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# Proceedings of the 2nd International Conference on Progress in Electrically Active Implants for Tissue and Functional Regeneration (ELAINE 2024)

Elaine

electrically active implants

SFB 1270

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Proceedings of the

# Conference on Progress in Electrically Active Implants

## Tissue and Functional Regeneration
## ELAINE 2024





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# Contents

# Introduction

In March 2024, the 2nd edition of the International Conference on Progress in Electrically Active Implants for Tissue and Functional Regeneration (ELAINE 2024) was held at the University of Rostock, Germany. We were delighted to bring together 73 esteemed researchers, scholars, and professionals in the Hanseatic City of Rostock from 20 to 22 March 2024. This interdisciplinary event served as a hub for discussing the latest advancements in therapeutic and regenerative electrical stimulation, implant development, energy harvesting, and material design.

This year's conference took place in two distinguished venues at the University of Rostock; the historic main building's auditorium and the modern facilities of the Campus Südstadt. The program offered a diverse and enriching exchange of ideas, spanning from multi-scale modelling and simulation to *in vitro* and *in vivo* studies in bone, cartilage, and deep brain stimulation.

The conference featured four dedicated sessions:

- **Session I** – Multiscale Modeling for Electrically Active Implants and Implant Reliability
- **Session II** – Technological Developments and Future Directions for the Development of Electrically Active Implants
- **Session III** – Role of Molecular Signaling in Biophysical Stimulation for Regenerative Medicine
- **Session IV** – Innovations and Therapeutic Applications of Neurostimulators for Deep Brain Stimulation and Neuronal Disorders

Additionally, a Poster Session provided further opportunities for discussion and collaboration on emerging research topics. Beyond the scientific program, participants engaged in social events, including a Social Evening with DJ Paule Paulsen and an Excursion on a boat featuring live music by saxophonist Lydia Harder. These activities fostered networking and a sense of community among attendees. Postdoctoral researchers of the Collaborative Research Center ELAINE proudly organised this conference. We extended our deepest gratitude to the organising committee, contributors, and sponsors who made this event possible. We also appreciated the enthusiastic participation of our attendees, whose dedication continued to drive innovation in the field. On behalf of the organising committee, we warmly welcomed everyone to the conference and looked forward to a productive and inspiring exchange.

*The ELAINE 2024 Conference Committee*

# Keynotes

## 2.1 Bergita Ganse

### Smart Implants for Bone Fracture

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Delayed healing and non-union of bone fractures are massive socio-economic problems. The Werner Siemens Foundation funds the interdisciplinary research project "Smart Implants", based at Saarland University, with 8 million Euros. The project's aim is to develop new implants for bone fracture healing that have sensing and acting capabilities to track the healing progress and to actively stimulate and improve fracture healing in a control loop. To reach this goal, the use of shape memory alloys such as nitinol wires has been explored to change the implant stiffness and to stimulate the fracture gap by axial micromovement. Extensive multimodal motion analyses and the use of AI algorithms have enabled the development of parameters that help to predict healing through implant-based live sensor data analyses. In addition, force combined with computed tomography data in finite element analyses was used for implant design and to determine the needed micro-movements to reach ideal strain values in different fracture types. The team has also developed new methods to measure fracture-healing progress in human patients *in vivo*, including non-invasive perfusion measurements.

Bergita Ganse is a professor and head of the Werner Siemens Foundation Endowed Chair for Innovative Implant Development (Fracture Healing) at Saarland University in Germany. In her talk, she will explain the work progress and achievements four years into the project. She will also address current challenges, considerations and ideas to lay a foundation for fruitful discussions with and among the congress participants to go beyond biomechanics into physiology and future collaborations.

## 2.2 Julia Glaum

### Microstructural design and chemical stability of piezoelectric BaTiO3 ceramics in the context of load-bearing biomedical applications

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**Introduction:** The ability to convert an electrical field into a mechanical perturbation and vice versa makes piezoelectric materials interesting for fundamental studies and industrial applications. In recent years, research towards biomedical applications, as for bone tissue repair or *in vivo* sensors, has gained significant momentum. However, the boundary conditions these materials must meet to function in an *in vivo* environment differ greatly from their established industrial applications. Among the many facets of biocompatibility, I will focus on the microstructural design and chemical stability of piezoelectric BaTiO3 ceramics intended as bone replacement material.

**Methods:** To combine the functional properties of piezoelectric materials with the mechanical properties of medically accredited metals, we employed Aerosol Deposition as a coating method. For the development of porous structures beneficial for tissue ingrowth, we utilized freeze casting and additive manufacturing. Chemical stability was tested via Inductively-Coupled-Plasma Mass-Spectrometry.

**Results:** Aerosol-deposited coatings show very good substrate-coating adherence. Subsequent heat treatments lead to an improvement of the dielectric response, as well as the onset of ion diffusion towards the coating

surface, causing significant grain growth. Freeze casting and Additive Manufacturing of capillary suspensions provide versatile methods to tailor the porosity – and, with this, the functional properties. Even for highly porous structures, solid piezoelectric performance is observed. Exposure to water-based liquids initiates the dissolution of mainly barium. Dissolution kinetics are very fast within the first hour and slow down afterwards, hinting towards a transition to a diffusion-controlled process.

**Conclusion:** Piezoelectric ceramics can be manufactured in a broad variety of ways, e.g., as functional coatings on medically accredited materials or as porous structures that can allow tissue ingrowth. This makes them very adaptable for many types of applications. The dissolution of Ba upon contact with aqueous media must be taken into account during implant design to allow the development of safe and stable implant materials.

## 2.3 Sahba Mobini

### Novel Applications of Low-Intensity Bioelectrical Stimulation

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The past two decades have witnessed a growing focus on studying the fundamental role of physical forces (e.g. mechanical, electrical, and architectural cues) in controlling biological processes with the aim of harnessing the power of cell therapy.

Electro-modulation of therapeutic cells has been considered a promising strategy to guide cellular responses, which gives rise to numerous applications in regenerative medicine. Several attempts have been made to demonstrate the relevance of electro-modulation in preclinical and clinical settings. Both direct approaches, where electrical stimulation (ES) devices are implanted to foster tissue regeneration and integration, as well as indirect approaches, where ES is employed *in vitro* to prime therapeutic cells before implantation, have been tested.

In this presentation, I will review the primary accomplishments and challenges associated with the application of ES in regenerative medicine, incorporating insights from our laboratory. I will delve into current methodologies involving ES, exploring their role in cell differentiation, tissue remodelling, and the cultivation and maturation of CNS organoids. Lastly, I will introduce innovative and promising applications, specifically highlighting the use of electrical stimulation in manipulating the cell secretome.

## 2.4 Jens Volkmann

### Spatiotemporal Retuning of Motor Disease Networks by Deep Brain Stimulation

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In recent years many brain disorders have been reinterpreted from a network perspective, where motor and non-motor symptoms can be characterized as dysfunctions in task-specific brain circuits. This paradigm shift from local effects to distributed network alterations allows a unifying pathophysiological classification of neurological and psychiatric symptoms and, importantly, the development of a common approach for network-specific neuromodulation therapies. Our Transregional Collaborative Research Center TRR295 was launched in July 2020, with the overarching goal of improving the treatment of brain circuit disorders by retuning abnormal network activity using neuromodulation. The founding hypothesis of TRR295 was that neuromodulation therapies allow brain signalling to be retuned and motor function to be restored by either eliminating pathological network activity, enhancing normal interareal communication, or activating compensatory circuits. In the long term, we propose that through a better understanding of the neurobiological basis of abnormal network communication in brain disorders, our approach will lead to individualized, symptom-specific, and brain state-adaptive neuromodulation of motor and non-motor disorders.

Significant progress has been made in defining the functional anatomical networks underlying specific motor symptoms in common movement disorders. More recently, the focus of research has shifted to the dynamic nature of network interactions, plasticity mechanisms, and the durability of state changes induced by neuromodulation. Neurophysiological biomarkers of motor symptoms have been characterized in space and time using functional connectivity measures in patients with deep brain stimulation (DBS) therapy and in rodent models of disease. Within the TRR295 three milestone achievements allow us to explore motor network dynamics with enhanced spatiotemporal resolution: (i) simultaneous cortical and subcortical human recordings using subdural strips and multisegmented DBS electrodes; (ii) chronic neuronal recordings from sensing-enabled DBS devices; (iii) chronic recordings in rodent models of PD and dystonia that extended over the entire disease trajectory, from symptom onset to the advanced disease state. The latter now provides a platform for validating dynamic interventions (e.g., patterned for adaptive stimulation) in preclinical disease models, and for refining the timing of intervention before entering a clinical trial phase.

In this lecture, I will outline how deep brain stimulation will benefit in the future from a better definition of temporal and contextual frameworks for targeted interventions. We strongly believe that multimodal prediction algorithms – informed by imaging data, individual chronic electrophysiological signatures acquired by out-of-hospital, long-term recordings, and objective symptom assessments using wearable motion sensors or other kinematic measures – will help to tailor neurostimulation parameters to the needs of individual patients in everyday life. As a consequence, DBS is currently undergoing a transformation from open-loop static informational "lesioning" of motor symptom circuits towards augmentative neuromodulation through a highly dynamic, personalized brain-computer interface technology.

# Talks

## 3.1 Highly electrically conductive PEDOT:PSS films via layer-by-layer electrostatic self-assembly

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The surface coating of an implant should be an adequate bio-interface and promote cell adhesion and proliferation. To support health, the implant should be able to transport electrical impulses. The Layer-by-Layer (LbL) method – the sequential adsorption of oppositely charged macromolecules or nanoparticles – has proven effective in coating a surface. Polyelectrolytes are poor at conducting charges; therefore, electrically conductive nanoparticles are required. PEDOT:PSS nanoparticles are used. LbL films are built from polyanion PEDOT:PSS and polycation polydiallyldimethylammonium (PDADMA) by dip coating and a flow cell. The film prepared with flow cell exhibits lower roughness and constant electrical conductivity (230 kS/m), regardless of the number of PEDOT:PSS bilayers deposited. Films prepared with dip-coating have lower conductivity (26 kS/m), and greater roughness. However, the electrical conductivity is constant (230 kS/m) and independent of the number of deposited PEDOT:PSS/PDADMA bilayers. The coating exhibits ohmic behaviour. By clever choice of the coating method and the number of bilayers, the sheet resistance can be tuned by two orders of magnitude.

**References:**

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# 3.2 Identification of non-motor symptoms in an α-synuclein-overexpressing rat model of Parkinson's disease

***Hanna Weber***[1]***, Meike Statz***[1]***, Sarah Pfeisinger***[1]***, Alexander Storch***[1,2,3]***, Mareike Fauser***[1]

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**Introduction:** Parkinson's disease is the second most prevalent progressive neurological disorder in humans with accumulation of the α-synuclein protein as a critical initiation of the disease. The development of a novel transgenic rat model expressing the entire human SNCA sequence in Sprague-Dawley rats provides an opportunity to expedite research in the realms of symptomatic progression and symptom control. Prior to embarking on additional experiments, it is imperative to thoroughly characterize this animal model. This project aims to characterize non-motor symptoms in the α-synuclein-overexpressing rat model of Parkinson's disease (SNCA rats) to identify the course of symptom development in this model. The results will contribute to a better understanding of disease progression in this model to optimize age selection for subsequent research questions.

**Methods:** Specific behavioural tests were conducted to identify various non-motor symptoms in SNCA rats. The Light/Dark Box Test was employed to investigate anxiety-like behaviour, the Sucrose Preference Test examined (an)hedonic behaviour, while the Buried Pellet Test assessed olfactory function in SNCA rats. Additionally, histological studies were conducted to determine the progressive degeneration in the dopaminergic system in this model.

**Results:** Significant differences between wild-type and SNCA animals were observed starting at the age of nine months. For instance, increased anxiety in the animal model was discerned. Histological analyses revealed a significant dopaminergic degeneration in the nigrostriatal system as late as at the age of twelve months.

**Conclusion:** The model is suitable for research questions regarding non-motor and early motor symptoms when utilizing rats from the age of nine months onwards.

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## 3.3 OSS-DBS v2.0: Towards a realistic volume conductor model for deep brain stimulation

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**Introduction:** Deep Brain Stimulation (DBS) has emerged as an effective treatment for Parkinson's Disease, dystonia, Alzheimer's disease, and other neurodegenerative disorders. However, the optimal selection of targets and stimulation parameters remains challenging [1]. Computational models are essential to address these challenges. They can improve our understanding of the underlying mechanisms and help to optimize preoperative planning and postoperative therapy, including stimulation device programming. This requires reliability, patient-specificity, and efficient computation.

**Methods:** Our open-source software, OSS-DBS v2.0, integrated into the Lead-DBS v3.0 framework [2], enhances handling, accuracy, and efficiency. Utilizing the finite element method, OSS-DBS v2.0 accurately computes the electric field induced during DBS by solving the electro-quasistatic approximation of Maxwell's equations. Implemented with the open-source Python package NGsolve [3], medical imaging data is mapped into the computational domain to create a complex volume conductor model of the brain. Different meshing strategies, including local and adaptive refinement, are used to create a precise solution while maintaining computational efficiency. The selection of effective solvers and preconditioners paired with shared-memory parallelization allows for efficient use on personal computers and high-performance clusters.

**Results:** These improvements enable the exploration of large parameter spaces for individual patients within a reasonable time. This includes quantifiable outcomes like the Volume of Tissue Activated (VTA) or detailed Pathway Activation Models (PAM) for specific fiber tracts. Whereas the calculation of a VTA takes less than one minute, the more complex PAM for 4873 axons took about four minutes (Intel(R) Xeon(R) Gold 6136 CPU @ 3.00 GHz).

**Conclusion:** OSS-DBS v2.0 is a valuable tool that provides insights into DBS and estimates the stimulation effect on neural tissue with high accuracy and computational efficiency. Its applicability to different clinical scenarios makes it a valuable tool for researchers and clinical users.

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[3] Joachim Schöberl. "C++ 11 implementation of finite elements in NGSolve". In: *Institute for analysis and scientific computing, Vienna University of Technology* 30 (2014).

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## 3.4 Challenges in electrical stimulation of human stem cells

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**Introduction:** The complex field of electrical stimulation (ES) of cells is a rapidly expanding area of tissue regeneration research. Despite numerous studies, a clear dose-response relationship has yet to be established. This is crucial for the successful application of electrical stimulation in therapy. Electrical stimulation combined with an implant could be an alternative for treating critical bone defects. To this purpose, basic laboratory studies are needed to investigate the effects of electrical stimuli on cells, but the methodology faces many challenges.

**Methods:** Our method of electrical stimulation is constantly being refined and improved to achieve the most reproducible results possible. In addition to an integrated measurement system, a new electrode has been developed for stimulation experiments on human stem cells in a homogeneous electric field (AC/20 Hz/sinusoidal waveform). The gold electrodes, in the form of a plate capacitor, will be studied in laboratory experiments under technical monitoring and tested in special 3D-printed chambers. Biological analyses, such as the investigation of cell metabolic activity or cell differentiation, will allow conclusions to be drawn about the effectiveness of the electrical stimulation. The parameter analysis will help to identify ideal electrical stimulation conditions for developing an electrically active implant system to treat critical mandibular defects.

**Results & Conclusion:** Initial investigations with a titanium electrode in rod form under technical real-time monitoring during stimulation experiments have shown that the resulting current (from applied $1\,V_{rms}$, $2\,V_{rms}$, $3\,V_{rms}$) does not behave linearly. The formation of a double layer at the electrode interface, which has a major effect at low frequencies, creates impedances that cannot be detected without an integrated measurement system. Continuous monitoring of the electrical parameters (voltage, current, impedance, phase shift) increases the reproducibility of ES experiments and provides transparency, but also shows the limitations of the system. A new electrode configuration has, therefore, been developed and tested. This new development allows cells to be stimulated in a homogeneous, controllable electric field. It will be used in the future to learn more about the effects of electrical stimulation on stem cells.

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# 3.5 Numerical modelling and simulation of electro-stimulating bone implants for maxillofacial and orthopaedic applications

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**Introduction:** The development of electro-stimulating implants to regenerate large bone defects in maxillofacial or orthopaedic applications is a key aspect of the SFB 1270/2 ELAINE. Critical-size defects and non-unions require advanced surgical or therapeutic measures to achieve bone regeneration. Electrical stimulation, which mimics the naturally occurring electric fields in bone as a bioelectric material, can act as an adjunct to these approaches and improve bone regeneration.

**Methods:** Finite element simulations are conducted on 3D models of large bone defects in the lower jaw and the femur. Our study is based on the hypothesis that sinusoidal electric fields between 5 V/m and 70 V/m at a frequency of 20 Hz are beneficial for bone regeneration, as suggested in the literature. By using a homogenisation approach that ignores bone microstructure in favour of modelling uniform cortical and cancellous bone, we have confined the analysis to the mesoscale. Uncertainty quantification methods are utilised to determine the most influential parameters within the numerical model.

**Results:** The numerical models serve to identify and optimise feasible implant designs for their respective application areas. The electrode geometry parameters and the stimulation voltage are optimised to achieve a maximum volume of beneficially stimulated tissue for a critical-size defect in the mandible and a nonunion in a femoral bone, respectively. Furthermore, the findings will support assessing the validity of the hypothesised beneficial field threshold by numerically reproducing the electrostimulation setup from the literature that was the basis for this threshold.

**Conclusion:** This study is a significant advancement in designing reliable electro-stimulating implants for bone regeneration, as it explores the corresponding electric field distribution and recommends appropriate stimulation parameters.

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## 3.6 Data-driven 3D reconstruction for absolute electrical impedance tomography

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**Introduction:** The application of deep learning (DL) methods for absolute electrical impedance tomography (EIT) image reconstruction has increased significantly. The reason for this is that it offers advantages over numerical methods. This contribution provides a proof of concept for absolute 3D imaging. The final reconstruction model consists of a variational autoencoder (VAE) and a mapper.

**Methods:** To reconstruct the conductance distribution, the ill-posed nonlinear inverse EIT problem is solved using a combination of a VAE and a mapper. Experimental data is collected using a Sciospec-EIT device, wherein an acrylic glass ball is positioned at various locations within a phantom tank. The phantom tank has two levels of 32 electrodes, which yields 4096 potential values per measurement. The true conductivity distribution is known due to the experimental condition. The VAE is a generative model that learns a latent representation of the true conductance distribution. This way, a statistical model is learned for the potential solutions, which acts as a regularizer for the inverse problem. The mapper projects the measured potential values onto the latent space. It is trained using the latent space representations of the conductivity distributions in the training dataset. The final model has around a million parameters. For achieving the absolute 3D image reconstruction, unknown measurement data can be fed into a successfully trained reconstruction network.

**Results:** The evaluations of the trained models indicate that absolute 3D image reconstruction is feasible. Unseen test data could be reconstructed with good agreement to the true conductance distribution.

**Conclusion:** The provided results agree with the assertion that DL methods appear to overcome the limitations of existing numerical model-based methods. In the next step, more complex geometries with varying sizes are examined.

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## 3.7 Towards a flexible research platform for electrical tissue stimulation supporting various application domains

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**Introduction:** The ageing population demands innovative medical solutions. Implantable active devices play a crucial role in overcoming these challenges by monitoring patients' health status and electrically stimulating tissue to alleviate symptoms and support the body's regenerative processes. For instance, Deep Brain Stimulation (DBS) is a well-established therapy for various neurodegenerative diseases, and ongoing research aims to improve its effectiveness further. Additionally, the effects of electrical stimulation on other target areas, including the regenerative treatment of bone and cartilage defects, are currently under investigation for clinical use. Given the diverse and expansive application potential, there is an urgent need for a flexible research platform to uncover the underlying mechanisms of electrically stimulated tissue.

**Methods:** Our research targets a modular, fully implantable research platform allowing novel investigations in the field of electrical stimulation across different tissue types. The platform addresses critical aspects, including multimodal stimulus generation, efficient power management strategies, integrated self-diagnostic tests, safety features, and compact size while ensuring long-lasting runtime for multiple *in vivo* applications.

**Results:** In preliminary *in vitro* experiments, our research platform has demonstrated high flexibility in controlling stimulation profiles for brain, bone, and cartilage. It enabled precise electrical signal generation with a wide range of forms, strengths, and frequencies. The integrated diagnostic test has reliably detected integrity issues that may arise during stimulation, providing a robust mechanism to ensure replicable studies. Notably, the research platform has shown ultra-low power consumption while generating various signals, enabling long-term experiments even in size-critical implants.

**Conclusion:** Our research platform provides a comprehensive toolkit for studying the impact of electrical stimulation on tissue. Insights gained from these investigations can enhance the development of effective electrical stimulation therapies across various medical applications.

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# 3.8 Effect of polymer electrode coating on local field potentials recorded from implanted deep brain electrodes

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**Introduction:** PEDOT:PTS coatings of implanted electrodes are used in long-term electrophysiological methods, including local field potential (LFP) recording. However, the impact on the electrode-tissue interface is not fully understood. This study combined *in vivo* impedance recording, immunohistology, and *in silico* methods to understand the effect of electrode coatings on the electrode-tissue interface in recording applications.

**Methods:** Impedance of coated (N= 6) and uncoated (N= 7) deep brain stimulation electrodes implanted in 13 adult Wistar rats of both sexes was recorded over 8 weeks, LFPs were recorded at 0, 4 and 8 weeks and brain tissue astrocytosis (GFAP), neuroinflammation (Iba1) and neurodegeneration (NeuN) assessed at 8 weeks. An *in silico* model of the electrode interface and a finite-element model of the rat brain were used to simulate LFP signals from surrounding neurons. The amplitude and signal-to-noise ratio of the simulated signals were compared for coated and uncoated electrodes. The influence of electrode impedance on the electrode detection volume and the effect of coating on LFP signal quality were examined under three conditions representing different combinations of encapsulation tissue thickness and neuron distribution.

**Results:** *In vivo* electrode impedance was higher for uncoated than coated electrodes from 3 weeks onward. The signal-to-noise ratio was also higher for coated electrodes, and astrocytosis, neuroinflammation and neurodegeneration were reduced compared to untreated electrodes.

While electrode impedance had little effect on the detection volume of the electrode *in silico*, variations in neuron location had a substantial effect on the detected signal. Simulated distributions where neurons were located closer to the coated electrodes were found to closely resemble the experimental electrophysiological and histological results.

**Conclusion:** The results suggest that the improved performance of PEDOT-coated electrodes can mainly be attributed to reduced encapsulation tissue and neuronal loss in the electrode vicinity, causing functional neurons to persist close to the electrode.

# 3.9 Validation-oriented modelling of electric cell-substrate impedance sensing chip for tissue engineering

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**Introduction:** Electric cell-substrate impedance sensing (ECIS) chips have been employed in various cell experiments. This study aims at validation-oriented modelling of the ECIS chip using the concept of digital twins and investigates whether the chips are suitable for electrical stimulation.

**Methods:** Electrical impedance spectroscopy (EIS) was conducted to characterise the ECIS chips. The electro-quasistatic field equation [1] was solved using the Finite Element approach to derive the impedance. Sensitivity analysis was performed to examine the impact of the electrode thickness and conductivity.

**Results:** Impedance measurements reveal large variations in the total impedance of different wells due to the influence of the lead resistance of the connecting trace. Moreover, each chip exhibited a distinct lead resistance. Consequently, one must subtract the corresponding trace resistance to obtain a corrected impedance. The difference between the corrected measured impedances and the simulation is less than 10The sensitivity analysis reveals that when the electrode thickness is below 600 nm, the variation in the impedance of the system due to differing electrode conductivity becomes significant. In alternative applications, for example, estimating the dielectric properties of the medium, evaluation of the medium impedance is required. However, it poses a challenge because different media with different conductivities can potentially yield a relatively similar impedance.

**Conclusion:** The ECIS chip may not be ideal for cell stimulation due to potential uncertainties arising from variations in the impedances of the electronic circuits. To achieve an accurate correction, measuring the trace resistance of each chip is essential. However, this becomes impractical as the chip cannot be reused for cell experiments once conductive silver paint is applied. Careful consideration and attention to electrode thickness and conductivity are crucial during chip manufacturing. Without it, the measured system impedance may not yield meaningful insights into the medium's conductivity or the cells' different states.

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# 3.10 Subthalamic nucleus deep brain stimulation induces functional deficits in forebrain norepinephrinergic neurotransmission in a Parkinson's disease model

***Meike Statz*[1], *Sarah Pfeisinger*[1], *Hanna Weber*[1], *Frederike Schleuter*[1], *Maria Kober*[1], *Henning Bathel*[2], *Franz Plocksties*[3], *Ursula van Rienen*[2,4,5], *Dirk Timmermann*[3], *Alexander Storch*[6], *Mareike Fauser*[1]**

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**Introduction:** Deep brain stimulation of the subthalamic nucleus (STN-DBS) has been repeatedly linked to cognitive impairment and other non-motor symptoms, such as depression or apathy, in Parkinson's disease. Since both dopaminergic and norepinephrinergic neurotransmissions play important roles in certain cognitive functions/non-motor symptoms, we analysed morphological alterations of the catecholaminergic system as well as effects of STN-DBS on norepinephrine and dopamine availability in different brain regions in the 6-hydroxydopamine rat model of Parkinson's disease.

**Methods:** We applied six weeks of continuous unilateral STN-DBS or sham stimulation, respectively, in groups of healthy and 6-hydroxydopamine-lesioned rats to quantify catecholaminergic cell counts in the substantia nigra pars compacta, ventral tegmental area and locus coeruleus. In addition, we analysed norepinephrine and dopamine contents in the striatum, olfactory bulb and dentate gyrus after one week of STN-DBS in a second cohort.

**Results:** The 6-hydroxydopamine lesion significantly reduced dopamine levels in the striatum and dentate gyrus as well as norepinephrine levels in all of the examined regions. While 6-hydroxydopamine significantly reduced midbrain dopaminergic neuron counts, as intended, norepinephrinergic neuron numbers remained unchanged. Consequently, dopamine levels in the striatum and dentate gyrus were significantly reduced, however, an additional decrease in norepinephrine levels was detected in all of the examined regions. Six weeks of STN-DBS did not alter catecholaminergic neuron counts in mid- and hindbrain regions and dopaminergic fibre density in the dorsal and ventral striatum. However, one week of STN-DBS decreased norepinephrine levels in forebrain regions, i.e., the striatum and olfactory bulb in 6-hydroxydopamine-lesioned animals; in contrast, dopamine levels were reduced in the dentate gyrus. We found no effects of STN-DBS on catecholamine systems in any of the examined regions in healthy animals.

**Conclusion:** STN-DBS modulates norepinephrinergic neurotransmission in forebrain regions in a PD rat model. This mechanism might contribute to cognitive impairment related to the treatment, but this relationship must, of course, still be confirmed by suitable behavioural studies.

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# 3.11 Field-assisted sintering of load-bearing Ti6Al4V-barium titanate piezoelectric scaffolds for bone tissue engineering

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**Introduction:** A critical-size bone defect in load-bearing areas is a challenging clinical problem in orthopaedic surgery. Currently, used titanium alloy (Ti6Al4V) scaffolds feature high biomechanical stability but lack electrical activity, which hinders their further use. In preliminary studies, we fabricated piezoelectric and biocompatible calcium titanate and barium titanate ceramics through field-assisted sintering. The piezoelectric properties of fabricated scaffolds were analysed and compared with the piezoelectric properties of natural bone. Our recent study is focused on fabricating Ti6Al4V-barium titanate bulk composite scaffolds to combine the biomechanical stability of Ti6Al4V with electrical activity through barium titanate.

**Methods:** A hollow cylindrical Ti6Al4V is additively manufactured by electron beam melting and combined with barium titanate powder for joint processing in field-assisted sintering. The manufactured test specimens were analysed with regard to their mechanical and piezoelectric properties.

**Results:** Scanning electron microscope images on the Ti6Al4V-barium titanate composite scaffold interface showed that after sintering, the Ti6Al4V lattice structure bounded with the barium titanate matrix without its significant deformation. The Ti6Al4V-barium titanate scaffold had average piezoelectric constants of $(0.63 \pm 0.12)\,\mathrm{pC/N}$ directly after sintering due to partial dipole alignment of the barium titanate tetragonal phase, which increased to $(4.92 \pm 0.75)\,\mathrm{pC/N}$ after a successful corona poling. Moreover, the nanoindentation values reveal that the Ti6Al4V is the harder and stiffer part in the Ti6Al4V-barium titanate composite scaffold [1].

**Conclusion:** The fabricated scaffold can potentially be used to treat critical-size bone defects in load-bearing areas and guide tissue regeneration by piezoelectric stimulation.

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# 3.12 Development of scale separation maps for multiscale modelling of electrically active implants

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**Introduction:** The numerical simulation of electromagnetic fields is essential for designing and practically implementing electrically active implants. The efficacy of these implants depends mainly on the resulting field distribution in the stimulated tissue or organ, which in turn depends upon multiple factors, such as the design of the electrode, the electrical stimulation protocol, emerging electrical double layers, tissue encapsulations, the dielectric tissue properties, and their stochastic uncertainties. In addition, the hierarchical structure of the biological tissue adds to the complexity such that only a numerical formulation as a multiscale problem, linking processes at the microscopic and macroscopic levels, can meet the character of the object of investigation. Selecting a scale separation method to connect two simulation models operating at distinct scales is crucial in multiscale modelling. The initial phase of the process commences with developing a scale separation map, a step essential for guaranteeing reliable and realistic outcomes. By scrutinising this map, a clear overview emerges, revealing the modular structure of the macroscopic and microscopic scales inherent in the problem. This comprehensive and deeper understanding sets the stage for a more profound multiscale analysis. The scale separation map also serves as a roadmap for identifying fundamental interactions and dependencies between different scales, enabling a systematic exploration of the multiscale system.

**Methods:** This work adopts multiscale analysis with homogenisation and insertion techniques. Besides space separation, the approach includes time scale separation to describe different time processes in the macroscopic and microscopic models. This process can be handled efficiently by MUSCLE3 [1], which offers modularity and flexibility at the same time.

**Results:** In the focus of our research, three scale separation maps are developed, specifically tailored for deep brain stimulation, as well as the regeneration of cartilage and bone. Each map has different characteristics, offering a perspective on the multiscale dynamics of these intricate processes.

**Conclusion:** Particularly for the case of deep brain stimulation, the scale separation map is employed as an early study for discerning the intricate relations between tissue activities at the macroscopic level and cellular responses at the microscopic level due to electrical stimulation. Likewise, the map can show the constellation of tissue-level electrical activities and the cellular processes orchestrating regeneration resulting from electrical stimulation in the regeneration of cartilage and bone.

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# 3.13 Monitoring of implant secondary fixation using acoustic-mechanical methods

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**Introduction:** Hip implant loosening is currently diagnosed using imaging techniques such as X-rays. However, these methods often offer a low sensitivity and specificity of around 80%, as the presence of the metallic implant makes diagnosis more difficult [1]. Acoustic-mechanical methods have been proposed to improve the detection of implant loosening [2, 3]. The principle is to acoustically excite the implant and record the generated sound waves with accelerometers attached to the skin. Different frequency spectra are intended to provide information on the implant loosening state. However, it has been shown that the reproducibility of the external measurements is low. Recently, a hip endoprosthesis with a self-sufficient energy supply was proposed [4], which allows intracorporeal acceleration measurements to be studied. Therefore, this work aimed to acquire frequency spectra directly at the hip stem.

**Methods:** A simplified test setup was created for the first investigations. A titanium rod to simulate the hip stem was implanted in a cylindrical artificial bone. Three different defects in the upper proximal region of the artificial bone were examined (Defects 0 to 2). The excitation of the titanium rod was performed with an exciter attached directly to the tip of the titanium rod, playing an exponential sine sweep (50 Hz to 20 kHz). The data was recorded using three broadband accelerometers attached directly to the titanium rod at different distances from the exciter.

**Results:** There are initial visual differences in the shapes of the recorded accelerometer signals between the defects (Fig. 3.1). Furthermore, with growing distance from the exciter, the amplitudes of the signals decrease.

**Conclusion:** The visual differences in the recorded signals encourage further analysis and support the initial hypothesis. Further emphasis will be placed on extracting other features, like frequency responses, and training machine learning models to detect loosened states.

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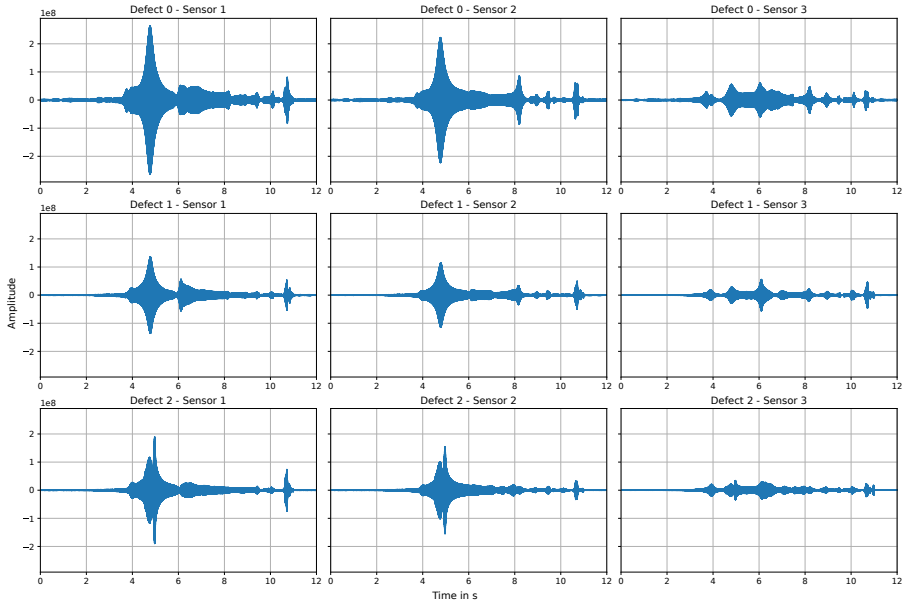


Figure 3.1: Results of the signal response over time.

# 3.14 Predicting cell differentiation on a mechanically stimulated structured hydrogel scaffold using an FSI simulation

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**Introduction:** 3D hydrogel scaffolds can be used to treat cartilage and bone defects. In tissue engineering, the formation of cartilage and bone can be specifically stimulated by mechanical stimulation. In this study, we applied a transient one-way FSI model that can predict cell differentiation on the entire surface of a 3D-structured hydrogel scaffold seeded with cells due to dynamic compressive load stimulation.

**Methods:** A structured scaffold was created using CAD. The FE model included three parts: piston, scaffold, and support. The piston could move vertically to compress the scaffold. The scaffold material model was based on experimental tests of pure ADA-GEL. The applied compressive load was sinusoidal with a frequency of 1 Hz. CFD setup was based on laminar, Newtonian, and incompressible flow. For the FSI setup, a transient, one-way co-simulation strategy was employed. The modified mechanoregulation theory of Prendergast was implemented into the model to predict cell differentiation.

**Results:** Average octahedral shear strain ($OSS_{avg}$) and area-weighted averaged wall shear stress ($WSS_{avg}$) were computed during one loading cycle for different compression amplitudes from 1% to 10%. The cell phenotypes were predicted at the simulation time points when the maximum values of average stimuli ($S_{avg}$) occurred. Bone cell differentiation decreased with increasing compression amplitude. Cartilage cell differentiation initially increased in the range of 2 % up to 7 % compressions and then decreased. Fibrous cell differentiation was predicted from the compression aptitude of 5 % up to 10 %.

**Conclusion:** The presented model can predict cell differentiation based on both the mechanical deformation of the scaffold and the compression-induced fluid flow during dynamic compressive stimulation. Therefore, the model can be used to study the effects of, for example, different scaffold designs and stimulation parameters on cell differentiation in mechanically stimulated 3D-structured scaffolds.

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## 3.15 Intracellular signalling processes and cell migration after physical stimulation

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**Introduction:** Regenerative medicine is a significant research focus and relies on interdisciplinary research. Developing new biomaterials and medical devices for tissue and cell treatments is a growing area in this context. We use biophysical stimulation techniques to induce changes in cellular functions such as proliferation and differentiation.

**Methods:** AC stimulation of human pre-osteoblasts (MG-63) and stem cells was performed using the commercially available IonOptix and the self-manufactured Mobini chamber. Furthermore, the application of mechanical forces, physical plasma, and light of different wavelengths was investigated regarding the cell-physiological impact. Here, we focus, on the one hand, on the study of adhesion and migration processes and the membrane receptors required for these processes. On the other hand, intracellular protein translocation is investigated in more detail.

**Results:** Electrostimulation leads to a significantly enhanced osteoblastic cell adhesion after 10 min and increased $Ca^{2+}$-mobilisation. Especially, mechanical forces have direct effects on central cell signalling pathways for osteogenic differentiation and cell adhesion to biomaterial surfaces. Physical plasma promotes tissue regeneration and tight junction opening for better drug uptake, while light of different wavelengths also improves wound closure and tissue repair by influencing stem cell fate. Although different stimuli were applied, a common cell signalling pattern regarding the involvement of ROS and intracellular $Ca^{2+}$ was described. Investigation of ROS-dependent NF-$\kappa$B signalling revealed a time-dependent translocation of this protein to the nucleus.

**Conclusion:** Although treatment approaches vary, these physical stimuli activate cell signalling via calcium ions and reactive oxygen species (ROS). A better understanding of the cellular response to the applied physical stimuli will help develop efficient treatment strategies and optimised device settings.

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## 3.16 Feasibility of monitoring periprosthetic bone quality using EIT

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**Introduction:** Periprosthetic bone loss is a common cause of aseptic loosening in hip stem implants that is difficult to detect using current methods. Electrical impedance tomography (EIT) is a non-invasive imaging technique that is used to monitor conductivity changes within the body and has been suggested for bone and implant monitoring [1, 2]. If EIT can detect the changes in bone conductivity that accompany osteolysis [3, 4], it could be applied for the early detection of implant failure. Here, we investigate whether changes in bone conductivity are detectable by EIT if the conductivity of surrounding tissue changes.

**Methods:** EIT data for various conductivity changes in a model of a human thigh are simulated using the EIDORS toolbox [5] to generate forward models using the finite element method. Difference voltages are calculated between two states: a reference state where bone and surrounding tissue have the conductivity of healthy bone and muscle, and various scenarios with conductivity changes in the bone and muscle. Principal component analysis (PCA) and support vector machines (SVM) are used to detect changes in bone conductivity directly from EIT voltages in the presence of simultaneous conductivity changes in surrounding tissue and additive noise. Sensitivity and specificity for the detection of bone defects are calculated for different changes in muscle conductivity and different noise levels. We investigate scenarios with and without a titanium hip stem implant in the femur.

**Results:** Low bone conductivity changes in simulation data are detectable with high sensitivity using PCA and SVM, even in the presence of conductivity change of surrounding tissue, if noise levels are sufficiently low.

**Conclusion:** The analysis of simulated bone conductivity data shows the feasibility of using EIT to monitor bone quality. In the presence of implants, this approach can be used to monitor the periprosthetic bone to detect implant failure.

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## 3.17 Osteoblast response upon short time AC-stimulation with commercially available IonOptix chamber

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**Introduction:** An area of research in regenerative medicine is electrical stimulation (ES) and its effects on biological systems. The focus here is on the mechanism of action of ES, i.e., which physical parameters influence the surrounding medium and the cells. The aim was, therefore, to gain new insights into why ES contributes to cell activation during the regeneration of bone tissue.

**Methods:** To answer this question, human MG-63 osteoblasts were electrically stimulated for 10 min using a commercially available multi-channel system (IonOptix) with a pulsed alternating current (AC-stimulation) upon a voltage of 1 V or 5 V and frequencies of 20 Hz, respectively. The osteoblasts were cultured in a medium containing FCS (10 The ES of suspended cells was performed immediately after seeding, and *in vitro* investigations were conducted by microscopy (FE-SEM, cLSM) and flow cytometry within 24 h.

**Results:** ES positively affected the process of cell attachment and initial adhesion, as well as intracellular calcium ion signalling of suspended osteoblasts. Furthermore, ES influenced the expression of aquaporin channels in the cell membrane, which are relevant for water passage and small molecule transport. However, we could exclude fluid-mediated effects, as the AC stimulation did not change the medium's pH, temperature, oxygen, or hydrogen peroxide content.

**Conclusion:** A short-term AC stimulation of osteoblasts is sufficient to promote cell adhesion, membrane transport, and signalling. The influence of ES on the environment is crucial for comparing and evaluating *in vitro* studies.

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## 3.18 The effects of AC-induced electrochemical byproducts on osteoblasts' intracellular reactive oxygen species

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**Introduction:** Electrical stimulation (ES) enhances bone fracture healing in non-union patients. With direct contact ES, the electric field can influence cellular reactions and electrochemical by-products. Electrically conditioned culture medium influenced cellular behaviour in vitro, e.g., due to reactive oxygen species (ROS) [1, 2]. ROS can surpass the cell membrane via aquaporin channels, which are well-regulated but can be inhibited by metal ions such as $Ag^{+}$, $Hg^{2+}$, and $Au^{3+}$ [3]. The question arose whether metal ions released from the electrodes may also have an influence.

**Methods:** Human osteoblastic MG-63 cells were stimulated with 20 Hz and 6 mA biphasic pulses via L-shaped platinum electrodes [4] for 2 h. The additional effect of hydrogen peroxide ($H_2O_2$) or platinum ions was examined. In addition, cells were seeded in an electrically conditioned medium. The impact on intracellular ROS was examined via flow cytometry and microscopy.

**Results:** While both direct stimulation and AC-conditioned medium impacted cell adhesion and spreading, only the direct stimulation enhanced the intracellular calcium ions and ROS significantly. ES led to changes in the culture medium, including the generation of $H_2O_2$. Flow cytometry analysis showed little influence of the ES medium on intracellular ROS. However, the incubation with hydrogen peroxide led to a significant increase in ROS. The detailed regulation of ROS generation and uptake is to be examined.

**Conclusion:** The electrical stimulation of the culture medium alone did not induce the same cellular effects as the direct stimulation of cells, indicating the impact of the electric field. The generation of $H_2O_2$ alone is not accountable for the cellular reactions of an electrically stimulated medium.

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# 3.19 Tailoring a hard-to-soft transition interface on 3D porous titanium alloy scaffolds

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**Introduction:** Titanium implants are essential in modern medicine and are indispensable when replacing bone in the load-bearing area. However, titanium is an inert biomaterial with no bioactive properties that actively promote implant integration into the bone. Here, we supplement 3D porous gyroid scaffolds with a Bioglass-loaded hydrogel coating to actively encourage cell ingrowth in the scaffolds and bonding of the implant to the bone through a hydroxy carbonated apatite layer.

**Methods:** Using electron beam melting, small plates and 3D porous scaffolds made of different gyroid unit cell sizes were manufactured from Ti6Al4V alloy. The scaffolds were coated with various hydrogel formulations in a dip-coating process. Alginate dialdehyde-gelatine (ADA-GEL) was used as the basic hydrogel, which was filled with bioactive glass (BG) particles (45S5) in concentrations of 0, 0.05, and 0.1 wt.%. The coated samples were examined concerning the homogeneous adhesion of the coating, the swelling and degradation behaviour, the bioactivity, and the mechanical properties.

**Results:** The addition of BG to ADA-GEL led to a slight increase in effective stiffness and delayed the degradation of the hydrogel, attributed to the additional crosslinking from released calcium ions from BG. Furthermore, the bioactive properties of the hydrogel coating after immersion in simulated body fluid were confirmed by X-ray diffraction and scanning electron microscopy for the BG-loaded hydrogel. Moreover, upon adding BG to the hydrogel, the adhesion strength of the coating to the titanium substrate was improved.

**Conclusion:** Our study demonstrates the feasibility of coating highly porous titanium scaffolds of various gyroid unit cell sizes with BG-loaded ADA-GEL, facilitating a hard-to-soft transition. The addition of BG to the hydrogels enables a tailorability of the resulting coating properties and exhibits potential for further advancements, such as employing ion-doped BG to introduce additional functionalities.

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## 3.20 Towards a boundary element multi-trace formulation for quasi-electrostatic, composite problems in electrical impedance tomography

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**Introduction:** Numerical simulations are commonly used in bio-electromagnetic problems, for example, to predict the outcome of physical experiments or to generate synthetic data that can be used to train neural networks. Electrical impedance tomography (EIT) is a promising measurement tool for detecting the loosening of hip implants, albeit reconstructing the dielectric properties of the measured tissue-implant compounds is a complex inverse problem. To solve the inverse problem, machine learning techniques can be used, requiring, however, a large amount of data, measured or synthetic.

**Methods:** The boundary element method (BEM) has been a popular choice when the problem can be described by a set of compartments with constant dielectric properties, since it reduces the number of unknowns and simplifies the meshing process when compared to methods like the finite element or finite difference methods. Recently, so-called multi-trace formulations have been introduced. We adopt this multi-trace formulation to bio-electric scenarios in the electro-quasi-static regime, where electrodes and floating potentials must be modelled. To verify our formulation, we have derived semi-analytic solutions to canonical problems, such as two touching hemispheres in a homogeneous field, where one is a perfect conductor.

**Results:** Both the semi-analytical solution and the numerical method converge. When the numerical method is applied to model problems with known analytical solutions, we converge towards the same solution.

**Conclusion:** The newly derived multi-trace formulation shows, first, promising results that form a basis for simulating more complex geometries and the actual EIT measurement setup.

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# 3.21 Impact of deep brain stimulation on neuronal network mechanisms in generalised dystonia

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**Introduction:** Pallidal deep brain stimulation (DBS) is an effective treatment for generalised or cervical dystonia, which improves dystonia severity by up to 60 %. However, the outcome for the individual patient remains unpredictable due to unknown mechanisms of the DBS treatment. With our electrophysiological and immunohistochemical experiments, we want to clarify the mechanism of DBS dystonia, which might lead to higher treatment success rates.

**Methods:** We are investigating the synaptic transmission and network activities within the cortico-basal ganglia-thalamo-cortical as well as the cerebello-thalamo-cortical pathways in an animal model of paroxysmal generalised dystonia affected by DBS. For this purpose, we implanted bipolar stimulation electrodes bilaterally into the $dt^{sz}$ mutant hamster's globus pallidus internus. We fully implanted the STELLA stimulation system [1] in the hamster's flank for continuous long-term DBS (130 Hz, 50 µA) over 11 days. We defined two experimental groups: a) the DBS group, with activation of DBS three to four days after surgery, and b) the sham group, where the DBS remained turned off over the total period. We use field potential, patch clamp, and high-density microelectrode arrays for our electrophysiological recordings of acute brain slices. Moreover, the effect of short-term DBS on the neuronal activity of multiple brain regions was examined after three hours using fluorescence immunohistochemistry and molecular genetic analyses.

**Results:** Our results, summarised in Fig. 3.2, indicated unexpected effects of pallidal DBS on the thalamus by upregulating the excitatory tone rather than direct inhibitory projections. The inhibitory tone on striatal medium spiny neurons (MSN) is also raised through DBS. Additionally, our measurements demonstrated a decreased frequency of excitatory synaptic currents on the MSN. Moreover, we found a mean firing rate in the spinocerebellar cortical network that was within the range of healthy control hamsters. At the same time, the neuronal activity within the deep cerebellar nuclei, which we detected by c-Fos expression, was decreased after short-term DBS.

**Conclusion:** Our results confirmed our hypothesis of a global network effect of DBS rather than a local impact on the stimulation target.

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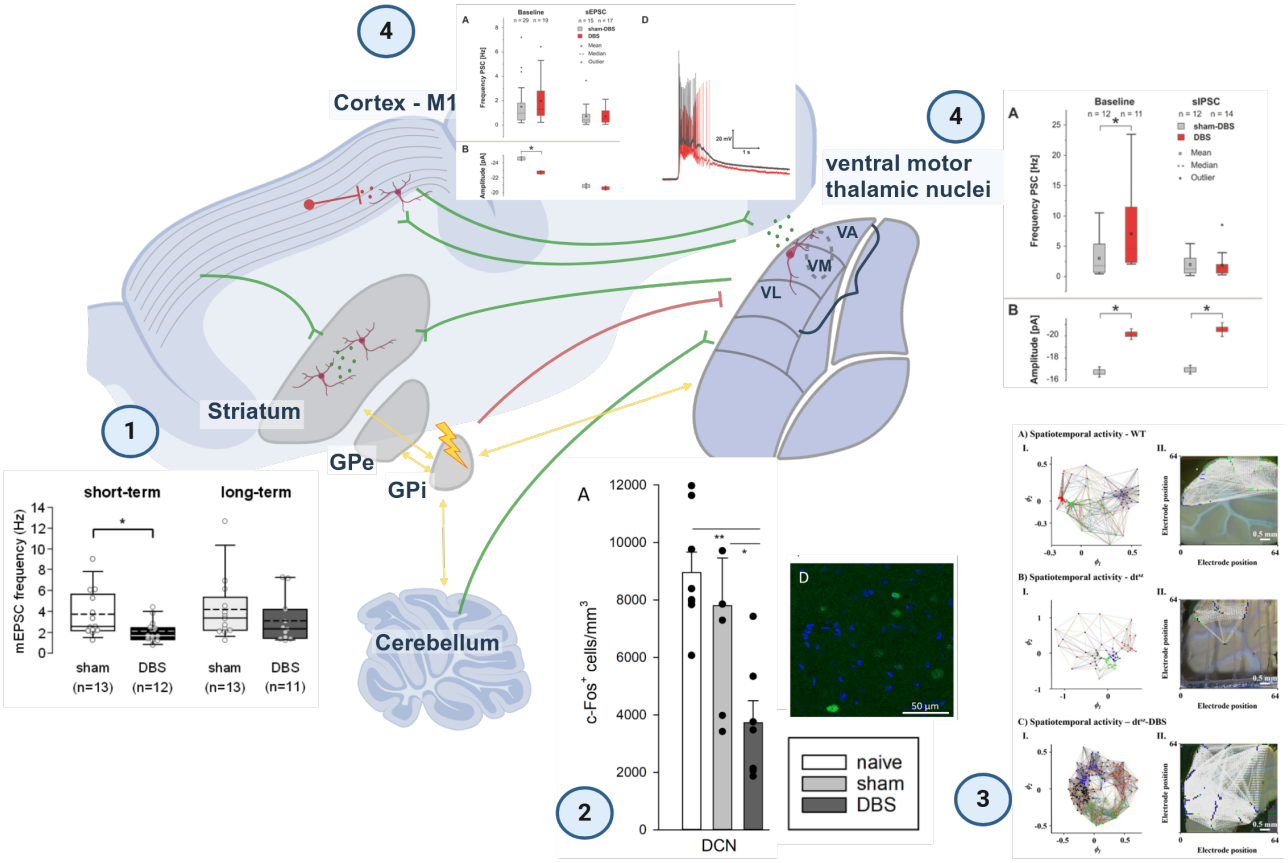


Figure 3.2: Network-wide effects of pallidal deep brain stimulation. (1) increased frequency of miniature excitatory postsynaptic currents (mEPSC) in Striatum (published in [1]). (2) decreased c-Fos expression in deep cerebellar nuclei (DCN) (published in [2]). (3) improved network connectivity in the cerebellum (published in [3]). (4) modulation of synaptic plasticity and spike patterns in ventral motor thalamic and motor cortical neurons (published in [4]).

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# 3.22 The nanomorphology of neural stem cells investigated by scanning ion conductance microscopy

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**Introduction:** Deep brain stimulation (DBS) is a treatment method for neurological disorders such as Parkinson's disease that requires the implantation of electrodes in the brain and an understanding of the method's mechanism of action. The biocompatibility and electrical conductivity of the electrode surface are important for the mediation between ions and electrons and cellular response.

**Methods:** We investigate murine adult neural stem cells (NSCs) from the subventricular zone to see how they interact with different materials and respond to electrical stimulation. NSCs can differentiate into different types of neuronal and glial cells. Their nanomorphology, i.e., their shape and structure in the nanometer range, is supposed to evolve in the course of differentiation and function. We use scanning ion conductance microscopy (SICM) to characterise the nanomorphology of NSCs. The SICM is a contactless scanning probe microscopy technique with high resolution and low mechanical stress.

**Results:** SICM visualises filopodia, thin, finger-like protrusions that are involved in cell-cell interaction and cell migration. Furthermore, characteristic surface features of NSC can also be observed.

**Conclusion:** By analysing the nanomorphology of NSCs, it may be possible in the future to determine whether a cell is already differentiated. We are discussing the role of polyelectrolyte-based surface coatings as substrates that exhibit better biocompatibility and electrical conductivity than previously established materials. We hope that in the future, we will be able to use surface coatings to stimulate cells via the surface.

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# 3.23 Quantification of motor symptoms using automated gait analysis in a Parkinson rat model

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**Introduction:** Parkinson's disease (PD) is one of the most common neurodegenerative diseases, occurs predominantly in advanced age, and is characterized by a chronic-progressive course. One successful therapeutic option, especially for advanced PD, is deep brain stimulation (DBS), often applied in the subthalamic nucleus (STN). This therapy is symptom-oriented and currently used for treating motor symptoms, resulting in improved quality of life in PD patients. However, the underlying mechanisms of action of DBS are not fully understood. Therefore, there is an urgent need for further research in which animal models might contribute significantly to the understanding of DBS's modes of action. However, motor symptom quantification has been challenging in small animal models, especially regarding DBS-related improvements, with additional limitations due to stimulation devices. The study aims to establish a commercially available rodent gait analysis system (MotoRater®) to quantify motor symptoms in a PD rat model.

**Methods:** Gait analyses were conducted repeatedly using MotoRater in healthy and PD rats. The animals were captured from three different sides while walking through a transparent corridor made of plexiglass. Three videos with three consecutive steps each were analysed for each animal.

**Results:** The preliminary results of the gait analysis showed differences in the motor behaviour of healthy versus PD rats. Furthermore, the results indicate that it will also be possible to investigate the influence of STN-DBS on motor behaviour in this animal model.

**Conclusion:** The gait analysis system was successfully established to quantify certain motor symptoms in a PD rat model. In the future, it will be possible to use gait analysis to investigate motor outcomes of other PD models on the one hand and the influence of different therapies in these models on the other.

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# 3.24 In silico investigation of electrode-tissue interface dynamics in deep brain stimulation

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**Introduction:** Clinicians and device manufacturers emphasise the critical role of the electrode-tissue interface encompassing the electrical double layer and glial encapsulation – in maintaining the functionality of deep brain stimulation (DBS) electrodes. Developing precise computational models to enhance the efficacy and safety of DBS electrodes and stimulation protocols requires accurately depicting the electrode-electrolyte/tissue interface. The interface undergoes distinct stages based on applied charge density, transitioning from a polarisable (non-Faradic) state to a non-polarisable (Faradic) state with charge separation, leading to reversible and subsequent irreversible redox reactions. This study specifically aims to identify the threshold current amplitude at which segmented DBS electrodes shift from the non-Faradic charge transfer to the Faradic charge transfer.

**Methods:** The finite element model of the segmented DBS electrode includes the influences of nonlinear resistive and capacitive properties of the electrical double layer. Solving for the unknown potentials at the electrode-tissue interface employs the time-harmonic quasi-static formulation of Maxwell's equations with an iterative approach. The study utilises stationary polarisation to investigate the shift from linear to nonlinear behaviour in the EDL as current increases at various frequencies. Finally, the research determines the transition point to the Faradic charge transfer and predicts maximum charge density and charge per phase by employing nonlinear polarisation curves and Shannon tissue damage criteria.

**Results:** The results indicate that the faradic region is reached at clinically used stimulation intensities in human DBS and below the Shannon safety limit. Prolonged electrode operation within this nonlinear region may result in irreversible damage to the electrode and surrounding tissue.

**Conclusion:** The inclusion of nonlinear EDL in DBS models provides a more complete picture of electrode stability in long-term stimulation and can be used to optimize electrode design for high electrochemical stability.

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# 3.25 Defining the effects of electric field (EF) stimulations and oxygen tension (pO2) interplay on osteogenic differentiation of human mesenchymal stromal cells (hMSC)

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**Introduction:** Exogenous electric field (EF) stimulation has been widely researched and applied sporadically in clinics to promote bone regeneration. Nonetheless, the "Effective Window" of EF to maximize bone regeneration remains ambiguous. Therefore, we aimed to recapitulate the different stages of bone regeneration in vitro by controlling $pO_2$ and applying EF at each stage to elucidate their effects on osteogenic differentiation of hMSC.

**Methods:** With an aim to recapitulate *in vitro* 1) the hypoxic niches in bone defects, 2) the slightly oxygenated niches in regenerating defects, and 3) regular *in vitro* incubator, EF was applied with various oxygen tensions (1 % to 16 %). Their effects on hMSC proliferation, osteogenic differentiation – based on alkaline phosphatase (ALP) activities – and gene expression profile are investigated. The hMSCs are seeded on type 1 collagen-coated glass coverslips and cultured in a hypoxic chamber with controlled $pO_2$ and pulsatile alternate current (AC) EF stimulation (0.34 V/m, 10 Hz, 12 h/d) for 21 days.

**Results:** Distinct differences to EF controls were observed: 1) Hypoxia (1 %) + EF had significantly reduced ALP but elevated cell proliferation, an effect in relation to the HIF pathway; 2) slightly oxygenated (8 %) + EF had balanced ALP and cell proliferation, similarly in EF controls; 3) highly oxygenated niche (16 %) + EF mimicking typical *in vitro* experiments had significant elevated ALP, but reduced cell proliferation. EF had also altered the cell morphologies: Condition 3 led to cells with the largest surface area.

**Conclusion:** Our results indicated that the competence of EF stimulation for bone regeneration is strongly affected by $pO_2$. Therefore, an "Effective Window" for EF application is expected and is being investigated more thoroughly. Ongoing research is also done on 3-dimensional (3D) scaffolds with different conductivity (cross-linked collagen/3D-printed polycaprolactone; nude versus mineralized) to gain a closer resemblance to the physiological niches.

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# 3.26 Adjusting the pores geometry of 3D printed polycaprolactone bone graft substitutes for modulated mechanical integrity, cell ingrowth and electrical field distribution

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**Introduction:** Healing critical bone defects can be supported with a bone graft substitute (BGS) by providing a provisional structure for bone cell proliferation and differentiation. Electrical stimulation (EF) can also stimulate and enhance osteogenic differentiation of mesenchymal stem cells (hMSC). Therefore, the internal design of a 3D-printed BGS should be adjusted to support modulated mechanical integrity, cell ingrowth, and electrical field (EF) distribution.

**Methods:** Polycaprolactone (PCL) was processed by Fused Deposition Modelling (FDM) to produce scaffolds with different pore geometries, namely triangular, rectangular, and spectral pores with 50 % infill densities. The influence of the pores' geometry was investigated in terms of compression tests and accelerated bulk degradation tests over 28 days in 2.5 M HCl. The dielectric properties of the scaffolds were determined by electrical impedance spectroscopy (EIS). Together with these results and µCT-scans of the 3D-printed scaffolds, EF distribution depending on pore geometry is simulated through mathematical modelling. This approach allows a better understanding of their interplay to ultimately enhance osteogenic differentiation.

**Results:** Even though mechanical stability was the highest with rectangular pores, degradation tests identified the triangular pores as the most suitable for mechanical integrity after bulk degradation (Figure 3.3). EIS measurements are expected to show the impact of the water uptake of PCL on dielectric properties, which are further considered in the mathematical model. The pores' geometry impacted the EF distribution, and simulations are currently underway in collaboration with Prof. van Rienen and Dr. Appali.

**Conclusion:** The pore geometry has a crucial impact on the suitability of 3D-printed scaffolds as BGS. Both mechanical integrity and EF distribution depend on this internal design and can be adjusted accordingly. This work contributes to developing scaffolds for electrically stimulated osteogenesis. The results will be used to estimate the cell response depending on cell localization and EF concentration.

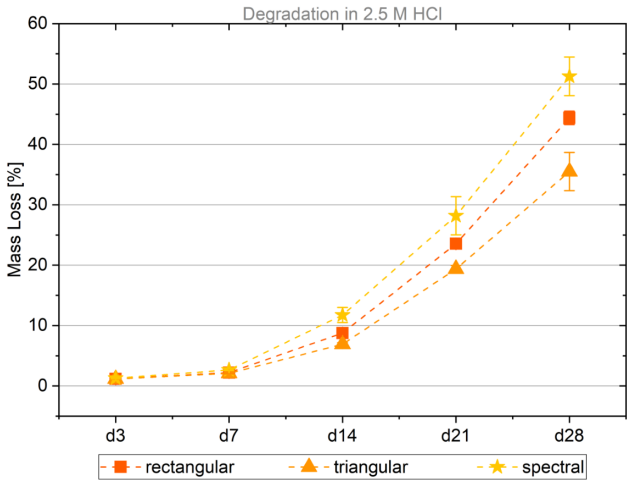


Figure 3.3: Scaffold integrity after bulk degradation. With bulk degradation, a smaller mass loss can be correlated to a higher mechanical stability.

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# 3.27 Measurement of the electrical potential in the articular cartilage using implanted electrodes

***Marco Stubbe***[1]***, Janine Waletzko-Hellwig***[1]***, Nils Arbeiter***[2]***, Henning Bathel***[2]***, Mario Jackszis***[1]***, Anika Jonitz-Heincke***[1]***, Ursula van Rienen***[2,3,4]***, Rainer Bader***[1,3,4]

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**Introduction:** Lesions of the articular cartilage can cause osteoarthritis, leading to reduced joint mobility and pain. The electrical stimulation of these lesions may induce a regenerative effect in the cartilage tissue. Therefore, the development of an electro-stimulative implant system for the *in situ* treatment of osteochondral lesions could be a promising approach. For this, the dielectric properties of bone and cartilage tissue and the electric field distribution in the implant area have to be characterised. This study aimed to develop a setup for the measurement of the electrical potential and current distribution at the cartilage surface, as well as the impedance of the bone tissues.

**Methods:** For these measurements, two bipolar electrodes were positioned in the subchondral bone region of porcine femoral heads. Electric potentials between $1\,V_{pp}$ and $3\,V_{pp}$ at frequencies of 1 kHz and 60 kHz were applied between the two poles of each of the electrodes to determine the electric potentials and the currents at defined positions at the cartilage surface. To obtain the dielectric properties of the subchondral bone, the impedance was recorded between one pole of the bipolar electrode and a measuring electrode positioned at the cartilage surface in the measuring range of 100 Hz to 1 MHz.

**Results:** The electric potentials and currents were measured at the surface of the cartilage, and the results were combined into a surface map of their distributions. Applied electrical potentials above $2\,V_{pp}$ and a frequency of 60 kHz were found to depict detailed maps of the electric potential and current distribution at the cartilage surface.

**Conclusion:** The measurements of the electrical potential and current distribution at the cartilage surface and the subchondral bone show that the subchondral positioning of an electro-stimulative implant equipped with bipolar electrodes may be feasible for the biophysical stimulation of osteochondral lesions.

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# 3.28 Influence of electrical stimulation on the proliferation and differentiation of murine adult neural stem cells in vitro

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**Introduction:** Electrical stimulation is a common therapeutic principle in neurology, for example, in deep brain stimulation (DBS) for movement disorders. Here, we investigate the influence of different stimulation parameters on the proliferation and differentiation of murine adult neural stem cells of the subventricular zone (SVZ-aNSCs) *in vitro*. Since stem cell proliferation, migration, and differentiation occur in parallel *in vivo*, the influence of electrical stimulation cannot be investigated separately. *In vitro*, this is possible to a certain extent. This study investigates the influence of electric fields on SVZ-aNSCs migration as well as effects on proliferative capacity and neuronal or glial differentiation, depending on the stimulation parameters.

**Methods:** The applied electric fields were analysed for all stimulation methods. The influence of electrical stimulation on cell migration was investigated using a single 6-hour DC stimulation in a galvanotactic chamber. Studies on the alteration of proliferation or differentiation of SVZ-aNSCs were carried out in a 6-well chamber using DC (1 h/d) or 130 Hz AC stimulation (12 h/d). Electrical stimulation was either applied during the proliferation (4 days) or differentiation phase (6 days) or over the entire period (10 days). We used established immunocytochemical methods to quantify the cell types generated.

**Results:** *In vitro*, SVZ-aNSCs showed migration towards the cathode under DC stimulation. Repeated DC stimulation did not affect proliferation or neuronal and glial differentiation *in vitro*. In contrast, 130 Hz AC stimulation mimicking DBS parameters used in clinical settings promoted cell differentiation. In particular, the number of neuronal cells increased, leaving the stem cell pool and glial differentiation unchanged.

**Conclusion:** This study provides evidence that electrical stimulation promotes neuronal differentiation of SNZ-aNSCs, although the underlying mechanism remains unclear. In particular, preconditioning during the proliferation phase of the cells could be involved.

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# 3.29 ECSO – An ontology for the documentation of electrical cell stimulation experiments

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**Introduction:** Research data emerge from every step of the scientific research process, from planning an experiment through experiment execution to analysis. To obtain and reuse such data efficiently, the FAIR guiding principles for scientific data management recommend comprehensive documentation using metadata. This also includes information about the particular processes executed during wet-lab experiments. Ontologies, as recommended ways to provide machine-interpretable metadata, implement capabilities for such representation. While domain-specific ontologies can already be used to document research data from most scientific fields, there is still a gap in electrical cell stimulation experiments.

**Methods:** We introduce an ontology for the semantic representation of electrical cell stimulation experiments to close this gap in vocabularies for experiments commonly performed in research collaborations such as the CRC ELAINE. The ontology is based on existing frameworks that allow the description of actions in biomedical experiments (EXACT2) [1], operating procedures in a generalized way (EP-PLAN) [2], and minimal information requirements for the documentation of electrical cell stimulation experiments [3]. The ontology is designed using the ontology editor Protégé and implements best practices in ontology design.

**Results:** Our work presents a preliminary version of the electrical cell stimulation experiment ontology (ECSO). This ontology framework provides a vocabulary to describe electrical cell stimulation experiments, used equipment, and the provenance of the research procedure [4], utilizing human and machine comprehensible semantic web technologies.

**Conclusion:** The ECSO ontology framework unifies multiple ontologies and provides a tailor-made description for electrical cell stimulation experiments conducted in biomedical laboratories. ECSO enables the documentation of research data generated from such experiments and provides a foundation for the FAIR publication of these. As a result, employing ECSO makes electrical cell stimulation experiments more reproducible and comparable.

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## 3.30 Data-driven identification of neural activity patterns

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**Introduction:** In this study, we used data-driven methods to map the activity of neuronal networks topographically. The data sets used for this purpose, which contained the neuronal firing rates, were obtained using high-density multielectrode arrays (MEA) with hamster brain slices.

**Methods:** We constructed Functional Connectivity Networks (FCN) by correlating the firing rates from the different electrode positions. Then, using a nonlinear manifold learning method called Diffusion Maps, we extracted a low-dimensional representation of the correlation matrices. This made it possible to represent the neural activity topographically. Different network measures were computed to reveal critical features of the underlying functional connectivity.

**Results:** Brain slices of three experimental groups were analysed: (1) healthy control hamsters, (2) dystonic hamsters, and (3) dystonic hamsters continuously treated with deep brain stimulation (DBS) for 11 days. Qualitative network properties were extracted in the three cases mentioned above.

**Conclusion:** Our method offers a low-dimensional representation of neural activity, allowing us to analyse spatio-temporal activity patterns. Network properties give new insights into the brain organisation during healthy, pathological, and DBS conditions.

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# Author Index