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ARTORG CENTER
BIOMEDICAL ENGINEERING RESEARCH

ARTORG CENTER
ANNUAL REPORT 2023

Foreword

Dear friends, colleagues, collaborators, and partners

2023 fills me with pride as our Center of Excellence for Biomedical Engineering Research is celebrating 15 years of existence!

In this decade and a half, we have achieved impressive educational, scientific, and translational successes. We have introduced 561 Master students to biomedical research methods and each of them has worked on a clinical implementation project with the conclusion of their studies. We have had the pleasure to accompany 143 talented and highly motivated PhD students during their first steps into independent research and have been stepping stone for countless postdoctoral students on their way into academic and industry careers.

Our research has impacted patient care through 30 patents filed and another 30 license agreements for our technology to enter healthcare. We had seen 7 start-ups spin out of our specialized research groups and created more than 140 jobs. Our inspirational and interdisciplinary research with innovative and ground-breaking approaches have made us the only Swiss center to have claimed three MedTech Awards.

At the brink of the new year, we are welcoming our new professor for Robotics and Micromechatronics, Manuela Eugster, who will establish her research group over the coming months. We are consolidating our successes in computational methods and artificial
intelligence, biomechanics, sensor technology, surgical instruments and biomicrofabrication, and look forward to many more success stories.

I hope you will enjoy delving into a selection of our projects on the following pages.

Sincerely,

Raphael Sznitman
ARTORG Director

Groups

↓
AIHN
Artificial Intelligence in Health Nutrition

↓
AIMI
Artificial Intelligence in Medical Imaging

↓
CVE
Cardiovascular Engineering

↓
CB
Computational Bioengineering

↓
GER
Gerontechnology and Rehabilitation

↓
HRL
Hearing Research Laboratory

↓
IGT
Image-Guided Therapy

↓
MIA
Medical Image Analysis

↓
MSB
Musculoskeletal Biomechanics

↓
OOC
Organs-on-Chip Technologies

↓
UGE
Urogenital Engineering

↓
MDP
Mechanical Design and Production

Master of Science
Artificial Intelligence in Medicine

Master of Science
Biomedical Engineering

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Research Profile

The Artificial Intelligence in Health and Nutrition (AIHN) laboratory focuses primarily on the interface between machine learning, artificial intelligence (AI), and their applications for improving health. The laboratory develops innovation to translate "data into knowledge" and "research into clinical practice." Our ongoing research activities include AI-powered innovative systems for:

- dietary monitoring, assessment, and management
- diabetes management and treatment optimisation
- diagnosis, prognosis, and management of acute and chronic lung diseases

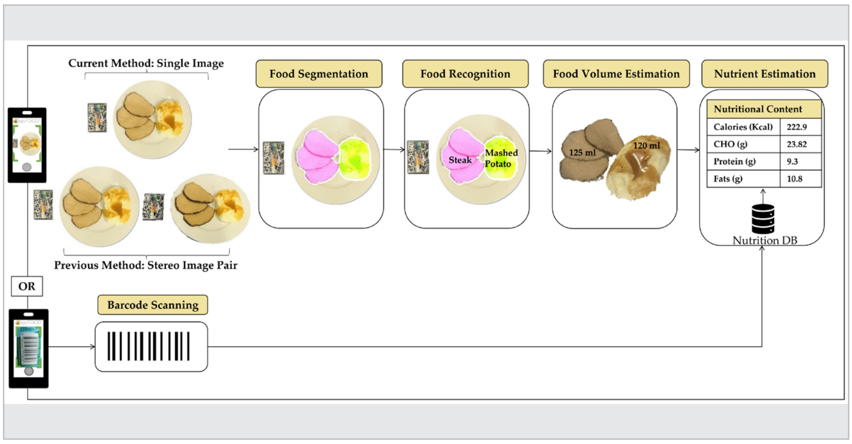

Fig. 1: The goFOOD™ system pipeline: The previous version of our system required two images from different angles as input, while the new one requires only a single image.

Nutrient intake monitoring and diet assessment

A healthy diet plays a pivotal role in preventing and managing diverse diseases and conditions like diabetes, obesity, and certain types of cancer. To maintain a healthy diet, the monitoring of dietary intake is essential. While conventional approaches to dietary assessment, such as food frequency questionnaires and 24-hour recalls, are extensively employed, they are time-consuming, costly, and error-prone. With the recent advances in AI and mobile technologies, and widespread adoption of mHealth, automatic dietary assessment is rapidly gaining momentum. Typically conducted through multimedia analysis based on food images or videos, sound, speech, and text, automatic dietary assessment is characterized by heightened user-friendliness and enhanced accuracy opposed to traditional methods.

For 15 years now, the AIHN laboratory has been striving towards the development, refinement, and democratization of AI-based technologies for performing automatic dietary assessment. Our first prototype, GoCARB, designed to support people with type 1 diabetes in their everyday life, was employed to automatically estimate the carbohydrate content of a meal from two images. Since then, a plethora of improvements have taken place. The new system, now rebranded as goFOOD™, not only continues to estimate the carbohydrates of a meal but has expanded its →

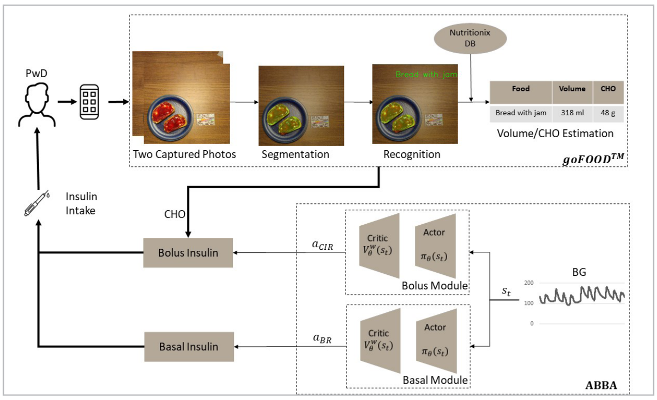

Fig. 2: The AI-based algorithm, integrated into a highly secured Android smartphone, takes input from either a blood glucose meter or continuous glucose monitors, and outputs the daily insulin treatment. The algorithm learns while being used by the patient and is able to provide personalised advice on the insulin treatment.

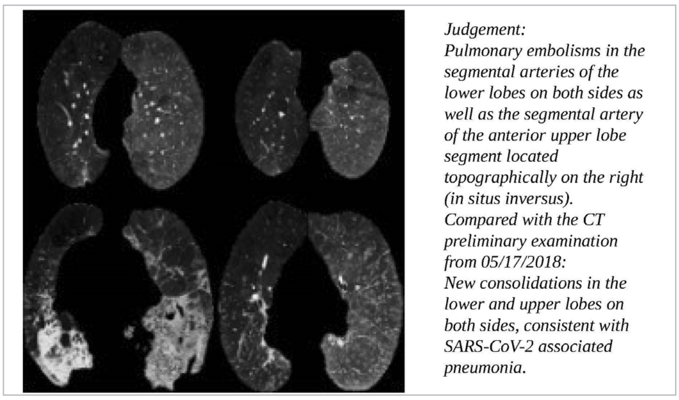

Fig. 3: Slices taken from a CT image during the pandemic with its respective report. The intricate lung details from the report are mapped to the corresponding pixels in the image.

functionalities to encompass the evaluation of energy, protein, and fat content.

The enhanced system exhibits advancements across multiple facets, including enhanced accuracy, user-friendliness, and reduced processing time. Comprehensive improvements have been implemented throughout the entire pipeline, commencing with food segmentation and the recognition of food items. This process carefully integrates user manual input within the framework of explainable and interpretable AI. Various methodologies were explored in the context of food volume estimation, ranging from traditional geometric approaches using two images to leveraging depth sensor data and employing convolutional neural networks based on a single image. This exploration aims not only to enhance accuracy but also to potentially alleviate user workload comparable accuracy.

Diabetes management and personalisation of insulin treatment

Treating type 1 diabetes and some cases of type 2 diabetes requires the infusion of exogenous insulin. Insulin, as a medicine, has side effects - mainly related to improper dosing, which may lead to sudden life-threatening events from severe hypoglycaemia or cause long-term complications from hyperglycaemia.

An innovative algorithm has been developed by the engineers of the AIHN laboratory and allows daily adjustment of the insulin treatment based on fluctuations in the patient's glucose and lifestyle-related information. Specifically, data from glucose monitoring devices (self-monitoring of blood glucose or continuous glucose monitors) and lifestyle (food intake) trackers provide input to the algorithm, which outputs basal daily insulin and boluses for the case of pump or insulin pen users. The newest version of the algorithm is under evaluation in the in-silico clinical trial for three months, under extreme scenarios of disturbances, uncertainties, and variabilities. After the in silico clinical trials, a feasibility study and a multicenter clinical trial involving 450 people with diabetes under insulin treatment will start within the next year.

AI and lung diseases

Interstitial Lung Diseases (ILD) are a heterogeneous group of more than 200 chronic, overlapping lung disorders, characterised by fibrosis and/or inflammation of lung tissue. The diagnosis of a suspected ILD is based on high-resolution computed tomography (HRCT) images and often presents a diagnostic dilemma. By achieving a reliable diagnosis on HRCT images, patients could avoid potential complications, as well as the high costs associated with a surgical biopsy. To this end, we investigate AI- and computer vision-based algorithms for the analysis of imaging, clinical/biochemical, other disease-related data, along with reports for diagnosis and management of ILDs. More specifically, algorithmic approaches for the fully automatic segmentation of lung and anatomical structures of the lung cavity, the segmentation and characterization of lung pathological tissue, and the calculation of disease distributions are introduced and continuously validated within the framework of research trials. The image analysis results along with the additional disease-related information are further analysed not only in order to support the faster diagnosis, but also for the more efficient disease management in the sense of treatment selections and disease progression.

COVID-19 and ILDs share similarities. Over the last years, we extended our research activities in the field of COVID-19 pneumonia detection, severity assessment (acute COVID-19), and prognosis (including long COVID-19). Utilizing modern AI techniques, we perform self-supervised AI techniques to map CT images to their respective radiological reports. These results allowed us to classify intricate lung details.

Selected Publications

1. Papathanail, I., Abdur Rahman, L., Brigato, L., Bez, N. S., Vasiloglou, M. F., van der Horst, K., & Mougiakakou, S. (2023). The Nutritional Content of Meal Images in Free-Living Conditions—Automatic Assessment with goFOODTM. Nutrients, 15(17), 3835. https://doi.org/10.3390/nu15173835
2. Dack, E., Christe, A., Fontanellaz, M., Brigato, L., Heverhagen, J. T., Peters, A. A., ... & Ebner, L. (2023). Artificial Intelligence and Interstitial Lung Disease: Diagnosis and Prognosis. Investigative radiology, 10-1097. 10.1097/RLI.0000000000000974
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4. Abdur Rahman, L., Papathanail, I., Brigato, L., & Mougiakakou, S. (2023). A Comparative Analysis of Sensor-, Geometry-, and Neural-Based Methods for Food Volume Estimation. In Proceedings of the 8th International Workshop on Multimedia Assisted Dietary Management. https://doi.org/10.1145/3607828.3617794
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Artificial Intelligence in Medical Imaging

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Research Profile

The Artifical Intelligence in Medical Imaging (AIMI) lab is focused on designing novel machine learning and computer vision methods to solve unmet clinical needs. With a strong focus on methodology that spans basic to translational research, the emphasis is on engineering solutions in a holistic fashion, whereby taking into account how new approaches can be integrated in routine clinical care. As an interdisciplinary research team, the AIMI lab is involved in several research projects encompassing research challenges in both diagnostic and interventional contexts.

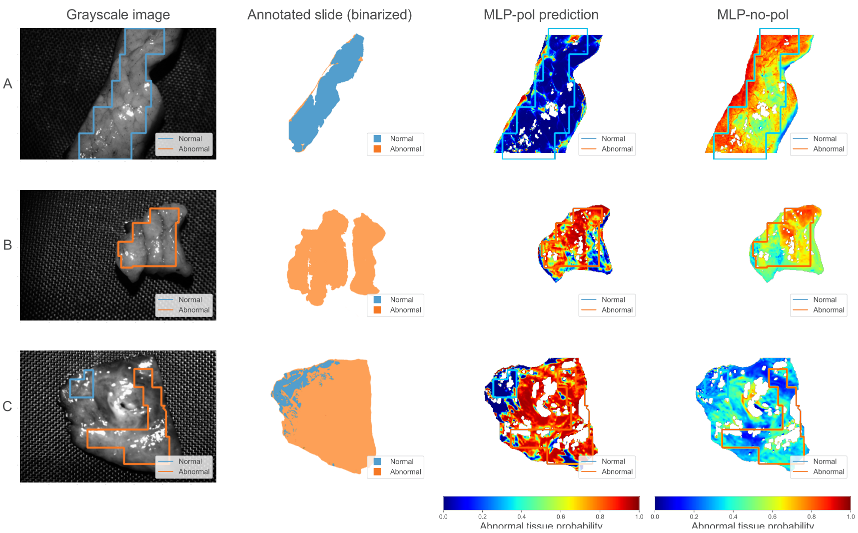

Fig. 1. Predictions results for three test samples: (A) entirely normal, (B) entirely abnormal, and (C) with both regions. The probability maps generated by MLP-pol correctly predicted the different tissue types with high confidence, including the two regions within the same sample. Predictions outside the annotated region matched the annotated slide. In contrast, the predictions of MLP-no-pol for samples A and B yielded scores with very low differentiation. On sample C, although it identified differences within the sample, it lacked the confidence presented by MLP-pol.

Müller matrix polarimetry for pancreatic tissue characterization

Polarimetry is an optical characterization technique capable of analyzing the polarization state of light reflected by materials and biological samples. In this study, we investigate the potential of Müller matrix polarimetry (MMP) to analyze fresh pancreatic tissue samples. Due to its highly heterogeneous appearance, pancreatic tissue type differentiation is complex. Furthermore, its challenging location in the body makes creating direct imaging difficult. However, accurate and reliable methods for diagnosing pancreatic diseases are critical for improving patient outcomes. To this end, we measured the Müller matrices of ex-vivo unfixed human pancreatic tissue and leveraged the feature-learning capabilities of a machine-learning model to derive an optimized data representation that minimizes normal-abnormal classification error. We show experimentally that our approach accurately differentiates between normal and abnormal pancreatic tissue. To our knowledge, this is the first study to use ex-vivo unfixed human pancreatic tissue combined with feature-learning from raw Müller matrix readings for this purpose (Fig. 1).

Logical implications for visual question answering consistency

Despite considerable recent progress in Visual Question Answering (VQA) models, inconsistent or contradictory answers →

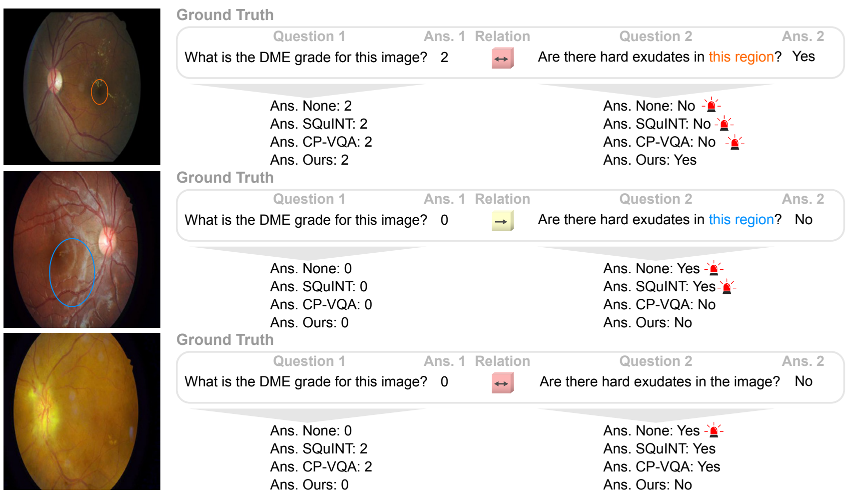

Fig. 2: Examples from the DME dataset and comparison of methods depend on the number of visual pathological features of the retina. Top and middle: Although all methods correctly predict the answer to the first question, some inconsistencies appear when a necessary condition is false. Bottom: Only the None baseline produces an inconsistency. Note that SQuINT and CP-VQA's answers do not produce inconsistent pairs because both questions were answered incorrectly, and those answers (``2" and ``yes") respect all known relations.

continue to doubt their true reasoning capabilities. However, most proposed methods use indirect strategies or strong assumptions on pairs of questions and answers to enforce model consistency. Instead, we propose a novel strategy to improve model performance by directly reducing logical inconsistencies. To do this, we introduce a new consistency loss term that can be used by a wide range of the VQA models and relies on knowing the logical relation between pairs of questions and answers. While such information is typically unavailable in VQA datasets, we propose inferring these logical relations using a dedicated language model and using these in our proposed consistency loss function.

Stochastic segmentation with conditional categorical diffusion models

Semantic segmentation has made significant progress in recent years thanks to deep neural networks, but the common objective of generating a single segmentation output that accurately matches the image's content may not be suitable for safety-critical domains such as medical diagnostics and autonomous driving. Instead, multiple possible correct segmentation maps may be required to reflect the true distribution of annotation maps. In this context, stochastic semantic segmentation methods must learn to predict conditional distributions of labels given the image, but this is challenging due to the typically multimodal distributions, high-dimensional output spaces, and limited annotation data. We propose a conditional categorical diffusion model (for semantic segmentation based on Denoising Diffusion Probabilistic Models to address these challenges. Our model is conditioned to the input image, enabling it to generate multiple segmentation label maps that account for the aleatoric uncertainty arising from divergent ground truth annotations. Our experimental results show that CCDM achieves state-of-the-art performance on LIDC, a stochastic semantic segmentation dataset, and outperforms established baselines on the classical segmentation dataset Cityscapes.

Unsupervised out-of-distribution detection for safer robotically guided retinal microsurgery

A fundamental problem in designing safe machine learning systems is identifying when samples presented to a deployed model differ from those observed at training time. Detecting so-called out-of-distribution (OoD) samples is crucial in safety-critical applications such as robotically guided retinal microsurgery, where distances between the instrument and the retina are derived from sequences of 1D images that are acquired by an instrument-integrated optical coherence tomography (iiOCT) probe. This work investigates the feasibility of using an OoD detector to identify when images from the iiOCT probe are inappropriate for subsequent machine learning-based distance estimation. We show how a simple OoD detector based on the Mahalanobis distance can successfully reject corrupted samples coming from real-world ex vivo porcine eyes. Our results demonstrate that the proposed approach can detect OoD samples and help maintain the performance of the downstream task within reasonable levels. MahaAD outperformed a supervised approach trained on the same kind of corruption and achieved the best performance in detecting OoD cases from a collection of iiOCT samples with real-world corruptions. The results indicate that detecting corrupted iiOCT data through OoD detection is feasible and does not need prior knowledge of possible corruptions.

Selected Publications

1. Sampaio P., Antuna M., Storni, F., Wicht, J., Sokeland, G., Wartenberg, M., Marquez Neila, P., Candinas, D., Demory, B-O, Perren, A., and Sznitman, R. "Muller matrix polarimetry for pancreatic tissue characterization", Nature Scientific Reports,2023
2. Tascon Morales, S., Marquez Neila, P. and Sznitman, R., "Logical Implications for Visual Question Answering Consistency". IEEE / CVF Computer Vision and Pattern Recognition (CVPR), 2023.
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4. Jungo, A., Doorenbos, L., Da Col, T., Beelen, M., Zinkernagel, M., Marquez-Neila, P., Sznitman, R. "Unsupervised out-of-distribution detection for safer robotically-guided retinal microsurgery", International Journal of Computer Assisted Radiology and Surgery - Special Issue: IPCAI, 2023

Cardiovascular Engineering

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Research Profile

The Cardiovascular Engineering (CVE) group studies biomedical flow systems to develop diagnostic and therapeutic technology for cardiovascular diseases. Our research aims to improve the durability and biocompatibility of therapeutic devices and implants and to develop novel diagnostic tools. These translational research projects address unmet clinical needs that were identified with our clinical partners who are closely integrated in the research teams from start to finish.

CVE operates a modern cardiovascular flow lab with state-of-the-art measurement technology to simulate physiological conditions in the heart and to measure hemodynamic parameters. This includes high-speed cameras and laser-based methods for flow quantification. Next to the experimental facilities, CVE develops and uses custom-tailored computer models of cardiovascular flows, including fluid-structure interaction and turbulent blood flow. Large-scale flow simulations are enabled by using high-performance computing infrastructure at the Swiss Supercomputing Center CSCS.

Fig. 1: Testing of heart valves in the Cardiovascular Flow Lab.

Heart valve replacement

Numerous designs of heart valve prostheses have been in use for more than half a century. Insufficient durability and biocompatibility of heart valve prostheses are limiting factors for the clinical use of these devices. In an ageing society where patients expect to be able to continue their active lifestyle after heart valve replacement, these limiting factors represent an unmet clinical need.

A detailed understanding of hemodynamic mechanisms governing valve tissue deterioration and blood trauma paves the way for the design of more durable and biocompatible devices. To this end, we have developed a sophisticated experimental and computational infrastructure for the study of heart valves. This includes mock loops replicating pulsating blood flow, compliant silicone phantoms of large blood vessels, and modern measurement technology for quantifying complex three-dimensional blood flow fields (Fig. 1). Our experimental approach is complemented by computational flow solvers for turbulent flow, which are coupled with finite-element models for soft tissue via the immersed boundary method. These models are optimized for high-performance computing platforms to provide unparalleled insight into the generation of turbulent blood flow past aortic valves. In recent studies, we established a direct connection between turbulent blood flow and valve calcification, and we investigated which valve designs are more prone to lead to blood clots. This information is used to design heart valve prostheses with higher durability and lower thrombogenicity. →

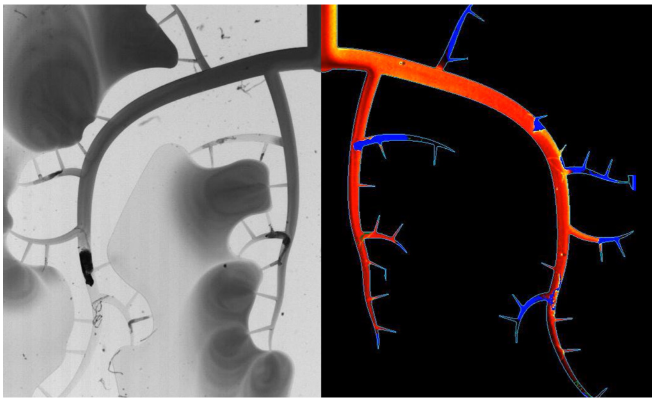

Fig. 2: Drug transport in a microfluidic model of the cardiac microcirculation with microthrombi.

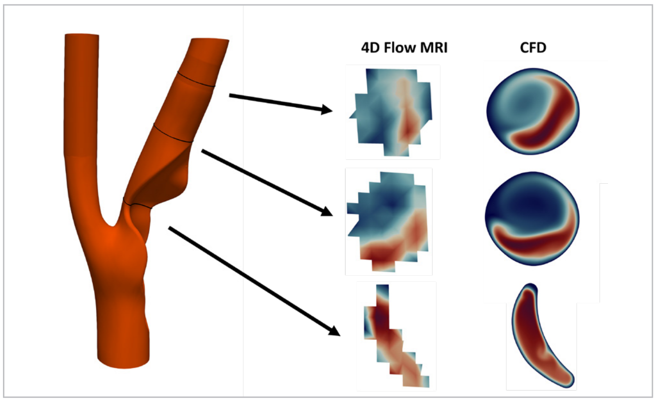

Fig. 3: Comparison of flow patterns in a carotid bifurcation measured with 4D-Flow-MRI and predicted by CFD.

→ Myocardial infarction

In myocardial infarction (heart attack), the supply of the heart muscle with oxygen and nutrients is blocked by an obstruction of a coronary artery. Even after recanalization of this artery, secondary obstructions in the cardiac microcirculation (Microvascular Obstruction, MVO) may lead to local underperfusion of the heat muscle and worsen the long-term patient outcome. MVO is an underdiagnosed condition because it cannot be detected during acute treatment in the catheter lab. Moreover, there exists no established treatment for MVO.

CVE addresses this unmet clinical need together with a larger academic consortium and a med-tech start-up. A multi-scale benchtop model of the coronary circulation allows us to study the pathophysiology of MVO and to develop novel diagnostic and therapeutic methods for MVO. This model comprises a microfluidic chip-mimicking vessels of the cardiac microcirculation (Fig. 2). It is used to study transport of drugs in the myocardium and to optimize infusion protocols for catheter-based treatment of MVO.

Microvascular blood flow regulation

Oxygen and nutrient exchange between blood and surrounding tissue takes place in the capillary networks of the microcirculation. They comprise capillaries as small as 5 micrometers, such that red blood cells must squeeze through these vessels. In contrast to blood flow in larger blood vessels, capillary blood flow follows different physical laws and the mechanics of red blood cells plays a dominant role. We study blood flow in complex capillary networks as they may be found, for instance, in the brain, and investigate how the network topology affects the distribution of red blood cells in the network and how the system reacts to local vasodilation and to obstructions (e.g., micro-strokes).

Computer-augmented 4D-Flow-MRI

4D-Flow-MRI is a method for non-invasive and non-ionizing measurement of blood flow patterns in large blood vessels. It has great potential to be used for the diagnosis of cardiovascular diseases such as carotid stenosis. However, the lack of sufficient spatial resolution limits the applicability of this imaging modality in the clinic and it is known that luminal wall-shear stress (an important factor in atherosclerotic plaque progression) is underpredicted by 4D-Flow-MRI. We seek to combine data from 4D-Flow-MRI with advanced computational models to enhance the predictive quality of these measurements (Fig. 3). This includes classical CFD models which are used to regularize the measured flow fields and statistical machine learning models which are trained with CFD data to yield very fast and accurate predictions of luminal wall-shear stress patterns that can be used in clinical practice.

Dielectric elastomer augmented aorta

Together with the Center for Artificial Muscles from EPFL, we are working on a novel cardiac assist device in a project supported by the Werner-Siemens Stiftung. In contrast to classical ventricular assist devices (VADs) that use rotary blood pumps, the Dielectric Elastomer Augmented Aorta (DEAA) directly compresses and dilates a section of the aorta to support the function of the heart by reducing the afterload. We are using an in vitro benchtop model with a circulatory mock loop and in vivo trials to optimize the design and actuation pattern of the device.

Selected Publications

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Computational Bioengineering

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Osman Berk Şatır
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Research Profile

The Computational Bioengineering group tackles challenges in medical research with modern computer simulation tools. We focus not on the computational methods themselves, but on their appropriate application to address practical and fundamental clinical questions. Numerical methods are combined with experimental and clinical research to create personalized biomechanical models.

Together with our collaborators, we form a strong team covering a wide range of research topics. In addition to our core expertise in applying finite element analysis to study skeletal biomechanics, we seek to improve surgical planning by developing numerical models of soft tissues, such as the cornea or arteries.

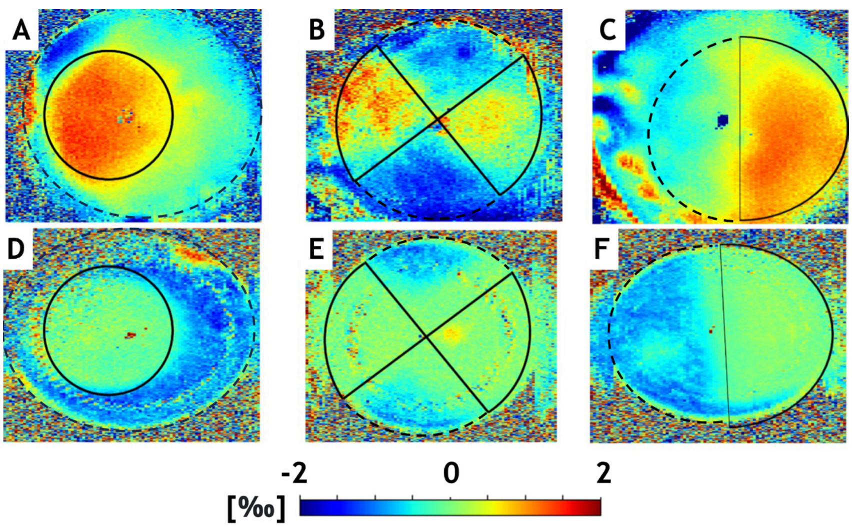

Fig. 1: Optical changes in the cornea are achieved by local stiffening using structured cross-linking. Optical coherence tomography was used to quantify corneal strain 30 minutes (A-C) and 36 hours (D-F) after treatment. Different irradiation patterns were used, such as circular (A), bow-tie (B), or semi-disc (C).

Refractive effects of local corneal stiffening

Optical coherence tomography (OCT) has become widely used in ophthalmology over the past two decades and has become a valuable tool for visualization of ocular tissue structures, playing a critical role in the evaluation and monitoring of various ocular diseases. Based on phase-sensitive deformation tracking algorithms, OCT elastography has emerged as a novel method for studying the mechanical deformations of tissues under controlled loading conditions.

We used state-of-the-art OCT imaging technique to determine the optomechanical changes caused by local corneal crosslinking (CXL) on ex vivo tissues. Different patterns were used to induce local corneal stiffening, e.g., in the shape of a bow tie or a half disk (Figure 1). Our results show that the cornea also undergoes geometric changes during stiffening, which in turn affect its refractive properties. We have quantified the relationship between the energy delivered to the tissue and the resulting refractive change. In addition, we have shown that OCT is an effective tool for studying high-resolution dynamic mechanical processes that the tissue undergoes during CXL.

The experimental data collected demonstrate that OCT is an innovative approach to quantify the mechanical properties →

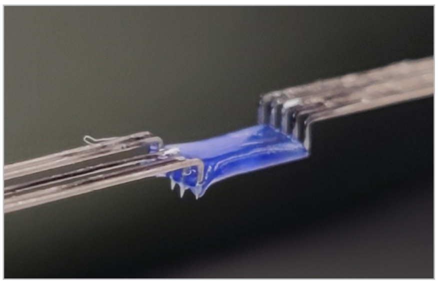

Fig. 2: Samples prepared with a laser at different depths of the human cornea were characterized mechanically.

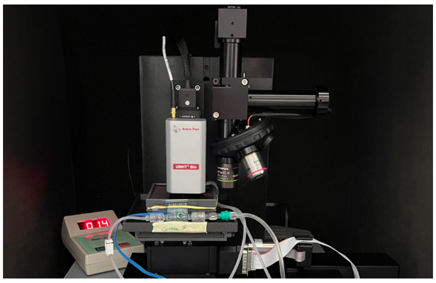

Fig. 3: The viscoelastic properties of the human cornea under physiological conditions were quantified by indentation.

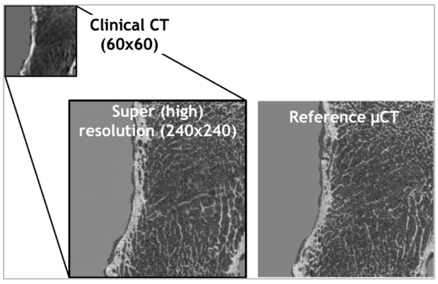

Fig. 4: Image super-resolution is used to reconstruct the trabecular structure of µCT images from clinical CT datasets.

of the cornea. When combined with biomechanical models of the tissue, this information provides new insights into the mechanical characterization of the cornea and could be useful in planning CXL treatments and refractive surgery.

Depth-dependent properties of the human cornea

The prevalence of myopia is rising sharply, leading to an increase in elective refractive surgery. Since the cornea accounts for about two-thirds of the optical power of the eye, small changes in its shape or curvature have a significant impact on vision. Each person has a unique corneal structure and biomechanics, making general surgical planning ineffective for predicting the outcomes of refractive surgery. Currently, these surgeries still result in double-digit under- or overcorrections. Therefore, numerical modeling is proposed to improve surgical planning and optimize the results of laser vision correction, which requires an accurate biomechanical characterization of the human cornea.

Over the past year, we have used different approaches to quantify corneal biomechanics. First, corneal samples were taken from young patients undergoing laser vision correction. The corneal lenticules taken during surgical correction were used in a uniaxial test setup to characterize their properties. As these samples were taken from the most anterior part of the cornea, an additional sample source was required to quantify the properties of the posterior cornea. For this evaluation, corneal grafts that were not intended for transplantation were used (Figure 2). In this case, femtosecond lasers were used to cut thin samples at different depths of the cornea so that the depth dependence of corneal biomechanics could be investigated. Our results show that the stiffness of the cornea decreases linearly with the depth of the human cornea, with the anterior part of the tissue being about 40 % stiffer than the posterior part.

In addition to the uniaxial tensile test, we quantified the mechanical properties of the cornea using tissue indentations (Figure 3). In this technique, a small spherical indenter is pressed onto the corneal surface to record the relationship between the force exerted by the indenter on the tissue and its displacement. Specimens were subjected to physiological intraocular pressure during indentation to account for the natural preload of the cornea, and both dynamic and cyclic loads were used to characterize the viscoelastic response of the human cornea.

This information is used to create numerical tissue models that take into account the known orientation of collagen fibers in the tissue, which are isotropically distributed in the corneal plane, while they are oriented along the corneal curvature and have little dispersion outside the corneal plane. Accurate characterization and modeling of the human cornea is essential to explore better refractive surgery for the population undergoing these treatments, to develop in silico models that account for corneal biomechanics when planning refractive surgery, and to provide a basis for improving visual outcomes in the rapidly growing population undergoing these treatments.

Virtual µCT from clinical CT image

Image-based modeling is a popular approach for performing patient-specific biomechanical simulations. Accurate modeling is critical for orthopedic applications to evaluate diagnostics, implant design, and surgical planning. It has been shown that bone strength can be estimated from bone mineral density and trabecular bone structure. However, these findings cannot be directly applied to patient-specific modeling because only bone mineral density values can be derived from calibrated clinical CT, but no information on the trabecular bone structure is available to the clinician.

Image super-resolution is a computer vision task involving the enhancement of high-resolution images from low-resolution counterparts. With the rapid development of deep learning techniques in recent years, deep learning-based super-resolution models have been actively explored and often redefine the state of the art in various benchmarks.

In this work, we proposed and implemented a method based on generative adversarial networks to predict the structure of the trabecular bone from the clinical CT scan of the patient based on a deep learning super-resolution model applied to three-dimensional datasets (Figure 4).

Selected Publications

1. Matteo Frigelli, Philippe Büchler, Sebastian Wolf, Martin Zinkernagel, Sabine Kling, "Optomechanical Assessment of Photorefractive Corneal Cross-linking via Optical Coherence Elastography", Front. Bioeng. Biotechnol., 2023, 11:1272097. https://doi.org/10.3389/fbioe.2023.1272097
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3. Matteo Frigelli, Philippe Büchler, Sabine Kling; Dynamic Evaluation of the Mechanical and Refractive Effects of Corneal Cross-Linking using Optical Coherence Elastography. Invest. Ophthalmol. Vis. Sci. 2023;64(8):4386.
4. Malavika Nambiar, Theo G Seiler, Philippe Büchler, "Depth-dependent, experimental characterization of the human corneal stroma", Ophthalmology & Visual Science, June 2023, Vol.64, 1685
5. Nambiar, Malavika H., Layko Liechti, Harald Studer, Abhijit S. Roy, Theo G. Seiler, and Philippe Büchler. "Patient-Specific Finite Element Analysis of Human Corneal Lenticules: An Experimental and Numerical Study." Journal of the Mechanical Behavior of Biomedical Materials 147 (November 2023): 106141. https://doi.org/10.1016/j.jmbbm.2023.106141.

Gerontechnology and Rehabilitation

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Research Profile

The interdisciplinary Gerontechnology and Rehabilitation Research group is a collaborative research effort with the goal of developing and evaluating novel, flexible, and cost-efficient technologies to improve diagnostics, monitoring, and therapies of neurological and psychiatric disorders in the hospital, in the instrumented apartment and at home. Core methodologies include digital biomarkers, telemonitoring and telerehabilitation technology. The research group partnered with the department of neurology (Prof. Claudio Bassetti) to establish the NeuroTec Loft, which is an instrumented apartment within the sitem NeuroTec to monitor human behaviour and to investigate how neurological and psychiatric disorders influence daily life.

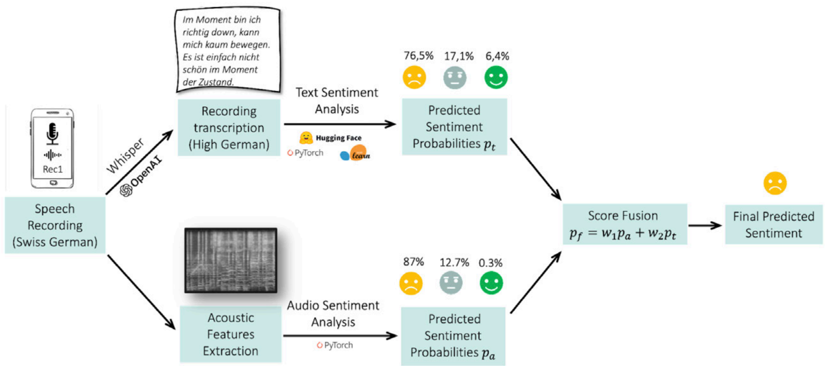

Fig. 1: Example of workflow of the AI pipeline. Given a speech recording, mood detection is performed by fusing resulting scores of speech-based and text-based models. Example of workflow of the AI pipeline. Given a speech recording, mood detection is performed by fusing resulting scores of speech-based and text-based models.

Speech-based digital biomarkers in the patient's home: Emotion in parkinson's disease

With increasing life expectancy, the number of people affected by neurodegenerative disease (e.g., Parkinson's disease) will continue to grow, as aging is one of the primary risk factors. The presence of motor (e.g., bradykinesia, tremors) and non-motor symptoms (e.g., neuropsychiatric symptoms) can severely affect the patient's quality of life. Even though neuropsychiatric fluctuations can be more disabling than motor symptoms, they are poorly recognized and, thus, inadequately treated. There is, indeed, a need for methods and tools to assess non-motor symptoms over time that do not rely only on the subjective reports of patients or caregivers. Treatments like Deep Brain Stimulation (DBS) have been studied as a solution to lessen symptoms, even neuropsychiatric symptoms. However, to work optimally, they must dynamically adapt their parameters (e.g., type and amount of stimulation) according to the patient's current health status (e.g. closed-loop DBS). In this context, we aim to develop a multimodal (audio and context) AI-based pipeline [Fig. 1] that continuously detects the emotion state and mood from Swiss-German spontaneous speech collected several times daily at home using patients' smartphones. This method will allow clinicians to develop a patient-tailored →

Fig. 2: Living room in the instrumented apartment (sitem Neurotec Loft).

Fig. 3: Kitchen with a number of contact-free sensors (sitem Neurotec Loft).

Fig. 4: Bedroom with integrated sensors (sitem Neurotec Loft).

treatment by gathering information on both motor and non-motor symptoms remotely and continuously over the day.

Sensor-based digital biomarkers in the hospital: Digital care assistant

Currently, there is a shortage of skilled workers and pressure to reduce costs in the health care system, which is particularly evident in the personnel-intensive and time-consuming care characteristic for acute geriatric psychiatric hospitals but also nursing, and care homes. Furthermore, as the number of patients, especially the number of dementia patients is steadily growing in the context of increasing life expectancy and the baby boomer cohort retiring, the shortage of nurses will further escalate. Sensor-based digital biomarkers have the potential to be used in a clinical setting to provide objective and reproducible data about the patient's status and to support healthcare professionals at the ward. Especially remote continuous monitoring of patients allows to immediately detect slight changes in health status. We developed an unobtrusive sensor system, a so-called digital care assistant, that monitors behavioral and physiological parameters to support and ease the workload of medical professionals of an old age psychiatric ward (Fig. 5). We have equipped twenty patients rooms with sensors (e.g., bed sensor, lidar sensor, and radar sensors). A smartphone-based app displays information about the patient's status and helps healthcare professionals (e.g. nurses) to keep an overview of all patients of their ward. We are currently testing acceptance and effectivity of the sensor-based digital care assistant.

Sensor-based digital biomarkers in the instrumented apartment and in the patient's home: Fatigue in multiple sclerosis

The autoimmune disease multiple sclerosis (MS) is one of the most prominent causes of nontraumatic neurodegenerative disorders with a typical onset in young adults. Currently, in Switzerland, approximately 110 out of 100'000 people suffer from MS, whereas the prevalence in the last years was on the rise. The severity of MS symptoms considerably varies between patients, occurring in relapsing or progressive forms, and can be classified as motor (e.g., unsteady gait, tremor, weakness) and non-motor symptoms (e.g., vision issues, sensory disturbances, fatigue). We use sensor-based digital biomarkers in the instrumented apartment (fig. 2- 4) and in the patient's home to measure patient's actions. There are two related research questions. First, to better understand the relationship between established clinical scores (e.g., Expanded Disability Status Scale) and the actual daily function of the patient. Second, the long-term behavioural data will help us to better understand the phatophysiology of fatigue in MS.

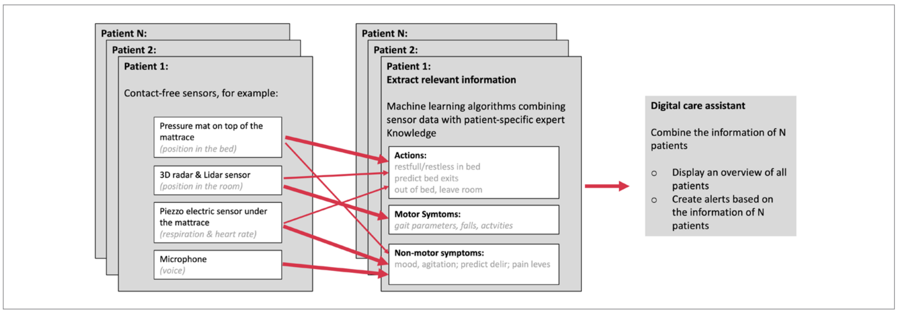

Fig. 5: Schematics of the digital care assistant under clincial evaluation at the university hospital of old age psychiatry.

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1. Schütz N, Knobel SEJ, Botros A, Single M, Pais B, Santschi V, Gatica-Perez D, Buluschek P, Urwyler P, Gerber SM, Müri RM, Mosimann UP, Saner H, Nef T. A systems approach towards remote health-monitoring in older adults: Introducing a zero-interaction digital exhaust. Nature Digital Medicine (NPJ), 2022
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4. Ruettgers N, Naef AC, Rossier M, Knobel SEJ, Jeitziner MM, Grosse Holtforth M, Zante B, Schefold JC, Nef T, Gerber SM. Perceived sounds and their reported level of disturbance in intensive care units: A multinational survey among healthcare professionals. PLoS One. 2022 Dec 30;17(12):e0279603. doi: 10.1371/journal.pone.0279603. PMID: 36584079; PMCID: PMC9803129.
5. Naef AC, Gerber SM, Single M, Müri RM, Haenggi M, Jakob SM, Jeitziner MM, Nef T. Effects of immersive virtual reality on sensory overload in a random sample of critically ill patients. Front Med (Lausanne). 2023 Oct 4;10:1268659. doi: 10.3389/fmed.2023.1268659. PMID: 37859854; PMCID: PMC10582722.

Hearing Research Laboratory

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Research Profile

The human ear stands as a testament to nature's ingenuity, seamlessly weaving the threads of acoustics, biomechanics, fluid dynamics, biochemistry, and neural processing. To delve into the mysteries of the auditory world, we recognize the need for a multidisciplinary approach that converges expertise from diverse fields.

As otologic procedures place unique demands on human tactile and locomotive capabilities, the HRL, jointly with the Department for Otolaryngology at the Inselspital, is committed to developing tools that assist surgeons in these complex tasks. Our focus lies on creating technology that seamlessly integrates into established workflows. We design, test, and refine innovative surgical tools specifically engineered to overcome these challenges. Concurrently, we develop algorithms that harness a range of sensory data, for instance from cochlear implant telemetry, providing us with insights into the surgical process and leading toward the realization of personalized approaches to hearing restoration and rehabilitation.

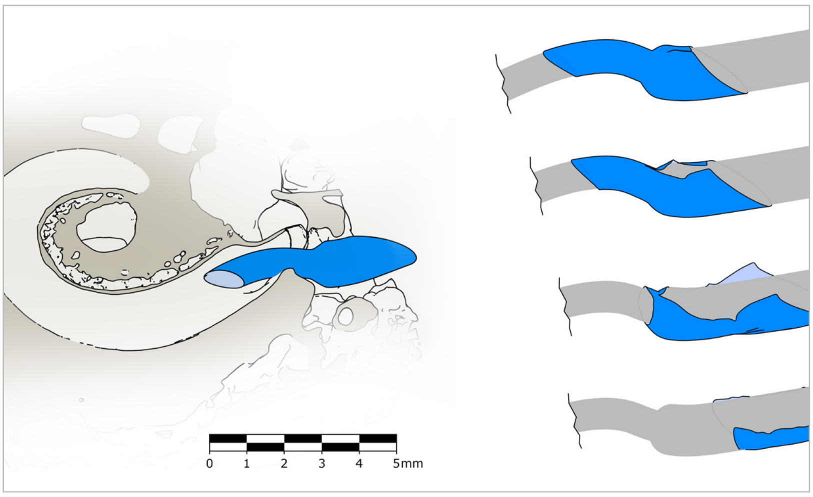

Fig. 1: Illustration of a compliant guiding tool that allows to optimize the insertion trajectory of cochlear implant electrodes arrays. It is designed with a tear-open mechanism, for post-surgical removal.

Advancing surgical solutions for cochlear implantation

Cochlear implants have transformed hearing restoration by electrically stimulating auditory sensory cells within the cochlea. These devices have evolved into the gold standard for treating severe to profound hearing loss, and their applications are expanding to encompass patients with residual hearing. Preserving the structural integrity of the hearing organ is of paramount importance for such cases.

At the threshold of hearing, we find the inner hair cells' stereocilia moving with astonishing subtlety, just nanometers in distance. The stapes, that transmits vibrations from the eardrum to the inner ear, is the smallest bone in the human body and yet dwarfs this delicate movement by a millionfold.

Given these scale extremes, our team engineers surgical instruments to address these constraints, aiming to directly integrate into existing procedures. For instance, we have designed a sleeve-based, compliant guiding tool that enables surgeons to redirect the implant's electrode array onto a favourable trajectory, bypassing anatomical constraints (Fig. 1).

Moreover, we've developed a device for the robot-asisted insertion of the electrode array that minimizes intracochlear pressure transients while offering highly accurate force measurements, exhibiting significantly enhanced sensitivity beyond the surgeon's sensory perception (Fig. 4). →

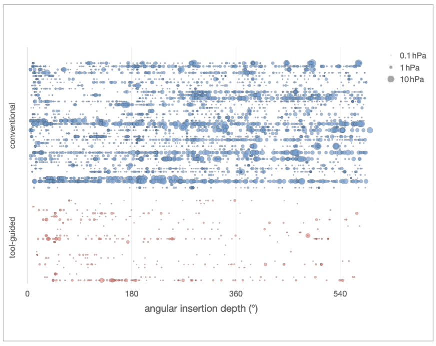

Fig. 2: The validation of a novel surgical tool shows a reduction of pressure transients in cochlear implantation by 29 dB compared to the conventional surgical approach.

Fig. 3: A Segmentation of the ossicular chain obtained from dynamic synchrotron phase-contrast imaging of the middle ear also illustrates a complex vascular system.

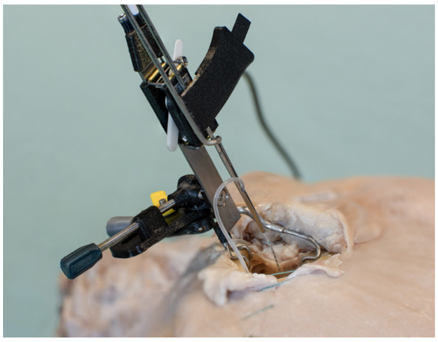

Fig. 4: A prototype for the robot-asisted insertion of cochlear implant electrode arrays.

Enhancing feature detection in electrocochleography

The cochlea, concealed within the temporal bone, presents a unique surgical challenge as it is a hidden cavity inaccessible to direct observation. To address this issue, we employ a process called electrocochleography, where the ear is acoustically stimulated, and the implant measures the auditory response, allowing for real-time monitoring of auditory preservation during the surgical procedure. However, interpreting these signals is a complex task, even for experienced professionals.

Our research focuses on the development of algorithms for robust real-time feature detection within these intricate signals. The ultimate goal is to provide surgeons with a user-friendly system, akin to a simple traffic-light indicator, which can offer immediate insights into adverse events occurring during surgery. This approach streamlines the surgical process, simplifying the interpretation of the surgical procedure, and ensuring better outcomes for patients (Fig. 2).

Radiation-free cochlear implant localization

At present, confirming the position of a cochlear implant necessitates a post-operative computed tomography scan. Our team pioneers an innovative approach that relies on impedances measured by the implant to extract data about the intracochlear environment. Using machine learning algorithms, we work towards accurately estimating the implant's position without the need for medical imaging.

This radiation-free method ensures sub-millimeter precision in implant placement and offers immediate intraoperative verification of the surgical procedure. Moreover, this enables use in vulnerable populations such as children and pregnant women, eliminating potential health risks associated with radiation. Finally, the technology enables long-term monitoring of implant migration.

Predicting speech understanding in cochlear implant patients

Cochlear implant patients exhibit a wide spectrum of hearing outcomes, with some mastering speech comprehension even in challenging listening situations while others experience limited benefits from the implant. Our research delves into understanding these disparities by analyzing brain activation patterns with functional near-infrared spectroscopy.

We have observed significant differences in brain activation during auditory tasks between normal hearing individuals and cochlear implant patients. For instance, cochlear implant patients may exhibit substantial activation in the auditory cortex, when engaging in activities like lip reading. These findings guide us in our search for biomarkers that can predict the expected hearing outcome, allowing for more personalized approaches to cochlear implant treatment and rehabilitation.

Dynamic imaging of the middle ear

The middle ear serves as a pivotal component in the acoustic pathway, responsible for transmitting vibrations from the tympanic membrane to the cochlea. We employ synchrotron phase-contrast imaging to capture the dynamic motion of the entire middle ear with micrometer resolution during acoustic stimulation (Fig. 3).

This not only enhances our understanding of the precise mechanics of auditory stimulation but also holds the potential to shape the development of novel and more efficient auditory prostheses.

Selected Publications

1. Aebischer, P., Weder, S., Mantokoudis, G., Vischer, M., Caversaccio, M., & Wimmer, W. (2023). A Sleeve-Based, Micromotion Avoiding, Retractable and Tear-Opening (SMART) Insertion Tool for Cochlear Implantation. IEEE transactions on bio-medical engineering, 70(3), 860–866.
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3. Talon, E., Wimmer, W., Hakim, A., Kiefer, C., Pastore-Wapp, M., Anschuetz, L., Mantokoudis, G., Caversaccio, M. D., & Wagner, F. (2022). Influence of head orientation and implantation site of a novel transcutaneous bone conduction implant on MRI metal artifact reduction sequence. European archives of oto-rhino-laryngology, 279(10), 4793–4799.
4. Andonie, R. R., Wimmer, W., Wildhaber, R. A., Caversaccio, M., & Weder, S. (2023). Real-Time Feature Extraction From Electrocochleography With Impedance Measurements During Cochlear Implantation Using Linear State-Space Models. IEEE transactions on bio-medical engineering, 70(11), 3137–3146.
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Image-Guided Therapy

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Research Profile

The Chair for Image Guided Therapy is leading technical advancements in various fields like simulation, modeling, imaging, sensing, visualization, and robotics from research into clinical care. The innovations focus on areas like radiology, ENT, neuro, and hepatobiliary surgery, and have the potential to boost human operation in medical procedures. The aim to revolutionize these procedures reflects in treating previously difficult or untreatable conditions by leveraging technology over human limitations, resulting in zero morbidity and minimal invasiveness. Tight collaborations with clinical co-investigators at the Inselspital and other national and international partners are essential for translating technological solutions into standard clinical practices and validating them through direct patient care.

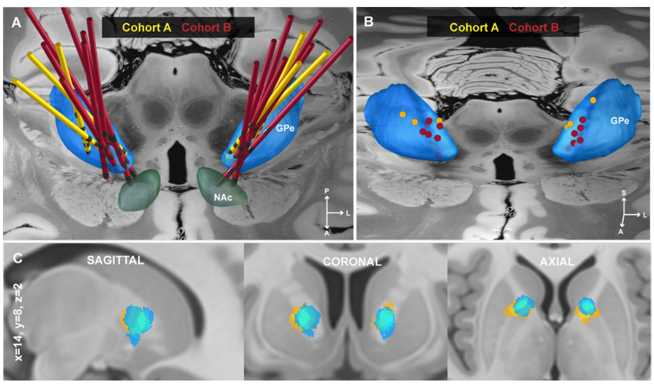

Fig. 1: Studying deep brain stimulation for obsessive-compulsive disorders. (A) Electrode location of two cohorts implanted in the nucleus accumbens (NAc) and external globus pallidus (GPe) area. (B) Highlighting the active contacts of the electrodes as in A). (C) Stimulated areas for three different perspectives in group space.

Mapping and modelling of deep brain stimulation

(SNSF Ambizione 186142)

The objective of this project is to improve patient care by developing computer-assisted programming for deep brain stimulation. For movement disorders and Parkinson's disease, we applied deep learning techniques to stimulation data from two centers, Inselspital Bern and University Hospital Cologne, in a retrospective analysis. Preliminary results have been promising, and more validation is needed. With this approach, we drastically improved the performance of computer-assisted programming over our previous approaches with sweet spots and sweet tracts. Specifically, we were able to suggest the best electrode level and best electrode contact with more than 90 percent accuracy, and the current amplitude with an average error of 0.1 mA. For psychiatric disorders, such as treatment-resistant depression and obsessive-compulsive disorders, we have continued our work with patient-specific tractography together with our clinical partners. Adding more patient data over a longer period has helped to better understand the tracts implicated in improvement for these disorders (Fig. 1).

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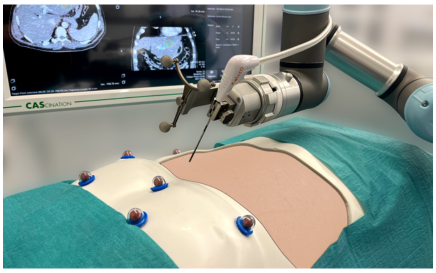

Fig. 2: Robotic system for configurable ablation integrates a robotic arm, an optical navigation system, and an ablation probe.

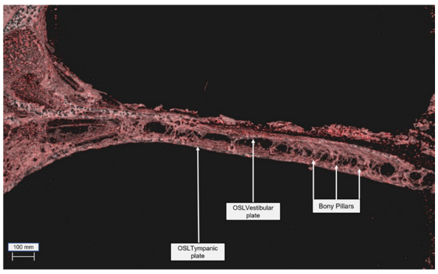

Fig. 3: Using the 2.3- µm voxel size, the OSL bony pillars, vestibular and tympanic plates are demonstrated.

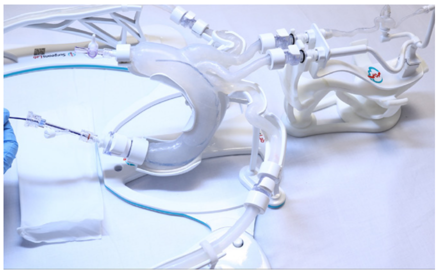

Fig. 4: Endovascular simulator micro device deployment.

➔ Fighting liver cancer

(H2020 MSCA-ITN 722068, Innosuisse 37855.1 IP-LS, NTN Innovation Booster Robotics)

Percutaneous thermal ablation for treatment of very early to early-stage liver tumors faces challenges in treating larger, non-spherical, or critically located tumors due to risks of over-ablation and potential damage to surrounding structures. Current clinical practice favors smaller and spherical tumors, and struggles with cases requiring overlapping ablation volumes, which can lead to tumor recurrence. To address these issues, we aim to develop a system that integrates image-based planning, stereotactic probe navigation, and robotic ablation, which can dynamically modulate ablation power and probe velocity to create configurable tumor-fitted ablation volumes (Fig. 2). The aim is to investigate repeatability and enhance outcome reproducibility in complex cases, potentially advancing the treatment for both standard and complex treatments, while reducing reliance on physicians' experience.

Approaching human osseous spiral lamina using microCT

The osseous spiral lamina (OSL), an inner bony structure projecting from the modiolus from base to apex, plays a crucial role in separating the cochlear canal into the scala vestibuli and scala tympani. Recently, scientists have turned their attention to the porosity of the OSL, recognizing its potential impact on overall sound transduction. Conventional histopathological studies often struggle to capture the bony pillars between the vestibular and tympanic plates of the OSL adequately. Utilizing microCT, we achieved a groundbreaking anatomical demonstration of the OSL, providing unprecedented 3D detail. Our approach involved calculating width, thickness, and porosity at increasing nominal resolutions, reaching up to a 2.5-µm voxel size. Moreover, we created intricate 3D models of the individual plates at the basal and middle turns, as well as the apex, enabling a comprehensive 3D reconstruction of the bony pillars between the OSL plates. This innovative methodology not only enhances our understanding of the OSL but also contributes to advancing our knowledge of hearing mechanisms. The detailed insights gained can further improve the precision and efficacy of cochlear models, marking a significant step forward in auditory research.

High-fidelity neuroendovascular simulator

(Innosuisse 51144.1 IP-LS, Swiss Heart Foundation FF20061, Siemens Foundation, Gerber Ruef Foundation)

There is a global need for more well-trained surgeons and interventionists. Conventional ways of learning intricate head and neck microsurgeries have limitations in imparting practical knowledge to residents and senior surgeons regarding complex procedures. Current training methods and complex case planning are not quantified, and one's performance is not currently measured. To address these concerns, the research group is developing mixed reality 4D micro interventional simulators to train for complicated microsurgeries in head and neck surgeries in an immersive environment like an operating room (Fig. 4). This ensures that residents can access real-life surgical procedures and operations through a detailed learning module and patient-specific exercises derived from actual patients. The high-fidelity simulators are equipped with an AI-powered performance matrix for the user, allowing them to assess the level of their skills and surgeries, such that a surgeon's quality can be measured and quantified. In such a way, in the future, a surgeon's performance will be rated and reviewed based on the treatment outcomes driving towards value-based health insurance policies providing quality healthcare to the patients.

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Medical Image Analysis

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Research Profile

The Medical Image Analysis group develops advanced medical image analysis technologies, and related translational biomedical engineering technologies, to quantify, diagnose, and follow-up diseases and disorders. The group develops novel techniques for multimodal image segmentation and analysis of brain lesions, presently including glioblastoma multiforme, brain metastases, and related conditions. The results of these developments are aimed at advancing the discovery of innovative non-invasive imaging biomarkers used to characterize disease and guide the decision-making process, as well as in radio-therapy, neuro-surgery, drug-development, etc. A special focus is to develop algorithms and methodologies to improve the robustness and interpretability of AI-based solutions for medical image analysis. The developments revolve around the vision of scalable, adaptable and time-effective algorithms developed with a strong focus on clinical applicability.

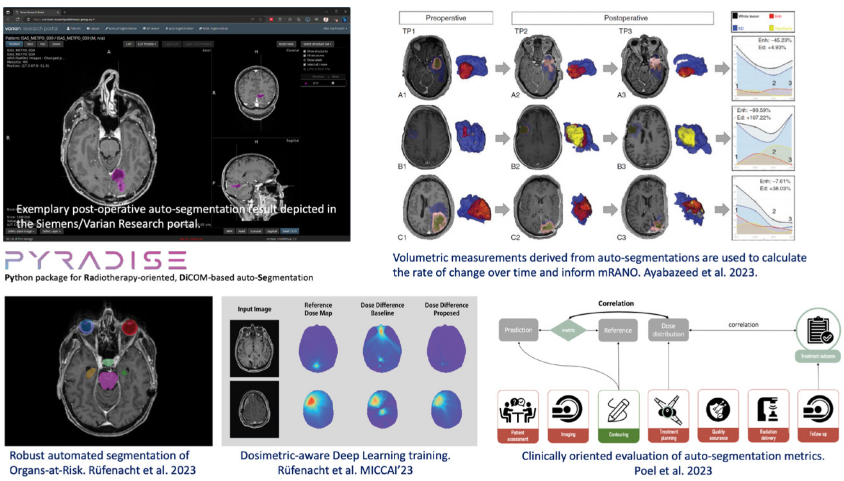
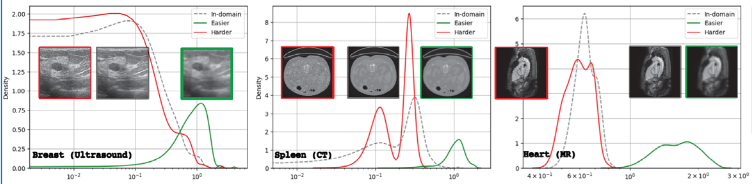


Fig. 1: Robust and accurate AI-based segmentation for clinically relevant and translational objectives.

Accurate, robust and clinically translated ai-based quantification in medical image computing

Magnetic Resonance Imaging (MRI) and its variants are a powerful imaging modality that encompasses rich anatomical and physiological information at a high resolution. In neurosciences, these modalities have become a standard in clinical practice. However, the interpretation of the images requires the combined use of different modalities, which leads to the need of computer-assisted technologies.

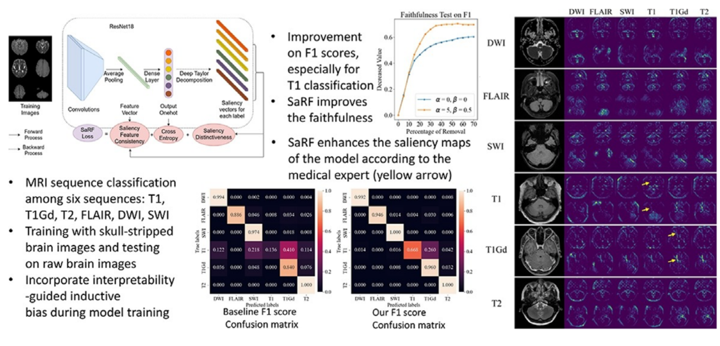
Based on AI technologies our group has developed methods and produced related translational technologies to automate the delineation of brain tumors. We have made these technologies available for the research community but also further developed them for future clinical use. In 2022, in collaboration with the US-based start-up Neosoma, our group further got this technology FDA approved (510k). During 2023, we continued working on expanding the technology for its utilization in brain metastases. Currently, we are performing a multicenter clinical multi-criteria evaluation of the technology. During 2023 we further developed a new learning paradigm focusing on radiation-therapy that employs deep learning metrics derived from the clinical-end goals. Furthermore, our team has developed AI-based quality assurance technology focusing on dosimetric →



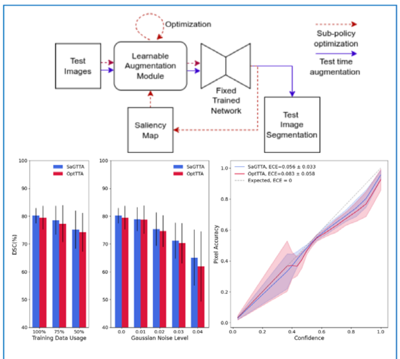
Understanding the role of U-Net's skip connections and model robustness. Kamal et al. MICCAI'23.

Data set	Texture level	AGU-Net	U-Net	NoSkipU-Net
Breast (Ultrasound)	Harder	0.645 (0.291)	0.723 (0.281)	**0.735** (0.268)
	In-domain	**0.795** (0.206)	0.762 (0.261)	0.761 (0.258)
	Easier	**0.799** (0.200)	0.735 (0.244)	0.748 (0.243)
Spleen (CT)	Harder	0.310 (0.226)	0.074 (0.152)	**0.558** (0.265)
	In-domain	**0.927** (0.092)	0.745 (0.275)	0.606 (0.265)
	Easier	**0.809** (0.201)	0.394 (0.354)	0.486 (0.292)
Heart (MRI)	Harder	0.139 (0.242)	0.500 (0.316)	**0.815** (0.126)
	In-domain	**0.929** (0.055)	0.900 (0.080)	0.833 (0.111)
	Easier	**0.889** (0.073)	0.805 (0.129)	0.823 (0.103)

Mean (standard deviation) of Dice scores for each of hard, in-domain and easy textures on the Breast (Ultrasound), Spleen (CT) and Heart (MR) data sets.



Interpretability-guided Deep Learning training via Saliency regularized feature learning (SaRF). You et al. 2023



Interpretability-guided Test-Time Augmentation under Domain Shift. You et al. 2023

Fig. 2: Interpretability-guided medical image segmentation and classification. Our group has developed novel methodologies to employ information derived from interpretability to further boost the performance, robustness and generalization of AI systems.

compliance that informs physicians in nearly real-time how their segmentation modifications might impact dosimetry.

Interpretability of deep learning-based medical image analysis

Next to accuracy, the robustness of computer-assisted technologies is fundamental for their effective deployment and integration in medicine. Particularly, it is crucial to develop technologies that can cope with computer errors stemming from the large heterogeneity of medical images, the complex pathophysiology of disease, among other factors. Towards a better understanding and clinical adoption of medical imaging AI technologies, our group is researching on interpretability approaches to leverage our understanding on the underlying learning mechanisms of AI systems, as well as to identify areas where their robustness is affected in clinical imaging scenarios. Beyond interpretability approaches, our group has further developed strategies to employ interpretability information of AI systems to guide their learning, performance and robustness.

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10. Kamath, A., Poel, R., Willmann, J., Ermis, E., Andratschke, N. and Reyes, M., 2023, July. ASTRA: Atomic Surface Transformations for Radiotherapy Quality Assurance. In Proceedings of the International Conference of the IEEE Engineering in Medicine and Biology Society, Sydney, Australia (pp. 24-27).
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Musculoskeletal Biomechanics

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Research Profile

Motivated by prevention, diagnosis, and treatment of degenerative diseases, the research of the Musculoskeletal Biomechanics group focuses on multi-scale structure-function relationships of bone from the extracellular matrix to the organ level. Combined theoretical, experimental, and numerical approaches are applied to model, validate, and simulate the mechanical behaviour of bone tissue and bone-implant systems during growth, aging, disease and treatment. The group supervises master theses, provides biomechanical testing services, and cooperates with local, national as well as international partners from academia, hospitals, and industry to help reduce the burden of bone diseases and failure of the bone-implant interface.

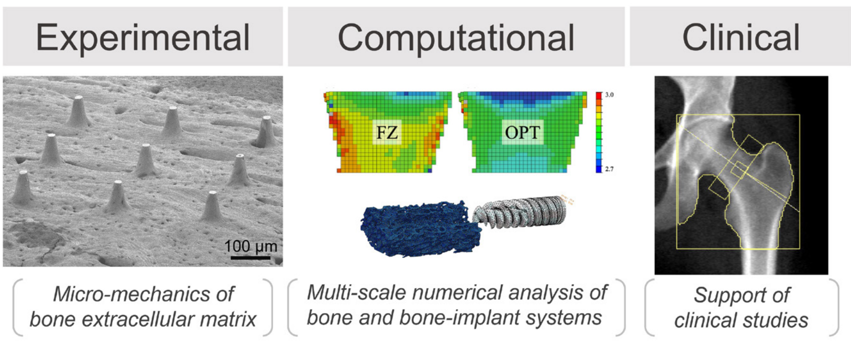

Fig. 1: Overview of MSB research.

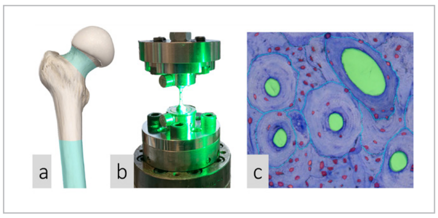

Fig. 2: Femoral sample overview (a) with mounted sample for tensile tests (b) and image with automatic segmentation of bone micro-structural components (c).

Contribution of bone tissue properties to strength of the ageing human hip *(SNF grant # 200365 with EMPA, PSI & VUT)*

This study examines local variations in bone tissue quality at the proximal femur in relation to age. Ninety-four femurs were scanned with micro-CT, giving access to morphology and mineral content. After sample preparation, structure-property relationships were explored through histological staining and tensile tests on native and demineralized samples (Fig. 2). Age-related changes were observed in structural components such as increasing cement line density, while the organic fraction and mechanical properties remained age-independent. Synchrotron experiments with PSI explore bone ultrastructure and mechanical properties at the femoral neck. This project also improves a finite element model to simulate the hip's mechanical behavior from physiological loading up to a fall impact.

A fragility fracture integrative risk model for ct recycling *(SNF grant # 183584 with HUG, IS, & MUG)*

The project aims to develop a hip fracture risk model based on the risk of falling and a calibrated CT examination. To validate the model, a clinical study has been running for two years. In June, the last participants have been examined, and the →

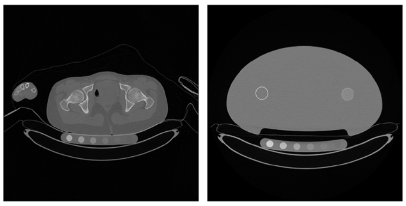

Fig. 3: Left: CT scans with patient and phantom (synchronous calibration). Right: with phantom only (asynchronous calibration).

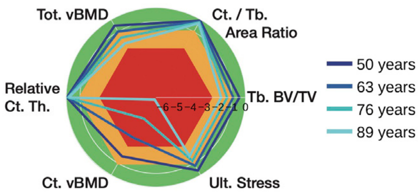

Fig. 4: Sex- and site-specific size-invariant bone properties. Radial coordinates designate standard deviations with respect to young controls.

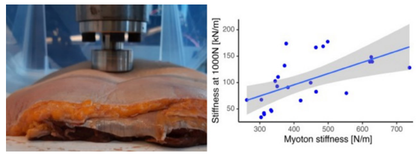

Fig. 5: Left: mechanical testing of a trochanteric soft tissue sample. Right: comparison of laboratory and clinical stiffness measurement modalities.

→ baseline data from 374 participants is being analysed. In the last year, a script for CT calibration was developed (Fig. 3). In addition, a method for extracting the thickness and composition of soft tissue from CT scans was developed. The CT scans will be used for femoral strength computations through an automated finite element pipeline. Together with fall risk estimations and newly gained insight about the soft tissues during an impact, this data will be used to explore novel mechanistic ways to predict hip fracture risk.

HR-pQCT-based diagnosis of osteoporosis *(with IS)*

High Resolution peripheral Quantitative Computed Tomography (HR-pQCT) is an imaging technique used to quantify the morphological, densitometric and mechanical properties of the distal radius and tibia with a resolution of 61 µm. We aimed to collect reference data with a new multi-stack protocol and identify size-independent structural and strength parameters to improve the continuous assessment of bone health. We conducted exploratory statistical analysis stratified for sex and anatomical site on 276 healthy participants who were previously measured at the Policlinic for Osteoporosis of the Inselspital. Our findings highlight that cortical volumetric bone mineral density (Ct.vBMD) of the weight-bearing tibia is the most sensitive variable with age. We propose a set of size-independent variables that provides a synthetic and intuitive overview of distal bone health for practical diagnostics in a clinical setting (Fig. 4).

Biomechanical testing and master theses

Mechanical testing was used in several research projects and Master's thesis e.g., validating a preoperative marker for safe screw placement in bone conduction hearing implants, revealing correlations between the marker and mechanical properties. Areal bone mineral density (aBMD) and trabecular bone score (TBS) were measured in lumbar vertebrae compressed uni-axially to decipher the potential role of vertebral fractures in these standard clinical measures. Tissue properties of the human distal tibia were evaluated by nano-indentation to characterize different microstructural compartments for improved finite element analysis. In a computational study, intramedullary geometry of the human proximal femur was classified using a statistical shape modeling approach to help improve custom total hip arthroplasty.

Biomechanical stability of dental implants and bone screws *(with AO)*

Immediate post-surgery loading is of high interest in dental implantology and orthopedics. The MSB laboratory offers computational models validated by experiments, to assess the primary stability of dental or orthopedic implants in human bone tissue. Based on high-resolution µCT scans of specific anatomical sites, these models provide deep insights into implant behaviour according to their geometry, material and insertion protocols under various loads. Those models are typically used to develop new prototypes.

Role of hip soft tissues in fracture risk *(with MUG)*

Trochanteric soft tissues attenuate the impact force on the femur following a sideways fall. A deeper understanding of the mechanical behavior of these tissues during an impact and the use of appropriate measurement tools may improve hip fracture risk prediction. We examined the mechanical response of excised human trochanteric soft tissues at low force using a handheld device and at high impact force using a mechanical testing system (Fig. 5). Finite element models of these structural experiments were created to identify material constants of these soft tissues.

Atlas of the hip and spine *(with IS)*

A large dataset of whole-body postmortem CT images containing a calibration phantom (Fig. 3) was used to create atlases of the proximal femur and thora-columbar spine. The first project looked at the evolution of BMD distribution and cortical thickness in the proximal femur with age and BMI. In the second project, the bone strength of aging thora-columbar vertebral bodies was computed using homogenized finite element analysis.

Selected Publications

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Organs-on-Chip Technologies

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Jan Schulte
Arunima Sengupta
Pauline Zamprogno
Soheila Zeinali
Negar Vahdani
Lisette van Os
Tobias Weber

Research Profile

The Organs-on-Chip Technologies group focuses on the development of advanced in vitro models, called organ-on-chips. Such devices aim at reproducing the smallest functional unit of an organ, by mimicking the cellular composition and the cellular microenvironment. The group particularly focuses on modeling the human lung and microvasculature, in healthy and disease states. To achieve this, multidisciplinary research is performed at the interface of cell biology, biomechanics, microtechnology, and microfluidics. These systems are deemed to be implemented for precision medicine, in which the treatment efficiency can be tested with the patient's cells to individualize and optimize the therapy.

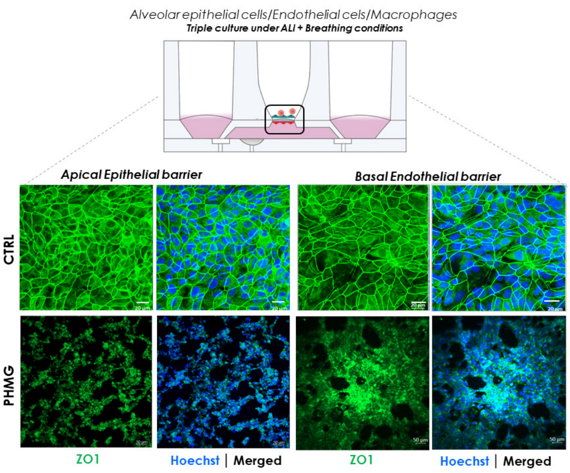

Fig. 1: Cross-section of the lung-on-chip with the alveolar epithelial barrier exposed to PHMG. Bottom: Comparison of healthy (CTRL) and PHMG-exposed conditions, with normal and damaged epithelial and endothelial layers, shown by tight junctions (ZO1) expression. (Ref: Sengupta et al. Front Pharm. 2023).

Aerosol lung toxicity prediction

In 2011, South Korea faced a severe lung illness epidemic due to PHMG, a humidifier disinfectant supposedly non-harmful when inhaled as an aerosol. It would have been invaluable to be able to predict its harmful effects in advance. As part of a European project, we have partnered with our spin-off AlveoliX, Vitrocell and the lung clinics of the University Hospital of Bern to develop an innovative in vitro lung inhalation model. The toxicity of PHMG and other chemical agents that can be inhaled was investigated using primary human alveolar epithelial cells (Fig. 1). An aerosol with the agent to be tested was created using the Cloud AX12 from Vitrocell, in which the AlveoliX lung-on-chip was located. Our research findings revealed a remarkable synergy of the air-blood barrier sensitivity, cytotoxicity, and inflammation when combining air-liquid interface and cyclic stretch culture conditions. We also demonstrated that inhaled corticosteroid effectively reduced PHMG-induced inflammation. To our knowledge, this is the first in vitro inhalation exposure system for the distal lung that incorporates a breathing lung-on-chip technology. The Cloud AX12 model is now an advanced preclinical tool for evaluating inhalation toxicity risks, drug safety and efficacy. →

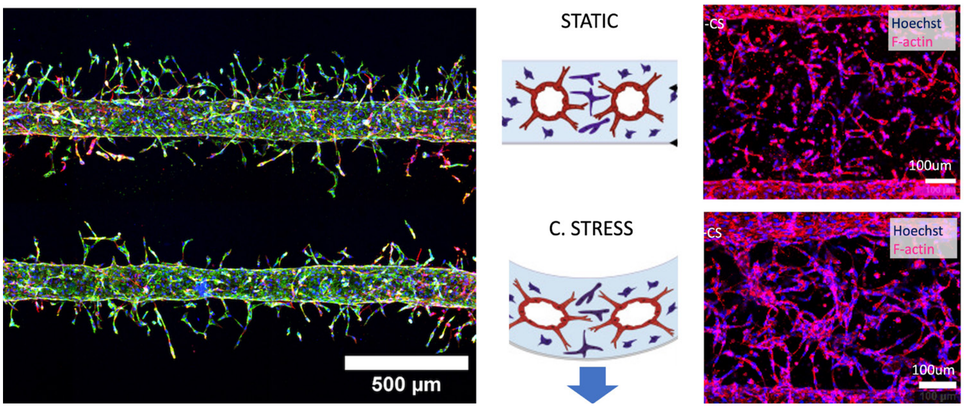

Fig. 2: Left: Two parallel vessels with angiogenic sprouting. Right: Comparison between the self-assembly process of endothelial cells cultured between the two vessels exposed or not to the cyclic stress (CS) of respiratory movements (Ref: Ferrari et al. iScience. 2023).

→ Complex microvasculature-on-chip

The endothelium of blood vessels is an important organ that reacts to subtle changes in stiffness and mechanical forces from its environment, called the extracellular matrix (ECM). When these biomechanical factors are altered, endothelial cells activate signaling pathways that control vascular remodeling. We have succeeded in recreating a complicated microvasculature consisting of two parallel vessels and a self-assembled capillary network, allowing us to study the individual or combined effects of biomechanical and biochemical stimuli (Fig. 2). The vessels were created in fibrin hydrogels with two different degrees of stiffness, demonstrating that even small differences in stiffness significantly influence the creation of new blood capillaries. In addition, we showed that the physiological stretching induced by the breathing increases the capillary density, potentially leading to increased oxygenation of the tissues. Gene expression analysis confirmed that cyclic stretch promotes expression of the ANGPTL protein family, which plays an important role in angiogenesis, but also in cancer progression and metastasis.

Immune response to acute lung injury

Acute respiratory distress syndrome (ARDS) is a severe lung disease associated with a high mortality rate and is often triggered by various factors, including lung infections. Currently, there is no specific treatment, and more research is needed to better understand the underlying mechanisms of ARDS. Most lung-on-chip models designed to mimic the air-blood barrier have a horizontal barrier that allows immune cells to migrate vertically, making it difficult to visualize and study their movements. In addition, these models often lack a natural protein-derived extracellular matrix (ECM) barrier suitable for live cell imaging to study ECM-dependent immune cell migration, a crucial aspect of ARDS. In this study, we present an innovative inflammation-on-chip model to monitor live immune cell extravasation and migration during lung inflammation. The three-channel, perfusion-enabled inflammation-on-chip system mimics the endothelial barrier of the lung, the ECM environment, and the inflamed epithelial barrier of the lung (Fig. 3). By creating a chemotactic gradient within the ECM hydrogel, immune cells migrate through the endothelial barrier. The results of this study demonstrate that immune cell extravasation depends on the presence of the endothelial barrier, ECM density, stiffness, and flow profile.

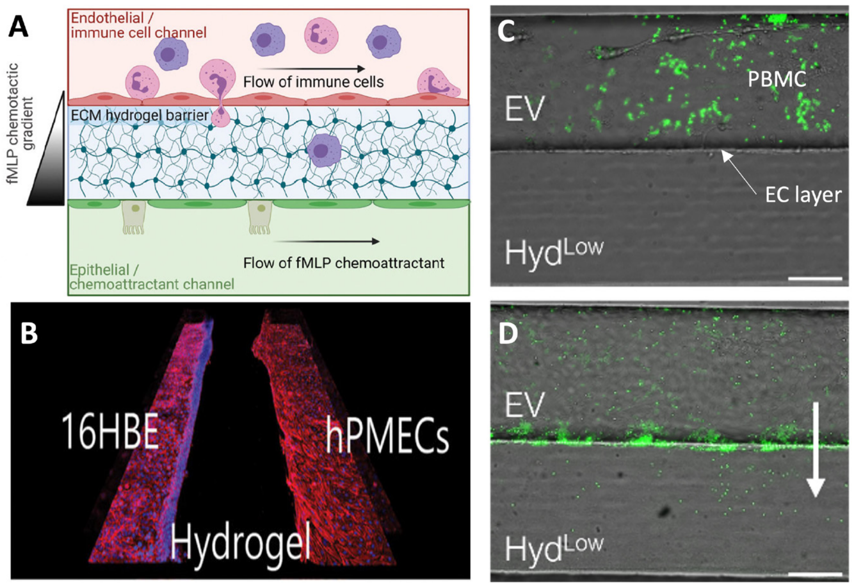

Fig. 3: A. Schematic of the inflammation-on-chip system, with the endothelial channel separated from the epithelial channel with a hydrogel barrier. B. Confocal view of the endothelial (hPMLEC) and the epithelial (16HBE) barriers. C. Peripheral blood mononuclear cells (PBMC) perfused through the endothelial vessel (EV) , and D. exposed to a chemotactic gradient, which induces the PBMC migration. (van Os et al., Eur J Pharm Sci. 2023).

Selected Publications:

1. Sengupta, A., et al., „A multiplex inhalation platform to model in situ like aerosol delivery in a breathing lung-on-chip." Front Pharmacol. 2023, 6;14:1114739.
2. van Os, L. et al., „Immune cell extravasation in an organ-on-chip to model lung inflammation." Eur J Pharm Sci. 2023, 1;187:106485.
3. Ferrari, D. et al., „Effects of biomechanical and biochemical stimuli on angio- and vasculo-genesis in a complex microvasculature-on-chip." iScience. 2023, 13;26(3):106198.
4. Van Os, L. et al., „Integration of immune cells in organs-on-chips: a tutorial." Front Bioeng Biotechnol. 2023 Jun 1;11:1191104.
5. Zamprogno, P. et al., „Lung-on-a-Chip Models of the Lung Parenchyma." Adv Exp Med Biol. 2023;1413:191-211.
6. Nizamoglu, M. et al., „Innovative three-dimensional models for understanding mechanisms underlying lung diseases: powerful tools for translational research." Eur Respir Rev. 2023 Jul 26;32(169):230042.

Urogenital Engineering

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Shaokai Zheng

Research Profile

The urinary tract (UT) includes two kidneys, two ureters, a bladder and one urethra. To achieve normal urination, all components of this system must work in a synergetic and correct way. The Urogenital Engineering (UGE) group aims at developing novel engineering-based solutions to improve the insight, the diagnoses and the treatments of UT diseases, many of which have a significant impact on health and quality of life. Our special research focus is on urinary obstructions (e.g., kidney, ureteral stones), underactive bladder, overactive bladder and urinary incontinence. Our translational projects address unmet clinical needs, which are identified and discussed with our clinical partners who are fully integrated in the project teams. In parallel to our computational fluid mechanical investigations, our biomedical flow experiments involve cutting edge technologies such as computer-controlled setups, various sensors (pressure, flow, volume, impedance), high-speed cameras and laser-based flow measurement systems.

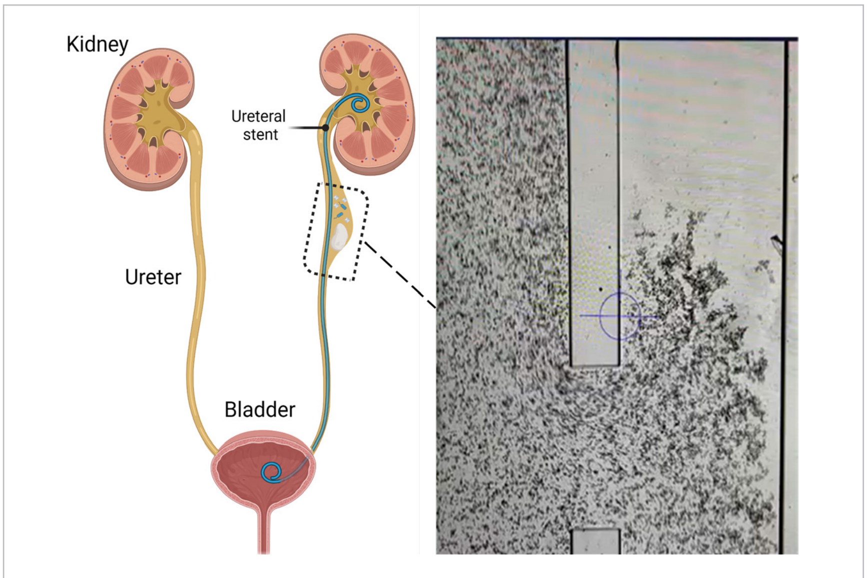

Fig. 1: Schematic of Urinary tract (UT) and microfluidic UT model (inset) to investigate crystal deposition in urinary stents and catheters.

Urinary tract modelling

A deep understanding of the normal UT function and its alteration due to pathologies is key to develop novel medical devices that can help patients. To this end, we have developed innovative platforms combining in-silico, in-vitro and ex-vivo modelling. Theses platforms mimic the fluid mechanical environment (pressure and flow) of UT and aim at: i) improving the insight on local fluid mechanics, ii) identifying the critical aspects of current medical devices and iii) testing new solutions. These platforms can be combined with an index matched fluid to allow particle image velocimetry (PIV) measurements for full fluid mechanical characterization. They can be used to test various medical devices such as urine drainage devices (urinary stents and catheters), devices for incontinence (artificial sphincters) and for urinary retention (see section 'New solutions to urinary retention'). Moreover, we have recently produced several microfluidic UT models to investigate, at microscale level, the dynamics of chemical and biological phenomena involved in encrustation and biofilm in urinary stents and catheters (see next paragraph).

Encrustation and biofilm in ureteral stents

Ureteral stents are frequently used in clinical settings to maintain the drainage of urine in the presence of ureteral obstructions (e.g., stones, tumours). Once in place, ureteral stents extend along the whole ureteral length, with side holes positioned at regular intervals. Encrustation and biofilm →

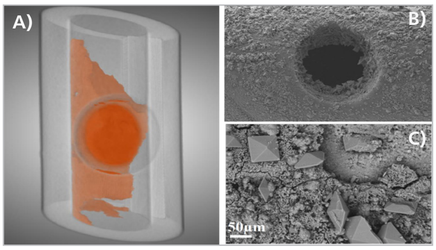

Fig. 2: Encrustation (orange) in ureteral stent (A). Examples of scanning electron microscopy (SEM) images of typical crystal found on stents (B and C).

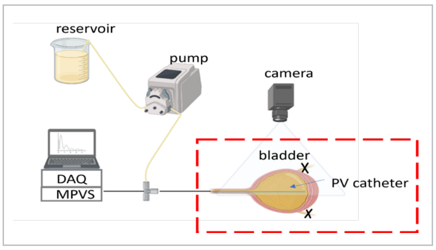

Fig. 3: Schematic of the ex-vivo setup for bladder pressure and volume measurements.

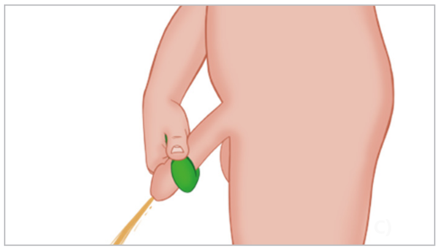

Fig. 4: Our handheld device, based on impedance pumping, for male patients suffering from urinary retention.

➔ are considered the main causes of stent failure, and our research is showing that their development in stented ureters is strongly influenced by local fluid mechanics (e.g., shear stresses). Ureteral stents, once implanted in patients, are exposed to complex fluid mechanical and biochemical environments. Location and extent of encrustation/biofilm in ureteral stents for different diseases may be informative for patient management and for the development of newer stent generations. In this context, current projects at UGE involve: i) the use of micro–computed tomography (µ-CT), combined with semantic segmentation, to quantify the encrustation/biofilm volume on ureteral stents, retrieved from patients and ii) scanning electron microscopy (SEM) combined with energy dispersive X-ray analysis (EDX) for morphological and chemical characterizations of the crystals. These investigations aim at: i) identifying the regions of the stents that are more prone to develop encrustation and ii) linking these regions to the local fluid mechanics (Fig. 2).

Improving the diagnosis of overactive bladder and incontinence

Patients suffering from overactive bladder (OAB) live with a continuous urge to urinate even at low bladder filling volumes, often leading to urinary incontinence. OAB has an enormous impact on the quality of life of affected patients. Despite the high prevalence, the understanding of the mechanism underlying OAB remains limited and, as a consequence, treatment options are scarce. UGE has developed several tools that aim to identify specific patterns in bladder pressure and bladder nerve signals associated with overactive bladder. For example, we have developed an algorithm that generates alarms before the start of an unwanted bladder contraction. The algorithm was successfully tested first in rats and then in patients using classical urodynamic signals. It could be used to warn the patients about an impending bladder contraction (to act against incontinence) or/and to trigger conditional sacral nerve stimulation (i.e., stimulation of bladder nerves to inhibit the bladder contraction). Moreover, our group has recently shown that catheters designed to measure cardiac volumes and pressure could be used in urology to better diagnose and treat lower urinary tract dysfunctions. These catheters could enable the evaluation of the bladder contractile function and the identification of local changes of bladder volume (e.g., during non-voiding bladder contractions). Non-voiding bladder contraction being typical in OAB patients, our approach can lead to more tailored treatment options (Fig. 3).

New solutions to urinary retention

We are developing non-invasive solutions to urinary retention. Patients suffering from urinary retention are unable to empty their bladder because of either a weak bladder muscle or/and a bladder outlet obstruction (e.g., enlarged prostate in men). The main complaints from these patients are pain, urinary tract infections, continuous sleep disruption, the necessity to plan for awareness of the location of toilets, impairment of social life, embarrassment, and reduced self-esteem. To date, catheters are the most common therapy for bladder emptying. However, catheters are invasive and very often cause urinary tract infections. Hence, a non-invasive solution for bladder emptying that does not lead to urinary tract infections is highly desirable. Our patent-pending technology is based on an innovative pumping principle (impedance pump), which generates urine flow by applying an external intermittent compression on the urethra (the outlet tube of the bladder) such that direct contact with urine is avoided. Being urine-contactless and non-invasive, this solution can drastically reduce urinary tract infections. This research has led to the development of an external/handheld prototype which has been tested in 10 male patients (i.e., first-in-man study). The same principle can also be applied to female patients. URODEA AG (www.urodea.com) is a spinoff of the ARTORG Center and is focusing on bringing this technology to the patients.

Selected Publications

1. Jahren S.E., Obrist D., Haenggi M., Burkhard F., Clavica F. „Can Cardiac Pressure-Volume Catheters Improve Urodynamic Assessment? An Ex-Vivo Proof-of-Concept." Frontiers in Urology 2023, 3, DOI:10.3389/fruro.2023.1258649
2. Zheng S, Amado P, Obrist D, Burkhard F, Clavica F., „An in vitro bladder model with physiological dynamics: Vesicoureteral reflux alters stent encrustation pattern." Frontiers in Bioengineering and Biotechnology, 2023. DOI:10.3389/fbioe. 2022.1028325
3. Zheng S., Obrist D., Burkhard F., Clavica F. , „Fluid mechanical performance of ureteral stents: The role of side hole and lumen size." Bioengineering & translational medicine Wiley, 2022. DOI: 10.1002/btm2.10407
4. Zheng, S., Amado, P., Kiss, B., Stangl, F., Haeberlin, A., Sidler, D., Obrist, D., Burkhard, F., Clavica, F. „Quantitative Evaluation of Encrustations in Double-J Ureteral Stents With Micro-Computed Tomography and Semantic Segmentation." Front. Urol. 2:836563, 2022. DOI: 10.3389/fruro. 2022.836563
5. Zheng, S., Carugo, D., Mosayyebi, A., Turney, B., Burkhard, F., Lange, D., Obrist, D., Waters, S., Clavica F. „Fluid mechanical modelling of the upper urinary system." WIRES Mechanisms of Disease, 2021. DOI: 10.1002/ wsbm.1523
6. Häberlin A., Schürch K., Niederhauser T.; Sweda R., Schneider M. P.; Obrist D., Burkhard F. C.; Clavica F. (2018). „Cardiac electrophysiology catheters for electrophysiological assessments of the lower urinary tract-A proof of concept ex vivo study in viable ureters." Neurourology and Urodynamics 87-96, 2019. DOI:10.1002/nau.23816
7. Niederhauser, T., Gafner, E., Cantieni, T., Grämiger, M., Haeberlin, A., Obrist, D., Burkhard, F., Clavica, F. „Detection and quantification of overactive bladder activity in patients: Can we make it better and automatic?" Neurourology and Urodynamics, 1 - 9, 2018. DOI: 10.1002/ nau.23357

Mechanical Design and Production

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Urs Rohrer
Piravin Jeyendran
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Meret Ruch
Jan Christen
Killian Brennan

Research Profile

The primary function of the Mechanical Design and Production (MDP) group is the co-development and manufacturing of mechanical and electro-mechanical components related to the research pursuits of the ARTORG Center. The MDP group supports all levels of the design and manufacturing process from concept to production. This includes Computer Assisted Design (CAD) modelling, prototyping and production with technical drawings, standard tooling, Computer Assisted Manufacturing (CAM), a CNC-milling-machine and a CNC-lathe (Computerized Numerical Control). We also support industrial and academic external research collaborators with their mechanical design and production needs.

Fig. 1: Overview of the MDP workshop at sitem-insel.

Training and Education

The MDP group has a second role in training. This training encompasses the skills required to operate machine shop tooling and equipment safely and proficiently, the knowledge required to achieve the best results with a variety of materials and the skills needed to efficiently manage the design and production workflow.

In 2022, we selected Lio Ritschard as our new apprentice, and he started his basic training on August 1, 2023, in the workshop of the Institute of Physics, University of Bern, and will join us in the workshop in spring 2024.

Our apprentice Piravin Jeyendran completed his basic training exam at the end of the second year with the partial exam and we congratulate him. In the coming two years, his training will focus more on CAD-CAM technologies and on manufacturing more ambitious parts.

Janosch Schär completed his four-year appreticeship with a grade of 5.1 and achieved one of the best results in the Bern-Biel Mittelland district. We congratulate him on this huge success. We employed him in our machine shop as a polymechanic until next year.

This year MDP has seen a big turnover in staff. Meret Ruch left at the end of April to take on a new challenge. We thank her for her commitment over the last two and a half years and wish her much success and all the best in her future. →

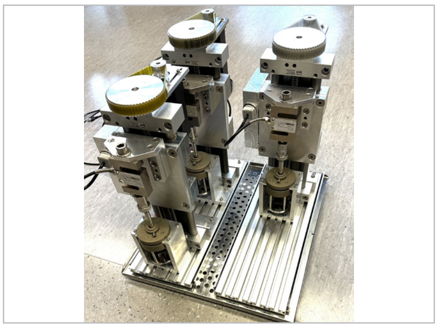

Fig. 2: Suprareactors for Orthopaedics.

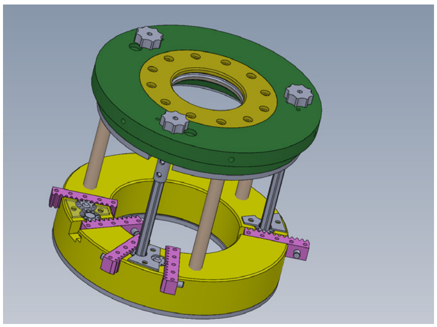

Fig. 3: New Mitral Valve Unit.

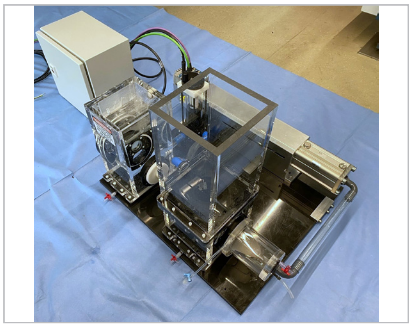

Fig. 4: Flow Loop built for Mitral Valve Unit.

Many ongoing projects necessitated a quick succession for Meret in the workshop and were able to welcome Jan Christen to our MDP team at the beginning of March. He decided to take a new direction in his career and left at the end of September. During his employment with us, he performed administrative tasks and increased team productivity. We thank him for his excellent work and support in our workshop.

Due to a high workload, we recruited a polytechnician, Killian Brennan as alternative civilian service employee at the end of this year. He performed administrative tasks and increased the productivity of our team. We thank him for the work he has accomplished in our workshop.

Research Equipment Design and Manufacturing

This year we were only able to work on a few small projects for ARTORG and hope that next year and in future we will again be able to work on more internal projects. A promising approach is the collaboration with the new research group for Robotics and Micromechatronics at the ARTORG Center led by Manuela Eugster.

The requirements for a workshop supporting research in biomedical engineering are as diverse as the research field itself. The diversity of topics researched at ARTORG and by external research partners results in a range of different design and production requirements, from prototypes for clinical and surgical tools to fixtures for mechanical, biological, and kinematic testing to accessories for imaging systems and calibration equipment. The following illustrations show some of this year's projects.

Inselspital, Department of Orthopaedic Surgery and Traumatology

In this project we were required to reconstruct and rebuild an already existing fixture device. The original function of the device was focused on the tensile load from the anterior cruciate ligaments and was manufactured in 2016.

The whole structure of the drive had to be reworked and the sample chamber parts had to be equipped for tensile tests of shoulder tendons. In 2022, we realized the first prototype of the device in collaboration with Dr. Slavko Corluka and master's student Manuel Garnier.

After the first tests showed positive results, we were able to optimize this first prototype. Following the positive results, we built two more units. By the end of this year, we have also constructed the device to be able to produce the fabric samples following the tensile tests (Fig. 2). In a next project, it is planned to manufacture one more device and to operate them in an incubator. We are sure that we will overcome any technical and practical challenges encountered during this process.

Inselspital, Department of Cardiology Echo Cardiovascular Center

One of the methods used to examine the heart muscle is ultrasound. With this procedure, cardiac activity, and the function of the four heart valves can be examined and visualized in real time. The parts for this mitral valve unit, which we designed, manufactured, and assembled in collaboration with Michael Stucki and Dr. med. Eric Buffle this year, make it possible to examine the function of the mitral valve. When using ultrasound, there must be no metallic objects in the sound field, as these interfere with the imaging. For this reason, this device had to be made from different special plastics (Fig. 3).

A first device of this nature had already produced by us in 2021, but it had been shown that the way in which it was constructed is not sufficient to simulate the malpositions of the mitral valve, which is located between the left atrium and main chamber of the heart and is intended to prevent oxygenated blood from flowing back into the atrium.

Physics for Medicine Paris

As in 2020, this year we were again able to produce a flow loop for use with the mitral valve unit described above and shown in Figure 3. A flow loop is used to simulate a small blood circuit of the left ventricle for research into the functions of the heart valves and has a modular design so that the corresponding valves can be installed if required. This research with our 2023 flow loop is being carried out by Dr. Eric Buffle at the Institute Physics for Medicine in Paris and we are looking forward to the results.

Dissertations

Yannick Rösch
Cardiovascular Engineering
Efficiency of intracoronary drug infusion into myocardial microcirculation with microvascular obstruction: in vitro study with a multiscale flow model

Klaus Schürch
Hearing Resaerch Laboratory
Advancements in Electrocochleography: Towards Improved Reliability and Objective Assessment

Benjamin Voumard
Musculoskeletal Biomechanics
Biomechanical Investigation of Dental Implant Stability and the Aging Femoral Neck

Lisette van Os
Organs-on-Chip Technologies
Immune cell migration during infection in organs on chip

Suhang You
Medical Imaging Analysis
Segmentation and Quality Control, Understanding Confounders Leading to Failure Modes in Medical Image Analysis with Deep Learning

Eduardo Villar Ortega
Motor Learning and Neurorehabilitation
Combining somatosensory stimulation with robotic training to enhance neurorehabilitation

Robert Poel
Medical Imaging Analysis
Radiotherapy oriented quality control for deep learning based fully automated segmentation of intracranial targets and organs at risk

Elias Rüfenacht
Medical Imaging Analysis
Data-centric and Clinically-relevant AI-based Segmentation of Intracranial Tumors and Organs-at-Risk for Radiotherapy

Aileen Näf
Gerontechnology and Rehabilitation
The Development, Application, and Evaluation of Virtual Reality Technology to Decrease Sensory Overload in the Intensive Care Unit

Noëlle Harte
Hearing Resaerch Laboratory
The spiral shape of the cochlea: Transverse flow visualizations and emerging phenomena in idealized models

Malavika Harikrishnan Nambiar
Computational Bioengineering
Material Characterization of the cornea: Towards Personalised Refractive interventions

Emile Talon
Hearing Resaerch Laboratory
Image-guidance for optimized bone conduction implantation

Alice Dudle
Musculoskeletal Biomechanics
DXA- and QCT-based modeling of the human proximal femur towards improved hip fracture prediction

Matthias Fontanellaz
AI in Health and Nutrition
From diagnosis to disease management: The use of AI in medical decision support systems

Oriella Gnarra
Gerontechnology and Rehabilitation
A New System of Wearables and Nearables to Monitor Sleep: from the Lab to Real-World Application

Research Partners

UNIVERSITY OF BERN

AlveoliX In-vitro models inspired by nature

AO Foundation

Bern University of Applied Sciences

CASCINATION

CHUV

City of Hope

CorFlow Therapeutics

csem

Danderyds Sjukhus

DEBIOTECH

DLR

DOMO CARE

EMPA Materials Science & Technology

ENIUS

EPFL

ETH zürich

INSELSPITAL UNIVERSITÄTSSPITAL BERN HOPITAL UNIVERSITAIRE DE BERNE BERN UNIVERSITY HOSPITAL

force dimension

GERIATRISCHE KLINIK ST.GALLEN

HFR hôpital fribourgeois freiburger spital

HIPS HELMHOLTZ Institute for Pharmaceutical Research Saarland

Lucerne University of Applied Sciences and Arts HOCHSCHULE LUZERN

Hocoma a DIH brand

HUG Hôpitaux Universitaires Genève

Inria INVENTEURS DU MONDE NUMÉRIQUE

Imperial College London

Kantonsspital Aarau

Karolinska Institutet Anno 1810

luzerner kantonsspital

McGill UNIVERSITY

MDC MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE IN THE HELMHOLTZ ASSOCIATION

MED-EL

Newcastle University

sitem-insel

UKBB University Children's Hospital Basel

Optimeyes

Oslo University Hospital

OVIVA Freude am Leben

PAUL SCHERRER INSTITUT PSI

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UNIVERSITÄRE PSYCHIATRISCHE DIENSTE BERN

ulm university universität uulm

UZA

UniversitätsSpital Zürich

VASCULAR INSTITUTE SWITZERLAND

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