

**Conference on Progress in Electrically Active Implants  
Tissue and Functional Regeneration  
(ELAINE 2020)**




**Rostock, Germany  
29.09.–30.09.2020**

Proceedings of the  
**Conference on Progress in Electrically Active Implants**  
Tissue and Functional Regeneration  
ELAINE 2020


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## Introduction

In September 2020, the Conference on *Progress in Electrically Active Implants - Tissue and Functional Regeneration (ELAINE 2020)* was held at the University of Rostock, Germany. Due to the COVID-19 situation, the conference was held virtually on 29.–30. September 2020 using the interactive Hopin conference platform.

In recent years there has been a sharp rise in the use of experimental electric stimulation in medical purposes, in terms of both novel material development and new technology applications. In particular therapeutic and regenerative medicine increasingly utilise wearable and implantable devices. Moving forward, implantable devices have empowered novel therapeutic interventions to develop well-established treatments, such as promoting bone healing in critical-size bone defects, deep-brain stimulation for movement disorders, cochlear implants for hearing loss and visual prosthetics.

The conference on *Progress in Electrically Active Implants - Tissue and Functional Regeneration (ELAINE 2020)* focused on novel methods in the electric stimulation of bio-material compounds of living cells and implantable electric stimulation devices. ELAINE 2020 provided international scientists a virtual platform to discuss the latest achievements in the form of invited presentations, selected talks from abstract submissions, and virtual poster sessions. In addition, we particularly invited critical reviews and contributions with negative results or unsuccessful replications to foster the scientific discussion and explicitly encourage young scientists to contribute and submit their work.

the ELAINE Conference Programme Committee

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Monique Zwar  
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## Call for Abstracts



## Progress in Electrically Active Implants – Tissue and Functional Regeneration

On behalf of the Collaborative Research Centre 1270 Electrically Active Implants – ELAINE we cordially invite you to

the *virtual* Conference on Progress in Electrically Active Implants - Tissue and Functional Regeneration 2020  
(ELAINE 2020)

29.–30. September 2020

in Rostock, Germany

At ELAINE 2020, we want to discuss the latest achievements and advancements in the field of electrically active implants. We expect a highly attractive scientific programme, covering all aspects of therapeutic and regenerative electrical stimulation and implant development for bone, cartilage and deep brain stimulation—from multi-scale modelling and simulation, cell and tissue mechanisms *in vitro* and *in vivo* to energy harvesting and electrically conductive and piezoactive materials.

The aim is to discuss the latest achievements in the field in form of invited presentations, selected talks from abstract submissions, and virtual poster sessions. In addition, we particularly invite critical reviews and contributions with negative results or unsuccessful replications to foster the scientific discussion. We explicitly encourage young scientists to contribute and submit their work.

We kindly invite the growing community of researchers, engineers, and medical practitioners from around the world working in the field of electrically active implants, with focus on brain, bone and cartilage stimulation, to submit abstracts for virtual presentation or poster sessions. The conference will serve as a platform for interdisciplinary scientific exchange and networking opportunities with experts, researchers, and up-and-coming leaders in the field of engineering, medicine and life sciences. Topics include, but are not limited to:

- Multi-scale modelling and simulation
- Therapeutic and regenerative electrical stimulation
- Tissue regeneration
- Energy harvesting
- Bioactive implants
- Electrical conductive and piezoactive materials

Due to the current COVID-19 situation across the world, the ELAINE 2020 conference will be going ahead as a 2 day virtual conference. It is a pleasure to present you live-streamed keynote lectures by renowned speakers and selected talks from abstract submission, as well as an interactive poster session and an online networking platform.

We are looking forward to welcoming you (virtual shaking hands) at the ELAINE 2020 conference.



# Progress in Electrically Active Implants – Tissue and Functional Regeneration

**Tuesday - Sept 29<sup>th</sup>**

**09:00 – 09:05 Welcome**

**Keynote Lecture I**

**09:05 – 09:35 Thomas Stieglitz - Neural implants in bioelectronics medicine: tools for diagnosis and novel treatment options**

**Session I: Developments in Electrical Neurostimulators**

- 09:35 – 09:45 John Fleming Clinically-viable approaches for closed-loop deep brain stimulation in Parkinson’s disease
- 09:45 – 09:55 Kevan Hashemi An Implantable, Battery-Powered, Wireless, Stimulator
- 09:55 – 10:05 Franz Plocksties Towards an Energy Autonomous Implant for Closed-loop Neurostimulation
- 10:05 – 10:15 Maria Kober Development of a fully implantable rodent DBS system for long-term neurostimulation

**10:15 – 10:35 Discussion**

**10:35 – 10:45 Coffee Break**

**Keynote Lecture II**

**10:45 – 11:15 María Angeles Pérez Ansón - Multiscale simulation of bone tissue regeneration**

**Session II: Multiscale Modelling and Simulation in the field of Implantology and Tissue Regeneration**

- 11:15 – 11:25 Hendrikje Raben Numerical Model of an Electro-Stimulating Implant for a Porcine Mandibular Critical Size Defect
- 11:25 – 11:35 Bojana Rosic Bayesian multiscale analysis describing mechanical response of bone tissue
- 11:35 – 11:45 Wiebke Radlof Predictability of the mechanical behaviour of additively manufactured porous structures for the application in load-bearing implant structures
- 11:45 – 11:55 Abdul Razzaq Farooqi Computational Modeling of Electroactive Hydrogels for Cartilage-Tissue Repair Using Electrical Stimulation

**11:55 – 12:15 Discussion**

**12:15 – 13:15 Lunch Break**

**Keynote Lecture III**

**13:15 – 13:45 John G. Hardy - Electroactive Biomaterials for Drug Delivery, Tissue Engineering and Regenerative Medicine**

**Session III: Describing Therapeutic and Regenerative Electrical Stimulation – From Idea to Reality**

- 13:45 – 13:55 Kai Budde Documenting an Electrical Cell Stimulation Experiment–Guidelines at Work
- 13:55 – 14:05 Abijeet Mehta Physiological electric fields induce directional migration of mammalian cranial neural crest cells
- 14:05 – 14:15 Judith Evers Characterisation of the electrode-tissue interface of chronically implanted stimulated and un-stimulated deep brain stimulation electrodes
- 14:15 – 14:25 Konstantin Butenko Stochastic optimization of deep brain stimulation in the entopeduncular nucleus in a hamster model

**14:25 – 14:45 Discussion**

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## Progress in Electrically Active Implants – Tissue and Functional Regeneration

**Wednesday – Sept 30<sup>th</sup>**

**09:00 – 09:05 Welcome**

### Keynote Lecture IV

**09:05 – 09:35 Yiannos Manoli - The Vision of Deep-Brain Recording neuroDSM – a Digital Fully-Immersible Silicon Neural Probe**

### Session IV: Electrical Conductive and Piezoactive Materials and Energy Supply to Electrically Active Implants

09:35 – 09:45	Sofiane Bouhedma	Bioheat-based thermoelectric power supply to electrically active implants
09:45 – 09:55	Dennis Flachs	Biocompatible energy-harvester based on FEP-piezoelectrets
09:55 – 10:05	Amir Azinfar	Tuning the surface morphology of polyelectrolyte multilayer films by changing the chain length of the PSS macromolecule on a nanometer scale and examining its mechanical properties in pure water and NaCl solution
10:05 – 10:15	Thomas Distler	Enzymatically Crosslinked Oxidised Alginate Gelatine Hydrogels for Cartilage Tissue Engineering and their Potential for Conductive Hydrogel Derivatives

**10:15 – 10:35 Discussion**

**10:35 – 10:45 Coffee Break**

### Live Poster Session

**10:45 – 11:15 Abstract #1-12**

**11:15 – 11:45 Abstract #14-34**

**11:45 – 12:15 Abstract #36-49**

**12:15 – 12:30 Closing**

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## Progress in Electrically Active Implants – Tissue and Functional Regeneration

### Live Poster Session

<b>A 10:45 – 11:15</b>		<b>Abstract #1-12</b>
#1	Hans-E. Lange and Daniel Kluess	Piezoelectric energy harvesting concept for an orthopaedic implant - Simulation & Implant fatigue testing
#2	Anika Lüttig, Stefanie Perl, Maria Paap, Rüdiger Köhling, Markus Morawski and Angelika Richter	Immunohistochemical examinations of the effects of short-term deep brain stimulation on neuronal activity and components of perineuronal nets in the dtsz hamster
#3	Franziska Sahn, Vivica Frein Grote, Thomas Kreller, Rainer Detsch, Rainer Bader and Anika Jonitz-Heincke	Long term stimulation of osteoblasts with low-frequency alternating electrical fields
#4	Maria Paap, Stefanie Perl, Anika Lüttig, Franz Plockstieß, Christoph Niemann, Dirk Timmermann, Christian Bahls, Ursula van Rienen, Denise Franz, Monique Zwar, Marco Rhode, Rüdiger Köhling and Angelika Richter	Deep brain stimulation as a therapeutic option in dystonia: effects of different frequencies in a phenotypic animal model by using an optimized stimulator
#5	Wenzuo Wei and Juergen F. Kolb	Analysis of Impedance Properties of Trabecular Bone Based on Cole-Cole Analysis, Linear Discriminant Analysis and Effective Medium Approximation
#7	Yogesh Deepak Bansod, Maeruan Kebbach, Daniel Kluess, Rainer Bader and Ursula van Rienen	Multiscale finite element analysis of strain-adaptive bone remodelling with considering bone piezoelectricity
#8	Simone Krüger, Rika Uphoff, Anika Jonitz-Heincke and Rainer Bader	Electrical stimulation leads to enhanced chondrogenic differentiation in co-cultured human mesenchymal stem cells and chondrocytes
#9	Jonathan Dawson, Ursula van Rienen and Revathi Appali	Theoretical framework to study the influence of electric field on the mesenchymal osteogenic differentiation and osteoblast migration
#10	Revathi Appali	Comparison of FitzHugh-Nagumo Model and Heimburg-Jackson Model of Nerve Pulse Propagation
#11	Julius Zimmermann and Ursula van Rienen	Uncertainty quantification for electromagnetic models of biological cells
#12	Kiran Kumar Sriperumbudur, Revathi Appali, Rainer Bader and Ursula van Rienen	Modeling Anisotropic Electric Conductivity of Porous Bone Tissue Using Image-Based Method
<b>B 11:15 – 11:45</b>		<b>Abstract #14-34</b>
#14	Poh Soo Lee, Revathi Appali, Aldo Boccaccini, Vera Hintze and Ursula van Rienen	Investigating the potential of electric field (EF) stimulations and bioactive glass nanoparticles (BGN) to enhance osteogenic differentiation of human mesenchymal stem cells (hMSC)
#15	Sven Neuber, Annetkatrin Sill, Peter Nestler, Heiko Ahrens, Katja Fricke and Christiane A. Helm	Electrically conductive layer-by-layer assembled films using oxidized carbon nanotubes and polycations
#20	Jakob Heller, Pia Wilsdorf, Christoph Niemann, Franz Plocksties, Adelinde M. Uhrmacher, Christian Haubelt and Dirk Timmermann	Assisting Early Design Decision For Implantable Neurostimulators Through Virtual Prototyping
#22	Karthik Sridhar, Judith Evers and Madeleine Lowery	A computational study on the effect of chronic stimulation on the electrode-tissue interface of deep brain stimulation electrodes
#25	Imke Reich, Monique Zwar, Marco Rohde, Valentin Neubert, Stefanie Perl, Lüttig Anika, Franz Plocksties, Angelika Richter, Rüdiger Köhling and Denise Franz	Viability of striatal and pallidal parvalbumin-positive neurons after deep brain stimulation
#26	Konstantinos Spiliotis, Jens Starke, Denise Franz, Angelika Richter and Rüdiger Köhling	Basal Ganglia Network Dynamics in Deep Brain Stimulation - A Frequency Dependent Analysis
#29	Francia Molina, Mareike Fauser, Julius Zimmermann, Kai Budde, Adelinde M. Uhrmacher, Ursula van Rienen and Alexander Storch	In vitro effects of direct current electrical stimulation on forebrain adult mouse neural stem cells
#30	Nikolai Weis, Mareike Fauser and Franz Markert	Dopaminergic plasticity induced by deep brain stimulation in the subthalamic nucleus
#31	Vishnu Prathapan, Peter Eipert, Revathi Appali, Ursula van Rienen and Oliver Schmitt	Modeling and simulation of neural signal activity in a connectome for the study on Multiple Sclerosis
#33	Christian Polley, Caroline Scheufler, Fukun Shi, Thomas Distler, Rainer Detsch, Aldo R. Boccaccini, Jürgen Kolb and Hermann Seitz	Functionalization of 3D printed, piezoelectric barium titanate-hydroxyapatite composite scaffolds with bioactive glass
#34	Max Ulbrich, Christian Völkner, Issam Assi, Regina Lange, Martina Grüning, Barbara Nebe, Ingo Barke and Sylvia Speller	Mapping charge and current distributions on osteoblasts via Scanning Ion Conductance Microscopy

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## Progress in Electrically Active Implants – Tissue and Functional Regeneration

### Live Poster Session

C	11:45 – 12:15	Abstract #36-49
#36	Max Ulbrich, Christian Völkner, Regina Lange, Heiko Lemcke, Robert David, Martina Grüning, Barbara Nebe, Ingo Barke and Sylvia Speller	Local membrane height dynamics of live cells
#37	Christian Völkner, Issam Assi, Martina Grüning, Regina Lange, Barbara Nebe, Ingo Barke and Sylvia Speller	Nanoprobing of osteoblasts adhered to micro-contact printed dendrimer and protein layers
#38	Monique Zwar, Marco Heerdegen, Denise Franz, Valentin Neubert, Franz Plocksties, Christoph Niemann, Dirk Timmermann, Christian Bahls, Ursula van Rienen, Maria Paap, Stefanie Perl, Anika Lüttig, Angelika Richter and Rüdiger Köhling	Increase of striatal inhibitory tone by pallidal deep brain stimulation in awake dystonic hamsters
#39	Chengdong Yuan, Gunasheela Sadashivaiah, Dennis Hohfeld and Tamara Bechtold	System-Level Modelling Approaches of a Miniaturized Thermoelectric Generator for Electrically Active Implants
#42	Valentin Neubert, Monique Zwar, Denise Franz, Marco Heerdegen, Lüttig Anika, Stefanie Perl, Jakob Heller, Christoph Niemann, Franz Plocksties, Frank Krüger, Sascha Spors, Dirk Timmermann, Angelika Richter and Rüdiger Köhling	Identification of Biomarkers for Progression and Amelioration of Disease in a Hamster Model of Dystonia
#43	Alexander Riess, Alina Weizel, Simone Krueger, Anika Jonitz-Heincke, Rainer Bader and Hermann Seitz	A novel device for combined electrical and mechanical stimulation of human cartilage cells
#45	Susanne Staehlke, Fiete Haack, Anna-Christin Waldner, Dirk Koczan, Caroline Moerke, Adelinde M. Uhrmacher and J. Barbara Nebe	Defined micro-topography regulates osteoblasts Wnt/ $\beta$ -catenin transcriptional activation
#46	Sebastian Schick, Max Schröder, Antje Meuser, Frank Krüger and Sascha Spors	Data Management Planning in Large Collaborative Research Consortia
#47	Andrea Andree, Konstantin Butenko, Mareike Fauser, Maria Kober and Ursula van Rienen	In silico characterization of the electric field distribution of deep brain stimulation in a detailed volume conductor model
#48	Sascha Spors, Simon Adrian, Daniel Kluess and Lisa Krukewitt	Exploring the potential of electrical impedance tomography for monitoring of revision total hip replacements
#49	Mohamed Elhensheri, Michael Dau, Vivien Engel, Dirk Timmermann, Franz Plocksties, Rainer Bader, Bernhard Frerich, Peer W. Kämmerer	Electrical direct stimulation for induction of bone regeneration in critical-size mandibular Defects - a preliminary in vivo model

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## Keynotes

**Thomas Stieglitz**

**Neural implants in bioelectronics medicine: tools for diagnosis and novel treatment options**

Laboratory of Biomedical Microtechnology, Department of Microsystems Engineering–IMTEK, University of Freiburg  
Bernstein Center Freiburg, University of Freiburg 79098, Freiburg, Germany

“Our vision is the restoration of lost body functions” said Thomas Stieglitz from the University of Freiburg and on this note, he will open ELAINE 2020 by a lecture about neural prostheses and neuromonitoring.

**María Angeles Pérez Ansón**

**Multiscale simulation of bone tissue regeneration**

Multiscale in Mechanical and Biological Engineering (M2BE), University of Zaragoza, Zaragoza, Spain

María Angeles Pérez Ansón is leading the M2BE group (Multiscale in Mechanical and Biological Engineering) at Zaragoza University and will give a presentation about computational modelling in mechanobiology of skeletal tissue.

**John G. Hardy**

**Electroactive Biomaterials for Drug Delivery, Tissue Engineering and Regenerative Medicine**

Department of Chemistry and Materials Science Institute, Faraday Building, Lancaster University, Lancaster, LA1 4YB, UK

John G. Hardy, head of the Materials Science and Engineering Research Group at Lancaster University, is focused on materials that interact with electricity, light and magnetism for a variety of technical and medical application tissue engineering and regenerative medicine.

**Yiannos Manoli**

**The Vision of Deep-Brain Recording neuroDSM – a Digital Fully-Immersible  
Silicon Neural Probe**

Hahn-Schickard-Gesellschaft für angewandte Forschung e.V., Villingen-Schwenningen, Germany  
Fritz Huettinger Chair of Microelectronics, Department of Microsystems Engineering - IMTEK, University of Freiburg,  
Freiburg, Germany

Yiannos Manoli will talk about the evolution of tissue-penetrating probes for high-density, deep-brain recording of in vivo neural activity. He presents a modular and scalable architecture that integrates the analog-to-digital conversion under the electrodes.

## Talks

### **Clinically-viable approaches for closed-loop deep brain stimulation in Parkinson's disease**

***John Fleming***<sup>1</sup> and ***Madeleine Lowery***<sup>1</sup>

<sup>1</sup> Neuromuscular Systems Laboratory, UCD School of Electrical & Electronic Engineering, University College Dublin, Dublin, Ireland

`john.fleming@ucdconnect.ie`

Closed-loop deep brain stimulation (DBS) for Parkinson's disease (PD) has demonstrated promising results in preliminary clinical studies. So far these studies have focused on utilizing pathologically elevated beta-band oscillatory power derived from the subthalamic nucleus local field potential (LFP) to modulate the amplitude of stimulation. To date, these clinically investigated approaches have been straightforward, with the stimulation amplitude either linearly increasing, decreasing or remaining constant as LFP beta-band power was measured above, below or within a target threshold. In process control literature, there exists a multitude of alternative approaches which may provide improved performance over current clinical control strategies. Proportional-integral (PI) control is a closed-loop strategy extensively used in industrial control applications, however, has as of yet not been translated to clinical investigations of closed-loop DBS. The performance of the PI controller is sensitive to the identification of suitable parameters, or controller gains. Poorly chosen PI parameters may lead to either rapid fluctuations or slow changes in the DBS amplitude, corresponding to potential stimulation side-effects in the former or poor symptom suppression in the later. In this study, a new rule-tuning method is presented for selecting clinically-viable PI controller gains. The rule-tuning method utilizes upper and lower amplitude bound values, the clinically tolerable rate limit for varying the stimulation amplitude and the rate of emergence of the pathological beta-band power to derive suitable PI controller gain values. The PI controller and current clinical closed-loop approaches were tested in a computational model of the cortical basal ganglia network which simulated the subthalamic LFP, the DBS extracellular field and temporal variations in network beta-band activity. Of the controllers tested, the PI controller displayed superior performance for regulating network beta-band activity whilst accounting for clinical considerations and suggests that further investigation of the controller in patients is warranted.

## **An Implantable, Battery-Powered, Wireless, Stimulator**

***Kevan Hashemi***<sup>1</sup>, ***Pishan Chang***<sup>2</sup>, ***Maria Fitzgerald***<sup>2</sup>, ***Seth Lieberman***<sup>3</sup> and ***Chris Schaffer***<sup>4</sup>

<sup>1</sup> Open Source Instruments Inc., USA

<sup>2</sup> Department of Neuroscience, Physiology and Pharmacology, University College London, UK

<sup>3</sup> College of Veterinary Medicine, Cornell University, USA,

<sup>4</sup> Department of Biomedical Engineering, Cornell University, Ithaca, New York, USA

hashemi@opensourceinstruments.com

The Implantable Stimulator-Transponder (IST), manufactured by Open Source Instruments Inc. (OSI), and developed in collaboration with University College London and Cornell University, is a battery-powered, implantable, wireless stimulator. With displacement volume 0.9 ml and mass 1.5 g, the IST is small enough to implant in a mouse. Its 30-mm loop antenna serves both as a command receiver and acknowledgement transmitter. Its two flexible, fatigue-resistant, stainless-steel, helical leads provide 20 mA to a light-emitting diode (LED) for optogenetic stimulation, or 3.7 V for direct, bipolar, electrical stimulation. A single wireless command defines the stimulus pulse length, pulse frequency, and stimulus duration. The same command can initiate the stimulus and request an acknowledgement that will act as confirmation that the stimulus took place during continuous, long-term experiments with little or no human interference. The IST can be implanted for up to eight weeks, ready to deliver a stimulus at any time, before it exhausts its battery. Once explanted, the IST's lithium-polymer (lipo) battery may be re-charged through its stimulation leads, and it is ready to be implanted again. When implanted along side a telemetry device, such as the 0.65-ml Subcutaneous Transmitter (A3028P1) manufactured by OSI, the IST makes possible long-term experiments in which we deliver stimulus in response to biometric signals, or observe biometric signals in response to stimulation. Implanted alone, the IST delivers on-demand stimulus with no human contact.

## Towards an Energy Autonomous Implant for Closed-loop Neurostimulation

***Franz Plocksties<sup>1</sup>, Christoph Niemann<sup>1</sup>, Jakob Heller<sup>1</sup>, Christian Haubelt<sup>1</sup> and Dirk Timmermann<sup>1</sup>***

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Electrically active implants are capable to alleviate symptoms and pain in various parts of the body, assisting and substantially improving the quality of human life. As the underlying effects of electrical stimulation are not fully understood, preclinical studies with animal models are required. However, current stimulation devices for animals suffer from high power consumption leading to short stimulation duration or large batteries affecting the animals well-being. Our research led to an ultra-low power and highly adaptable stimulation platform called STELLA allowing unprecedented long term studies of especially brain diseases such as Parkinson and dystonia in small animals. With  $24.8 \mu\text{W}$  for bilateral DBS Parkinson stimulation in rats, for the first time energy autonomous operation only driven by harvesting ambient energy is in reach. This enables completely new studies where long-term stimulation is necessary. Besides, the STELLA architecture includes basic sensory readout as well as a bidirectional wireless data communication module. Its open access to soft- and hardware invites global communities to usage and modifications. Our further research goal is to extend the STELLA architecture by modules that allow for extensive therapy exploration through sensory readout, working towards closed loop stimulation, all while remaining fully implantable to enable undisturbed animal studies. Due to the stringent constraints resulting from closed loop scenarios, a simultaneous optimization of the energy management and the sensor data processing is mandatory. Hence, novel virtual prototyping and model-based design approaches will be investigated for ultra-low power electrostimulating implants.

## Development of a fully implantable rodent DBS system for long-term neurostimulation

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Deep brain stimulation (DBS) is a neurological treatment option applying electrical high-frequency stimulation through chronically implanted electrodes into specific brain structures. It is most commonly used in a variety of movement disorders. Underlying mechanisms of action of DBS remain enigmatic even more than thirty years after its initial clinical implementation. Regarding the growing field of possible applications, investigations into functional mechanisms are necessary. Especially for preclinical long-term studies, the development of a reliable chronic animal model is essential. Compared to the human situation, rodent studies present special difficulties, e.g. the requirement of miniaturized devices, biocompatible encapsulation and particularly low costs. For this purpose, an implantable chronic DBS device for long-term stimulation in small rodents was developed. It delivers reliably current-driven and charge-balanced stimulation pulses to two channels. A programming interface allows the stimulation parameters to be adjusted for any given study. A special encapsulation technique with epoxy resin leads to a smooth lightweight and corrosion resistant implant. This encapsulation already passed a four-week corrosion test in a PBS-H<sub>2</sub>O<sub>2</sub> solution, successfully. In a pilot study in Wistar-Han rats, the novel implantable stimulation device yielded reduced animal strain compared to standard external stimulators with improved postoperative weight gain with good wound healing. We are therefore the first to present a long-term fully implantable neurostimulation device for chronic rodent stimulation studies, a paramount prerequisite for future mechanistical studies in preclinical settings.



## Numerical Model of an Electro-Stimulating Implant for a Porcine Mandibular Critical Size Defect

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Electrical stimulation is a promising therapeutic approach for the regeneration of large bone defects. Innovative electrically stimulating implants for critical size defects in the lower jaw are under development and need to be optimized in silico and tested in vivo prior to application. In this context, numerical modelling and simulation are useful tools in the design process. In this study, a numerical model of an electrically stimulated minipig mandible was established to find optimal stimulation parameters that allow for a maximum area of beneficially stimulated tissue. Finite-element simulations were performed to determine the stimulation impact of the proposed implant design and to optimize the electric field distribution resulting from sinusoidal low-frequency ( $f=20\text{Hz}$ ) electric stimulation. Optimal stimulation parameters of the electrode length  $h_{el} = 25\text{mm}$  and the stimulation potential  $V_{stim} = 0.5\text{V}$  were determined. These parameter sets shall be applied in future in vivo validation studies. Furthermore, our results suggest that changing tissue properties during the course of the healing process might make a feedback-controlled stimulation system necessary.

## **Bayesian multiscale analysis describing mechanical response of bone tissue**

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The predictive modelling of bone mechanical response as a heterogeneous material requires more realistic mathematical models. This is especially true when describing the nonlinear material behaviour, which is not fully resolved unless observed on multiple scales going from micro-to macro-scale descriptions. As the detailed description on the macroscopic level is not computationally feasible for large scale structures, the multi-scale approaches are often utilized in the numerical practice. In this paper only macro- and meso-scale descriptions of bone tissue will be considered, however, lower scales can be introduced as well. In this talk physics based multi-scale processes governed by their own principles for evolution or equilibrium on each scale are coupled by matching the stored energy and dissipation, in line with the Hill-Mandel principle. In our view the correct representations of stored energy and dissipation is essential for the representation of irreversible material behaviour. The small scale, here the meso-scale, is assumed to be described probabilistically. Therefore, the macro-scale also admits a probabilistic form that is further identified in a Bayesian setting, reflecting the randomness of the meso-scale, the loss of resolution due to upscaling, and the uncertainty involved in the Bayesian process. In this way multi-scale processes become hierarchical systems in which the information is transferred across the scales by Bayesian identification on coarser levels. For this purpose high dimensional meso-scale stochastic simulations are first reduced, and then are mapped to the macro-scale models by employing a generalized version of the Kalman filter. As a result, the probability distributions of macro-scale material parameters are determined, reflecting the aleatory uncertainty at the meso-scale level.

## **Predictability of the mechanical behaviour of additively manufactured porous structures for the application in load-bearing implant structures**

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Additively manufactured porous structures have a great potential to be applied in load-bearing implant structures. Due to the high degree of freedom in design of the additively manufacturing process, the architecture of the unit cells of the porous structures can be adjusted to achieve desired mechanical properties, e.g. to match the elastic modulus of human bone, to reduce stress shielding or to obtain desired ultimate limit and fatigue strength. The predictability of the mechanical behaviour of additively manufactured porous structures is especially important for a safety application as load-bearing structures under quasi-static as well as cyclic load cases. An essential factor influencing the numerical investigation of porous structures are the nonlinearities caused by manufacturing. Besides material nonlinearities, due to different build directions, geometrical nonlinearities have a considerable influence on the predicted mechanical behaviour. In this study, the workflow for the numerical investigation of an additively manufactured porous structure under compression loading is presented. This includes the derivation of a constitutive model as well as damage model on solid hourglass samples, which were produced with the same manufacturing process as the porous structures investigated later. To consider process related geometrical imperfections, like strut diameter variations or strut waviness in the numerical models, digital microscopy and micro computed tomography were used for identification of these imperfections. The numerical models were compared with experiments and reveal that a consideration of the imperfections is essential for an accurate prediction of the mechanical properties of additively manufactured porous structures.

## Computational Modeling of Electroactive Hydrogels for Cartilage–Tissue Repair Using Electrical Stimulation

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The self-repair capability of articular cartilage is limited because of non-vascularization and low turnover of its extracellular matrix. Regenerating hyaline cartilage remains a significant clinical challenge as most non-surgical and surgical treatments provide only mid-term relief. Eventually, further pain and mobility loss occur for many patients in the long run due to further joint deterioration. Repair of articular cartilage tissue using electroactive scaffolds and biophysical stimuli like electrical and osmotic stimulation has the potential to heal cartilage defects occurring due to trauma, osteoarthritis, or sport-related injuries. The application of electrical stimulation results in the movement of ions and the opening of voltage-gated calcium channels. The increased activity of intracellular-calcium concentration activates the underlying mechanisms that facilitate cell growth, proliferation, and differentiation in a tissue-engineered sample. In this regard, a model for the numerical simulation of electroactive hydrogels for the cartilage-tissue repair is presented as the first step towards an optimized experimental design. The multiphysics transport model that includes the Poisson–Nernst–Planck equations and the mechanical equation is used to find the electrical stimulation response of the polyelectrolyte hydrogels. Based upon this, a numerical model on electromechanics of electroactive hydrogels seeded with chondrocytes is presented employing the open-source software FEniCS, which is a Python library for finite-element analysis. We analyzed the ionic concentrations and electric potential in a hydrogel sample and the cell culture medium, the osmotic pressure created due to ionic concentration variations and the resulting hydrogel displacement. The proposed mathematical model was validated at various steps with examples from literature. The presented formulation for the electrical and osmotic stimulation of a hydrogel sample can serve as a model for the development and analysis of a cartilaginous scaffold employing electrical stimulation. By analyzing various parameters, we pave the way for future research on a finer scale using open-source software.

## Documenting an Electrical Cell Stimulation Experiment—Guidelines at Work

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Using electrical stimulation (ES) as a treatment option in a variety of medical applications has been studied for centuries [1]. However, researchers are still trying to better understand the effects of ES [2] as well as endogenous electric fields that appear within living matter [3]. Basic research in this field includes in vitro experiments with cells that play a vital role in the tissue to be treated (e.g., neural or mesenchymal stem cells for deep brain stimulation or bone/cartilage regeneration, respectively). In addition to the uncertainty of established wet-lab experiments, for instance, due to the variability of cells, the complexity and uncertainty inherent to the ES instrumentation have to be considered. For example, electrolytic processes or double layer effects may significantly influence the applied voltage or current. Therefore, thorough documentation is a prerequisite for the replication of ES experiments. It also supports the translation of the setup and findings of these experiments into computer simulations such as the simulation of electric field strengths or intracellular signaling pathways. This will eventually lead to a better understanding of ES. We have extended the Minimum Information About a Cellular Assay (MIACA) guideline with ES-specific parts and presented the advantages of using ELNs [4]. Now, we will show our documentation approach at work for an alternate current stimulation experiment of neural stem cells where voltage- and current-controlled stimulation are compared.

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## Physiological electric fields induce directional migration of mammalian cranial neural crest cells

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During neurulation, cranial neural crest cells (CNCCs) migrate long distance from the neural tube to their terminal site of differentiation. The pathway traveled by the CNCCs defines the blueprint for craniofacial construction, abnormalities of which contribute to three-quarters of human birth defects. Biophysical cues like naturally occurring electric fields (EFs) have been proposed to be one of the important guiding mechanisms for CNCC migration from neural tube to identified position in the branchial arches. Such endogenous EFs can be mimicked by externally applied EFs of physiological strength that have been previously reported to guide migration of amphibian and avian neural crest cells (NCCs). However, behavior of mammalian NCCs in external EFs has never been reported. This study is the first instance of directional migration of a mammalian CNCC line (O9-1) that are shepherd towards the anode by single-axis direct current (DC) EFs of physiological strength. Polarity switch reverses the directedness. The response threshold was 30mV/mm and the migration directedness, distance travelled, and displacement rate increased with the increase in the EF strength. Primary mouse CNCCs also showed similar electrotaxis behavior. Notably, the electrotaxis of CNCCs was not affected by neighboring cell population. Collectively, our results demonstrate for the first time that mammalian CNCCs respond to physiological EFs by robust directional migration towards the anode in a voltage-dependent manner.

## Characterisation of the electrode-tissue interface of chronically implanted stimulated and unstimulated deep brain stimulation electrodes

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**Introduction** Long-term efficacy of deep brain stimulation (DBS) electrodes is affected by changes at the electrode-tissue interface including impedance, neuroinflammation, neurodegeneration and glial scarring. However, the exact mechanisms, in particular the influence of current/voltage applied during active stimulation, are not fully established. The aim of this study was to compare the electrode-tissue interface in chronically implanted stimulated and un-stimulated electrodes in subthalamic nucleus (STN) DBS, an established symptomatic treatment for Parkinson's Disease.

**Methods** Bipolar concentric electrodes were implanted in the STN of 16 male Wistar rats (400g). 9 rats received DBS (130Hz, 100 $\mu$ A, 60 $\mu$ s, 6 hours per day) and 7 received no stimulation for 8 weeks. Impedance spectroscopy (20–300.000Hz) was performed  $\geq 3$  times per week. Brains were fixed by cardiac perfusion with 10% neutral buffered formalin and 5 $\mu$ m sections were labelled for astrocytes (GFAP), neurofilament, neuron specific enolase (NSE) and microglia (Iba-1) by immunohistochemistry. Impedance data was compared using two-way repeated-measures ANOVA and histological data was assessed using custom programs (Matlab 2019b). Experiments were approved by the UCD Animal Research Ethics Committee and licenced by the Health Products Regulatory Authority of Ireland.

**Results** Baseline impedance at 1kHz was 24.5k $\Omega$  (11.1k $\Omega$ (SC), 2.9k $\Omega$ (SEM)). After the first 2 weeks, impedance was significantly lower in the stimulation group (P=0.02). The stimulation induced impedance drop was reversible (N=1). There was a mild increase in astrocytosis to 200 $\mu$ m surrounding stimulated electrodes versus non-stimulated (p=0.03) and a slight increase in activated microglia. Neurofilament and NSE staining revealed no differences in neurodegeneration between the two conditions.

**Conclusions** An effect of stimulation on the surrounding parenchyma and the electrode-tissue-interface beyond the foreign body response was shown. This might include both the electric double-layer at the electrode-electrolyte interface and astrocytosis of the brain parenchyma. Impedance changes might influence novel stimulation protocols where the stimulation intensity is continuously adjusted or active contacts switched. Increased astroglial proliferation might be related to stimulation induced astrocyte activity.

## Stochastic optimization of deep brain stimulation in the entopeduncular nucleus in a hamster model

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Mechanisms and efficiency of deep brain stimulation for dystonia treatment still remain unclear. Clarification is supported by experimental research including stimulation in genetically dystonic hamsters. However, significantly smaller dimensions of their brain structures constrain the implantation possibilities. In case of stimulation of the entopeduncular nucleus, even the exact targeting results in considerable neurological damage to the nucleus by the electrode lead. Therefore, the stimulating electrode contact is placed just above the entopeduncular nucleus. However, the resulting proximity of the electrode to the thalamus could cause undesirable side effects of the stimulation. Such side effects must be avoided if possible, as they would distort the experimental results and make it difficult to validate the experimental hypotheses.

The primary goal of this study is to achieve a precise focalization of the electric field in the entopeduncular nucleus by optimizing the delivered current and configuring a novel design of the stimulating electrode. In that, we start off from a commercially available electrode by Microprobes and modify the outer contact and the tapering. The computational problem takes into account heterogeneous, anisotropic and dispersive properties of the hamster brain tissue. During the optimization, the uncertainties in the tissue conductivity are considered using the combinatorial stochastic annealing algorithm with Hammersley sampling to reduce the total amount of computations. As a result, we provide a new robust protocol for targeted stimulation of the entopeduncular nucleus by a distally implanted electrode.



## Bioheat-based thermoelectric power supply to electrically active implants

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The fraction of elderly citizens in German population is ever increasing. By 2050, over 30 % of the total population will be over 65 years old. Therefore, there is an increasing demand for the development of new medical technologies, mainly electrically active implants with a long lasting power supply. In the last two decades, the power requirements for these implants decreased drastically. Therefore, we investigate the potential of thermoelectric energy harvesting for powering these implants from temperature gradients inside the human body. Thermoelectric generators (TEG) convert the thermal energy into electrical energy.

This contribution proposes a novel implantable medical device with a continuous power supply of around 30  $\mu$ W from a temperature difference of a few degree, typically to be found across the subcutaneous fat layer. It addresses the design and numerical modelling of the TEG integrated within a biocompatible housing. We found that a representative tissue model (including only skin, fat and muscle layer) can be used, which is derived from a more detailed bioheat model based on realistic geometries.

We propose several simplifications on the TEG model, which enable computationally efficient and detailed parametric studies. Electrical power delivery is determined from the generated voltage, considering a resistive load with a matched resistance. Convection, radiation, and evaporation effects on the skin surface are applied to identify the heat transfer effects between the human body and the environment. Additionally, metabolic heat generation in all tissue layers has been implemented as well. A thorough parametric study has been performed to define the key parameters impacting on the system power output. Additionally, an experimental investigation of a commercially available TEG has been performed under different temperature gradients and demonstrated that the TEG in question can deliver the required power for the application.

## **Biocompatible energy-harvester based on FEP-piezoelectrets**

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Implantable medical devices, like pacemakers and deep brain neurostimulators, are powered by batteries with a limited lifetime. To avoid battery exchanges, it is highly desirable to provide sustainable sources to power such devices. The human body itself is a source of abundant energy, with an example being the movement of internal organs (e.g. heartbeat and lung motion). Energy-harvester can use this motion to convert this mechanical energy into electrical power.

Our approach for energy-harvesting is the usage of so-called piezoelectrets. Piezoelectrets are electrically charged cellular polymers that generate electrical power under mechanical force. Over the last decade, their performance with respect to their piezoelectric coefficient, has shown a tremendous increase with values of up to several thousand of pC/N. Typical piezoelectret materials are polytetrafluoroethylene (PTFE) and fluoroethylenepropylene (FEP). Especially the latter encouraged the development of FEP-based vibration-energy-harvesters, which are emerging in the mW/cm<sup>2</sup> range. These values – after further improvement – promise future applications for implanted electronics, namely energy-harvesters. Another striking argument for polymer-based piezoelectret foils is that major drawbacks known from classic piezoelectric ceramics, such as difficult processing and brittleness, are here no issue.

In this work we present a microfabrication process for FEP foils (12.5 μm) based on silicon-thermoforming masters, which enables to tailor the piezoelectric properties of the device. Further, as charge decays rapidly in humid environment as prevalent in the body, we investigate the encapsulation of piezoelectrets to improve their long-term stability. This process however unavoidable deteriorates the mechanical properties and thus the energy output of the harvester. Here, we decided for polydimethylsiloxane (PDMS) as encapsulation material, spin-coated in thin layers. Measurements of the piezoelectric d<sub>33</sub>-coefficient show that encapsulation as expected reduces the piezoelectric constant of the device. However, values for the d<sub>33</sub>-coefficient of several hundreds of pC/N are a promising result.

## **Tuning the surface morphology of polyelectrolyte multilayer films by changing the chain length of the PSS macromolecule on a nanometer scale and examining its mechanical properties in pure water and NaCl solution**

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While polyelectrolyte multilayers (PEMs) are widely used for biomedical and technical applications, it remains a challenge to understand the layer-by-layer self-assembly. By using AFM microscopy, we observed a buckling pattern on the surface of polyelectrolyte multilayer films, in water and air. The PEMs consisted of multilayers of polydiallyldimethylammonium (PDADMA) and polystyrene sulfonate (PSS) exhibiting non-linear and linear growth regimes. The length of the PDADMA chain was always kept constant during film preparation. Both, in water and air, buckling patterns on the film surface appeared, when a short PSS chain with a molecular weight below a threshold value ( $< 33.8$  kDa) was used. The periodicity of the pattern was the same in air and in water. For PSS with a molecular weight above the threshold value, the surfaces were smooth and laterally homogeneous. Moreover, we could show that during film formation using a short PSS chain, the surface structure and the periodicity of the pattern could be controlled also by increasing the number of deposited PDADMA/PSS bilayers. The Young's modulus of the films was determined by colloidal probe force microscopy in pure water and also for different ionic strengths of NaCl. Pattern formation is attributed to stress relaxation of thin films with a low Young's modulus on a hard substrate which cannot move laterally.

## Enzymatically Crosslinked Oxidised Alginate Gelatine Hydrogels for Cartilage Tissue Engineering and their Potential for Conductive Hydrogel Derivatives

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The engineering of hydrogel platforms to enable long-term cell cultivation to induce cartilage tissue formation remains a significant challenge in biomaterials research. While oxidised alginate-based hydrogels proved suitability for various tissue engineering applications [1], the usability of this hydrogel system for cartilage tissue engineering applications remains unexplored. Here, we present enzymatically crosslinked oxidised alginate gelatine (ADA-GEL) hydrogels which offer long term stability *in vitro* (> 30 days), cytocompatibility towards various cell types, and tuneable mechanical properties [2]. We show that the use of microbial transglutaminase in combination with divalent calcium cations as crosslinkers can control the mechanical stiffness and degradation behaviour of ADA-GEL hydrogels. Moreover, it is possible to process the hydrogel precursor via bioplotting to create three-dimensionally (3D) printed open-porous hydrogel scaffolds. The hydrogels allow for adhesion and proliferation of mouse teratocarcinoma ATDC-5 and fibroblast NIH-3T3 cells similar to tissue culture polystyrene controls [2]. In addition, the hydrogels can be used to prepare electroactive ADA-GEL polypyrrole polystyrenesulfonate (PPy:PSS) hydrogel composites, with potential applications for electrical stimulation assisted cartilage regeneration. Our results demonstrate that enzymatically crosslinked ADA-GEL can be a cost-efficient hydrogel matrix with great potential for advanced cartilage engineering applications.

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## Posters

### **Piezoelectric energy harvesting concept for an orthopaedic implant - Simulation and Implant fatigue testing**

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To further improve the current clinical outcome of total hip arthroplasty, implants with additional passive monitoring sensors or active functions for therapeutic measures have been investigated. The development of such instrumented smart implants is strongly connected to the question of an adequate energy supply. Shortcomings of batteries and external power sources promote research towards energy harvesting concepts within implants. In this study we continued our work on a piezoelectric energy harvesting concept for an energy autonomous instrumented hip implant.

By means of experimental testing and finite-element analysis we evaluated the metallic component of our current implant design with regard to mechanical safety in a worst case situation. Based on the set-up of ISO 7206-4:2010, we loaded three modified hip stems in a quasi-static experiment followed by the prescribed structural fatigue test. After successful completion, the test was repeated and incremental increase of the loading level was conducted up to 4.7 kN without effecting fracture of any of the three samples. Additionally, we simulated the stress distribution within the modified hip stem and validated the data with strain gauge measurements from the quasi-static experiments. The percentage deviation between experiment and simulation is 13% and assumed to mainly result from geometric inaccuracies (strain gauge placement, specimen embedding). The numerical results show a stress concentration inside the introduced cavity of 417 MPa von-Mises stress. This is higher than for the previously reported physiological situation but slightly below reported literature fatigue data. It reveals the importance of worst case considerations and the need of our experimental testing.

The fatigue results militate in favour of a safe implant modification, especially considering the more than double numbers of cycles and with additional load levels up to twice as high as required.

## **Immunohistochemical examinations of the effects of short-term deep brain stimulation on neuronal activity and components of perineuronal nets in the dt<sup>SZ</sup> hamster**

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Deep brain stimulation (DBS) is an important therapeutic treatment for patients with dystonia, Parkinson disease and other neurological disorders. While the molecular effects of DBS are nearly unknown, it has been hypothesized that slow normalization of synaptic plasticity or re-organization of the basal ganglia network in addition to immediate effects on neuronal activity are important for beneficial effects in dystonia.

Therefore, we focus on the examination of neuronal activity using fluorescence immunohistochemistry (IHC) of c-Fos, an indirect marker for neuronal activity. IHC is performed in dt<sup>SZ</sup> hamsters after receiving DBS of the entopeduncular nucleus (EPN) or the subthalamic nucleus (STN) with different frequencies (130Hz EPN, 40Hz EPN, 130Hz STN). During EPN-DBS, the severity of dystonia was significantly lower using 130Hz, while 40Hz were less effective and 15Hz and STN-DBS did not exert significant effects. Therefore, we expect a different extent of c-Fos changes in these groups.

For IHC analyses, we focus on the cortico-basal ganglia network but also consider further regions such as the lateral habenula, deep cerebellar nuclei and brainstem nuclei.

A further aim is the investigation of effects of EPN- and STN-DBS on the expression of perineuronal nets (PNs), which play an important role in neuronal plasticity. First data in the DYT1 knock-in mouse model, indicated subtle basal changes of brevican expression, a chondroitin sulfate proteoglycan within the PNs. Brevican levels may play an important role in synaptic plasticity.

With regard to the successfully completed in vivo short-term DBS, we are confident that our IHC investigations will reveal further insights into the mechanisms of DBS. Our additional studies including long-term DBS and its effects on neuronal activity and PN's will complement these findings.

## Long term stimulation of osteoblasts with low-frequency alternating electrical fields

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Bone deformation induce intrinsic voltages in bone and by using the inverse piezo effect, mechanical modification can be formed through an external electrical field. A clinical applied electroinductive screw system uses this effect to treat bone defects. Despite the positive results in clinical studies little is known about the fundamental processes acting during electrical stimulation of bone. Therefore, basic research needs to be done to understand the implication of electrical fields on cells involved in bone formation.

The ASNIS III s screw served as a template to design a Ti6Al4V electrode for studying the effects of electrical fields in vitro. Collagen coated coverslips were placed centered under each electrode and seeded with human osteoblasts. Cells were stimulated 3x45 min/d with a sinusoidal alternating voltage of 700 mV and 20 Hz over 28 days. Metabolic and alkaline phosphatase (ALP) activity, as well as calcification and protein release were examined.

Using the mentioned settings no changes in metabolic and ALP activity could be found. The calcification processes under electrical stimulation were donor dependent as alizarin red staining revealed different amounts of calcified matrix with electrical stimulation. A higher concentration of IL-6, DKK-1 and OPN in the supernatant could be found when cells were cultivated under electrical stimulation. Other bone remodeling marker proteins like OPG, RANKL, Leptin, BMP-2, IL-1 $\beta$  and TNF- $\alpha$  revealed no change in the concentration.

The investigations showed that long term electrical stimulation had no impact on the cell metabolism and on most of the typical bone remodeling markers. However, changes in IL-6, DKK-1 and OPN showed that the osteoblasts perceive the electrical field and that this field leads to changes in the cells. Therefore, further studies in mono- and co-culture will be done with different voltages and frequencies to evaluate the best electrical field for bone formation.

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## **Deep brain stimulation as a therapeutic option in dystonia: effects of different frequencies in a phenotypic animal model by using an optimized stimulator**

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Deep brain stimulation (DBS) of the entopeduncular nucleus (EPN) obtained importance for the treatment of generalized dystonia, a severe movement disorder. Disadvantages of commonly used “high frequency stimulation” (130 Hz) are the lack of benefit in some cases, the high energy consumption and the long latency to improvement. Pathophysiological, the mechanisms of DBS are unknown and it is questionable if lower frequencies are effective. Therefore, we performed studies on the effects of EPN-DBS with different frequencies on the severity of dystonia in the phenotypic dt<sup>sz</sup>-hamster, a model for paroxysmal dystonia.

Based on previous electrophysiological data, we hypothesized that different frequencies (130 Hz, 40 Hz, 15 Hz) of EPN-DBS improve dystonia in the dt<sup>sz</sup> hamster. We used optimized stimulators (50  $\mu$ A, 60  $\mu$ s) allowing precise bilateral electrical stimuli using SNEX-100 electrodes. Since the individual highest severity of dystonic episodes is reached within 3 hours after application of mild stress, the duration of DBS was 180 min. The severity scores reached within each hour during DBS were compared to scores reached during sham-stimulation (inactive stimulator) and pre-sham stimulation in the same animal.

During DBS with 130 Hz, the severity of dystonia was significantly lower within the 3rd hour ( $p < 0.05$ ) in comparison with the severity score reached during pre-sham and sham stimulation. Stimulations with 40 Hz only exerted a trend to antidystonic effects during the 3rd hour compared to pre-sham ( $p < 0.05$ ) but not to sham-stimulation, while 15 Hz aroused no effects.

These results indicate that short-term DBS is effective in the dystonic hamster at the chosen stimulation parameters when using 130 and 40 Hz. Therefore, it represents a suitable model to further investigate the effects of long-term DBS and to give insights into the underlying mechanisms.



## **Analysis of Impedance Properties of Trabecular Bone Based on Cole-Cole Analysis, Linear Discriminant Analysis and Effective Medium Approximation**

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The understanding of local field distributions and current pathways in treated bone is decisive for the success of electrical stimulation (especially via hip implant) and for the patient-specific choice of stimulation parameters. This necessitates an improved spatially-resolved characterization of dielectric properties of osseous tissue, which is an inherently highly inhomogeneous and anisotropic material. In the study, an unambiguously discrimination of dielectric properties of trabecular bone, i.e. femur head, neck and greater trochanter, was obtained by a Cole-Cole and Linear Discriminant Analysis (LDA). The mechanism behind the distinction for different regions, i.e. the possible contributions to the discrimination, could be interpreted from both methods, e.g. from the coefficients at the investigated frequencies. However, an improved and advanced model that can correlate the microstructure and their dielectric properties is still needed. This can be realized by the Effective Medium Approximation (EMA) that considers the contribution of each component (water, fat and porosity) to the bulk dielectric properties. Results show that the microstructural parameters, i.e. bone volume fraction (the ration of bone volume to tissue volume, BV/TV) derived from the EMA is comparable to the one determined by micro-CT.

## **Multiscale finite element analysis of strain-adaptive bone remodelling with considering bone piezoelectricity**

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For therapies using electrically active implants, numerical analysis plays an important role in determining and optimizing the resulting electric field distribution in the region of interest of the targeted tissue. Biological processes such as bone remodelling or cartilage regeneration are hierarchical and thus it is advisable to model them using multi-scale approaches. Bone remodelling is the mechanism that regulates the relationship between bone morphology, bone mineral density distribution and external mechanical loads applied to the bone. In fact, bone tissue possesses piezoelectric properties and thus is capable of transforming mechanical stress into electrical potential. The generation of piezoelectricity in bone is a complex phenomenon and has been shown to play a vital role both in bone adaptation and remodelling. Thus, for better understanding the interplay between mechanical and electrical stimulation during these processes, strain-adaptive bone remodelling models without and with considering the piezoelectric effect were simulated using the Python-based open-source packages. To discretise the bony geometry and its properties, a finite element method was employed for the spatial variables and an explicit Euler scheme for the temporal derivatives. The predicted bone density distributions were evaluated against the radiographic scan of a proximal human femur and the bone density calculated using a bone mineral density calibration phantom. The simulation results demonstrated that the electrically stimulated bone surface enhanced bone deposition and mechanical stimuli due to daily physical activities could be partially replaced by therapeutic electrical stimulation to reduce bone loss in osteoporosis. The bone remodelling algorithms implemented using an open-source framework facilitates reproducible research by providing the necessary data and code to reproduce the analyses.

## Electrical stimulation leads to enhanced chondrogenic differentiation in co-cultured human mesenchymal stem cells and chondrocytes

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**Introduction** The therapy of cartilage lesions represents a considerable clinical challenge. The combination of cells, biomaterials and external biophysical stimuli may be appropriate to restore the native physiological properties of the injured articular cartilage (Awad et al. 2004; Vaca-González et al. 2019; Przekora 2019). The co-cultivation of human mesenchymal stem cells (MSCs) and human chondrocytes (Qing et al. 2011; Zuo et al. 2013; Meretoja et al. 2012; Cho et al. 2018) and their stimulation by electrical fields (Hiemer et al. 2018) has been shown to improve cartilage matrix formation. The aim of our study was to examine the effects of capacitively coupled electrical field stimulation on chondrogenic differentiation of co-cultured human MSCs and chondrocytes.

**Methods** For this purpose, chondrocytes, MSCs and their co-culture (ratio 50:50) were seeded on Collagen 1-based scaffolds and integrated in a stimulation device as previously described by Krueger et al., 2019. After seven days of stimulation (1 kHz and 100 mVeff), cellular activity and expression of chondrogenic markers (Collagen 1, Collagen 2, MMP-13) were investigated.

**Results** The results of our study suggest that the used electrical field has desired effect on the co-cultured cells. Although the co-cultured cells were seeded on Collagen 1-based scaffolds a reduction of collagen 1 gene expression compared to stimulated chondrocytes was detected after electrical stimulation. This is appropriate, as a decreased Collagen 1 gene expression indicates a reduction in the undesirable formation of fibrous cartilage.

**Conclusion** During in vitro cultivation, electrical field stimulation could improve differentiation capacity of co-cultured MSCs and chondrocytes and therefore could enhance cell-based therapies for cartilage repair. In further studies, the optimisation of parameter combinations as well as the elucidation of the underlying cellular mechanisms should remain in focus.

## **Theoretical framework to study the influence of electric field on the mesenchymal osteogenic differentiation and osteoblast migration**

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Fracture healing and bone regeneration is a highly complex and tightly regulated process. Mesenchymal osteogenic differentiation and osteoblast migration play an important role in fracture healing. Electrical fields are known to influence both osteogenic differentiation and osteoblast migration. As a result, electrical stimulation via bio-implants is being successfully used to treat bone defects. However, so far the mechanisms of osteoblast activation and migration and how electrical fields influence these remain unclear. We present theoretical approaches to study the dynamics of osteoblasts. Our theory is based on in vitro experimental studies of the influence of electric fields on mesenchymal osteogenic differentiation and osteoblast migration. We show that simple mean-field and particle based models, capturing key cellular processes, can describe the experimentally observed dynamical behavior of osteoblasts. Our framework allows us to study the influence of applied electrical field on the cellular processes of osteoblasts, both in osteogenic differentiation and osteoblast migration.

## Comparison of FitzHugh-Nagumo Model and Heimbürg-Jackson Model of Nerve Pulse Propagation

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In 1952, the origin of action potential in the nerve membrane was described by the Hodgkin-Huxley model. However, the computational complexity of this model has led to several simplifications such as FitzHugh-Nagumo model. The FitzHugh-Nagumo model abstracts all of the electrical characteristics of Hodgkin-Huxley model and is computationally less expensive. This model eases the usage of fitting parameters of the Hodgkin-Huxley model through its two coupled first-order differential equations with five fitting parameters.

In 2005, a new interpretation of nerve's action potential as a density pulse has been proposed by Heimbürg and Jackson. The corresponding mathematical model, Heimbürg-Jackson model, describes the neural signal as a density pulse. This alternative mathematical model has described all of the action potential properties including the reversible heat. In addition, this model is free of fitting parameters as all of the parameters are taken from the experiments.

The nerve models play an important role in the in-silico studies of electrically active neural implants such as deep brain stimulation, cochlear implants and retinal implants. In this contribution, a mathematical comparison of FitzHugh-Nagumo model with the Heimbürg-Jackson model will be presented. The importance of biophysical interpretation of these mathematical models will be discussed.

## Uncertainty quantification for electromagnetic models of biological cells

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Developing reliable models to understand the interaction between electromagnetic fields and biological cells is a challenging task due to a lack of precise data. We present an approach to estimate the induced transmembrane potential. The approach is based on the electroquasistatic formulation of Maxwell's equations and requires knowledge of the conductivity and relative permittivity of the different constituents of the system under investigation (that is cell membrane, cytoplasm and extracellular medium). The values of the different parameters and their uncertainties are based on experimental data. Starting from the parameters' uncertainty, the uncertainty of the model output is estimated in a mathematically rigorous fashion. The modelling outcome enables us to suggest possible electrical stimulation experiments to test different hypotheses on the mechanism of interaction.

## Modeling Anisotropic Electric Conductivity of Porous Bone Tissue Using Image-Based Method

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Bioactive implants such as cochlear implants and stimulators for fracture healing operate through bone interfaces. Often in in silico studies, interfaces like the femoral bone or cochlear modiolus, which are porous, are assumed as homogenous and non-porous bone structures to overcome the modeling complexities. However, such assumptions would lead to incorrect results of numerical simulation. Therefore, we have used an image-based method to model the porosity and anisotropic conductivity of bone tissue. In this contribution, we compare the electric field distribution in the region of interest in four modeling scenarios: first, homogenous bone structure with isotropic conductivity, second, homogeneous bone structure with anisotropic conductivity, and third porous bone structure with isotropic conductivity and fourth, porous bone structure with anisotropic conductivity. In this context, we point out the advantages and pitfalls of using the actual porosity modeling approach over the effective conductivity approach in in silico studies.

## Investigating the potential of electric field (EF) stimulations and bioactive glass nanoparticles (BGN) to enhance osteogenic differentiation of human mesenchymal stem cells (hMSC)

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**Introduction** In bone, short-term injury potentials and load-dependent electric fields (EFs) are generated by streaming potentials and piezoelectricity of collagen molecules and hydroxyapatite. Despite its role in bone homeostasis, EFs are not widely applied in bone tissue engineering and the underlying mechanisms inducing osteogenesis remain poorly understood. Besides the extrinsic stimulants, the material of bone implants is equally important. Specifically, bioactive glass nanoparticles (BGN) have garnered abundant attentions for its osteoinductivity, osteoconductivity, biocompatibility and potential to form a hydroxyapatite layer that bonds strongly with native bone. Specifically, the release of Si<sup>4+</sup> and Ca<sup>2+</sup> ions over time also have notable enhancing effects for osteogenic differentiation and cell proliferation. In this study, the potential complementary effects of EFs and BGN to enhance osteogenic differentiation of hMSC are investigated. This is further coupled with variable EF stimulation regimes to identify an effective combination. Based on these results, the effects will be simulated through macroscale modelling.

**Methods** Glass coverslips (Ø13 mm) coated with 2 mg/mL collagen type I (COLI) and BGN are cultured in osteogenic differentiation medium for 28 days. Specifically, dexamethasone is omitted to elucidate the efficacy of EFs and BGN to induce osteogenic differentiation. Pure EF is exerted through a Transformer-Like Coupling (TLC) system. An effective EF stimulation regime (frequency = 10 Hz, field strength = 0.36 V/m, pulse width = 7 ms, 28 days) that enhance osteogenic differentiation in our previous studies is applied. The duration of EF stimulation is further investigated: 1) Intermittent (4 h EF / 4 h Pause), a reference point from previous studies, 2) Continuous (12 h EF / Pause), 3) Spaced interval (24 h, once every 4 days). Corresponding samples without EF stimulation are used for comparison.

**Preliminary Results** Osteogenic differentiation is increased on coverslips coated with COLI+BGN. Further experiments with intermittent EF stimulation are on-going.



## **Electrically conductive layer-by-layer assembled films using oxidized carbon nanotubes and polycations**

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Surface functionalization by ultrathin films is becoming increasingly important for technological and biological applications such as the electrically active implants. nm-thick films were made by sequential adsorption of different polycations (strong polycation PDADMA; weak polycations PAH and branched PEI) and oxidized carbon nanotubes (CNT). The degree of oxidation of CNTs was determined by XPS, FTIR and UV-vis absorption spectroscopy. Quartz crystal microbalance and ellipsometry have shown that film structure depends on the used polycation. AFM-Images showed a predominantly horizontal orientation of CNTs. Ohmic behavior with constant electrical conductivity of each CNT/PE film was constant, values up to  $5.9 \times 10^4$  S/m were found, an order of magnitude better than reported for LBL films up to now, yet one order less than found for  $\mu\text{m}$ -thick films made from pure CNTs.

## Assisting Early Design Decision For Implantable Neurostimulators Through Virtual Prototyping

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The demand for neurostimulators is growing globally as electrical stimulation is used as a therapy option for a growing number of neurological disorders. To understand the operational principles of these disorders, neurostimulators have to be adapted for animal testing and the implementation of additional sensory units. However, most stimulators are driven by a non-rechargeable battery under a tight power consumption and volume constraint, deeming ultra-long runtimes impossible. Consequently, the adaption of existing stimulators has to meet a formerly unmet level of optimization. To further runtime and power optimization we utilized virtual prototyping.

This simulative approach allows us to model the combined behavior of different subsystems, which is not observable in conventional prototyping. This includes different power supply and voltage configurations along with their respective influence on power consumption and consequently, runtime. Additionally, we are able to simulate the impedance change of the electrode through gliosis as a circumstance affecting the overall power consumption of the implant.

The overall model combines different submodules with varying abstraction levels on the digital as well as analogue domain. This work proposes a power model for a developed neurostimulator, based on a time-continuous battery model and power state machines. The SystemC-AMS implementation was validated against discharge-measurements of a state of the art neurostimulator called Software Defined Implantable Platform (STELLA).

This simulation-based architectural exploration revealed a possible runtime extension for split voltage levels on the micro-controller and stimulation unit. The ingrowth of the electrodes into the surrounding tissue and thus the needed voltage headroom on overall power consumption was identified as a non-neglectable factor for runtime estimation. Additionally, the trade-off between battery runtime and volume has been assessed for optimal working points.

Therefore, virtual prototyping can be used to further the understanding of nonlinear interaction between subsystems on the implant and thus extend runtime and optimization.

## **A computational study on the effect of chronic stimulation on the electrode-tissue interface of deep brain stimulation electrodes**

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The electrode tissue interface (ETI) is an important functional feature of deep brain stimulation (DBS) electrodes for stimulating and recording of neural tissues. Both clinical and preclinical studies observe increased electrode impedance following chronic implantation and a reduction with the start of electrical stimulation. However, under chronic stimulation, it not well established whether observed electrode impedance changes are due to changes in ETI properties surrounding the electrode. Moreover, the encapsulation tissue properties implemented in state-of-the-art DBS models are resistive in nature. The aim of this study was to investigate effect of electric stimulation on the ETI surrounding electrode and its effect on the voltage distribution in the surrounding tissue.

Experimentally recorded impedance data were used in combination with a 3D finite element model of the rat brain to estimate dispersive properties of the encapsulation tissue and ETI surrounding a concentric bipolar electrode. Electrode encapsulation tissue properties were first estimated from the experimental data under non-stimulation conditions. The electrical double layer properties during stimulation were then estimated from the experimental stimulation data assuming protein dissolution over the active electrode surface during stimulation (D Merrill et al, 2005).

The influence of dispersive encapsulation tissue properties on the voltage waveform in the surrounding tissue can be seen when pulse duration exceeds 400 $\mu$ s for current control stimulation. The estimated effective surface area (ESA) for stimulation condition was 55% higher compared to non-stimulating condition. The increase in the ESA may be due to repulsion of proteins and cells from the electrode, which in turn increase the ETI capacitance and decrease electrode impedance. In conclusion, computational models of rat DBS have been developed to help identify the electrical properties of the ETI and encapsulation tissue in stimulation and non-stimulation conditions. These DBS models correlated with pre-clinical outcomes can be a critical for developing closed loop DBS.

## Viability of striatal and pallidal parvalbumin-positive neurons after deep brain stimulation

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Striatal parvalbumin-positive (PV+) interneurons are drastically reduced in the dtsz-hamster, an genetic animal model of generalized dystonia, and are suggested to provoke the hyperkinetic movement disorder. Despite their low portion of striatal neurons with 3-5 %, the PV+ interneurons innervated up to 50 % of striatal medium spiny neurons (MSN) and mediated the main feedforward inhibition. Decline of the PV+ interneurons lead, among other things, to disinhibition of the MSN, which results in increased projection of direct pathway MSN to the globus pallidus internus (GPi). Deep brain stimulation (DBS) of the GPi (related to entopeduncular nucleus in rodents) diminished the severity of dystonia in dtsz-hamsters. However, the underlying mechanisms of DBS are still not clear. The viability of PV+ neurons was verified by immunohistochemical staining with Anti-Parvalbumin in order to preclude cell damage through tissue modification by the implanted electrode and the electrical stimulation. Awaken dtsz-hamsters with bilaterally implanted DBS-electrodes were treated with 50  $\mu$ A current-pulse and frequency of 130 Hz for 3 h. Acute coronal brain slices were subsequently prepared. The number of PV+ neurons in the striatum and the globus pallidus externus, which is innervated by the stimulated GPi, was compared with native and sham-stimulated (implanted electrode, no stimulation) dtsz-hamsters. Due to no significant discrepancy between the three groups, we exclude harmful effects on striatal and pallidal PV+ interneurons through DBS. This result allows for further examinations on the main inhibitory interneurons at molecular and single cell level to elucidate the pathophysiology of dystonia and mechanisms of DBS.

## Basal Ganglia Network Dynamics in Deep Brain Stimulation - A Frequency Dependent Analysis

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A computational large-scale biophysical model related to Parkinson disease (PD) and deep brain stimulation (DBS) treatment is proposed. Using complex network theory and Hodgkin Huxley neurons, four areas of the basal ganglia (BG); the globus pallidus (externa / interna) (GPe-GPi), the subthalamic nucleus (STN) and the thalamus, are modelled. Macroscopic quantities such as the synchronization index and the mean synaptic activity can be derived from the model.

We show, in accordance with dopaminergic deficit in PD, how different levels of striatal inhibition to BG areas switch the system dynamics from "normal" to a "parkinsonian", i.e. switching from faithful to disturbed transfer of information through the network. The computational model includes the effect of DBS in the STN, and explains how high-frequency stimulation influences the whole network. Specifically, during DBS conditions, the model reproduces a de-synchronisation or declustering of GPe and GPi activity which is projected to the thalamus. Defining and quantifying the response efficacy of thalamic activation during DBS, we deduce ranges of stimulation frequencies optimal for therapeutic success. The entropy calculation of the synchronization index and mean synaptic activity confirms the results of the response efficacy.

## **In vitro effects of direct current electrical stimulation on forebrain adult mouse neural stem cells**

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Deep brain stimulation of the subthalamic nucleus (STN-DBS) enhances adult neurogenesis *in vivo*, but mechanisms still remain unknown. Since network modulations through electrical stimulation are based on alterations of cellular and neurochemical activity, *in vitro* studies of adult neural stem cells (aNSCs) should be helpful for understanding the phenomenon. Here we investigated the effects of intermittent direct current (DC) electrical stimulation (ES) on aNSCs derived from the murine subventricular zone (SVZ-aNSCs) *in vitro*. Cells were kept in an adherent monolayer culture system and submitted to 1 h of 1.5 V DC stimulation daily during either proliferation (4 days) or differentiation phase (6 days) or both using a 6-well stimulation chamber with platinum L-shaped electrodes in a parallel circuit. The resulting electric current was continuously monitored during stimulation. Short-term DC stimulation induced cathodal migration in aNSCs, while chronic application led to a stabilization of stem cell state indicated by Nestin expression without increased proliferation exclusively at the cathodal side. When submitted to differentiation conditions, DC stimulation induced differentiation into both tubulin+ neurons and GFAP+ astrocytes without changing the proportion of newly-generated cell types, though these results are again confined to regions close to the cathode. Here, we demonstrate that intermittent DC stimulation alter neural stem cell behavior on both the stem cell level and in their downstream differentiation properties.

## Dopaminergic plasticity induced by deep brain stimulation in the subthalamic nucleus

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**Objective** Deep brain stimulation (DBS) is a well-established therapy for mid- to late-stage Parkinson's disease (PD), though the choice of the optimal target region is still under debate, since both DBS in the subthalamic nucleus (STN) and the internal globus pallidus (GPI) have proven effective for the alleviation of motor deficits. In addition, a potential disease-modifying effect has been suspected from studies of STN-DBS in both toxin-based and viral vector-induced PD animal models, though it has so far not been assessed in GPI-DBS.

**Methods** Rats were injected with 6-hydroxydopamine into the median forebrain bundle to induce degeneration of the dopaminergic nigrostriatal and mesolimbic system. After development of a stable phenotype, rats underwent bilateral electrode implantations into either the STN or GPI, respectively, and were submitted to either chronic DBS or sham stimulation for a total of 5 weeks. Animals were sacrificed at 6 weeks and histological analyses of total neuron counts in the targets regions and the Substantia nigra as well as a quantification of dopaminergic cell numbers performed.

**Results** Both STN- and GPI-DBS did not alter total neuron counts as indicated by Nissl staining in both the respective target regions and the Substantia nigra compared to sham stimulation. Though, STN-DBS increased the number of TH+ dopaminergic neurons in the nigrostriatal and mesolimbic dopaminergic systems of the Substantia nigra and ventral tegmental area, respectively. Accordingly, TH+ fiber density was increased in the corresponding projection sites in the striatum and Nucleus accumbens. Interpretation: Our data support the putative neuroprotective effect of STN-DBS in a mechanistically relevant model of PD, though this effect seems to be limited to the stabilization of the dopaminergic phenotype and is confined to a specific stimulation site.

## Modeling and simulation of neural signal activity in a connectome for the study on Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating condition affecting the brain and spinal cord. Despite being the most prevalent disabling adult neurological diagnosis in Europe and the US, our understanding of its cause, pathogenesis and pathophysiology is still incomplete, and no treatments are currently available that arrest disease progression. A greater understanding of MS pathology is necessary to allow more effective disease management and therapeutic intervention, yielding improved patient outcomes. So far, there exists no MS model at the scale of neuron populations. Here, we aim to investigate the relation of network architecture, dynamic models, and disease progression. The latter appears to spread neuronal pathologies, namely anterograde trans-synaptic/trans-neuronal degeneration and retrograde trans-synaptic/trans-neuronal degeneration. This has direct functional effects on brain regions connected through axons with changed myelination and axonal damage. Myelin sheaths are electric isolators wrapped around the nerve fibre and are also responsible for the fast propagation of neuronal signals. One hypothesis is that demyelination affects multiple primary and secondary target regions of a connectome. Therefore, the objective of this study is to predict the dynamic changes in target regions in a connectome.

An accurate model is needed to accomplish an appropriate simulation of demyelination and remyelination processes [1]. Hence we model the myelination of axons as a parameter that allows us to mimic different clinical subtypes of MS. Here, the integrate and fire neuron model (quadratic, leaky, exponential) and the axonal cable model is considered to adapt the dynamics of myelination in the weighted and directed connectome data [2]. Then the compartmental modeling is incorporated to propagate the action potential. The simulation is carried out in a JAVA application platform (NeuroVIISAS) where the myelin and axonal properties could be altered at specified neurons in a connectome.

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## Functionalization of 3D printed, piezoelectric barium titanate-hydroxyapatite composite scaffolds with bioactive glass

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The fast and stable integration of synthetic bone replacement materials at the implantation site is one of the main challenges in bone tissue engineering. Through the combination of tailored biomaterials and advanced manufacturing technology such as 3D printing, numerous breakthroughs have been achieved in recent years to specifically improve the osteointegration of such synthetic scaffolds. In the study presented here, we aim to combine electrical stimulation capacity and bioactivity in barium titanate/hydroxyapatite/bioactive glass (BT/HA/BG) scaffolds. Based on a barium titanate and hydroxyapatite composite scaffolds were 3D printed, followed by infiltration and coating using bioactive glass (45S5) slurry via a dip coating process. Different groups of scaffolds, sintered after infiltration (900 °C and 1000 °C) and unsintered, were analysed with respect to their porosity, the distribution of the 45S5 particles, their mechanical, dielectric, and piezoelectric properties. The dip-coating process was able to homogeneously infiltrate the scaffolds, and 45S5 particles could be identified in cross-sections via scanning electron microscopy coupled with electron dispersive X-Ray spectroscopy. With respect to the dielectric and piezoelectric properties, a slight decrease of the relative permittivity and a slight increase of the electrical conductivity with a simultaneous reduction of the piezoelectric constant  $d_{33}$  could be observed compared to the non-infiltrated BT/HA control. BT/HA/BG scaffolds showed promising piezoelectric functionality. The results pave the way for future investigations of the formation of hydroxy-carbonated apatite in contact with simulated body fluid to evaluate the bioactive performance of the scaffolds.

## Mapping charge and current distributions on osteoblasts via Scanning Ion Conductance Microscopy

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In SICM an ion current through a nanopipette opening of ~50 nm serves as interaction signal to keep the probe at nanoscopic, constant distance to the cell surface. The main observable is the 3D nanomorphology on the apical membrane of live, adhered cells [1]. The method can be augmented to render it sensitive to the imaging of cell surface charges and ion channels. This is done via online comparison of forward and backward currents. A transmembrane ion current would not change sign upon bias reversal, unlike the Faradaic ion current through the nanopipette [2]. The strategy is to use a DC bias plus a modulated AC voltage in order to obtain transmembrane current sensitivity and to acquire respective maps on the surface of adhered osteoblasts. Since osteoblasts are considered non-electrifiable, this concerns in the first-place quasi-static ion channels, though action potential firing cannot be fully excluded [3]. In a first step we changed the modulation frequency to 200 Hz in order to achieve the fastest possible topography imaging, which is limited by capacitive currents. In a second step we acquire pairs of apparent topographies at two bias polarities on surfaces with heterogenous zeta potential. The third step we seek to raise the frequency into the kHz regime to allow a faster imaging of live osteoblasts, while obtaining charge information as well as the topography.

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## Local membrane height dynamics of live cells

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Cellular membrane fluctuations are considered for monitoring physiologic and pharmacologic effects [1]. Scanning Ion Conductance Microscopy (SICM) is a nanoprobe method to acquire morphologies on live cells. We operate the nanopipette-probe on fixed lateral locations and record SICM time traces in order to assess membrane fluctuations and cell activities with regard to processes [2]. Height variations of live osteoblasts and cardiomyocytes are analyzed in time and frequency domain. To that end we inspect scaling exponents as slopes in log-log plots of the power spectral density versus frequency. Osteoblasts show in average lower scaling exponents than expected from pure membrane bending stiffness [3], however with substantial spreading. Cardiomyocytes show scaling exponents around -2.5, besides a pronounced frequency response behavior due to the electromechanical action. We discuss the origin of the spreading in terms of position on the cell and cell fitness.

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## Nanoprobing of osteoblasts adhered to micro-contact printed dendrimer and protein layers

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Chemical and physical surface gradients to control local cell adhesion and migration may allow to find routes to improve osseointegration of implants. Therefore, the local as well as the mesoscopic responses of living osteoblast-like cells (MG-63) were studied by means of Scanning Ion Conductance Microscopy (SICM) [1] and Fluorescence Microscopy, respectively. To achieve molecular landscapes with a small topographic corrugation height, amine-terminated PAMAM dendrimers and albumin were deposited in a stripe pattern on glass cover slips by direct micro-contact printing [2]. A distinct spindle shape oriented parallel to the surface pattern as well as a preferential adhesion of the cells on the glass site is observed when the width of the stripes is in the regime of 20 microns. SICM-measurements reveal a high ruffle density on the plasma membrane at the cell poles.

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## **Increase of striatal inhibitory tone by pallidal deep brain stimulation in awake dystonic hamsters**

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There is strong evidence that the development of the movement disorder dystonia is based on a dysfunction of the basal ganglia and the associated thalamo-cortical network. Despite the assumption that a reduced GABAergic inhibition may be responsible for this, the precise understanding of the underlying pathomechanism of dystonia is largely unknown. Hence, the therapeutic options for treating the symptoms of most types of generalized dystonia are also inadequate. Deep brain stimulation (DBS) in the globus pallidus internus (GPi) is considered to be the most relevant treatment option for patients with severe dystonia. It is supposed that GPi-DBS affects disruption of the striatal control of the globus pallidus, possibly leading to disinhibition of the thalamus. The hypotheses range from a general silencing of the target nuclei (e.g. due to a depolarization block), via various changes in thalamic fire behavior, to disruption of the oscillatory activity in the beta-range.

We hypothesize that DBS alters the function of the striatal network through axonal backfiring or indirectly through thalamic coupling. The dtsz hamster, an animal model of spontaneous generalized dystonia, was used to test this hypothesis.

Stimulation electrodes were implanted bilaterally in both dystonic dtsz hamsters and non-dystonic controls to target the entopeduncular nucleus (EPN), the equivalent of human GPi. DBS and sham-DBS were performed in awake and freely moving hamsters for three hours. Immediately after EPN-DBS, brain slices were prepared from these animals in order to measure the excitability of the network, and its inhibitory control after GABA receptor block by recording potentials of the synaptic cortico-striatal field.

After DBS, cortico-striatal responses were increased in both non-dystonic and dystonic tissue. However, the inhibitory control was influenced differently: DBS increased the inhibitory control in dystonic and decreased it in non-dystonic tissue, possibly via presynaptic mechanisms. DBS possibly restores striatal inhibitory tone.

## System-Level Modelling Approaches of a Miniaturized Thermoelectric Generator for Electrically Active Implants

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The increasing aging population poses a serious challenge to the healthcare system and motivates the development of medical technologies. In the last decades, implantable medical devices have been widely used and developed, e.g. cardiac pacemakers, deep brain stimulators and cochlear implants. However, their limited battery capacity is always a key challenge. In order to supply lifetime power to implants, the miniaturized thermoelectric generator (TEG) is utilized to harvest the thermal energy from temperature gradients inside human body. In this work, an accurate human body thermal model is constructed by considering the physiologically correct thermal transfer effects, such as internal heat transfer and external heat transfer effects. Moreover, temperature-dependent realistic material properties are applied to the tissues and to the components of TEG. To enable efficient human body temperature simulation, we investigate the feasibility of nonlinear model order reduction methods such as proper orthogonal decomposition and dynamic mode decomposition methods. For an efficient design optimization of TEG, the compact human body model is applied within the submodeling approach. The temperature distribution results are back-projected as boundary conditions for the TEG submodel. Furthermore, we present an optimization strategy for TEG based on replacing the detailed device by a dummy one. The fill factor, a geometry parameter defining the amount of area occupied by the thermocouples in relation to the total device size, is modeled as the equivalent thermal conductivity of the thermoelectric material. The parametric model order reduction method is applied to yield a highly accurate and compact parameter-independent reduced TEG model. To maximize the power output of TEG, a system-level co-simulation circuit is constructed based on the reduced TEG model and parametric studies of the fill factor and the thermal boundary conditions are performed.

## Identification of Biomarkers for Progression and Amelioration of Disease in a Hamster Model of Dystonia

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**Introduction** Electrocorticography and electroencephalography (ECoG/EEG) allow for recording brain activity. By implanting wireless devices, brain signals of small rodents can be visualized during different stages of behaviour, e.g. sleep or resting, over periods up to several months. A trade-off between number of electrodes, sampling rate and battery life has to be considered before conducting experiments. While single electrodes implanted on the cortex' surface allow for reducing sampling rates and longer battery life, the implantation of electrode arrays or multichannel electrodes and reasonable sampling rates require a cable tethered solution. Recordings are often prone to artifacts, with chewing, grooming and movement contaminating the signals. ECoG/EEG patterns predictive of disease progression over several days have not been identified yet.

**Methods and Results** 7 dtsz hamsters, as a model organism of dystonia exhibiting dystonic attacks, were equipped with EEG recording devices by subcutaneous implantation. Electrodes were placed on the motor cortex above EPN and referenced against the visual motor cortex as caudally as possible. ECoG and video was recorded for up to 7 days continuously.

ECoG recordings were examined visually and artifacts were annotated. Several dystonic attacks were identified visually. No obvious patterns or changes during the attacks could be identified.

**Outlook** Considering the large amount of data and annotations, we will

1. create a database of annotated patterns for future use and automated artifact detection and recognition, aiming for species independence
2. use Machine Learning methods to distinguish ECoG patterns between dystonic vs. non-dystonic phases
3. use Machine Learning methods to predict impending dystonic attacks (timescale preferably from hours to seconds prior) by identifying predictive patterns
4. simplify detection of said patterns and incorporate into event-triggered electrically active implants.

## **A novel device for combined electrical and mechanical stimulation of human cartilage cells**

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This work presents a device for combined mechanical and electrical stimulation of human cartilage cells. The device is designed for use under various atmospheric conditions, in particular inside incubators with high humidity and elevated temperature. It enables the individual stimulation of up to twelve cell seeded scaffolds based on a timetable. In order to facilitate operation, a graphical interface was created that allows the user to define the schedule and control the device. A microcontroller is used for real-time implementation of the control tasks, which connects the various system components with one another via interface cards designed in-house. Compression and shear are implemented as mechanical stimuli, which can be used separately or in combination with electrical stimulation. The compression is exerted by plungers and is path-based with frequencies up to 10 Hz, limited by the scaffold height (10 mm). It can be configured independently for each sample. The shear stimulation takes place equally for all samples via a horizontal drive unit. Electrical stimulation is provided by sinusoidal signals with frequencies of up to two MHz and peak-to-peak voltages of up to 42 V (electrical field strengths of a few V/m). The signal is introduced into the sample by means of capacitive coupling via a pair of planar electrodes. The signal source is a circuit developed in-house, including an associated circuit board based on function generators. We aim to examine the influence of individual electrical and mechanical stimuli and their combination on chondrogenic differentiation of cells seeded on various scaffold materials. Due to the high degree of automation and the possibility to apply different stimulation parameters to each individual well, it is possible to efficiently investigate their influence. This allows to establish an optimized ex vivo 3D cultivation of human chondrocytes and mesenchymal stem cells on collagen- and hydrogel-based scaffolds.



## Defined micro-topography regulates osteoblasts Wnt/ $\beta$ -catenin transcriptional activation

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The physico-chemical surface design of implant materials effects the surrounding cells. Defined sharp-edged micro-topographies affects the osteoblasts morphology, actin cytoskeleton organization, Ca<sup>2+</sup> mobilization, induced a cellular stress reaction with low adenosine triphosphate (ATP) level and ultimately impaired osteogenesis. Further in-vitro analysis of MG-63 osteoblasts on defined titanium-coated micro-pillars (5 × 5 × 5  $\mu$ m) indicated an elevated cellular stress level and an activated state of the Wnt/ $\beta$ -catenin pathway. The impact of sharp-edged topography on the Wnt/ $\beta$ -catenin pathway in combination with the cells' stress response has not been clear. Here we present a combined in-vitro and in-silico study to analyses the cellular and transcriptional response mechanism in MG-63 osteoblasts on defined micro-topography. MG-63 osteoblasts on micro-pillars produced a significant higher reactive oxygen species (ROS) amount after 1 and 24 h. While  $\beta$ -catenin protein accumulated in the cytosol and translocated into the nucleus, gene profiling indicated an antagonism mechanism of the transcriptional activity of  $\beta$ -catenin due to an increased expression of inhibitors like ICAT (inhibitor of  $\beta$ -catenin and transcription factor-4) or SOX17 (SRV-related HMG box transcription factor). In silico analyses offered a detailed view on how transcriptional activity of Wnt signaling is coordinated in response to the oxidative stress (ROS) induced by the defined micro-topography. Due to coordinated expression of regulatory elements of the Wnt/ $\beta$ -catenin pathway, MG-63 osteoblasts are able to cope with an increased accumulation of  $\beta$ -catenin on micro-pillars and suppress an unintended target gene expression. In additional,  $\beta$ -catenin can be redirected into other signaling pathways to support defense mechanisms against ROS.

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## Data Management Planning in Large Collaborative Research Consortia

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Research Data Management (RDM) is an essential part of today's research processes and beneficial for the quality of the scientific results and, thus, also for the reproducibility [1]. The aim of RDM is to ensure that the principles of good scientific practice are respected, that data is securely stored in all phases of the research life cycle, and that data sharing is possible. Furthermore, the comprehensibility of the research experiments is promoted by the documented administration of research data. Data Management Plans (DMPs) are an integral part of research data management and thus often requested by funders. DMPs are documents that describe the data that are created (format, types, volume, . . .) during the research investigation and potential standards, methods and specifications that are used. Furthermore, questions concerning ethical aspects and intellectual properties are treated. DMPs also describe the implemented plans for storage and backup of data and how data exchange and access are provided. Finally, a strategy for the long-term archiving of the data is documented in data management plans. The Infrastructure support project of the CRC 1270 ELAINE developed a template for DMPs specifically tailored for the application in large collaborative research consortia following the recommendations of Michener [2]. While this template does not focus on the CRC as a whole, it aims at documenting the data management in particular sub-projects. On the one hand, this distributes the effort for the creation and maintenance and on the other hand allows more specific descriptions of the data management processes. The Research Data Management Organizer (RDMO) is employed as a tool for the creation and maintenance of digital DMPs. It supports the planning, implementation, and administration of all tasks concerned with the planning of RDM.

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## **In silico characterization of the electric field distribution of deep brain stimulation in a detailed volume conductor model**

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Deep brain stimulation (DBS) is an effective symptomatic treatment of Parkinson's Disease. Especially interrelating in vivo and in silico models enables for a controlled environment, in which the effects of DBS can be studied and provide the means to understand its therapeutic and side effects. The mechanisms of DBS can be studied in vivo in a rat model of Parkinson's disease. By applying the finite element method, the induced stimulating field caused by DBS can be characterized in silico. An essential simulation result of the volume conductor model (VCM) is the electric potential. Combined with multicompartment cable models of neurons the volume of tissue activated can be computed. Thereby, the neuronal effects of DBS can be estimated. In order to compute realistic stimulating field distributions, it is necessary to create anatomically correct geometries defining the modeling domain of the VCM. Therefore, we created a full tissue rat head model based on Magnetic Resonance Imaging (MRI) and (Micro-) Computer tomography ( $\mu$ CT and CT). The resulting geometries comprise:

- the brain (gray and white matter as well as the Cerebrospinal Fluid filled ventricles) derived from MRI data of the Waxholm Space Atlas of the Sprague Dawley Rat Brain,
- the subarachnoidal space,
- the skull, as a simplified geometry derived from  $\mu$ CT scans,
- the soft tissues of the rat head (muscles, tendons and so on were lumped as one tissue), and
- the skin, defined as an offset of 0.5 mm of the soft tissue.

By using a combination of the software Materialise Mimics and 3-matics as well as Matlab, a NIFTI file is created based on the geometries. This approach allows for a voxel based mapping of the dielectric properties of the respective tissues into a VCM and a reasonable discretization using for example OSS-DBS and its adaptive mesh refinement.

## Exploring the potential of electrical impedance tomography for monitoring of revision total hip replacements

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Total hip arthroplasty is one of the most common inpatient procedures with an expected increase in numbers due to the aging society. As a consequence, the probability of a revision surgery is also expected to rise. Aseptic loosening is the most frequent late complication after total hip arthroplasty. It is a consequence of periprosthetic osteolysis leading to a continuing reduction of cortical and cancellous bone mass. The standard diagnosis methods do not guarantee accurate diagnosis.

Certain physiological and mechanical properties of bone are related to its electrical permittivity and conductivity. Electrical Impedance Tomography (EIT) is a noninvasive, radiation-free imaging technique for the electrical impedance of body parts. An array of conducting surface electrodes is placed on the skin in order to inject high-frequency electrical current and sense the resulting potentials. The volumetric impedance is then inferred from these surface measurements. So far EIT has not been applied to the diagnosis of hip stems. We therefore aim at exploring the potential of EIT for assessing the state of osseointegration and periprosthetic bone quality. Reconstructing the absolute impedances is a challenging task due to the non-linearity and ill-posedness of the underlying inverse problem. However, recent advances using data-driven post-processing of EIT data show promising results for thorax imaging.

In this in-silico study we present the reconstruction of impedances in a simplified model of a hip-stem replacement. The impedances are computed from the electrode signals using a common Gauss-Newton solver. The resulting impedances show a low spatial resolution not allowing to differentiate between bone and implant. The impedance data is then post-processed by a neural network in order to increase its resolution. The results show that the combination of established EIT techniques in combination with data-driven methods is a promising path for the monitoring of hip-stem replacements.

## Electrical direct stimulation for induction of bone regeneration in critical-size mandibular defects - a preliminary in vivo model

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Electrical therapeutically stimulation in field of regenerative medicine holds significant promise for tissue regeneration, but maintenance of cell differentiation and osteogenetic in vivo are still major obstacles for bone formation in critical-size bone defects. This preliminary study was carried out in order to test bone regeneration via electrical stimulation in a porcine mandibular critical-size defect. Electrical stimulation has been demonstrated to increase cellular osteogenic differentiation in vitro [1],[2],[3] and promote bone healing in clinical settings [4], but the ideal stimulation characteristics remain uncertain.

This animal model study was conducted on 4 Aachener Mini pigs under general anaesthesia. After submandibular surgical incision, a tricortical (3.5 x 1.5 cm) mandibular bone defect was created bilaterally and an electrically active implant [5],[6] was inserted in order to bridge the defect (each animal sham versus test). In n=2 animals, stimulation with 500 mv and 20 Hz (45 minutes stimulation period / 8 hours) started right after closing the wound, whereas in n=2 animals, stimulation started at the 4th day after surgery. In cases of immediate stimulation, wound healing disturbances and abscess formation occurred at the test site whereas a non-disturbed wound healing was detected in the group with delayed stimulation. Here, the study is still in progress for 3 weeks followed by animal euthanization for further radiological and histopathological investigation.

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