes represent a decisive step towards a heart valve implant with growth capability for the treatment of young children.
Biomechanical Properties of Textile Scaffold Structures for Biohybrid Implants

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Introduction
To date, purely tissue engineered implants have been limited by their mechanical strength and (re)producibility. Biohybrid implants can overcome these limitations by incorporating a textile scaffold structure to reinforce the biological material. However, the design of these structures is highly dependent on know-how, and currently there are no established tools or specifications for their development based on physiological requirements. The aim of this research study is to develop a model for the biomechanical and morphological design of tubular warp knitted scaffold structures.

Methods
A statistical design of experiments was employed to investigate the effects of manufacturing parameters on the biomechanical and morphological properties of the scaffold structures. Biomechanical properties were characterised using longitudinal, circumferential, and biaxial tensile tests, while morphological properties were determined by analysing porosity and pore size distribution using light microscopy. The results of the statistical analysis were transformed into a mathematical model to determine the correlations between the manufacturing parameters and the morphological and biomechanical properties of the scaffold structure.

Results
The results showed that all investigated process parameters, such as lapping, stitch course density, wale density, and yarn count, had statistically significant effects of varying magnitudes on the morphological and biomechanical properties of the scaffold structures. Within the investigated process window, the effects were sufficiently linear to allow for interpolation between test points. Therefore, a linear regression model was created to describe the correlations between the process parameters and the textile properties.

Conclusion
The results provide a targeted starting point for setting the process parameters for designing textile scaffold structures for new biohybrid implants. As a result, the quality of the scaffold structure can be improved and the development time can be reduced.
Track:
Magnetic Methods
Fast and Sensitive Magnetic Immunoassays utilizing Magnetic Particle Spectroscopy with Adjustable Offset Fields

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Introduction

The field of magnetic immunoassays (MIAs), using magnetic nanoparticles (MNPs) as markers, has seen a lot of promising concepts over the years. Recent research on MIAs, induced by the SARS-CoV-2 pandemic, has shown that magnetic assays could provide an alternative to ELISA for antibody tests, rapid antigen kits for antigen testing, and potentially even serve as a substitute for certain rtPCR applications. One promising technique for a fast, sensitive and extraction-free binding detection with MNPs is magnetic particle spectroscopy (MPS). Its feasibility with a compact MPS device has been demonstrated by several groups.

Methods

In MPS, the MNP markers are exposed to an alternating magnetic field of sufficiently large amplitude to generate higher harmonics due to non-linear dynamic magnetization. Upon binding of MNPs to analytes their hydrodynamic size increases. The reduced Brownian particle mobility leads to a significant alteration of the detected harmonics. To further increase the sensitivity of MPS towards binding detection, one may utilize the dc field dependency of the dynamic magnetization process, as was suggested by other groups.

During the early pandemic, we realized a first iteration of a low-cost, self-contained, benchtop “immunoMPS” device. The now improved version of the system especially addresses sensitivity and long-term stability, and incorporates the following hardware improvements: (i) adjustable static offset field, (ii) passive transmit-side T-bandpass for extra 20 dB harmonics suppression and (iii) improved coil system design and material selection for increased sensitivity and thermal stability (using glass-reinforced material)
Results

Here, we introduce the second generation “immunoMPS” system and demonstrate its use for selected immunoassay applications, continuing to improve on previous results.

Conclusion

Sensitive MPS hardware is a critical building blocks for the realization of fully optimized, highly sensitive and rapid magnetic immunoassays.

Keywords: Magnetic Particle Spectroscopy, Magnetic Nanoparticles, Immunoassay
Cobalt ferrite nanoparticles as thermal markers on lateral flow assays

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Introduction
Using magnetic nanoparticles (MNP) for therapeutic hyperthermia, safety restrictions concerning the external magnetic field apply. For extracorporeal heating purposes, larger field amplitudes and thereby particles with higher coercivities ($H_C$) can be used. Therefore, we studied in detail the synthesis of hard magnetic cobalt ferrite (CoFe$_2$O$_4$) nanoparticles as novel potential thermal markers on lateral flow assays.

Methods
First, the influence of synthesis parameters of the co-precipitation process on the resulting particles was studied, by varying the temperature during NaOH addition ($T_{add}$), duration of addition ($d_{add}$), end temperature of the reaction ($T_{end}$), overall reaction duration ($d_{react}$) and atmosphere (air or nitrogen). Second, the cobalt content $x$ was altered, resulting in particles with the formula Co$_x$Fe$_{3-x}$O$_4$ to tune the magnetic behaviour towards soft magnetic magnetite (Fe$_3$O$_4$). Particles were characterized using magnetometry, XRD, Mössbauer spectroscopy, TEM and measurements of their specific absorption rate (SAR).

Results
Necessary conditions were identified to synthesize pure cobalt ferrite nanoparticles. $T_{add}$ may not exceed 65 °C while $T_{end}$ needs to exceed 85 °C to prevent the formation of non-magnetic hydroxides detected by XRD and Mössbauer spectroscopy. Increasing $d_{add}$ leads to an increasing $H_C$ and decreasing saturation magnetization ($M_S$). The use of nitrogen atmosphere increases $M_S$ and lowers $H_C$. Variation of the cobalt content $x$ results in a non-monotonic trend of $H_C$, with a maximum $H_C$ of 37 kA/m (@ 300K) for $x = 0.8$ and a decrease in $H_C$ for higher $x$. SAR values up to 480 W/g were measured, limited by the available magnetic field amplitude. Particle size ranged from 10 to 18 nm.

Conclusion
By controlling synthesis conditions and varying cobalt content, cobalt ferrite particles with high coercivities, adjustable to the used external magnetic field, are promising candidates for extracorporeal heating applications, like thermal markers on lateral flow assays.
Magnetically shielded setup for presenting visual stimuli during OPM-MEG

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Introduction
Magnetoencephalography (MEG) measures magnetic fields generated by electric currents in the brain. Conventional MEG sensors are helium-cooled and arranged in universally fitting helmets. New sensors called optically pumped magnetometers (OPMs) do not require cooling and can be mounted onto the subjects’ head. This increases signal strength and source localization accuracy and allows for more complex experiments.

Many MEG experiments require visual stimulation (VS) inside a magnetically shielded room (MSR). Because electronics distort the weak magnetic fields of the brain, VS is usually realized using a projector outside the MSR and optical elements. We present a more flexible VS setup housed in a portable shield and placed inside the MSR, improving image quality.

Methods
The VS setup consists of a Raspberry Pi 4b running PsychoPy and a Texas Instruments DLPDLCR230NPEVM projector, both battery-powered and inserted in a cylindrical Twinleaf MS-2 magnetic shielding. Visual stimuli are projected through holes in the end caps of the shielding onto the inner wall of the MSR. We compared an empty-room measurement to measurements with our setup and a varying number of end caps during VS. We also exposed four subjects to reversing checkerboard paradigms generated by our VS setup and measured their brain signals using OPMs.

Results
Our results show no significant difference in noise spectra measured in an empty room versus a fully shielded VS setup. Decreasing the number of end caps revealed distortion signals generated by the electronics. We found the expected brain activity in the visual cortex during visual stimulation.

Conclusion
Our VS setup can be integrated into any MSR and supports the new possibilities of OPM-MEG. Because no optical elements are required, it is more flexible and provides better image quality than existing setups. Our measurements show that brain signals can be stimulated with our setup and that distortion signals are well contained.
First Experiences with an Enhanced Compact Magnetic Shielding for Magnetoencephalography using Quantum Magnetometers

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Introduction
Emerging quantum magnetometers, e.g. based on nitrogen-vacancy centers in diamonds, have demonstrated their ability to detect subnanotesla biomagnetic signals, like those generated by muscles and nerves. These sensors show substantially smaller construction volumes when compared to superconducting quantum interference devices. This enables the application of magnetic shielding with smaller dimensions and fewer layers of highly-permeable material, which can be additionally combined with cost-effective room-sized active compensation systems.

Methods
A commercially available magnetic shielding for magnetoencephalography using zero-field OPMs (Fieldline Inc., Boulder, USA) was installed in early 2023 at the Bosch Corporate Research Center in Renningen, Germany. The tubular shielding consists of two mu-metal layers, a single Al layer, and is closed on one side. Additionally, the laboratory room was equipped with an active compensation system (MR-3, Stefan Mayer Instruments, Dinslaken, Germany). Unshielded measurements were performed using a fluxgate magnetometer (MFG2S-LC, Magson GmbH, Berlin, Germany), while shielded measurements were performed with a zero-field OPM (QZFM Gen 1, QuSpin, Louisville, USA).

Results
The magnetic noise spectrum outside and inside the shielding was dominated by drifts (< 1 Hz), 12.5 Hz (Filter-Fan-Units), 50 Hz (powerline), 9 Hz (unknown) and 16.7 Hz (Railway electrification) signals. The active compensation system reduced the noise level for volumes close to the feedback sensor, e.g., from 5 nT/sqrt(Hz) @ 9 Hz to 0.5 nT/sqrt(Hz), while the noise level inside the shielding was substantially lower (e.g. < 600 fT/sqrt(Hz) @ 9Hz, non-actively compensated).

Conclusion
Small construction volumes of quantum magnetometers allow for the design of compact magnetic shielding, which can be further enhanced by active compensation systems. This advancement in biomagnetic signal detection offers potential for improved diagnostic and research applications.

We thank Fieldline Inc., USA, and Stefan Mayer Instruments, Germany for setting up the passive and active shielding. Support was granted by the BMBF initiative QSENS:QHMI (FZ03ZU1110DD).
Anatomically adapted drive field coil design for human-scale magnetic particle imaging

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Introduction

Technical challenges possessed by the transfer of magnetic particle imaging (MPI) to the human scale require careful development of each component of the scanner hardware. This paper demonstrates an optimization procedure for the head drive field coil unit based on the stream functions approach and anatomical information.

Methods

The design concept implies accessibility for the clinicians to the patient and simplicity of positioning. Base surfaces for the coil windings were developed with open-access statistical data (HF-STD-001) to find average human head dimensions. As the major optimization tool, we employed bfieldtools package.

Results

With the stream function approach, we synthesized a drive field coil set with a complex shape for the human head region. Numerical simulations with a target average field value of 6 mT have shown that following the head anatomy reduces the coil volume and leads to energy-efficient wire structures.

Conclusion

The approach provides tremendous flexibility for parameter optimization. However, it has some drawbacks related to the inability to control the distance between the wires directly. This complicates its direct implementation for MPI where a balance must be struck between wire thickness, windings density, and field uniformity.

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Keywords: Magnetic Particle Imaging, LF magnetic field, Optimisation, medical imaging, stream functions
Sensitivity Analysis of EEG/MEG Skull Conductivity Calibration

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Introduction
The inter-individual variation of head tissue conductivities and especially of the skull conductivity leads to a significant uncertainty in the results of EEG source analysis. To reduce this uncertainty, individual skull conductivity calibration based on combined EEG and MEG measurements of evoked brain activity has been proposed. The benefit of an individual estimation of the skull conductivity has, e.g., been shown in the evaluation of epileptic activity. However, it has not been investigated yet whether skull conductivity calibration actually improves source analysis for arbitrary source positions and in how far the skull conductivity estimate is influenced by uncertainties of other head tissue conductivities.

Methods
We simulated EEG and MEG measurements of evoked brain activity (somatosensory, auditory, visual) for randomly drawn tissue conductivities and with varying noise levels. For the same tissue conductivities, we simulated measurements of brain activity for arbitrary source positions. Following, we performed EEG/MEG skull conductivity calibration based on the simulated evoked potentials as previously proposed, i.e., the other conductivities are set to literature values. To evaluate the benefit of the conductivity calibration, we performed EEG source analysis of the simulated measurements for arbitrary source positions and determined in how far the uncertainty of the EEG source analysis was reduced.

Results
Our results show the benefit of EEG/MEG skull conductivity calibration to reduce the uncertainty of EEG source analysis. However, we find that the benefit of the conductivity calibration is not equally distributed but depends on the location of the reconstructed source. Furthermore, the conductivity calibration does not necessarily exactly reconstruct the actual skull conductivity, but the calibration result is also influenced by variations of other head tissue conductivities.

Conclusion
EEG/MEG conductivity calibration is a valuable tool to reduce uncertainty in EEG source analysis and should be applied when possible.
Linear magnetic nanoparticle structures for theranostic applications in magnetic hyperthermia and magnetic particle imaging

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Introduction
Novel magnetic theranostic cancer treatment approaches aim at combining magnetic particle imaging (MPI) and magnetic hyperthermia (MH) to enable imaging-based control of thermoablation of tumors. Such a therapy is realized with a fiber-based nanomodified polymer stent that once implanted is heated up to destroy cancer tissue. MPI and MH rely on the excitation of magnetic nanoparticles (MNP) in an alternating magnetic field (AMF). Here, we analyse the influence of linear MNP structures in the fibers on the MPI and MH performance.

Methods
Linear structures were produced by extrusion of hybrid fibers consisting of polypropylene and MNP. Further, hydrogels with linear MNP structures were prepared by exposing the hydrogel to a static magnetic field during the synthesis. Linear structure formation was examined via transmission electron microscopy. All samples were investigated with a custom-build MH setup and Bruker MPI system to evaluate the heating and tracer performance. Measurements were performed for different orientations of the fibers and hydrogel samples relative to the main reference frame of the MH and MPI devices. Numerical simulations were additionally conducted to model the behaviour of linear structures in an AMF.

Results
The MH heating output as well as the harmonic frequencies and amplitudes of the measured MPI signal was dependent on the linear MNP structure orientation. The highest performance was achieved when linear structures were aligned with the direction of the AFM, e.g. a relative temperature increase of 40% for hydrogels and 60% for fibers was obtained. Simulations confirmed the dependencies derived from experiments.

Conclusion
Alignment of linear MNP structures with the direction of AMF excitation increases their tracer and heating agent performance. This is beneficial for MH, since for the same AMF settings, the same performance is achieved with lower MNP concentrations. To improve MPI resolution, MNP orientation must be considered in image reconstruction.
Active compensation of a shielded room with an optically pumped magnetometer as inside sensor

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For linear operation of open-loop optically pumped magnetometers (OPM) of the SERF type slowly varying fields need to be in a range of less than 1 nT. This is achieved in two-layer mu-metal rooms by adding an active compensation. Here an existing coil set at the outside edges of a magnetically shielded room is used to reduce the fluctuations inside the room.

An OPM operated inside the room is connected to a PI controller driving a current source connected to the outside coil. Since fluctuations normal to the Earth plane are strongest only this direction is compensated here. A fluxgate mounted on the outside is used as an alternative sensor for compensation.

Using the OPM as control sensor achieves a reduction of the field fluctuation amplitude in the range of 25-30 dB. Since the OPM requires a nulling procedure the starting point of the compensation setup has an influence on the performance. Using the fluxgate achieves a slightly lower performance around 25 dB.

Using an internal sensor to compensate fluctuations in a magnetically shielded room using an outside coil is an effective method to allow linear OPM operation. The alternative of using an outside fluxgate does not need the nulling of the sensor and is slightly easier to operate, but is not adaptable to changing experimental conditions.
Optimization of an Iron Core Selection Field Generator for Human-scale Magnetic Particle Imaging

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Introduction
Magnetic particle imaging (MPI) is currently on the verge of moving from a pre-clinical to a clinical imaging method. In 2019 the first version of a head-scanner and its selection field generator was shown [1]. The selection field (gradient field) is used to achieve spatial encoding, by generating field free regions.
An improvement from the old two-coil setup was introduced by Foerger et al [2], which contains 18 coils with iron cores that can be driven separately. In this abstract this idea is taken up and different coil geometries are simulated and evaluated.

Methods
To find the optimal setup, a set of parameters has to be identified and evaluation methods developed to achieve the best selection field setup, in regards to low power consumptions and high magnetic field. Furthermore the selection field generator must comply with several limits to meet clinical standards and safe use in humans.
For the simulations the software COMSOL and Matlab are used.

Results
By implementing an optimization algorithm the field free region can be driven to a wanted position with a predefined gradient strength. With this, the field free region is driven in a spiral trajectory and different coil and soft iron topologies are evaluated. The achieved gradient is 0.5 T/m with a power consumption of below 500 W.

Conclusion
On basis of these simulation results a setup which fulfills the conditions is found.

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References
Current Control System for coupled Coil Arrays in MPI

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Introduction

Magnetic Particle Imaging (MPI) is a novel real-time capable biomedical imaging technique which measures the spatial distribution of superparamagnetic nanoparticles. Recently a new energy-efficient multi coil array Selection and Focus field generator (SeFo) topology was presented. To shift the field free region needed for imaging, varying currents up to 30 A with frequencies up to 10 Hz are needed. Trivial but cost-intensive solutions include using 4-quadrant amplifiers for each coil.

In this abstract a cost-efficient and modular approach providing controllable bipolar currents is shown.

Methods

Custom PID-controller boards measure the current and control commercial regenerative motor drivers. A RedPitaya IO Cluster provides the current setpoint to the controllers and output filters lower ripple currents. A capacitor bank allows reuse of energy stored in the coils. Two DC sources supply up to 120 A to the system.

The current was measured with a current clamp and compared to the applied setpoint.

Results

The current in the coils can be accurately controlled and inductive coil cross coupling is suppressed.

Conclusion
The system shows an inexpensive, modular solution to drive inductively coupled coil arrays of multicoil SeFo topologies.

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**Keywords:** Magnetic Particle Imaging, LF magnetic field, medical imaging
High-scale synthesis of magnetic nanoparticles for biomedical applications using turbulent mixing in a continuous millifluidic system

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Introduction
Magnetic nanoparticles (MNP) must meet application-specific requirements such as high magnetic saturation and strong magnetic response to alternating magnetic fields to be useful as e.g., heating agents in magnetic fluid hyperthermia (MFH) and as contrast agents for magnetic resonance imaging (MRI). Promising imaging and hyperthermia applications were reported for scaffolds with incorporated MNP. For their fabrication, MNP must be produced with a yield in the order of several hundred grams with reproducible properties. Here, an approach for the scalable and automated synthesis of MNP is presented.

Methods
A continuous and millifluidic modularly built manufacturing setup was designed: Two peristaltic pumps feed the reactants base and iron salts into a jet mixer, enabling their turbulent mixing (mixing unit). The resulting mixture flows in a tube, in which temperature is controlled. Here, the reaction takes place and MNP are formed (crystallization unit). MNP are then coated with citric acid (coating unit) and the MNP suspension is purified (downstream unit). Synthesis parameters were variably set in each unit such as iron ion ratio, flow rate and temperature. The MNP were then analyzed using dynamic light scattering, transmission electron microscopy, MFH, MRI and magnetic particle imaging (MPI). The iron concentration was determined photometrically based on complexation of Fe³⁺.

Results
The unique setup design allowed for process control in each unit, which facilitated the investigation of optimal combination of synthesis parameters to tailor the MNP core sizes. MNP with approx. 10 nm, 50 nm, respectively 100 nm in diameter resulted in size-dependent signals in MRI and MPI, and different heating outputs in MFH.

Conclusion
The automated synthesis approach enabled MNP optimization for MFH, MRI and MPI applications. Importantly, it is high yielding and provides several processing advantages compared to a batch process at scale showing favorable prerequisites for clinical translation.
Track:

Education and Training
Learning Outcome of Different Digital Learning Objects in the Field of Regulatory Affairs for Medical Devices

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Introduction
For engineering students heading for the medical device industry, knowledge in engineering subjects should be complemented by the basic concepts of regulatory affairs for medical devices (RA for MDs). Since the development of digital learning objects (DLOs) needs time and money, the type of DLO should be carefully chosen to achieve high pedagogic quality. Former work led to a list of types of DLOs, which are suitable to deliver teaching content in the field of RA for MDs. Each item included a preliminary estimation of its acceptance by students. This work aims at giving a first impression of the influence of the type of DLO on the learning outcome of the participants.

Methods
For three different topics in the field of RA for MDs, three different DLOs with high popularity rankings were investigated:
1. A text was provided in a webbased format with junctions and possibilities to go into more detail.
2. Lecture with embedded quizzes
3. Animated picture story with characters
The material provided the same information for each topic in each of the different DLOs. Additionally, a pre- and a posttest for each topic was conducted. Ten different participants went through the following procedure:
- Pre-test for the first topic,
- Usage of one of the DLOs (1-3),
- Post-test.
This procedure was repeated for all three topics. The order of the three topics was the same for all participants.
To estimate the learning outcome the results of the pre- and posttests were compared.

Results
The procedure provided a ranking of the DLOs (1-3) with regard to their effectiveness in the learning process.

Conclusion
The effect on the learning outcome as a selection criteria is added to the suitability and the popularity ranking. Thus it enlarges the basis for decision regarding the selection of DLOs in the field of RA for MDs.
Light detection for simulator based endoscopic training in colonoscopy

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Introduction
Colonoscopy is considered as gold standard in colorectal cancer screening with the highest sensitivity and specificity. The quality indicators of colonoscopy are reaching the caecum, a withdrawal time over 6 minutes, and an adenoma detection rate (ADR) of ≥ 20%. ADR can be significantly improved by training. The goal of this work is to develop a colonoscopy training model for intraprocedural polyp detection with feedback. The simulator will be evaluated with a study.

Methods
Colorectal datasets were first processed using graphics software, transition areas were designed and polyps implemented. The organs were 3D printed, immersed in latex, and photoresistors were attached. The positioning and morphology of the polyps are according to human pathology. The organs were fitted into a foam block and a chassis, followed by installation and programming of the electronics. The recorded data in comma-separated values format were analysed with Excel.

Results
The colonoscopy simulator was evaluated with n = 29 participants. The developed model is suitable for colorectal examination and detection of pathologies. Intubation of the caecum and measurement of the withdrawal time are possible. Further, the user interface provides numerical and visual information about the required time and the number of detected polyps. The model achieved a score of 1.6 (Scale: very good to not realistic, 1 – 6). During the standardized examination, the participants required an average of 7.4 minutes for withdrawal and detected 6.6 of 10 polyps. Participants with a withdrawal under 6 minutes detected 48% of the polyps. Participants with a withdrawal over 6 minutes detected 74.7% of the polyps.

Conclusion
With this mechanical model, colonoscopy training can be performed in a good, standardized manner with the detection of polyps by implemented photoresistors. The evaluation provides a good suitability of the simulator for training. The results show a higher number of polyps detected with an examination time over 6 minutes.
Thorax simulators reloaded: Anatomically correct training models of the chest cavity

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Introduction
The project aims to develop a realistic training system for thoracic surgery, applicable for both open and minimally invasive procedures.

Methods
Central components are (I) a modular thorax model based on real CT data, whose ribs are connected by a plug-in system, and a (II) simulation trainer for abdominal interventions. The design process was based on the guidelines of the VDI and the usability requirements of the MDR. Various concepts were designed and manufactured. The selection of a preferred variant was made by the head of the thoracic surgery department at Magdeburg University Hospital. The components were manufactured additively with PETG and TPU, to provide a flexible organ tray.

Results
The training system consists of a holder on which a right hemithorax and a synthetic skin can be attached. It can be combined with a P.O.P Trainer (Optimist GmbH), which allows the use of animal organs including their perfusion as a Wet Lab application. A flexible grid is connected to the bottom to keep animal organs in an anatomically correct position. The evaluation employed criteria that were derived from general requirements for medical training systems. In addition, a tabular comparison was made with other products. The model met the criteria and convincingly represented clinical conditions compared to other thoracic simulators. The geometry and modular system of the thoracic model provides advantages over other systems. Furthermore, it mimics the arrangement and functioning of organs more realistically, especially by imitating the vertical movement of the heart through pulmonary ventilation. Therefore, the proof of concept could be carried out successfully.

Conclusion
The design should be improved in order to simplify handling and the soft tissue shell should become more realistic. Aligning with high standards set by VDI and MDR creates the prerequisites for future approval as a valid training option.
Introducing Gamification to a Biosignal Processing Course on Bachelor Level

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Introduction
Keeping up student engagement throughout a whole-semester course is a challenge which can be addressed by including gamification into the course structure. We evaluate the application of gamification to a second-year B.Sc. "Biosignal Processing" course (5 ECTS, 3 semester hours/week) in an Applied Computer Science study degree. We analyze whether there were different types of learners and the impact on student satisfaction.

Methods
We applied gamification by providing different ways to earn points (max: 1,405) as prerequisite for the exam. Students were eligible upon reaching 600p. These could be earned by taking a quiz after each lecture (first 50p, then 5p each), submitting solutions for Jupyter Notebook exercise sheets (100p each), presenting a solution orally in front of the class (100p), or answering questions to a scientific paper as a group task (100p). For each student we compared the achieved points to the grade in an online, open-book exam. Additionally, we conducted a questionnaire evaluation at the end of the course using Likert scales (1-6).

Results
The exam was taken by 22 students with an average of 75% (std: 21%, range: 54-96%). During the course, we observed different types of behavior, e.g. "competitive" (aim: maximize points) vs. "cost-effective" (aim: reach 600 points), and roles, e.g. "busy bees" (early submissions) vs. "procrastinators" (late submissions). The course was evaluated by 7 students with an average of 2.0 for the whole course and 1.7 for the combination of lectures and gamification tasks. 6/7 rated the various options as motivating and 3/7 expressed that they tried to earn as many points as possible.

Conclusion
The overall evaluation of the course was improved by 0.6 compared to previous years with the same content but without gamification. In the future we will incorporate more types of tasks appealing to more types of learners.
Introductory practical course on machine learning for students of biomedical engineering

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Introduction
Machine learning (ML), especially neural networks (NN), play an increasingly important role in medicine. This implies the integration of this topic into the curriculum of the course of study in biomedical engineering and related courses of study. At the Westsächsische Hochschule Zwickau a practical course was developed, which introduces the students to the concept of ML.

Methods
The practical course takes place in a computer room. For the exercises, the students create web-based interactive Jupyter Notebook documents and program in the language Python. Basic programming skills are a prerequisite. Each unit of the course takes 90 minutes and covers a different topic of ML. It was taken care, that there are no special requirements regarding the hardware and that the used software is free of charge.

Results
In total, six units were developed for the course covering topics such as introduction to important Python libraries (Numpy, Matplotlib and Pandas), supervised learning applied to tabular data of diabetic patients using the k-NN-algorithm and supervised learning applied to tabular data using deep learning realised with the library Keras (including the development and evaluation of a model for a NN). In two final units supervised learning implemented with the library TensorFlow is used to classify image data like CT images of brain tumours.

Conclusion
The practical course covers selected important topics of ML and is able to teach the concept of this field. Despite the limited period of time the students are able to solve practical problems in a unit. Students of biomedical engineering evaluating the course listed the programming as the biggest challenge, which is likely due to their limited education in computer science. They also stressed the importance of an accompanying lecture teaching the theoretical background of ML.
Track:

Robotics and Society
Optical Non-Contact-Based Vital Sign Monitoring for Care Robots

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Introduction
The nursing crisis is becoming increasingly acute. According to the Federal Statistical Office, the number of people in need of care in Germany will rise from 5.1 million to around 6.8 million in 2055. The increase in the number of people in need of care is matched by an insufficient number of nursing staff. In this context, intelligent assistance systems based on machine learning offer the possibility of relieving nursing staff of routine tasks and supporting them through digitisation.

Methods
In this work, a camera-based robotic measurement system is developed to provide automated and non-contact measurement of vital signs, including heart rate and respiratory rate. The robot is able to respond to various situations and interact with the care recipients. Remote photoplethysmography is used to measure heart rate by detecting pulse-related subtle skin colour changes from RGB images. The method includes advanced tracking, individual skin colour detection, and adaptive filtering. For respiratory rate determination, prominent features in the chest area are tracked using optical flow, followed by filtering, principal component analysis, and frequency analysis. To promote a higher level of privacy and counteract data traffic, the images are processed on edge devices.

Results
The implementation is demonstrated and evaluated under realistic scenarios. Various lighting conditions, subject movements, as well as angles and distances between the robot and the subject are examined. The automatic recording of vital signs in combination with AI-supported data analysis and the achieved fast and local processing allows emergency situations or changes in the care situation to be detected.

Conclusion
The non-contact monitoring of heart and respiration rates using nursing robotics offers considerable benefits for use in care. It reduces the workload of nursing staff and increases their productivity through digitisation and AI-supported evaluation. At the same time, it supports a self-determined life in the field of Ambient Assisted Living.
Track:

Optical Systems and Biomedical Optics
Investigation on correlations between optical tissue properties and MRI relaxation times

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Introduction
Knowledge about the optical tissue properties is essential for calculating light distribution within tissue and thus precise estimation of the light dosimetry in light-based therapies like interstitial photodynamic therapy (iPDT). So far, for this application, homogeneous tissue are assumed and specified with assigned literature values of tissue optical properties for use in dosimetric concepts. However, these literature values give only an estimate of the actual optical conditions. There is a lack of estimations of how the optical tissue properties may vary in the same tissue type and for individual persons.

Methods
The present study aimed to investigate whether MRI-information can be used to derive tissue optical properties for the target tissues. A 3T-MRI was used to determine the T1 and T2 NMR-relaxation times of porcine tissue samples (brain, liver) and optical tissue phantoms. The samples were diluted with different ingredients in a concentration-dependent manner. The ingredients used (water, Lipovenös®, blood) are related to the optical tissue properties (e.g. absorption, scattering). Samples undergo T1 and T2 NMR-measurements and integrating sphere measurements, with which the optical tissue properties, the absorption coefficient $\mu_a$ and the reduced scattering coefficient $\mu_s'$ are determined for the wavelength range 450-750 nm. NMR-values and optical values were compared.

Results
An increasing water concentration resulted in a decrease of $\mu_a$ and an increase of $\mu_s'$, maybe due to an increase of air in the sample after the mixing process. A prolongation of both NMR-relaxation times (T1, T2) was observed for increasing the water content. With increasing Lipovenös® concentration $\mu_s'$ increased, and a shortening of T1 and T2 was observed. An increase in the blood fraction caused increased absorption and prolongation of T1 while T2 shortened. In addition, tissue phantom recipes that combine NMR-relaxation times and optical tissue properties of different brain tissue could be derived.

Conclusion
The extraction of a direct correlation of optical tissue properties and NMR-relaxation times may not be possible. However, by using the differences or occurrence of changes in T1 and T2 within the same tissue type, differences in optical tissue properties may be estimated as both are affected macroscopically by the samples’ water and lipid content. Further investigations may focus individually on the curves’ steepness as intermediate property for each tissue to estimate changes in optical properties dependent on T1 and T2.
Regression-based Correction for Infrared Thermography in Neonatal Incubators

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Introduction
Neonatal incubators provide an ideal thermal environment for premature infants. However, adhesive temperature sensors compromise interaction and increase infection risk. Infrared thermal imaging is a non-contact alternative, but its accuracy, varying between 2°C and 5°C, remains a challenge. Developing more accurate thermal imaging techniques can be highly beneficial for continuous monitoring of preterm infants in neonatal intensive care units.

Methods
This work explores a regression-based accuracy improvement approach for contactless surface temperature measurement in a neonatal incubator with the Optris PI640 infrared camera. The camera used for measurement was placed on top of the hull, enabled by a novel research incubator with a built-in infrared window. A custom-made passive reference with a clinically used temperature sensor covered with a highly emissive foil was placed inside the incubator to enable live temperature correction. In addition, an active black body with high-precision temperature sensors replaced the infant, allowing infrared camera accuracy testing. In total, 26 measurements, each lasting 9 hours with realistic temperature ranges from clinical settings, were carried out with spatial variations on the incubator mattress and then divided into six folds for cross-validation. Finally, a regression-based algorithm was developed using the temperature data from the passive reference as features to improve the temperature measurement of the infrared camera.

Results
A linear regression with feature interactions provided the best results and improved the infrared camera’s accuracy for temperature measurement inside a neonatal incubator. The mean absolute error decreased from 0.91°C to 0.17°C (81% improvement), maximum error of corrected measurements from 4.85°C to 0.73°C (85% improvement).

Conclusion
The regression-based correction algorithm presented in this work has significantly improved the accuracy of infrared thermography. The results indicate that infrared cameras have the potential to be used effectively for non-contact temperature measurement in neonatal incubators by applying the proposed correction algorithm.
A lateral scanning fiber-based common-path optical coherence tomography system for obtaining algorithm training data from pituitary gland and adenoma tissue samples

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Introduction
Resection of pituitary adenoma is usually performed through transnasal surgery using an endoscope. Discrimination of gland and adenoma tissue in this process is currently based on visual inspection. Here, optical coherence tomography (OCT) can become an important tool. We present a lateral scanning fiber-based OCT system suitable for measurement of paraffin embedded tissue samples.

Methods
To provide information on pituitary tissue during surgery, an endoscopic approach must be followed. Therefore, in this work we developed a fiber-based common-path OCT system employing a measurement fiber that can be used in an endoscope with only minor modifications. The fiber assembly consists of a single-mode fiber with an attached GRIN lens. The GRIN length was optimized to obtain a depth of focus corresponding to the first 1.5 mm within the sample. Further, for acquiring training data, two motorized translation stages were programmed in order to obtain OCT scans at different pre-defined lateral positions of the sample. Additionally, the position of the light spot on the sample is recorded, facilitating a later correlation procedure with histopathological data.

Results
Although paraffin is causing a strong background signal, a first pituitary tissue sample could be visualized with high contrast using our OCT system. A-scans were recorded at different lateral points of the sample and analyzed regarding different parameters (signal intensity, attenuation coefficient, fractal dimension, spectral properties) which can be used for training a classification algorithm. En-face visualizations of our OCT data are in good agreement with microscope images of the same sample.

Conclusion
The OCT device developed in this work enables data collection from a large number of points on pituitary tissue samples, which is essential for an automated tissue discrimination algorithm. Thus, we are confident that this device will contribute to establishing endoscopic OCT as supporting tool for the surgeon during pituitary adenoma resection.
Spectral skin color measurement by LED reflectometry

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Introduction
In recent years, there have been approximately 60,000 to 80,000 limb amputations per year in Germany. In addition to anatomical adaptation, color matching to the natural skin tone also plays an important role in the acceptance of prostheses.
In orthopedic practice today, skin color is usually determined by comparing the skin color with color sample charts. However, this procedure is not only very time-consuming, but also highly subjective and shows a high dependence on the spectrum of the incident ambient light.

Methods
Most existing hand-held colorimeters rely on the tri-stimulus approach to measure skin color in a three-dimensional color space (RGB or CIE-Lab). We argue that a full measurement at multiple wavelengths is required for a natural appearance of skin prostheses under varying ambient light conditions. To this end, we developed a novel handheld spectrometer device to measure the fraction of reflected light from 12 light-emitting diodes (LEDs) at their respective discrete wavelengths (462-640nm) using a photodiode (TSL2591 sensor) and an ESP32 microcontroller. Spectral profiles of 3 skin phantoms (pale, reddened, medium brown) and 4 volunteers (24-41yrs, European skin types) were acquired.

Results
Reflectivity was between 19.3% and 38.6% at the lowest wavelength (462nm) and gradually increased to 46.0% and 62.1% at the maximum wavelength (640nm), showing a trend inverse to melanin absorption. Reflectivity of the paler inner forearm was generally higher when compared to the darker outer side. The pale skin phantom showed high agreement to some volunteer reflectivity spectra.

Conclusion
Our results suggest the viability of this novel approach for low-cost spectral skin color measurement. For application to prosthesis coatings, further studies with reference silicone materials and patients are needed to improve robustness. In the longer term, LED reflectometry may certainly improve production quality of silicone materials for color-matched prostheses independent of the ambient light spectrum.
Combining the benefits of NIR-signals for biosensing with sensitive Si-based detectors

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In the context of biomedical applications, optical signals in the near infrared (NIR) region are superior than those in the visible range. Because of reduced absorption and scattering, as well as minimized autofluorescence, signal-to-noise ratios are high and interfering background is low. Carbon nanotubes (CNT) serving as optical biosensors exhibit NIR-fluorescence depending on analyte interaction. The emission peaks of CNTs with (6,4)- and (6,5)-chirality fall exactly on the edge, where the sensitivity of Si-detectors ends and the sensitivity of InGaAs-detectors begins. Due to the several advantages of silicon detectors, like low noise and low-cost, it is of interest to evaluate them for CNTs emitting between 900-1000 nm.

At first, a detailed simulation of the fluorescence scenario with different detectors was performed, where CNT signal, background and noise were calculated. Further, fluorescence experiments in a microscope setup with Si- and InGaAs-based cameras and photodiodes were carried out. Different CNT concentrations and the fluorescence change of analytes were evaluated and compared.

The simulation results show that Si-detectors are more sensitive than InGaAs-detectors, due to their lower background and noise. This is especially interesting for imaging, when using (6,4)-CNTs (880 nm) with standard Si-cameras. (6,5)-CNTs (990 nm) on the other hand are better imaged with an InGaAs-camera. If no spatial information is needed, silicon pin-photodiodes outperform InGaAs. In experiments similar responses between InGaAs and low-cost Si-photodiodes for (6,5)-CNTs were detected, which matches the simulation results.

To conclude, we show the technology to detect beneficial NIR-signals with low-cost commercial cameras and detectors, which opens many opportunities for biosensing.
Optical calibration of a common path optical coherence tomography device for measurement of tissue attenuation coefficients

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Introduction
In contrast to other OCT methods, common-path (CP) OCT works with a built-in reference, e.g. the interferometric reference arm is provided by the same optical single mode fibre that is used for the measurement. This is an advantage for endoscopic surgery applications, where single point measurements can be applied for discriminating different tissue types or diseased (cancerous) from normal tissue. A good parameter for tissue discrimination is light attenuation. Unfortunately, there are many parasitic effects, like the fibre-sample distance, ghosting, etc. that make it difficult to measure the exact value of the attenuation coefficient. In this work it is shown how to properly and reproducible calibrate the OCT signal for correct attenuation coefficient measurement with a standardised Formazin solution. Different effects and measurement conditions that are detrimental to the calibration are discussed.

Methods
Calibration measurements are performed on different concentrations of a standardised Formazin colloid solution used in nephelometry, at different fibre-sample distances. From the A-scans the attenuation coefficients at different depths below the sample surface are calculated via the depth resolved algorithm from Vermeer. In contrast to the true attenuation of the Formazin standard, which is independent of the depth, the measurement shows depth dependence. This can be corrected via calibration based on the assumption of homogeneity and linearity between backscattering and Formazin concentration. A cross-check was performed with samples showing stepwise constant attenuation profiles at different depth ranges.

Results
After calibration, the attenuation data from cross-check samples are independent from fibre-sample distance and from the position below the sample surface.

Conclusion
The calibration of CP-OCT measured attenuation coefficients for tissue discrimination via Formazin solution was shown to be feasible and reproducible due to the near constant properties of the applied Formazin standard. Stabilized Formazin solutions can be applied more conveniently, as the non-stabilized Formazin segregates relatively fast.
Real-time smartphone-assisted EEG electrode localization and augmented reality application

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Introduction
Electroencephalography (EEG) electrode digitization is essential for accurate source localization, connectivity analysis, and EEG cap evaluation. Existing commercial systems are costly, cumbersome, and labor-intensive. Although affordable photogrammetry-based alternatives exist, their widespread application is hindered by manual post-processing and computational demands. We present a novel approach using live electrode identification from smartphone camera images and sparse 3D reconstruction without dense model calculation, augmented by sensor information on live images.

Methods
We developed a smartphone app (Android) with custom image processing for automated electrode detection and identification using Kotlin, C++ and OpenCV. 3D reconstruction from sparse electrode locations was conducted using the structure from motion approach (COLMAP library).

Results
Our approach achieved live electrode detection, labeling, and 3D reconstruction (30+ frames/second) on a mid-tier smartphone, with the capability to store sensor labels and template coordinates for different cap layouts. The operator launches the app on an ordinary Android smartphone, aims the camera at three particular electrodes and then moves around the subject to capture the remaining electrodes around the head. We tested and validated the system extensively with regards to accuracy, repeatability, and various head sizes. Measurements with a commercial infrared-optical stylus-based system took around 15 minutes and scan-rescan errors exceeded 3 millimeters for individual electrodes. In contrast, measurements with our smartphone-based approach took less than two minutes of acquisition time and all electrodes from caps with 65 channels were located with sub-millimeter accuracy.

Conclusion
The proposed smartphone app facilitates widespread EEG sensor digitization in medical research and clinical settings. Augmented reality offers operators rapid guidance and potential for further enhancements, such as displaying interfacial impedance values.
Reproducible and Easy-To-Use Optical Phantom for Biomedical Polarization Imaging

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Introduction
Biomedical polarimetry is an emerging technique for analyzing polarization of light in biological tissues, providing valuable insights into tissue microstructural organization and physiological state. As polarimetric applications advance toward clinical and commercial stages, there is an urgent need for calibration, quantification, and standardization of polarimetric instruments. This necessitates the development of well-calibrated phantoms and standards.

Methods
The phantom comprises a glass vessel filled with an intralipid solution to generate Rayleigh scattering, and a suspension of microspheres to create Mie scattering properties. The size and concentration of microspheres are varied to modulate scattering extent. A birefringent target is embedded within the phantom to produce a defined retardation effect. The phantom is specifically designed for reflection-based polarization imaging, but can also be used in transmission. To measure the phantom, it is illuminated with monochromatic, circularly polarized light from a xenon lamp. To capture the polarization-dependent intensities, a special polarization-sensitive camera sensor is used (IMX250MZR, Sony, JAP).

Results
The developed optical phantom demonstrates potential for mimicking the optical properties of biological tissues in polarization imaging, particularly depolarization and retardation, with easy-to-procure components. Although the phantom does not cover the effect of dichroism due to its application specificity, it provides a preliminary standardized platform for calibration and validation of polarimetric instruments.

Conclusion
The proposed optical phantom offers a simplified and reproducible approach for validating and calibrating polarization imaging devices, addressing the need for standardization in the field. While further refinement is necessary, this optical phantom could facilitate the development of reflection-based polarization instruments and ultimately contribute to the advancement of polarized light applications in medicine.
Track:
Imaging Technologies and Analysis
Mapping the Anisotropy of Tissue Magnetic Susceptibility from Single-Orientation Magnetic Resonance Imaging

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Introduction
In magnetic resonance imaging (MRI), the magnetic susceptibility of the biological tissue causes tiny perturbations to the magnetic field. In the highly aligned white matter of the human brain, magnetic susceptibility is anisotropic and must be described with a susceptibility tensor, rather than a scalar. The apparent susceptibility on the tensor’s main diagonal leads to field perturbations distributed in a characteristic magnetic dipole pattern. The off-diagonal elements of the susceptibility tensor, however, produce a markedly different spatial fingerprint in the field maps.

In this work, we present a deep learning-based technique that separates the three components of the magnetic susceptibility tensor that are apparent under a single direction in the main magnetic field.

Methods
We extended the physical model of QUASAR, which itself is an extension to quantitative susceptibility mapping (QSM), by adding the sources from the off-diagonal susceptibility tensor $\chi$:

$$f = \chi_{33}d_{33} + \chi_{23}d_{23} + \chi_{13}d_{13} + f_\rho,$$

where $f$ is the observed frequency shift, $d_{xy}$ are the respective magnetic dipole kernels, and $f_\rho$ represents the nondipolar frequency shifts. We simulated synthetic training data adhering to this model and trained deep neural networks to solve the inverse problem by mapping from $f$ to either of the sources $\chi_{xy}$ (analogous to Jochmann2019ISMRMp0320, but with anisotropy).

We evaluated the method in simulations and applied it to real data.

Results
We built a method that maps the anisotropy of tissue magnetic susceptibility from single-orientation MRI. The resulting maps highlighted white matter tracts, known to be anisotropic.

Conclusion
Since magnetic anisotropy in white matter is a result of the highly aligned tissue, e.g., the myelin sheaths, our novel method is sensitive to alterations where the microstructural integrity is damaged, even before the bulk constitution of the tissue is changed. Our work lays the ground to study single-orientation anisotropy mapping as a marker for structural integrity of white matter.
Fiber-Based Impedance Spectroscopy as an Integrated Sensor System for Real-Time Monitoring of Oxygenators

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Introduction
Extracorporeal membrane oxygenation (ECMO) is the last measure to ensure survival for patients with lung failure. The most common indications are severe ARDS and COPD exacerbations. During ECMO, the main complications include blood clot-induced events, as clot-related failures occur in nearly 30% of all treatments. Even though various methods exist for monitoring the ECMO system (e.g. pressure difference or oxygen saturation) they are not sufficient. In 10% of all treatments, an acute thrombus-induced life-threatening system failure occurs.

Methods
In this work a fiber-based measurement system for real-time monitoring of blood coagulation in the oxygenator is proposed. For this purpose, conductive fibers are integrated into the hollow fiber mats of the oxygenators. By measuring the impedance between these conductive fibers, changes in the blood composition can be detected. The measurement allows conclusions about successful priming and clots forming between the fibers.

Titanium fibers are integrated into a hollow fiber mat. Six of these mats are integrated into the oxygenator at different levels. The change in impedance between the fibers is determined using 4-point impedance measurement. Four fluids (air, water, NaCl, and citrate blood) were passed through the oxygenator with a flow of 5 l/min. Subsequent to the experiments utilizing blood 10 ml of Calcium gluconate 10% MPC solution was injected to the blood to stimulate coagulation. The resulting clotting was monitored at a single position over time.

Results
The functionality of the fiber-based measurement system was successfully demonstrated for all Fluids. Significant differences in impedance were observed in the frequency spectrum of 10^2 to 10^6Hz

Conclusion
The determined data illustrates that a fiber-based impedance sensor system can provide helpful information about the fluid composition in the oxygenator. By spacially distributing the fibers within the oxygenator a sensor system, able to indicate the size and position of air bubbles and clots in the oxygenator, can be achieved.
Development of a PET/MRI system with long axial field-of-view (LAFOV) and dedicated local PET detectors enhancing the spatial resolution – Introduction of the HD-MetaPET-Project

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Introduction
Positron Emission Tomography (PET) systems with long axial field-of-view (LAFOV) have been introduced in recent years, considerably increasing sensitivity. By now, these PET systems are exclusively combined with CT. The HD-MetaPET project [1] aims to develop the first LAFOV PET/MRI, enabling superior soft-tissue contrast and the benefits of simultaneous imaging, e.g., motion correction. In addition, HD-MetaPET is working on methods to locally boost the PET image's spatial resolution, enabling the detection of smallest lesions or tissue changes.

Methods
HD-MetaPET integrates a clinical wide-bore 1.5 Tesla-MRI with a stationary LAFOV PET ring featuring dedicated local detectors. The PET electronics is based on the MR-compatible Hyperion III-PET-platform [2]. The local PET detectors, which can be freely placed within the field of view, provide a highly increased spatial resolution of ~ 1 mm. Therefore, the PET spatial resolution is locally increased at these regions of interest. DOI information at both the local detectors and the stationary ring will ensure almost uniform spatial resolution throughout the entire field of view. Currently, segmented and light-sharing detector concepts are tested and will be compared, especially regarding system applicability and detector performance (i.e., positioning, energy, and timing resolution).

Results
We present the current progress of the HD-MetaPET project, including measurement results for both the stationary and local PET detectors as well as MR-compatibility studies of the Hyperion III-PET-platform.

Conclusion
HD-MetaPET enables simultaneous LAFOV PET/MRI imaging with a local enhancement of the PET spatial resolution.

Funding
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References
ProtoTOF: A scalable DOI-capable detector prototype aiming for 100 ps timing resolution in time-of-flight positron emission tomography systems

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Introduction
Especially for organ-dedicated time-of-flight (TOF) positron emission tomography (PET), correcting for parallax errors caused by an unknown depth of interaction (DOI) of the γ-photons is essential for a high signal-to-noise ratio in the tomographic image. Additionally, achieving a coincidence time resolution (CTR) of 100 ps (FWHM), i.e., a spatial resolution of 1.5 cm along the line of response, can boost the noise-equivalent count rate by a factor of about 5 compared to state-of-the-art clinical systems with a CTR of 214 ps. The project ProtoTOF aims for such a TOF- and DOI-capable detector prototype.

Methods
We propose a scalable detector unit using light-sharing between two detector pixels to encode the DOI similar to known concepts. The units consist of LYSO:Ce,Ca crystals (3x3x20 mm³) and novel NUV-MT silicon-photomultipliers by FBK and Broadcom, which showed that reaching a CTR of 100 ps (FWHM) is possible, exceeding the current state of the art [1]. The unit is read out by adapted high-frequency (HF) electronics [2,3] to characterize its TOF limits and system-applicable electronics, i.e., the TOFPET2c ASIC by PETsys Electronics.

Results
Within the ProtoTOF project, overall nine light-sharing concepts were investigated and their TOF and DOI capabilities evaluated. The best concepts achieved a CTR of about 230 ps (FWHM) and a DOI resolution of about 3 mm (RMSE) with system-applicable electronics. Using HF electronics, the CTR was pushed to about 150 ps (FWHM).

Conclusion
Using the TOFPET2c ASIC, the best unit achieved a DOI resolution of few millimeters and state-of-the-art TOF resolution. Upscaled HF electronics would offer to push the timing performance towards the goal of 100 ps. The status of the project will be presented at the conference.

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Deep Learning Enables a Novel Magnetic Resonance Imaging Contrast that Unveils Chemical and Microstructural Brain Tissue Changes Through Nondipolar Larmor Frequency Shifts

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Introduction

In magnetic resonance imaging (MRI), the name-giving resonance of the protons exhibits tiny local frequency shifts. In the human brain, these shifts have been attributed mainly to iron and myelin, but theoretical and experimental evidence suggests additional frequency shifts from chemical exchange and microstructure. These additional components differ from iron and myelin by their spatial fingerprint on the frequency maps: they do not present with a dipole-shaped distribution; hence, we termed them nondipolar frequency shifts.

We developed DEEPOLE QUASAR, a method that maps nondipolar frequency shifts in vivo, creating a new MRI contrast (Jochmann ISMRM2019p0320). Here, we investigated the contrast in the normal human brain and in multiple sclerosis (MS) lesions.

Methods

We simulated synthetic data training based on QUASAR, an extended physical model of quantitative susceptibility mapping (QSM). With this data, we trained a deep neural network (U-Net) to solve the inverse problem (source separation and deconvolution).

MRI scans were acquired at 3T and analyzed for 12 healthy volunteers. Additionally, MS lesions from 8 patients were selected, labeled, and analyzed for contrast patterns.

Results

Nondipolar frequency shifts were observed extensively throughout the normal human brain and in MS lesions. Our findings challenge the traditional interpretation of MRI frequency contrast, which solely considered dipolar frequency shifts. Lesions in MS patients displayed diverse contrast patterns in the nondipolar frequency maps, indicating the potential to distinguish lesion subclasses that conventional MRI cannot tell apart.

Conclusion

The presence of nondipolar frequency shifts in brain tissue calls for reevaluating previous conclusions regarding iron accumulation and demyelination. Our novel DEEPOLE QUASAR contrast reveals clinically relevant brain tissue alterations and enables the study of molecular processes associated with brain disease and aging. Given its low adoption barrier and compatibility with established QSM methodology, DEEPOLE QUASAR is poised to impact clinical and research settings.
Ventilatable thorax-lung model of the rat to optimize electrical impedance tomography for small animals

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Introduction
Electrical impedance tomography (EIT) is widely used in clinical and pre–clinical research in humans and large animals. Though the technique is easily transferrable to large animals there is currently no dedicated solution to monitor the ventilation state of small animals with EIT even though small animals account for the vast majority of pre-clinical studies. In this context, adaptation of EIT for the application in small animals would require a significant amount of animal lives in order to establish and approve measuring and image reconstruction algorithms. With the goal to reduce the number of animal lives dispensed in pre-clinical research, we developed a physical model of the rat thorax that could be connected to a small animal ventilator and used instead of live animals.

Methods
The model is comprised of a latex balloon filled with saline-infused agar agar incorporating a two-compartment lung surrogate. The lung consisted of a balloon that was divided into two parts by a longitudinal latex strip. The two compartments filled sequentially leading to a distinct ventilation pattern, which facilitated validation of EIT image reconstruction. For EIT imaging, the thorax-lung model was equipped with sixteen equally spaced subdermal hook needle electrodes connected to a Sciospec EIT32 system.

Results
The physical model was successfully connected to the EIT device and manual and mechanical ventilation of the model could be visualized. A sequential filling pattern and the location of the lung surrogate compartments inside the model given by reconstructed EIT images was confirmed by its visible light reflection pattern.

Conclusion
Our new model is capable of simulating regional ventilation in small animals. With the presented model, it would be possible to optimize and refine peripheral hardware configuration for EIT, study different current injection patterns and adapt the reconstruction algorithms to rat anatomy and physiology without performing animal experiments.
Parameter evaluation and image data analysis for the development of medical diagnostic Multi-Energy X-ray

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Introduction
Due to the nature of digital radiography (DR) as a planar projection, three-dimensional information of overlapping anatomical structures is reduced into a two-dimensional transmission projection, thereby limiting tissue differentiation. Recently, the advancement of dual-energy usage led to the clinical application of dual-energy X-ray and dual-energy CT, resulting in improved diagnostic performance [1]. According to Hounsfield [2], Alvarez and Macovski [3], it enables the differentiation of materials and quantification of material mixtures. The underlying motivation of this research is to transfer and extend this knowledge to planar radiography creating a diagnostic benefit with minimization of dose and costs, especially for mobile X-ray applications. This work focuses on parameter studies regarding the development of a single-exposure multi-energy rapid kVp-switching sequence.

Methods
To set an adequate database for the investigation and parameterization of the technical implementation and development of an image processing algorithm, a series of measurements were carried out in an experimental DR System (Siemens Healthineers) including a flat-panel detector (Canon). Multispectral image datasets were obtained by subjecting various phantoms to X-ray imaging within a range of several energy levels. First, a purpose-built liquid container phantom filled with different materials was X-rayed to investigate the attenuation behavior of materials according to physical fundamentals. Furthermore, an estimation of exposure parameters with an acrylic phantom and its data validation using the anthropomorphic thorax phantom LUNGMAN were realized [4].

Results
Exposure parameters for rapid kVp-switching via pulsed mode are verified and reviewed. Moreover, the multispectral data obtained from the liquid phantom were suitable for material characterization and differentiation by using a specially developed algorithm based on the material decomposition model approach.

Conclusion
Initial data collection and analysis suggest the feasibility of multi-energy X-ray imaging and its diagnostic benefit. Further phantom parameter studies aim to improve the algorithm and transfer it to clinical applications.
Enhanced PET/MRI Insert for High-Resolution Breast Cancer Imaging

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Introduction
The ongoing quest to improve the spatial resolution and system sensitivity of PET systems has led to the introduction of total-body PET/CT systems, which offer a fourfold increase in sensitivity for a single organ. However, these systems still face physical limitations with a spatial resolution of about 3-4 mm. The EU-H2020 project HYPMED aims to overcome these limitations by developing a PET insert for a clinical MRI for breast cancer imaging.

Methods
The HYPMED insert consists of a combination of local receive coils and two local PET rings that allow simultaneous imaging of the female breast. To better follow the thoracic contour, the two local PET detector rings are arranged at an out-of-plane angle of +/- 20°. Each ring consists of 2×14 detector stacks. A three-layer crystal array design was chosen to achieve high and homogeneous resolution across the FOVs. The MR-compatible detector is based on the Hyperion III platform and features a sensor tile with 12x12 individual channels of DPC-3200 (Philips) forming a sensitive area of ~48×48 mm².

Results
The PET electronics have been successfully tested for gradient and B₀ interference. At the highest slew rates and duty cycles of the MRI system, only a slight temperature effect on the detector stacks was observed. Flood maps of the 3-layer detector stack were measured and demonstrated an excellent ability to identify each of the 3,425 crystals. First simultaneous measurements of PET and MRI show the high spatial resolution, which was compared with a commercial 3T PET-MRI scanner (Siemens).

Conclusion
Local PET detectors in combination with a stand-alone clinical 1.5T MRI system are a promising approach for high-resolution clinical PET-MRI of single organs, such as the female breast. With its higher sensitivity and improved spatial resolution, this system offers an attractive alternative to commercial integrated PET-MRI systems.
Polyvinyl Alcohol based Ultrasound Phantoms with Magnetic Microparticles for the Development of Magnetomotive Ultrasound Algorithms

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Introduction
A promising approach for local cancer treatment is magnetic drug targeting (MDT) with superparamagnetic iron oxide nanoparticles (SPIONs) in combination with a magnetomotive ultrasound (MMUS) based monitoring system. MMUS can determine the spatial distribution of SPIONs inside the tumor. Polyvinyl alcohol (PVA) based ultrasound phantoms interspersed with SPIONs are commonly exploited for baseline studies. However, SPIONs are not visible in B-mode images, and strong magnetic fields are needed to induce periodic particle movements as required for MMUS. An alternative use of magnetic microparticles (MMPs) could address these disadvantages. In this contribution, we describe the phantom manufacturing process and evaluation results using B-mode imaging.

Methods
The phantoms contained mixtures consisting of deionized water, Elvanol 71-30 PVA and CUT150 iron powder, hardened by the freeze-thaw method with two cycles. First, a gel was prepared from deionized water with 10 wt% PVA by heating and stirring, and subsequently filled into several containers according to the required weight. The MMPs were then mixed into the individual gels by weight. Finally, the resulting mixtures were filled into several molds, with the openings sealed with plastic foils. This prevented leakage and allowed the mixtures to expand due to icing of the water. To achieve uniform distributions, continuous rotation of the molds during the hardening process was required. We produced cube-shaped phantoms with an edge length of 2 cm and iron powder concentrations between 10 wt% and 35 wt%.

Results
High contrast B-mode images showing the interspersed area were observed for all phantoms, but with increasing acoustic attenuation caused by scattering.

Conclusion
MMPs allow to sonographically analyze the interspersed area due to sufficient echogenicity. Furthermore, particle movements in the interspersed area can be induced with weaker magnetic fields than those required for SPIONs. This would enable the design of simple electromagnets that meet the specific requirements for MMUS algorithm development.
Measurements of the Pressure Loading Response of the Gluteal and Sacral Skin Tissues when Lying in Bed Using Camera-based Techniques

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Introduction
Camera-based systems offer the opportunity of not only being contactless but also being able to perceive wavelengths beyond the capabilities of the human eye up to the infrared spectrum. Additionally, they enable objective assessments making them a promising tool for medical diagnostics such as early detection of pressure ulcers. This type of chronic wound is highly prevalent at the lower back and buttocks of especially older people due to pressure and stress while lying on the back for a longer time. However, the manifestation of wounded tissue in camera-based measurements is overlaid by a normal, healthy effect of increased pressure and temperature on the skin tissue. Measuring this response will allow for source separation and lead to a more profound diagnosis during wound studies.

Methods
A camera setup including an RGB camera, a hyper-spectral camera and an infrared thermology camera has been used to record the effect of lying in bed for one hour on 11 old and 10 young healthy subjects to analyze a normal bed-response. The snapshots were taken before lying down and 1min and 10min after the end of the lying phase. The preliminary results of two probands including a correlation analysis and visualization are presented.

Results
Pressure relief and cooling after the lying phase lead to changes in the skin temperature profile, oxygenation and tissue absorbance.

Conclusion
This small study shows the effect of lying in bed on successive camera-based measurements regarding temperature, oxygenation and the short-wave infrared spectrum, quantifying a pressure loading-response for the subtraction of a healthy baseline during the examination of wounds or other tissue abnormalities in this region.
Exploring the Orientation Dependency of Nondipolar Frequency Shifts in Magnetic Resonance Imaging: An Approach to Unveil Chemical Exchange and Tissue Microstructure in the Brain

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Introduction

In magnetic resonance imaging (MRI) of the brain, the resonance frequency demonstrates tiny local perturbations. Traditionally, these perturbations have been explained with paramagnetic iron and diamagnetic myelin imprinting a frequency shift in the shape of a magnetic dipole. We recently showed that brain tissue also exhibits frequency shifts with nondipolar distributions, that could be caused by chemical exchange or the tissue’s magnetic microarchitecture (JochmannISMRM2019p0320). To investigate the origin of the nondipolar frequency shifts in brain tissue, we studied their dependency on the orientation relative to the main magnetic field.

Methods

We used the DEEPOLE QUASAR method to map nondipolar frequency shifts and tissue magnetic susceptibility from frequency maps that were derived from gradient-echo MRI. We studied the orientation dependency in regions of the brain that are known to be structurally anisotropic (cortical gray matter, white matter tracts) and the liquid-filled (isotropic) lateral ventricles. We used MRI scans from eight patients, measured under 11-29 orientations to the main magnetic field (Shi2022NeuroImage). Nonlinear co-registration of the data to the MNI152 standard brain was performed using ANTs. Approximations of each voxels main tissue orientation was obtained from the HCP-1065 DTI template.

Results

We mapped the orientation dependency of nondipolar frequency shifts in the human brain which allows us to conclude which biophysical mechanisms dominate the contrast in different parts of the brain: cortical gray matter had low orientation dependence, potentially from chemical exchange with randomly oriented proteins. White matter tracts (optic radations) had the strongest orientation dependence, suggesting microstructure-related effects from the anisotropic water compartments in and around myelinated axons.

Conclusion

The orientation dependency in brain tissue unveils tissue differences that were previously only visible via histology. The deeper understanding of the causes of nondipolar frequency shift will increase the specificity of the estimated tissue alterations when studying neurodegenerative diseases.
Mechanical energy and intensity of ventilation and its association with pulmonary neutrophilic inflammation

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Introduction
Mechanical ventilation is used in intensive care therapy to ensure adequate gas exchange in patients with acute respiratory distress syndrome (ARDS). However, inadequate settings of ventilatory settings may result in increased pulmonary complications, pro-longed necessity of ventilation and length of stay at intensive care units, so called ventilator-induced lung injury (VILI). Mechanical energy (ME) and power of ventilation had been suggested as a surrogate for VILI incorporating relevant ventilatory settings. This association was evaluated locally using computed tomography (CT) derived ventilation maps.

Methods
Lung injury was inducted using surfactant depletion in 24 pigs. Directly before randomization and after mechanical ventilation for 12h at different levels of positive end-expiratory pressure (PEEP), whole lung static CT scans, during approx. ten-second holds, at plateau pressure and PEEP, respectively were performed (1mm³ voxel volume, kernel B70f). After co-registration using the ANTs library, ME was determined from tidal ventilation image and mechanical intensity (MI) was considered as ME normalized by end-expiratory aerated lung volume. Pulmonary neutrophilic inflammation was used as a surrogate for VILI as determined by positron emission tomography after administration of ¹⁸F-FDG labelled microspheres (200MBq) to determine the change of uptake rate (ΔKi). Global change of inflammation was calculated as the sum over the whole lung and global ME was derived from respiratory signals measured at the ventilator.

Results
ME and MI were highest and were positively associated with ΔKi only in animals ventilated at PEEP=5cmH₂O, while in the PEEP=10cmH₂O and the group with PEEP titrated according to open-lung approach there was no association between those measures. Over all paired measurements ME and MI were positively associated with ΔKi.

Conclusion
Mechanical energy and mechanical intensity of ventilation may be derived using static lung CT scans. This study suggests that the association between mechanical energy/intensity and VILI may depend on the level of PEEP.
Track:

Application in Artificial Intelligence
Early Input Error Detection in Prototypical Networks

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The training of deep-learning-based models for digital pathology requires metadata gained from time-consuming, error-prone annotation by medical experts. Few-shot approaches, which employ only small amounts of reference data, are a possible solution to this problem. However, current evaluation approaches of few-shot models rely exclusively on the output (e.g. F1 score), disregarding evaluation during the training process.

To enable direct evaluation of input data, we introduce a quality assessment approach for prototypical networks, a few-shot method that uses a pre-trained encoder to map exemplary samples of each class into the feature space. Based on the assumption that erroneous sample annotations affect the cluster structure of the feature vectors in the feature space, we use cluster validity indices to detect such errors.

To test this approach, we adapt six classifiers by adding 32 correct samples in eleven classes, and then finally one sample containing an error (mislabeled annotation of tumorous and healthy urothelial tissue with varying size and morphological features). We qualitatively evaluate how the cluster validity indices (Silhouette, Calinski-Harabasz, Davies-Bouldin, S_Dbw, Dunn) respond to these errors by comparing the indices and F1 scores before and after adding the erroneous sample with the indices and scores of an error-free classifier.

In the conducted experiments, the Silhouette, Calinski-Harabasz and Davies-Bouldin indices were the most consistent with the difference of F1 scores, i.e. were best at recognizing erroneous input. The less morphologically similar the switched annotation classes, the better the error was detected (e.g. muscle and neuroendocrine). Switches in very similar classes (e.g. inflammation and neuroendocrine) were not detected well by any of the indices.

The results show that our quality assessment approach has the potential to detect many errors in input data as it is added, enabling real-time feedback to the user on the impact of their annotations.
Deep transfer learning for faster reconstruction in 2D magnetic particle imaging

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**Introduction**
Magnetic particle imaging (MPI) is an emerging medical imaging technology, displaying the concentration distribution of super-paramagnetic nanoparticles. The conversion between particle signal and concentration image can be achieved with the system matrix (SM), which is acquired in a time-consuming calibration scan by measuring the signal response of a particle sample placed at equidistant positions in the scanner. For clinical translation, it is inevitable to reduce this calibration time, either by (partly) modeling the SM or using a reconstruction method without SM. In this work, we propose a neural network framework that can both model single SM measurements (recovery) or directly reconstruct the concentration image (reconstruction).

**Methods**
The proposed framework consists of an encoder network and two decoder networks. For the recovery task, the input to the network is an SM measurement at position \((x,y)\) and the network predicts the measurement at position \((x,y+1)\), corresponding to a 50\% reduced SM acquisition time. In the reconstruction task, weighted linear combinations of SM measurements are the input and the network predicts the weighting factors. Both tasks are trained independently until convergence before the encoder weights are exchanged between the tasks and the training is continued.

**Results**
This transfer learning approach achieves a performance improvement of about 33\% for the recovery task. For the reconstruction task, the performance is compared by predicting the concentration image of single SM measurements, where an improvement of about 3\% is achieved. However, SM-based reconstruction provides more than four times higher accuracy.

**Conclusion**
This work shows that direct reconstruction with neural networks can provide a rough estimate of the concentration distribution in MPI. For more accurate results, an SM is required whose acquisition can be accelerated by deep learning. As training data is scarce for MPI, transfer learning can be leveraged to improve both tasks.
Detection of Ventricular Tachycardia Using Artificial Intelligence

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Introduction
Cardiovascular diseases are the leading cause of death worldwide. The associated ventricular tachycardias are currently diagnosed via long-term electrocardiogram (ECG) recordings. This work explores the potential of using Artificial Intelligence for real-time classification of ventricular tachycardias with a few selected features directly on such a device.

Methods
In this study, Einthoven leads I and III are used to extract 49 heart rate variability (HRV) features from the time, frequency, and time-frequency domains using the Pan-Tompkins algorithm. Additionally, 26 features based on signal morphology and 26 statistical features are extracted. Sequential forward selection, feature importance from Gemini index, and ANOVA tests are used for selecting the best features and Artificial Neural Networks (ANN), Random Forrest (RF), and Support Vector Machines (SVM) for classification. The applied Charité data set consists of 447,774 signals recorded with an event recorder. To account for the unbalanced data set, oversampling of the data with ventricular tachycardia is performed.

Results
On an independent test dataset, the ANN demonstrates the best classification performance, achieving an area under the receiver operating characteristic curve (ROCAUC) of 0.71, RF 0.7, respectively, and SVM 0.68. The most relevant features selected for classification are based on HRV, including the percentage of consecutive RR intervals below 50 ms. When atrial fibrillation patients are excluded, the ANN achieves a best ROCAUC of 0.74. Compared to results reported in the literature for other datasets, the ROCAUC is relatively low. This can be partly attributed to the poorer signal quality of the event recorders.

Conclusion
The classification accuracies presented in this study are not yet sufficient for practical use. The algorithms need to be adapted to account for the poorer signal quality of event recorders. The study demonstrates that HRV features have a significant impact on classification, and strong overlaps with atrial fibrillation patients are present.
Tumor vessel delineation using U-Net: A sparse labeled deep learning approach for semantic segmentation of histological images

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Introduction
Semantic segmentation is an important imaging analysis method enabling the identification of tissue structures to be targeted e.g. for image-guided interventions. Histological image segmentation is particularly challenging having large structural information while providing only limited training data. Additionally, labeling structures to generate training data is time consuming. To overcome these challenges, U-NET architecture was designed. Here, we demonstrate the feasibility of semantic segmentation using U-NET with sparse labeling for the reconstruction of 3D-models of vascular networks from a stack of tumor slices.

Methods
With the above-mentioned method, images are segmented into six classes: vessel walls, vessel lumen, tissue, corrupted tissue, debris, background. The data was split into 60-20-20 fractions for training, test and validation sets, respectively. Data augmentation was applied to the training set. To counteract the high class imbalance, the classes tissue, destroyed tissue and background were undersampled and higher class weights were added to walls and lumen. The network was based on U-NET architecture with four levels and a bridge containing two convolutions each. Additionally, attention gates, residual and recurrent links and dropout regularization were incorporated. The reconstruction algorithm tracked individual vessels in the stack of segmentation images and yielded 3D-models.

Results
The segmented images show accurate delineation of vessels. The applied data augmentation makes the algorithm robust to staining variations and counteracts the sparse labeling, but areas of high structural ambiguity (vessel walls, thrombi, bleedings) are still difficult to delineate. This characteristic is attributed to limited training data and high class imbalance.

Conclusion
Our method yields detailed segmentations for histological images. With focus on vessel segmentation, the results enable reconstructing realistic vascular tumor models to use e.g. in biosensing or drug delivery applications. Larger training data sets with more types of labeled structures will further increase segmentation robustness. The method is versatile and can be applied to different stained images.
Advancing Cardiovascular State Estimation: A Machine Learning-Based Extended Kalman Filter Approach

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Introduction
The aging of the population leads to an increasing number of people suffering from terminal congestive heart failure. Due to the shortage of donor organs, the implantation of mechanical ventricular assist devices (VADs) is replacing heart transplantation as gold standard therapy. In clinical practice, VADs are usually driven at constant speed. Thus, they are not adaptive to changes in hemodynamic conditions, which may result in complications such as ventricular suction or insufficient blood flow. Controlling VADs based on physiological parameters like stroke work could improve patient quality of life. However, current methods require additional invasive sensors to determine such parameters, for example by measuring ventricular volume, which makes them unlikely to be implemented in clinical practice in the near future.

Methods
We propose the use of an extended Kalman filter (EKF) with a physics-based heart model and a machine-learned error circuitry to estimate cardiovascular states such as ventricular volume. For this purpose, ventricular as well as aortic pressure and VAD flow are chosen as state variables of the EKF and compared to the corresponding measured values. In contrast to a pure soft sensor, comparing the measurable state estimates to the corresponding measurements allows to correct the ventricular volume estimate. Furthermore, the Kalman filter can effectively filter noisy measurements.

Results
The findings demonstrate that the EKF is capable of accurately estimating ventricular volume in-silico as well as in-vivo in animal case studies. However, due to the high variability between the individual animals, the prediction performance improves by 35.18 % when the artificial neural network is trained exclusively on data of the respective animal rather than using data from multiple animals.

Conclusion
Based on these findings, the EKF can be used to design a suitable physiological control approach for VADs, which holds promise for application in clinical practice.
Interpretable decision support system for an automated and objective interdisciplinary gait-assessment of stroke patients

Authors
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Introduction
Gait rehabilitation after stroke requires a personalized therapy based on interdisciplinary decision-making. An intelligent but transparent decision-support system built on interdisciplinary knowledge would allow for tailoring therapy based on concrete, objective, and interpretable insights extracted from measurements. In this study, the collective assessments of an interdisciplinary medical-board on the walking ability of hemiparetic stroke patients are reconstructed using decision-trees. This yields a white-box model with an excellent goodness-of-fit.

Methods
100 hemiparetic stroke patients received a clinical examination and a full-body instrumented gait-analysis. An interdisciplinary board of medical experts assigned each patient a Stroke Mobility Score (SMS) [1]. From the measurements, 904 pairs of gait cycles (ipsilateral and contralateral) and 752 gait features were extracted. The dataset was split 70/30 for training and testing in a stratified manner. Univariate filter selection methods were used to obtain feature subsets of reduced dimensionality. Breiman’s CART decision-tree regression algorithm was used as learning model. During training, a nested cross-validation procedure was carried out to tune the model hyperparameters and select the optimal feature subset. Testing was carried out for each SMS sub-score by averaging the predictions for all available gait cycles of each patient.

Results
The model predicted the SMS for the testing data set with a coefficient of determination $R^2$ of 0.83, while the average $R^2$ of the individual medical experts with respect to the board’s decision is 0.85.

Conclusion
The white-box model predicts the SMS with an excellent goodness-of-fit. The resulting decision-trees render interpretable decision chains based on the extracted features.

References
Blood pressure determination by means of ballistocardiogram and artificial intelligence

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Introduction
In non-invasive blood pressure measurement, using an inflatable cuff and a stethoscope or sphygmomanometer is currently considered the gold standard. However, both procedures are uncomfortable and have limitations regarding accuracy and speed. We, however, introduce a ballistocardiogram-based measurement method, which is recorded by means of an acceleration sensor at the carotid artery to estimate blood pressure values.

Methods
A satisfying placement of the accelerometer on the carotid artery while breathing in a supine position was determined by the examination of subject body positions (supine position, sitting, standing) on different body locations (carotid artery, chest, abdomen). The recorded raw data were subjected to average subtraction and filtering. An abstraction by extracting times, amplitudes, and gradients among other features was used to increase the interpretability and facilitate neural network learning. The most important features were identified by sequential forward/backward selection, recursive feature elimination and the principal component analysis. For the subsequent machine learning, a problem-adapted fully connected feedforward neural network, with three hidden layers and at most 384 neurons, was trained and tested. Reference values were obtained using a Finapress Nova Plus medical device for continuous blood pressure measurement.

Results
Feature extraction, principal component analysis, and hyperparameter optimization were used to estimate blood pressure with an MAE of 6.3 mmHg for systolic pressure and an MAE of 3.4 for diastolic pressure. These results were accomplished with a leave one group out cross validation on a dataset of 15 subjects.

Conclusion
These results are on a quality level with other more complex experimental methods such as those using a combination of ballistocardiogram, electrocardiogram, and photoplethysmography. In comparison to traditional methods, our blood pressure estimation does not need a cuff and generates a Beat-to-Beat continuous blood pressure estimation based only on one low cost, small and energy efficient sensor.
Towards the practical use of artificial intelligence (AI) in medical applications and diagnostics, a strong foundation of trust and understanding of neural networks has to be built. This work presents an approach to improve the understanding of electrocorticogram (ECoG)-signals and the decision basis of neural networks by localizing signal segments relevant for classification. In a previous work, a rat model of Parkinson’s disease was investigated. Micro-electrocorticogram ECoG readings on the dura above the motor cortex and sensorimotor cortex were recorded for rats during basal activity and after an injection with the dopamine receptor antagonist haloperidol, showing a change in oscillatory activity within theta, beta and gamma bands. The resulting ECoG-signal dataset was previously used to train a convolutional neural network for binary classification, achieving up to 92% accuracy.

In this work, the gradient-based post-hoc explanation method Grad-CAM is applied on this network and variations, resulting in saliency maps for signal samples showing the relative influence on the network’s classification decision. Evaluation revealed correlations between signal segments in saliency maps of networks with different input lengths. Furthermore it was shown that, relative to the absolute input signal length, only small percentages of the input signal are relevant for classification, with increasing percentage for shorter input signals. These results were verified by removing signal segments below selected thresholds prior to inference. Additionally, binary classification model was shown to have a strong bias towards one class, reducing the information value of the saliency map for that class respectively.

By applying this method on a variety of networks and datasets, signal areas significant for classification can be localized and extracted. With further inspection of these signal segments, e.g. clustering by properties, a common basis for decision making of neural networks for ECoG-classification can be found, supporting medical research.
Track:

Model-based and automated Medical Systems
The best of both worlds – An automated molecular PoC-system for infection detection combining the advantages of laboratory diagnostics and antigen-based rapid tests for individual- and mass-testing

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Introduction
Despite measures including “hands-face-space”-campaigns and vaccination, the past years with SARS-CoV-2 have demonstrated that the fast detection of infections remains one of the most crucial tools to control and prevent outbreaks involving pathogens with epidemic or pandemic potential. PCR-based tests have been shown to be much more sensitive and reliable than antigen-based methods. However, conventional PCR is generally reserved for central laboratories incurring critical diagnostic delay due to sample shipment, and considerable costs as well as limited capacities that disqualify laboratory diagnostics for mass-application.

Methods
In accordance with this paradigm of sensitivity and speed, we have been focusing on a point-of-care-testing approach comprising four elements: 1. The development of a mobile PCR-based detection system including a microfluidic cartridge, 2. the integration of a collaborative robot to enable fully-automated and high-throughput sample-analysis, 3. an intelligent data transfer strategy that links automated data transfer to the involved stakeholders with data privacy and data usage control of individuals, and 4. technical and approval concepts that are in line with open platform specifications to facilitate global collaboration and evolution of the system.

Results
Measurements using synthetic ssRNA and a commercial RT-PCR kit for SARS-CoV-2 detection showed, that the developed system allows a valid analysis in under 15 minutes. A clinical performance study is currently being performed to evaluate the diagnostic sensitivity and specificity. Moreover, a collaborative robot was equipped with the necessary hard- and software to perform automated sample-preparation and subsequent transfer to the analysis cartridge. The total process from self-sampling to the dissemination of test results was successfully demonstrated.

Conclusion
The approach described combines the advantages of both centralized laboratory diagnostics and antigen-based rapid testing. It represents a step towards a new generation of molecular PoC-tests that are sensitive, fast, mobile, affordable, and available for individual- or mass-testing in outbreak and disease screening scenarios.
Trusting “autonomous” medical Devices

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Trusting “autonomous” medical Devices

Introduction
Staff shortage might affect the quality of medical treatment in the future. Physical stress and the unergonomic design of the equipment further decreases the attractivity of healthcare professions. The usage of medical devices which have a certain degree of autonomy for mechatronic movements might help.
However, to increase the market acceptance of these solutions, staff and patients must trust these mechatronic features.

Methods
Up to now, psychological aspects have only partially been considered during the development of mechatronic features for medical devices. Therefore, it is important to understand how trust is generated.
IEC/TR 60601-4-1 introduces levels of autonomy for medical devices. However, concentrating on mechatronic movements the presented 16 degrees are too complex. Thus, a simplified matrix for this use case was created.

Results
Over- and under-trust is one aspect which must be considered. Often misjudgment occur due to a different understanding of autonomy. The presented matrix can be used for communicating the degrees of autonomy of a certain mechatronic feature. Furthermore, it visualizes who is responsible for a certain task. At the same time, this information defines which safety requirements must be met by the developers.
It is important that the roles of the user and the machine are well-defined. During a certain workflow the responsibilities might change. For this reason, hand-over-points must be intuitive.
Finally, a roadmap for medical devices based on different levels of autonomy helps to generate trust and increase user acceptance.

Conclusion
Trust in autonomous medical devices is important for market acceptance. The definition and communication of autonomy levels reduces the risk of over- and under-trust. Furthermore, the matrix defines the roles between humans and machines. For the developer, the degrees of autonomy define the safety architecture of the mechatronic feature. Roadmaps can introduce autonomy to users gradually.
Real-time FPGA Implemented Image Analysis Algorithm for Target-RGC Selection

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Introduction
Current retinal implants stimulate all of the locally available Retinal Ganglion Cells (RGCs) indiscriminately, only linearly dependent on the respective pixel brightness. To mimic natural vision more closely, it is necessary to process the optical input of the implant in a way the underlying retinal network would do it, to receive cell-type selective activation functions.

Methods
A widely used mathematical representation of RGC behaviour is the Difference of Gaussian (DoG) algorithm. For an ON-RGC, it can be described as

\[ \text{DoG}_{\text{ON}}(x,y,t) = I(x,y,t) \ast \left[ \frac{1}{2\pi \sigma_{c}^2} e^{-\frac{x^2+y^2}{2 \sigma_{c}^2}} - \frac{1}{2\pi \sigma_{s}^2} e^{-\frac{x^2+y^2}{2 \sigma_{s}^2}} \right] \]

where \( I(x,y,t) \) represents the input frame, dependent on its x and y pixels and its timestep t. The size of the cell-type dependent receptive field (RF) is defined by the parameters \( \sigma_c \) and \( \sigma_s \). Together with other mathematical operators, this operation is to be realized in FPGA logic with minimum resource requirements.

Results
For an efficient implementation, it is not required to store an entire image frame into internal FPGA memory. Instead, the serial data output of a camera can be used to perform the image analysis sequentially, while only three first-in first-out (FIFO) registers are required to enable the analysis of RF sized structures, reducing the required parallel convolution units to three. The correlation coefficient between the model output and natural RGC behaviour was 0.969 (ON-transient), 0.915 (ON-sustained), 0.986 (OFF-transient) and 0.83 (OFF-sustained).

Conclusion
The shown implementation of the DoG-algorithm can differentiate between eight different RGC-subtypes extracted out of greyscale images. At a fixed frame rate, the maximum image size is dependent on the FPGA's master clock frequency. If a frequency of 200 MHz is used, the maximum image size is 5 megapixels, making this implementation superior to event cameras, that are also usable for this task. This implementation is thus very suitable for use in future retinal implants, as the algorithm's potential lies way above currently available stimulator resolutions.
Detailed anatomical neck model for electromagnetic simulations

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Introduction
The development of individualized electric stimulation applications is substantially dependent on detailed anatomical models and electromagnetic simulations. Such model simulations enable stimulation parameter adjustments and optimization based on the evaluation of stimulated and co-innervated nerves. We aim at building an anatomical volume conductor model of the neck for evaluating electric phrenic nerve stimulation with a higher level of detail.

Methods
We created an anatomical model based on tissue compartments from the BodyParts3D platform (male, 22 years, 173 cm, 65 kg, https://lifesciencedb.jp/bp3d/?lng=en). The model incorporates 68 muscles, 20 bones, 2 cartilages, 8 intervertebral discs, 30 nerves, 22 blood vessels, thyroid, esophagus, trachea, skin, and connective tissue. The smallest structures were nerves and blood vessels with a diameter of 1 mm. Additionally, subcutaneous fat and internal air were manually modeled. Each compartment was converted from the provided obj-format via stl-mesh to solids and pre-processed to create a uniform surface, to repair surface defects, and to eliminate tissue intersections. The model was implemented in COMSOL Multiphysics 6.0. Electrical stimulation of the phrenic nerve was realized using two surface electrodes (edge length 1 cm, spacing 1.5 cm) under steady-state conditions with a stimulation current of 30 mA.

Results
A detailed and modular model of the neck, representing the section between the clavicle and the maxilla, was created with the aforementioned tissues. Electromagnetic simulations were performed using a mesh with about 30 million tetrahedral elements, with tissue material parameters derived from literature. The maximum calculated electric field at the phrenic nerve was about 40 V/m and can lead to nerve activation. Co-innervated nerves were the auricular and the transverse cervical nerve with an electric field of up to 240 V/m.

Conclusion
With this detailed volume conductor model of the neck, the electrode positions can be optimized to maximize the stimulation of the phrenic nerve and to minimize the co-innervation.
Assessing Hematopoietic Cell Classification Performance with Domain-Adapted Deep Learning Models: Insights from a Multi-Center Evaluation

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Introduction
The task of hematopoietic cell classification of image data obtained from microscopy images is essential in automatizing clinical workflows of medical experts in the field of hematology. Computed whole-slide image statistics can give quick indications for a multitude of different diseases. Several studies have proposed processing pipelines, nevertheless, evaluation methodology issues w.r.t. real-world applicability remain, e.g. dataset splitting, number of classes, used staining procedure, or microscope resolution.

Methods
To ameliorate the effects of these issues we present a facility cross-validated evaluation of hematopoietic cell classifiers based on the DenseNet121 and ResNet152 architectures using four different datasets with different amounts of white and red blood cell classes. The datasets were extracted from bone marrow and peripheral blood and stained using the Pappenheim and faster Wright-Giemsa protocol. We analyze them for variability concerning H&E staining vectors and statistical criteria concerning color and cell size. Paired with cross-validation, we employ model ensembling, augmentation, and normalization to train domain-adapted models for each clinical site. We set our evaluations into practical context by performing an inter-rater analysis on a multi-labeled dataset of neutrophilic granulocytes and additionally evaluate using known metrics accounting for tolerable intra-lineage confusions.

Results
We achieve accuracies of \(67.1\% \pm 0.622\%\) in 13-, 8-, and 5-class cross-validation setups, using different amounts of data each. Incorporating confusion tolerance yields accuracies of \(88.36\% \pm 6\%\), whilst ensembling site-specific classifiers increases scores in a similarly significant manner as training on larger combined datasets. Inter-rater agreement makes for accuracy of \(66.5\%\).

Conclusion
Our study shows that models trained without appropriate color augmentations experience severe performance drops when evaluated on data from other sites. Especially brightness, contrast, hue, and saturation augmentations outperform staining augmentation and normalization approaches. Whilst our results show slightly better agreement with annotations compared to medical experts, careful analysis of the distribution of confusion remains essential to judge clinical applicability.
An Automated emotion detection system using Texture Features from Spectrogram-based Phasic Segmentation of Electrodermal Activity Signals and Machine Learning

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Introduction

Early detection of negative emotion can lead to timely intervention and effective treatment, thereby reducing the risk of long-term mental health problems such as chronic depression and anxiety disorders. In this study, we aim to develop an automated emotion detection system using electrodermal activity (EDA) signals.

Methods

Initially, we obtained EDA from the publicly available Continuously Annotated Signals of Emotions dataset and segregated them based on the participants’ mean valence and arousal ratings to classify them into four categories: High-Valence High-Arousal, High-Valence Low-Arousal, Low-Valence High-Arousal, and Low-Valence Low-Arousal. Then, EDA were decomposed into tonic and phasic components using the cvxEDA decomposition algorithm. The phasic component was divided into two halves, and each was further segmented into five equal parts. Further, spectrograms were generated using short-time Fourier transform for each segmented part of the phasic signal. Texture features that capture the distinct patterns and structures within a spectrogram are extracted using the gray-level co-occurrence matrix and gray-level run length matrix. Finally, we built Random Forest (RF) Machine Learning (ML) models to classify emotions and evaluated the models using stratified 10-fold cross-validation and performance metrics.

Results

The results showed that the RF classifier using texture features from the second half of the phasic EDA yielded the highest classification results, with an average classification accuracy, sensitivity, specificity, precision, and f-score of 78.5%, 52%, 84.6%, 57.3%, and 53.4%, respectively.

Conclusion

To validate the results of our proposed pipeline, we will extend this study with more transform techniques (Mel frequency cepstral coefficients and continuous wavelet transform), feature extraction methods (Hu and Zernike Moments), and ML models (Logistic regression, support vector machine, and Extreme gradient boosting). Our study shows that texture features from spectrograms and machine learning can detect emotions in real time from EDA signals, with potential applications in psychology, human-computer interaction, and health monitoring.
Track:

Micro- and Nanosystems
[18F]Fluorodeoxyglucose in functional characterization of the renal barrier in a proximal tubule model

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Introduction
Kidneys as dose-limiting organ for radiopharmaceutical administration should undergo in vitro evaluation with functional renal equivalents, which can be integrated into microphysiological systems (MPS). We generated a model of the proximal tubule using human renal proximal tubule epithelial cells (RPTEC) and human umbilical vein endothelial cells (HUVEC). To assess renal barrier function, we measured transepithelial/transendothelial electrical resistance (TEER) and permeation of [18F]Fluorodeoxyglucose (FDG).

Methods
The investigations were conducted in transwell inserts with a permeable membrane. The viability and density of the cellular bilayer were assessed using calcein staining. RPTEC and HUVEC were seeded on the apical and basolateral sites of the membrane, respectively. TEER was utilized to measure the ionic conductance in the cell layers. The basolateral-apical passage of [18F]FDG was quantified using a gamma counter and presented as percent passage.

Results
After 3 to 4 days, the cellular bilayer in the proximal renal tubule model reached confluence, as indicated by calcein staining. The barrier exhibited higher electrical resistance of 533±47 Ωcm² across the cellular bilayer compared to 306±26 Ωcm² across transwell blanks. These results were corroborated by the low basolateral-apical passage of [18F]FDG (4±1 %) through the intact cellular bilayer compared to transwell blanks (13.5±1.5 %). Morphological, electrical, and functional assessments verified the integrity of the renal barrier in this model.

Conclusion
This study shows that measuring [18F]FDG passage tests the renal barrier function in a proximal renal tubule model. The TEER value indicates the ionic conductance of the paracellular pathway, while [18F]FDG passage indicates paracellular water flux and tight junction pore size. Next, apical-basolateral [18F]FDG transport will be investigated to characterize reabsorption via SGLT2 in the proximal renal tubule. After characterizing the model in a static system, it will be integrated into a fluidics system with a liver equivalent and tumor spheroid for radiopharmacological assays.
Deposition methods of biodegradable polymer as a future inflammation sensor for the cochlear implant

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Introduction
After cochlear implant (CI) surgery, patients might be suffering post-surgical inflammation (e.g. interleukin-6 or interleukin-21). MIP sensors on a CI electrode are suitable for this inflammation detection. Additionally, these MIP could be conductive for further improvement of sensitivity. Since the long-term use of electrodes is stimulation, biodegradability of the MIP layer is required. In recent research, MIPs or nanoMIPs are being investigated for implant applications, with either biodegradable or conductive MIPs. These two required properties, as well as biocompatibility for the inflammation sensors, can be achieved by embedding conductive nanoMIPs in a biodegradable layer or by corrosion of conductive MIPs. In this work, MIPs were deposited by electrochemical polymerization to investigate the corrosion of conductive MIPs. As part of a preliminary nanoMIP investigation, biodegradable MIPs were deposited by dip coating. Since interleukin and its epitopes are expensive, ibuprofen was initially used as a template.

Methods
For the dip-coating method, a platinum electrode was immersed in an acetic acid-ethanol solution containing chitosan and ibuprofen. For the electrochemical polymerization, poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) was selected as conductive polymer. Deposition was performed via cyclic voltammetry. To detect ibuprofen, the MIPs were then washed in ethanol and an impedance measurement was realized. PEDOT:PSS was then corroded in phosphate buffered saline (PBS) solution by additional impedance measurements. Finally, the PBS solution was measured using a bio-drop spectrometer.

Results
A homogeneous layer with adjustable thickness could be achieved by electrochemical polymerization but not by dip-coating. The ibuprofen detection was possible using MIPs. The PEDOT:PSS was successfully corroded with an impedance shift occurring during corrosion. The corroded monomers and polymer molecules could be measured in the PBS solution.

Conclusion
To improve distinctness in ibuprofen detection, the production processes have to be optimized. In addition, corrosion of the polymer needs further investigation to only release monomers, e.g. by lowering the voltage.
Controlled therapeutic nucleic acid delivery: From smart DNA-circuits to out-of-equilibrium systems

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Introduction
DNA-circuits are artificial nanodevices composed of short DNA strands, designed to perform computational and signal processing tasks. Renewable DNA-circuits can revert to their original state by addition of DNA-strands. These circuits have potential applications in nanotechnology and biotechnology, and can regulate drug delivery by enabling kinetic control over drug release.

Methods
Here, an enzyme-based DNA-circuit was designed for delivering CpG-oligodeoxynucleotides (CpG-ODNs) that stimulate the immune system. A complementary DNA-strand (cDNA) hybridizes to CpG-ODN and temporarily deactivates its biological function, while T7-exonuclease hydrolyzes the cDNA to release active CpG-ODN. Factors affecting the circuit’s kinetic profile and temporal behaviour, including cDNA design and the DNA-duplex and T7-exonuclease concentrations, were investigated using FRET-based reporter system. In-vitro performance was studied in HEK-engineered cells and J774A.1-macrophages.

Results
We demonstrated successful deactivation/activation of CpG-ODN using the DNA-circuit. Kinetic parameters were established and in-vitro activation resulted in toll-like receptor-9 stimulation in HEK-engineered cells, as well as tumor necrosis factor-alpha release in macrophages. Compared to a system without controlled release, the circuit provided acute and potent immunostimulation with altered pharmacological profile. The DNA-circuit was transformed into an out-of-equilibrium dissipative system through repetitive addition of the cDNA strand at defined timepoints. This resulted in successful multiple loading/release cycles with defined kinetic parameters.

Conclusion
We present the first example of a drug delivery system exploiting a DNA-circuit programmed to trigger distinct biological responses in comparison to a non-programmed system. This paves the way for interactive DNA-circuits utilizing cell-owned signals (i.e. endogenous enzymes) as a trigger, to replace T7-exonuclease in the current conceptual design. Signals that differ between healthy and diseased tissue would be valuable in targeting various disorders for time-controlled manipulation of the biological response. Additionally, one-time DNA-circuits can be converted to renewable dissipative systems that operate out-of-equilibrium, which can be programmed to stimulate the target receptors multiple times with potential autonomous control.
Active Stents – Development of a systems approach towards versatile condition monitoring implants

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Introduction
Cardiovascular diseases represent the first cause of mortality in Germany and worldwide. They are mostly associated with a decreased organ perfusion caused by a narrowing or occlusion of a blood vessel, such as in critical organs like the heart and the brain. Catheter-based interventions allow for a minimally invasive treatment of diseased vessels. For instance, they are used to re-open stenotic coronary as well as carotid arteries by means of balloon-expandable and self-expandable stent, respectively. This kind of implant aims at keeping the vessels open but might invoke serious hazards such as in-stent thrombosis and inflammatory vessel reaction triggered by foreign material reaction, fluid dynamics disturbances and mechanical stress. We believe that (self-)monitoring functions potentially integrated in stents would crucially improve patient safety. This work uses the concept of reverse translation to review current knowledge of mechanical material-tissue interaction, engineering approaches of electronics and system integration and derive mandatory requirements of building blocks for condition monitoring in vascular stents.

Methods
System review of existing technologies was done with respect to size, rigidity/flexibility and powering of active and passive components. Definition and design of building blocks of application specific integrated circuits was investigated to balance chip size with geometrical constraints. Analysis was complemented by coils and chip integration strategies into flexible substrates.

Results
System requirements have been broken down into building blocks. Placement rules of ASICs have been transferred into substrate designs, integration methods considering a separate coil as well as the stent itself as antenna. Target specifications are transferred now towards developments.

Conclusion
Comprehensive system design supports biocompatible long-term integration of electronics on highly deformable, self-expandable and catheter-navigable vascular implants for condition monitoring. Such active stents will not only help to improve patient safety but also allow for new approaches in diagnosis and treatment.
PEDOT:PSS coating for improved electric cell-substrate impedance sensing assays

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Introduction
In multicellular systems, numerous biological processes depend on tightly regulated cell migration, for which dynamic changes in the focal adhesions of cells are fundamental. In various pathologies such as neurodegenerative diseases or different forms of brain tumors, the migration of neurons can be disturbed by non-uniform dynamics of cell adhesion in their microenvironment, making their observation highly interesting. Electric Cell-Substrate Impedance Sensing (ECIS) is a powerful method for in vitro monitoring of cultured cells, especially for adhesion and migration. Due to the metal-electrolyte interface of commercial ECIS electrodes, the measured impedance increases sharply with decreasing frequency, which effectively desensitizes the electrode for monitoring cell layer kinetics without powerful amplification systems.

Methods
In the present study, we coated commercial gold 8W1E-ECIS chips (Applied BioPhysics, Inc.) with poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) by electropolymerization. Subsequently we seeded two different cell lines (A172 and N2a) on both coated and uncoated electrodes. Immediately after adding the cell suspension, we performed impedance measurements at a fixed frequency of 1 kHz for 14 hours to record the impedance effect of the cellular layer on the electrode-electrolyte interface. The impedance measurements were performed using a low-cost potentiostat (EmStat Pico Development Kit, PalmSens).

Results
The PEDOT:PSS coating reduced the 1 kHz impedance magnitude drastically, increasing the measured current by almost two decades. On the coated electrodes, we recorded a clear increase of 500 ohms by the large A172 cells, while the small N2a cells showed an increase of 250 ohms. The uncoated electrodes revealed only a slight increase by 100 ohms due to the attachment of the A172 cells.

Conclusion
In this study, we demonstrated two fundamental improvements by PEDOT:PSS coating on commercial ECIS chips, namely the possibility of successful adhesion measurements even on small cells and also that ECIS measurements can be performed with a low-cost and portable potentiostat.
Method to Predict Microelectrode Impedances during Runtime for Electrical Stimulation and Recording in Future Neural Implants

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Introduction
Modern neural implants and brain-computer interfaces rely on microelectrode arrays. Microelectrode arrays are used to interface biological tissue and electrical circuits for stimulation and recording in the research of neural devices. In these applications, the electrode performance and hence its impedance may change during the runtime. Exact knowledge of the electrode performance is crucial for an efficient stimulation and the evaluation of the neural interface. Therefore, we present a modelling approach based on numerical simulations of in-vitro experiments using penetrating probes for retinal experiments to predict the characteristic electrode impedance. Then, impedance spectroscopy (EIS) is used to identify the bulk volume impedance and the electrode-tissue interface impedance. Characteristic parameters of both impedance contributions are extracted by fitting equivalent electrical circuit models to measurement data.

Methods
Penetrating probes with 12 iridium-oxid electrodes were considered*. A realistic 3D geometry of the electrodes immersed in phosphate-buffered saline (PBS) according to the experiment was built. The impedance was computed using the finite element method. Impedance data were retrieved by EIS and Fourier analysis of transient current and voltages recordings. The Python package ImpedanceFitter (Zenodo: 10.5281/zenodo.5116618) allows to extract the impedance for each run in order to identify the aforementioned parameters.

Results
From simulation, a modelled tissue resistance in a range of 8.4 and 11.1 Kiloohm was predicted for a conductivity of 1.5 to 2 S/m, matching the values in the temperature range of the experiment. A Randles circuit was used for determining a PBS resistance of 10.1 Kiloohm, which is in very good agreement with the numerical prediction.

Conclusion
Our approach is a step towards an adaptive implementation of more complex stimulation patterns for selective stimulation. This enables a better control and selection of suitable electrodes during runtime. Furthermore, a direct link to a biophysical model of the stimulation can be established.
Fabrication process of hexagonally arranged needle electrodes for direct retinal contact

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Introduction

Current retinal implants are still not able to restore natural vision due to several challenges linked to spatial resolution of electrical stimulation. The reasons for this include low electrode density, high distance between target cells and electrodes and high crosstalk between adjacent electrodes. One approach to address these problems are penetrating needle electrodes, which are implanted epiretinally into the tissue. Here, a concept for a CMOS compatible fabrication process is presented, where needle electrodes are arranged in a hexagonal array with a local ground configuration to reduce the crosstalk and enable local stimulation.

Methods

The fabrication process can be divided into two sections. First an internal wiring is fabricated by depositing and etching a conductive material. The conductive lines are passivated and then planarized by a CMP process. Subsequently, vias are etched into the passivation and filled with tungsten. On top TiN is deposited and patterned to form planar electrodes as a base for the needle electrodes. In the second phase cylindric openings in a thick film lithography process are created as templates for the needles. They are are filled with a metal by electrodeposition. The released metal cores are encapsulated with a thin ALD layer, which is structured afterwards to isolate the electrodes from each other. The resulting electrode array is characterized by EIS and CV measurements. Additionally, first biocompatibility experiments are performed on the integrated materials.

Results

The fabrication of the flat base electrodes was performed successfully to create a hexagonally array of electrodes while the optimization of the second fabrication part is still in progress. The first biocompatibility experiments showed promising results and will be continued with structured chips.

Conclusion

The approach of using penetrating needle electrodes in a hexagonally arrangement with local returns can improve the confinement of electrical field and reduce crosstalk to enable higher electrode densities.
Systematic Design of DNA Strand-Displacement-Based Magnetic Immunoassays - a Bottom-Up Approach

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Introduction
A key element in diagnostic analysis is the sensitive and specific detection of nucleic acid sequences, such as viral RNA, microRNA and cell-free DNA. A promising approach to detect these biomarkers in complex samples in an extraction-free manner are magnetic immunoassays (MIAs). These MIAs combine the properties of magnetic nanoparticles (MNPs) and DNA nanotechnology and can be customized for a variety of diseases. Functionalized MNPs are crosslinked using complementary DNA to form magnetic clusters. These can subsequently be disassembled via toehold-mediated DNA strand displacement (TM-DSD) in the presence of one specific target sequence. The resulting change in hydrodynamic size and dynamic magnetic properties of the magnetic clusters can be monitored by magnetic particle spectroscopy (MPS). For MIAs to compete with established detection platforms, it is essential to determine the ideal characteristics of the basic components of a MIA to construct a highly sensitive, specific and rapid MNP-based catalytic system.

Methods
Here we focus on the TM-DSD-based disassembly kinetics of MIAs and the utilization of the spontaneous dissociation of specific DNA strands, which will be used in future MIA designs to improve the limit of detection. Therefore, we investigate the influence of the length of distinct DNA domains, reaction conditions, such as temperature and buffer composition, as well as the influence of targeted base pair mismatches. Furthermore, an approach to recycle the target sequence is investigated, which improves the limit of detection of the MIA, measured with a tailored immunoMPS system, but bears the risk of false positive results if designed improperly.

Results
The investigated MIAs generate a concentration dependent signal change. Based on our studies we create guidelines on how to systematically establish a complex and reliable DNA nanosystem, based on its fundamental components.

Conclusion
The systematic design of these components is essential for optimal MIA kinetics and stability.
Chemofluidic Circuits for Clinical Diagnosis

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Introduction
Traditional molecular diagnostics use large instruments or require significant manual labor. Lab-on-a-chip technology, in contrast, offers simple, fast, low-cost, on-site diagnostics and high integration for applications such as personalized medicine. But even LOC systems require bulky off-chip control for complex fluidic operations.

Our concept of chemofluidic circuits uses smart materials to build intelligent and autonomous systems with novel actuator and sensor functionalities. We are using the technology to develop a rapid test for infectious diseases like influenza and Covid-19. Additionally, we aim to use chemofluidics for single-cell analysis of cancers, such as acute myeloid leukaemia (AML), to enable faster and more precise diagnosis compared to current microscopic evaluation.

Methods
We developed hydrogel-based closing valves that swell upon liquid contact and block liquid transport after a certain time. Polymer-based soluble opening valves allow fluid transport after a defined time. Chemofluidic transistors can be opened and closed repeatedly. When combined in fluidic circuits, these valves facilitate diagnostic assay operations such as basic fluidic operations for diagnostic tests like mixing, incubation, and transport. Fluidic chips are fabricated by laser patterning and assembling polymer foils, which enables large-scale production.

Results
We use computational methods to design chemofluidic LOCs with integrated valves, which were fabricated in laboratory scale. Opening and closing time of the valves, and consequently the fluid volumes passing through can be precisely adjusted (between 10s and 10min) with low variation (relative standard deviation below 10%). We were able to significantly reduce reagent consumption (down to 10%) for various applications, such as protein quantification, cell sorting, and nucleic acid compared to off-chip assays.

Conclusion
Our chemofluidic LOC concept promises to enable complex diagnostic assays on a miniaturized test chip at the point-of-care. This technology has the potential for the high integration, making it possible to revolutionize the diagnosis and treatment of diseases through single-cell analysis.
Track:
Neural Implants and Engineering
Neurostimulation artifact removal algorithms to improve control of a tactile feedback prosthesis

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Introduction
To achieve reliable bidirectional control of a multifunctional upper limb prosthesis by the end user, tactile feedback to the brain is essential. One approach to providing tactile feedback is to implant electrodes around residual nerves, allowing for direct nerve stimulation based on sensor information from the prosthetic device. Furthermore, modulation of the stimulation is necessary to achieve a more natural sensation and richer information. However, the proximity of the nerve electrodes to the muscular electrodes can cause electric artifacts during stimulation, which degrade the quality of the electromyographic (EMG) signal and reduce the reliability of the myoelectric control.

Methods
We propose a novel algorithm for removing modulated stimulation artifacts by using a statistical model-based approach due to strictly limited memory within a self-contained embedded prosthetic system. The algorithm adapts the filter based on the modulated amplitude of the stimulation, allowing the relative artifact template to be subtracted from the EMG signals. Offline analysis of recorded EMG signals containing modulated stimulation artifacts was conducted to train the algorithm and evaluate its performance in artifact removal. To assess the algorithm’s real-time performance, it was implemented on an embedded prosthesis controller, and experiments were conducted with a participant implanted with intramuscular electrodes for myoelectric control and nerve cuffs for tactile feedback.

Results
The experimental results demonstrate that the proposed filtering algorithm partially removes offline the modulated stimulation artifacts and helps to restore the original EMG signal for control. The improved signal quality enhanced the performance of the neural network classification for myoelectric control during standardized online motion tests by 38% (from 8/25 to 11/25 correct classifications with 5 possible classification classes).

Conclusion
The algorithm can filter modulated stimulation artifacts partially, to enable more reliable myoelectric control and tactile stimulation simultaneously. However, further research is needed to reach a more reliable classification accuracy.
Reliability of non-hermetic PDMS encapsulation for implantable ceramic interconnections between the micro and the macro world

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Introduction
In the field of neural implants, the quest for ever smaller components with high spatial resolution, long-term stability, and low invasiveness is a strong driving force. Implantable, reliable connection adapters built with thin-film technology are needed to bridge these miniature parts to the macro world, e.g. to implantable or extracorporeal stimulators.

Methods
To investigate the long-term stability of non-hermetically encapsulated bridge elements, sputtered platinum (Pt) thin film metallized alumina ceramics (Al\textsubscript{2}O\textsubscript{3}) were encapsulated with silicone (PDMS). The influence of adhesion promoters (silicon oxide (SiO\textsubscript{2}), silicon nitride (Si\textsubscript{x}N\textsubscript{y})) on the strength of the encapsulation was investigated by accelerated aging (in phosphate buffered saline (PBS) at 60 °C for 10 weeks, n = 5 per test day and sample type) and weekly tensile shear tests. Bare alumina ceramics were prepared for reference and statistical evaluation.

Results
In direct comparison over an aging period of 70 days (~ one year at 37 °C), metallized ceramics without adhesion promoters exhibited the lowest initial bond strength of 3 MPa. This value was increased with SiO\textsubscript{2} and Si\textsubscript{x}N\textsubscript{y} coatings, to 4 MPa and over 5 MPa, respectively. The reference reached an initial value of 5 MPa which decreased by -0.021 MPa/day over the period studied. While SiO\textsubscript{2} adhesion promotion decreased similarly, this was -0.014 MPa/day for sputtered Pt and -0.033 MPa/day for Si\textsubscript{x}N\textsubscript{y}.

Conclusion
The results present linear decrease in adhesion in the observed time frame for all species. Depending on the implantation duration, crossover points can occur where initially stronger material bonds fall behind another material pair over time of aging. These experiments give a good indication that the adhesion promoters do increase PDMS adhesion to the underlying metallized substrate compared to bare sputtered Pt over the simulated time period of a year at 37 °C. Further experiments are required to predict longevity over decades of life-time.
Development of a biocompatible circuit board as basis for ultrasonic energy supply of neural implants

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Introduction
Implants in Bioelectronics Medicine aim to be miniaturized and implanted deeper into the body. This requires alternative forms of energy transmission than inductive coupling. Ultrasound is taken as an alternative approach to power deep-seated implants. 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. However, new challenges arise with non-hermetic encapsulations, such as the use of biocompatible materials to which the silicone adheres well over long periods of time.

Methods
This approach presents the design and development of a biocompatible circuit board based on Alumina (AL2O3), with sputtered tungsten titanium (WTi) and platinum (Pt) traces on both surfaces, interconnected by electrical vias. The vias were cut into the alumina substrates by a nanosecond laser, followed by sputter-deposition of WTi as adhesion promoter and Pt as conductive path. Metal was then selectively removed by the laser, leaving only the traces to the vias. Indentations were created as predetermined breaking points on the perimeter of the substrate by laser structuring. The circuit boards were then mechanically separated.

Results
Vias with a size of 190 µm and a resistance of 38 Ω were fabricated. The lowest reproducible resistance in the vias was found with a deposition of 100 nm Wti and 1000 nm Pt. Here, the chamber was heated to 400°C for the WTI deposition; the conducting paths could be reliably produced with a separation of 100 µm.

Conclusion
In this work, biocompatible double-sided circuit boards were fabricated using a clean room process. The circuit boards are suitable as a basis for mechanical and electrical assembly of ultrasonic transducers and thus serving as a basis for miniaturized implants since Alumina is well known to establish good contacts with PDMS.
On the structural and optical differences between 3D-printed and spin-coated poly-dimethylsiloxane (PDMS)

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Introduction
In the scope of PDMS-based neural implants, various fabrication techniques have been developed to further improve additive manufacturing methods. These developments aim to reduce material costs and machine complexity and increase automation. Spin-coating is one method for polymer processing, which requires further complex and time-consuming fabrication steps, e.g. laser patterning. With applications in cranial window methods for neurovascular imaging in mind, this study aimed to develop a fabrication protocol for 3D-printing PDMS samples that exhibit similar optical and mechanical properties to those produced by spin coating.

Methods
This work investigated the material properties of 3D-printed and spin-coated PDMS. Cured samples from both methods were optically examined by microscopy and transmission measurements to investigate surface morphology. Furthermore, mechanical tension was applied and the elongation/damage of specimens was observed. In the case of printed samples, the mechanical responses were also observed as tension was applied along different directions of the printed fibers i.e. perpendicular or parallel.

Results
Samples of 200-800 µm thickness and within 200-400 mm² size were produced using each process. In the 3D printing process, a suitable parameter combination (pressure, printing speed, and gap height) was used to produce specimens for optical and mechanical testing. The printing protocol was adjusted to produce samples with no significant differences in mechanical elongation or optical transmission from spin-coated samples.

Conclusion
To sum up, the selected printing parameters led to similar optical and mechanical characteristics of the samples, and no measurable differences were observed between them. The results presented proof of the feasibility of the less costly printing process for future applications of manufacturing cranial windows. This promises the possibility of personalized brain interfaces with optical functionality that require less production time and material costs.
Combined QCM and Ellipsometry In-situ Measurement for Area-Selective Atomic Layer Deposition for Use on Active Implants

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**Introduction**

Atomic layer deposition (ALD) is a cyclic coating process applicable for manufacturing of highly conformal, defect-free, and thin layers. Selective coating is achievable by pre-treatment or by exploiting the chemical-physical properties of substrate surfaces without misplacement and complex lithography steps as the layers are grown only on desired surfaces. This powerful bottom-up process is already used in the semiconductor industry to produce smallest structures on nanometer scale.

With respect to medical applications, selective atomic layer deposition offers outstanding potential for use on implants. Performant barrier layers deposited on selected implant surfaces could be achieved without time-consuming and costly lithography steps.

However, a deeper insight and understanding of the growth kinetics of the ALD layers on the substrates is required, correlating with the necessity of a real-time in-situ monitoring, combining a quartz crystal microbalance (QCM) and ellipsometry, presented in this work.

**Methods**

An ellipsometer and a QCM are used for real-time monitoring of growing ALD layers. The beam of the ellipsometer radiates directly onto the sample surface which is examined. After each ALD cycle an ellipsometric measurement determines the layer thickness using a suitable model. The QCM serves as a reference. Differences in coating thickness between the two measuring methods give the selectivity on the different surfaces.

**Results**

In initial experiments, a gold surface was vapourised with propanthiol to prevent the growth of titanium oxide on it. The ellipsometer showed a delayed growth in the first ALD cycles until a failure of the passivating effect of the propanthiol was detected and the titanium oxide grew normally.

**Conclusion**

With a combined measurement setup of QCM and ellipsometry, real-time monitoring of the area selectivity of the growing ALD layers on substrate surfaces is possible. Coating of the QCM with different materials will lead to more measurement options.
Definition of critical load conditions for highly conformable circuit integration using a vascular model for the advancement of active stents

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Introduction
Further advancement in stent technology towards condition monitoring is necessary, as drawbacks in medical application such as in-stent thrombosis and restenosis are still present. Hence, a monitoring implant is not only crucial for implant efficacy, but for patients' safety. Consequently, a continuous monitoring device consisting of electrically active components manufactured with Chip-in-Foil technology will be integrated on a braided stent and investigated with respect to stability under mechanical load and deformation. This will provide first insights of occurring motion modes in an active stent allowing quantitatively determination of mechanical load conditions. The evaluation is essential for mechanical longevity of highly conformable integrated electrical components.

Methods
Simplified representatives of electronic circuits were designed for integration into a stent. Platinum thin film metallization for conductive traces were encapsulated by polyimide (PI) layers on a silicon (SI) wafer used as a carrier substrate during the micromanufacturing process steps. Singularized samples were integrated into a stent. After implantation in a vascular model and integration in a pulsatile circulatory mock loop, the highly integrated system was evaluated and recorded under microscopy in straight and bent configuration. Additionally, radial deformation and delivery force in catheter were tested.

Results
The visual recordings of the system within the vascular model led to fracture points in the circuit leading to critical motion modes based on cardiovascular circulation. Deformability tests demonstrated the limits of mechanical load, and optical examinations provided information about the correlation between motion modes and impact on the integrated circuit.

Conclusion
Using a vascular model for simulating the moving environment of an electrically equipped stent the determination of critical fracture points was possible. The information of the mechanical load conditions allows to estimate optimum placement sites for electronic components for integration into a stent, setting the basis for realization of an "active" stent prototype.
Closed-loop control of a non-invasive neuroprosthesis for automatic adaption of grasp patterns

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Introduction
For restoration of a useful grasping function in people with high-level spinal cord injury, the intensity of up to four electrical stimulation (ES) channels of a non-invasive neuroprosthesis needs to precisely coordinated. In particular, the channel specific pulse width at predefined states in the grasp generation cycle need to be individually adjusted, which is typically done in a iterative process by clinical experts. To automate this task, a camera-based closed-loop system was developed.

Methods
The finger kinematics were recorded by a LeapMotion controller (Ultraleap Inc., Mountain View, CA, USA) in a lower arm positioning frame. The absolute coordinates calculated by the LeapMotion software of the most distal finger segments were compared in real-time with reference ES-generated grasp patterns (lateral and palmar grasp) from five non-disabled individuals not involved in the evaluation. A self-developed software enabled calculation of deviations of the fingertip coordinates from the reference and adjustment of the pulse widths at two distinct grasp states in real time. The time required to adjust the grasp patterns and the number of passes per grasp state were evaluated.

Results
The feasibility of the closed-loop system was tested in ten non-disabled study participants with ten repetitions per grasp and subject. The average time to execute the automatic adaptation for the two grasp patterns ranged from 12 to 387 seconds, and the number of iterations ranged from 1 to 35.

Conclusion
A camera-based automatic adaption of two grasp patterns seems to be feasible. A calibration time of less than 7 minutes before the neuroprosthesis use is a realistic option for everyday use, not only for the initial setup, but also for regular re-adaptation and as needed by the neuroprosthesis users themselves.
Compliant and transparent neural implants for simultaneous neurophysiology and imaging

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Introduction
The ultimate goal of neural implants is to interact with the nervous system and provide treatments for neurodegenerative diseases. Microelectrode arrays are often used as the main interface to record and stimulate the activity of neuronal targets. However, when combining electrophysiology with optical imaging modalities such as two-photon imaging, the metal feedlines, and electrodes of state-of-the-art neural implants generate shadows and light artifacts, thereby exposing the need for transparent implants. 1-6

Methods
Standard surface micromachining processes, photolithography, and colloidal lithography processes were explored to fabricate parylene-C-based micro electrocorticography electrodes (µECoGs) containing mesh metal structures and soft electrode coatings based on PEDOT: PSS. The transparency, shadow cast, and behavior towards light-induced electrical artifacts were investigated in vitro and subjected to one-photon and two-photon imaging, as well as electrochemical characterizations. Additionally, the performance of the implants was assessed in vivo upon implantation in mice by performing combined electro- and optophysiological measurements in awake mice with minimal photo-induced artifacts or optical interference upon tactile and visual stimuli.

Results
Metal-mesh and PEDOT: PSS structures showed an improved transmittance behavior. Electrodes based on PEDOT: PSS exposed lower light artifacts when combined with electrophysiology. In in vivo experiments, PEDOT: PSS implants showed the feasibility of imaging directly under the electrodes and feedlines while recording neural activity. While the performance of mesh implants started degrading after two weeks, implants based on only PEDOT:PSS have shown long-term stability for more than three months.

Conclusion
This study demonstrates the advantages of transparent implants made of PEDOT: PSS or holy metal structures for parallel electrical recording and optical imaging for in vivo neural applications. In in vivo settings, the transparent PEDOT:PSS implants showed the best overall compromise between electrical and optical properties as well as long-term stability.

1 Donahue, et. al., eNeuro, 2018
2 Dijk, et. al., Microsyst Nanoeng, 2022
3 Qiang, et. al., Sci Adv, 2018
4 Renz, et. al., Adv Healthc Mater, 2020
5 Kuzum et. al., Nat Commun, 2014
6 Park, et. al., Nat Commun, 2014
Development and validation of 3D multisite neural implants

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Introduction
Neural implants provide access to the peripheral and central nervous system aiming to understand and treat neurodegeneration or to artificially restore sensory inputs. Among other challenges, low spatial resolution due to a small number of electrodes is a limiting factor. Therefore, our group proposes fully-customizable, flexible 3D multisite electrode arrays which penetrate the neural tissue to simultaneously record and stimulate the target cells.

Methods
Implants are fabricated using thin-film technology and surface micromachining processes. To create 3D probes from 2D flexible polymer substrates such as Parylene-C, two approaches were followed: A) Kirigami (with a cut and fold principle), and B) 3D printed implants by 2-photon polymerization and template-assisted electrodeposition of Au and PEDOT:PSS. The electrochemical characteristics of the electrodes were evaluated by electrochemical impedance spectroscopy (EIS). Cadaveric, in-vitro and in-vivo validations were conducted with healthy wild-type (WT) and diseased RCS rats’ retinae and cortex.

Results
Kirigami implants contain 128 electrodes equally distributed over 32 shanks, which were folded simultaneously at a 90° angle. Shanks’ heights of up to 1000 µm are feasible. 3D printed implants are highly flexible in terms of design choices with high aspect ratios (up to a height of 300 µm and a diameter down to 12 µm). Both types of implants showed mechanical stability over more than 10 insertions into tissue. During in-vitro and in-vivo experiments, it was possible to obtain 3D recordings of the same neuronal column. Additionally, the implantation of retinal penetrating implants was successfully validated in cadaveric rats’ retinae.

Conclusion
Our 3D flexible implants offer advantages over related methods ([1][2]), such as design versatility, a high number of electrodes, and fast processing, pushing further the next generation of 3D flexible electrode arrays to treat neurodegenerative diseases.

[1] Lee et al., npj Flexible Electronics, 2022
Intra-operative test electrode and electrical auditory brainstem response after pre-operative assessment in cochlear implant candidacy

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Introduction
Over the last years, in doubt of cochlear implant (CI) candidacy, assessment of excitability of the auditory nerve is performed with pre-operative tests. These tests are the pre-operative (pre-op.) performed electrical auditory brainstem (EABR) and the late response (EALR) recorded with trans-tympanic promontory stimulation in local anesthesia. But in some cases after such preoperative tests there is still doubt about the excitability of the auditory pathway. The most reliable EABR is recorded with using stimulation via the CI. However, before CI implantation, an intra-cochlear test electrode could be used to achieve similar EABR results.

Methods
In doubtful cases of patients who underwent pre-op. EABR, we performed EABR by a test electrode, part of the auditory nerve test system. This measurement was used to confirm the pre-operative results just before CI implantation. Additionally, EABR using CI stimulation was performed intra-operatively right after the CI implantation to confirm EABR using the test stimulation electrode results.

Results
Six subjects were included. They were tested by pre-op. EABR (n=6), pre-op. EALR (n=5), intra-op. EABR using test electrode (n=6), intra-op. EABR via CI (n=6), and post-op. EABR (n=2), and post-op. EALR (n=2). In two cases, intra-operative EABR showed a positive (=clearly measurable) response whereas there was a doubtful response in pre-op. EABR. Intra-op. EABRs (test electrode and CI stimulation) showed the same results in all cases. Waveforms of EABR using test electrode look similar to EABR using CI stimulation but with more defined peaks compare to the pre-op. EABR. In one case with all-over positive EABR, pre- and post-operative EALR were matching.

Conclusion
Intra-op. EABR using test electrode was easy to record and it shows similar results to EABR using CI stimulation. Intra-op. EABR using test electrode may help in confirming the results of unclear pre-op. EABR with minimal increase in recording time.
Re-evaluation of LA-TT-EABR “PromBERA” in cochlear implant candidacy

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Introduction
The trans-tympanic electrically evoked auditory brainstem response measurement in local anesthesia (= LA-TT-EABR) has been shown as a useful tool in doubtful CI candidacy to objectively evaluate the excitability of the auditory pathway up to the brainstem. Previous studies in this matter were of relatively low subjects number. To update the knowledge of the reliability of LA-TT-EABR, we re-evaluated the latest results from a bigger subjects dataset from our clinic and follow up regarding hearing sensation post-operatively.

Methods
LA-TT-EABR was performed, as described in previous publications, with a trans-tympanic golf-club electrode in the round window niche for pre-operative stimulation in local anesthesia and with an evoked potential device for EABR recording. Hearing sensations were monitored in the implanted CI subjects.

Results
39 of 40 planned subjects were included in this study. In 22 subjects, a positive LA-TT-EABR was recorded. In 11 subjects, the response was insecure. In 6 subjects, no response was recorded. One subject was excluded because of pain during the paracentesis. Among them, 19 were implanted with a CI, and 18 had hearing sensations with a hearing prosthesis post-operative. The sensitivity and specificity of LA-TT-EABR in estimating the excitability of the auditory nerve pre-operatively are both 100%.

Conclusion
LA-TT-EABR was shown as a reliable pre-operative test to objectively evaluate the auditory brainstem response. In addition to LA-TT-EABR, an analysis of the auditory cortex using LA-TT-EALR may provide correlation and confirmation of LA-TT-EABR results and additional information about cortical reorganization after long deafness.
Track:

Biosignal Analysis and Data Aggregation
Data Acquisition System for Multichannel FSCV Measurements

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Introduction
A high-performance, multichannel stimulation and data acquisition system for real-time detection of neurotransmitters is presented. Existing devices suffer from limitations in terms of number of channels, sampling rate and flexibility. In a joint project, Fraunhofer IMS (Duisburg, Germany), Fraunhofer USA Center Midwest (East Lansing, USA) and Fraunhofer USA Center Mid-Atlantic (Riverdale, USA) cooperate to overcome these bottlenecks. The system described here is designed to apply arbitrary programmable waveforms with a sampling rate of up to 250 kS/s and a maximum slope of 1200 V/s to a multi-electrode array. Up to 16 electrodes establish electrical contact to neural brain cells and enable the measurement of neurotransmitters such as dopamine or others by fast-scan cyclic voltammetry (FSCV).

Methods
This paper focuses on the hardware and firmware development performed by Fraunhofer IMS, which is based on high performance A/D and D/A converters controlled by a Xilinx Zync 7000 FPGA device. This enables real time control of the components and convenient processing of large data streams.

Results
The sensitive analog hardware for stimulation and recording is located on a separate PCB close to the electrode array. The connection to a standard host computer is made via a USB link. The key features of the system include 16 parallel output and input channels with an update and sampling rate of 250 kSps, 16-bit D/A and A/D resolution, +/-2.5 V applied voltage range and a current response spanning ≤ 10 nA up to 1 µA in magnitude. The system supports continuous measurements with a programmable duration of up to 2 hours.

Conclusion
The system development is currently in its final phase. Once connected with electrode arrays it will allow to deepen our understanding of the brain and its inner working by fast measurements of neurotransmitter release.
Comparison of Feature Extraction Methods for Spike Detection with Artificial Neural Networks: A Focal Epilepsy Case Study

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Introduction
In focal epilepsy, EEG is used for non-invasively measuring epileptic activity as one of the standard diagnostic modalities for presurgical epilepsy diagnosis. In the diagnostic process, interictal epileptiform discharges (IED) are marked by experts in the EEG data. This manual marking is a time-consuming, subjective and tedious work, leading also to larger variability between different expert markers. Therefore, it would be beneficial to develop and train systems that can automatically detect IED in the EEG data. In our talk, we show how this can be achieved via training machine learning algorithms with EEG data.

Methods
We present a new automatic detection and Artificial Neural Networks (ANN) classification procedure together with detailed preprocessing steps. We survey the possibility of representing the data with new features without direct classification and show how advantageous it is to use these features. The complex, statistical and frequency features are represented in the multichannel EEG with epochs of smaller size and used for training the network.

Results
The multi-input ANN trained with multichannel EEG data achieved 71.81% accuracy and 70.18% precision. Training the ANN with the new features increased the success of classification and achieved 98.23% accuracy and 98.25% precision.

Conclusion
For IED detection, the proposed method increases the success and speed of classification. Furthermore, automatic detection embeds well in the expert inter-rater variability.
Amplitude fluctuations in the averaged photic driving in the electroencephalogram correspond to burst occurrence in single trials

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Introduction
Frequency entrainment and resonance phenomena are frequently studied in research as well as in various pathologies, such as migraine, and epilepsy. Despite the long history of application, the underlying mechanisms are not yet fully understood. The purpose of this study was to investigate photic driving in unaveraged signals. This analysis should lead to a better understanding of frequency entrainment and resonance phenomena with their observed amplitude fluctuations in the averaged signals.

Methods
Intermittent photic stimulation (IPS) was presented to 14 volunteers at eight stimulation frequencies (\(f_{\text{stim}}=7.8,8.8,12.8,13.4,14.4,18,19,23\) Hz), 64-channel EEGs were recorded during stimulation. Preprocessing consisted of cleaning the EEG data, bandpass filtering (1-40Hz), and re-referencing to common average reference. With a complex Morlet wavelet, time-frequency maps of one-second length with a frequency band of \(f_{\text{stim}}\pm5\)Hz, were calculated. Transient high-amplitude events within the time-frequency maps were detected. The probability density estimate of the detected transient events over time was correlated with the time course of the main frequency within the averaged time-frequency window.

Results
Contrary to averaged photic driving signals, the unaveraged single-trials did not show a continuously enhanced amplitude at the respective stimulation frequency. However, single transient events with increased amplitude were observable for all one-second windows and all stimulation frequencies. The median correlation coefficient (±SEM) across all volunteers and stimulation frequencies was 0.88±0.01. Especially stimulation frequencies within the alpha band showed very high correlation coefficients (\(0.97±0.01\) at \(f_{\text{stim}}=7.8\)Hz) and (\(0.96±0.01\) at \(f_{\text{stim}}=8.8\)Hz), compared to lower correlation coefficients in the beta band (\(0.79±0.04\) at \(f_{\text{stim}}=18\)Hz), \(0.86±0.01\) at \(f_{\text{stim}}=19\)Hz), and (\(0.84±0.02\) at \(f_{\text{stim}}=23\)Hz).

Conclusion
Photic driving in unaveraged recordings consisted of transient high amplitude events which on average resulted in the well-known continuous amplitude increase. Correlation coefficients between the temporal distribution of bursts and the amplitude course over time provided an explanation of the earlier described amplitude fluctuations in the time-frequency domain.
A 3D-printed ventilator for small animals

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Introduction
For animal experiments in a research context, mainly commercial ventilators for small animals or syringe anesthesia have been used. These ventilators are expensive, available in limited quantities and distributed internationally only by a few manufacturers. Syringe anesthesia cannot be used for all small animals.

As a minimum requirement, the system should be able to ventilate a mouse with a tidal volume of 0.2 ml and a ventilation pressure of approximately 20 cmH2O. For the system to be easily replicated, it should be reproducible with the classic fusion layer print.

Methods
The major parts of the system were made airtight by PLA printing and mounted on a wooden board. The driving unit is approx. 36cm·10cm·5cm and the control unit approx. 14cm·20cm·14cm. Via a pre-chamber, the ventilation gas is aspirated by syringe and then applied to the animal to be ventilated. The actual ventilation takes place via a stepper motor, which is connected to the syringe plunger. A pressure sensor ensures that no pressure above 30mgH2O occurs within the system. The movement of the ventilation gas within the system is controlled by electric valves. The CO2 content of the exhaled air is measured with an environmental gas sensor. The control of the stepper motor and the processing of the sensor data is done by an RP2040.

Results
The tightness of the system and the ability to draw in and move gases was tested and proven with test smoke. The running safety of the system was carried out with several measurements of 30 minutes against a resistance consisting of a water column. Measurements are pending to accurately determine the gas volume and pressure sensor accuracy.

Conclusion
This ventilator can theoretically ventilate a small animal. For final suitability, both the safety functions and the usability of assembling the device require further improvement.
Optimization of the deep selectivity of PPG signals in the context of PTT determination

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Photoplethysmography (PPG) has become an indispensable tool in modern clinical practice. A PPG signal is obtained by illuminating the skin tissue with a light emitting diode (LED) and detecting the transmitted or reflected light. The cause of the PPG signal are periodic volume changes in the blood vessels. Light can penetrate the tissue to depths depending on the wavelengths of the selected LED. With the depth information, the pulse wave transit time (PTT) can theoretically be calculated at only one measurement point.

To improve the measurement of the PTT at one measurement point, a new type of sensor is introduced to find the optimal emitter-detector spacing by varying the spacing of LEDs and photodiodes. For this purpose, the system has been divided into two circuit boards. One with the components for the emitter consisting of a digital-to-analog voltage converter and five LEDs with wavelengths in the range of 465 nm to 940 nm, and a second board for the detector consisting of a photodiode array, an analog-front-end for signal amplification and filtering, an analog-to-digital converter, and a microcontroller for signal processing. The entire assembly is mounted on two optical platforms, and the circuit boards are positioned in a way that the LEDs and photodiode are adjacent to each other in parallel. By means of an adjustment screw, the emitter-detector distance can be adjusted.

The proposed method enables the measurement of reflected multispectral pulse waves with varying emitter-detector distances. Further measurements still have to be performed in order to ensure the functionality of the sensor. In conjunction with an analytical model and further simulations, the ideal transmitter-detector distance in terms of pulse transit time will be verified experimentally in the future.
Pilot study on the effect of a transocular alternating current stimulation on the steady-state pattern-reversal electroretinogram

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Introduction
Transocular alternating current stimulation (ACS) with weak currents (≤ 2 mA) has gained attention for the treatment of neurodegenerative retinal diseases. However, until today it is unknown which and how retinal cells react to the current. Transcranial ACS showed frequency-dependent effects on visual evoked potentials. With the present pilot study, we aim to test the effects of transocular ACS on the steady-state pattern-reversal electroretinogram (ssPERG) as an evaluation method for investigations of frequency-dependent effects of such stimulation on the retinal cells.

Methods
Five participants were stimulated in two different sessions (48 h between) with a transocular ACS (sinus, 800 µA, 20 Hz, 20 min) applied using one electrode surrounding one eye and one electrode over the visual cortex. The sessions included ssPERG measurements at baseline and after ACS using 20 or 30 reversals-per-second (rps; randomized order) to stimulated with the ACS frequency and the next highest possible frequency of the system, which triggers a ssPERG response. Changes in the maximum of the power spectrum of the ssPERG and in the median inter-trial coherence (ITC), as a parameter for phase consistency over trials, were used to compare baseline and after ocular ACS conditions.

Results
The median ITC in ssPERG measurements was higher after the transocular ACS for 20 rps and 30 rps, in 4 out of 5 participants. After the stimulation, the maximum in the power spectrum of the 20 rps ssPERG was reduced in 3 out of 5 participants, while the maximum in the 30 rps measurements was higher in 4 out of 5 participants.

Conclusion
Transocular ACS induced changes in the ITC and the maximum of the power spectrum of the ssPERG. Thus, this method is applicable to study the effects of ACS on retinal cells and can be used for larger studies in the future.
Transmissive transcranial ultrasound as a novel approach for the non-invasive assessment of the intracranial pressure status

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Introduction

Invasive intracranial pressure (ICP) measurement is a key parameter for monitoring traumatic brain injuries (TBI) at the intensive care unit (ICU). Due to its invasive procedure, economical and personal costs, alternative methods for the assessment of ICP are desirable. To date, no non-invasive method has been proven to be convincing for ICP assessment [1]. We present transmission transcranial ultrasound (TTUS) measurements as an alternative approach for the fast, non-invasive and reliable assessment of the ICP status.

Methods

Patients with severe TBI were prospectively enrolled in the ICU. Reference ICP, arterial blood pressure, heart rate and TTUS measurements were simultaneously recorded in situations with and without elevated ICP. TTUS was measured using two ultrasound probes placed at the skull between EEG positions T3-T5 and T4-T6 respectively. The signal was calculated based on Time of Flight measurements of high frequency signals. A binary supervised Random Forest classifier was implemented based on measurements from 10 patients with increased ICP (>15 mmHg, ICPinc) and normal ICP (<10 mmHg, ICPnorm). The model was validated in a leave-one-subject-out procedure.

Results

25 patients aged 61.6 ± 17.6 years were enrolled from October 2021 to October 2022. The median ICP of the population was 10.4 mmHg. 19 measurements were used for training of the classification algorithm (n ICPinc = 10, n ICPnorm = 9). The trained model yielded a sensitivity of 100% for the ICPinc group and a specificity of 78% for the ICPnorm group. From 27 measurements in the test set, automated analysis successfully identified increased ICP values >15 mmHg (sensitivity 100%, specificity 47%).

Conclusion

TTUS measurements were able to detect elevated intracranial pressure non-invasively with higher sensitivity compared to other non-invasive approaches [1] If the results can be confirmed in a clinical trial with a larger study population, TTUS have the potential to partially replace invasive ICP measurements and to avoid unnecessary ICP probe placements.

Characterization of time-delay in inline blood gas sensors

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Introduction
ECMO therapy is characterized by a high degree of personnel expenditure and a low degree of automation. The implementation of automated control concepts can be facilitated by a safe and simple continuous measurement of blood gases. For this reason, we utilized a newly designed fluorescence optical in-line measurement system called Organ Life Vent (OLV), which is equipped with three sensor tips for PCO₂, PO₂ and pH-value. We observed the time-delay of OLV compared to the established shunt blood gas monitor Terumo CDI 500 when entering a step input in gas fraction.

Methods
An in vitro test setup (n=3) consisting of blood pump, oxygenator, and silicone tubing was constructed. The circuit was flushed with Ringer’s solution and filled with porcine blood obtained during slaughter process. Measurement was conducted at a blood flow of 500 ml/min and a gas flow through the oxygenator of 2 l/min. Blood gas composition was adjusted by altering fractions of N₂, O₂ and CO₂ in a gas mixer to three discrete step levels (F O₂/F CO₂ in %: 22/7; 35/2; 7/10) and altering blood temperature levels (34, 37, 40) °C. Delay time was determined by measuring the time for the step response of the system to reach 63 % of its final value.

Results
A total of n=46 step responses were evaluated. We observed comparable results between the measurements performed with OLV and CDI sensors in terms of time (mean time-delay ± standard deviation OLV vs. CDI; O₂: (64 ± 39) s vs. (75 ± 24) s, CO₂: (91 ± 16) s vs. (74 ± 19) s, pH: (94 ± 35) s vs. (89 ± 35) s).

Conclusion
The OLV sensors exhibit comparable behaviour to the CDI 500 but offer significantly improved usability. Next steps will focus on blood gas control based on these sensors to improve patient safety in an ECMO setting.
An interactive tool for analysis of electrical heart axes using 2D vector loops of 6-lead ECGs

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Introduction

The electrical heart axis (EHA) is an important parameter for diagnosis of certain pathologies. Vectorcardiography (VCG) allows for a visual identification of the EHA based on a 2D vector loop and can be reconstructed from conventional electrocardiography (ECG). Building upon this concept, we propose an open-source tool for EHA analysis. It is freely available at https://gitlab.gwdg.de/GOESTERN-0228132/ptb-xl.git.

Methods

The application is developed in R (version 4.1.2) using libraries "manipulate" (1.0.1) and "colorspace" (2.0-3). The tool offers a graphical user interface with two visualizations and a menu for adjusting them interactively.

The right-hand visualization shows any lead of the 6-lead ECG in time domain. The left-hand visualization shows the 2D vector loop as plot with leads \(I\) and \(-m\cdot aV\!F\), where \(m=2/\sqrt{3}\), as x- and y-axes. The menu offers choosing the projection angle of the 2D-VCG and the start and end of the ECG signal. A sample of interest is highlighted and the corresponding polar coordinates (using atan2) are shown.

We used the PTB-XL dataset (https://physionet.org/content/ptb-xl/1.0.2/) for evaluating the proposed software and used the WFDB-package for bringing the data in a suitable format. Our tool offers to load this data as well as a general method for selection of a subset of ECG signals with similar metadata (e.g. SCP codes).

Results

We manually analyzed PTB-XL signals without pathological findings and confirmed the majority of reported EHAs. Inspecting loops of patients with heart diseases showed QRS-loops with a broad range of corresponding angles.

Conclusion

The proposed tool gives a detailed insight in the limb leads and might be useful for analyzing cases with abnormal EHAs, e.g. fragmented QRS. In future work we will add more interactive functionalities and the chest leads to complete the 12-lead ECG.
Signal analysis and classification of interictal epileptiform discharges from EEG with machine learning

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Electroencephalography (EEG) is an important tool for the detection and treatment of patients with epilepsy. The detection of interictal epileptiform discharges (IEDs) is often an important, time-consuming, manual task. In addition, a high level of expert knowledge is required. For this reason, and to ensure continuous improvement, we want to automate the detection of IEDs using machine learning techniques.

A machine learning pipeline with multiple parameters is built. First, a freely available, already annotated dataset with different virtual montages is read into the pipeline. To increase the number of individual samples, the dataset is augmented. Feature engineering is then performed using one of the dimensionality reduction methods, principal component analysis (PCA) or dynamical component analysis (DyCA), and persistent homology or time series analysis to extract topological or time series features respectively. A radial kernel support vector machine (SVM) is used to classify the features of the one-second EEG segments.

The results of this study are obtained from one evaluation dataset strictly isolated from the training dataset. Using SVM, an accuracy of 85.6 % (sensitivity of 80.7 %) is achieved. The best results are obtained with PCA, while DyCA is more robust to parameter variations in the machine learning pipeline. The use of topological features achieves a lower performance (accuracy of 83.5%) than the results with time series features, but the results with topological features show a higher sensitivity (up to 89.5%).

The classification results show that the developed machine learning pipeline with interpretable features leads to a good classification of IEDs or no IEDs. The use of deep learning approaches achieves higher sensitivities up to 93%, but it is limited in interpretability [Lourenço, doi: 10.1007/978-3-030-31635-8_237]. Before the IED detection system is ready for clinical use, quality improvements are needed and the applicability to other data needs to be verified.
A Cut finite element method for the tDCS forward problem

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Introduction

The forward problem for transcranial direct current stimulation (tDCS) describes the cortical current density distribution induced by a set of scalp electrodes, a result that can be used for the creation of individually optimized stimulation montages. It is represented by a partial differential equation (PDE) which can be solved through the use of a finite element method (FEM). FE methods are able to accurately model individual volume conduction properties such as multiple compartments and tissue anisotropy. However, they require a volumetric discretization, a mesh, of the human head. Such meshes are usually made up of either hexahedral or tetrahedral elements. Both however have certain strengths and limitations. Hexahedra for example are inadequate for curved structures while tetrahedra require nested, closed surface triangulations that are free of self-intersections.

Methods

Aimed at solving these issues, this work introduces a cut finite element method (CutFEM) to tDCS forward modeling. It is part of a category of unfitted finite element approaches where the mesh is disentangled from the geometry which is only represented by level set functions. Following a description of the method, we will employ it in controlled spherical scenarios as well as a set of 19 realistic cases where CutFEM is used for calculating optimized multi-channel stimulation montages.

Results

In sphere models, CutFEM outperforms a geometry adapted hexahedral model with regard to numerical accuracy and memory consumption. It is also able to mesh arbitrarily touching compartments which occur in realistic head models.

Conclusion

CutFEM strikes a balance of numerical accuracy, computational efficiency and ability to model complex geometries that was previously not available in FEM-based tDCS forward modeling.
Analysis of Varying Light Conditions on Camera-based Non-Contact Vital Sign Monitoring

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Introduction
Smartwatches and wearables have been extensively explored for long term pulse rate monitoring. Photoplethysmography (PPG) requires skin-contact to ensure seamless data acquisition. Recently, camera sensors are explored for remote PPG (rPPG) acquisition. In existing studies, rPPG signals are acquired in a controlled environment with proper lighting conditions. Hence, there is a necessity to evaluate the effect of varying light effect for rPPG extraction in wild conditions.

Methods
We propose a framework to monitor pulse rate on a simple front-facing camera with varying lighting conditions. For this, $N = 10$ volunteers (5 females) recorded their facial videos in three different conditions (whitelight, sunlight and shade). Camera is placed 1 meter away from the eye level of the users. Subjects are asked to rotate their head in horizontal direction. Recorded videos fed to mediapipe face tracking algorithms and faces are detected. Region of interest (RoI) namely forehead and cheek is extracted. Furthermore, green and hue channels are extracted from each ROI frame. The hue channel signals are preprocessed and subjected to Fast Fourier Transform. The highest frequency is considered as the pulse rate of the subject in beats per minute (BPM).

Results
The proposed approach is able to extract rPPG signal in varying light conditions. The hue channel signals are consistent in assessing the pulse rate of subjects. Maximum variations are observed in sunlight condition. This may be due to the intensity of sun light. The white light is found to be accurate in obtaining rPPG. Further, it is observed that the heart rate measured using our algorithm has no significant bias or random error in comparison to groundtruth.

Conclusion
The results showed a considerable impact of lighting conditions on the accuracy of rPPG signal extraction. This work emphasizes the need of controlled illumination and reliable algorithms to handle light variability.
Inter-Subject Differences in orientations and locations of stimulation targets in the visuo-motor network

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Introduction

Transcranial electric current stimulation (tES) is a non-invasive technique to modulate neural activity, which effectively reduces symptoms of neurological or mental health disorders. Variations in stimulation effects of standard TES applications can be reduced with individually optimized montages for (multichannel-)tES, which account for the target location and orientation. Preparing to stimulate the visuo-motor network, we examined the distributions of target locations and orientations between subjects in the visual area right V5 and the right Frontal Eye Field (FEF) and compared resulting montages.

Methods

For 19 healthy participants, we collected fMRI data and simultaneous EEG/ MEG data during an oculomotor pursuit task. The target locations were extracted from the fMRI data, while the orientations were estimated from EEG and MEG data with a Linearly Constrained Minimum Variance beamformer with Unit-Noise-Gain constraint. Exploiting the respective strengths of each modality, the estimated orientation resulted from the superposition of the tangential component (estimated from MEG data) and the radial component (estimated from EEG data). The required solution of the forward problem was based on a realistic, 6 compartment finite element headmodel, including white matter anisotropy and individually calibrated skull conductivity. Montages were optimized with a multichannel distributed constrained maximum intensity algorithm.

Results

Between subjects, we found substantial varieties in target locations over a limited cortical area and in target orientations for both, FEF and V5. The optimized montages are consequently different from each other, but also from the standard montage. Current flow would therefore be neither maximal nor oriented optimally in the targets for most subjects, when applying standard tES.

Conclusion

Our results suggest, that standard tES would lead to suboptimal stimulation effects in most of the participants and therefore individual montages are highly recommended to optimally stimulate the visuo-motor network.
Facial responses to physiological stress in thermal infrared imaging

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Introduction
When humans are stressed or experience arousal, it causes visible perspiration in multiple areas of their body or slight temperature changes of the skin due to sympathetic nervous system activation. One common method of measuring stress is by non-invasively measuring electrodermal activity (EDA) on the hands. EDA measures changes in the electrical conductivity of the skin, which is affected by sweat gland activity, when the stress is triggered. Additionally, the forehead, upper lip, and cheeks are areas of the face where perspiration may be noticeable during times of stress. To investigate these facial areas for signs of perspiration or changes in temperature, thermal imaging can be used. In this study, the feasibility of using thermal infrared imaging to detect stress is evaluated by examining the reactions of five subjects.

Methods
The subjects in this study were stressed with a combination of audio-visual and thermal stimuli. To measure electrodermal activity (EDA), the Shimmer3 GSR+ was attached to one of the subject's hands, which allowed for the extraction of tonic and phasic activity from the EDA signal. Additionally, a thermal infrared camera was directed at the face, while a close-up was simultaneously recorded. To track and analyze facial changes, several regions of interest (ROI) were defined using an infrared facial landmark model.

Results
The comparison between the electrodermal activity (EDA) signals and the temperature signals from thermal camera regions of interest (ROIs) allowed for the evaluation of phasic event trends in each signal to extract the response to each stimulus. By analyzing the slope of the phasic events, it was possible to calculate a correlation that indicates whether the stimulus is noticeable in both modalities. In this analysis, r-values exceeding 0.7 were attained.

Conclusion
The present study showcased the potential of thermal imaging as a noncontact method for recording physiological activity of the sympathetic nervous system, making it a promising tool for e.g. driver monitoring systems that can detect stressed drivers unobtrusively.
Comfortable dry EEG using Flower electrodes

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Introduction
Dry electrodes have contributed to faster, simplified electroencephalography (EEG), avoiding the need for skin preparation and gel application. Wearing comfort of state-of-the-art dry electrodes is considered lower than for conventional gel-based electrodes, thus limiting their application to short recordings in upright body position. We propose a novel type of dry electrode made of Silver-Chloride coated polyurethane. The soft material and the specific shape, which we call Flower shape, enable high adaptivity and improved comfort. We integrated 64 Flower electrodes in an EEG cap and compare its performance with a commercial dry electrode cap.

Methods
The novel Flower dry EEG cap and the commercial Multipin dry EEG cap comprise 64 channels. EEG was recorded sequentially on 20 healthy volunteers with both caps using a referential EEG amplifier. We acquired resting state EEG with open eyes, closed eyes, and triggered eye blinks in sitting and in supine body position. A visual evoked potential was recorded in sitting condition. The EEG was compared between both dry electrode types using established signal quality metrics. Moreover, we assessed electrode-skin impedance and wearing comfort.

Results
Application time, channel reliability, and electrode-skin impedance of both electrode types are comparable in sitting and supine position. No statistical differences are evident between a) power spectral densities of the resting state EEGs (1-40 Hz) in the sitting position, b) global field power amplitude and latency of the VEP, c) signal-to-noise ratio estimations of the VEP. The wearing comfort of the novel Flower electrode was significantly improved before, during, and at the end of the EEG recordings as well as during recordings in supine position.

Conclusions
The Flower electrode improves the wearing comfort of dry EEG while maintaining reliability and signal quality, enabling new fields of application for dry EEG in sensitive populations and long-term recordings.
Wearable healthcare sensor-system for the treatment of patients with Diabetic Foot Syndrome

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Introduction
One of the most common and severe secondary diseases of diabetes is diabetic foot syndrome (DFS), which results from poor sensation in the feet and can lead to irreversible physical consequences, including amputations. The current treatment for DFS involves immobilization and offloading of the wound, but it is limited in its ability to measure medically relevant parameters between visits and prevent deterioration.[1]

Methods
To address this limitation, a smart wearable monitoring and feedback system has been developed as an additional support for traditional DFS care.[2] This system includes a miniaturized flat PCB sensor part connected with a flexible bridge to a communication unit, which is seamlessly integrated within the DFS foot dressing. The sensor continuously measures temperature, humidity, and pressure in the wound area and provides instant active feedback to the patient's smartwatch in case of wound overstressing or critical changes within the wound area. The system demonstrated an energy-efficient operation, continuously maintaining data acquisition, processing, and connection to the watch and server for up to 2 months without additional maintenance.

Results
In a randomized study involving twenty participants with DFS, the developed system was tested. Participants received audio-visual warnings over the smartwatch when the predefined pressure limit was exceeded, providing biofeedback to compensate for the incomplete sensation in their feet. As a result, participants were able to adjust their behaviour and avoid incorrect pressure loads on their feet, potentially positively influencing the wound healing process.

Conclusion
Based on the case-by-case analysis of this pilot study, it can be concluded that the sensor-system is appropriate for sensor-based treatment of patients with DFS.

1. D. Hochlenert et al. Diabetic Foot Syndrome: From Entity to Therapy. Cham: Springer, 2018
Track: Ultraschall
A new matrix-array based ultrasound neurostimulation system

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Introduction
Deep brain stimulation (DBS) is a well established method for therapy of brain-related neurological disorders (Parkinson’s, essential tremor). It consists in inserting an electrode designed for delivering a stimulus into the brain. Ultrasound can be a non-invasive alternative to these surgical methods. While HIFU therapy (high intensity ultrasound) will permanently damage brain tissue by coagulation, LIFUP (low-intensity focused ultrasound pulsation) therapy is based on a neuromodulating or –suppressing effect while being in the energy range of diagnostic ultrasound.

Methods
The TRUST-system (MR-Instruments Inc., Licensed by Fraunhofer IBMT) is a novel multi-channel electronics device including two matrix array transducers for 3D beam steering developed by Fraunhofer IBMT. The 256 transmit channels with up to 16 W/channel and DC up to 100% can be individually programmed. The matrix arrays have 256 elements in a circular configuration and allow steering up to 20°. The probes allow integration into an MR head coil and are equipped with MR markers for easy localization in MR planning data. Each probe is equipped with an active cooling, so that heating of the aperture is prevented.

Results
Pressure distribution field measurements were performed to characterize the system. A focal pressure of >8 MPa was obtained for a focus of 3 mm x 20 mm (x/z respectively). The acoustic output inter-element variability was less than 20 % (standard deviation). The array allows steering in a range of approximately +/- 20°. The system safety was assessed both when it comes to compliance with medical device standards (IEC 60601) and thermal aspects (system, probe and cable heating).

Conclusion
A novel ultrasound neuromodulation system based on a programmable multichannel platform with high DC capabilities and two matrix array probes allowing precise focusing with more than 8 MPa focal pressure has been developed, characterized and tested according to medical device standards.
Nonspherical Microbubbles for Ultrasound-Assisted Drug Delivery

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Introduction

The blood-brain barrier (BBB) is a major physical barrier for drug delivery. Sonopermeation, which refers to the combination of ultrasound (US) and microbubbles (MB), has been used to permeabilize the BBB and improve drug delivery to the brain. In order to enhance sonopermeation, MB design parameters such as size, shell composition and active targeting have been investigated. In this study, we investigated the role of MB shape, a new design parameter, to potentiate sonopermeation-mediated drug delivery across BBB.

Methods

Spherical MB were synthesized by anionic polymerization of n-butyl cyanoacrylate. Rod-shaped MB were synthesized by stretching spherical MB unidirectionally above their glass transition temperature. Rod-shaped and spherical MB were studied to systematically compare their margination profiles, blood half-life and the magnitude of BBB permeation upon US treatment.

Results

Cryo-SEM and confocal microscopy confirmed successful formation of spherical and rod-shaped MB. Upon flowing these MB in a microfluidic chip, we observed that rods showed stronger margination both in the absence and presence of blood. Real-time US monitoring in mice demonstrated that rods have a significantly higher blood half-life time than spheres. Likely as a direct result of these phenomena, rod-shaped MB in combination with focused US almost doubled the degree of BBB permeabilization and drug delivery as compared to spheres. Finally, via functionalizing the MB surface with brain endothelium-binding anti-CD71 antibodies, we demonstrate that active targeting of rod-shaped MB enhances BBB permeabilization and drug delivery even more, by up to a fourfold.

Conclusion: This is the first study to exemplify the importance of MB shape in margination, circulation half-life and ultrasound-mediated drug delivery. These findings indicate that tailoring MB shape is a promising strategy for potentiating US-mediated opening of BBB to improve brain disorder treatment.
Towards a multi-platform flexible neuronavigated MRgFUS Neuromodulation system – 3MP-FUS system

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Transcranial focused ultrasound has become of great importance for neurological treatments. Magnet Resonance-imaging guided Focused Ultrasound (MRgFUS) is of interest due to real-time co-registration of targeted brain regions with ultrasound transducer, as well as possible direct visualisation of FUS-effects. Based on the need for versatile mobile MRgFUS systems for any MRI, this study presents first steps towards a clinical MRgFUS neuronavigated system.

MRgFUS research system consists of rolling table for flexible transportation with monitor and amplifier for connection of MR-compatible and beam steering capable mobile FUS-system with a 256-channel matrix transducer (MRInstruments). Transducer size of 10x10x11 cm fit into most head coils. To identify optimal insonation window for FUS to cross the patients skull, phase aberration was investigated on human calvaria in a self-built acoustic scanning tank with fiber optic hydrophone (Precision Acoustics). System is equipped with MR-compatible optical tracked navigation system (Localite). For MR-based transducer tracking semi-active resonant fiducial markers were improved at the transducer housing and investigated for directionality and visibility in T1-weighted gradient-echo sequences (GRE, *fl2d1*, FA=1°,10°,20°,40°,60°,90°, TR=100ms, TE=3.53ms, FoV=133*214mm, AM=0±192±120°, FS=3T). MR measurements were performed in Biograph mMR PET/MRI (Siemens Healthineers) based on modified ASTM sequences. Treatment planning and transducer placement was tested on a phantom using ACCESS head coil, and DuoFlex Quadrupole coils (MRInstruments).

The integrated semi-active MR markers showed a >12 times increased brightness of >4095 at FA=10° compared to standard passive Gd-filled markers at 338. The SNR in air ranged from 531 (FA=1°) to >1165 (FA=90°). Most components of the set-up were made from mostly 3d-printed plastic parts with non-magnetic electronic components, thus achieving full MR-compatibility.

The feasibility of the mobile versatile MRgFUS-system was shown and various measurements are being performed to verify that a safe operation on human subjects is possible in the particularly difficult and sensitive area of the brain.
The Artificial Vision Symposium – The international Symposium on visual Prosthetics
Quantum Dot Integrated Photovoltaic Neurostimulation Devices

S Nizamoglu

Optoelectrical Stimulation of Neurons via Near-Infrared Light by Using Quantum Dots

Bioelectronic medicine provides a method for treating illnesses by stimulating cells without the need for drug delivery or genetic alterations to the native tissue. One useful type of device for neurostimulation is the photovoltaic biointerface, which is wireless and battery-free, eliminating the need for wires and surgical battery replacement. Silicon photovoltaic biointerfaces have been successful in restoring vision in patients with age-related macular degeneration, but they require a rigid, 30 μm-thick photoactive layer due to low silicon absorption coefficients in the near-infrared spectrum. Optoelectronic devices that are thin and flexible offer a better alternative to fit into tissue curvature. Organic pigments and polymers have been developed as photoactive layers for flexible photocapacitors as cuff electrodes on peripheral nerves and implants that conform to the curvature of the retina.

Colloidal quantum dots offer an alternative to silicon photovoltaic biointerfaces due to their unique properties, such as a size-tunable bandgap through a quantum confinement effect, high absorption coefficient, and solution-processable fabrication. They also have high optical stability with minimal photobleaching or chemical degradation.

In this study, we developed flexible biointerfaces that are sensitive to near-infrared light by using quantum dots. Specifically, they integrated an ultra-thin layer of 25 nm lead sulfide quantum dots into a multilayered photovoltaic architecture to create a capacitive photoresponse, which safely injects charges for extracellular neurostimulation. The biointerfaces were able to generate precise action potentials in hippocampal neurons with over 80% success rates up to a stimulation frequency of 20 Hz, all within the ocular safety limits. Additionally, the biointerfaces showed resistance to various stress tests and chronic photoexcitation, as well as low cytotoxicity for in vitro hippocampal neuron cultures. Overall, the biointerface architecture using near-infrared-sensitive quantum dots has great potential for creating minimally invasive neurostimulators for retinal stimulation.
The PRIMA bionic vision system in patients with geographic atrophy

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Introduction: The PRIMA bionic vision system is designed to partially restore vision in patients suffering from geographic atrophy due to age-related macular degeneration (AMD). A camera mounted on a pair of glasses captures images from the environment. After processing, this information is sent by an infrared projector onto a subretinal photovoltaic implant. The 378 pixels of the implant convert the infrared light into electrical pulses which stimulate the remaining inner retinal neurons.

Methods: PRIMA has been implanted in 5 subjects with atrophic AMD in a feasibility trial in France. After mechanical, optical and electronic adjustment of the external components, the subjects were trained to use the device. Subjects underwent visual testing, including Octopus visual field, visual acuity tests with Landolt rings and ETDRS charts. Subjects were able to benefit from the image processing, including zoom. We report about the follow up over up to 48 months.

Results: In all 5 patients, the implant has been successfully placed under the central retina. The visual field test demonstrated that all subjects had perception elicited by the implant in the scotoma area. Visual acuity measurement with Landolt rings demonstrated an improvement of up to logMAR 0.87 (with vs without the system). ETDRS measurement demonstrated that subjects are able to recognize letters and sequences of letters with a visual acuity improvement of up to 37 letters (logMAR 0.74). The peripheral visual acuity did not decline after the surgery over a review period of up to 48 months following surgery.

Conclusions: The subretinal implantation of PRIMA in subjects with geographic atrophy due to AMD is feasible and safe, with no reduction of natural peripheral visual acuity. Visual acuity measures showed that patients are able to reliably recognize letters and sequences of letters with a clinically meaningful visual acuity improvement.
A Novel Wireless and Scalable Cortical Visual Prosthesis

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Introduction
Cortical Visual Prostheses (CVP) suffer from limited channels, complex surgery due to wires, and lack of mechanical compliance.

Methods
We designed a novel CVP composed by thousands of wireless, ultra-miniaturized and free-floating CMOS implants for intracortical microstimulation. The CMOS implants were designed in Cadence and fabricated by TSMC 180-nm technology. The 3-coils Inductive Power Transfer (IPT) system and the CMOS circuits were characterized with standard electronic instrumentation.

A craniotomy was performed in one Non-Human Primate (NHP) and the chamber was fixated over the primary visual cortex of the right hemisphere of the macaque. Two Pt/Ir microelectrodes were coated with Pt-black by electrodeposition, glued in a bipolar configuration and inserted through the chamber.

Results
The IPT link simultaneously delivers power and data at 433 MHz with a 10% duty cycled transmission safely receiving a SAR-constrained power of 150 µW using a squared receiving coil with a 200 µm lateral size implanted at 12 mm from the transmitting coil. With this wireless approach up to 1024 CMOS implants can be powered at the same time. CMOS simulations and measurements demonstrate stable 1.1 V supply from low incident RF-voltage at the receiver. A 4 kHz unbalanced relaxation oscillator with a combinational circuit generates the biphasic stimulation waveform with a burst rate up to 1 kHz. Electrical stimulation has been successfully used in one NHP to elicit phosphenes in precise and distinct locations of the visual field. Preliminary experiments show that phosphenes can be reliably evoked using biphasic current burst with ± 100 µA, pulse width of 200 µs, burst rate of 200 Hz and 50 ms burst duration.

Conclusion
This technology enables thousands of parallel stimulating sites, covering large cortical surface corresponding to a wide visual field size with high spatial resolution. This solution could provide useful artificial vision to blind patients.
Fabrication of a MEA with embedded microfluidic channels for in-vitro and ex-vivo testing

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Introduction
Retinopathia pigmentosa (RP) is an inherited retinal disease in which photoreceptors degrade that ultimately leads to blindness. Due to a lack of photoreceptor input retina remodeling occurs. This remodeling hinders successful electrical stimulation and recording of retinal implants. Gene electrotransfer (GET) is a therapeutic procedure in which plasmids are precisely and locally injected into cells under the application of an electric field. GET can be used to counteract retinal remodeling.

Methods
A microelectrode array (MEA) was attached to a microfluidic structure. The microfluidic structure consists of two layers SUEXTM hardresist (K25, micro resist technology GmbH, Berlin). The MEA was fabricated by ZMNT (RWTH Aachen University) by evaporation of 30 nm Ti/ 150 nm Au followed by electroplating. A 10 µm Parylene-C isolation layer finishes off the MEA. Holes were etched into the layers using two consecutive reactive-ion etching (RIE) steps with oxygen and sulphur hexafluoride in order to access the electrodes and microfluidics. Electric and fluidic contact were established through a specially designed printed circuit board (PCB) carrier and a test platform containing medical tubing and battery contact pins.

Results
The MEA consists of 60 electrodes each with a surface area of 1 760 µm² that are 125 µm apart. Microfluidic openings with a diameter of 30 µm are integrated between each of the electrodes. The final MEA has a thickness of 60 µm.

Conclusion
The MEA presented provides a platform to interface cells and tissue electrically as well as microfluidic. It can be used to study diseases such as retinitis pigmentosa, to perform GET, and to stimulate and record neuronal tissue in-vitro and ex-vivo.
Classification of Retinal Ganglion Cell Subtypes Using Deep Learning Approaches

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Introduction
In future electronic retinal implants, the selective stimulation of specific Retinal Ganglion Cell (RGC) subclasses will be of great importance to mimic the natural response of neurons to light. To be able to determine the selectivity success of the stimulation, a robust cell-type classification of evoked spiking activity is required. To achieve this, a deep learning neural network approach is used.

Methods
To ensure a robust classification, a sufficient amount of recorded light stimulation responses is required as training data for the neural network. This data, which is already labeled with the respective cell-type class, was acquired from the “RGC Typology Database”, which is available at rgctypes.org. The dataset was split into ON-/OFF-clusters to ensure a homogeneous spike distribution within the respective recording, having a standardised length of 1 second. Afterwards a fully connected deep learning model was trained using the raw neural spike train recording as its input and the matching cell-type as its output.

Results
It was determined that the most effective configuration for this task was a neural network incorporating three hidden layers, utilising the ReLU activation function for the hidden layers and the SoftMax function for the output layer. A dropout rate of 10% was used to prevent overfitting. Using this configuration, a correct classification rate of 92% could be reached on average for a broader distinction into functional cell classes (ON/OFF, transient/sustained, DS). Applying a specific distinction into the respective subtypes (n = 42), an average accuracy of 72% could be reached.

Conclusion
Neural networks are a powerful tool for the classification of contained cell-types within raw neural recordings. For 1 second spike trains a satisfying accuracy could be reached, enabling this approach to be used for closed-loop retinal stimulation systems. Future trainings will focus on single spike classifications and the hardware integration of the resulting model.
Closed-loop feedback visual prosthetics

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Introduction
The Newcastle Visual Prosthesis project aims to develop an optogenetic visual prosthesis. This architecture of this involves a headset to capture and encode the visual scene. Data is then transmitted to a subcutaneous controller, which commands implants to stimulate neurons in the early visual cortex (V1).

Conceptually the entire process described above is feedforward. i.e. the stimulus intensity is purely a function of the visual signal rather than considering the background activity of the visual cortex. However, the architecture of the visual system consists of many feedback processes. It is, therefore, our hypothesis that the efficiency of visual data transfer can be improved by implementing such feedback processes into the prosthesis.

Methods
In addition to our efforts on visual cortical prosthetics, we recently developed a prototype system for suppressing seizure activity in epileptic brain tissue. This prototype used a phase shift algorithm to constructively and destructively interfere with the existing brain signals to suppress or increase activity. We have therefore adapted this closed-loop model for the visual prosthesis to explore the benefits and problems of such an approach.

Results
We have experimental evidence of closed-loop control of neural activity for the epilepsy case. We were only able to stimulate optogenetically, but even then could demonstrate an increase or decrease up to +/- 5dB. These results have been validated across theoretical models.

The transfer of visual information is not a fixed target as with epilepsy, but we can essentially overlay the visual information on top of the suppressed activity. The two key outcomes we aim to show at the conference are reduced stochasticity (improved contrast) and reduced stimulus requirement (reduced phototoxicity effects).

Conclusion
We believe that closed-loop feedback will improve visual return and reduce stimulus-induced damage to the tissue in the long term.
Dual-mode electronic and optogenetic visual cortical prosthetics

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Introduction
Visual prosthetics have shown some promise in restoring sight to patients. By inducing the electrical activities of neurons and generating a biomimetic vision directly in the visual pathway. Attempts to develop real-time, high-resolution devices have been made, but they are far from stable and reliable patient application devices. Many studies have successfully yielded some degree of vision based on electrical stimulation. However, the electrical stimulation has limited cell specificity, which is unacceptable in the visual system with a complex range of cells and functions. Optogenetics supports cell recognition and enables stimulation with high spatial and temporal resolution. However, the light is scattered, the direction is limited to a forward arc from an emitter, and the LED consumes ~100x more power than electrical stimulation.

Method
The intensity of light and electric field will be controlled subthreshold to ensure that neurons would not release spikes without any of them, as when these stimuli work together. The ChR2 will be expressed in pyramidal cells in the 4th layer of the primary visual cortex. The LED will be placed over the cortex, and the light will stimulate vertically. The electrodes will be penetrated inside, and the current will stimulate horizontally.

Result
The system realizes a high resolution and cell-specific stimulation while reducing power consumption. The shunt current in the biphasic current steering is limited by the sensing ground structure. The local field potential is recorded to monitor the action of the neuron population.

Conclusion
The dual-mode visual cortical prosthetics based on electrical and optical stimulation circuit is tested. Functional PCB and ASIC will be developed and tested with animal experiments.
Convolutional Neural Network-based Inverse Encoder for Optimization of Retinal Prosthetic Stimulation

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Introduction

The resolution of the electrode array in retinal implants is a bottleneck in the signal transmission pipeline from the camera to the brain. To address this issue, we applied an inverse model as a preprocessing step before transmitting signals to the electrode array. We investigated the performance of a neural network-based inverse model as the encoder in a retinal implant. Our rationale for this study is that downsampling input images to the resolution of the electrode array does not construct an inverse function, which in theory is the optimal encoder.

Methods

Using two psychophysically validated computational models, scoreboard and axon-map, we generated percepts from images (or stimulations, which are the current signals on the electrode array) from the MNIST dataset and two randomly generated datasets of continuous values and ternary values {0, 0.5, 1}, respectively. Ideally, the percept should be identical with the input image. With this assumption, the convolutional neural network-based inverse model, which was trained from stimulations to percepts, received the original image as input and generated the encoded stimulation signals on the electrode array as output during inference. The loss function used was the pixel-wise mean squared error (MSE).

Results

We evaluated the reconstruction performance between the normalized input image and the predicted percept using MSE on the test set. With the scoreboard model, we achieved MSEs of 0.016 and 0.009 using a 3-level and a 5-level U-Net, respectively. With the axon-map model, we achieved MSEs of 0.0013 and 0.0005 using a 2-block and a 4-block VGG, respectively.

Conclusion

Our results suggest that the convolutional neural network-based inverse encoder is feasible for optimizing the retinal prosthetic stimulation signals on the electrode array with different datasets, both visually and numerically.
An actor-model framework for visual sensory encoding

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Introduction
Sensory encoding converts information from sensors into stimulation parameters of sensory prostheses. In visual implants, one key aspect of image encoding is to downsample the images captured by a camera to match the specifics of implantable neural interfaces. Although several studies developed image encoding pipelines, the natural transformation occurring within the retina is generally not considered.

Methods
We utilized a learning-based approach with a neural network for the optimization of the downsampling process. The model consists of an actor-network prepended to a forward-network, both of which are convolution neural networks. The forward-network acts as the digital twin of a biological retina which we used to optimize the actor-network. We first train the forward-network using experimental data of retinal ganglion cells' response to projected images. Then we train the actor-network to downsample a given image in a way that, when presented to a retinal, elicits a neuronal response similar to that of a high-resolution image.

Results
Here we show that with a learning-based approach accounting for the retinal image transformation, our model could distil pertinent features of effective downsampling. Compared with the performance of a learning-free approach like pixel-space averaging, our proposed method generated higher neuronal reliability validated both in-silico and ex-vivo. These results indicate that our method generates downsampled images which elicit a neuronal response more similar to the high-resolution images. We also reveal contrast as a crucial feature for effective downsampling.

Conclusion
The implications of our research are far-reaching and we anticipate our method will serve as a guide for future image encoding research to account for biological processes using a learning-based image encoding approach. Ultimately, this study holds promise in aiding the advancement of retinal prosthesis, bringing us closer to a future where retinal prosthesis can help restore vision to those who have lost it.
BioAdhere: tailor-made bioadhesives for epiretinal visual prostheses

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Introduction: Visual prostheses, i.e. epiretinal stimulating arrays, are a promising therapy in treating retinal dystrophies and degenerations. An innovative method for epiretinal fixation of stimulator arrays is required. We developed tailor-made bioadhesive peptides (peptesives) for fixating epiretinal stimulating arrays omitting the use of traumatic retinal tacks.

Methods: Binding motifs on the stimulating array (poly[chloro-p-xylylene] (Parylene C)) and in the extracellular matrix of the retinal surface (collagens I and IV, laminin, fibronectin) were identified. The anchor peptides cecropin A (CecA), KH1, KH2 (author’s initials) and osteopontin (OPN) were genetically fused to reporter proteins to assess their binding behavior to coated microtiter plates via fluorescence-based assays. Domain Z (DZ) of staphylococcal protein A was used as a separator to generate a bioadhesive peptide. Direct and non-direct cytotoxicity testing (L-929 and R28 retinal progenitor cells) was performed. Lastly, the fixating capabilities of the peptesives were tested in proof-of-principle experiments.

Results: The generation of the bioadhesive peptide required evaluation of the N- and C-anchoring of investigated APs. The YmPh–CecA construct showed the highest activity on Parylene C in comparison with the wildtype phytase without the anchor peptide. eGFP–OPN was binding to all four investigated ECM proteins (collagen I, laminin > collagen IV, fibronectin). The strongest binding to collagen I was observed for eGFP–KH1, while the strongest binding to fibronectin was observed for eGFP–KH2. Direct and non-direct cytotoxicity testing of the peptide cecropin-A–DZ–OPN using L-929 and R28 cells showed good biocompatibility properties. Proof-of-concept experiments in post-mortem rabbit eyes suggested an increased adhesion of CecA–DZ–OPN–coated stimulating arrays.

Conclusion: While the fixation of macroscopic objects using bioadhesives was shown firstly, further biomechanical testing, and bond strengthening is needed to fulfill requirements for the in-vivo application.
Results from cadaveric eye experiments using the newly developed 3D-PLAPS ophthalmic surgical instrument for implantation of large retinal stimulators

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Introduction
In treatment of blindness causing retinal dystrophies i.e., Retinitis pigmentosa (RP) retinal implants showed promising results. In recent years, larger devices restoring a greater field of vision were introduced. With larger size, implantation became more difficult. In this study, a novel implantation device was developed, fabricated, and tested in ex-vivo implantation surgeries in porcine & rabbit eyes. The goal was to demonstrate a reproducible, safe, and compared to current methodology, superior implantation method.

Methods
3D design software was used for design, modeling, and fabrication. Anatomical dimensions of rabbit, pig and human eyes were collected from anatomical and histological data sources. The 3D-printed large-array port system (3D-PLAPS) was fabricated using 3D printing. Implantation surgery was performed on cadaveric porcine as well as rabbit eyes. 3D-PLAPS was tested for implantation of a large-array epiretinal stimulator, developed by this group. A standardized ophthalmologic surgical procedure was established. Intraocular pressure was measured at different time points during surgery.

Results
3D PLAPS was manufactured with a length of 9.0 mm and adapted to the curvature of an emmetropic human eye with a diameter of 24.0 mm. The elliptically shaped aperture is 7.0 mm long and 1.0 mm wide at its widest points. Apertures for scleral fixation were added. Further, a sealing plug closing the central aperture was introduced. In ex-vivo experiments, 3D-PLAPS improved the stability of the eye, sealed the incision, and withstand increased intraocular pressures during surgery. It is suitable for foldable retinal stimulators up to 14.0 mm and up to 7.0 mm in diameter in non-foldable state, respectively.

Conclusion
The new implantation device proves to be feasible for implantation of large epiretinal stimulators. The newly established implantation methodology will be tested in further in-vivo experiments. The project is funded by the Research Training Group 2610/1 of the German Research Foundation (DFG).
Multi-modal evaluation of neuronal integrity in the visual pathway after retinal degeneration in RCS rats

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Introduction
Retinitis pigmentosa (RP) is a class of inherited disorders caused by the progressive death of photoreceptors in the retina, for which treatments remain limited. Retinal prostheses are a therapeutic approach to restore vision for RP patients, which rely on an intact and organized visual pathway. Alterations of anatomy and function along the visual pathways from the retina to the visual cortex upon blindness are well studied. However, little is known about plasticity on a molecular level.

Methods
The Royal College of Surgeons (RCS) rats were used as the retinal degeneration model for this study. Along the process of retinal degeneration, experiments were conducted at P30 (30 days), P50, 3M (3 months), 6M, and 12M of age. Optomotor response was tested to track the visual performance of the RCS rats. We further analyzed the receptor density of GABAAR, mGluR5, and 5-HT2AR, as they were implicated in cortical plasticity, by the specific binding of selective radioligands [3H] Flumazenil, [3H] ABP-688 and [3H] MDL100907, respectively, on brain slices.

Results
In RCS rats at P30 and P50, scotopic and photopic vision were comparable to wild-type rats. Scotopic vision was initially completely lost in 6M RCS rats with some detectable photopic vision at contrast 1. This high contrast photopic vision was subsequently completely impaired at 12M. A transient increase of 30% of GABAAR density was found in the superior colliculus of RCS rats at P50, compared with wild-type rats, but not in the visual cortex. The GABAAR density in RCS rats dropped to a normal level at 3M. No difference was found in the receptor density of mGluR5 and 5-HT2AR between RCS and wild-type rats.

Conclusion
Scotopic and photopic vision were completely impaired in 6M and 12M RCS rats, respectively. A transient increase in GABAAR density was found in the superior colliculus of RCS rats at P50.
Electroporation-based transfection of rd10 and wild-type retinas: anatomical and cell biology studies

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Introduction
Artificial vision to treat retinitis pigmentosa is based on directly stimulating surviving retinal cells to create visual perceptions. However, retinal degeneration is associated with remodeling processes, which impair the efficacy of artificial vision. Gene therapy is a promising approach to treating retinal diseases. Our aim is to develop an efficient and safe gene therapy to counteract the process and effects of retinal remodeling. We have analyzed non-viral Sleeping Beauty (SB) transposon-based gene transfer into degenerated retinas using electroporation.

Methods
Different stages of rd10 mouse retinas (P25 to P180) and age-matched wild-type (WT) retinas (C57BL/6J) were electroporated with the SB100X transposase plasmid and the pT2-CAGGS-Venus transposon plasmid using NEPA21 electroporator. Transfection efficiency was assessed by fluorescence microscopy one day after incubation. Retinal integrity and transfected cell types were evaluated and identified by hematoxylin & eosin and immunofluorescence staining, respectively. Fluorescein isothiocyanate-dextran (FITC-dextran, 4 kDa) was used to further investigate the electroporation effect.

Results
The ideal electroporation settings were: 10 V (voltage), 5 ms (length), 50 ms (interval), 2 (number), 10% (decay rate), +/- (polarity) for the poring pulse; 10 V (voltage), 50 ms (length), 50 ms (interval), 5 (number), 40% (decay rate), +/- (polarity) for the transfer pulse. Transfection efficiency was improved using 0.1 µg/µl plasmid mixture with Opti-MEM electroporation buffer. Retinas from rd10 mice older than P61 were easily transfected. Thickness and number of retinal cell layers were maintained under the optimal electroporation parameters. The transfected cells were Müller cells. Retinas from young rd10 (P25) and WT mice were difficult to transfect; however, FITC-dextran was able to enter both young rd10 and WT retinal cells after electroporation.

Conclusion
This non-viral electroporation-based gene transfer enables distinct transfection in degenerated rd10 retinas. Increased Müller cell transfection might be due to hypertrophy of Müller cell endfeet during the process of retinal remodeling in rd10 mice.
Machine learning-based surrogate models predict optic nerve fiber firing rates and enable automatic optimization of electrical stimulation parameters

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**Introduction**

Optic nerve stimulation has the potential to produce visual perceptions spanning the whole visual field, providing thus a valuable alternative to retinal and cortical stimulation. Nonetheless, the produced phosphenes are very elongated and it is difficult to organize them into meaningful perceptions. Automatic optimization of stimulation based on biophysically-accurate computational models would allow to explore in an efficient way the large space of stimulation parameters, but its use is limited by the complexity of said models. Here, we propose how to substitute biophysically-accurate models with machine learning-based surrogate models to enable stimulation optimization.

**Methods**

We propose to predict the firing rate of optic nerve fibers under the independent electrical stimulation from multiple stimulating sites using machine learning. Specifically, we compare support vector machines, multilayer perceptrons, random forests, and more recent machine learning algorithms like XGBoost and LightGBM in terms of accuracy and speed of prediction. Finally, we propose cascading a classifier to predict recruitment with a regressor to find the firing rate of recruited fibers.

**Results**

We find that random forest-based methods excel both in terms of accuracy and speed of prediction (LightGBM, RMSE for active fibers: 6.27 Hz, RMSE for inactive fibers: 3.00 Hz). The goodness of predictions is further improved on inactive fibers cascading a classifier and a regressor (LightGBM classifier then regressor, RMSE for active fibers: 6.44 Hz, RMSE for inactive fibers: 1.80 Hz). The use of such methods increases the speed of prediction of several orders of magnitudes with respect to traditional models (0.2 s for 25,000 samples), and enables the in silico optimization of stimulation parameters in an automatic way in a simplified model of optic nerve stimulation.

**Conclusion**

Machine learning-based surrogate models allow to accurately predict the firing rates of optic nerve fibers and can replace traditional models enabling automatic, model-based optimization of electrical stimulation parameter.
Phosphene synchrony in simulated artificial vision

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Introduction
Phosphenes in electrically-based visual prostheses are created from microstimulation to individual contacts in electrodes implanted in the visual pathway so as to bypass the impaired site and provide restoration of function. Objects are conveyed through patterns of stimulation driven by images from the external world, subject to device designs that can, for example, limit the number of simultaneously activated electrodes. In this experiment, we investigate the effect of temporal skew of individual phosphenes on perception in a simulation of artificial vision, with quantitative measurements made through a reading task. We hypothesized that synchronously presented phosphenes will result in higher performance than asynchronous phosphenes.

Methods
We had normal, sighted subjects perform a simple reading task based on the MNREAD test of visual acuity, viewed through a high-performance simulation of artificial vision. Sentences in the task were presented at varying font sizes (1.1–1.4 logMAR) to measure reading performance under different levels of phosphene temporal noise.

Results
Phosphene temporal noise significantly affected reading performance: higher levels of asynchrony created lower reading scores. A significant negative impact on reading scores was also observed for an overall increase in phosphene latency.

Conclusion
Text perception, and by extension, object binding, is optimized with synchronously presented phosphenes, and degrades with increasing levels of asynchrony. Our observations are important for the design of effective stimulation patterns required for high-fidelity artificial vision.
An implantable control system for visual cortical prosthetics

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Introduction
Serious eye diseases significantly impact the lives of those affected. Eye correction devices and surgical procedures have been developed to address these challenges. However, these do not provide a definite solution for severe eye conditions such as glaucoma. Instead, cortical prostheses have possible solutions. These aim to restore vision by stimulating the visual cortex because stimulation in the cortex produces phosphenes, and thus the vision of light flashes within the visual field. This abstract discusses our progress in developing our custom vision prosthetic system to restore partial vision where the patient can recognize objects by boundaries.

Methods
Our design comprises four modules, 1) headset, 2) subcutaneous control unit, and 3) optogenetic probes driven by 4) our custom ASIC design. The headset with a camera captures incoming visuals (images at a defined framerate) for bio-inspired processing and powers the control unit using wireless power transmission. The processed visuals are then sent (in a compressed form) to the control unit using Bluetooth Low-Energy (BLE). This unit therefore embodies the BLE module, a low-power microcontroller (MCU) and a wireless power receiver with dedicated power management.

Results
The MCU first decompresses these images and then based on the contents of each image dynamically reconstructs the frame map used to drive the ASIC and then the probes. This is done to be sure that the probes operate with an even power distribution to avoid excessive current damage to the tissues. Finally, the control unit transmits the generated frame map to the ASIC, which controls the probes blinking (temporally and spatially) to stimulate the nerves, drives LEDs for optogenetic stimulation, drives electrodes to recording, resulting in closed-loop control.

Conclusion
Preliminary experimental results show that the processed images, which reduce the instantaneous peak power by 30-50%, are ready to be tested in a future controlled environment.
Differences in the non-viral electroporation-based transfection of glial cells in suspension or adherent state

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Introduction
Retinopathy pigmentosa is an inherited retinal dystrophy that leads to blindness. Previous retinal prostheses have had limited efficacy, in part because the remaining retinal layers remodel as the disease progresses. In recent years, gene therapy has emerged as a promising approach to treat genetic disorders. Currently, viral vectors are the main method for gene transfer; however, they also have drawbacks. Here, the non-viral Sleeping Beauty (SB) transposon system was used to transfer the genes encoding yellow-fluorescent protein, pigment epithelium-derived factor (PEDF), and brain-derived neurotrophic factor (BDNF) by electroporation, resulting in stable integration into the cell genome.

Methods
The SB100X transposase plasmid and the corresponding transposon plasmid (1:16 ratio, 420 ng/µl) were introduced into the glioblastoma cell line A-172. Two electroporation devices were used: a capillary-based system for cells in suspension and a system for adherent cells. Transfection efficiency, transgene expression, and cell viability were assessed by flow cytometry, ELISA, qPCR, and a luminescence assay.

Results
The best transfection efficiency (62.4%) for cells in suspension was achieved at 1100 V, 30 ms, and 2 pulses. Increasing the voltage resulted in higher transfection efficiency but lower cell viability. An increase in PEDF/BDNF transgene expression and protein secretion was observed compared to non-transfected cells. For transfection of adherent cells, voltages of 125 V to 275 V were used. A poring and a transfer pulse (+ or +/- polarity) were applied. The best efficiency (4 %) was observed with a poring pulse with + polarity and a transfer pulse with +/- polarity at 200 V for 5 ms.

Conclusion
Transfection of cells in suspension resulted in higher efficiencies than adherent cells, which might be due to a better distribution of the electric field. Nevertheless, transfection of adherent cells helps in further development of intraocular chips with a dual function of electroporation and stimulation.
POLYRETINA restores light responses in blind Göttingen minipigs

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Introduction
Retinal prostheses have shown the restoration of a coarse form of vision in patients affected by retinitis pigmentosa, such as letters discrimination and object recognition. However, despite some progress in retinal prosthetics, several challenges remain open.

Methods
POLYRETINA device exploits photovoltaic wireless stimulation to overcome these challenges. For the preclinical validation of the POLYRETINA prostheses we used blind Göttingen minipigs.

Results
We generated a model of retinal blindness by intravenous injection of iodoacetic acid (IAA) in Göttingen minipigs. Anatomical and physiological alterations were verified using in-vivo spectral-domain optical coherence tomography (SD-OCT), in-vivo evoked electroretinograms (fERGs) and flash visual evoked cortical potentials (fVEP), and postmortem histological assays. Then, we developed a minimally invasive injection procedure to insert the large epiretinal implant into the eye through a 6.5-mm long corneal incision. The epiretinal fixation was achieved using two custom-made stainless-steel retinal tacks. Postoperative echography images showed that POLYRETINA matched the eye curvature with tight adhesion to the retina.

Then, we showed that POLYRETINA restores light-evoked cortical responses at safe irradiance levels in blind Göttingen minipigs unilaterally implanted. We recorded flash electrical evoked potentials (fEEPs) to demonstrate the recovery of light responses in implanted blind Göttingen minipigs. Electrophysiological recordings were performed acutely before (fVEPs) and after (fEEP) POLYRETINA implantation. Recordings before surgery showed no detectable fVEPs induced by light. After POLYRETINA implantation, fEEPs were recovered. Last, postmortem histological assays showed a low level of acute immune response compared to normal minipigs (2 weeks after implantation). The level of immune response was comparable to unimplanted minipigs but treated with IAA. We concluded that POLYRETINA does not worsen the inflammatory state caused by degeneration.

Conclusion
These results indicate that POLYRETINA holds the potential for artificial vision in totally blind patients affected by retinitis pigmentosa.
Towards in-vivo validation of 3D retinal implants: An in-vitro and cadaveric validation

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Introduction
Throughout the last decades, researchers worldwide have been trying to artificially restore vision in blind patients affected by retinal degenerative diseases. Our group has been pushing forward a new generation of retinal implants: Flexible bidirectional microelectrode arrays (BiMEAs), penetrating the retinal tissue for simultaneous recording and stimulation. With the aim of in-vivo trials in mind, this work presents the in-vitro and cadaveric validation of 3D retinal implants.

Methods
Flexible implants are fabricated using thin-film technology and surface micromachining processes. Experiments were carried out with healthy wildtype (WT) rats, and additionally with diseased RCS rats as a model for retinitis pigmentosa. An Open-Sky approach and pars-plana implantation were tested in a cadaveric setting as surgical methods. Resistivity measurements at the implantation site are used to prove successful insertions.

Results
3D flexible implants were successfully tested in ex-planted in-vitro WT and RCS retinae to prove their recording and stimulating feasibility. The resistivity values were mapped to electrophysiological recordings showing spontaneous activity when the electrode was close to the ganglion cell layer and no activity when placed at deeper locations. The resistivity values peak at the OPL/ONL layer with values of 1.68 +/- 0.12 for RCS and 2.89 +/- 0.15 W m (mean +/- SEM) for WT rats. In cadaveric rats and rabbits, the feasibility of an open-sky and pars-plana surgical approach were tested using the resistivity measurements to demonstrate the implantation depth.

Conclusion
Proving the surgical implantation by resistivity measurements in cadaveric settings for healthy and diseased retinae paves the way for future in-vivo validation with 3D retinal implants.
Novel silicon-nitride photonic integrated circuit-based microelectrode array system for in-vitro characterization of retinal samples using high resolution optical stimulation

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**Introduction**
To study the functionality of \textit{in-vitro} prepared retinas, we propose a novel measurement system based on a silicon-nitride photonic integrated circuit (SiN-PIC) technology that allows for optical stimulation of single retinal cells (photoreceptors). SiN-PICs are particularly suitable for the visible light spectrum, where photoreceptor cells are most sensitive. Among other things, they support very compact co-implementation of complex optical and electrical circuits, including wavelength filtering, phase tuning, light distribution, and surface emission from multiple apertures.

**Methods**
In this study, we have developed a passive SiN-PIC integrated with a microelectrode array (MEA) for optical stimulation and electrical recording of retina ganglion cell activity \textit{in vitro}. The SiN-PIC includes an edge coupler to couple light from an external laser source with a central wavelength of 520 nm, a light distribution network to manipulate light propagation within the PIC, and grating emitter-based aperture arrays that scatter light out-of-plane toward the retina sample on the MEA system.

**Results**
Here we present a measurement system based on optical grating emitters that can generate arbitrary illumination patterns using beam focusing with the subcellular beam diameter or beam steering by tuning the input laser source wavelength and using phase shifters. In addition, we use Mach-Zender interferometric (MZI) switches in the light distribution network that actively control light propagation by applying electrical signals to micro-heaters located on the MZI optical switches. We demonstrate the design of the PIC system as well as the specific grating emitters and compare them with measured characteristics.

**Conclusion**
The subcellular resolution and beam steering capability of the PIC-integrated MEA system allow stimulation of single cells in the retina, and thereby enables new possibilities in the study of \textit{in-vitro} retinal samples.
Towards an addressable active electrode array embedded in a flexible implant for stimulating the ganglion cells of the retina

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Introduction:
Retinitis pigmentosa (RP) affects the retina of approximately 1.5 million persons around the world. As RP progresses, the photoreceptor cells degenerate, eventually resulting in total blindness, whereby the state of degeneration is different in each patient. Numerous teams around the world are pursuing individualized technical, genetic, and stem cell strategies. One approach is electronically stimulating the ganglion cells projecting into the visual cortex by an epi-retinal implant. To improve the resolution towards a full vision perception, more than 1000 electrodes would be required. Clearly, it is very challenging to address each microelectrode individually with a conventional wiring method. We are working on an addressable matrix concept towards high-density electrode arrays inside a flexible epiretinal implant.

Method:
A 32x32-crossbar transistor array is fabricated on a silicon-on-insulator (SOI) wafer as a first proof-of-concept. The drains of the transistor array are connected with stimulating electrodes coated with Iridium oxide. The process involves the fabrication of an addressable transistor matrix and stimulation electrodes, backside thinning of the SOI wafer, and transfer of the chiplets into a flexible, multilayer polyimide substrate to integrate the addressable arrays into a flexible foil.

Results:
As a first step, the design and used materials (Polyimide PI2611, Parylene C) are approved by implanting in cadaver eyes. In the first test process, backside etching of the SOI wafer, separation of the silicon part into small chiplets (1x1cm) and then transferring them into a polyimide foil are executed to maintain the flexibility of the implant. Simultaneously, the 32x32 transistor array is also fabricated on an SOI wafer, while its active features are transferred into the flexible foil.

Conclusion:
The main process steps and their challenges for the fabrication of a functional high-density electrode array inside a flexible implant are discussed. Eventually, this work will be the foundation of the next generation of epi-retina implants with enhanced resolution.
Reduced complexity optical phased array for artificial vision goggles

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Introduction
To restore the vision artificially, including the natural stimulation approach, we present a two-device solution: a pair of goggles with Optical Phased Arrays (OPA) combined with a retinal implant chip with a Biocompatible Dense Photodiode Array (BPDA). The OPA generates an image which is neuro-electronically applied to the retina by the BPDA. This approach targets Macular Degeneration (MD) and Retinitis Pigmentosa (RP) patients. Existing Si-photodetector-based implants only benefit fully blind patients. In our two-stage solution, the initial stage RP patients are envisioned to only use goggles and will not require complex implant surgery. However, the fully blind patient will need a chip implant. The OPA scales up low-pixelated image resolution by rapid beam scanning, excites the retina directly without needing intra-ocular amplification, and results in the wireless implant circumventing sclera-crossing.

Methods
The OPA consists in an array of Grating Emitters (GE) tuned by Thermal Phase Tuners (TPT). It is fabricated as a Silicon Nitride (Si3N4) Photonic Integrated Circuit (PIC) that is transparent in the visible spectrum. An optically addressable Liquid Crystal (LC) cell integrated on the top of the OPA enables 2-D beam steering by nonlinear beam mixing.

Results
Conventional OPA technology is not scalable, since TPTs for Si3N4 PICs are large and consume substantial electrical power. Our novel OPA architecture with LC cell makes it scalable by reducing the number of TPTs required for an N×N OPA from N2 to a number that can be as small as 2N in a fully populated array. As a proof of concept, we have designed and sent to fabrication a first OPA with 100 GEs that requires only 32 TPTs.

Conclusion
We have significantly reduced the control complexity of an N×N OPA from N2 to ON TPTs. This integrated photonics advancement directly benefits artificial vision prostheses by resulting in realizable goggles.
Engineering a biohybrid neural interface for vision restoration.

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Introduction
Blindness caused by damages to the optic nerve is currently an irreversible condition. To restore functional vision in these patients, direct stimulation of the primary visual centers in the brain is required. The lateral geniculate nucleus (LGN) would be an ideal stimulation target since it receives direct retinotopic input from most retinal ganglion cells (RGC) of a healthy retina. However, the LGN is located deep inside the brain and therefore hard to access. Moreover, current deep brain stimulation electrodes do not have the stimulation resolution required to restore any functional vision.

Methods
Here, we propose a novel implantable biohybrid neural interface with the goal of restoring functional vision in the blind without an optic nerve. Our interface uses living on-chip grown retinal neurons as relays to convert electrical signals from a stretchable microelectrode array into synaptic stimulation of a thalamic target tissue. This approach overcomes the limitations of current deep brain stimulation electrodes, which have a low resolution and often cause an inflammatory foreign body reaction that reduces their functionality over time.

Our interface is based on a stretchable microelectrode[1] array onto which we align axon guiding microfluidic structures that enable unidirectional guidance and merging of axons to form an artificial optic nerve.

Results
We show that retinal neurons seeded onto our device form an artificial optic nerve that is several mm long and can transit from the device into a matrigel-based target structure in vitro. Moreover, we present the first in vitro data on how our device[2] will enable synaptic modulation of thalamic target neuron activity in vitro.

Conclusion
To conclude, our preliminary results demonstrate the feasibility and functionality of our biohybrid device in vitro, which paves the way for future in vivo studies.
Stimulating and recording the retina from the inside

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Introduction
Visual prostheses that stimulate electrically the retina have allowed partial vision restoration in blind patients with retinal degenerative diseases. Nonetheless, current retinal implants do not give feedback on the efficiency of electrical stimulation therapies and do not adjust to the remodelling processes of the diseased retina. To improve the efficiency of electrical stimulation, this work builds upon the bidirectional approach proposed before [1] and characterizes further the capability of evoking electrical responses from the inside of the retina with different current-controlled stimulation configurations.

Methods
Parylene-C-based intraretinal probes [2] with four 145-185 µm-long penetrating shanks, each one containing three 15-µm diameter-recording electrodes (REs) and one 25-µm diameter-stimulating electrode (SE) are used in vitro in explanted healthy (WT) and diseased rd10 mouse retinae. Intraretinal placement comprises SEs at the inner plexiform layer and REs along the inner retina and ganglion cell layer. Monopolar/bipolar, biphasic, and first cathodic vs. first anodic pulses were tested with stimulation currents between ± 0.5–10 µA and pulse widths between 0.1–5 ms.

Results
Simultaneous recording and stimulation inside the retina are feasible with charge injection thresholds as low as 0.05 nC. Excitatory and inhibitory, monotonic, non-monotonic, and saturated neural responses, are captured upon electrical stimulation. Electrically evoked potentials with latencies between 5–25 ms to 150 – 400 ms are captured, implying therefore indirect responses of the retina. Furthermore, the excitability of WT and rd10 retinae is increased for both when using bipolar biphasic first-anodic charged balanced pulses. Moreover, the use of bipolar stimulation uncovered the possibility of significant responses within single neuronal columns.

Conclusion
Multisite intraretinal probes allow simultaneous recording and electrical stimulation of the retina, exposing electrically evoked neural responses using electrodes with single-cell dimensions and low-charge injection thresholds.

FEM Model of a hexagonally arranged Needle Electrode Array with Local Return for a Retinal Implant

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Introduction
With current retinal implants, the spatial resolution of stimulation is still a major technical challenge to create sufficient visual perception. This is linked to a limited electrode density, high cell distance and high crosstalk between adjacent electrodes due to a limited field confinement. To enable a localized stimulation knowledge about the electrical field is necessary. Here, we present a simulation model where a simplified cellular model is stimulated by an electrode array to compare the field confinement of different electrode configurations in a more natural way.

Methods
The simulation consists of a time-dependent 3D FEM model in Comsol Multiphysics. The Poisson equation is solved for the extracellular and intracellular space respectively. A biphasic pulse is injected at a needle electrode, which generates the electric field for stimulation. In this field a simplified cell consisting of axon and soma is modelled. At the cell boundary the Hodgkin Huxley kinetics are implemented to describe the transmembrane voltage as a set of ordinary differential equations with voltage depended ion channel conductivities. This model is used to compare different electrode configurations of an array with different return electrodes. Especially local flat electrodes and needle return electrodes are investigated.

Results
Based on the transmembrane voltage the necessary threshold for triggering action potentials (AP) as a function of distance and stimulation current. Furthermore, it can be shown that there is very low field confinement from one pixel into adjacent pixels with only a common return. With local needle electrodes the maximum range for triggering AP is improved to only half of the pixel pitch.

Conclusion
The implemented model can be used to compare different electrode configurations in a better approximation to nature. Based on this, the positive influence of local return electrodes in the tissue can be shown, which is becoming increasingly important especially for high electrode densities.
Modeling the Effects of Realistic Electrode Geometries on Layer-5 Pyramidal Cell Microstimulation

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Introduction
Intracortical microstimulation (ICMS) is a technique for restoring lost sensory perception, such as vision and touch, and for relieving the symptoms of certain neurological disorders. To recreate complex firing patterns, ICMS devices should have a large number of small electrodes that can stimulate at high spatial resolution. This work aimed to use computational modeling both to study neuron responses to intracortical electrical stimulation and to compare various stimulating electrode geometries (carbon fiber electrode, Utah electrode, and an ideal point source) with realistic 3D morphologies.

Methods
A biophysical model of a cortical neuron was combined with a volume conductor model of the head, with several realistic electrode designs included. The neuron model is a multi-compartmental conductance-based cable model of a pyramidal neuron with realistic 3D morphologies from Blue Brain library. The head volume conductor is finite element model of a head with four layers. Anodic-first, cathodic-first and cathodic-first asymmetric charge balanced biphasic single pulses were used with pulse widths of between 50 µs and 2 ms. Electrodes were placed at 80 different locations around the pyramidal neuron in a 3D grid. Threshold in µA for a given pulse width was calculated at each electrode location.

Results
The average threshold difference between a carbon fiber electrode and an ideal point source was less than 5.3%, 4.1% and 4.2% for anodic-first, cathodic-first and cathodic-first asymmetric charge balanced biphasic pulses respectively. Utah electrode had thresholds 38%, 37% and 38% times higher than the carbon fiber electrode. Moreover, cathodic-first pulses consistently activated the neuron with lower thresholds compared to anodic-first pulses. It was also seen that threshold current is directly proportional to the distance between the electrode and action potential initiation point. Chronaxie and rheobase calculations supported findings related to threshold predictions. Utah electrode thresholds predicted by the model are similar to clinical findings.

Conclusion
This study demonstrates the importance of using realistic electrode geometry for modeling ICMS. Additionally, the use of realistic neuron models with 3D morphologies are promising instead of simpler models.
Factors underlying sensitivity differences to high frequency stimulation across RGC types

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Introduction
To improve psychophysical outcomes with retinal implants, it will be necessary to better reproduce the complex signaling patterns used naturally by the retina. Re-creating such patterns with a prosthesis is challenging however as neurons are heterogeneous and closely spaced and therefore individual cell types need to be selectively targeted. Unfortunately, thresholds to conventional pulsatile stimulation are similar between different types of RGCs. However, different RGC type exhibit sensitivity differences to stimulation delivered at higher rates, e.g., 2000 Hz. The factors shaping these differences are not well understood and are investigated here.

Methods
A combination of cell-attached and whole-cell patch clamp recordings were used to correlate spiking and voltage responses to both low and high frequencies of stimulation. A computational model was then developed that allowed the biophysics underlying observed responses to be examined.

Results
Low frequencies produced hyperpolarization of Vm regardless of amplitude while higher frequencies tended to produce hyperpolarization at lower amplitudes but depolarization at higher amplitudes. Conditions that produced hyperpolarization also generated robust spiking while those that produced depolarization, especially at stronger levels, resulted in weaker spiking responses. Modeling revealed that the depolarizing vs. hyperpolarizing shifts arose from changes in the relative contributions of voltage-gated sodium vs. potassium channels. Interestingly, ON cells enter depolarization block at a more depolarized level of Vm than OFF cells. While this suggested that OFF cells should reach depolarization block at a lower level of stimulus amplitude, the level of depolarization produced by a given level of HFS was higher in ON cells, with the result that the peak responses of ON cells occurred at lower stimulus amplitudes than those of OFF cells.

Conclusion
These results suggest that previously reported non-monotonic responses arise from depolarization block and that the sensitivity differences between ON and OFF types arise from differences in the properties of intrinsic ion channels.
Assessment of retinal function in patients with advanced retinitis pigmentosa (RP) using a combination of transcorneal electrical stimulation (TES) test and square localization test

T Morimoto - needs to be confirmed

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Purpose: Evaluating visual function in advanced RP patients for retinal prosthesis candidacy is challenging using conventional ophthalmologic exams. This study investigates the combined effectiveness of TES and localization tests in evaluating visual function in advanced RP patients.

Methods: Eighteen right-handed patients (10 men, 8 women) with advanced RP, mean age 64.4 ± 11.5 years, participated. Visual acuity ranged from hand motion to bare light perception. Informed consent was obtained, and the study was approved by the Ethics Committee of Osaka University Hospital. TES used a stimulating electrode, measuring electrical current thresholds for initial phosphene perception. The square localization test involved touching white square targets with a 10° visual angle on a monitor screen, measuring the average absolute deviation. Tests were performed one eye at a time, focusing on right eye results. If the right eye couldn't perceive phosphenes, left eye results were used. Correlations between visual acuity, phosphene threshold, and localization test results were calculated.

Results: The mean threshold for initial phosphene perception was 1.25 ± 0.6 mA (±SD). Mean absolute deviation was 16.0 ± 6.7°. No significant correlations were found between visual acuity, TES results, and localization test results. Patients were divided into four groups based on a threshold of 1 mA and a deviation of 15 degrees. The group with deviation <1 mA and >15 degrees showed the highest potential for visual function improvement with a retinal prosthesis.

Conclusions: Combining the TES and localization tests can effectively evaluate visual function and identify suitable retinal prosthesis candidates among advanced RP patients where traditional ophthalmologic exams are insufficient.
Early functional outcomes for the first human with the Intracortical Visual Prosthesis (ICVP)

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Introduction
The ICVP is a novel device for creating visual percepts in blind individuals. We tested the hypothesis that the implantee could discriminate horizontal and vertical orientations of smallest gratings of Berkeley-Rudimentary-Vision-Test (BRVT).

Methods
The ICVP consists of multiple wireless floating microelectrode arrays (WFMAs), each with 16 stimulating electrodes. Twenty-five WFMAs were implanted in the right occipital visual cortex of a participant with only bare light perception in an FDA-approved Phase 1 clinical trial (NCT04634383). Groups of electrodes within WFMAs were evaluated across 9 months to measure current thresholds and phosphene positions and persistence (at 200 Hz, 200 µs cathodic phase duration and currents up to 60 µA). An off-the-shelf pair of glasses with an integrated camera was used for stimulation with 6 selected WFMAs. During 2 days of exploratory testing, the 50 M BRVT grating was tested at 25 cm in front of the participant (0.15 cycles/degree) in either horizontal or vertical orientation, with 30 balanced, randomized forced-choice trials.

Results
Thresholds under 60 µA were found for 233 electrodes. Thresholds varied across days, but remained stable on average. Of the 6 WFMAs used for camera testing, 4 produced phosphenes within a 4° cluster centered 4° below and left of fixation, and the others located 4° below and 20° left of the central cluster. Phosphene sizes varied within 0.3–6° across, generally increasing in size with distance from fixation. The participant correctly determined the orientation of the 50 M grating in 27/30 trials (p < 10⁻⁵, binomial test), corresponding to an acuity of 2.3 logMAR or better, responding within 24 s on average (range: 6–91 s). In recent tests, the participant successfully placed checkers pieces on magnetic boards, located small objects and walked a short mobility course.

Conclusion
In the first human-implanted ICVP system, patients achieved a grating acuity of 2.3 logMAR or better.
Pharmacological suppression of pathological oscillations in the retinitis pigmentosa mouse model rd10

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Introduction:
In the rd10 mouse model, an intrinsic oscillatory activity is observed at a frequency of 3-6Hz in the local field potential and retinal ganglion cell (RGC) firing that compromises the efficiency of electrical stimulation. It was suggested that the loss of photoreceptor-mediated glutamatergic input causes depolarization of ON cone bipolar cells and through electrical coupling, also of AII amacrine cells (AII), allowing the activation of voltage-gated Na⁺ channels and oscillations. As oscillations compromise the stimulation efficiency, in this study, we seek to identify approaches to abolish oscillations.

Methods:
In vitro recordings from retinas of 5-6 months old C57BL/6J wild-type (wt) and rd10 mice were obtained using multi electrode arrays. The effect of different pharmacological drugs on the oscillatory activity was determined.

Results:
Blocking excitatory ionotropic glutamate receptors or decoupling gap junctions abolished oscillations. However, both methods reduced RGC spiking, indicating that RGCs might be less excitable. The inhibitory neurotransmitters GABA and glycine also abolished oscillations, probably by shifting the AII membrane potential to a range that does not allow oscillations.

Oscillations were abolished by activating specifically GABA_A receptors using benzodiazepines and THIP, but not by targeting GABA_B receptors or by increasing the GABA concentration in the synapse by blocking either GABA re-uptake or GABA catabolism.

Conclusion:
Our data indicate that the activation of GABA_A receptors abolishes oscillations. Clinically approved GABA_A receptor agonists like benzodiazepines would be suitable candidates to improve stimulation efficiency of a retinal implant.
Transcorneal Electrical Stimulation: An Electroceutical for Retinitis Pigmentosa

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Introduction

Retinitis pigmentosa (RP) comprises a group of inherited retinal diseases associated with progressive visual loss. Currently, there is no standard treatment available. To preserve or restore vision, gene-replacement therapies, stem cell therapies, optogenetic therapies and electronic implants are under development. An alternative treatment route is neuroprotective therapy using transcorneal electrical stimulation (TcES). In an exploratory analysis, the hypothesis of a current-strength dependent slowing of loss of visual field area (VFA) by TcES was tested (Stett et al., Trans. Vis. Sci. Tech. 2023).

Methods

The data for the a posteriori analysis come from a study conducted at the University of Tübingen from 2011 to 2014 (Schatz et al., IOVS, 2017). In the randomised controlled trial (clinicaltrials.gov: NCT01837901), 52 RP patients were monocularly stimulated with biphasic current pulses (pulse duration 5ms/5ms, amplitudes 0.0 to 1.0 mA, 20 Hz) with the OkuStim system once a week for one year. In the reanalysis the percentage reduction in VFA (measured with semi-automatic kinetic perimetry) at the end of treatment was compared with the untreated contralateral eyes and correlated with current amplitude.

Results

After one year, the TcES-treated eyes had a mean VFA loss of 2.1%, while the untreated contralateral eyes had lost 5.8% and the placebo-treated eyes had lost 7.5%. Thus, the loss of VFA was 64% less in the stimulated eyes than in the untreated contralateral eyes ($p = 0.013$) and 72% less than in the placebo-treated eyes ($p = 0.103$). The slowing effect correlated linearly with current amplitude ($p = 0.047$), and the visual field was stable on average in patients receiving 0.8 - 1.0 mA.

Conclusion

TcES is an electroceutical that can slow down the progressive VFA loss in RP. Further studies are needed to confirm its long-term effectiveness and to elucidate the neuroprotective mechanism of action of TcES treatment.
Reading text works better than watching videos to improve acuity in a simulation of artificial vision

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Introduction
Simulations of artificial vision are used in visual prosthesis design, with normal-sighted subjects performing psychophysical tasks to give insight on capabilities and the trajectory of improvement over time. Previously, we observed substantial training effects in a longitudinal study of daily practice with a reading task. Here, we sought to quantify and compare the training effects in a more passive task, with the expectation that activities like watching videos are likely to dominate post-implant experience.

Methods
Eight subjects used a simulation of a thalamic visual prosthesis with 1000 phosphenes to watch episodes of classic American television in daily, 25-minute sessions, for a period of about one month (21 total episodes) while we periodically measured their reading accuracy and reading speed through a simple reading task using six font sizes (logMAR 0.9-1.4). Sigmoidal fits to reading task performance across font sizes allowed estimation of equivalent acuity that was longitudinally tracked. A carefully designed schedule allowed independent extraction of the learning effects of video viewing from the interleaved reading tests.

Results
Population reading accuracy improved significantly with passive experience leading to a 0.15 ± 0.05 logMAR visual acuity change. When normalized by the amount of time spent training, the per-minute improvement was about one third the rate of the interleaved reading tests. Population reading speed, on the other hand, did not change significantly over the duration of the experiment.

Conclusion
While passive viewing tasks may be useful for post-implant rehabilitation, active tasks are likely to be substantially more effective.
Progress on Electronic Intraocular Visual Prosthesis for Corneal Blindness

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Introduction
An intraocular implant with wireless video reception and projection function provides a solution to intractable corneal blindness free from the limitations of current treatments which require tissue transplantation. Since demonstration of our wired proof of concept, we have continued to refine the design to produce a wireless and completely intraocular device 100x smaller than prior.

Methods
We designed a completely intraocular implant which consists of a laser light source, two micromirrors and associated optics and electronics to allow for wireless reception of video and power and projection of imagery in focus approximately 16 mm away from device. Implantation surgery was demonstrated in cadaveric eyes.

Results
We completed benchtop demonstration of the optoelectronic system including 1x size lens and projection hardware. The device is a short cylinder approximately 10mm in diameter and 4 mm in thickness. Its weight is approximately 250 mg. These are similar to that of the natural crystalline lens. Power usage under 150 mW. Projection pitch is 10 um which corresponds with 20/40 image quality. We are working on custom ASIC to complete device encapsulation and start animal safety and efficacy experiments.

Conclusion
A completely intraocular projection visual prosthesis is a potential treatment for intractable corneal blindness, a condition which affects millions of people.
A window of opportunity for localized epiretinal electrical stimulation?

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Introduction:
Electrical retinal implants have been employed for partial restoration of sight in the past. However, although partially successful, the visual percepts restored so far have not been proven useful enough in the day to day life of patients. Therefore, optimal stimulation protocols avoiding stimulation at remote positions are still highly needed. In this sense, achieving preferential and local activation of retinal ganglion cells is assumed to provide a sufficiently high acuity of the visual percept.

Methods:
In this study, we search for a window of opportunity, which efficiently stimulates retinal ganglion cell (RGC) somata while avoiding activation of axons of passage in ex vivo retinas of a photoreceptor-degenerated (rd10) adult mouse model of retinitis pigmentosa. We make use of a CMOS-based microelectrode array which allows for continuous electrical stimulation and simultaneous electrical recording of RGC spiking activity. The CMOS-MEAs used here enable precise localization of RGC somata and of axons at a spatial resolution of 16 µm. Sinusoidal electrical stimulation was applied to electrodes positioned underneath the cell soma or underneath the axons.

Results
We were able to identify RGC spiking during electrical stimulation. Variation of the sinusoidal stimulation frequency and amplitude allowed us to identify cell-specific stimulus-response relations and to identify a window of opportunity for stimulation of the cell somata while avoiding axons.

Conclusion:
Our results indicate specific parameters, i.e. a window of opportunity which might be used in future to avoid axonal stimulation in epiretinal prostheses.