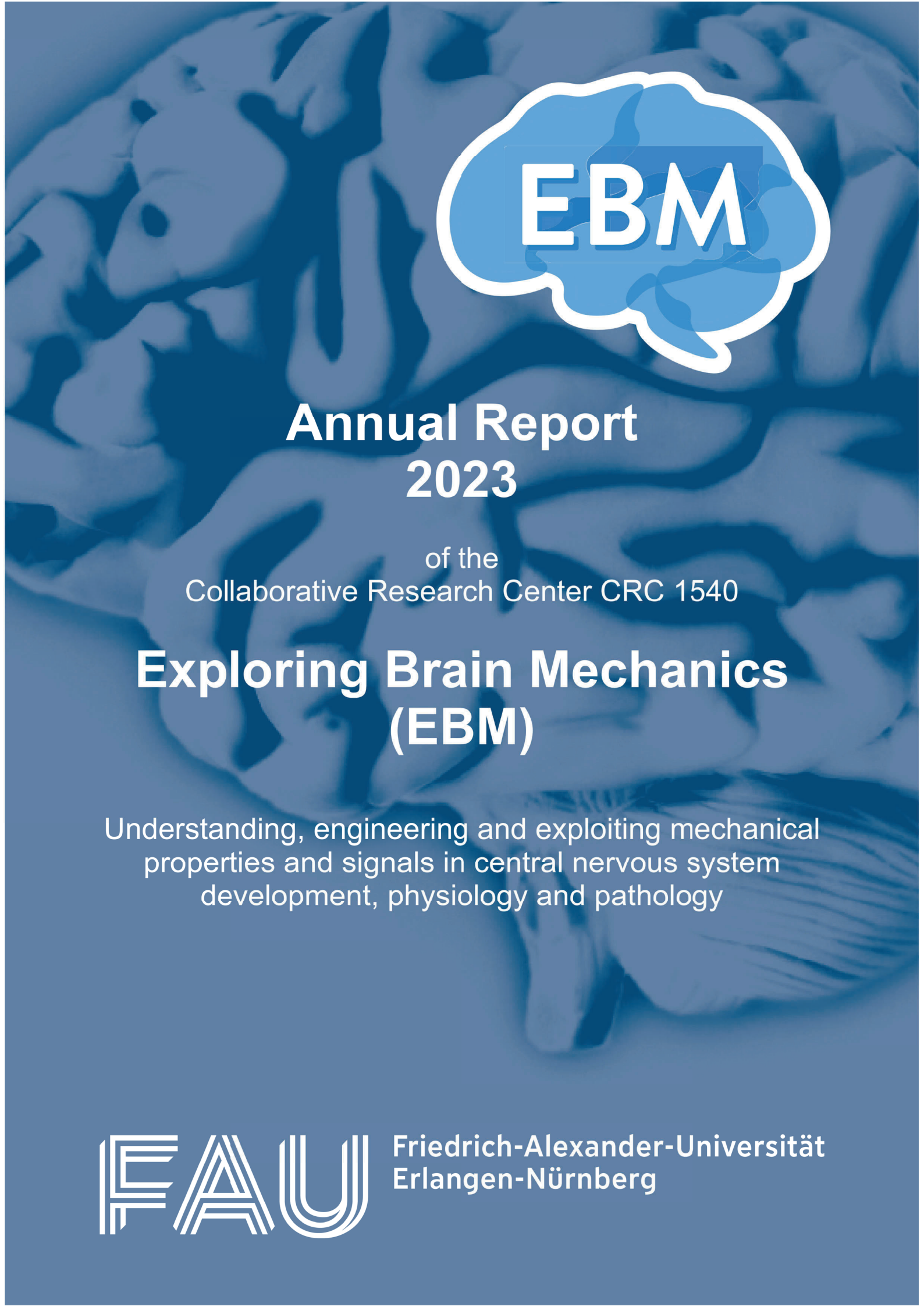

Annual Report 2023

of the
Collaborative Research Center CRC 1540

Exploring Brain Mechanics (EBM)

Understanding, engineering and exploiting mechanical properties and signals in central nervous system development, physiology and pathology

Friedrich-Alexander-Universität
Erlangen-Nürnberg

Annual Report

of the Collaborative Research Center CRC 1540

Exploring Brain Mechanics (EBM)

Understanding, engineering, and exploiting mechanical properties and signals in central nervous system development, physiology and pathology

at the

Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)

Prof. Dr.-Ing. Paul Steinmann (spokesperson)

Prof. Dr.-Ing. Silvia Budday (co-spokesperson)

2023

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Preface

At the beginning of 2023, after several years of focused and intense preparation and approval by the DFG in November 2022, the time had finally come: our CRC 1540 "Exploring Brain Mechanics" could officially start! Now it was time to fill the scientific positions, organize the coordination and administration, and bring the integrated Research Training Group to life. In fact, together we all managed to realize a real kick-start here. This report looks back on the first, already very successful year of our joint research and scientific and non-scientific interactions to explore brain mechanics. At the same time, this annual report is intended to whet the appetite for EBM's upcoming and guaranteed exciting research in the coming years.

Erlangen, December 2023

Paul Steinmann

Silvia Budday

CONTENT

Figure 1: Group photo at the 1st EBM-Retreat in Bad Windsheim on September 21, 2023. (Image: S. Schmitzer)

1 RESEARCH PROGRAM

The CRC1540 EBM focuses on unraveling the mechanical aspects influencing the central nervous system (CNS). Despite advancements in understanding biochemical and genetic regulations, many CNS processes and diseases remain elusive. The program addresses challenges such as unpredictable axon growth, imprecise diagnosis of CNS-related diseases, and the promotion of neuronal regeneration post-spinal cord injuries.

Researchers associated with EBM, and a few other groups worldwide, have recently identified the significant impact of mechanical signals on CNS cell function. Examples include the influence of brain tissue mechanics on axon growth, the role of mechanical forces in cortical folding, and the link between brain stiffness and age-related remyelination issues. These insights suggest that mechanics plays a vital role in diverse CNS functions, interacting intensely with chemical signals at cellular and tissue levels.

EBM brings together a multidisciplinary team of engineers, physicists, biologists, medical researchers, and clinicians in Erlangen. Leveraging advanced techniques across various time and length scales, the team aims to understand how mechanical forces and properties like stiffness affect CNS function, with a specific focus on cerebral, spinal, and cellular mechanics.

In vivo and i*n vitro* studies provide fundamental insights and identify key mechano-chemical factors. *In silico* models enable hypothesis testing without extensive experiments, facilitate data transfer across species and scales, and optimize parameters for the development of In vitro brain tissue-like matrices. Ultimately, EBM seeks to exploit mechanics-based approaches to enhance our understanding of CNS function, laying the groundwork for improved diagnosis and treatment of neurological disorders.

1.1 RESEARCH PROJECTS

EBM is structured into three focal research areas (FRA) focusing on cerebral (**A**), spinal (**B**), and cellular mechanics (**C**), and an overarching cross-sectional research area (**X**RA).

FRA A – Cerebral Mechanics:

FRA **A** focuses on brain development with special emphasis on brain malformations associated with neurological disorders such as epilepsy. Computational modeling in **A01** will help systematically understand physical mechanisms underlying brain malformations and benefits from quantitative characterization of human brain malformations in **A02** and the *In vitro* and *in vivo* insights gained for brain development in *Xenopus* (**A03**/**A05**) and organoids (**A03**/**A04**) based on engineered brain tissue-like matrices.

FRA B – Spinal Mechanics:

FRA **B** focuses on spinal cord injury and disease with special emphasis on mechanically stimulated regeneration of CNS function. Computational modeling of spinal cord injury, disease and regeneration in **B01** assists and builds on unraveling regeneration/disease-promoting/limiting characteristics and determinants of its mechanical landscape in **B02**, **B03**, **B04**, and exploration of *in vivo* mechanical manipulation in **B05**.

FRA C – Cellular Mechanics:

FRA **C** focuses on the role of mechanics in cell-matrix interactions. Computational modeling of cell-matrix-interactions in **C01** targets the role of mechanics for neuronal “plasticity”, seizure-like hyperactivity and cellular differentiation investigated in **C02**, **C03** and **C04**, all informed by the versatile experimental platform established in **C05** and corresponding insights into mechanosensing and -transduction.

XRA – Cross-Sectional Projects:

The overarching cross-sectional projects in **X**RA will focus on the standardization and integration of *in vivo* and *ex vivo* testing data across scales (**X01**), the transferability of data from different species and experimental methods through advanced machine learning techniques (**X02**), and the design of engineered substitute materials for brain tissue (**X03**)

Table 1 subsumes EBM's projects:

Table 1: EBM projects

FOCAL RESEARCH AREA A: CEREBRAL MECHANICS		
A01	*In silico* modeling of brain malformations	S. Budday
A02	Quantitative characterization of brain malformations	I. Blümcke, A. Dörfler, F. Paulsen
A03	*In vitro* model for the mechanics of early brain development	A. Schambony
A04	The role of mechanics in orchestrating neural lineage decisions	M. Karow, S. Falk
A05	*In vivo* model for the mechanics of brain development	K. Franze
FOCAL RESEARCH AREA B: SPINAL MECHANICS		
B01	*In silico* modeling of spinal cord regeneration	P. Steinmann, S. Budday
B02	Pre and post-metamorphosis spinal cord regeneration in frogs	K. Franze
B03	The determinants of spinal cord mechanics in homeostasis	J. Guck, S. Möllmert
B04	Spinal cord mechanics in a mouse model of multiple sclerosis	S. Kürten
B05	*In vivo* mechanical manipulation of spinal cord regeneration	D. Wehner
FOCAL RESEARCH AREA C: CELLULAR MECHANICS		
C01	*In silico* modelling of mechanical cell-matrix interactions	V. Zaburdaev, P. Steinmann
C02	The role of mechanics for neuronal "plasticity"	R. Frischknecht
C03	The role of matrix mechanics in synchronized neuronal activity	K. Kobow
C04	Cellular differentiation in brain tissue-like matrices	A. Bosserhoff
C05	Molecular mechanisms of neuronal mechanotransduction	B. Fabry
CROSS-SECTIONAL RESEARCH AREA X: CROSS-SECTIONAL PROJECTS		
X01	Model-based reconciliation of *ex vivo* and *in vivo* test data	J. Guo, I. Sack, P. Steinmann, K. Willner
X02	Data analysis and machine learning for heterogeneous, cross-species data	A. Maier, K. Breininger
X03	Engineering brain tissue-like matrices	A.R. Boccaccini
Y	Establishing magnetic resonance elastography at FAU	A. Dörfler, F. Laun, J. Guo, I. Sack

1.2 PROJECT REPORTS

A01 Inverse mechanical characterization of human brain tissue

Jan Hinrichsen, Nina Reiter, Silvia Budday

The overall goal of project **A01** is the implementation of a computational model to predict cortical malformations. An important preliminary step to this is the mechanical characterization of human brain tissue. We have therefore used inverse parameter identification to obtain region-specific hyperelastic parameters [1]. Next, we combined these with the results of enzyme-linked immunosorbent assays (ELISA) that quantify specific tissue components. We have found strong correlations between hyperelastic parameters and levels of Iba1, collagen IV, collage VI, and GFAP (see Figure 3) [2]. Furthermore, we have investigated how we can accelerate the computationally demanding inverse parameter identification. To this end, we have incorporated recurrent neural networks as surrogate models for viscoelastic finite element simulations. However, it is still necessary to run simulations in order to produce pairs of in- and output data that are crucial for the training of these data-driven models. Therefore, we have implemented a Monte-Carlo dropout-based active learning approach that seeks to select the next best point in the parameter space during training. Our hybrid approach incorporates the surrogate model for parameter identification and effortlessly transitions into a higher precision finite element model. This results in dependable accuracy and computational economy. Figure 2 shows the final viscoelastic model output for experimental data from the human frontal cortex. Our next steps aim at the integration of the insights that we have gained so far into the folding model. Especially the availability of cell density data from project **A02** is highly valuable for the development of patient specific models to predict cortical malformations.

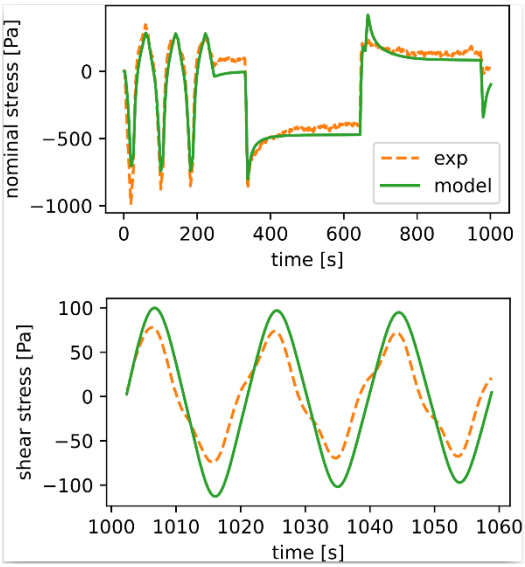

Figure 2: Final model output for the viscoelastic characterization for experimental data from the human frontal cortex.

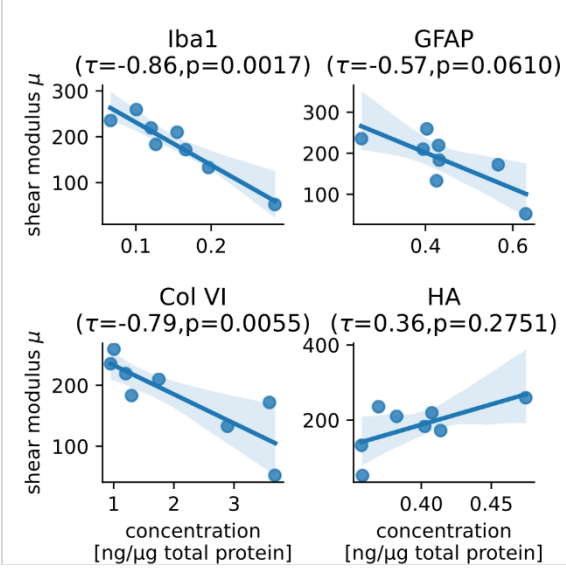

Figure 3: Correlation of the shear modulus μ from fitting the one-term Ogden model and component concentrations.

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A02 Quantitative characterization of brain malformations

Sophia Auer, Erica Cecchini, Stefan Rampp, Lucas Hoffmann, Ingmar Blümcke, Arnd Dörfler, Friedrich Paulsen

WP1: The generation of normal/healthy human brain datasets commonly usable for EBM members

The primary objective in this WP is to create comprehensive brain datasets using healthy human brain samples. So far, we obtained three brains from healthy human body donors (two males, 66 and 77 years old, one female, 83 years old). All brains were scanned *ex vivo* by 3T as well as 7T MRT (see below, WP2.2.2). Selected anatomical regions were dissected and mechanically tested by our EBM partners from **A01** (see report therein). All tissues were fixed in formalin, embedded into paraffin and serially sectioned into 4µm thin sections (WP3). This tissue collection effort will continue in the upcoming years to further enrich our common dataset of healthy human brain tissue and which serves as essential reference for understanding mechanical abnormalities in the epileptogenic brain. We also shared five surgical tissue samples from patients submitted to epilepsy surgery, including hippocampal sclerosis and Focal Cortical Malformations. The same pipeline of presurgical MRI scanning at 3T (WP2), mechanical testing *ex vivo* by **A01** and histopathology analysis of all available tissue samples was implemented (WP3).

WP2: (Ultra-) High-field imaging of human brain malformations

We established a standardized protocol for annotation and co-registration in WP2.1.1. MRI datasets were obtained from the HARNESS epilepsy protocol clinically applied in the presurgical evaluation of patients with medically refractory focal seizures at the University Hospital Erlangen, incl. 3D T1, FLAIR, Inversion Recovery, Diffusion Weighted Imaging, and partially also DTI. In addition, MRI postprocessing was added to each dataset. Segmentation and standardization to several anatomical atlases was performed. So far, data from 20 patients with FCD, 5 with MOGHE and 1 patient with double cortex syndrome were processed and annotated.

Work in WP2.2.1 has so far focused on optimizing MRI protocols for the evaluation of patients with cortical malformations. To optimize sequences and protocols for quantitative MRI (i.e. CEST, QSM) and evaluation of patients with cortical malformations, 10 healthy controls were scanned at 3 Tesla and 7 Tesla field strength, respectively. In addition, 7T CEST imaging was performed on 5 patients with brain tumors. Results are part of the manuscript “Comprehensive 7T CEST – a clinical MRI protocol covering multiple exchange rate regimes” submitted by Fabian et al. to NMR in Biomedicine, which is currently under review.

Furthermore, functional MRI (fMRI) acquisitions in 18 healthy participants were acquired at 3T and 7T to evaluate advantages of higher field strengths in the analysis of functional connectivity using resting state fMRI. The results were published just recently in Frontiers in Neuroscience 2023 by S. Kreitz et al.: “3T vs. 7T fMRI: capturing early human memory consolidation after motor task utilizing the observed higher functional specificity of 7T”.

In WP2.2.2, brains of three body donors were scanned (see above). To compare 3T and 7T scanners and to establish an optimal scanning protocol, specimens were each scanned at different scanners, including a 3T Magnetom Prisma, 3T Magnetom Vida and a 7T Magnetom Terra, respectively (all Siemens Healthineers, Germany). In addition, 5 surgical specimens of resected brain tissue were scanned at 7T ultrahighfield MRI (WP 2.2.2).

Based on these data, further work on optimization of scanning protocols and handling of specimen is currently in progress. Specifically, a 3D-printed brain-holder device is under construction, which will allow reliable positioning of brain specimen in the MR scanner to allow for high-quality ex-vivo scans.

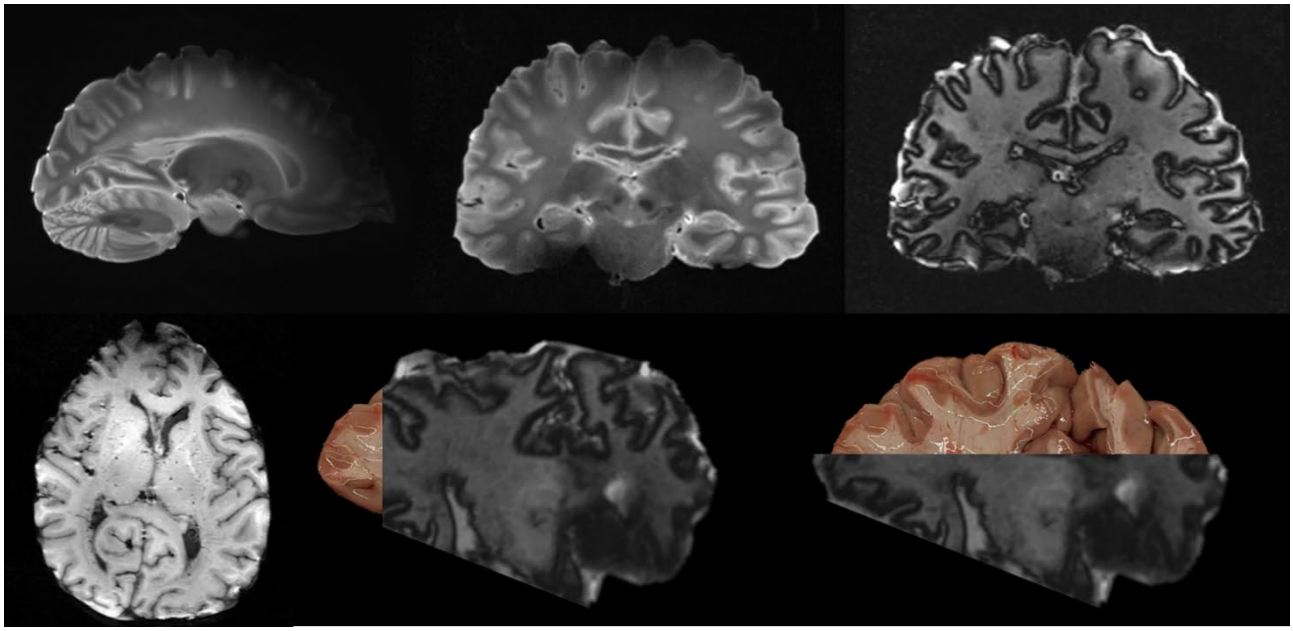
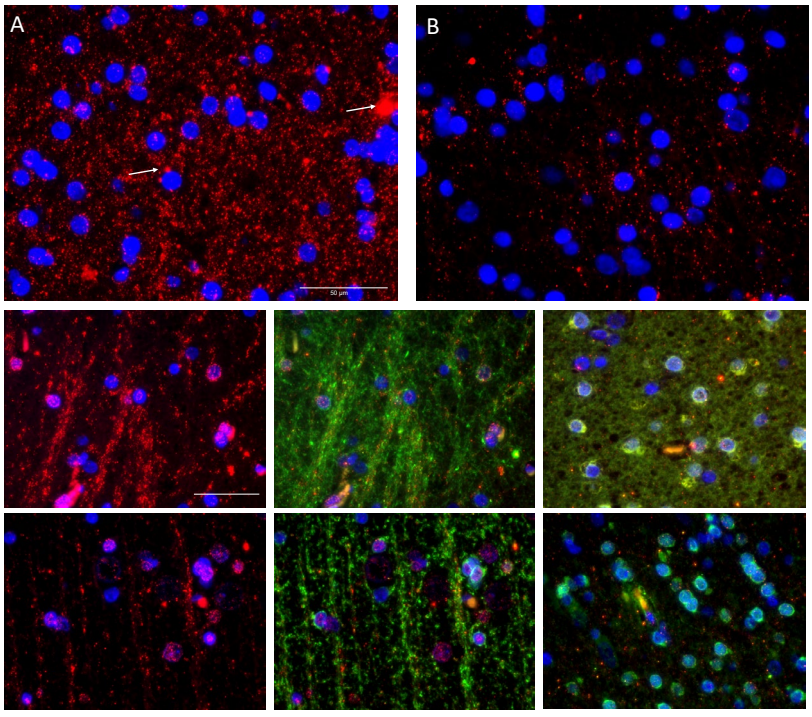


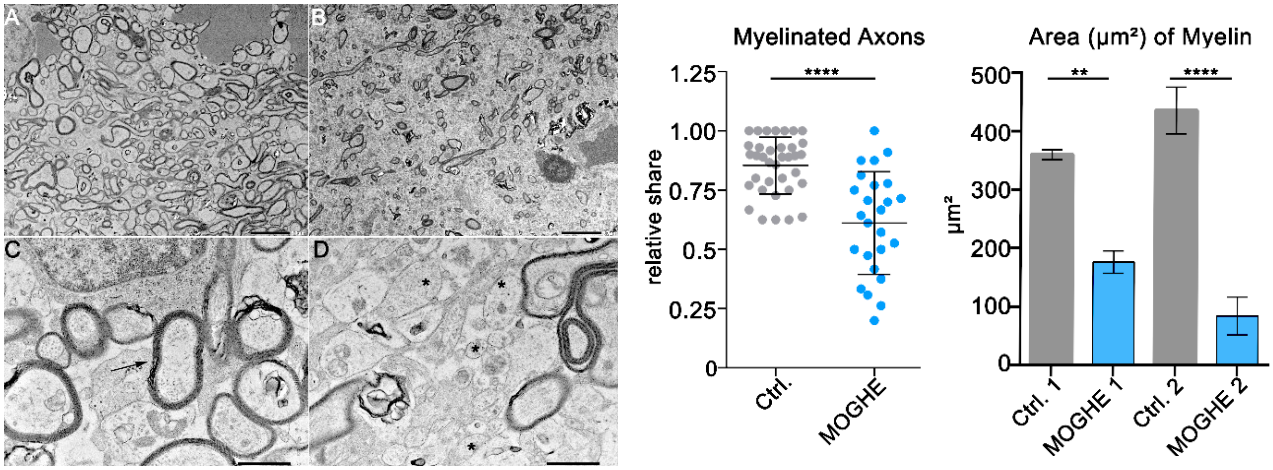
Figure 4: Examples of first 7T body donor scans. The two panels on the lower right show co-registration results of MRI and photographs of unfixed post mortem brain slices used for mechanical testing (A01).

WP3: Deep histopathology phenotyping of genetically characterized human MCD

The investigations that have been carried on for the purpose of the project can be summarized into four main tasks. Since the starting of the research period, much focus has been put on the testing of a newly produced polyclonal antibody directed against the N-terminus of the SLC35A2 epitope. The main goal is to identify the normal and aberrant expression pattern of the protein produced by the SLC35A2 gene, encoding for a UDP-Galactose transporter, carrying variants in almost 50% of MOGHE cases. Immunofluorescence analyses performed on MOGHE and control cases revealed a main localization of the protein within perinuclear and extracellular area and a clear reduction of the protein signal within the MOGHE cases compared to control ones (Figure A, B). Furthermore, double immunofluorescence labelling has been performed to identify association and/or co-localization of the protein with perinuclear and extracellular structures. Starting from the assumption that MOGHE samples display patchy areas of hypo myelination within the white matter when stained with myelin-associated antibodies, to provide further evidence at the ultrastructural level, electron microscopy (EM) analyses have been made (Figure A, B, C, D below; in cooperation with FP from WP4). These studies confirmed myelin loss in MOGHE samples compared to control. This opens the question on how SLC35A2 loss of function affects the MOGHE histopathological phenotype and clinical outcome. Part of the project includes the search for new genetic candidate markers. We have retrospectively collected 145 cases, of which 33 have been identified carrying pathogenic loss-of-function variants within the SLC35A2 gene. In addition, Copy Number Variation (CNV) plots calculated from DNA methylation array data are suggesting a role of the Y chromosome, as several cases display a CNV increase of Y chromosome



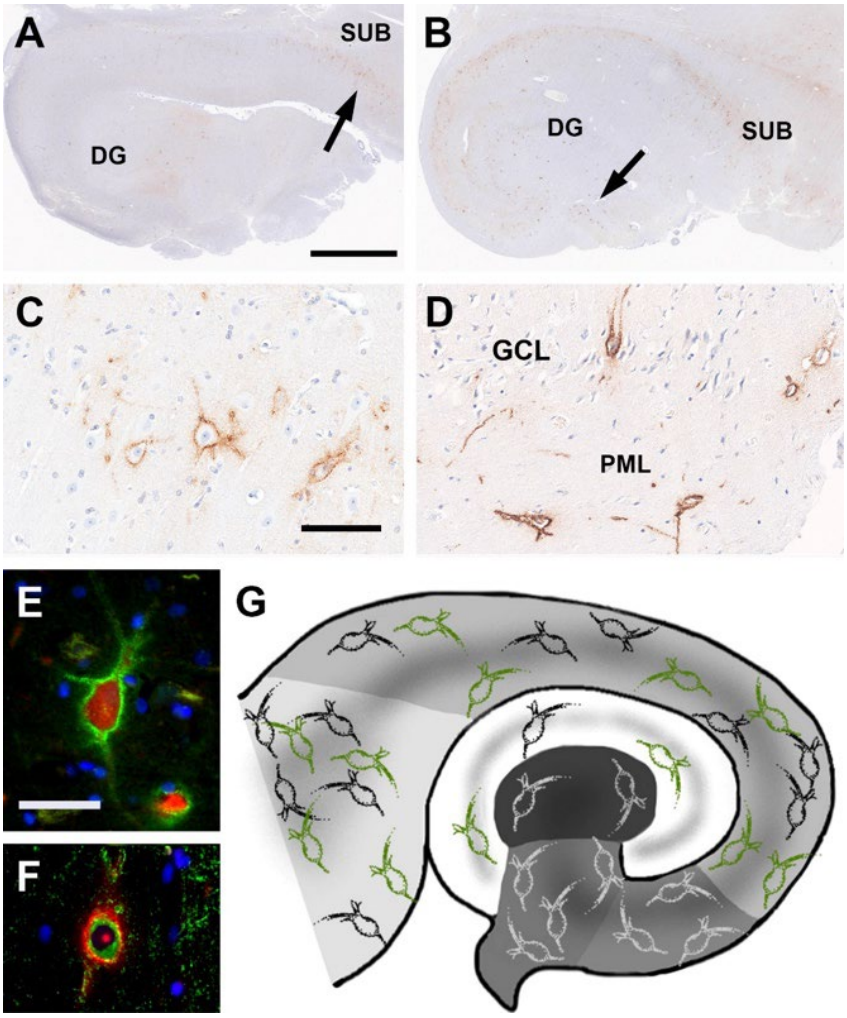
(unpublished data). Within the next months, in situ hybridization analyses will be carried out to better visualize alterations of the Y chromosome in our patient cohort. In addition, spatial transcriptomics in surgical MOGHE samples will be performed to further characterize the abnormal cellular structure together with the extracellular matrix (ECM) composition.



WP4: Deep extracellular matrix (ECM) quantification and phenotyping in healthy human brain and cortical malformations

Within Work Package 4, our focus is on the in-depth quantification of the extracellular matrix (ECM) and the comparison of the ECM profile between healthy human brains and brains with cortical malformations. To gain an initial understanding of the proteins present in the brain's ECM, we have initiated the collection of tissue samples of distinct brain regions from body donors (n=2) and surgical patients with MCD (n=2). The tissue samples will undergo thorough proteomic analysis to comprehensively characterize the protein composition, with particular emphasis on ECM-related proteins. To achieve this, we have established a collaboration with a specialized company in proteomic studies to maximize the information obtained from these tissue samples. Our investigation will particularly concentrate on patients with FCD, MOGHE, and Hippocampal sclerosis (HS).

Another component of WP4 involves the qualitative and quantitative description of perineuronal nets (PNN) in the human neocortex. PNNs are highly specialized ECM structures that primarily encase GABAergic interneurons. Within WP4, we have started to determine whether PNNs exhibit any structural, functional, or molecular alterations in human brain malformations, such as FCDs or MOGHE. We are quantitatively characterizing PNN in cortical samples of postmortem controls and epilepsy samples. Utilizing immunohistochemical and immunofluorescence techniques we have first results in the staining, quantification, and comparison of PNN between the control and epileptogenic conditions. The studies compare well with a recently submitted manuscript of **A02** addressing PNN in the developing human hippocampus compared to patients with temporal lobe epilepsy, which showed an age-dependent increase of this peculiar ECM compartment which appears to also mature precociously in the epileptic brain (Lehner et al, submitted, with reference to EBM).



Distribution of perineuronal nets in the human hippocampus. A: 26-year-old patient with epilepsy and HS ILAE type 1 (SUB-subiculum; DG - Dentate Gyrus). B: 53-year-old patient with epilepsy and HS ILAE type 3. C: Higher magnification of PNN in the subiculum of the patient shown in A. D: Higher magnification of PNN in the Dentate Gyrus of the patient shown in B. E: Triple immunofluorescence image showing a Parvalbumin-immunoreactive neuron in green, covered by an aggrecan-immunoreactive PNN in red fluorescent dye. F: Triple immunofluorescence image showing a GAD-immunoreactive neuron in green, covered by an aggrecan-immunoreactive PNN in red. G: Schematic drawing of our major observation of increased PNN in the epileptic human hippocampus. Anatomical distribution patterns of PNN are depicted in black and white color. Green PNN represent the epileptic condition. Scale bar in A = 2.5 mm, applies also to B. Scale bar in C = 100µm, applies also to D. Scale bar in E = 50 µm, applies also to F. Taken from Lehner et al., submitted for publication.

A03 *In vitro* model for the mechanics of early brain development

Clara Froidevaux, Alexandra Schambony

The brain develops from a flat sheet of dorsal ectoderm, the neural plate, which undergoes extensive morphogenesis and shape changes to form the three primary ventricles of the brain and the spinal cord. We are developing and characterizing an organoid model system derived from *Xenopus laevis* neural plate tissue to investigate the interplay of mechanics and biochemical signaling in early brain morphogenesis.

WP1.2: Characterizing the Extracellular Matrix of neural plate organoids

Since there is limited knowledge of the composition and stoichiometry of the ECM during early neurogenesis in *Xenopus laevis*, we aim at quantitatively analyzing the matrisome of the neural plate and its immediate surrounding tissues during this phase. We have modified our initial strategy to implement data-independent acquisition [1] for a higher depth of analysis and faster measurements. Currently, we are in the process of experimentally testing and optimizing sample preparation for our needs. In addition, we are expanding the initially planned matrisome analysis to include mouse and human brain samples, which are of high interest to other members of EBM.

WP2: Analyzing the influence of global mechanical cues on brain morphogenesis and tissue mechanics

In this part of the project, investigating how mechanical properties of substrates and environment influence early neural morphogenesis and differentiation is the central aim.

Table 2: Length-width ratio of organoids grown on different substrates at 0h, 24h and 48h of culture at 18°C, L/W ratio is given as average ± standard deviation.

Substrate and functionalization	Number of organoids	Ratio (L/W)		
		0h	24h	48h
Glass	7	1,37 ±0,18	1,92 ±0,66	2,34 ±0,29
Glass + Fibronectin	14	1,70 ±0,13	1,74 ±0,63	1,86 ±0,42
Alginate Hydrogel	10	1,51 ±0,25	2,12 ±0	2,33 ±0,16
Alginate Hydrogel + Fibronectin	8	1,38 ±0,26	2,06 ±0,47	2,56 ±0,08

In collaboration with project **X03** we prepare different types of hydrogels with tunable mechanical properties. *Xenopus* cells and tissues have quite different requirements to osmolality and temperature than mammalian cells (18-25°C, approximately 240 mosmol/kg [2]), conditions which turned out to markedly reduce hydrogel swelling of both OHA and Alginate hydrogels. A long-time degradation study under incubation conditions and parallel mechanical testing using the *CellScale* Microtester is planned once the maintenance of the Microtester is completed. In parallel the DR and Miriam Mager, master student working in the project, have been trained to prepare neural plate organoids from early *Xenopus laevis* embryos. For initial experiments, we have chosen alginate hydrogels with a concentration of 1,5% (w/v) and an expected stiffness of around 0.4 MPa [3] and compared organoid growth on hydrogel and on glass

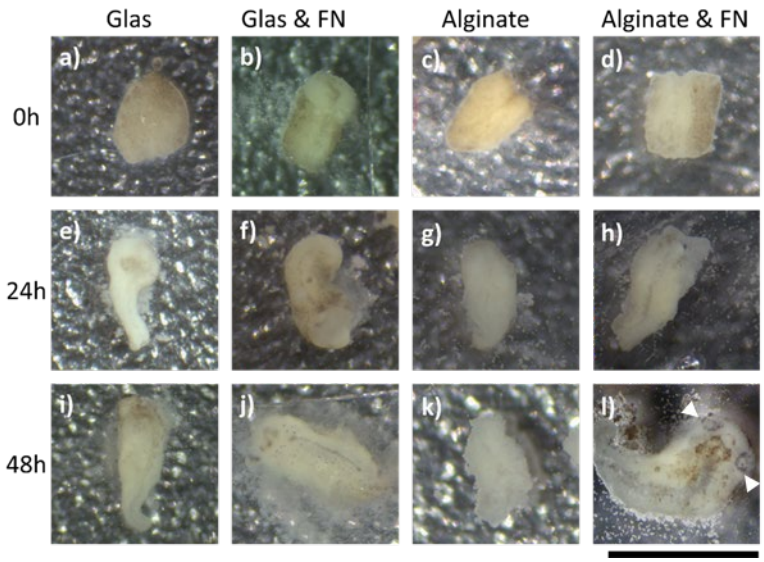


Figure 5: Xenopus Organoids on different substrates at either 0h, 24h or 48h of incubation. Scale bar = 1cm, arrows mark the eyes.

over 48h. Both substrates have been tested with Fibronectin (FN)-functionalization and non-functionalized. Interestingly the strongest elongation of organoids was observed on glass without FN and on hydrogels with FN (Table 2 and Figure 5a-l). Notably, organoids cultured on FN functionalized alginate hydrogels showed the highest degree of visible differentiation as these organoids developed eye primordia with pigmented retinae (Figure 5l, arrows). The characterization of differentiation marker gene expression such as *sox2* or *neurogenin1* is ongoing.

WP3: Analyzing the impact of PCP defects on the mechanical properties of brain primordia

The local application of labelling agents, reagents or drugs is an important tool for manipulation of cellular mechanics or signaling in a limited area of an organoid. The µkiss methodology [4] was developed to apply reagents to very small subcellular areas. We plan to use the same principle. However, organoids are significantly larger, multicellular systems. Already the manipulation of one or a few cells requires scaling of the flow envelope, even more so if targeting larger areas, e.g., the neural plate border or the entire prospective forebrain region. Moreover, a larger field of view and working distance is required when working with organoids as compared to a monolayer cell culture. Accordingly, the workflow needs to be adapted to use on a stereomicroscope. We are currently in the process of making the required modifications and establishing the workflow for routine applications.

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A04 The role of mechanics in orchestrating neural lineage decisions

Michael Tranchina, Sven Falk, Marisa Karow

Objectives

The overall goal of A04 is to understand how changes in the mechanical properties of the environment impact on human neural stem cell lineage decisions and to elucidate the molecular counterparts relaying this information. We are using human induced pluripotent stem cell (hiPSC) - derived brain organoids and neural cells derived thereof to address this question. Ultimately, we aim to chart the molecular landscape modulated in neural stem cells by the mechanical environment to determine molecular key nodes responsible for orchestrating neural stem cell lineage decisions.

Main achievements and conclusions

In a series of experiments in collaboration with the team of Silvia Budday, we obtained the first exciting evidence for a brain organoid resident neural progenitor cell fate change upon an acute mechanical manipulation. By using a rheometer for both, impacting on and measuring the forces acting on individual brain organoids coupled with a newly developed unbiased analysis pipeline quantifying protein levels in organoids with spatial information, we revealed a transient upregulation of the neural stem cell controlling protein SOX2 upon mechanical manipulation. Intriguingly, this modulation of SOX2 was strongly dependent on the localization of the cells with neural stem cells closer to the apical surface of the ventricle as well as cells outside of the neural stem cell containing ventricular zones reacting strongest. As a consequence, compressed cells alter their lineage decisions and rather stay stem cells than differentiate to postmitotic neurons. Dissecting the molecular changes induced by compression using bulk RNA-sequencing we found major alterations in the expression of genes associated with patterning processes pointing towards shifting in the regional identity of cells in brain organoids upon mechanical manipulation.

To further dissect this lineage and developmental time-specific regulation we now extend these results with single-cell resolved molecular characterization. Mock-control and compressed organoids derived from hiPSCs of two individuals were subjected to single-cell RNA-sequencing (scRNA-seq). We now can deconstruct the impact of mechanics on different cell types and lineages and start to

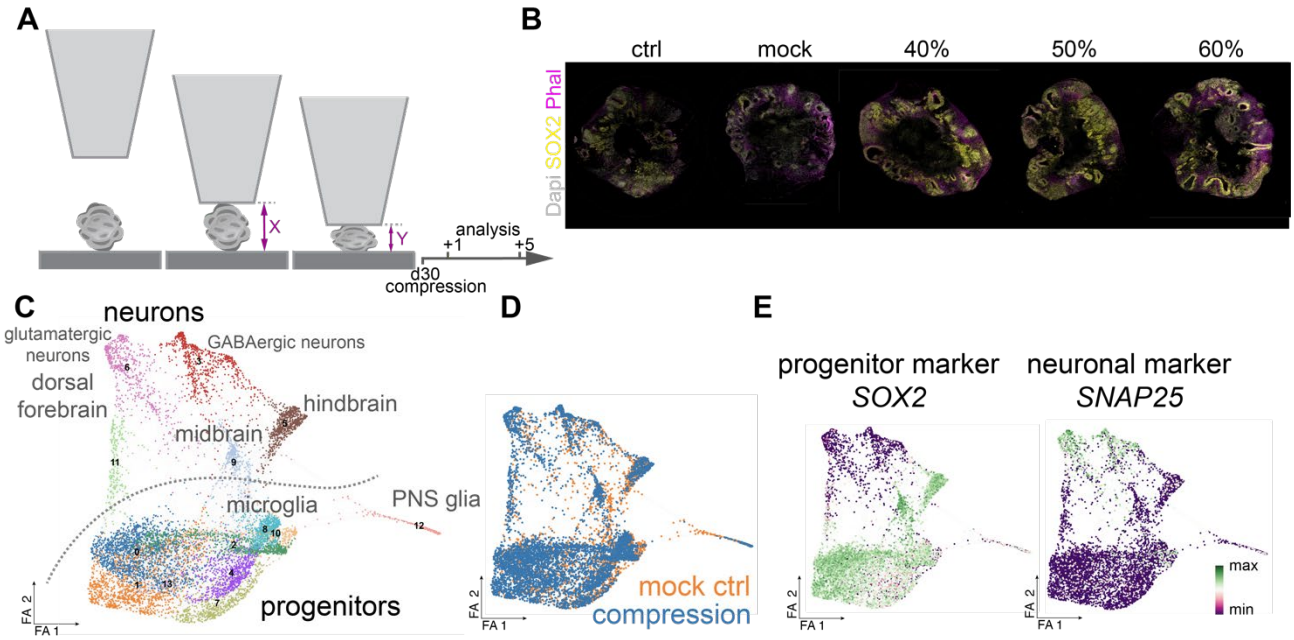

*Figure 6: **A)** Experimental scheme for organoid compression and analyses timepoints. **B)** Immunofluorescence images of brain organoid slices assessed for the neural stem and progenitor marker SOX2 (yellow) across all conditions 24h after compression. Phalloidin marks actin filaments. Ctrl organoids were left untreated, mock organoids were placed on the rheometer platform but not compressed. Organoids in this panel were compressed for 40%, 50% or 60%. **C)** Force directed graph embedding of cells derived from dissociated organoids. Leiden clustering was used to show in different colors transcriptionally different clusters. Note the existence of distinct neural lineages. **D)** Indication of mock (2344 cells) and compressed cells (5447 cells). **E)** The expression of the progenitor marker SOX2 and the neuronal marker SNAP25 was projected onto the embedding of C.*

prioritize molecular key nodes explaining the changes in the molecular landscape induced by mechanical manipulation.

In parallel, in collaboration with the team of Aldo Boccaccini, we set up the conditions to generate hydrogels (2.5 wt.% oxidized hyaluronic acid, 2.5 wt.% gelatin cross-linked with 15% microbial transglutaminase solution in PBS) for brain organoid embedding. The physical properties of such hydrogels can be systematically varied to test the impact of changes in the physical environment on brain organoid development as opposed to the rheometer-induced acute impact. Organoids will be compared to organoids embedded in the current gold standard, Matrigel. First encouraging experiments have shown that hydrogels can indeed be used to embed brain organoids (d11 of the protocol) and that the formation of organoids is per se not affected.

Outlook

We are currently analyzing the scRNA-seq data with the goal to determine genes and regulons specifically deregulated following compression and potentially being responsible to relay the cellular information to induce global transcriptome changes.

Furthermore, we will systematically test hydrogels with defined physical properties for their impact on brain organoid formation. Analyses will include both molecular and cellular phenotyping of the resulting brain organoids compared to Matrigel-embedded organoids.

A05 *In vivo* model for the mechanics of brain development

Sebastián Vásquez-Sepúlveda, Jana Sipkova, Kathrin Welsch, Kristian Franze.

Objectives

1. Characterize brain viscoelasticity *in vivo*.
2. Determine mechanics and morphology of brains with gene mutations leading to malformations.
3. Rescue brain mechanics and test the effect on brain morphology and malformations.

In 2023 most of the work was aimed towards animal handling, setting up protocols for work with *Xenopus laevis* tadpoles and adult frogs, as well as ordering required solutions and reagents for experimental work on the model. On Friday 25th of August the Felasa certification was completed, allowing the work on the animal model.

Specifically for Objective 2, the techniques for brain extraction, nuclear staining and labelling of the optic tract using the lipophilic dye DiI have been established successfully. The results of this methodology are shown in Figure 7.

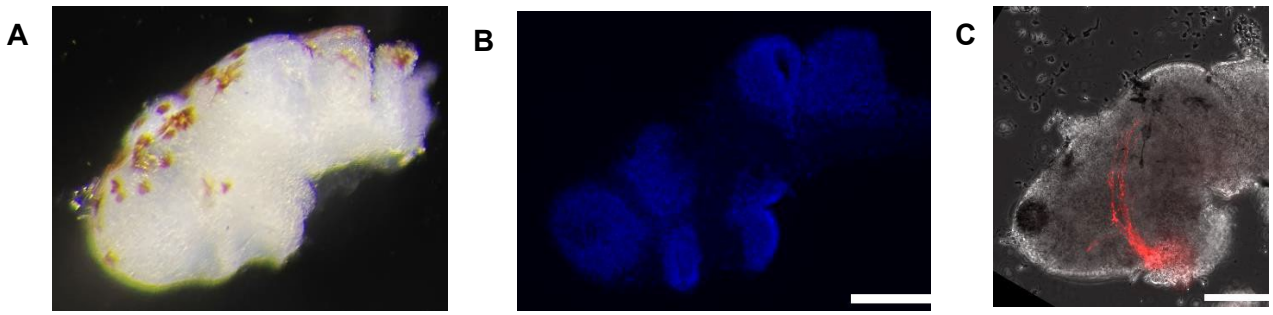

Figure 7: ***Extraction and labelling of Xenopus laevis brain.*** *A) Exemplary image of an isolated fixed brain of Xenopus tadpole at stage 40. B) Stage 40 tadpole brain slice of 50 µm stained with Hoechst 33342 for nuclei. C) DiI labelled optic tract on a stage 40 tadpole. Scale bar 200 µm.*

Two gene expression manipulation candidates, Slc35A2 and Nprl3, were selected. Tools for labeling and modifying gene expression have been designed and will be tested as they are delivered.

As of November 2023 S.V. has presented the overview of the project at Franze/Paluch Lab Symposium at Cambridge, UK on June 8, 1st EBM Retreat on September 22, and an extensive look at the theoretical framework of this research at the EBM Doctoral researchers seminar on November 23.

The methods set up during this first period are the foundation of project A05, and the proper establishment of protocols for handling of frogs and tadpoles, brain extraction, and labeling of cellular components are key for effective advancement in all three objectives proposed in this research. With the arrival of all ordered reagents, techniques for modifying gene expression and labeling of mRNA will be established, which will allow for the start of experimentation.

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aA05 Mechanical interactions between neural stem cells and their niche

Kathrin Welsch, Sebastián Vásquez-Sepúlveda, Jana Sipkova, Kristian Franze

Objectives

Characterize morphology and mechanical properties of neural stem cells (NSCs) extracted from adult mouse brains *in vitro*: Wild type versus FoxO1/3/6 knock out in 2D and 3D culture systems with varying mechanical properties.

Investigate tissue stiffness of the dentate gyrus in wild type mice versus FoxO1/3/6 knock out *in vivo* using Atomic Force Microscopy (AFM).

Determine the influence of a FoxO1/3/6 knock out on the composition of the extracellular matrix (ECM) *ex vivo*, specifically the role of TGM2.

Since the beginning of this project, we set up a cell culture laboratory using fibroblasts as a training cell line and familiarized all non-biologically trained staff with general methods in cell culture.

We established a protocol to generate hydroxy-polyacrylamide hydrogels ranging in stiffness from 100Pa to 10kPa. Exact rheological measurements are currently being performed in order to confirm these values.

In first experiments we cultured fibroblasts on hydrogels coated with Poly-D-Lysin and Fibronectin with positive results.

Kathrin Welsch was taught how to passage NSCs at the laboratory of Prof. Lie at the Institute of Biochemistry (FAU) and all necessary equipment and reagents were obtained to establish NSC culture at our institute.

Outlook

Before the end of the year, NSCs are supposed to be taken in culture, expanded and frozen in order to generate a cell stock for future experiments.

First tests will include evaluation of their growth and morphology on aforementioned hydrogels, determining membrane tension using an Optical Tweezer set up and immunofluorescence staining for apoptosis, glia and neuronal markers.

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B01 *In silico* modeling of spinal cord regeneration

Stephen Melly, Oskar Neumann, Silvia Budday, Paul Steinmann,

This report provides a comprehensive summary of the objectives, key findings, preliminary conclusions and potential prospects of the ongoing experimental and computational investigations in project B01. Current scientific efforts are focused on gaining insights into the mechanical properties of human spinal cord tissue through a combination of experimental testing and computational modelling.

Within the scope of work package 1, the experimental investigations successfully addressed various aspects. Mechanical testing was executed on ten specimens derived from the cervical, thoracic, and sagittal segments of the human spinal cord. These specimens underwent diverse loading conditions, including compression, tension, and torsional shear. The rheometer served as the testing apparatus, and collaborative efforts were undertaken with researchers from project A01 and the affiliated Institute of Continuum Mechanics and Biomechanics. In addition, nanoindentation tests were conducted on porcine spinal cord. The mechanical sensitivity of the tissue was analyzed in relation to loading rate, holding time and temperature as well as the relaxation behavior. The experimental work also included the development of an experimental setup and protocol tailored to the nanoindentation of brain tissue, combined with comprehensive digital documentation facilitated by an electronic laboratory notebook (ELN). This was done in close collaboration with researchers from the University of Bonn (project B04). Moreover, the project encompassed the creation of post-processing software designed for the localization of indentation points and the implementation of data filtering, smoothing, and segmentation techniques. In this context, established software tools from the Max Planck Institute for the Science of Light, as recommended by researchers in project B03, were seamlessly integrated. Expanding the scope, a multi-modality experimental pipeline was established for brain tissue. This pipeline includes nanoindentation, magnetic resonance elastography (in collaboration with researchers from project X01) and multimodal mechanical testing with the rheometer.

To summarize, our preliminary experiments highlight that the testing machine (Chiaro Nanoindenter, Optics11 Life) appears to be suitable for gaining insights into the regional mechanical properties of spinal cord tissue. Initial data indicate that the grey matter in the spinal cord is stiffer than the white matter. Exemplary results are shown in Figure 8.

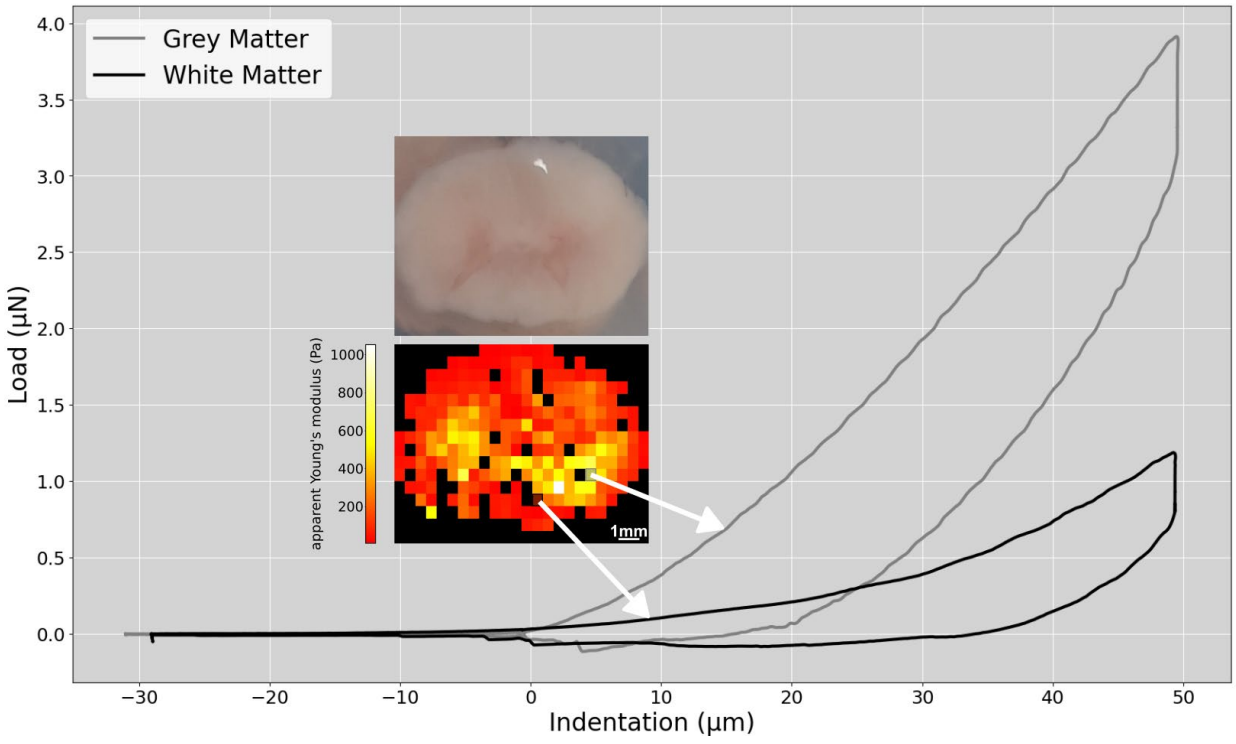

Figure 8: Exemplary force-displacement curves for nanoindentation of grey and white matter with a tip radius of 100 µm and a loading rate of 10 µm/s. The insert shows the transverse plane of a porcine spinal cord slice and the apparent Young' Modulus derived by fitting a Hertzian contact model to the curves of a grid scan of the whole area.

Upcoming efforts will include further mechanical testing, including already established techniques like nanoindentation and multimodel mechanical testing combined with magnetic resonance elastography and other available *in vivo* and *ex vivo* methods like Brillouin microscopy (B02) and atomic force microscopy (B02/B03).

The following paragraph highlights the computational objectives and achievements of project **B01**.

The computational aspect of the project aims to achieve accurate simulations of the mechanical response exhibited by human spinal cord tissues. To this end, a computational model was implemented that employs an isotropic material response for both elastic and viscoelastic behaviors, incorporating a modified one-term Ogden model and generalized Maxwell element(s). Material parameters are determined through an inverse identification scheme integrating optimization routines and finite element simulations of the different testing setups with their exact boundary conditions.

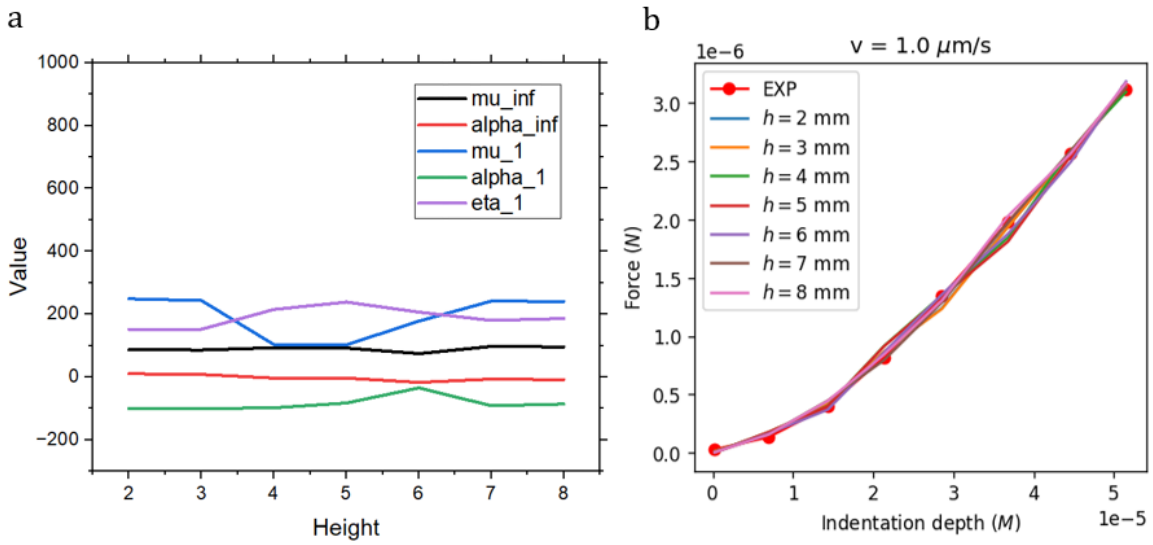

Figure 9: (a) Visualization of optimized parameter values across various heights in the 3D model, and (b) a comparison of force-indentation curves at different heights.

A primary challenge is the substantial computational cost of the inverse identification scheme, prompting efforts to compromise between simulation accuracy and computation time. Multiple simulation runs were conducted to assess the influence of specimen dimensions and element sizes.

In addition, we are currently implementing an axisymmetric model, a 2D reduction of the 3D model, promising significant reductions in computational costs. Figure 9 shows the current results of these efforts.

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B02 Pre and post metamorphosis spinal cord regeneration in frogs

Maria Tarczewska, Kristian Franze

Objectives

The primary objective of the project work in the reporting period was to learn the spinal cord dissection and investigate spinal cord anatomy and protein expression in Xenopus laevis tadpoles and adult frogs. The project aims to optimize protocols for spinal cord dissection, tissue sectioning, and fluorescent staining and imaging of agarose embedded sections. The project also sought to learn and apply Atomic Force Microscopy (AFM) techniques to quantify tissue stiffness in specific regions of grey and white matter.

Main Achievements

Significant progress was made in learning and optimizing protocols for spinal cord dissection from Xenopus laevis tadpoles (Figure 10), as per the technique published in Nature Protocols [1]. This method was successfully implemented for immunofluorescence (IF) stainings (Figure 11). Further, spinal cord dissection, sectioning, and staining of adult Xenopus laevis frogs were performed to compare anatomy and protein expression between tadpoles and adult frogs.

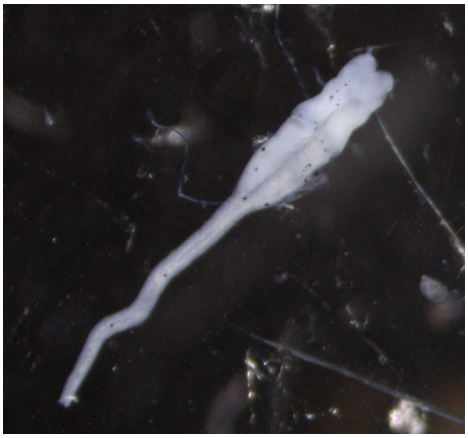

Figure 10: Spinal cord isolated from Xenopus laevis tadpole at stage 45.

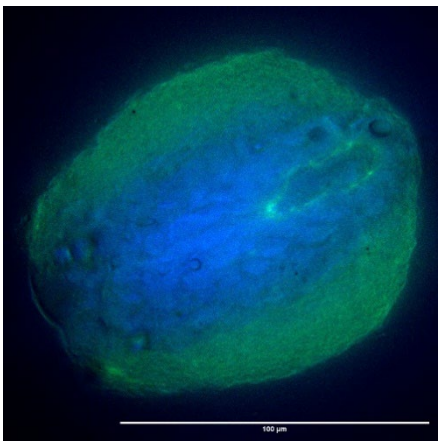

Figure 11: Immunofluorescence imaging of transversal section of stage 45 Xenopus laevis tadpole. Stained with Hoechst (blue) and phalloidin (green).

The project focused on the optimization of vibratome sectioning and fluorescent staining and imaging of agarose embedded sections of adult and tadpole Xenopus laevis. Stainings primarily included phalloidin and alpha-tubulin.

A stay at the University of Cambridge facilitated learning of AFM, which was then applied to create a stiffness map of a transversal section of Xenopus tadpole. This initial attempt requires further optimization and was an important step towards quantifying tissue stiffness in specific regions of grey and white matter.

Conclusions

The project has successfully implemented and optimized several protocols for studying the spinal cord in Xenopus laevis. The application of AFM, although requiring further optimization, has opened new possibilities for quantifying tissue stiffness, which could provide valuable insights into spinal cord injuries.

Outlook

The project plans to improve the immunofluorescence staining through OCT sample preparation. Future IF imaging will investigate molecular changes between regenerative and non-regenerative stages, including markers such as collagen IV, laminin, GFAP, vimentin, and Sox2/3+ cells [2][3].

The project also aims to implement HCR to investigate the expression of Small leucine-rich proteoglycans, recently identified to alter the mechanical properties of spinal lesions in zebrafish [4], in injured and uninjured tadpoles.

Further optimization of AFM experimental design is also planned, with future attempts including both regenerative and non-regenerative stages of injured and uninjured tadpoles.

Additional Skills

During the course of the project, a FELASA course was completed to enable work with animals.

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B03 The determinants of spinal cord mechanics in homeostasis

Jana Bachir Salvador, Jochen Guck, Stephanie Möllmert

Introduction

The objective of project **B03** is to characterize the mechanical properties of the zebrafish spinal cord *in vivo*. This entails a quantification of these properties, the identification of their determinants, and an examination of their relevance in homeostasis. Our focus is on the cellular constituents and the extracellular matrix contributing to the mechanical attributes of the spinal cord. To manipulate the composition and structure of the spinal cord in live zebrafish, we utilize biochemical and optogenetic techniques. This manipulation will involve targeted deposition of extracellular matrix components and the reduction of cell bodies. Subsequently, we will conduct *in vivo* Brillouin microscopy measurements on these manipulated specimens to extract the viscoelastic properties from the longitudinal modulus. We will investigate the same conditions and manipulations *ex vivo*, employing both Brillouin microscopy and Atomic Force Microscopy (AFM)-enabled indentation measurements on freshly sectioned tissue [1]. This approach aims to bridge multiple spatiotemporal scales, as established in various projects within this consortium, and potentially enable the extrapolation of *in vivo* mechanical properties from *ex vivo* measurements. In conjunction with these mechanical assessments, we will correlate the findings with structural and compositional analyses of the spinal parenchyma. These analyses will rely on histological, microscopic, and genetic tools, with machine learning techniques aiding in data interpretation. Ultimately, our research will not only contribute to a comprehensive data set allowing the prediction of distinct mechanical characteristics of spinal cord tissue based on histological data and proteome analysis but also enhance our understanding of the mechanical factors crucial for modifying pathological outcomes following injury or disease.

Methodology

We first employ optogenetically-mediated cell ablation in four-day-old zebrafish larvae. A confocal fluorescence microscope enables targeting distinct regions within the larval spinal cord with high spatiotemporal resolution. The TetON system was used to induce a tissue-specific expression of the photosensitizer KillerRed in the living zebrafish larvae upon incubation in doxycycline (DOX) [2]. The specificity of the ablation, such as cell type or spatial dimension, is achieved by either choosing fish lines in which only a distinct subset of cells expresses the protein, or by the user settings defined in the confocal fluorescence microscope, or a combination of both. In the transgenic line. We subjected specimens to 561 nm laser light in either the entire spinal cord cross-section only a defined volume in the dorsal section of the spinal cord or in all motor neurons. The KillerRed photosensitizer is a red fluorescent protein that then generates cytotoxic reactive oxygen species (ROS) which in turn causes irreversible oxidation of cellular components [3], leading to cell death within the illuminated area. We then proceed by measuring the response of these specimens by Brillouin time-lapse measurements using the Brillouin microscope based on the setup in [4] and AFM-based indentation measurements. The acquired Brillouin microscopy images and indentation curves are analyzed by custom-written software that wasprevious ly established in the lab.

Results

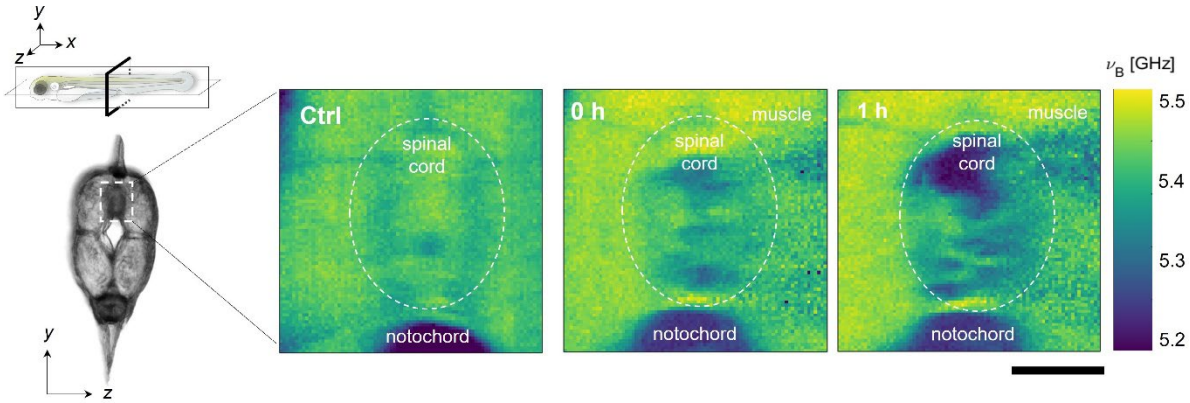

Figure 12: a) Brillouin frequency shift maps of the larval zebrafish spinal cord cross-section, surrounding muscle tissue and notochord for a non-ablated control, and for 0h and 1h after ablation, scale bar: 25 µm.

Our results show that by ablating with different laser intensities, targeting different cell types, or considering individual regions of interest in the spinal cord, we can dose the treatment and thereby tune the Brillouin frequency shift change in either direction.

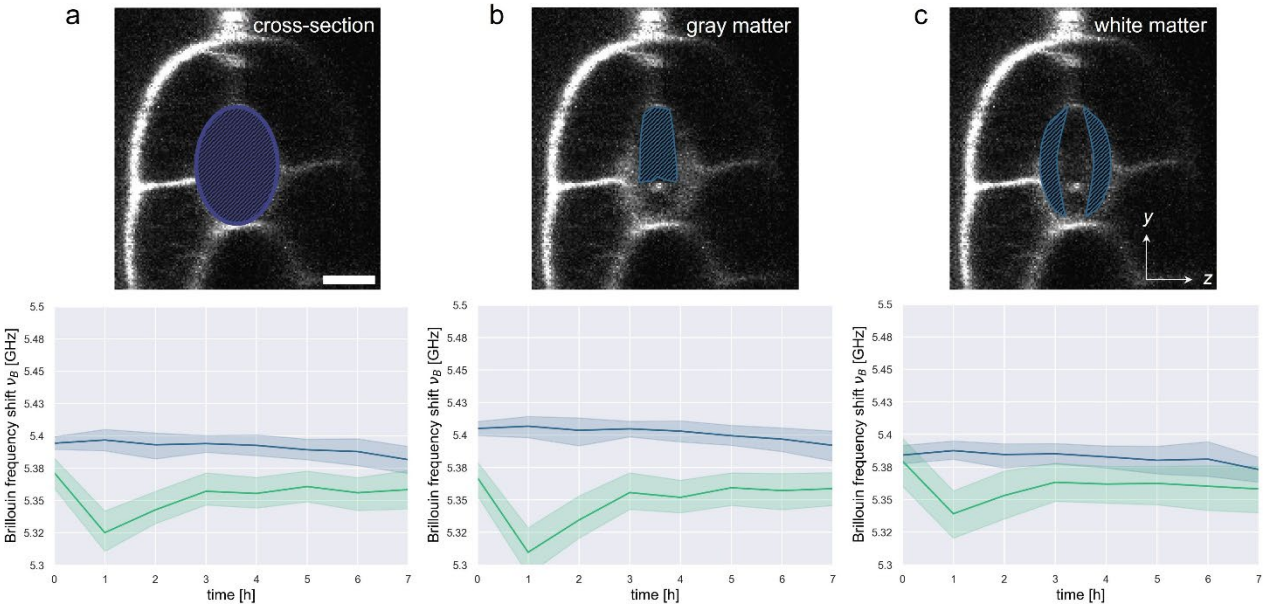

Figure 13: Time-lapse Brillouin microscopy, representative area for a) whole spinal cord cross-section, scale bar: 100 µm, b) gray matter, c) white matter, and the respective Brillouin frequency shift values after panneuronal ablation (shown in the green line), and for non-ablated controls (shown in the blue line).

Figure 13 shows different individual highlighted sections in the spinal cord, and their respective average Brillouin frequency shift values in a time-lapse measurement. It is shown that although the entire spinal cord section was ablated using the 561 nm laser, at 5% power, different regions show varied dose responses, which serves as a basis for further histological investigation. Moreover, to complement the *in vivo* measurements, AFM- based indentation measurements are per- formed on acute fresh spinal cord tissue sections that have undergone the same ablation. Preliminary results from the force- indentation curves of the apparent Young's modulus are shown in Figure 14.

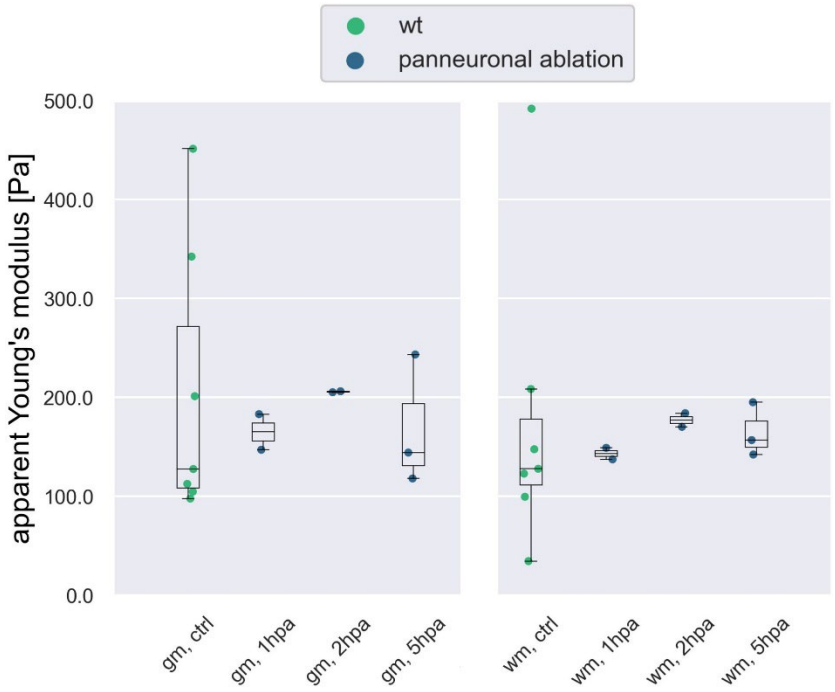

Figure 14: Apparent Young's modulus for gray matter (gm) and white matter (wm) regions for wild-type non-ablated controls, and panneuronal ablated larvae at different hours post ablation (hpa).

Outlook

Histological investigation will complement the Brillouin frequency shift changes with structural and compositional analysis, and thereby offer unprecedented insight into the determinants of tissue mechanical properties in the central nervous system. Artificially induced cell proliferation, for instance, is positively correlated with an increased Brillouin frequency shift, whereas cell death by ROS and concomitant accumulation of interstitial fluid is linked to a decreased Brillouin frequency shift. Further experiments include the manipulation of individual ECM components as well as chemical and physical perturbations of the spinal cord tissue. Moreover, *ex vivo* AFM measurements in addition to Brillouin measurements on sections of treated spinal cord tissue. Our results provide the basis for identifying potential targets to deliberately change tissue mechanical properties at will. This knowledge will eventually be used to initiate or benefit regenerative outcome after injury.

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B04 Spinal cord mechanics in a mouse model of multiple sclerosis

Maik Hintze, Rittika Chunder, Stefanie Kürten

Multiple sclerosis (MS) is a chronic neuroinflammatory demyelinating disease of the central nervous system (CNS) which is said to be autoimmune in nature [1]. Although the precise causes and nature of disease onset and progression remains unclear, it is generally accepted that infiltration of peripheral immune cells into the CNS may be the trigger of neuroinflammation in MS patients [2]. Distinct immune cell types, including antigen-specific T cells and B cells, drive disease pathology at different stages of MS by exerting their effector functions within the CNS. Destruction of myelin triggered by autoreactive immune cells leads to axonal insult, followed by axon loss and neuronal cell death eventually causing irreversible disease progression [2]. The cell loss during the late phase of MS is accompanied by formation of a so-called glial scar, wound-induced CNS tissue formed mainly by astrocytes. Reactive astrocytes are one of the main players in chronic non-resolving glial scar formation pathology [3].

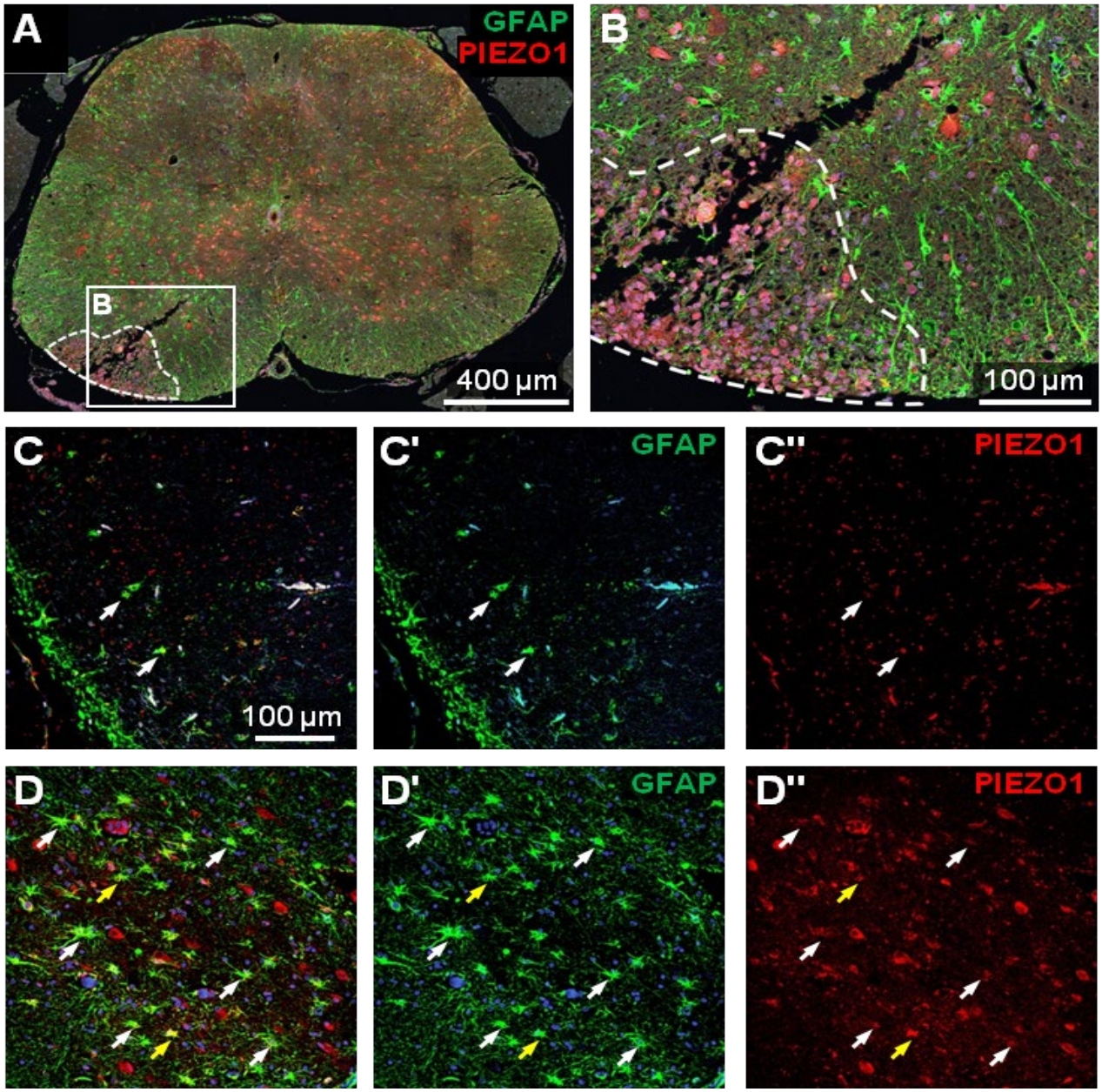

Figure 15: ***Reactive astrocytes upregulate PIEZO1.*** *A, B, mouse spinal cord with EAE immune cell infiltrate (dashed outline) shows no overlap of GFAP and PIEZO1 staining. C-C'', healthy human brain shows GFAP⁺ astrocytes lacking PIEZO1 staining (white arrows). D-D', MS patient brain shows PIEZO1⁺ astrocytes (yellow arrows) along with GFAP⁺ PIEZO1⁻ astrocytes (white arrows). Scale bar in C applies to C-D''.*

Given the wide range of homeostatic, trophic and mechanic functions of astrocytes within the CNS, we hypothesize that astrocyte-specific mechanosensation might be a contributing factor to MS pathology. One of the major cellular mechanosensors is the ion channel Piezo1 [4]. Piezo1 is known to be expressed on astrocytes, and can regulate Ca^{2+} oscillations and cytokine release *In vitro* [5]. Moreover, individual astrocytes have been shown to be "softer" than neurons [6], and tissue remodeling in CNS lesions leads to overall reduction of tissue stiffness at the lesion site [7]. Taken together, these observations suggest that MS-associated tissue remodeling likely leads to altered mechanical properties in MS lesions, which can then be sensed by astrocytes and may contribute to further disease progression.

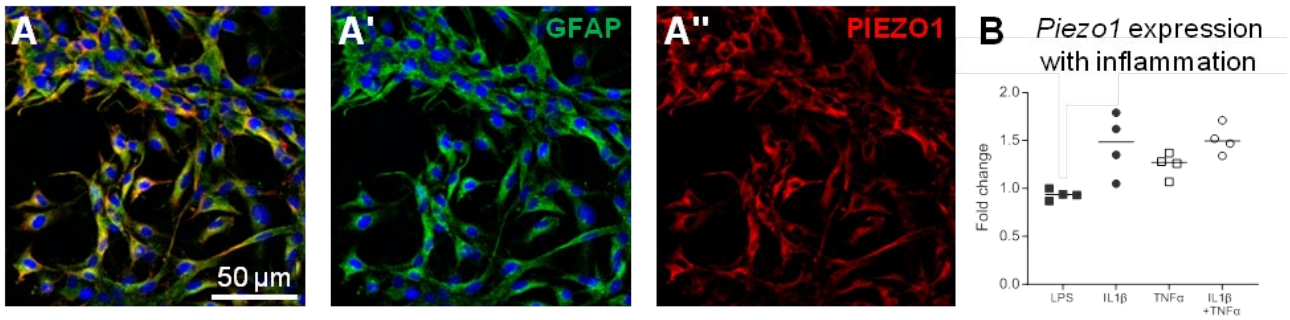

*Figure 16: **U87-MG glioblastoma cell line expresses.** A-A", immunocytochemistry shows that U87-MG cells express PIEZO1 along with the astrocyte marker GFAP. Scale bar in A applies to A-A". B, after 48 h stimulation with inflammatory stimuli as indicated, Piezo1 mRNA expression is upregulated, without reaching significance. Data points show fold change of Piezo1 mRNA expression compared to untreated sample.*

To this end, we first set out to test for astrocytic expression of Piezo1 *in vivo*. In mouse spinal cord from an animal with acute experimental autoimmune encephalitis (EAE), a mouse model that recapitulates various aspects of the human MS [8], we did not observe overlap between Piezo1 and the astrocyte marker GFAP, both within immune infiltrates and in surrounding healthy tissue (Figure 15A, B). Thus, under early (acute) disease conditions, Piezo1 expression on astrocytes is either low or absent at least in mouse spinal cord. Next, we tested human brain tissue and could indeed observe individual astrocytes showing Piezo1 expression (GFAP/PIEZO1 double positive) specifically in MS patients (Figure 15D), but not in healthy control tissue (Figure 15C). This indicates that in MS, specific populations of activated astrocytes can upregulate Piezo1 expression. To investigate Piezo1 expression change at a molecular level, we used the human astrocyte-like glioblastoma cell line U87-MG. On the one hand, we were able to show Piezo1 expression on these cells by immunocytochemistry (Figure 16A). On the other hand, we asked whether inflammatory stimuli which are present in the CNS during MS can affect Piezo1 expression levels. Indeed, some inflammatory stimuli displayed a trend towards upregulation of Piezo1 expression in U87-MG cells (Figure 16B), consistent with an inflammation-induced increase of Piezo1-dependent currents in a cerebellar mouse astrocyte cell line [9].

In the following experiments we will use these U87-MG cells in addition to primary human astrocytes for further investigation of Piezo1-mediated effects on astrocytes by applying the Piezo1 activator Yoda1, or the inhibitor GsMTx4. Using enzyme-linked immunosorbant assay (ELISA), quantitative PCR (qPCR), and scratch assay, we want to study the effects of Piezo1 activity on different astrocyte behaviors such as immune signaling and cell migration, especially in the context of MS. To dissect the effects of astrocyte-specific Piezo1 signaling *in vivo*, we are currently generating an inducible astrocyte-specific conditional Piezo1 knockout mouse (Piezo1-cKO). We will induce both acute and chronic EAE in Piezo1-cKO mice to test disease outcome by clinical and histopathological parameters. Using atomic force microscopy (AFM) and Brillouin microscopy, we will investigate the mechanical changes associated with EAE lesion development in EAE lesions in Piezo1-cKO animals with Piezo1-deficient astrocytes compared to EAE lesions in wild-type littermates.

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B05 *In vivo* mechanical manipulation of spinal cord regeneration

Olga Lyraki, Julia Kolb, Daniel Wehner

Project **B05** is testing the hypothesis that local mechanical tissue properties are critical for successful nerve fiber (axon) regeneration after spinal cord injury (SCI), and that the specific composition of injury-associated extracellular matrix (ECM) deposits confers these properties. To that aim, B05 utilizes the vertebrate species zebrafish, which different to humans and other mammals, is capable of long-distance axon regeneration and functional recovery after central nervous system (CNS) injury.

In the current reporting period, we focused on the identification of injury-associated ECM factors, which confer mechanical properties to central nervous system (CNS) lesions adverse to axon growth. To this aim, we first mapped the changes in ECM composition after SCI in regeneration-competent zebrafish using mass spectrometry-based quantitative proteomics. We next compared the zebrafish proteomics dataset with that of rats after SCI to identify interspecies differences in the ECM composition that could account for the ability of severed axons to regrow after CNS injury. We identified 61 matrisome proteins (ECM factors) that were down-regulated or not significantly regulated after SCI in zebrafish but enriched in the rat lesion site. Among the differentially regulated matrisome proteins that showed low abundance in the zebrafish spinal lesion site were the neurite growth-inhibitory factors neurocan and 16 components of the basal lamina. These data demonstrate the value of cross-species comparative approaches in identifying inhibitory components of the mammalian injury ECM. The comparative dataset further revealed seven members of the highly conserved small leucine-rich proteoglycan (SLRP) family to be enriched in the rat spinal lesion site but down-regulated or not significantly regulated after SCI in zebrafish (Figure 17A). Analyses of rodent, zebrafish and human (spinal cord and brain) specimens supported that the abundance of the SLRP family members Chad, Fmod, Lum, and Prelp in the injury ECM reciprocally correlates with the CNS regenerative capacity (Figure 17B). To determine if SLRPs are inhibitory to CNS regeneration, we investigated the effect of experimentally increasing SLRP protein levels in the zebrafish injury ECM on axonal regrowth and functional recovery after SCI (Figure 17C). We found that axonal regrowth and functional recovery was strongly impaired in the presence of either Chad, Fmod, Lum, or Prelp proteins, identifying SLRPs as previously unknown inhibitors of CNS axon regeneration *in vivo* (Figure 17D). Functional experiments indicated that SLRPs neither inhibit regeneration through i) direct (biochemical) interactions with the axonal growth cone (i.e., ligand-receptor interactions), nor ii) prevention of inflammation resolution, nor iii) altering the composition of the fibroblast-derived injury ECM. In contrast, utilizing atomic force microscopy (AFM)-based nanoindentation measurements, intravital cross polarized optical coherence tomography (CP-OCT) and Brillouin microscopy showed that the presence of individual SLRP family members in the injury ECM leads to changes in the structural (Fmod, Lum, Prelp) and mechanical (Lum, Prelp: reduced longitudinal modulus; Fmod, Lum, Prelp: reduced apparent Young's modulus; Fmod, Prelp: reduced apparent viscosity) properties of the lesion environment, which coincides with an impaired regenerative capacity of axons (Figure 17E). This indicates that SLRPs inhibit CNS regeneration by conferring mechano-structural properties to the injury ECM adverse to axon growth. Our study provides the first *in vivo* evidence for a direct relationship between tissue mechanics (longitudinal modulus, apparent Young's modulus, apparent viscosity) and regenerative outcome upon CNS injury, and identifies SLRPs as modulators of the inhibitory viscoelastic response of mammalian CNS lesions. These results were published in Nature Communications (doi.org/10.1038/s41467-023-42339-7), and involved collaborations with the EBM projects **A02**, **B03**, **C02**, and **C03**.

Currently, we are concentrating on the identification of factors that confer the regeneration-permissive mechanical properties to the injury ECM in zebrafish CNS lesions. To this aim, we are using pharmacological and genetic manipulations (gain-of-function / loss-of-function) of specific candidate ECM molecules (e.g., type XII collagen) identified in our mass spectrometry analysis, in order to correlate mechanical read-outs (Brillouin microscopy, atomic force microscopy) with regenerative success.

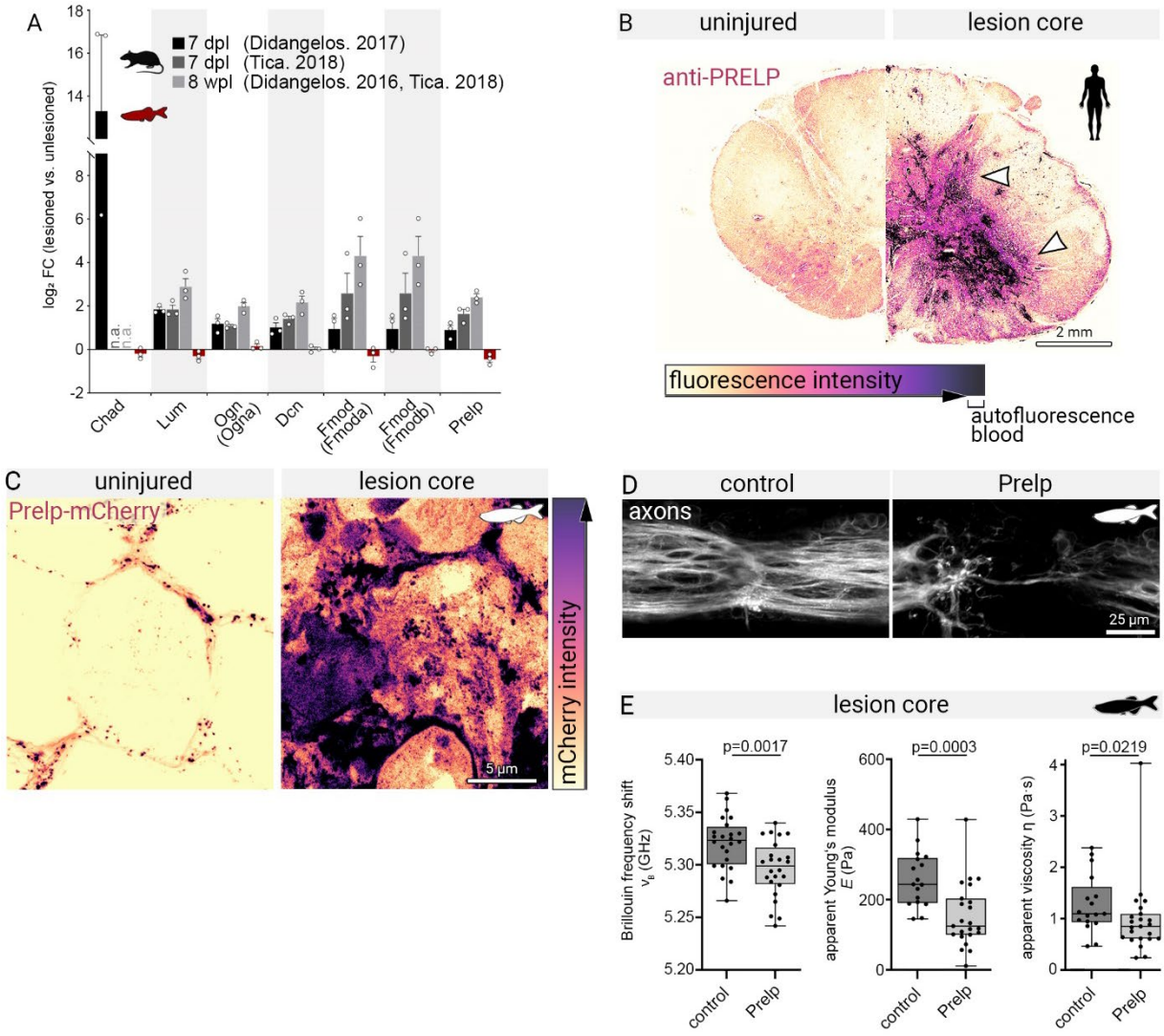

Figure 17: A) Comparative analysis of indicated proteomics datasets reveals differential enrichment of SLRP proteins after SCI in rat (grey tones) and zebrafish (red), including Prelp. (B) anti-PRELP immuno-reactivity is increased in the injured human spinal cord (arrowheads; transversal view). (C) Experimental enrichment of Prelp-mCherry fusion proteins in the zebrafish spinal lesion site (arrowhead; transversal view). (D) Targeting Prelp proteins to the zebrafish spinal injury ECM inhibits axon regeneration (white) in larval zebrafish (lateral view of the spinal cord). (E) Targeting Prelp proteins to the zebrafish spinal injury ECM reduces the Brillouin frequency shift, apparent Young's modulus and apparent viscosity of the lesion environment.

C01 *In silico* modelling of mechanical cell-matrix interactions

Soheil Firooz, Pritha Dolai, Paul Steinmann, Vasily Zaburdaev

On continuum modelling of cell aggregation phenomenon

The main objective of the **C01** project is to model and simulate the cell-ECM interaction. In doing so, as a preliminary work that could serve as a template, we examine cellular aggregate formation phenomenon. Cellular aggregates play a significant role in the evolution of biological systems such as tumor growth, tissue spreading, wound healing, and biofilm formation. Analysis of such biological systems, in principle, includes examining the interplay of cell-cell interactions together with the cell-matrix interaction. These two interaction types mainly drive the dynamics of cellular aggregates which is intrinsically out of equilibrium

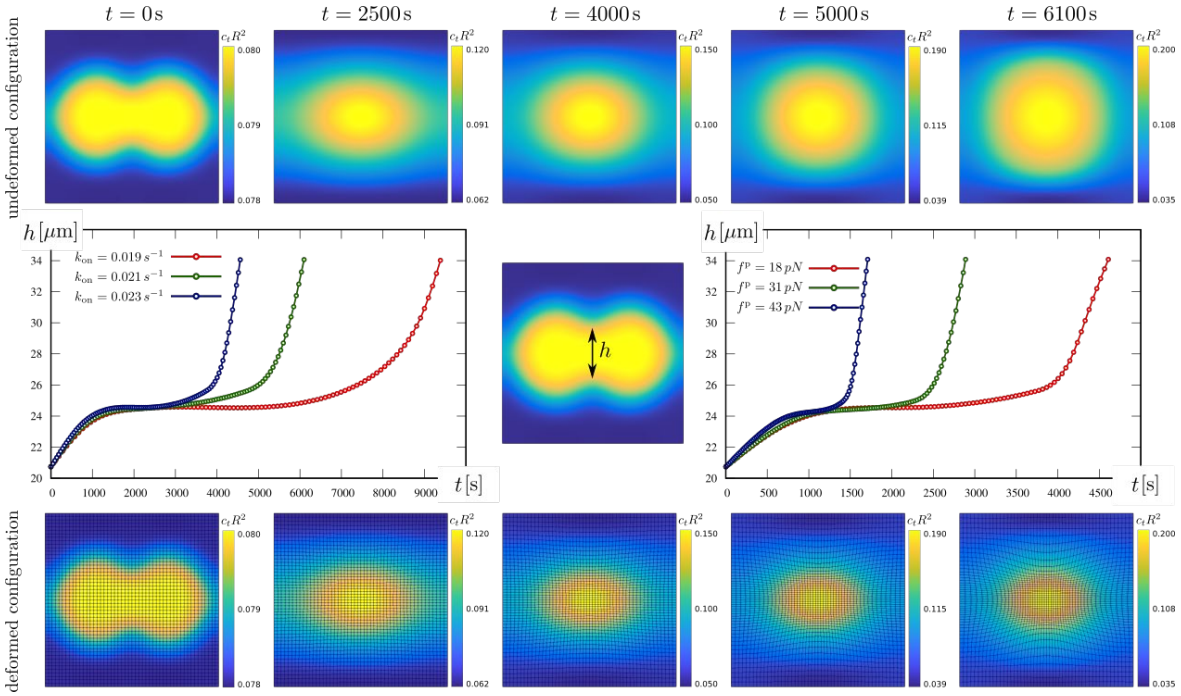

Figure 18: Five snapshots of the colony coalescence process in undeformed and deformed configurations. The parameter h measures the bridge length between the two merging colonies. The center plots render the effects of k_{on} and f_p on the evolution of the bridge.

In this project we proposed a non-linear continuum mechanics formulation and the corresponding finite element simulation framework to model the physics of cellular aggregate formation [1]. Via describing the aggregation process as an active phase separation phenomenon, we develop a continuum description of the problem which is of a convection-diffusion type [2]. To interact with the environment and with each other, cells use multiple long and thin retractable filaments, called pili. Pili can extend from the cell body, attach to the substrate or other cells and retract. Figure 18 investigates the influence of the pili-pili binding rate k_{on} and the pili-pili mediated attractive force f_p on the size of the bridge between two micro-colonies. It is observed that increasing any of pili-pili binding rate or pili-pili mediated attractive force yields a faster growth in the bridge length between the two micro-colonies.

Towards modelling cell matrix interactions in brain tissues

In another branch of this project, we would like to unravel the effect of cell-matrix interactions in the context of brain tissue. It is experimentally observed (in the group of Katja Kobow and Ben Fabry) that cell-cell and cell-matrix interactions play an important role in the hippocampal cell-network formation. There are few processes which are involved in network formation namely growth and shrinking of neurites, interactions or merging between neurites of different cells and clustering of cell bodies. As a first step, we are trying to develop an agent-based model for growth processes. Neurite growth process can happen in two ways: (a) via linear growth and (b) via traction forces. These two processes are explained below. Our model consists of a cell body of radius R_c and N_e number of extra-cellular matrix (EC) particles of radius r_e. The neurites are represented by beads of radius r_b

($r_b < r_e < R_c$) connected by spring. Neurite growth can happen at a certain rate α. To start a growth process, an angle θ is chosen randomly and a bead is added at the center of the cell with a spring. The initial spring (rest) length l is set to zero. Once the spring length l becomes larger than some critical value l_0, another bead is added at the center of the previous bead. A spring force act on the beads along the growth direction. The model system is illustrated in Figure 19 (left panel) containing a cell and two beads. There is excluded volume interaction acting between all pairs of particles: cell-bead, bead-bead, cell-EC, bead-EC and EC-EC. Figure 19 (right panel) depicts a typical simulated snapshot of a cell containing 5 neurites and each having 4 beads and embedded in a sea of EC particles. In the next few months, we would like to implement the shrinking processes and the interactions between the neurites of different cells.

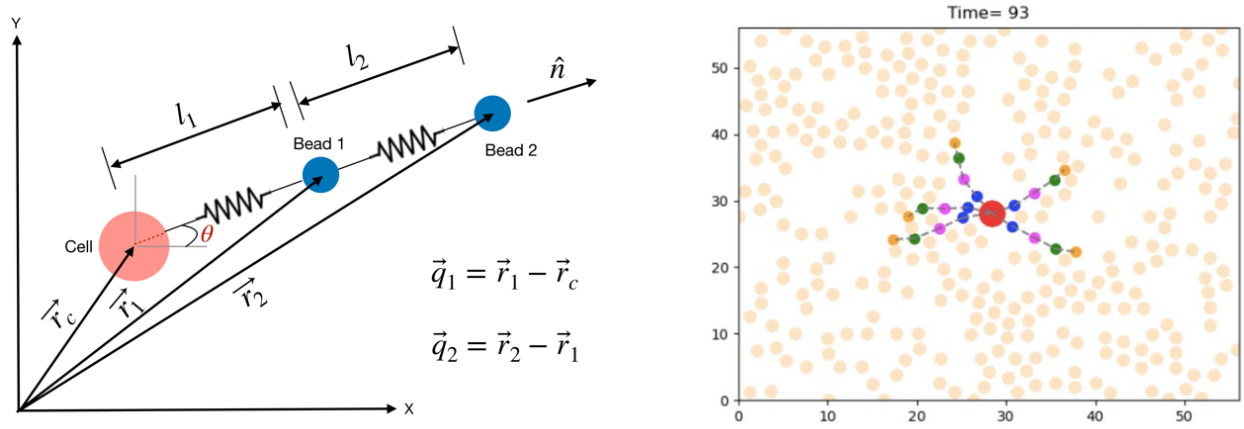

Figure 19: Left: Schematic diagram of a neurite. Right: Typical simulated snapshot of the system.

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C02 The role of mechanics for neuronal “plasticity”

Bartomeu Perelló Amorós, Ezgi Erterek, Renato Frischknecht

The perineuronal extracellular matrix (ECM) is responsible for regulating neuronal "plasticity" in the adult brain, though the precise mechanisms remain largely unknown. This study aims to test the hypothesis that the mature brain's ECM creates an unfavorable mechanical environment for neuronal plasticity and structural rearrangements. The hypothesis will be investigated using a three-work package approach. **WP1** aims to examine the mechanical properties of different brain regions by investigating the contribution of the ECM. A set of methods to modify ECM properties in both vitro and vivo settings will be created in **WP2**, evaluating their effects on brain mechanics. WP3 will investigate the influence of tissue stiffness on neuronal “plasticity” using these methods. During the first period, we mainly worked on WP2 and WP1. This report details our progress.

WP1: Contribution of the ECM to the mechanical properties of cortical layers

In collaboration with **B03**, we intend to clarify the contribution of the ECM to local differences of the mechanical properties of brain tissue. For that purpose, we want to measure brain stiffness in cortical layers of adult mice in acute brain slices and in 3D cultures of dissociated neurons using Brillouin microscopy. In a first attempt, we measured cortical neurons cultured in hydrogels provided by **X03** that were fixed and stained using cytoskeletal markers prior to Brillouin imaging. The obtained experience is now used to optimize the setup and cell culture system. Further, we started to characterize the ECM density using immunohistochemistry within the mouse cortex as a basis for the planned measurements of their mechanical properties in collaboration with **B03**.

WP2: Development of tools to alter ECM properties *in vitro* and *in vivo*

In WP2 we are pursuing two strategies to develop tools to manipulate the mechanical properties of the ECM to control neuronal outgrowth, synapse formation and synaptic plasticity. In collaboration with **X03** we tested OHA/GEL (oxidized hyaluronan) hydrogels with different mechanical properties for their ability to foster neuronal outgrowth. OHA was chosen to mimic the perineuronal ECM, in which hyaluronic acid is a central molecule. In addition to the OHA/Gel composition, we also varied the culture setup. First, we cultured neurons embedded in the matrix to obtain a 3D culture system; second we cultured neurons on top of the OHA/Gel; and third, we printed the hydrogel on a culture dish using a 3D printer and seeded neurons on the dish to monitor the ability of neurons to invade hydrogels with different mechanical properties. We found that gels containing higher concentration of OHA deterred neuronal outgrowth, while neurons exhibited normal outgrowth in gels with lower OHA concentrations. In these 3D cultures, neurons formed an elaborated neuronal network with numerous synapses and could be cultured for up to 3 weeks. Similarly, neurons were able to invade 3D-printed gels with low but not high concentration of OHA. However, to date we had little success culturing neurons on top of the hydrogel. Obtained results were recently summarized in an article published in BioSpectrum together with **X03** (Kuth et al., BioSpektrum 07.23). We are currently further characterizing the 3D culture system, which will be our main experimental system using hydrogels. Next goal is to stimulate mature neurons to induce synaptic plasticity and monitor structural changes of neurons depending on the mechanical properties of the hydrogel as part of WP3, which we have not yet started.

In collaboration with **B05,** we investigated the potential of ECM proteins selected based on their regulation after spinal cord injury for their potential to influence neuronal outgrowth. To this end, these ECM proteins were applied as a substrate for cortical neurons by being coated onto glass coverslips. Axonal growth was measured under varied conditions, and we observed no influence of the tested proteins on neurite extension. These findings suggest that these substrates do not induce classical biochemical signaling in this context. Together with a series of experiments conducted by **B05,** these studies aided in identifying the mechanical property variances in the damaged spinal cord that are accountable for spinal cord regeneration. The latest findings of this study, led by **B05** have been published [1].

A further technique to modify mechanical properties is to induce clustering of ECM proteins optogenetically. To accomplish this, we are cloning a fusion protein of cryptochrome2 (Cry2) and the abundant CNS-specific ECM protein brevican. Cryptochrome2 from Arabidopsis thaliana oligomerizes

reversibly under blue light exposure and has previously been used to investigate protein homo-oligomerization in cells. We have connected Cry2 to a red fluorescent protein (mCherry) to aid visualization. We are currently developing an assay to investigate the ability of the brevican-Cry2-mCherry construct to generate oligomers on the surface of eukaryotic cell lines. Following successful testing of the construct, we intend to overexpress it in neuronal cultures and manipulate the mechanical properties of the ECM near the neuron as part of WP3, which will commence in the coming year.

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C03 Exploring the mechanics of neuronal network formation

Kristina Karandasheva, Katja Kobow

Aim: To investigate mechano-biological aspects of neuronal circuit function under normal and pathophysiological conditions in mechanically tuneable engineered brain tissue

WP1: Mechanics of primary neuronal network formation

We used a rat primary neuronal cell culture in mechanically tuneable matrices. We specifically tested Matrigel with and without growth factors, Vitrogel with and without supporting adhesion molecules, Collagen I (C05), Hyaluronic acid (X03), and Alginate-gelatin hydrogels (X03) and compared neuronal maturation, migration, and network formation in 3D to previously established 2D cultures seeded on poly-D-Lysin (PDL), PDL+Laminin, and PDL+Fibronectin. The primary challenge extended beyond achieving viable cell cultures to creating conditions where neuronal cells spontaneously formed functional networks within the intricate spatial dynamics of 3D matrices. A reproducible protocol enabling such network formation within Matrigel was established, with cell cultures remaining viable for over 15 days. These established 3D cultures now serve as a benchmark, guiding ongoing efforts to explore the potential of tuneable matrices. Matrigel with Collagen I as well as Collagen I alone also supported survival and neuronal network formation, however, to a lesser extent (more dead cells, less connections within the network, changed cellular morphology). Major limiting factors that do not support neuronal survival, network formation and function in all other matrices tested so far are: an incompatible pH, use of bivalent cations to polymerize hydrogels, lack of adhesion molecules. Supporting experiments in 2D suggest that Laminin, when provided as adhesion molecule, helps to increase cell viability through support in cell adhesion and migration, with subsequent stable network formation. Additionally, collagen IV will be tested.

Next, approaches for the quantitative measurement of cellular and network characteristics were established. A collaborative effort, leveraging time-lapse microscopy with the expertise of partner C05 and the Optical Imaging Centre Erlangen (OICE), was undertaken to systematically monitor and quantify cellular motility. Time-lapse recordings captured dynamic cell movements over distinct temporal intervals (0-12 hours, n=3425; 0-48 hours, n=32; 24-125 hours, n=14) in 2D cell cultures seeded on poly-D-lysine (PDL) and Matrigel coatings. The data generated from these recordings were used to then develop a custom computer-vision-based algorithm for the extraction and quantification of cellular and network parameters from respective recordings, including 1) identification of cell types, 2) tracking of cell movement trajectories, and 3) delineation of axonal pathways. This will provide the technical framework for understanding the intricate dynamics of cellular behavior within the specified experimental conditions. Data will be shared with partner C01. Immunofluorescence staining with neuronal marker MAP2 and glial marker GFAP corroborated conclusions regarding *in silico* cell type prediction. In addition, initial traction force microscopy measurements in 3D neural networks embedded in collagen and collagen and Matrigel combinations were performed with C05.

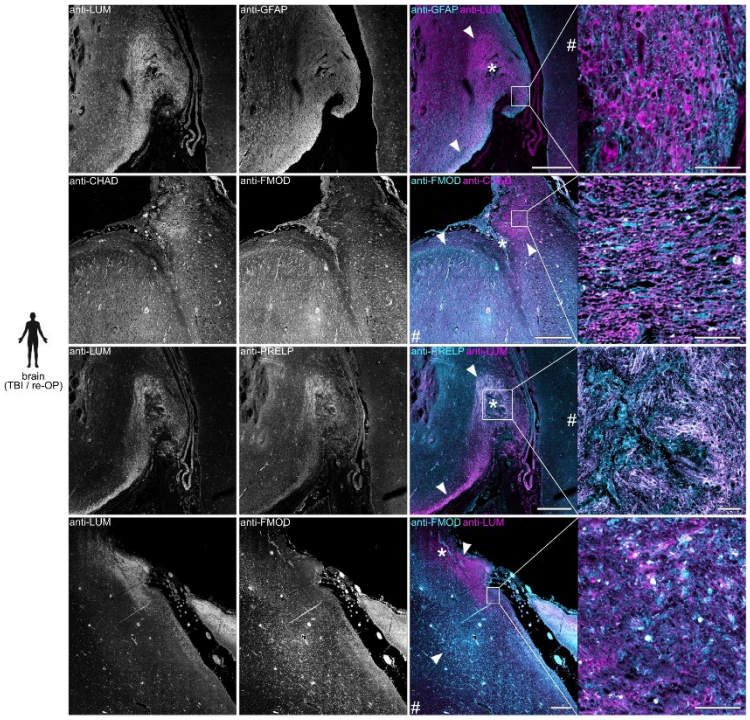
WP2: Mechanical aspects of ictogenesis

Together with B03 we performed Brillouin microscopy *in vivo* in the optic tectum of fluorescently labelled zebrafish larvae (4dpf, Her4:GFP;elavl:mKate) immobilized in agarose gel and treated with 15 µM PTZ to induce acute seizures. Optimal concentration for PTZ treatment was identified treating freely moving zebrafish in their normal media with final PTZ concentrations ranging between 5 and 60 µM. Only at 15µM all zebrafish reproducibly showed seizure activity (as quantified during continuous video monitoring over swim distance and speed and abnormal movements). At higher PTZ concentrations zebrafish died during seizure activity. During initial tests for Brillouin microscopy during seizure activity, 10 ROIs were analyzed in the OT of each fish (n=4) with 1 measurement per minute over 20 minutes. Brillouin shift and line width were quantified and averaged per time point and fish. More fish need to be analyzed to conclude on potential changes in viscoelastic properties of brain tissue during ictogenesis. Other seizure inducing agents (e.g., high K+, 4-aminopyridin, glutamate) will be tested and mechanical measurements complemented with atomic force microscopy measurements.

WP3: Mechanical aspects of epileptogenesis

In collaboration with B05 analyzed and compared the ECM composition of human, rodent and zebrafish CNS scars. Human brain samples were derived from focal epilepsy patients with brain

malformations adjacent to a scar (i.e., FCD 3D) and a known history of traumatic brain injury, intrauterine infarctions, or repeated surgery, who underwent surgery for the treatment of their epilepsy. We further had access to lesioned and unlesioned human, rodent, and zebrafish spinal cord samples. We analyzed the expression of small leucine-rich proteoglycans (SLRPs) and demonstrated that the SLRPs chondroadherin, fibromodulin, lumican, and prolargin were enriched in rodent and human but not zebrafish CNS lesions. Next, the study revealed SLRPs as inhibitory ECM factors that impair axon regeneration by modifying tissue mechanics and structure. Results were successfully published [1]. Within this study, we further identified that in unlesioned mammalian brain and spinal cord, but also in primary neuronal cell cultures, lumican is endogenously expressed in neurons, while another ECM component of mammalian scars (currently under investigation) was under “normal” non-lesional conditions exclusively expressed in glia. These preliminary results lead to the question what the functions and binding partners of respective ECM molecules are in physiological and pathological conditions and whether they do play a role in normal and aberrant circuit and network function.



Finally, we explored existing data sets from DNA methylation profiling studies in human lesional focal epilepsy focusing on a cohort of FCD 3D and investigating the potential functional consequences of disease- and pathology-associated epigenetic signatures towards gene expression. Differential methylation in FCD 3D with loss of layer 4 mapped explicitly to biological pathways related to neurodegeneration, biogenesis and organization of ECM, axon guidance, and regulation of the actin cytoskeleton. We also found SLRPs to be targeted by DNA methylation changes related to FCD 3D and epilepsy. Our data suggest that DNA methylation signatures in cortical malformations are phenotypically relevant, providing the molecular underpinnings of structural and histopathological features associated with epilepsy [2].

References

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C04 Cellular differentiation in brain tissue-mimicking matrices

Shanice Heidenreich, Anja Bosserhoff

C04 aims at using cell types with the same embryonic origin but distinct differentiation than brain cells, melanocytes and melanoma cells, to analyze the role of mechanics on cellular differentiation and de-differentiation. Melanocytes originate from the neural crest and display several characteristics typical of neural cells such as Schwann cells. Interestingly, melanoma cells are known to have the feasibility to transdifferentiate into Schwann cells ("Schwannian differentiation"). Comparison of cells from melanocytic origin to neural cells with regards to the impact of the different microenvironmental matrices on differentiation is therefore highly interesting. Further, melanoma cells actively metastasize into the brain in a high percentage of patients. Understanding of this process resembles a strong clinical need as brain metastases of melanoma are still not curable.

We have started to cultivate melanocytes in decellularized brain tissue and brain tissue-mimicking matrix (supported by **X03**, see Figure 20) and analyzed several molecular characteristics (e.g. differentiation-specific genes (MITF, E-Cadherin) to defined changes in the cells induced by the microenvironment. Interestingly, we observed strong change in expression of MITF and E-cadherin, already suggesting effects on cellular differentiation. We further plan to add more markers incl. markers for senescence and to perform RNASeq and bioinformatical analyses to define the brain-tissue-specific cell behavior and differentiation in an unbiased manner. By modeling of the matrix in follow-up experiments, its defined influence on molecular characteristics will be in focus. We already characterized Sox9 as an important regulator of melanocyte differentiation and their trans-differentiation to glial cells [1] and will also address the role of Sox9 in biomechanics in the brain. We finally aim to understand whether differentiation cues are mediated via biomechanics.

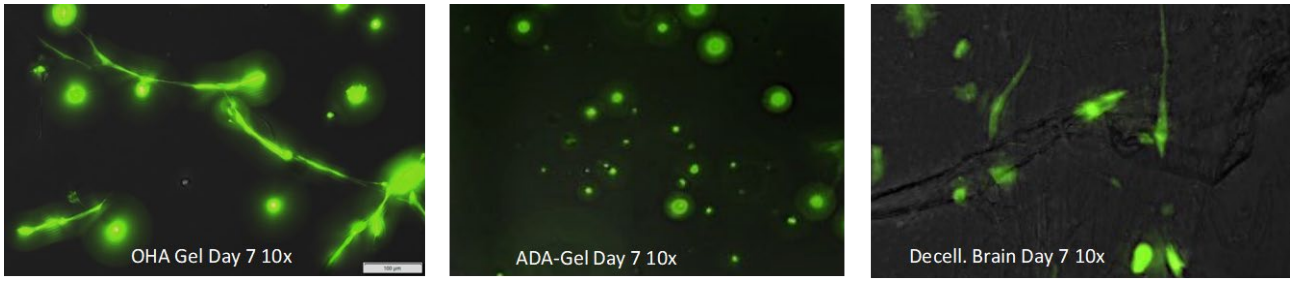

Figure 20: Melanocytes cultivated in three matrices revealed significantly different morphology.

In addition, molecular features and tumor cell characteristics of melanoma cells in brain tissue-mimicking hydrogels or decellularized brain tissue were started to be studied. Here, aim at getting insight into the role of mechanics during brain metastases of this aggressive tumor and want to finally understand whether the brain is an attractive soil for melanoma cells due to its mechanical properties.

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C05 Molecular mechanisms of neuronal mechanotransduction

Lars Bischof, Ben Fabry

The main objective of Project C05 is to investigate molecular mechanisms of mechanosensing and mechanotransduction in primary neurons in 3D environments. Hence as a first step we are establishing a 3D matrix composition that supports physiological growth of neurons while allowing mechanical analysis of interaction between cells and the extracellular matrix. We are currently exploring two different matrices, 1) collagen-based hydrogels that allow for traction force microscopy based on confocal reflection images (see Figure 21) without adding fiducial markers such as fluorescent beads, and 2) Matrigel. Both matrices have previously demonstrated to facilitate axonal growth [1,2]. Therefore, in close cooperation with Project **C03** who also provided us with primary neurons, we explored collagen, Matrigel, and collagen-Matrigel composite matrices with different protein concentrations and mixing ratios.

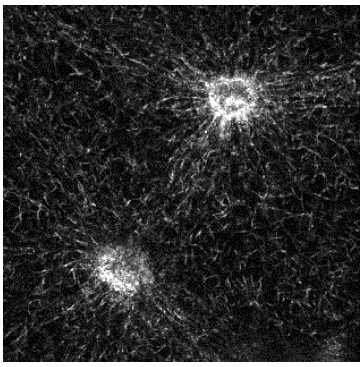

Figure 21: Two HC rat neurons on 1.2 mg/ml collagen hydrogel; confocal reflection image.

Primary hippocampal rat neurons were cultured in 3D extracellular matrices and monitored for multiple days. Time-lapse images were recorded (every 5 min) and analyzed by visual inspection based on neuronal interconnectivity. Neuronal cell interconnectivity was highest in Matrigel, slightly decreased in mixed collagen-Matrigel hydrogels, and almost completely absent in pure collagen hydrogels (see Figure 22). Further, 3D culture experiments in VitroGel also showed no neuronal network formation. So far, the results suggest Matrigel contains essential components for neuronal cell interconnectivity.

After optimizing neuronal growth conditions, we will proceed with traction force measurements, especially focusing on axonal growth by time lapse imaging of growth cones. Traction forces and growth persistence can be analyzed for various ECM properties: Mechanical stretching of collagen hydrogels results in fiber alignment and stiffening while variations in collagen concentration impacts fiber density, pore size and overall stiffness of the hydrogel.

In the long run, we will use all these ECM alterations to enable us guiding growing axons along predestined paths.

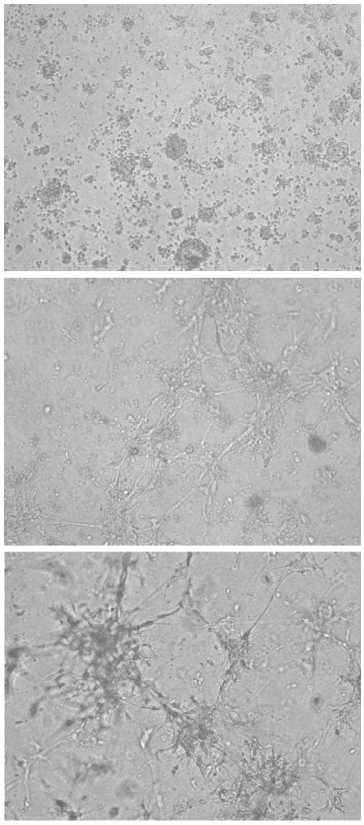

Figure 22: HC rat neurons cultured in 3D hydrogels; Neuronal growth after 5 days in 0.6 mg/ml collagen (top), 0.3 mg/ml collagen + 1 mg/ml Matrigel (middle) and 1:2 Matrigel.

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X01 Model-based reconciliation of *ex vivo* and *in vivo* test data

Laura Ruhland, Yashasvi Verma, Jing Guo, Ingolf Sack, Paul Steinmann, Kai Willner

Contradictory mechanical responses are a persistent problem concerning experimental studies of ultra-soft materials such as brain tissue when using different testing techniques. The project aims to tackle these inconsistencies via a two-pronged approach from the experimental and computational points of view.

One of the reasons for the inconsistent experimental responses is attributed to the varying testing conditions of the different techniques. Particularly challenging is the use of multiple time and length scales across the experiments. Experimental results have been conducted by two different testing methods. At the rheometer quasi-static experiments in the time domain were performed. A phantom material based on alginate (ALG) and gelatin (GEL), mimicking the viscoelastic behavior of the brain, was used for the measurements. The samples were analyzed under relatively large strains of about 15%. Based on a finite element model of the experiments in Abaqus the material parameters of the hydrogel were established. An identification procedure minimizing the least squares error between measured and modelled data was used to determine the optimal set of parameters. Figure 23 shows the hysteresis and stress relaxation data for compression, tension and shear loading of ALG-GEL and the calculated Abaqus results of the mechanical behavior.

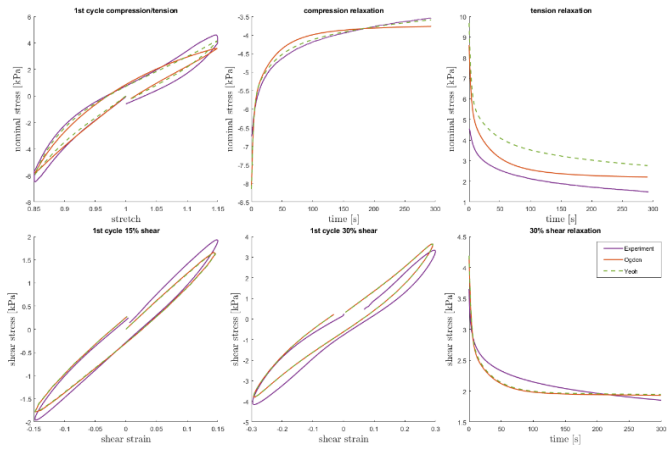

Figure 23: Mechanical behavior of ALG-GEL under cyclic loading and stress relaxation in compression-tension (first row) and shear (second row) and the calculated material responses by using a hyperelastic Ogden and Yeoh model both combined with a viscoelastic Prony.

In cooperation with our project partners Ingolf Sack and Jing Guo from Charité Berlin a table-top magnetic resonance elastography system was established to obtain material responses over a wide frequency range up to several kHz. The measurements were performed on a 0.5T magnet, which determines the vibration in the material induced by a piezoelectric actuator. With this measurement technique vibration data up to several kHz can be obtained. The material parameters of those experiments were identified by fitting the 1D-wave field of every frequency to the viscoelastic Maxwell or Kelvin-Voigt equations. Figure 24 shows the storage and loss module for ALG-GEL in a frequency range from 300Hz to 4100Hz.

An additional approach is to establish a computational model that can suitably predict the results of the various testing modes and methods.

In this effect, we employ a non-linear poroviscoelastic model of the brain [1]. This model is founded on the hypothesis that the brain is intrinsically biphasic in nature, and the porous and viscoelastic parameters interact with each other. It has previously shown promising results by predicting the contradicting nature of the stiffer white matter in indentation experiments, while the stiffer gray matter in large strain compression testing [2]. The model is implemented by using the deal.ii library and is being enhanced by including a full dynamic range over various time and length scales. This approach also involves a comprehensive consideration of specific loading, initial and boundary conditions tailored to diverse testing setups.

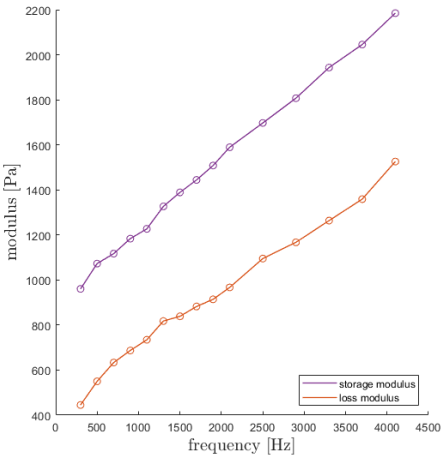

Figure 24: Storage and loss modulus of ALG-GEL calculated with the viscoelastic Maxwell model.

In this context, another important aspect is the inclusion of the vascular structure present in the brain into the model. The overlay of this discretized network and the integration of the blood pressure will serve as an enhancement of the model especially when *in vivo* measurements will be considered. The basis for adding the vascular tree into our model will be a library that generates a dendritic tree in blender software and a tool that exports it into deal.ii-readable meshes [3]. The vessels or inclusions will be coupled with a linear elastic material matrix using the reduced Lagrange multiplier method [4]. This mathematical coupling will be extended to the scope of our biphasic non-linear poroviscoelastic brain model in collaboration with Luca Heltai from SISSA, Italy.

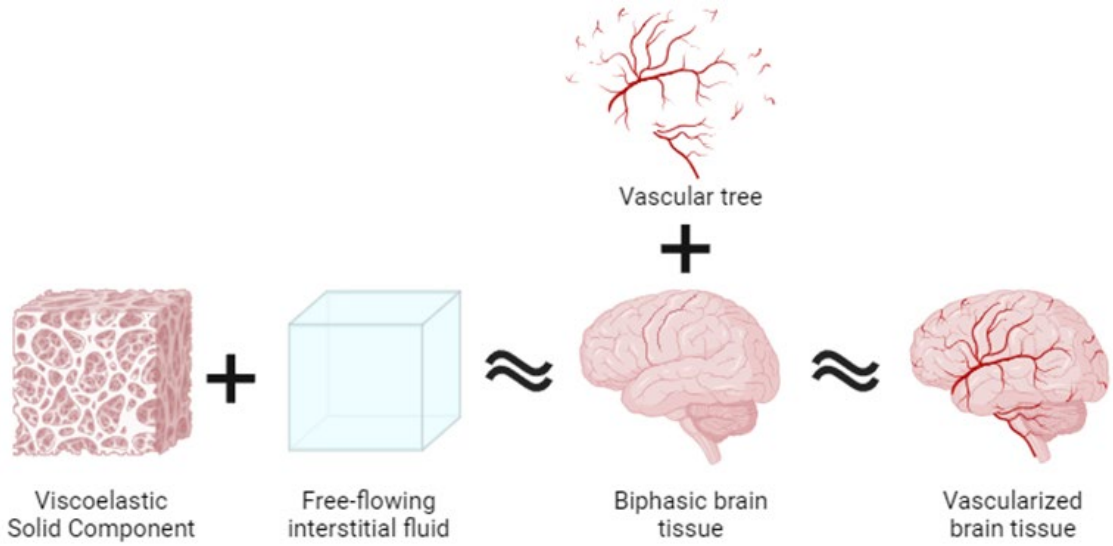

Figure 25: Approximation of the brain tissue in the computational model.

In addition to the aforementioned results, the Berlin team have performed *in vivo* multifrequency MRE to investigate the biomechanical progression of the female mouse brain over an age range of 6 to 18 months. it was observed that the whole brain underwent significantly softening over time ($p=0.023$) with increased viscosity ($p=0.004$). Both white matter ($p=0.002$) and gray matter ($p=0.045$) exhibited age-related brain softening; however, viscosity remained unchanged over time for these two regions. Our initial findings indicated that the overall brain underwent biomechanical degradation as it aged, resulting in a more fluid-like behavior with reduced rigidity and increased viscosity, consistent with the literature [5,6]. These biomechanical changes in the brain and cerebral subregions need to be further investigated and verified by histopathologic analysis. However, the preliminary results provide reference data needed to identify viscoelastic and poroviscoelastic models and will eventually guide our simulations.

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X02 Data analysis and machine learning for heterogeneous, cross-species data

Frauke Wilm, Zhaoya Pan, Mathias Öttl, Katharina Breininger, Andreas Maier,

The **X02** project focusses on the application of machine learning models on heterogenous cross-species data. In this context, trained models have demonstrated low robustness to domain shifts introduced by out-of-distribution data. Within the first report period of the EMB project, K.B. and F.W. took an active part in organizing the Mitosis Domain Generalization (MIDOG) challenge focusing on the detection of mitotic figures across different species and tumor indications. The challenge results were summarized in a manuscript, which is currently under review for publication in *Medical Image Analysis* [1], the corresponding dataset was published in *Scientific Data* [2].

During model training and development, tailored methodological approaches can be followed to make the algorithms less susceptible to data distribution shifts. Within this context, two student projects have focused on the implementation and validation of such methods:

Investigation of Domain Shift Effects in Histopathology Images for Vision Transformer-Based Segmentation (02/23 – 08/23)

Appearance-based Debiasing of Deep Learning Models in Medical Imaging (05/23 -11/23)

Additionally, experiments for an in-depth analysis of the domain susceptibility of specific deep learning architectures have been conducted. The results of these experiments are currently collected in a manuscript for submission at *Transactions of Medical Imaging*.

One of the primary goals of the **X02** project is the development of tools and models that facilitate the integration of machine learning/deep learning methods into different research projects within the EBM consortium. This entails the extension of the online annotation server EXACT. During the first report period, technical requirements have been collected and are currently structured as working packages and assigned with priorities. These include:

- Extend EXACT to read all required image formats within EBM
- Extend annotation formats to accommodate for new gold standard measurements within EBM
- Implement plugins to support the integration of data formats from other labelling tools
- Integrate the visualization of model inference results (and potentially enable inference directly within EXACT)

Overall, the **X02** has contributed to curating datasets that focus on various sources of domain shift and investigating methods to accommodate for out-of-distribution data during model development. Furthermore, progress has been made in laying the groundwork for integrating ML/DL techniques into the diverse array of projects within the EBM consortium. The upcoming report period will focus on the implementation of the defined working packages for EXACT and further investigate methods for robust DL model development.

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X03 Engineering brain tissue like matrices

Markus Lorke, Sonja Kuth, Aldo R. Boccaccini

Main objectives and achievements

Improving hydrogel stability while maintaining stiffness at a low (brain-mimicking) value

One of the main challenges in our newly developed OHA/GEL hydrogel system is their relatively low stability upon incubation at cell culture conditions. By qualitative assessment we determined an inhomogeneous crosslinking (CL) distribution, depending on the sample size, contributing to the poor stability. In an attempt for improvement, we adapted the crosslinking procedure (from postCL to *in-situ*CL). In that way, we were able to significantly improve the hydrogel stability (see Figure 26). At the same time, the effective stiffness was kept at the previously already low (and brain-mimicking) value (<1 kPa). With the improved crosslinking procedure, we are able to maintain the eff. stiffness at a constant level over a minimum time span of 28 days. The results of this study were recently submitted for publication [1].

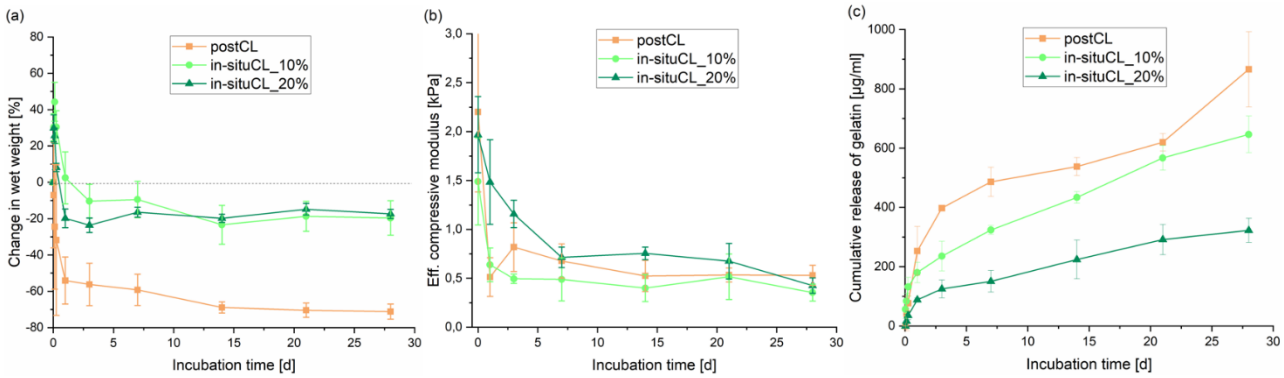

Figure 26: Degradation behavior of OHA/GEL samples crosslinked by postCL vs. in-situCL over 28 days of incubation in cell culture medium. (a) change of wet weight, (b) eff. compressive modulus, (c) cumulative release of gelatin [1].

Evaluation of long-term storing effects in terms of weight-loss and stiffness.

In the context of improving stability, we also assessed the long-term storing (4°C in PBS) ability in terms of weight loss and change of mechanical properties. We found that the samples undergo a weight loss of ~ 20% within the first 2 weeks and then maintain their weight for up to 10 weeks in total. In terms of stiffness, we found that the hydrogels can maintain the desired stiffness (0.1 – 1.5 kPa) for up to 10 weeks if stored accordingly. The found results were independent of the crosslinking concentration and technique. This shows us that the samples can be safely stored at 4°C for up to 10 weeks without major changes in the properties. This evaluation will have to be repeated in the case of future changes in hydrogel composition.

Establishing different techniques of cell culture

Evaluating the behavior of any cell in contact with our developed hydrogel matrix requires different testing approaches, depending on the experiment setups and goals of the study. We established 4 different testing setups (see Figure 27) to meet the requirements for our own experiments and those of our EBM collaborators. In the most straightforward approach, a film or “pillow” of the hydrogel matrix is prepared in tissue culture plates (TCPs). After crosslinking, the cells are added on top and cultivated in 2D. In a similar, but more advanced approach, a layer of hydrogel precursor (polymer solution prior to crosslinking) is added on top of these cells, to create a “sandwich”. This allows the attachment of cells if necessary, before fully surrounding them by the hydrogel matrix. In the third approach the cells are directly introduced to the hydrogel solution prior to crosslinking and homogenized by stirring. This allows control over the cell concentration in the hydrogel and generates an ECM mimicking 3D environment from the beginning of the study. In the 4th and last approach, the ability/tendency of the cells to migrate into/infiltrate the hydrogel matrix is assessed. By a 3D printing technique, single strands are printed into a coated TCP and crosslinked, leaving sections of the surface free of hydrogel. Similar to the first approach, cells are then seeded on top and cultivated. At a certain point during cell spreading/proliferation the cells growing on the coated TCP surface will interact with the hydrogel strand and either avoid or infiltrate it. This allows us to observe the ability

of cells to actively infiltrate/interact with the hydrogel matrix. All of the before mentioned approaches have been tested in our lab and/or with our EBM collaborators, as also reported in detail below.

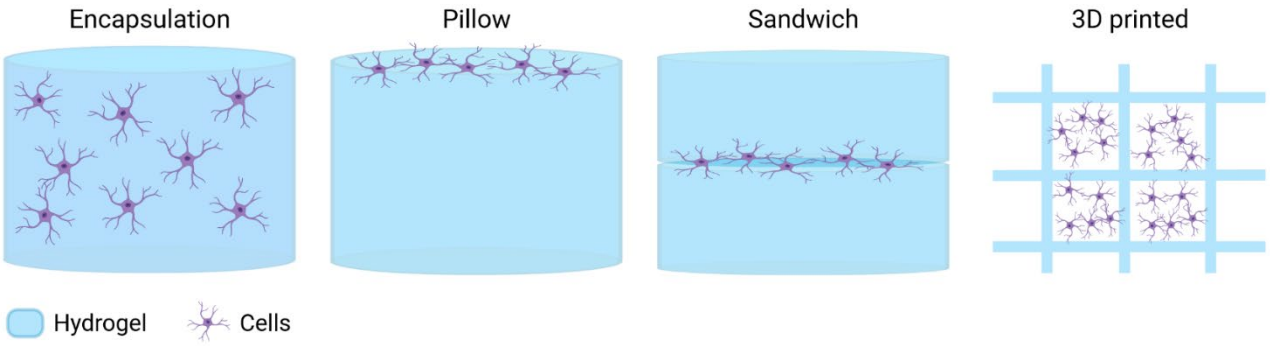

Figure 27: Schematic display of approaches for in vitro cell culture with the developed hydrogel matrix, as established in this project.

Protocol to rapidly dissolve the hydrogel matrix

Upon collaborating with EBM researchers, we became aware of the necessity for some sample evaluations to dissolve the hydrogel (with encapsulated cells) as quickly as possible, without damaging the cells in the process. This becomes necessary for example for PCR analysis of the encapsulated cells, which need to be freed from the hydrogel matrix for measurement. We assessed different enzymatic approaches and found that incubating the samples in a collagenase solution can fully dissolve the hydrogel matrix within 2 - 6 hours, depending on the hydrogel concentration.

Preliminary testing of established hydrogels in collaboration with different EBM researchers

A03: After assessing the possibilities and requirements of materials provided to **A03**, collaborators of **A03** were trained in the synthesis, sample fabrication, and handling of the hydrogels to allow an extensive collaborative material development in the future.

A04: We provided our established OHA/GEL matrix to **A04** and, in collaboration, succeeded in encapsulating the brain organoids developed in **A04** in a hydrogel bead. Further experiments could not be conducted due to unexpected contaminations of the samples.

B02: We have started the development of a suitable 3D hydrogel matrix for the cultivation of amphibian cells. Starting from the established hydrogel system, the matrix will be tailored to the needs of Xenopus retinal ganglion cells by creating a matrix with defined storage and loss modulus. This will be part of a joint supervision (Institute of Biomaterials, Institute of Medical Physics and Micro Tissue Engineering) of a Master thesis which started in mid-November.

C02: In collaboration with **C02** we tested the behavior of primary rat neurons in contact with the established OHA/GEL hydrogel matrix using different aforementioned approaches. We showed that primary neurons can develop in the OHA/GEL matrix provided the network concentration is kept at a low level. Higher concentrations were shown to hinder or deter neuronal development. In lower hydrogel concentrations, neurons can both, develop in a 3D matrix, and actively infiltrate the matrix. Parts of the results of this study were published in 2023 [2].

C03: We provided different concentrations of the established OHA/GEL matrix in two different thicknesses to test the behavior of mouse neuronal cells, seeded on top of the hydrogel “pillows” in dependency of the hydrogel stiffness and thickness of the bottom layer.

C04: In collaboration with **C04** we encapsulated melanocytes and melanoma cells in our OHA/GEL matrix. The samples were cultivated and assessed by **C04**.

X01: In collaboration with **X01** we have established a technique for MRE assessment of hydrogel matrices. Requirements that were achieved included bubble-free filling of the test tubes with hydrogel and storability of the filled test tubes without detaching of the hydrogel from the test tube walls. The values measured for OHA/GEL hydrogels were similar to those of human brain tissue.

Conclusion and outlook

In summary, the development of neuronal ECM-mimicking hydrogels for the use in cell culture was investigated. Several improvements in terms of long-term stability and cell culture approaches were developed for many different cell types and their specific requirements, as well as their analysis processes. The developed hydrogel matrix was tested in many collaborations with EBM researchers and showed sufficient results for the first implementation of this type of matrix. In the upcoming development phase, the aim is to establish a more precisely defined matrix, to collect more mechanical data, not only on a macroscopic but also on a microscopic level in order to further develop the hydrogels into an ECM-mimicking matrix. In addition, an approach for direct printing of cells will be investigated. In collaboration with B02 and A03, the use of the matrix for the cultivation of amphibian cells will be extended in addition to the existing mammalian cell cultures.

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Y Initialization phase for performing MRE in Erlangen

Arnd Dörfler; Frederik Laun; Ingolf Sack; Jing Guo

The aim of project Y is to establish magnetic resonance elastography (MRE) in Erlangen. While we have extensive multimodal magnetic resonance imaging (MRI) expertise in Erlangen, we had little expertise in MRE yet. For this reason, we teamed up with the very experienced MRE group of Ingolf Sack and Jing Guo from the Charité.

The first year has been devoted to the following activities:

Personal: For the works in Berlin, we were lucky to have a perfect match right from the start. We hired Steffen Görner who has been working as a technician in the Charité's MRE group already before and is very experienced in MRE. The search for the planned second technician, who was supposed to fill the second position in Erlangen, turned out to be extremely challenging due to the lack of qualified applicants. We therefore switched plans around mid 2023 and searched for a postdoc with MRE proficiency as we hoped to find a suitable researcher more easily and as a researcher might additionally enhance the project. The MRE field is rather small in comparison to the general MRI field and we experienced that the market is also very tight; and that this search for a postdoc was challenging. Therefore, it was a great opportunity to meet Elija von Houten from the University Sherbrooke, Canada, a pioneer in MRE, who gave a keynote lecture along with Silvia Budday on the Weierstrass workshop on Biophysics-based modeling in medical imaging in Berlin in August 2023. He referred us to a colleague, Guillaume Flé, a postdoc with a very good track record in MRE from the University of Montreal. Guillaume's contract at FAU starts on the 1st of January 2024. He is going to move to Erlangen in December.

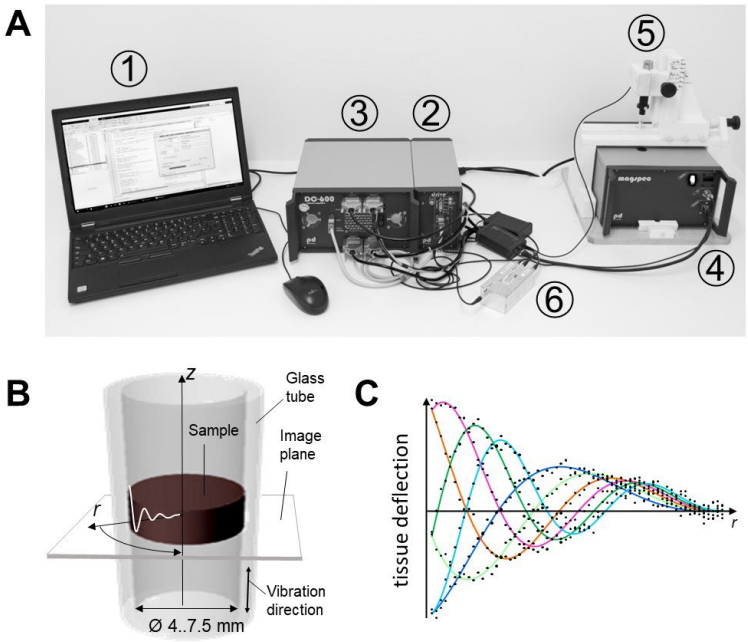

Figure 28: Experimental setup and data processing in tabletop MRE. (A) Compact MRI-MRE scanner. (1) Control computer with MRI operating system based on Matlab (Natick, MN, USA), (2) electronic cabinet, (3) gradient amplifier, (4) 0.5-Tesla magnet, (5) piezo-based actuator mounted to the sample tube, and (6) preamplifier. (B) Sample geometry in the glass tube sample holder, image plane and vibration direction. (C) Example multifrequency displacement data mapped onto one radial (r) axis and fitted by Bessel functions to obtain shear wave speed (SWS in m/s) and wave penetration rate (PR in m/s). Blue: 1kHz, light green: 1.2 kHz, orange: 1.4 kHz, magenta: 1.6 kHz, green: 1.8 kHz, light blue: 2.0 kHz.

Equipment: In Erlangen, we have all the MRI scanners necessary for the intended works, but did not have any dedicated MRE hardware at the start of the project. First, we bought the table top system, which is now installed and running in the Technical Faculty in Erlangen (c.f. Figure 28). Then we bought a first Vibro42 elastography setup from THEA-Devices GmbH. We want to run MRE experiments at two MRI scanners. First, at the research MRI scanner located in the *Zentrum für Medizinische Physik und Technik (ZMPT)*. Second, at the clinical 3T MRI scanner located in the Institute of Neuroradiology in the *Kopfklinikum* providing direct access to patients. The physical distance between these two locations is approximately 2 km by car and also well commutable by bike or by walking. Initially, we had planned to move the MRE devices back and forth between the two locations. This is possible with a small bus and we went for this option to minimize costs. Nonetheless, this approach is also quite cumbersome. In the first EBM retreat, we thus discussed this issue in the plenum. The Executive Board agreed to allocate the necessary budgets to allow the purchase of a second Vibro42 setup. We took this lucky opportunity and consequently purchased this second setup, which will let us work much more efficiently in the future. For the MRE experiments, it is necessary to use compressed air. At the clinical MRI scanner, compressed air is provided through an outlet in the scanner room. Since

pressured air supply is not available at the research scanner though, we purchased a fitting and adapted air compressor.

Works: Steffen Görner has worked on getting the tabletop system running. More prominently were his works on advancing this system, though. First, he has implemented a graphical user interface that facilitates working with the system (c.f. Figure 29). Previously, only shell-based interactions were possible. Second, we implemented several additional MRE models to fit the data, which are necessary for the intended research of the CRC.

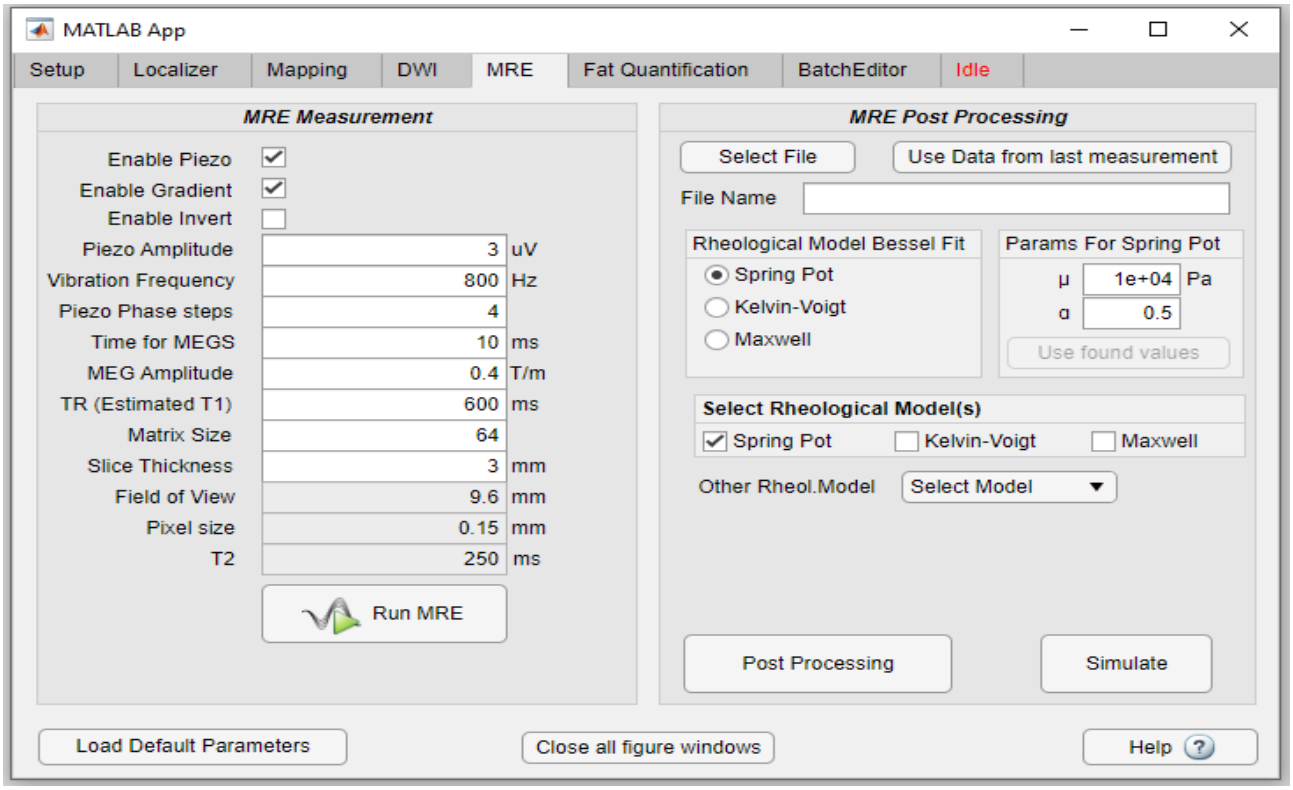

Figure 29: New graphical user interface for the table top system.

1.3 PUBLICATIONS

In the publication lists, **EBM members** are highlighted in bold. Publication lists are in alphabetical order.

1.3.1 PEER-REVIEWED ARTICLES, CONFERENCE CONTRIBUTIONS, BOOK PUBLICATIONS

[1] Bertalan, G., Becker, J., Tzschätzsch, H., Morr, A., Herthum, H., Shahryari, M., Greenhalgh, R. D., Guo, J., Schröder, L., Alzheimer, C., **Budday, S.**, **Franze, K.**, Braun, J., & **Sack, I.** (2023). Mechanical behavior of the hippocampus and corpus callosum: An attempt to reconcile ex vivo with in vivo and micro with macro properties. *J Mech Behav Biomed Mater*, *138*, 105613. https://doi.org/10.1016/j.jmbbm.2022.105613

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[27] Lehner, A., **Hoffmann, L.**, **Rampp, S.**, Coras, R., **Paulsen, F.**, **Frischknecht, R.**, Hamer, H., Walther, K., Brandner, S., Hofer, W., Pieper, T., Reisch, L. M., Bien, C. G., & **Blümcke, I.** Age-dependent increase of perineuronal nets in the human hippocampus and precocious aging in epilepsy. Epilepsia Open (submitted)

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2 INTEGRATED RESEARCH TRAINING GROUP (IRTG)

As EBM is exceptionally interdisciplinary, integrating disciplines such as experimental analyses, clinical studies, and bioengineering – all informed by advanced modeling and simulation – the integrated Research Training Group (**iRTG**) is particularly important for the CRC to bring the different disciplines together on a common basis.

The **iRTG** of EBM addresses this demanding interdisciplinary challenge by providing a structured mandatory qualification program and ensuring quality management and control for doctoral and postdoctoral researchers. This approach also nurtures their scientific independence and promotes their career development.

The comprehensive program encompasses a range of activities aimed at enhancing theoretical knowledge, methodological skills, soft skills, and fostering a collaborative research environment.

2.1 QUALIFICATION PROGRAM

The qualification program comprises

- EBM (Post-)Doctoral Researchers' Seminars
- EBM Harmonization Workshops (theory and methods)
- EBM Soft Skills Courses
- EBM Annual Retreats and EBM Update Meetings

as basic activities. These components are complemented by active participation in international conferences, the publication of at least one paper, participation in and organization of Lab Shadowing, and writing short contributions for the EBM homepage after organizing EBM-funded activities or travel. In addition, (post-)doctoral researchers have the opportunity to complete research stays abroad as part of the program.

Beyond these essential elements, additional activities are available for all EBM members, including

- EBM Virtual Breakfast Clubs and Lunches
- EBM Virtual Brain Talk
- EBM Seminar Talks

2.1.1 EBM (POST-)DOCTORAL RESEARCHERS' SEMINARS

Every two months, organized by two (post-)doctoral researchers in rotation, these two-hour seminars offer ample opportunities and valuable experiences for (post-)doctoral researchers to present their latest work-in-progress and results. The sessions facilitate discussions on current challenges and future research perspectives within a relaxed and interdisciplinary atmosphere. The seminars aim to foster networks among doctoral and postdoctoral researchers, catalyzing new research directions, approaches, and collaborations.

Originally, the concept was to hold the (post-)doctoral researchers' seminars monthly, with each month featuring a presentation by one (post-)doctoral researcher and the presence of the Principal Investigators. However, early in the EBM program, (post-)doctoral researchers expressed a desire for the seminar to be primarily internal among the doctoral cohort. In a closed circle, the doctoral researchers feel more at ease to ask questions, discuss uncertainties, and share their own experiences, fostering a more open and supportive environment.

Following feedback from the doctoral candidates during the EBM Retreat in September 2023, it was additionally decided to shift the seminar to a bi-monthly schedule due to time constraints. As compensation, it is now organized by two doctoral researchers who also deliver the presentations. This allows for a more efficient use of time for research work and other commitments.

To successfully complete the doctorate within the EBM iRTG 1540, it is mandatory to attend at least 4 of the 6 (Post-)Doctoral Researchers' Seminars per year.

Table 3: (Post-)Doctoral Researchers' Seminars

	Date	Organized by (name / project)	Title
01	19.04.23	Jan Hinrichsen / A01	Identifying region-dependent hyperelastic material parameters for human brain tissue through finite element analyses
02	24.05.23	Sophia Auer / A02	Quantitative characterization of brain malformations
03	26.05.23	Daniel Wehner / B05	Axonal regeneration in the injured spinal cord - a matter of ECM composition?
04	20.07.23	Sonja Kuth / X03	Engineering brain tissue-like matrices
05	23.11.23	Tomeu Perelló / C02	The role of mechanics for neuronal plasticity
06		Sebastián Vásquez / A05	Characterizing brain mechanics during development and neurodevelopmental malformations

Figure 30: Impressions of the (Post-)Doctoral Researchers' Seminars. (Images: S. Kuth, S. Auer, M. Lorke)

2.1.2 EBM HARMONIZATION WORKSHOPS

Trimestral half-day EBM Harmonization Workshops are focused introductions to interdisciplinary topics of key relevance for EBM. They aim to provide a common theory and methods basis for the doctoral researchers. Orchestrated by EBM PIs and postdoctoral researchers from different disciplines, the workshops cover a broad spectrum of theory and methods in a various formats (lectures, exercises, laboratories, tutorials, etc.).

To successfully complete the doctorate within the EBM iRTG 1540, it is mandatory to attend at least 8 of the 16 Harmonization Workshops (theory and methods) within 4 years.

Table 4: EBM Harmonization Workshops

	Date	Organized by	Subject
01	18.04.23	Friedrich Paulsen	Neuroanatomy
02	17.07.23	Stefanie Kürten	Anatomy of brain stem and spinal cord
03	19.07.23	Lucas Hoffmann	Neuropathology
04	09.11.23	Kristian Franze	Atomic force microscopy and frog brains

2.1.2.1 1st EBM Harmonization Workshop: Neuroanatomy

The brain, a subject of enduring fascination due to its mysterious nature and profound functions, has been a constant focus of research. As an engineer exploring the subconscious, the initial understanding of its anatomy was limited. The first harmonization workshop on April 18th, led by Friedrich Paulsen, significantly expanded knowledge.

The workshop commenced with a neuroanatomy seminar, elucidating the spatial arrangement of neurons in the brain and their intricate network overlay with blood vessels. The presentation illuminated various brain regions and functions, revealing the organ's complexity. The session transitioned to a hands-on brain dissection, a unique experience providing an opportunity to feel differences in materials among different brain regions.

The workshop concluded with a visit to the dissection lab, offering a transformative experience. Collaborating with medical experts, participants gained a concrete understanding of human (especially

Figure 31: EBM'S 1st Harmonization Workshop: Neuroanatomy. (Images: A. Dakkouri-Baldauf, S. Kuth)

brain) anatomy. This experience underscored the significance of the project, emphasizing the collective effort of doctors, scientists, and engineers dedicated to unraveling the processes that define human existence and contribute to the betterment of humanity. It highlighted the unique opportunity to collaboratively decode neurological processes.

(Based on a text by Yashasvi Verma, X01)

2.1.2.2 2nd EBM Harmonization Workshop: Anatomy of brain stem and spinal cord

An interdisciplinary training workshop has brought together EBM researchers from different disciplines at the Institute of Anatomy to explore the mysteries of the human brain, with a special focus on the intricate anatomy of the spinal cord. Led by Stefanie Kürten from the Neuroanatomy Department of the University of Bonn and esteemed experts Rittika Chunder and Maik Hintze, this workshop aimed to foster collaboration and enrich understanding of the complexity of the brain and spinal cord. Let's embark on a journey of discovery and unravel the mysteries of the spinal cord!

The workshop commenced with an engaging talk by Rittika Chunder. She provided a comprehensive introduction to the anatomy of the spinal cord, laying the foundation for participants to understand its essential components and functions.

Figure 32: EBM'S 2nd Harmonization Workshop: Anatomy of brain stem and spinal cord. (Images: O. Neumann)

Maik Hintze led the subsequent sessions. He conducted investigations on fixed spinal cord probes and human spinal cord samples, skillfully explaining the complicated anatomy of the spinal cord to the participants. Through hands-on experience, the researchers gained valuable insights into the structure and function of this important neural pathway. Hintze's expertise also extended to the anatomy of the brainstem, where he explained the functional background of the spinal nerves, the brainstem, and their intricate connections to the spinal cord. This lecture provided a holistic impression of how these components work together to enable vital bodily functions. In another exciting session led by Maik Hintze, participants were guided through examinations of brainstem and spinal nerves on fixed human specimens. This hands-on exploration allowed the researchers to deepen their understanding of the concepts discussed and to observe the anatomical structures.

Throughout the workshop, Stefanie Kürten provided valuable insights that enriched all discussions and investigations. The workshop fostered collaboration between researchers from different disciplines and emphasized the joint efforts needed to improve our understanding of the brain and its complex mechanisms.

(Oskar Neumann, B01)

2.1.2.3 3rd EBM Harmonization Workshop: Neuropathology

As part of the graduate program, the EBM researchers had the opportunity to gain hands on experience on the autopsy of the human brain. The workshop was hosted by the department of neuropathology of the university hospitals Erlangen and consisted of two parts, the first one being an online introduction on focal epilepsy caused by cortical malformations given by Ingmar Blümcke. The second part of the workshop was led by Lucas Hoffmann and showed the steps necessary to dissect a brain correctly and how to look for cues in the brain tissue showing possible brain diseases and damages, which helped the attendees to better understand the anatomy of the human brain. Searching the brain tissue for possible causes of death was a humbling experience, but nevertheless a fascinating one. All participants had the chance of having their questions answered and left the workshop with new ideas and motivation to continue their research.

(Clara Froidevaux, A03)

Figure 33: EBM'S 3rd Harmonization Workshop: Neuropathology. (Image: A. Schambony)

2.1.2.4 4th EBM Harmonization Workshop: Atomic force microscopy and frog brains

On November 9th, 2023, the Collaborative Research Centre (CRC) 1540 „Exploring Brain Mechanics (EBM)“, hosted an interactive workshop centered on Atomic Force Microscopy (AFM) and its

Figure 34: EBM'S 4th Harmonization Workshop: Atomic force microscopy and frog brains. (Images: A. Dakkouri-Baldauf, M. Hintze)

application to the study of frog brain. This event was organized by the group of Kristian Franze, situated at the Centre for Medical Physics and Technology (ZMPT).

The workshop, designed for postdoctoral researchers and doctoral candidates within the EBM consortium, encompassed two sessions. The first session featured a presentation by Kristian Franze, introducing the theoretical foundations of AFM and its utility in measuring mechanical properties, particularly in the context of biological samples. The talk highlighted noteworthy AFM findings pertaining to the influence of tissue mechanics dynamics on developmental processes.

The subsequent session, organized by Sebastián Ignacio Vásquez Sepúlveda, M.Sc., comprised a hands-on workshop where participants identified Xenopus embryo samples at different developmental stages. Attendees also assessed the brain anatomy, supplemented by an observation of the neuronal developmental trajectory within the Xenopus brain through fluorescence microscopy.

The objective of the workshop was to underscore the significance of AFM as a tool for mechanical measurements and the critical role played by tissue mechanics in various biological processes.

(Jana Bachir Salvador, C03)

2.1.3 EBM SOFT SKILLS COURSES

The half to full-day EBM Soft Skills courses primarily draw on the portfolio offered by the Graduate Center (GC) of FAU. In addition, the F³G network (Research Consortia for Promoting Equality at Friedrich-Alexander-Universität Erlangen-Nürnberg) provides various gender equality measures, including lectures and seminars on topics such as women's advancement and gender sensitivity, which members of affiliated research alliances can attend. EBM doctoral researchers have actively participated in both these offerings and others.

To successfully complete the doctorate within the EBM iRTG 1540, it is mandatory to attend at least one course on 'Good Scientific Practice,' one course on 'Scientific Writing,' and two additional Soft Skills Courses within four years.

Hence, in the first year of EBM, the course 'Good Scientific Practice' was exclusively organized and offered for EBM (post)doctoral researchers by the EBM coordination.

Table 5: Soft Skills Courses with EBM doctoral researcher participation

	Date	Content	Instructor	Offered by
01	03.04.23	Beating Impostor Syndrome	Francesca Carlin	Office of Equality and Diversity
02	17.04., 20.04., 24.04., and 27.04.23	Career Planning	Dr. Iris Köhler	Office of Equality and Diversity
03	03.05.23	Forschungsdatenmanagement – eine Einführung	Dr. Jürgen Rohrwild	GC
06	12.06.23	Effektives Stressmanagement für Promovierende	Dr. Christine Thiel	GC
07	13.06.23	Increase your Employability with a PhD – a Workshop on Becoming your own Marketing Manager	Wolfgang Leybold	GC
08	28.06. – 29.06.23	Working Effectively and Efficiently - Time and Project Management for Researchers	Dr. Daniel Friedrich	F³G
09	06.07.23	Effektives Stressmanagement für Promovierende	Dr. Christine Thiel	GC
10	12.07. and 19.07.23	How to Give a Good Talk	Sarah T. P. Andiel	GC
11	19.07.23	Zeitmanagement für die Promotion – Erfahrungen und Handlungsempfehlungen	Dr. habil. Tim Alexander Herberger	GC
12	28.09.23	My Visibility as a Scientific Expert on LinkedIn & ResearchGate	Katja Wolter	GC
13	05.10. – 06.10.23	The Essentials of Scientific Writing	Dr. Deborah Bennett	F³G
14	12.10.23	Good Scientific Practice	Dr. Christian Schmitt-Engel	EBM
15	26.10.2023	Grundlagen der Statistik	Dr. Felix Bauer	GC

2.1.3.1 EBM Soft Skills Course “Good Scientific Practice“

On the 12th of October, EBM Researchers were brought to the knowledge of the “Good Scientific Practice“ by Dr. Christian Schmitt-Engel (FAU) who held a lecture on the topic at the Interdisciplinary Center for Nanostructured Films (IZNF). After being introduced to the rules and regulations of Good Research Practice (from DFG, FAU, and Singapore-statement) students were split into groups to discuss some of the relevant aspects of the guidelines, followed by a presentation summarizing the thoughts of the group work. The day raised lots of questions and discussions among the DRs, which were promptly moderated by Christian Schmitt-Engel: from applying the ethical standards and methods of the scientific community to documenting data and results and acknowledging the contributions of others. The course represented a moment of note to ponder on the principles and values that should be integral parts of a good research scientist and on the importance of the regulations stated for ensuring quality, accountability, and integrity of scientific work.

(Erica Cecchini, A02)

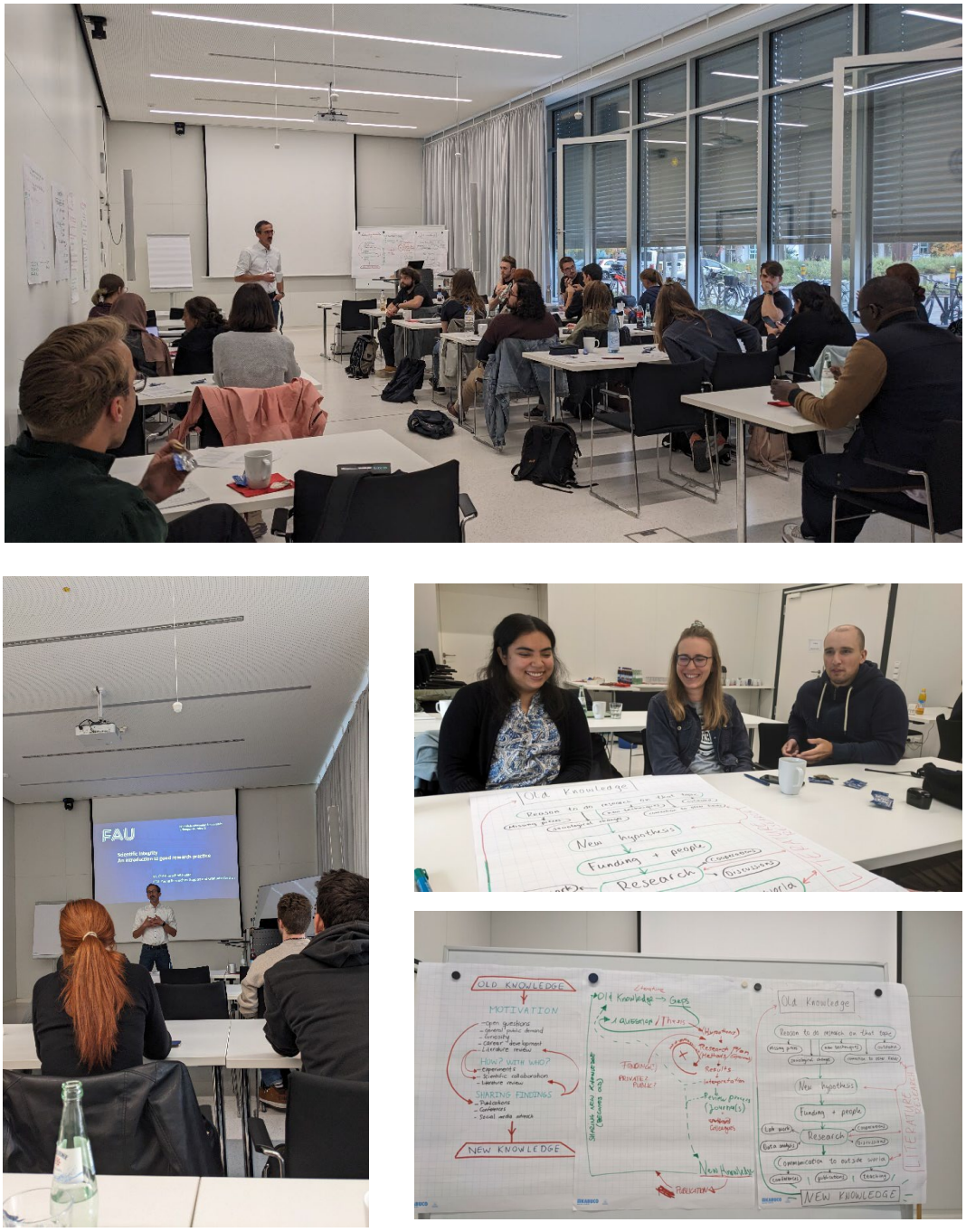


Figure 35: EBM Soft Skills Course "Good Scientific Practice". (Images: S. Kuth)

2.1.4 EBM RETREAT

Annual two-day EBM Retreats with mandatory attendance for **iRTG** members provide a forum for research progress presentations of the doctoral and postdoctoral researchers. The main focus is on the internal evaluation of scientific progress in the field of EBM and the promotion of the expansion of existing collaborations as well as the establishment of new collaborations between EBM projects.

These events are held at remote locations away from the FAU campus and include social activities to encourage informal interaction between participants.

To successfully complete the doctorate within the EBM iRTG 1540, it is mandatory to attend all annual Retreats.

Table 6: EBM Retreat

	Date	Type	Location
01	21.09. – 22.09.23	1. EBM Retreat	Hotel Arvena, Bad Windsheim

Program see Appendix 1

Figure 36: EBM members at the 1st EBM Retreat in Bad Windsheim. (Image: A. Dakkouri-Baldauf)

The 1st EBM Retreat took place from September 21st to 22nd, 2023 at the Hotel Arvena Reichsstadt in the small historic town of Bad Windsheim and provided a platform for scientific presentations primarily from doctoral researchers and postdoctoral researchers of the CRC 1540 „Exploring Brain Mechanics.“ The main objective of this conference was to present the current status of the 19 ongoing research projects and stimulate lively and constructive discussions to strengthen and further develop collaboration between various research projects.

The retreat started with a warm welcome by EBM's spokespersons Paul Steinmann and Silvia Budday. In a brief presentation, they provided an overview of the current status of the research consortium and an outlook on the program of the next two days. The first day of the retreat focused on presentations and discussions on topics such as the role of mechanics in cell-matrix interactions (projects of the focal research areas C), standardization and integration of in-vivo and ex-vivo test data across different scales (**X01**), transferability of data between different species and experimental methods through advanced machine learning techniques (**X02**), and the development of substitute materials for brain tissue (**X03**). Additionally, the current progress in establishing an MRE at FAU (project **Y**) was discussed.

During the extended coffee breaks, participants had the opportunity to exchange ideas and insights, leading to a fruitful exchange of knowledge. After the scientific presentations, there were simultaneous activities, including a brainstorming session for (post)doctoral researchers to develop ideas for the Long Night of Sciences 2023 and the quarterly meeting of the EBM Executive Board. The day concluded with a stroll through the picturesque “Fränkische Freilandmuseum”, allowing researchers to form closer connections in smaller groups.

This was followed by a delightful dinner and casual conversations, fostering the retreat's collegial atmosphere.

The second day began with a general assembly of the EBM, where all members gathered to discuss the latest developments and future directions. This included feedback from EBM leadership to members and vice versa, where EBM leadership received constructive and valuable feedback from doctoral students and project leaders.

Figure 37: Stimulating discussions at various locations. (Images: A. Dakkouri-Baldauf)

The day's program continued with presentations on brain malformations (projects of the focal research areas **A**) and spinal cord regeneration (projects of the focal research areas **B**). These presentations covered a wide range of topics investigated by various researchers. Lively discussions followed each presentation, facilitating the exchange of ideas and perspectives.

After the final scientific presentations, the doctoral researchers presented the results of their brainstorming session for the Long Night of Sciences program.

Figure 38: EBM members in the Franconian Open-Air Museum Bad Windsheim. (Images: A. Dakkouri-Baldauf)

Figure 39: Project presentations by the (post)doctoral researchers. (Images: A. Dakkouri-Baldauf)

The 1st EBM Retreat in Bad Windsheim was diverse, informative, and constructive, and provided ample time for discussion about science and other important aspects of life. The enthusiasm of the participants in actively and openly engaging in constructive discussions underscored the success of the retreat, fostered collaboration, and inspired all attendees.

2.1.5 EBM LAB SHADOWING

Ongoing EBM Lab Shadowing allows EBM doctoral researchers to conduct short-term collaborative stays at the laboratories of other EBM PIs, e.g., to participate in joined experiments, to learn experimental, modelling and computational techniques of common interest, and to prepare overarching, multi-disciplinary EBM publications and presentations.

2.1.5.1 Collaborative experiments between A01 and A02

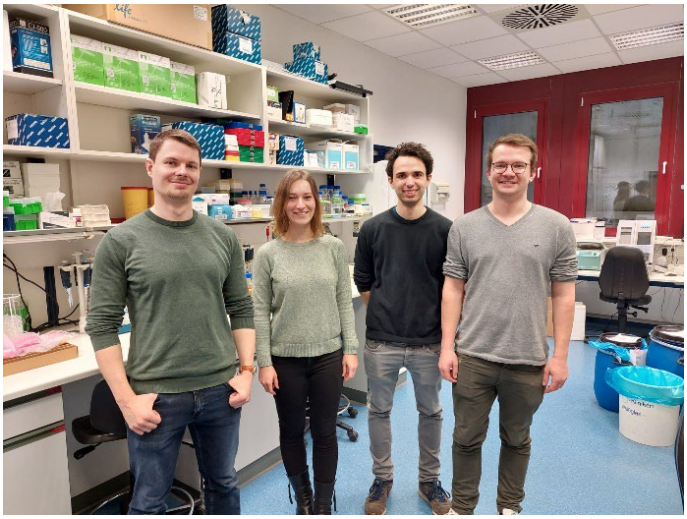


Figure 40; Members of Project A01 gain valuable insights during their visit to the lab of Project A02. (Image: private)

How does a brain tumor actually look in real life?

On February 13, 2023, Nina Reiter and Jan Hinrichsen from project **A01** (PI: Silvia Budday) visited the neuropathology where they were welcomed by Lucas Hoffmann (project **A02**, PI: Ingmar Blümcke). The opportunity to observe the daily process of cutting biopsy samples and ask questions to an experienced clinician was really valuable to connect abstract modeling with real material, such as brain tissue. We look forward to doing this more often in the future!

(Jan Hinrichsen, A01)

2.1.5.2 Collaborative experiments between X03 and C04

On March 21, 2023, project **X03** (Markus Lorke and Sonja Kuth, PI: A.R. Boccaccini) and project **C04** (Shanice Heidenreich, PI: A. Boßerhoff) performed their first collaborative experiments. The aim of this collaborative lab work was to familiarize ourselves with the different set-ups of experimental work. This will strongly help to design experiments with combined techniques in the future. We are looking forward to this collaboration in the scope of the CRC EBM!

(Sonja Kuth, X03)

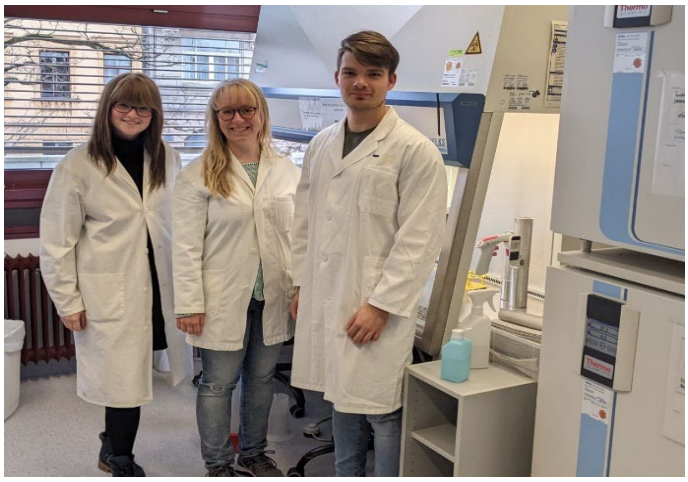


Figure 41: Collaborative lab work between X03 and C04. (Image: private)

2.1.5.3 Lab shadowing of X03 at C02 labs

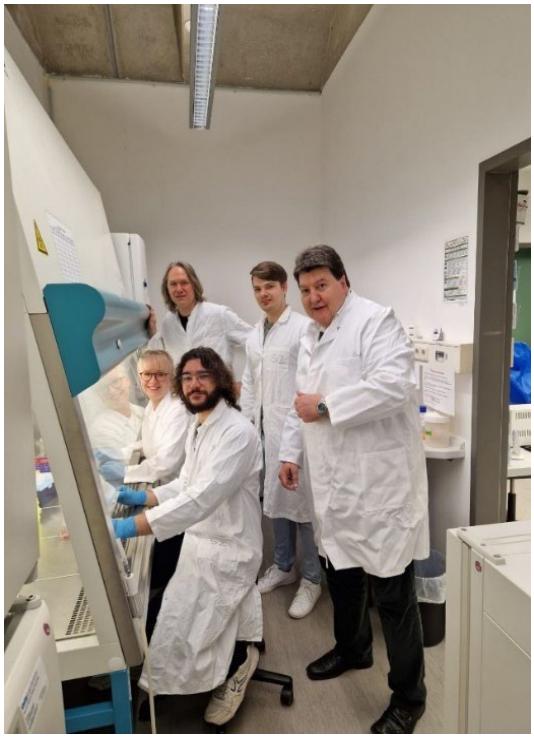


Figure 42: Members of Project X03 gain valuable insights during their visit to the lab of Project C02. (Image: private)

The team of **X03** Boccaccini (DR: Markus Lorke and Sonja Kuth) visited the team of **C02** Frischknecht (DR: Bartomeu Perelló Amorós) on March 31, 2023 at the animal physiology labs for a lab shadowing and discussion of the planned experiments in the scope of the CRC EBM. Planned experiments will investigate the behavior of primary neurons encapsulated in hyaluronic acid-based hydrogels.

(Sonja Kuth, X03)

2.1.5.4 Collaborative experiments between B01 and BRAINIACS

Figure 43: Nina Reiter during experiments with the spinal cord of pigs. (Image: O. Neumann)

On April 4, 2023, project **B01** (Oskar Neumann, PI: S. Budday) and Emmy-Noether research group BRAINIACS (Nina Reiter, PI: S. Budday) conducted some preliminary experiments on pig spinal cords. The main goal was to gain a feel for producing spinal cord samples and to become familiar with the experimental procedures for future experiments on human spinal cords. In fact, it was already very enlightening, as it proved to be quite challenging to cut the spinal cord into small pieces without deformation.

(Oskar Neumann, B01)

2.1.6 EBM SCHOLARS' VISITS

In 2023, EBM hosted short-term Scholars' Visits from two international EBM scholars, including an outstanding young scientist and an international student. The former contributed her current scientific expertise through a presentation in the framework of the EBM Virtual Breakfast Club and research collaborations with EBM projects. The latter experienced the lively and dynamic research spirit within the EBM initiative, particularly in collaboration with Jan Hinrichsen (**A01**).

EBM Scholar Visit: Carl Ferlay

We had the pleasure of hosting Carl Ferlay from the École Polytechnique in Paris, France, for his internship at the Institute of Continuum Mechanics with Silvia Budday. He stayed with us from 25.03.2023 to 15.07.2023 and was supervised by Jan Hinrichsen, who is part of the EBM project **A01**. Carl worked on implementing machine learning-based surrogate models to speed up inverse parameter identification for mechanical experiments on human brain tissue. He discovered that a recursive neural network is well suited for approximating viscoelastic finite element simulations. Additionally, he investigated how active learning techniques can be incorporated into the training of the surrogate models to select the most rewarding training points in terms of gained model accuracy, thus minimizing the required number of simulation runs. We enjoyed collaborating with Carl and are currently working on publishing the results of our joint efforts.

EBM Scholar Visit: Dr. Ester Comellas

Dr. Ester Comellas from Universitat Politècnica de Catalunya (UPC), Barcelona, Spain stayed at FAU from July 12 to August 9, 2023. As one of the principal developers of the nonlinear poro-viscoelastic finite element code in the open source library deal.II, her expertise and continuous support provides great value to EBM projects (e.g. **X01** and **B01**). During her research stay, we enjoyed thorough and lively discussions about the underlying model theory, worked on improvements regarding the visualization of our numerical results, resolved several computational issues and discussed concrete ideas for future publications. In addition, she contributed an invited lecture during the EBM Virtual Breakfast Club: "Nonlinear poro-viscoelasticity: modelling brain mechanics and joint formation".

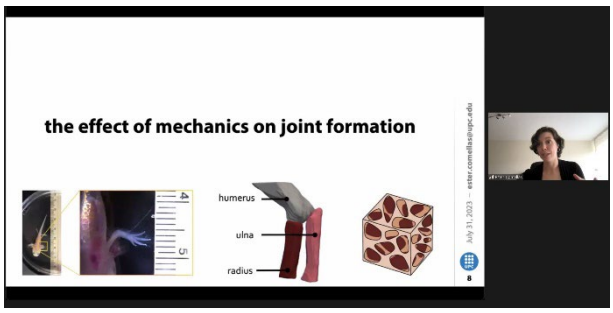


Figure 44: Ester Comellas during her presentation at the EBM Virtual Breakfast Club.

2.1.7 EBM RESEARCH SECONDMENTS AND SHORT-TERM RESEARCH STAYS

EBM Research Secondments, lasting several weeks and involving international academic hosts, including the EBM Mercator Fellows, enable the doctoral and postdoctoral researchers to acquire international experience, perspectives, and exposure. The research secondments support establishing networks for **iRTG** members and thus pave the way for future postdoctoral phases, both early and advanced.

Soheil Firooz

From / to	Institute visited	Local supervisor	Research activities performed and skills acquired during stay
01.04.23 / 31.05.23	Bilkent University	Ali Javili	Developing a computational framework for continuum-kinematics-inspired peridynamics
01.11.23 / 30.11.23	University of CapeTown	Daya Reddy	Finite element analysis convection dominated problems

On April 1st, Soheil Firooz traveled to **Ankara, Turkey** for a 2-month research stay at **Bilkent University**. The objective of this research stay was to collaborate with Prof. Ali Javili in order to develop a computational framework for the implementation of continuum-kinematics-inspired peridynamics aiming to investigate the non-local mechanical behavior of the brain tissue. His research stay at Bilkent University in Ankara was a remarkable experience, particularly as it allowed him to delve into the intricate realm of peridynamics. Collaborating closely with Professor Javili and his research team

Figure 45: Soheil Firooz (right) enjoying delicious Turkish cuisine with a friend. (Image: S. Firooz)

was both inspiring and intellectually stimulating. Bilkent University provided an exceptional academic environment, where state-of-the-art facilities and resources were readily available to support their research endeavors. Working alongside Professor Javili, he gained valuable insights into peridynamics, its diverse applications, and its potential impact on various fields such bio-mechanics. This collaboration not only deepened his knowledge but also opened up new research horizons, broadening his understanding of this innovative branch of mechanics. Apart from the academic pursuits, his return to Ankara also presented a nostalgic opportunity to reconnect with old friends from his time studying for his master's degree in the city. It was heartwarming to revisit familiar places and reminisce about their shared experiences. Ankara itself, as Turkey's capital city, offered a plethora of attractions and cultural treasures to explore. The city had much to offer from the historical significance of sites like the Anıtkabir Mausoleum to the vibrant local markets and Turkish cuisine. The delicious local food, including mouthwatering kebabs, baklava, and Turkish delight, was an irresistible culinary adventure he savored throughout his stay.

(Soheil Firooz, C01)

Figure 46: Daya Reddy (left) and Soheil Firooz (right). (Image: private)

In November 2023 Soheil Firooz did a research stay at the **University of Cape Town**, focused on finite element analysis of convection-diffusion problems. This research stay proved to be an intellectually invigorating experience. Collaborating closely with Professor Daya Reddy, a distinguished figure in this domain, expanded his understanding of this intricate field. Professor Reddy's guidance and the academic environment at UCT facilitated a deep exploration of complex problems, offering insights that have undoubtedly broadened the scope of his research pursuits. The exchange of ideas, coupled with access to cutting-edge resources, fostered a rich learning experience and laid the groundwork for innovative approaches to tackling convection-diffusion problems.

Amidst the research endeavors, exploring the scenic wonders of Cape Town was a highlight of his stay. The breathtaking beauty of Camps Bay, with its pristine beaches and vibrant atmosphere, provided a perfect retreat. Additionally, visiting the amazing Table Mountain and marveling at the panoramic views of the cityscape and surrounding landscapes was an awe-inspiring experience.

Cape Town's diverse attractions, from the historical significance of Robben Island to the cultural tapestry woven through its neighborhoods, offered a captivating glimpse into the city's heritage.

Embracing the local culinary delights, from savory Cape Malay dishes to the freshest seafood, added a delightful layer to his stay, enriching my cultural immersion and making each dining experience a culinary adventure.

This fusion of academic pursuit with the sensory pleasures of Cape Town's offerings created an unforgettable and holistic research journey.

(Soheil Firooz, C01)

Figure 47: Panoramic view of the city from Table Mountain. (Image: S. Firooz)

Jan Hinrichsen

From / to	Institute visited	Local supervisor	Research activities and skills acquired during stay
13.11.23 / 08.12.23	Living Matter Lab, Stanford, CA, USA	Ellen Kuhl	*Research topics*: • Using Bayesian neural networks to obtain uncertainty aware predictions of mechanical behavior of human brain tissue • Neural network based automatic viscoelastic model discovery for mechanical human brain data. *Acquired skills:* • model discovery using neural networks (iCANN) • Integrating bayesian methods to obtain uncertainty quantification

Nina Reiter

From / to	Institute visited	Local supervisor	Research activities and skills acquired during stay
13.11.23 / 08.12.23	Living Matter Lab, Stanford, CA, USA	Ellen Kuhl	*Research topics*: • Uncertainty quantification for mechanical characterization of human brain tissue • Automated viscoelastic constitutive model discovery for human brain tissue *Acquired skills:* • Bayesian neural networks • Python • CANNs

At the end of the first EBM year 2023, Jan Hinrichsen and Nina Reiter had the opportunity to stay in the **Living Matter Lab** of EBM Mercator Fellow Ellen Kuhl at **Stanford University in California, USA**. Their stay lasted four weeks, from November 13 to December 8. During their time there, they had the pleasure of meeting highly motivated people and engaging in exciting discussions about soft tissue mechanics. They learned more about automated model discovery approaches and are now working on applying these methods to human brain mechanics. These techniques have the potential to improve the understanding of the mechanical behavior of brain tissue under finite strain and to calibrate computational models.

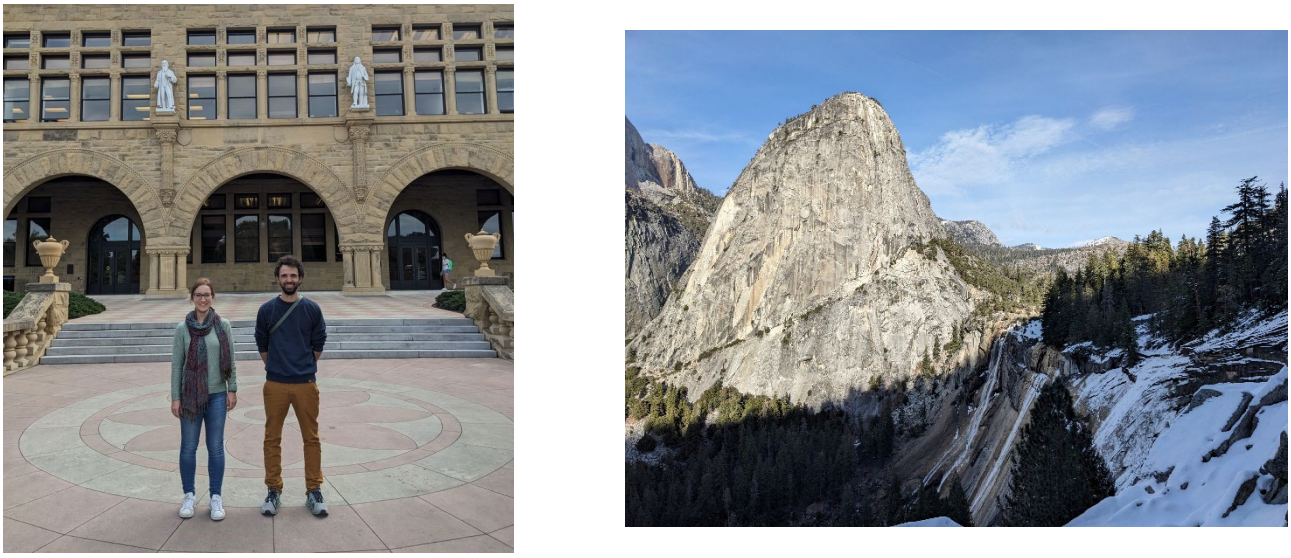


Figure 48: Jan Hinrichsen and Nina Reiter on the Stanford Campus (left) and the view during a hike in Yosemite (right). (Images: A. Ahern, left; J. Hinrichsen, right)

Outside of the inspiring atmosphere of the Stanford campus, they also found time to enjoy the beautiful weather that California is known for. They also found some snow on a trip to nearby Yosemite National Park, which offers beautiful scenery in the form of large cliffs and is home to the famous giant sequoias.

They return home with their minds full of new and exciting ideas that they are eager to apply to their projects back in Erlangen.

(Jan Hinrichsen and Nina Reiter, A01)

Laura Ruhland

From / to	Institute visited	Local supervisor	Research activities and skills acquired during stay
11.09.23 / 14.09.23	Institute for Radiology and Pediatric Radiology, Charité, Berlin, Germany	Steffen Görner	Introduction to Table-Top MRE

Maria Tarczewska

From / to	Institute visited	Local supervisor	Research activities and skills acquired during stay
06.11.23 / 17.11.23	University of Cambridge, UK	n/a	Learning atomic force microscopy

Sebastián Vásquez-Sepúlveda

From / to	Institute visited	Local supervisor	Research activities and skills acquired during stay
05.06.23 / 14.06.23	University of Cambridge, UK	n/a	Training in tadpole brain dissection and labelling

Yashasvi Verma

From / to	Institute visited	Local supervisor	Research activities and skills acquired during stay
05.11.23 / 18.11.23	SISSA, Italy	Luca Heltai	Computational model for vascular tree generation and coupling with poro-viscoelastic model of brain

2.2 FURTHER EBM ACTIVITIES

2.2.1 EBM VIRTUAL BREAKFAST CLUB

The digital format “EBM Virtual Breakfast Club” typically takes place on Monday mornings (excluding days with the scheduled EBM Lunch). Attended by all EBM members through Zoom in an informal setting, the original structure involved (post-)doctoral researchers taking turns presenting the latest scientific insights and open questions from their projects, leading to collective discussions. However, beginning in October, this was changed and the weekly updates on the individual projects were taken over by the respective project leaders. In addition to the project updates, these virtual meetings serve as a relaxed forum for informal discussions on organizational, administrative and current EBM-related topics.

In total, 21 EBM Virtual Breakfasts took place in 2023.

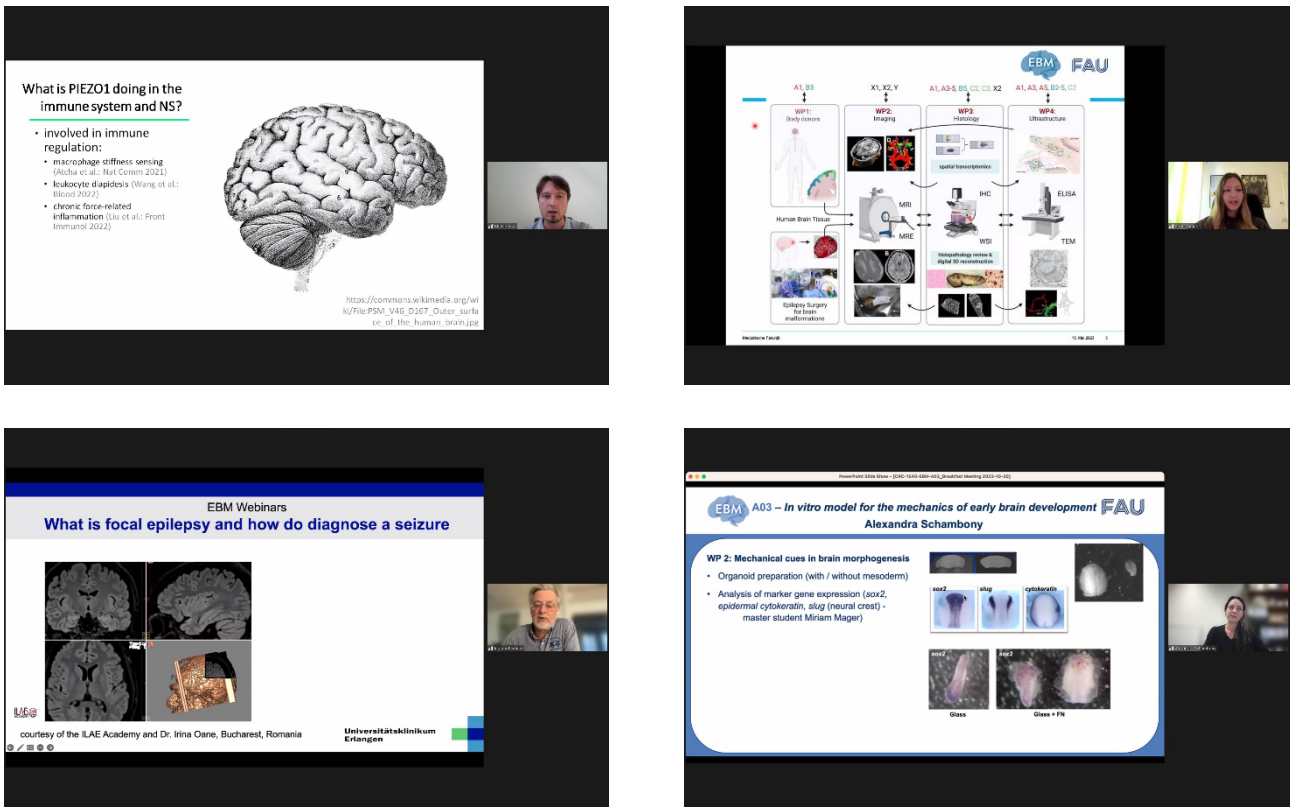


Figure 49: EBM Virtual Breakfast Club: Maik Hintze (top left), Sophie Auer (top right), Ingmar Blümcke (bottom left) and Alexandra Schambony (bottom right).

2.2.2 EBM LUNCH

On the first Monday of every month, all EBM members have the opportunity to meet for lunch together at a local restaurant. These EBM lunches provide a relaxed environment for informal discussions on organizational, administrative and current EBM-related matters. Not to mention the opportunity for social networking.

Figure 50: EBM members at their monthly joint lunch. (Image: A. Dakkouri-Baldauf)

2.2.3 EBM VIRTUAL BRAIN TALK SERIES

The EBM Virtual Brain Talk Series is a quarterly virtual, open-access event dedicated to exploring the latest advancements in mechanics-based approaches. Its primary focus is on enhancing our understanding of the functions of the central nervous system, laying the groundwork for future breakthroughs in the diagnosis and treatment of neurological disorders.

The approximately 45-minute presentations, distinguished by their high-quality content, are held by EBM members and invited scholars. These sessions are designed to foster a continuous exchange of results and ideas within the worldwide scientific community.

Despite being in its early stages, the event series has already proven to be a significant success. A substantial number of international participants, surpassing 50 in some instances, enthusiastically followed the engaging presentations by renowned experts and actively engaged in the lively discussions.

Table 7: EBM Virtual Brain Talks

	Date	Lecturer	Title
01	31.07.23	Paul Steinmann and Silvia Budday (Institute of Applied Mechanics and Institute of Continuum Mechanics and Biomechanics FAU Erlangen-Nürnberg, Germany)	*Exploring brain mechanics*
02	30.10.23	Johannes Weickenmeier (Stevens Institute of Technology, NJ, USA)	*Exploring the multiphysics of the brain during development, aging, and in neurological diseases*
03	11.12.23	Kristian Franze (Institute of Medical Physics, FAU Erlangen-Nürnberg, Germany)	*The mechanical regulation of brain development*

Figure 51: Speakers of the EBM Virtual Brain Talk Series.

2.2.4 EBM SEMINAR TALKS

For the EBM Seminar Talks, internationally renowned scientists were invited to give in-depth presentations on EBM-relevant research topics and then to actively engage EBM researchers in discussions and question-and-answer sessions.

	Date	Lecturer	Title
01	22.03.23	Peter Pivonka (School of Mechanical, Medical and Process Engineering, Queensland University of Technology, Brisbane, Australia)	*Computational simulation techniques for understanding bone remodeling*
02	27.03.23	Revathi Appali (Institute of General Electrical Engineering, University of Rostock, Germany)	*Multiphysics and multiscale modeling of electrically active implants*
03	24.10.23	Victor Borrell (Institute of Neuroscience, CSIC-UMH, San Juan de Alicante, Spain)	*Cellular and genetic mechanisms of cerebral cortex folding*

Figure 52: Viktor Borrell (hosted by Kristian Franze) during his EBM Seminar presentation. (Images: S. Kuth)

2.3 VISITING RESEARCHER PROGRAM

Table 9: Visiting researchers

From / to	Visiting researcher	Topic
22.03.23	**Prof. Peter Pivonka**, School of Mechanical, Medical and Process Engineering, Queensland University of Technology, Brisbane, Australia	Invited lecture within the EBM Seminar Talk series: “Computational simulation techniques for understanding bone remodelling”
27.03.23	**Dr. Revathi Appali**, Institute of General Electrical Engineering, University of Rostock, Rostock, Department of Ageing of Individuals and Society, Interdisciplinary Faculty, University of Rostock, Rostock, Germany	Invited lecture within the EBM Seminar Talk series: “Multiphysics and Multiscale Modeling of Electrically Active Implants”, online

From / to	Visiting researcher	Topic
27.03.23 / 14.07.23	**Carl Ferlay**, École Polytechnique, Paris, France	Collaboration with projects A01, B01: Developing metamodels for time-dependent finite element models of human brain tissue to address challenges in mechanical characterization, particularly related to softness and time-dependency, and to reduce computational costs.
12.07.23 / 09.08.23	**Dr. Ester Comellas**, Department of Mathematics, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain	Invited lecture within the EBM Virtual Breakfast Club: "Nonlinear poro-viscoelasticity: modelling brain mechanics and joint formation"
23.10.23 / 25.10.23	**Dr. Victor Borrell**, Laboratory Neurogenesis and Cortical Expansion, Developmental Neurobiology Unit – The Instituto de Neurociencias de Alicante, Spain	Invited lecture within the EBM Seminar Talk series: "Cellular and genetic mechanisms of cerebral cortex folding"
30.10.23	**Prof. Johannes Weickenmeier,** Stevens Institute of Technology, NJ, USA	Invited lecture within the Virtual Brain Talk Series: "Exploring the multiphysics of the brain during development, aging, and in neurological diseases"

3 EQUAL OPPORTUNITY MEASURES

Promoting equal opportunities for both women and men, along with advancing the careers of doctoral and postdoctoral researchers, is a key objective of EBM. This involves supporting early-career female scientists in strategically planning and advancing their careers, as well as facilitating the balance between research commitments and family life.
EBM's commitment to fostering equal opportunities, career advancement, and the holistic development of emerging scientists was underscored by its comprehensive measures under the **EBMequality** concept.

3.1 WORKSHOPS, SEMINARS

The F^{3}G network (Research Associations of Friedrich-Alexander-Universität Erlangen-Nürnberg for the promotion of equality) offers lectures and seminars on women's advancement, gender sensitization, etc., in addition to a variety of other gender equality measures, in which members of the affiliated research associations can participate. Consequently, some EBM members have taken advantage of these training opportunities and participated in the workshops already listed in Table 5.

3.2 FURTHER MEASURES

3.2.1 EBM FAMILY

- **KidsBox Acquisition:** Procuring a KidsBox to provide childcare services for the children of EBM members during EBM events.
- **Home Office Equipment Enhancement:** Upgrading home office equipment to foster family-friendly work practices.
- **EBM Retreat Childcare Expenses:** Covering childcare expenses during the EBM retreat for the convenience of participating members.
- **Conference Travel Childcare Coverage:** Providing financial coverage for childcare expenses incurred during conference travels for EBM members.
- **Financial Support for Holiday Childcare:** Providing financial assistance for vacation care services dedicated to the children of our EBM members.
- **F^{3}G Project Funding:** Offering financial support for specific projects under F^{3}G within FAU holiday childcare programs.
- **Pedagogic Enhancement:** Improving the pedagogic infrastructure at FAU daycare facilities to enhance the care provided to children.
- **Contribution to F^{3}G Coordination Costs:** Contributing to the coordination costs associated with F^{3}G initiatives.
- **Day Care Center Contingent Option:** Securing a contingent option for occupancy places at the day care center "Pfauennest II."

Figure 53: Children's activities during the EBM events with the EBM KidsBox. (Image: M. Schicht)

3.2.2 EBM ENCOURAGE

- **Young Talent Promotion:** Support for the "Formula 1 at school" project at Marie Therese Gymnasium, Erlangen, through our collaboration with F^3G as part of the promotion of young talent. Notably, the team, consisting of six pupils from Marie Therese Gymnasium aged between 16 and 18, won the F1 in Schools World Champions Trophy in Singapore in September 2023. This victory took place during the eighteenth world finals of the global STEM competition. The ”Recoil Racing Team” beat 67 other teams representing their respective regions and nations in the competition. Congratulations on this outstanding achievement!

- **CJT Impulstag – student visit**

  In October, Stefan Rampp and Nadia Müller-Voggel from the Department of Neurosurgery and the Department of Neuroradiology welcomed 30 8th grade students from the Christoph-Jacob-Treu-Gymnasium. During their visit, they were introduced to various aspects of brain anatomy and function and how these can be affected by brain disorders. A number of questions were raised in lively discussions: How big is the brain and how much does it weigh? How many nerve cells are there? What are the functions of the brain? How does the brain store memories? How does it produce and understand language? What are brain disorders and how can we detect them? ... and many more. Students explored MR images to find lesions ranging from obvious tumors to very subtle focal cortical dysplasia. Surgical approaches were then briefly discussed, including a brief tangent on awake surgery.

  In a second part, the students had the opportunity to visit the magnetoencephalography (MEG) laboratory of the Department of Neurosurgery. Here, patients with epilepsy are examined with EEG and MEG to record epileptic activity. The results are then used to localize the epileptic focus in order to tailor epilepsy surgery to the individual patient. The students not only had the opportunity to learn how the MEG system works, but also to experience a measurement themselves: Volunteers were scanned while their classmates watched their brain activity in real time.

  Although this was organized as a one-time event, plans are already underway to repeat it in 2024.

4 SELECTED HIGHLIGHTS

4.1 KICK-OFF MEETING

Figure 54: Detailed program see Appendix 2

On March 17th, 2023, the Collaborative Research Center (CRC) 1540 „Exploring Brain Mechanics (EBM)“ held its kick-off meeting at the Fraunhofer Institute for Integrated Systems and Device Technology (IISB) in Erlangen. The event was attended by researchers from the fields of engineering, physics, biology, medicine, and clinics who are involved in the project. The goal of the CRC 1540 “Exploring Brain Mechanics”‘ is to combine the expertise of professionals from Erlangen and Berlin and use mechanics-based approaches to improve our understanding of the central nervous system’s function. In the long run, this should lay the foundation for improving the diagnosis and treatment of neurological disorders.

The meeting began with presentations by the spokespersons of EBM, Paul Steinmann and Silvia Budday, who introduced the focal research areas and the overall structure of the research center.

Following this, Friedrich Paulsen, as spokesperson for the integrated Research Training Group, presented the integrated graduate program, focusing on the qualification program and upcoming events.

Afterwards, the project leaders introduced their respective projects in short presentations. During the coffee and lunch breaks, the participants had the opportunity to get information at the project posters while enjoying snacks and drinks and to exchange ideas with all the other researchers.

In the afternoon, the doctoral researchers‘ representatives were elected. Shanice Heidenreich was elected as the 1st doctoral researchers‘ representative and Soheil Firooz was elected as her deputy. During the same meeting, a social media group was formed, which will be responsible for managing the EBM Twitter and Instagram accounts. Simultaneously, the quarterly meeting of the EBM Executive Board was held.

Figure 55: Participants of the EBM Kick-Off Meeting. (Image: A. Greiner)

The kick-off meeting concluded with a joint dinner at an Italian restaurant in Erlangen.

Overall, the kick-off meeting of the CRC 1540 was a great success, providing a platform for researchers to exchange ideas and insights, while also fostering the development of a strong and cohesive research community.

Figure 56: Impressions of the EBM Kick-Off Meeting. (Images: A. Dakkouri-Baldauf, A. Greiner)

4.2 AWARDS AND DISTINCTIONS

(in alphabetical order of the award winners)

4.2.1 JANA BACHIR SALVADOR – BEST PRESENTATION AWARD

At the BioBrillouin conference, which took place from December 6 to 8, 2023 at Trinity College in Dublin, Ireland, Jana Bachir Salvador received the Best Presentation Award for her outstanding talk entitled "Deciphering the determinants of nervous tissue mechanical properties in vivo". This award underlines not only her excellent research work, but also her commitment and outstanding presentation skills.

We congratulate Jana on this well-deserved success!

4.2.2 ALDO R. BOCCACCINI ELECTED FELLOW OF BSE

Aldo R. Boccaccini, Head of the Institute of Biomaterials, Department of Materials Science and Engineering at University of Erlangen-Nuremberg (FAU) has been elected Fellow of Biomaterials Science and Engineering (FBSE), the highest honor the global biomaterials community can bestow on outstanding biomaterials scientists, which

The International College of Fellows of Biomaterials Science and Engineering

Figure 57: Prof. Dr. Aldo R. Boccaccini.

is awarded by the International Union of Societies for Biomaterials Science and Engineering (IUSBSE). The International College of Fellows of Biomaterials Science and Engineering (http://iusbse.org/fellows/) is a group of less than 500 of the most respected biomaterials scientists worldwide. The induction ceremony will take place at the 12th World Biomaterials Congress (WBC2024) to be held in Daegu, South Korea, May 26-31, 2024. Prof. Boccaccini said: "I am overwhelmed by this recognition as FBSE. This is indeed the result of many years of effective and successful work contributing to the biomaterials field which has been only possible by the contribution and hard work of former and current members of my research group, including PhD students, postdocs, academic colleagues as well as our large network of national and international collaborators. I thank them a lot for such great collaborations and support over the years and I look forward to playing a role in the activities of the International College of Fellows of Biomaterials Science and Engineering in the near future".

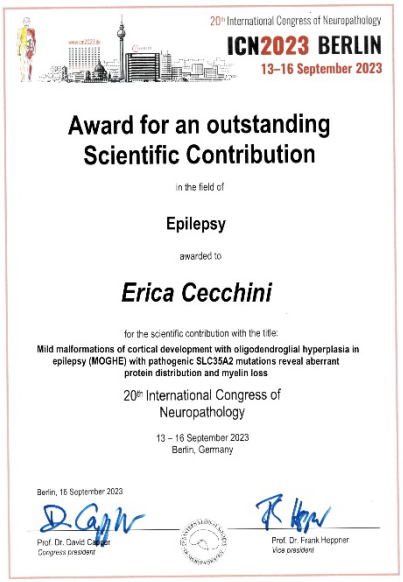
Congratulations, Aldo, on this well-deserved honor!

4.2.3 ERC STARTING GRANT 2023 TO SILVIA BUDDAY

EBM Co-Speaker Silvia Budday, Chair of Continuum Mechanics with a focus on Biomechanics, has achieved a significant milestone by being awarded the prestigious European Research Council (ERC) Starting Grant. This highly competitive grant, amounting to up to 1.5 million euros over a five-year period, serves as a testament to her outstanding contributions as a researcher. In her groundbreaking research, Silvia Budday investigates the behavior of extremely soft materials under mechanical influences, encompassing hydrogels and human brain tissue. The MAGERY project aims to prevent damage to brain cells caused by mechanical stresses, such as those occurring during brain surgeries. Using an innovative experimental setup and a combination of mechanical measurements, multiphoton microscopy, mathematical modeling, and simulation, the project seeks to determine the mechanical load levels our brain cells can withstand before sustaining damage or cell death. This research holds the potential to significantly impact neurosurgery by integrating findings into virtual or augmented reality solutions, allowing surgeons to predict and visualize stresses and potential damage in real time.

Figure 58: Prof. Dr.-Ing. Silvia Budday. (Image: FAU/Georg Pöhlein)

The entire EBM family congratulate Silvia on her impressive achievement!


20th International Congress of Neuropathology
ICN2023 BERLIN
13–16 September 2023

Award for an outstanding Scientific Contribution

in the field of

Epilepsy

awarded to

Erica Cecchini

for the scientific contribution with the title:

Mild malformations of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE) with pathogenic SLC35A2 mutations reveal aberrant protein distribution and myelin loss

20th International Congress of Neuropathology

13 – 16 September 2023
Berlin, Germany

Berlin, 16 September 2023

Prof. Dr. David Ca[illegible]
Congress president

Prof. Dr. Frank Hoppner
Vice president

4.2.4 ERICA CECCHINI – AWARD FOR AN OUTSTANDING SCIENTIFIC CONTRIBUTION

On September 21, 2023, Erica Cecchini was honored with the Award for an Outstanding Scientific Contribution. This prestigious award was in recognition of her remarkable presentation at the epilepsy session at the International Congress of Neuropathology in Berlin (ICN 2023). The title of her award-winning poster was “Mild Malformation of Cortical Development with Oligodendroglial Hyperplasia in Epilepsy (MOGHE) with Pathogenic SLC35A2 Mutations Reveals Aberrant Protein Distribution and Myelin Loss.”

Warmest congratulations to Erica on this achievement!

4.2.5 ERC SYNERGY GRANT 2023 TO KRISTIAN FRANZE

The European Research Council (ERC) has selected the UNFOLD project (Unfolding the dynamic interaction between mechanical and molecular processes in brain folding) as one of the 37 beneficiaries of the Synergy Grants program in 2023. This groundbreaking research project, involving the team of EBM PI Kristian Franze in collaboration with three other international scientists from the Institute of Neuroscience (Spain), the University of Liège (Belgium), and the Pasteur Institute (France), will receive over 10 million euros in funding. Together, these four partners are placing a special focus on the intricate interplay between biological and mechanical processes that drive brain folding, contributing to a deeper understanding of brain development and formation.

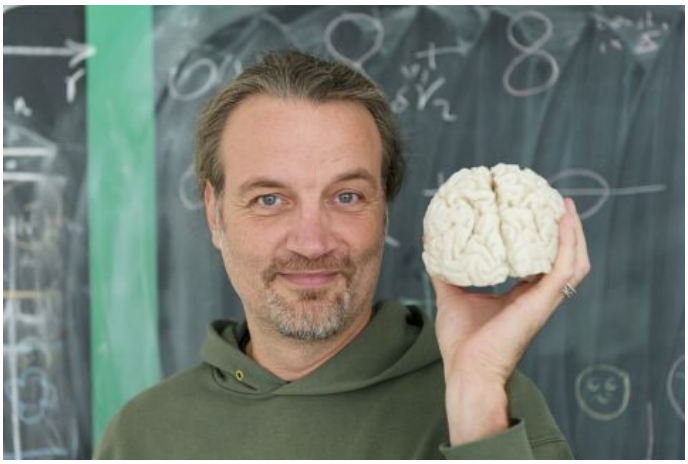


Figure 59: Prof. Dr. Kristian Franze. (Image: MPL/Stephan Spangenberg)

A heartfelt congratulations to our project leader Kristian!

4.2.6 CARL ZEISS LECTURE 2023 TO JOCHEN GUCK

The German Society for Cell Biology (DGZ) and ZEISS have awarded EBM PI Jochen Guck the Carl Zeiss Lecture 2023 in recognition of his extraordinary contributions to cell biology and his pioneering advances in microscopy technology. This prestigious award honors his internationally recognized achievements in the field of cell biology.

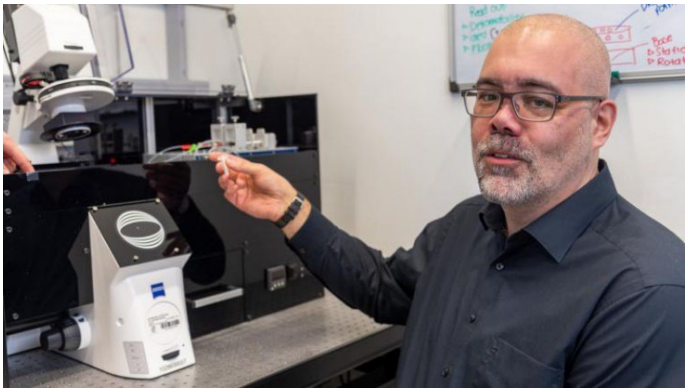


Figure 60: Prof. Dr. Jochen Guck. (Image: MPL/Max Kruse)

Jochen Guck's research focuses on the interface between biophysics and the synergy between physics and medicine. His research focuses on investigating the physical, mechanical and optical properties of living cells and tissues. Using microscopy and other innovative methods, he has done pioneering work in the field of biophotonics and microfluidics.

One of his notable contributions is the development of new techniques that use the stiffness of cells as a biomarker. With this innovative approach, he aims to identify pathologically altered or infectious cells. His research aims to improve our understanding of the fundamental units of biological systems - the cells - and their intrinsic properties.

Warmest congratulations to Jochen!

4.2.7 DOCTOR HONORIS CAUSA TO FRIEDRICH PAULSEN

EBM iRTG-Speaker Friedrich Paulsen was awarded a Doctor Honoris Causa from the Grigore T. Popa University of Medicine and Pharmacy (https://www.umfiasi.ro/en), Iasi, Romania, in May 2023. The award ceremony was hosted by the Rector Prof. Dr. Viorel Scripcariu. The laudatory speech was held by the anatomist Professor Dr. Anca Sava. Professor Paulsen was also made an honorary citizen by the Mayor of Iasi, Mihai Chirica. Prof. Paulsen has been associated with the University of Iasi for many years. When he took over the position of Secretary of the Anatomical Society in 2006, an intensive Romanian-German anatomical connection already existed in Iasi through Wolfgang Kühnel as former Secretary of the Anatomical Society and the anatomist Prof. Constantin Fatu. Friedrich Paulsen was subsequently able to expand this together with Anca Sava. An Erasmus partner-

Figure 61: Prof. Dr. med. Dr. h.c. Friedrich Paulsen (center). (Image: Grigore T. Popa University).

ship was successfully established between the University of Iasi and FAU, and over the years scientific networking has also increased. A joint doctoral student from Iasi is currently being supervised in a cotutelle procedure between the two universities in anatomy, working on neuronal networks in human laryngeal muscles. Through his honorary fellowship of the Romanian Anatomical Society, Friedrich Paulsen regularly takes part in the congresses of the Romanian Anatomical Society, as do numerous colleagues from Iasi at the congresses of the Anatomical Society.

Congratulations to Friedrich on this great honor!

4.2.8 NINA REITER – SPEAKER OF THE GAMM JUNIORS

Throughout the entirety of 2023, Nina Reiter held the esteemed position of Speaker of the GAMM Juniors. The GAMM Juniors is an exclusive group comprising 30 young researchers and GAMM members, distinguished by their outstanding diploma/master and/or PhD theses in the domains of Applied Mathematics or Mechanics. More information about GAMM Juniors can be found at https://www.gamm-juniors.de/.

Congratulations, Nina, on taking on this prestigious task!

4.2.9 JANA SIPKOVA – SCHOLARSHIPS FOR DEVELOPMENTAL BIOLOGY EXCELLENCE

Jana Sipkova was recognized for her active participation in the Society for Developmental Biology (SDB) conference in Chicago, USA. On May 7, 2023, she was awarded the **Society for Developmental Biology (SDB) International Student/Postdoc Scholarship**, a prestigious award that highlights her dedication and outstanding achievements in the field. This prestigious $2,000 scholarship is a testament to Jana's commitment to advancing knowledge in developmental biology.

In addition, Jana Sipkova was distinguished by receiving the **Cambridge Philosophical Society Travel Grant** on July 18, 2023. This grant of £250 enabled her to attend the Society for Developmental Biology conference in Chicago. The grant is not only a recognition of Jana's academic achievements, but also a testament to her commitment to scientific discourse and international collaboration.

Congratulations, Jana, on these well-earned recognitions!

4.3 PODCAST WITH KATJA KOBOW

Brain Tissue for Epilepsy Research - Neuropathology!

Katja Kobow, award-winning molecular neuropathologist and Assistant Professor involved in Project **C03** of EBM, recently participated in an interview, which was featured in a podcast published in August, 2023. The engaging discussion, led by Torie Robinson, was part of the podcast series titled "Epilepsy Sparks Insights."

In this interview she explained her research into unraveling the intricate interplay between epigenetic alterations and the development of epilepsy, specifically in the context of the adult post-mitotic brain.

The podcast covered various key topics related to neuropathology, obtaining and using human surgical brain tissue for research, molecular mechanisms in epilepsy, how to use molecular alterations to inform clinicians about patient histological/structural abnormalities, and new promising results on molecular diagnostic biomarkers in brain & blood. They also discussed science communication, the need to educate the wider public regarding epilepsy research, but also that a scientist in preclinical and clinical research needs to be careful in the management of patient dreams and expectations when talking about results.

For those interested, the full interview with Katja Kobow is available at this link: https://www.torierobinson.com/epilepsy-sparks-insights/katja-kobow-brain-tissue-for-epilepsy-research-neuropathology.

4.4 PODCAST WITH STEFAN RAMPP

What Are MEG Brain Scans?

Stefan Rampp, senior researcher involved in Project **A02** of EBM, recently participated in an interview, which was featured in a podcast published at the end of November. The engaging discussion, led by Torie Robinson, was part of the podcast series titled "Epilepsy Sparks Insights."

The interview delved into the realm of Magnetoencephalographies (MEGs), shedding light on their crucial role as brain scans with exceptional sensitivity. MEGs serve as a distinctive complement to traditional EEG and MRI scans, particularly in the preparatory stages of epilepsy surgery.

The podcast covered various key topics related to MEGs (Magnetoencephalography), including their fundamentals, advantages in epilepsy surgery preparation, comparison with EEG and MRI, identifying beneficiaries, the role in decision-making, addressing suboptimal options, risk minimization through normal brain activity localization, balancing risks and benefits in patient communication, and positive outcomes post-surgery. It emphasized the individualized work-up process leading to epilepsy surgery.

For those interested, the full interview with Stefan Rampp is available at this link: https://www.torierobinson.com/epilepsy-sparks-insights/stefan-rampp-meg-magnetoencephalography-benefits-epilepsy-neurosurgery.

5 OUTREACH ACTIVITIES

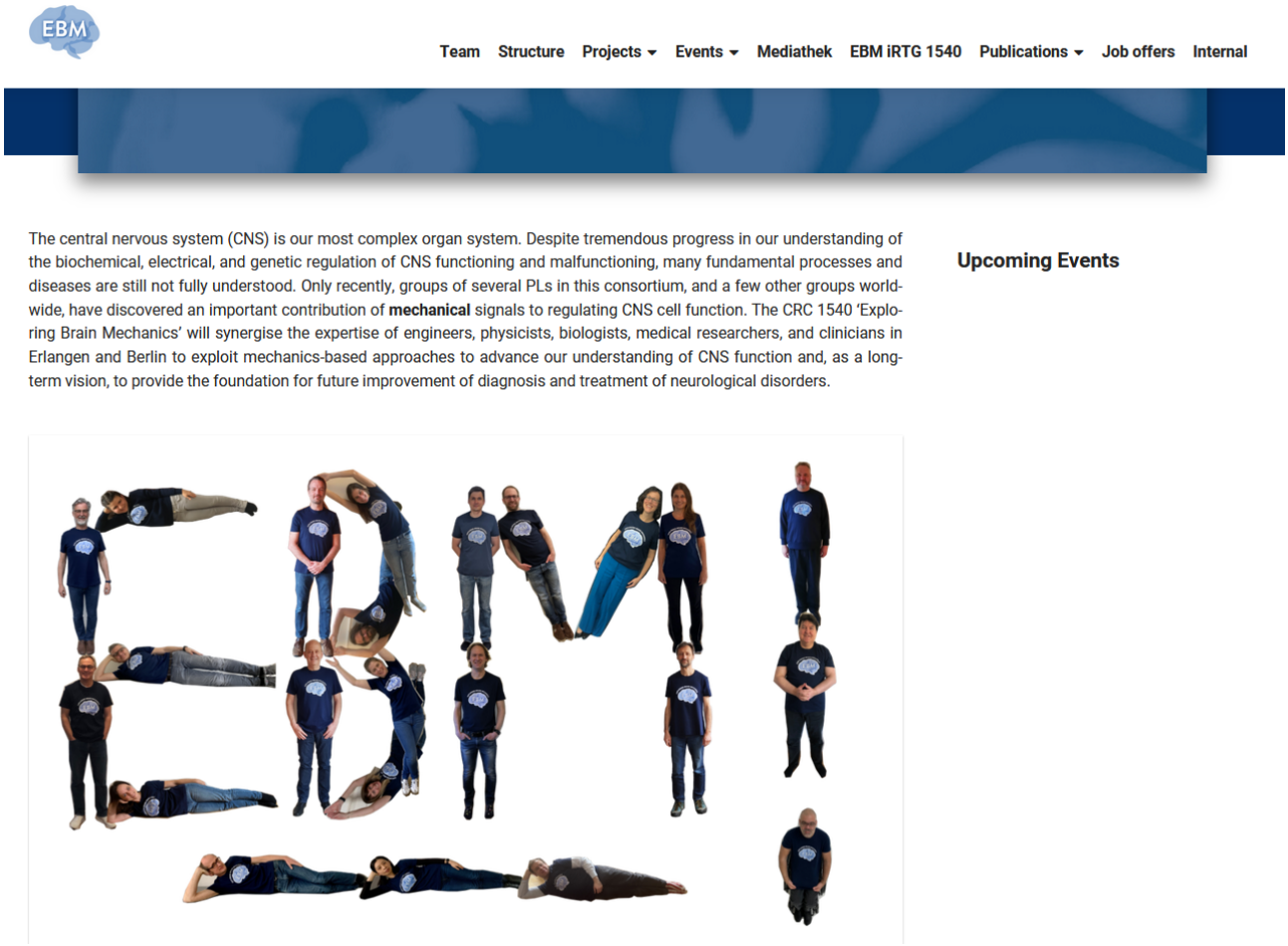
The primary objective of **EBMoutreach** concept is to achieve international, national, and regional visibility. This is intended to be accomplished through disseminating results and activities, thereby engaging both the broader public (**EBM2public**) and the world-wide scientific community (**EBM2peers**).

5.1 EBM2PUBLIC

The **EBM2public** initiative encompasses various channels to enhance public engagement and outreach:

5.1.1 EBM'S WEBPAGE

- EBM maintains an informative webpage at www.ebm.fau.de:



5.1.2 EBM SOCIAL MEDIA PRESENCE

- EBM actively manages social media channels on platforms such as X, LinkedIn, and Instagram.
- The Social Media Team, comprised of EBM doctoral candidates, the Co-Spokesperson, and the Scientific Coordinator, consistently updates these platforms.
- Throughout the year 2023, under the leadership of Sonja Kuth, all EBM projects were presented on these platforms. Updates on EBM activities, introductions of new publications, and the posting of the "#pictureoftheweek" were regularly featured.

5.1.3 EBM LAB VIDEOS

- Collaborating with FAU's Institute for Theatre and Media Sciences (ITM), EBM produces Lab videos.
- These videos are featured on EBM's website, providing an engaging visual insight into EBM's work.

5.1.4 EBM AT THE LONG NIGHT OF SCIENCES

EBM actively participated in the Long Night of Sciences, utilizing this event as an opportunity to interact with the public, showcase projects, and disseminate information.

Fascination Brain Mechanics: EBM at #NDW23

On October 21, 2023, the Collaborative Research Center CRC 1540 "Exploring Brain Mechanics" (EBM) participated in the Long Night of the Sciences in the Erlangen, Fürth, and Nuremberg region. In a captivating presentation, EBM opened its doors to the interested public, providing insights into various facets of its research. The event spanned across five locations:

At the main event venue, the Institute of Applied Mechanics (LTM), EBM provided a diverse range of stations in addition to the BRAINIACS group:

1. Interactive Activity: Touch Boxes - "Can you guess where we hid the brain?" Visitors had the opportunity to touch and guess the nature of the brain. It was a hygienically packaged brain, not of human origin but from a pig. Correct guesses were rewarded with gummy brain candies. This station illustrated the complex mechanics of the brain and how it behaves differently when pressed or pulled.
2. Engineering of Artificial Brain Tissue for Organ Phantoms: EBM explained how they imitated the extracellular matrix of soft tissue using hydrogels, which can create various levels of firmness. Visitors could touch the manufactured brain phantoms to determine which best imitated a real brain.
3. Brain Models from Anatomy: A 3D model of the human brain provided an opportunity to explore the fascinating complexity of this organ. Visitors were invited to disassemble and reassemble the model.
4. Horizontal Sections of a Real Human Brain: Visitors were particularly fascinated by the opportunity to view and touch real sections of a human brain and compare them to a 3D model.
5. Histological Stains of the Central Nervous System: Paraffin sections of the nervous system, treated with various stains to make specific cells and structures visible, were presented. Visitors could explore these sections under a microscope and study the different tissue structures.

6. 7T Neuro MRT Scan of the Human Brain – 3D Rendering: A fascinating glimpse into the latest technology in neuroimaging with a 7T Neuro MRI scan that displayed the human brain in 3D.
7. From the Neural Plate to the Brain: Visitors could trace the astonishing development of the brain from the neural plate to its full maturity in a video. This station illustrated how the brain changes during its development.

In addition to the main location, EBM was also present at four other locations at FAU:

- Institute of Biomaterials
- Chair of Biochemistry and Molecular Medicine
- Max Planck Institute for Physics and Medicine
- Department of Neurosurgery (University Hospital Erlangen)

At the last location, EBM, under the expert guidance of PD Dr. med. Stefan Rampp offered seven informative tours. More than 100 participants had the opportunity to visit the Magnetoencephalography (MEG) laboratory of the Department of Neurosurgery. MEG is an innovative tool used to detect subtle cortical lesions, such as focal cortical dysplasias, by pinpointing the location of epileptic activity in the brain. Visitors had the unique chance to observe the MEG device in its magnetically shielded room and examine the technical equipment used to study speech networks, motor functions, visual and auditory systems. Additionally, they witnessed a live demonstration of the MEG device's sensitivity. An information booth allowed visitors to gain exciting insights into clinical applications and ongoing research projects. Here, it was explained how functional measurements are combined with structural data to enhance our understanding of brain mechanics and mechanisms.

The presentation of CRC 1540 EBM attracted considerable attention throughout the night. The EBM (post)doctoral researchers impressed with their creative ideas and fresh presentations, effectively conveying the topic of brain mechanics to a wide audience.

Figure 62: Preparing for the Long Night of Sciences. (Images: A. Dakkouri-Baldauf)

Figure 63: EBM at the Long Night of Sciences. (Images: A. Dakkouri-Baldauf, S. Kuth, S. Lörentz, G. Pöhlein (FAU))

5.2 EBM2PEERS

- EBM Scientific Publications (see Section 1.3): All publications are freely accessible. Additionally, supplementary materials such as datasets are publicly available through the "Exploring Brain Mechanics - CRC 1540 EBM" community on the online storage service Zenodo.
- EBM Scientific Presentations at first-class conferences, workshops, and seminars (see Section 6.3
- EBM Virtual Brain Talks (see Section 2.2.3)

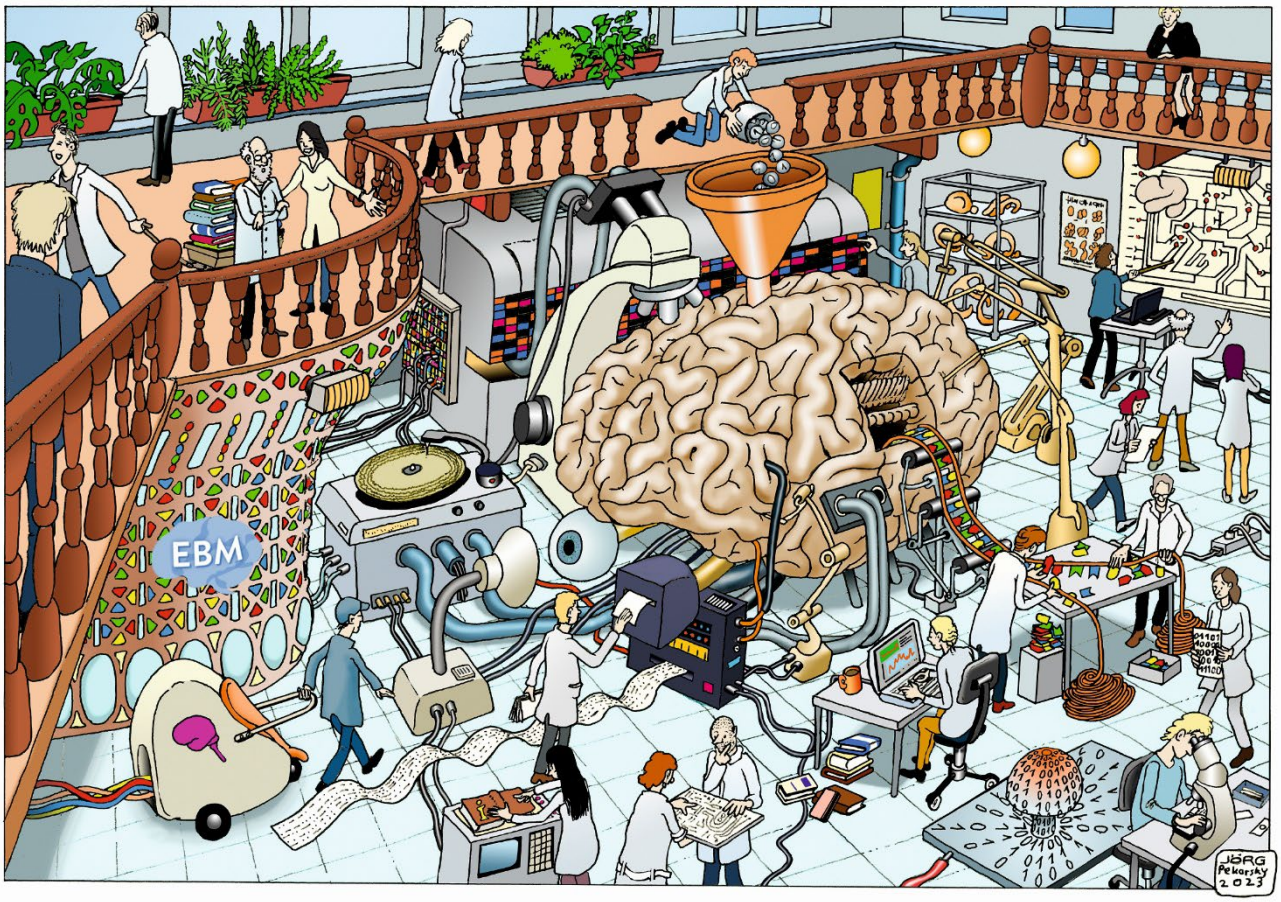


Figure 64: EBM-themed hidden object illustration drawn by Jörg Pekarsky, a member of Friedrich Paulsen's research group.

6 GENERAL INFORMATION

6.1 KEY DATA

6.1.1 GOVERNING BODIES OF EBM

Spokesperson
Prof. Dr.-Ing. habil. Paul Steinmann
Institute of Applied Mechanics
Egerlandstr. 5, 91058 Erlangen
+49 9131 8528501
paul.steinmann@fau.de

Co-Spokesperson
Prof. Dr.-Ing. Silvia Budday
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Egerlandstr. 5, 91058 Erlangen
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Scientific Coordination
Dr. rer. nat. Andrea Dakkouri-Baldauf
Institute of Applied Mechanics
Martensstraße 5a, 91058 Erlangen
+49 9131 85 20782
andrea.dakkouri@fau.de

EBM Executive Board
The EBM Executive Board consists of the Spokesperson, Co-Spokesperson, Scientific Coordinator, Chairs of the Focal Research Areas (FRA A, B, C) and the Cross-Sectional Research Area (XRA), the Principal Executive of the Integrated Research Training Group (iRTG), a representative from the Clinics, an Early Career Support Representative, an Equal Opportunity Representative, a (Post-) Doctoral Researchers' Representative, and the EBM assistance.

Members:

Spokesperson	Prof. Paul Steinmann
Co-Spokesperson	Dr. Silvia Budday
Scientific Coordinator	Dr. Andrea Dakkouri-Baldauf
Chair of FRA A	Prof. Kristian Franze
Chair of FRA B	Prof. Jochen Guck
Chair of FRA C	Prof. Ben Fabry
Chair of XRA	Dr. Jing Guo / Prof. Ingolf Sack
Clinics Representative	Prof. Arnd Dörfler / Prof. Ingmar Blümcke
Principal Executive of the iRTG	Prof. Friedrich Paulsen
Early Career Representative	Prof. Katharina Breininger
Equal Opportunity Representative	Prof. Marisa Karow
(Post-)Doctoral Researchers‘ Representative	Shanice Heidenreich (Deputy: Soheil Firooz)
EBM Assistance	Doris Bittner

6.1.2 PARTICIPATING RESEARCHERS

6.1.2.1 Principal investigators

Table 10: Principal investigators

Principal investigators (PIs)	Faculty	Home institution, location	Project
Blümcke, Prof. Dr. med., Ingmar	FAU-MedFak	Neuropathology, Schwabachanlage 6, 91054 Erlangen	A02
Boccaccini, Prof. Dr.-Ing. habil., Aldo R.	FAU-TechFak	Biomaterials, Cauerstr. 6, 91058 Erlangen	X03
Bosserhoff, Prof. Dr., Anja	FAU-MedFak	Biochemistry and Molecular Neurosciences, Fahrstr. 17, 91054 Erlangen	C04
Breininger, Prof. Dr.-Ing., Katharina	FAU-TechFak	Artificial Intelligence in Medical Imaging, Henkestraße 91, 91052 Erlangen	X02
Budday, Prof. Dr.-Ing., Silvia	FAU-TechFak	Institute of Continuum Mechanics and Biomechanics, Egerlandstr. 5, 91058 Erlangen	A01, B01, Z
Dörfler, Prof. Dr. med., Arnd	FAU-MedFak	Neuroradiology, Schwabachanlage 6, 91054 Erlangen	A02, Y
Fabry, Prof. Dr.-Ing., Ben	FAU-NatFak	Biophysics, Henkestr. 91, 91052 Erlangen	C05
Falk, Dr., Sven	FAU-MedFak	Biochemistry and Molecular Neurosciences, Fahrstr. 17, 91054 Erlangen	A04
Franze, Prof. Dr., Kristian	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	A05, B02
Frischknecht, Dr., Renato	FAU-NatFak	Animal Physiology, Staudtstr. 5, 91058 Erlangen	C02
Guck, Prof. Dr., Jochen	FAU-NatFak	Biological Optomechanics, Staudtstr.2, 91058 Erlangen	B03
Guo, Dr. rer. nat., Jing	Charité Berlin	Radiology, Charitéplatz 1, 10117 Berlin	X01, Y
Karow, Prof. Dr. rer. nat., Marisa	FAU-MedFak	Biochemistry and Molecular Neurosciences, Fahrstr. 17, 91054 Erlangen	A04
Kobow, PD Dr. rer. nat. Dr. habil. med., Katja	FAU-MedFak	Neuropathology, Schwabachanlage 6, 91054 Erlangen	C03
Kürten, Prof. Dr. med., Stefanie	FAU-MedFak	Anatomy and Cell Biology, Krankenhausstr.9, 91054 Erlangen and Universität Bonn, Institute of Neuroanatomy, Nussallee 10, 53115 Bonn	B04
Laun, Prof. Dr. rer. nat., Frederik B.	FAU-MedFak	Radiology, Maximiliansplatz 3, 91054 Erlangen	Y
Maier, Prof. Dr.-Ing. habil., Andreas	FAU-TechFak	Computer Science 15, Machine Intelligence, Martensstr. 3, 91058 Erlangen	X02
Möllmert, Dr. rer. nat., Stephanie	MPL	Biological Optomechanics, Staudtstr.2, 91058 Erlangen	B03
Paulsen, Prof. Dr. med., Friedrich	FAU-MedFak	Functional and Clinical Anatomy, Universitätsstr. 19, 91054 Erlangen	A02, IRTG
Sack, Prof. Dr. rer. nat., Ingolf	Charité Berlin	Radiology, Charitéplatz 1, 10117 Berlin	X01, Y
Schambony, Prof. Dr. rer. nat., Alexandra	FAU-NatFak	Schambony Lab, Staudtstr. 5, 91058 Erlangen	A03
Steinmann, Prof. Dr.-Ing. habil., Paul	FAU-TechFak	Applied Mechanics, Egerlandstr. 5, 91058 Erlangen	B01, C01, X01, Z
Wehner, Dr. rer. nat., Daniel	MPL	Biological Optomechanics, Staudtstr.2, 91058 Erlangen	B05
Willner, Prof. Dr.-Ing. habil., Kai	FAU-TechFak	Applied Mechanics, Egerlandstr. 5, 91058 Erlangen	X01
Zaburdaev, Prof. Dr., Vasily	FAU-NatFak	Mathematics in Life Sciences, Cauerstr. 11, 91058 Erlangen	C01

6.1.2.2 Associated principal investigators

Table 11: Associated principal investigators

Associated principal investigators (aPIs)	Faculty	Home institution, location
Hutter, Prof. Dr.-Ing., Jana	FAU-MedFak	Institute of Radiology, Henkestrasse 91, 91052 Erlangen
Riedl, Prof. Dr. med., Valentin	FAU-MedFak	Institute of Neuroradiology, Henkestr. 91, 91052 Erlangen

6.1.2.3 Postdoctoral researchers

Table 12: Postdoctoral researchers and assistant doctors

Postdoctoral researchers (PDRs)	Faculty	Home institution, location	Project
Dolai, Dr., Pritha	FAU-NatFak	Mathematics in Life Sciences, Cauerstr. 11, 91058 Erlangen	C01
Hintze, Dr., Maik	FAU-MedFak	Anatomy and Cell Biology, Krankenhausstr.9, 91054 Erlangen and Universität Bonn, Institute of Neuroanatomy, Nussallee 10, 53115 Bonn	B04
Melly, Dr., Stephen	FAU-TechFak	Institute of Continuum Mechanics and Biomechanics, Egerlandstr. 5, 91058 Erlangen	B01
Rampp, PD Dr. med., Stefan	FAU-MedFak	Department of Neurosurgery, Department of Neuroradiology, Schwabachanlage 6, 91054 Erlangen	A02
Shahryari, Mehrgan	Charité Berlin	Radiology, Charitéplatz 1, 10117 Berlin	X01
Wellge, Brunhilde	Charité Berlin	Medical Clinic, Department of Cardiology and Angiology, Charitéplatz 1, 10117 Berlin	Y

6.1.2.4 Associated postdoctoral researchers and assistant doctors

Table 13: Associated postdoctoral researchers and assistant doctors

Associated postdoctoral researchers and assistant doctors (aPDRs)	Faculty	Home institution, location	Project
Chunder, Dr. rer. nat., Rittika	FAU-MedFak	Anatomy and Cell Biology, Krankenhausstr.9, 91054 Erlangen and Universität Bonn, Institute of Neuroanatomy, Nussallee 10, 53115 Bonn	B04
Hoffmann, Dr. med., Lucas	FAU-MedFak	Neuropathology, Schwabachanlage 6, 91054 Erlangen	A02
Schicht, PD Dr. rer. nat. Dr. habil. med., Martin	FAU-MedFak	Functional and Clinical Anatomy, Universitätsstr. 19, 91054 Erlangen	A02
Scholz, Prof. Dr. rer. nat. Dr. habil. med., Michael	FAU-MedFak	Functional and Clinical Anatomy, Universitätsstr. 19, 91054 Erlangen	A02

6.1.2.5 Doctoral researchers

Table 14: Doctoral researchers

Doctoral Researchers (DRs)	Faculty	Home institution, location	Project
Auer, Sophia	FAU-MedFak	Functional and Clinical Anatomy, Universitätsstr. 19, 91054 Erlangen	A02
Bachir Salvador, Jana	MPL	Biological Optomechanics, Staudtstr.2, 91058 Erlangen	B03

Bischof, Lars	FAU-NatFak	Biophysics, Henkestr. 91, 91052 Erlangen	C05
Cecchini, Erica	FAU-MedFak	Neuropathology, Schwabachanlage 6, 91054 Erlangen	A02
Erterek, Ezgi	FAU-NatFak	Animal Physiology, Staudtstr. 5, 91058 Erlangen	C02
Firooz, Soheil	FAU-TechFak	Applied Mechanics, Egerlandstr. 5, 91058 Erlangen	C01
Froidevaux, Clara	FAU-NatFak	Schambony Lab, Staudtstr. 5, 91058 Erlangen	A03
Heidenreich, Shanice	FAU-MedFak	Biochemistry and Molecular Neurosciences, Fahrstr. 17, 91054 Erlangen	C04
Hinrichsen, Jan	FAU-TechFak	Institute of Continuum Mechanics and Biomechanics, Egerlandstr. 5, 91058 Erlangen	A01
Karandasheva, Kristina	FAU-MedFak	Neuropathology, Schwabachanlage 6, 91054 Erlangen	C03
Klingberg, Tim	FAU-NatFak	Mathematics in Life Sciences, Cauerstr. 11, 91058 Erlangen	C01
Kuth, Sonja	FAU-TechFak	Biomaterials, Cauerstr. 6, 91058 Erlangen	X03
Lorke, Markus	FAU-TechFak	Biomaterials, Cauerstr. 6, 91058 Erlangen	X03
Lyraki, Olga	MPL	Biological Optomechanics, Staudtstr.2, 91058 Erlangen	B05
Meyer, Tom	Charité Berlin	Radiology, Charitéplatz 1, 10117 Berlin	X01
Neumann, Oskar	FAU-TechFak	Institute of Continuum Mechanics and Biomechanics, Egerlandstr. 5, 91058 Erlangen	B01
Pan, Zhaoya	FAU-TechFak	Chair of Computer Science 5 (Pattern Recognition), Martensstraße 3, 91058 Erlangen	X02
Perelló Amorós, Bartomeu	FAU-NatFak	Animal Physiology, Staudtstr. 5, 91058 Erlangen	C02
Ruhland, Laura	FAU-TechFak	Applied Mechanics, Egerlandstr. 5, 91058 Erlangen	X01
Sipkova, Jana	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	A05
Tarczewska, Maria Weronika	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	A05
Tranchina, Michael	FAU-MedFak	Biochemistry and Molecular Neurosciences, Fahrstr. 17, 91054 Erlangen	A04
Vásquez Sepúlveda, Sebastián Ignacio	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	B02
Verma, Yashasvi	FAU-TechFak	Applied Mechanics, Egerlandstr. 5, 91058 Erlangen	X01
Wilm, Frauke	FAU-TechFak	Chair of Computer Science 5 (Pattern Recognition), Martensstraße 3, 91058 Erlangen	X02

6.1.2.6 Associated doctoral researchers

Table 15: Associated doctoral researchers

Associated doctoral Researchers (aDRs)	Faculty	Home institution, location	Project
Greiner, Alexander	FAU-TechFak	Institute of Continuum Mechanics and Biomechanics, Egerlandstr. 5, 91058 Erlangen	B01
Jordan, Jakob	Charité Berlin	Radiology, Charitéplatz 1, 10117 Berlin	X01

Öttl, Mathias	FAU-TechFak	Chair of Computer Science 5 (Pattern Recognition), Martensstraße 3, 91058 Erlangen	X02
Reiter, Nina	FAU-TechFak	Institute of Continuum Mechanics and Biomechanics, Egerlandstr. 5, 91058 Erlangen	B01
Welsch, Kathrin	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	A05

6.1.2.7 Associated master's students

Table 16: Associated master's students

Associated doctoral Researchers (aDRs)	Faculty	Home institution, location	Project
Butzke, Julia	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	A05
Gampl, Niklas	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	A05
Mai, Katharina	FAU-MedFak	Medical Physics, Henkestr. 91, 91052 Erlangen	B02

6.1.2.8 Student assistants

Table 17: Student assistants

Name	Supported researchers	Course / field of study	Funded member of EBM (from / to)	Tasks relating to EBM
Mayukh, Tikadar	Markus Lorke, X03	Nanotechnology	01.10.23 / 31.03.24	Help in determining the properties of hydrogels and synthesising precursors
Butzke, Julia	Kristian Franze, A05, B02	Physics	01.12.23 / 30.09.24	Help with identifying mechanotransduction pathways in neurons
Kashish Veda, Eluri	Soheil Firooz, C01	Computational Engineering	15.07.23 / 31.01.24	Investigation of thermal interfacial conditions at the cell-matrix interface
Feiler, Lea	Jan Hinrichsen, A01	Mechanical Engineering	01.05.23 / 30.06.23	Implementing neural network based surrogate models for the inverse parameter identification for human brain tissue.
Franke, Lorenz	Alexandra Schambony, Clara Froidevaux A03	Biology	1.04.23 / 31.12.23	Organoid Preparation, help with Xenopus Laevis handling and preparation of hydrogel substrates.
Gataulin, Radik	Kristian Franze, A05	Molecular Medicine	01.03.23 / 31.12.23	Help with PCR, Western blots and general wet lab duties
Gottipati, Taraswin	Jan Hinrichsen, Nina Reiter, A01	Computational Engineering	01.10.23 / 31.12.23	Automating the rheometer used for mechanical tests of brain tissue to improve the repeatability of results.
Hahn, Paula	Renato Frischknecht, C02	Biology	01.08.23 / 31.12.23	PCR and Cloning, Western blots, Immunohistochemistry
Hernandez Mora, Alejandro	Nina Reiter, A01	Mechatronic Engineering Sciences	01.05.23 / 31.07.23	Assistance in the analysis of specimens and data regarding the correlation between mechanics and microstructure in brain tissue
Karakuzulu, Basak Buse	Kristian Franze, A05, B02	Molecular Medicine	01.05.23 / 31.12.23	Help with PCR, Western blots and general wet lab duties

Name	Supported researchers	Course / field of study	Funded member of EBM (from / to)	Tasks relating to EBM
Kuhn, Arne	Alexandra Schambony, Clara Froidevaux A03	Biology	01.10. 23 / 31.12.23	Support in Xenopus Laevis handling and preparation of Organoids as well as Lab Data Management.
Lehner, Annika	Ingmar Blümcke, A02	Medicine	01.05.23 / 31.03.24	Technical lab support in studying perineuronal nets, sample selection and preparation (e.g. cutting of tissue slices)
Mai, Katharina	Kristian Franze, A05, B02	Medical Engineering	12.09.23 / 11.03.24	Help with the development of 3D gels
Modi, Sanskar	Oskar Neumann, Silvia Budday, A01, B01	Electromobility_ACES	01.09.23 / 30.11.23	Assistance in the experimental investigation of the mechanical properties of human spinal cord
Nasirli, Fatima	Kristian Franze, B02	Molecular Medicine	01.03.23 / 31.12.23	Help with PCR, Western blots and general wet lab duties
Rahnama Esfahani, Masoud	Soheil Firooz, C01	Computational Engineering	01.04.23 / 31.08.23 15.09.23 / 14.03.24	Developing a peridynamic code to explore non-local behavior of the brain
Rath, Alexander	Kai Willner, X01	Industrial Engineering and Management	01.03.23 / 31.05.23	Construction of the vibration table test stand
Roy, Sohini	Silvia Budday, A01, B01	Computer Science & Engineering	15.11.23 / 14.02.24	Sample preparation; Uniaxial tension tests; Material characterization; Modification of the experimental setup
Safaei, Behzad	Soheil Firooz, C01	Computational Engineering	01.09.23 / 29.02.24	Developing a peridynamic code to explore non-local behavior of the brain
Schaffer, Darius	Ben Fabry, C05	Medical Engineering	01.09.23 / 31.03.24	Setting up and programming a required microscope, as well as verifying and calibrating the planned measurement device
Seo, Minsu	Frauke Wilm, X02	Information and Communication Engineering	01.12.23 / 30.06.24	Assistance in the enhancement and maintenance of the EXACT annotation server
Settipalli, Sumanthreddy	Silvia Budday, A01, B01	Mechanical Engineering	15.11.23 / 14.02.24	Multimodal mechanical measurements using the rheometer
Shah, Rutvi	Jan Hinrichsen, Nina Reiter, A01	Computational Engineering	01.08.23 / 31.10.23 15.11.23 / 14.02.24	Establishing Docker containers to run deal.ii (C++ library for FE simulations) on local computers and especially on the FAU HPC cluster.
Surana, Harsh Vardhan	Oskar Neumann, B01	Computational Engineering	01.08.23 / 31.01.24	Assistance in the experimental investigation of the mechanical properties of human spinal cord

6.1.2.9 EBM Advisory Board

Table 18: EBM Advisory Board

Mercator fellows	Affiliation	Expertise
Franklin, Prof., Robin	Cambridge University, UK	CNS regeneration
Holzapfel, Prof., Gerhard	Institute of Biomechanics, Graz University of Technology, Austria	Mechanical testing and modeling of brain tissue mechanics
Kuhl, Prof., Ellen	Living Matter Lab, Stanford University, USA	Continuum modeling and simulation of the brain

Further board members		
Götz, Prof. Dr., Magdalena	Institute for Physiological Genomics, Ludwig-Maximilians-Universität München & Institute of Stem Cell Research, Helmholtz Zentrum, Munich, Germany	Neuroscience
Jayamohan, Dr., Jayaratnam (Jay)	Consultant Paediatric Neurosurgeon, John Radcliffe Hospital, and private practice at Nuffield Health Oxford, The Manor Hospital, Oxford, UK	Clinician
Schnell, Prof. Dr., Oliver	Neurosurgical Clinic, Chair of Neurosurgery, University Hospital Erlangen, Germany	Neurosurgery

6.1.3 COORDINATION AND ADMINISTRATION

Table 19: EBM Coordination and administration

	Work Address	Contact Data (Tel / Fax, Email, Web)	Work Area
Bittner, Doris	SFB 1540 EBM, Martensstraße 5a, 91058 Erlangen	+49 9131 85 20783 / -20785, doris.bittner@fau.de, www.ebm.fau.eu	EBM Administration
Dakkouri-Baldauf, Andrea, Dr. rer. nat.	SFB 1540 EBM, Martensstraße 5a, 91058 Erlangen	+49 9131 85-20782 / -20785, andrea.dakkouri@fau.de, www.ebm.fau.eu	EBM Coordination

6.2 NETWORK AND COOPERATION

Sophia Auer

Partner institute	Researchers involved	Research topic
Neuropathology	Ingmar Blümcke, Lucas Hoffmann, Annika Lehner.	Quantitative description of PNN in the human cortex.
Institute of Continuum Mechanics and Biomechanics	Silvia Budday, Nina Reiter, Anne-Mareike Schäfer	Modeling the finite viscoelasticity of human brain tissue based on microstructural information

Lars Bischof

Partner institute	Researchers involved	Research topic
Institute for Neuropathology, Univ. clinic Erlangen	Katja Kobow, Kristina Karandasheva	Neuronal growth in 2D and 3D matrices

Erica Cecchini

Partner institute	Researchers involved	Research topic
Institute of Continuum Mechanics and Biomechanics	Silvia Budday, Jan Hinrichsen, Nina Reiter	*In silico* modeling of brain malformations
Institut für Funktionelle und Klinische Anatomie	Friedrich Paulsen, Sophia Auer	Deep extracellular matrix (ECM) quantification and phenotyping in healthy human brain and cortical malformations, Electron microscopy
Epilepsiezentrum Neurochirurgie	Stefan Rampp	Human brain datasets and multimodal and multiparametric imaging

Ezgi Erterek

Partner institute	Researchers involved	Research topic
Institute of Biomaterials, FAU	Aldo Boccaccini, Markus Lorke, Sonja Kuth	Engineering brain tissue-like matrices
Max Planck Institute for the Science of Light, Erlangen	Jochen Guck, Stephanie Möllmert	Contribution of the ECM to the mechanical properties of cortical layers (m1-12)

Clara Froideaux

Partner institute	Researchers involved	Research topic
Institute of Biomaterials, FAU	Markus Lorke, Sonja Kuth, Aldo Boccaccini, Project X03	Hydrogels as substrates for explants
Max Planck Institute for the Science of Light, Erlangen	Stephanie Möllmert, Jana Bachir Salvador	AFM and Brillouin Microscopy measurements

Jan Hinrichsen

Partner institute	Researchers involved	Research topic
FAU, Institute of Continuum Mechanics and Biomechanics (Silvia Budday – A01/ B01)	Nina Reiter	Microstructure - Mechanics relation of human brain tissue
FAU, Institute of Functional and Clinical Anatomy (Friedrich Paulsen – A02, Lars Bräuer, Martin Schicht)	Sophia Auer (A02)	Mechanical characterization of human brain tissue from body donors. Correlation of tissue component concentration with mechanical properties.
Universitätsklinikum Erlangen-Neuropathologisches Institut (Ingmar Blümcke – A02)	Lucas Hoffmann (A02), Erica Cecchini (A02)	Mechanical characterization of human brain tissue from epilepsy surgery. Histological analysis of tested tissue. Investigating links between pathologies and mechanical behavior.
Universitätsklinikum Erlangen-Neurochirurgie (Arnd Dörfler – A02)	Stefan Rampp (A02)	MRT imaging of human brains prior to mechanical testing.
Biophysics Group, Department of Physics (Ben Fabry – C05)	David Böhringer	Mechanical characterization of collagen hydrogels.
ETH Zürich (Laura de Lorenzis)	Moritz Flaschel	Automated hyperelastic model discovery for human brain tissue (publication).
Institute of Medical Physics and Microtissue Engineering (Kristian Franze – B02/ A05)	Julia Becker, Alexander Winkel	Viscoelastic modeling of rat spinal cord AFM data.
FAU, Institute of Continuum Mechanics and Biomechanics (Silvia Budday – A01/ B01)	Alexander Greiner	Poroviscoelastic characterization of hydrogels.
FAU, Institute of Continuum Mechanics and Biomechanics (Silvia Budday – A01/B01)	Oskar Neumann (B01)	Mechanical characterization of human spinal cord tissue.
FAU, Institute of applied mechanics (Paul Steinmann – B01/C01)	Stephen Melly (B01)	Inverse parameter identification for AFM data.

Jakob Jordan

Partner institute	Researchers involved	Research topic
Charité Universitätsmedizin Berlin, Klinik für Pädiatrie m.S. Onkologie und Hämatologie	Anja Heeren Hagemann and group	MYCN and LM01 driven Neuroblastoma
Friedrich-Alexander Universität Erlangen-Nürnberg, Chair of Mathematics in Life Sciences	Vasily Zaburdaev and group	Bacillus Subtilis Biofilms
Charité Universitätsmedizin Berlin, Department of Neurosurgery with Pediatric Neurosurgery	Güliz Acker and group	Treatment of melanomas

Kristina Karandasheva

Partner institute	Researchers involved	Research topic
Institut für Physik der Kondensierten Materie	Ben Fabry, Lars Bischof	Quantification of neuronal network formation using time-lapse and traction-force microscopy
Max-Planck-Institut für die Physik des Lichts; Die Forschungsgruppe für Neuroregeneration	Daniel Wehner	ECM components in CNS scarring across species and tissues, specific role in regeneration and epileptogenicity
Max-Planck-Institut für die Physik des Lichts; Abteilung für biologische Optomechanik	Stephanie Möllmert, Jochen Guck	Investigation of seizure-like activity using confocal Brillouin microscopy
Department Biologie Lehrstuhl für Mathematik in den Lebenswissenschaften	Vasily Zaburdaev	*In silico* modelling of mechanical cell-matrix interactions
Neuropathologie	Ingmar Blümcke	Bioinformatic analysis for spatial transcriptomics
Institut für Biomaterialien; Departments Werkstoffwissenschaften	Aldo Boccaccini	Primary neuronal network formation in brain tissue-like matrices

Sonja Kuth

Partner institute	Researchers involved	Research topic
Chair of Animal Physiology, FAU	Renato Frischknecht	Neuroplasticity of primary rat neurons
Chair of Biochemistry and Molecular Medicine, FAU	Anja Bosserhoff, Shanice Heidenreich	Melanoma cells and melanocytes
Chair of Biochemistry and Molecular Neurosciences, FAU	Sven Falk, Marisa Karow, Michael Tranchina	Brain organoids
Institute for Neuropathology, Univ. clinic Erlangen	Katja Kobow, K. Karandasheva	Primary rat neurons in epilepsy
Department of Biology, FAU	Alexandra Schambony, Clara Froidevaux	Early brain development
Institute for Radiology and Pediatric Radiology, Charité, Berlin	Jing Guo, Pedro Augusto Dantas de Moraes	Magnetic resonance elastography

Markus Lorke

Partner institute	Researchers involved	Research topic
Chair of Animal Physiology, FAU	Renato Frischknecht, Bartomeu Perelló Amorós, Sonja Kuth	Primary rat neurons in contact to several hydrogel cultivation approaches
Chair of Biochemistry and Molecular Neurosciences, FAU	Michael Tranchina	Encasulating organoids in ydrogels
Chair of Biochemistry and Molecular Medicine, FAU	Anja Bosserhoff, Shanice Heidenreich	Cellular differentiation in brain tissue-like matrices

Charité Berlin	Jing Guo	Testing hydrogels in the MRE
Section of Developmental Biology, Department of Biology	Clara Froidevaux	Hydrogels as a growth platform for frog-organoids
Institute for Neuropathology, Univ. clinic Erlangen	Katja Kobow, Kristina Karandasheva	Influence of different hyaluronic acid-based hydrogels as a growth platform on primary neurons
Chair of Medical Physics	Kristian Franze	Development of a 3D hydrogel matrix for culture of Xenopus retinal ganglion cells

Oskar Neumann

Partner institute	Researchers involved	Research topic
Institute of Continuum Mechanics and Biomechanics, FAU	Jan Hinrichsen	Inverse identification of material parameters for human spinal cord tissue
Institute of Continuum Mechanics and Biomechanics, FAU	Nina Reiter	Multimodal mechanical testing on human and porcine spinal cord with the rheometer
Institute of Applied Mechanics, FAU	Laura Ruhland	Magnetic resonance elastography experiments on porcine spinal cord
Max Plank Institute for the Science of Light	Daniel Wehner	Scientific exchange on the mechano-biological aspects of spinal cord regeneration
Max Plank Institute for the Science of Light	Stephanie Möllmert	Scientific exchange on the mechano-biological aspects of spinal cord regeneration
Institute of Anatomy/Neuroanatomy, Uni Bonn	Maik Hintze	Scientific exchange on the experimental investigation and anatomy of spinal cord (staining, cutting and general questions)

Bartomeu Perelló Amorós

Partner institute	Researchers involved	Research topic
Institute of Biomaterials, FAU	Aldo Boccaccini, Markus Lorke, Sonja Kuth	Engineering brain tissue-like matrices

Nina Reiter

Partner institute	Researchers involved	Research topic
Institute of Functional and Clinical Anatomy	Friedrich Paulsen, Martin Schicht, Sophia Auer	Mechanical characterization and histological analysis of human brain tissue from body donors (connected to B01, A01, A02)
Neuropathology	Ingmar Blümcke, Lucas Hoffmann, Erica Cecchini	Mechanical characterization and histological analysis of human brain tissue samples from epilepsy surgery (connected to A01, A02)

Laura Ruhland

Partner institute	Researchers involved	Research topic
Institute of Biomaterials, FAU	Markus Lorke	Material testing of hydrogels

Yashasvi Verma

Partner institute	Researchers involved	Research topic
Charité, Berlin, Germany	Ingolf Sack, Jing Guo	MRE testing of brain samples and phantom materials
SISSA, Trieste, Italy	Luca Heltai	Computational-based embedding of vascular structure in brain model
B01-EBM	Nina Reiter	Compression-tension/Rheometer test on brain sample

Kathrin Welsch

Partner institute	Researchers involved	Research topic
Institute of Biochemistry FAU	Prof. Lie, Dr. Schäffner, Francesco Bambini	Adult neural stem cells and their interactions with their niche

Frauke Wilm

Partner institute	Researchers involved	Research topic
Technische Hochschule Ingolstadt	Prof. Dr. Marc Aubreville, Jonathan Ganz, Jonas Ammeling	Digital Pathology
Institute of Pathology, University of Veterinary Medicine, Vienna, Austria	Dr. Christof Bertram	Digital Pathology
Institute of Veterinary Pathology, Freie Universität Berlin, Germany	Prof. Dr. Robert Klopfleisch, Chloé Puget	Digital Pathology
Pathology Department, University Medical Centre Utrecht, The Netherlands	Nikolas Stathonikos	Digital Pathology

6.3 PARTICIPATION IN CONFERENCES AND CONGRESSES

6.3.1 CONFERENCES AND RESEARCH STAYS OF PRINCIPAL INVESTIGATORS

Table 20: Conferences and research stays of PIs

PI	Date	Conference	Title of own presentation / participation only
Blümcke, Ingmar	17.08.-23.08.23	Chinese Epilepsy Society Meeting and Summer School, Beijing and Chengdu, China	*Guiding principles in Neuropathology and Epilepsy Surgery FCD classification update 2022*
Blümcke, Ingmar	24.08. – 26.08.23	13th ILAE School for Neuropathology and Epilepsy Surgery Vienna, Austria	Organization and Leadership
Blümcke, Ingmar	12.09. – 16.09.23	20th International Congress of Neuropathology, Berlin, Germany	*Genotype-Phenotype Classification of cortical Dysplasia*
Blümcke, Ingmar	20.11. – 30.11.23	Cleveland Clinic Epilepsy Center, Ohio, USA, cooperation talks and lecture	*White matter terra incognita in cortical Dysplasia*
Bosserhoff, Anja	30.05. – 02.06.23	IPCC2023 (25th International Pigment Cell Conference), Bilbao, Spain	*Plasticity in melanoma*
Bosserhoff, Anja	06.09. – 08.09.23	ADO 2023, Hamburg, Germany	*Differenzierung und Aggressivität*
Bosserhoff, Anja	23.10 – 25.10.23	Hallmarks of Skin Cancer Conference, Heidelberg, Germany	*3D-modelling of melanoma by biofabrication to understand molecular processes in tumor dormancy*
Breininger, Katharina	10.02.23	Workshop Vienna, Austria	*A practical introduction to deep learning*

Breininger, Katharina	29.03. – 30.03.23	FAU – UCSF Workshop on AI Applications in Neurology, Oncological & Musculoskeletal Imaging, UCSF, San Francisco, USA	*Domain Generalization and Label-Efficient Learning in Digital Pathology and Beyond*
Breininger, Katharina	02.07. – 04.07.23	BVM Workshop 2023, Braunschweig, Germany	*Multi-Scanner Canine Cutaneous Squamous Cell Carcinoma Histopathology Dataset*
Breininger, Katharina	08.10. – 12.10.23	MICCAI 2023, Vancouver, Canada	*Adaptive Region Selection for Active Learning in Whole Slide Image Semantic Segmentation*
Breininger, Katharina	19.10. – 20.10.23	6th Conference on "Image-Guided Interventions" (IGIC), Mannheim, Germany	invited panel discussion: *AI use in medicine*
Budday, Silvia	13.02. – 14.02.23	Annual Meeting of the GAMM FA Computational Biomechanics 2023, Saarland, Germany	*On the importance of using region-dependent material parameters for full- scale human brain simulations*
Budday, Silvia	30.05. – 02.06.23	GAMM Annual Meeting, Dresden, Germany	*Multifield computational model predicts the interplay between cellular processes and geometrical instabilities in the developing human brain*
Budday, Silvia	09.07. – 12.07.23	ESBiomech 2023, Maastricht, The Netherlands	*Region-dependent material parameters for full-scale human brain simulations*
Budday, Silvia	30.08. – 01.09.23	Workshop BioPhysMed 2023, Berlin, Germany	*Biomechanical modeling of the human brain*
Budday, Silvia	18.11. – 26.11.23	Stanford, CA, USA	research stay
Falk, Sven	01.06. – 03.06.23;	Black Sea Neurogenesis Meeting; Varna, Bulgaria	*Molecular control of cellular identity acquisition*
Falk, Sven	19.06. – 22.06.23	EMBO workshop: X-chromosome inactivation: new insights on its 60th anniversary; Berlin; Germany	*X-chromosomal reactivation enhances female brain resilience*
Franze, Kristian	06.03. – 11.03.23	Spinal cord injury meeting, Houston, TX, USA	invited talk
Franze, Kristian	29.03. – 31.03.23	DPG Meeting, Dresden, Germany	*The physical regulation of brain development*
Franze, Kristian	11.05. – 12.05.23	Sorbonne Université, Paris, France	invited talk
Franze, Kristian	20.06. – 23.06.23	Mechanics of cells, tissues and embryos, Summer school, Lisbon, Portugal	invited talk
Franze, Kristian	04.07. – 10.07.23	Microscience Microscopy Congress 2023 (mmc2023) incorporating EMAG 2023, Manchester, UK	*Measuring and manipulating in vivo tissue mechanics using AFM*
Franze, Kristian	19.07.23	Scientific Symposium "Mechanical interaction of cells with their environment", Waischenfeld, Germany	invited talk
Franze, Kristian	13.10.23	Retreat of Clinical Scientist Program UKER, Waischenfeld, Germany	invited talk
Guck, Jochen	06.12. – 08.12.23	BioBrillouin, Trinity College, Dublin, Ireland	*Current applications of Brillouin microscopy – from sub-cellular mechanics to spinal cord repair*
Karow, Marisa	26.03. – 29.03.23	Co-Organizer COB Workshop Novel technologies for programming human cell fate; Eastwell Manor, UK	*Molecular control of cell identity acquisition*
Karow, Marisa	08.07. – 11.07.23	XVO European Meeting on Glial Cells in Health and Disease; Berlin, Germany	*Dissecting the molecular framework underlying pericyte-to-neuron conversion*
Karow, Marisa	04.09. – 05.09.23	Human Neurodevelopment Symposium; The Francis Crick Institute London, UK	*Dynamic X-chromosomal reactivation enhances female brain resilience*

Karow, Marisa	10.10. – 14.10.23	CSHL Meeting, USA,	*Querying the molecular determinants rendering iN reprogramming success or failure*
Kobow, Katja	20.06. – 24.06.23	EPNC 2023, Prague, Czech Republic	*The role of epigenetic mechanisms in the pathogenesis of drug-resistant epilepsy*
Kobow, Katja	28.08. – 01.09.23	WONOEP 2023, Kildare, Ireland	*Investigating the Role of the Extracellular Matrix in Epilepsy – Evidence from structural brain lesions and experimental models*
Kobow, Katja	02.09. – 06.09.23	IEC 2023, Dublin, Ireland	*Histopathological hallmarks and epigenetic background in MOGHE; Poster: Comparative analysis of brain and blood-derived DNA methylation signatures in MCD*
Kobow, Katja	04.10. – 06.10.23	Channelopathy meeting 2023, Tübingen, Germany	*Epigenetics for diagnosis and mechanistic understanding of drug-resistant focal structural epilepsies*
Kobow, Katja	16.11. – 18.11.23	GNP Jahrestagung, Dortmund, Germany	*Neocortical development and epilepsy: insights from focal cortical dysplasia and brain tumours*
Steinmann, Paul	27.10. – 05.11.23	The University of Queensland, Australia	research stay
Steinmann, Paul	05.12.23	Glasgow Computational Engineering Center (GCEC), Uni Glasgow, UK, Seminar Talk	*Modelling and Simulation of Bacterial Colony Formation: Challenges in Health and Computations*
Wehner, Daniel	09.07. – 14.07.23	Central Nervous System Injury and Repair Gordon Research Conference, Lucca, Italy	*Small leucine-rich proteoglycans inhibit CNS regeneration by modifying the structural and mechanical properties of the lesion environment*
Wehner, Daniel	03.09. – 06.09.23	ISRB Inaugural conference, Vienna, Austria	participation only

6.3.2 CONFERENCES OF (POST-)DOCTORAL RESEARCHERS

Jana Bachir Salvador

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
06.12.23 / 08.12.23	BioBrillouin	Trinity College, Dublin, Ireland	Talk: *Deciphering the determinants of nervous tissue mechanical properties in vivo*

Erica Cecchini

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
12.09.23 / 16.09.23	ICN2023	Berlin, Germany	Poster: *Mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE) with pathogenic SLC35A2 mutations reveals aberrant protein distribution and myelin loss*

Soheil Firooz

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
04.06.23 / 10.06.23	European Congress on Computational Methods in Applied Sciences and Engineering (ECCOMAS)	Oslo, Norway	Talk: *Computational continuum modeling of cell aggregation phenomenon.*

02.11.23 / 04.11.23	African Conference on Computational Mechanics (Africomp)	CapeTown, South Africa	Talk: *On continuum modeling of cell aggregation phenomenon.*
11.07.23 / 15.07.23	International Conference on The Evolving Nonlinear Continuum Panorama	Castro Urdiales, Spain	Talk: *Continuum-Kinematics-Inspired Peridynamics (CPD). A Novel Take on Nonlocal Continuum Modelling and Simulation.*

Jan Hinrichsen

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
10.09.23 / 13.09.23	GACM	Vienna, Austria	Talk: *Exploring the mechanical landscape of the human brain*

Jakob Jordan

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
06.07.23	ISMRM German Chapter	Berlin, Germany	Participation only
07.07.23	BIOQIC days	Berlin, Germany	Talk: *Optical time harmonic elastography (OTHE) - Versatile stiffness mapping from zebrafish larvae, to biofilms, to in-vivo human skin*

Sonja Kuth

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
04.08.23 / 08.08.23	ESB	Davos, Switzerland	Talk: *Designing a hydrogel for mimicking nervous tissue: development, optimization and application*

Olga Lyraki

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
02.09.23 / 06.09.23	Inaugural Meeting of the International Society for Regenerative Biology	Vienna, Austria	Participation only

Nina Reiter

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
03.05.23 / 05.05.23	CMBBE	Paris, France	Talk: *Mechanical characterization of human and porcine brain tissue and human brain organoids*
30.05.23 / 02.06.23	GAMM Annual Meeting	Dresden, Germany	Talk: *Modeling the finite viscoelasticity of brain tissue based on microstructural information*
09.10.23 / 11.10.23	GAMM Juniors Fall Meeting	Zurich, Switzerland	Talk: *Human Brain Mechanics in Health and Disease*

Sebastián Vásquez-Sepúlveda

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
08.06.23	Franze/Paluch Lab Symposium	Cambridge, UK	Talk: *Characterizing Brain mechanics during development and neurodevelopmental malformations*

Jana Sipkova

From / to	Name of conference	Location	Title of own presentation / title of own poster presentation / participation only
08.06.2023	Franze/Paluch Lab symposium	Cambridge, UK	Talk: *Mechanical regulation of Eph/ephrin signalling in the developing brain*
28.06.23 / 29.06.23	Invited talk - Laboratoire de Biologie du Developpement seminar series	Villefranche-sur-Mer, France	Talk: *Mechanical regulation of Eph/ephrin signalling in the developing brain*
20.07.23 / 23.07.23	Society for Developmental Biology 82nd Annual Meeting	Chicago, IL, USA	Talk: *Mechanical regulation of Eph/ephrin signalling in the developing brain*
11.09.23	Cambridge Morphogenesis Symposium	Cambridge, UK	Poster: *Mechanical regulation of Eph/ephrin signalling in the developing brain*
09.10.23 / 12.10.23	Invited talk – Stowers Institute for Medical Research	Kansas City, MO, USA	Talk: *Mechanical regulation of Eph/ephrin signalling in the developing brain*

6.4 SUMMER SCHOOLS / AUTUMN SCHOOLS

Soheil Firooz

From / to	Name of school	Location
23.10.23 / 26.10.23	CISM Advanced Course on Peridynamic Models for Material Degradation: from Fracture/Fragmentation to Corrosion; from Models to Computer Codes	International Centre for Mechanical Sciences (CISM), Udine, Italy.
16.10.23 / 20.10.23	CISM Advanced Course on Virtual Elements for Problems in Mechanics	International Centre for Mechanical Sciences (CISM), Udine, Italy.

Oskar Neumann

From / to	Name of school	Location
11.09.23 / 15.09.23	Biomechanics of soft tissues: From the heart to the cardiovascular system to the brain	TU Graz, Austria

Yashasvi Verma

From / to	Name of school	Location
11.09.23 / 15.09.23	Biomechanics of Soft Tissues: From the Heart to the Cardiovascular System to the Brain	TU Graz, Austria

7 APPENDICES

7.1 APPENDIX 1: PROGRAM OF THE 1ST EBM RETREAT

Program of the
1st EBM Retreat
September 21 – 22, 2023
Hotel Arvena Reichsstadt, Bad Windsheim

21 September 2023			
Time	**Project**	**Title**	**Lecturer**
9:30 – 9:50	WELCOME and INTRODUCTION by Silvia Budday and Paul Steinmann		
9:50 – 10:00	C01	*In silico* modelling of mechanical cell-matrix interactions	Soheil Firooz, Vasily Zaburdaev
10:00 – 10:15			*Discussion*
10:15 – 10:30	C02	The role of mechanics for neuronal 'plasticity'	Bartomeu Perelló Amorós
10:30 - 10:45	C03	The role of mechanics in synchronized neuronal activity	Kristina Karandasheva
10:45 – 11:00	C04	Cellular differentiation in brain tissue-like matrices	Shanice Heidenreich
11:00 – 12:00	IMPULSE DISCUSSION with a cup of coffee		
12:00 – 12:15	C05	Molecular mechanisms of neuronal mechanotransduction	Lars Bischof
12:15 – 12:30	X01	Model-based reconciliation of *ex vivo* and *in vivo* test data	Laura Ruhland Yashasvi Verma Jakob Jordan
12:30 – 12:45			*Discussion*
12:50 – 14:10	LUNCH BREAK		

21 September 2023			
Time	**Project**	**Title**	**Lecturer**
14:15 – 14:30	X02	Data analysis and machine learning for heterogeneous, cross-species data	Mathias Öttl
14:30 – 14:45	X03	Engineering brain tissue-like matrices	Markus Lorke
14:45 – 15:00	Y	Establishing magnetic resonance elastography at FAU	Frederik B. Laun
15:00 – 16:00	#NdW23 BRAINSTORMING || EBM EXECUTIVE BOARD MEETING with a cup of coffee		
16:00 – 18:00	WALK to the “Fränkisches Freilandmuseum” Bad Windsheim		
18:30 – 20:00	DINNER		
from 20:00	Joint evening with inspiring conversations		

22 September 2023			
Time	**Project**	**Title**	**Lecturer**
8:00 – 9:10	BREAKFAST		
9:15 – 10:15	EBM Members Plenary Meeting		
10:15 – 10:30	A01	*In silico* modeling of brain malformations	Jan Hinrichsen
10:30 – 10:45	A02	Quantitative characterization of brain malformations	Erica Cecchini Sophia Auer Stefan Rampp
10:45 – 11:00			*Discussion*
11:00 – 12:00	IMPULSE DISCUSSION with a cup of coffee		
12:00 – 12:15	A03	*In vitro* model for the mechanics of early brain development	Clara Froidevaux

22 September 2023			
Time	**Project**	**Title**	**Lecturer**
12:15 – 12:30	A04	The role of mechanics in orchestrating neural lineage decisions	Michael Tranchina
12:30 – 12:45	A05	*In vivo* model for the mechanics of brain development	Sebastián Ignacio Vásquez Sepúlveda
12:50 – 14:00	LUNCH BREAK		
14:05 - 14:15	B01	*In silico* modeling of spinal cord regeneration	Oskar Neumann Stephen Melly
14:15 – 14:30			*Discussion*
14:30 – 14:45	B02	Pre and post metamorphosis spinal cord regeneration in frogs	Maria Tarczewska
14:45 – 15:00	B03	The determinants of spinal cord mechanics in homeostasis	Jana Bachir Salvador
15:00 – 16:00	IMPULSE DISCUSSION with a cup of coffee		
16:00 – 16:15	B04	Spinal cord mechanics in a mouse model of multiple sclerosis	Maik Hintze
16:15 – 16:30	B05	*In vivo* mechanical manipulation of spinal cord regeneration	Daniel Wehner
16:30 – 17:00	CLOSURE AND OUTLOOK		
17:00	**Departure**		

Each EBM (post)doctoral researcher gives a **5-minute presentation**.
This is followed by a 10-minute discussion if there is only one presenter per project.
If there are two or more presenters per project, a total of 15 minutes is allotted for discussion.

7.2 APPENDIX 2: PROGRAM OF THE KICK-OFF MEETING

Program of the
EBM Kick-Off Meeting
March 17, 2023
Hans-Georg-Waeber-Saal, Schottkystraße 10, Erlangen

	Project	Title	Project leader(s)
9:00 - 9:40	WELCOME and INTRODUCTION by Silvia Budday and Paul Steinmann		
9:40 - 10:00	**iRTG**	Integrated Research Training Group on EBM	Friedrich Paulsen
10:00 - 10:20	COFFEE BREAK with discussion at posters		
10:20 - 10:30	**B01**	*In silico* modelling of spinal cord regeneration	Paul Steinmann, Silvia Budday
10:30 - 10:40	**B02**	Pre and post metamorphosis spinal cord regeneration in frogs	Kristian Franze
10:40 - 10:50	**B03**	The determinants of spinal cord mechanics in homeostasis	Jochen Guck, Stephanie Möllmert
10:50 - 11:00	**B04**	Spinal cord mechanics in a mouse model of multiple sclerosis	Stefanie Kürten
11:00 - 11:10	**B05**	*In vivo* mechanical manipulation of spinal cord regeneration	Daniel Wehner
11:10 - 11:30	COFFEE BREAK with discussion at posters		
11:30 - 11:40	**C01**	*In silico* modelling of mechanical cell-matrix interactions	Vasily Zaburdaev, Paul Steinmann
11:40 - 11:50	**C02**	The role of mechanics for neuronal ‘plasticity‘	Renato Frischknecht
11:50 - 12:00	**C03**	The role of mechanics in synchronised neuronal activity	Katja Kobow
12:00 - 12:10	**C04**	Cellular differentiation in brain tissue-like matrices	Anja Bosserhoff
12:10 - 12:20	**C05**	Molecular mechanisms of neuronal mechanotransduction	Ben Fabry
12:20 - 13:00	LUNCH BREAK with discussion at posters		

	Project	Title	Project leader(s)
13:00 - 13:10	X01	Model-based reconciliation of *ex vivo* and *in vivo* test data	Jing Guo, Ingolf Sack, Paul Steinmann, Kai Willner
13:10 - 13:20	X02	Data analysis and machine learning for heterogeneous, cross-species data	Andreas Maier, Katharina Breininger
13:20 - 13:30	X03	Engineering brain tissue-like matrices	Aldo R. Boccaccini
13:30 - 13:40	Y	Establishing magnetic resonance elastography at FAU	Arnd Dörfler, Frederik B. Laun, Jing Guo, Ingolf Sack
13:40 - 14:00	COFFEE BREAK with discussion at posters		
14:00 - 14:10	A01	*In silico* modelling of brain malformations	Silvia Budday
14:10 - 14:20	A02	Quantitative characterisation of brain malformations	Ingmar Blümcke, Arnd Dörfler, Friedrich Paulsen
14:20 - 14:30	A03	*In vitro* model for the mechanics of early brain development	Alexandra Schambony
14:30 - 14:40	A04	The role of mechanics in orchestrating neural lineage decisions	Marisa Karow, Sven Falk
14:40 - 14:50	A05	*In vivo* model for the mechanics of brain development	Kristian Franze
14:50 - 15:30	OPEN DISCUSSION moderated by Silvia Budday and Paul Steinmann		
15:30 - 16:00	ELECTION of the (POST-)DOCTORAL RESEARCHERS' REPRESENTATIVE (all PDRs and DRs)		
15:30 - 17:00	EXECUTIVE BOARD MEETING (Paul Steinmann, Silvia Budday, Andrea Dakkouri-Baldauf, Kristian Franze, Jochen Guck, Ben Fabry, Jing Guo / Ingolf Sack, Friedrich Paulsen, Katharina Breininger, Marisa Karow, DRs' representative, N.N.)		
18:00	JOINT DINNER (Location tba)		

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