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ARTORG CENTER
BIOMEDICAL ENGINEERING RESEARCH

ARTORG CENTER
ANNUAL REPORT 2022

Foreword

Dear friends, colleagues, collaborators, and partners

2022 was marked at the ARTORG Center by a spirit of renewed energy and excitement.

Our research and teaching activities were revitalized by in-person exchange, travel, learning experiences and the arrival of new members from diverse backgrounds and skillsets.
We successfully secured funding for prestigious and innovative projects, including European projects, in spite of Switzerland's current difficult status within EU research.
FDA approvals of medical technology solutions we developed and the 2022 Swiss Medtech Award win of the spin-off company AlveoliX testify to the continued excellent quality and translatability of ARTORG research into clinical care.

2023 marks the 15th anniversary of our Center of Excellence for Biomedical Engineering Research. With the beginning of this new year, we look forward to taking the ARTORG Center into the next decade of healthcare innovation through patient-centered engineering solutions and digital technologies.

With our newly formed Scientific Advisory Board (SAB) to help guide us towards this endeavor, and the establishment of a new professorship in mechatronics and robotics at the ARTORG in collaboration with our clinical partners at the Inselspital, Bern University Hospital, we are confident to hold an exciting and visionary portfolio of research.

I wish you all good health and an enjoyable read.

Sincerely,

Raphael Szitman
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

MLN
Motor Learning and Neurorehabilitation

MSB
Musculoskeletal Biomechanics

OOC
Organs-on-Chip Technologies

UGE
Urogenital Engineering

MDP
Mechanical Design and Production

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Artificial Intelligence in Medicine

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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

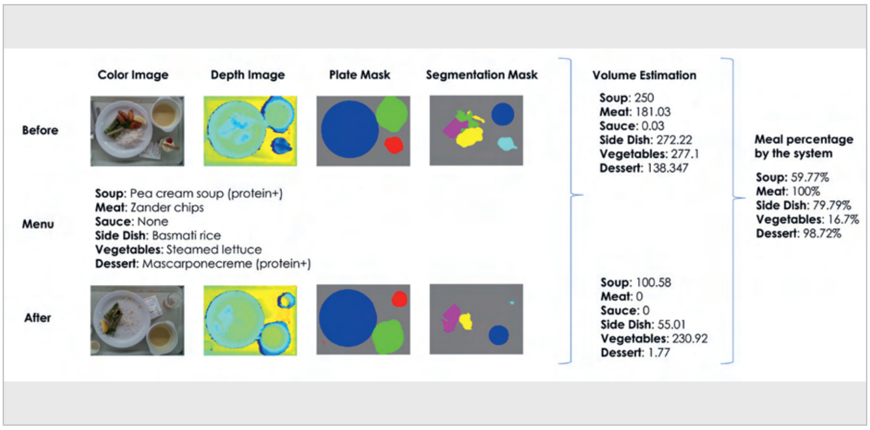

Fig. 1: Tackling hospitalised malnutrition: The system for hospitalised patients receives as input the daily menu and the tray images and estimates the volume of each dish before and after consumption.

Nutrient Intake Monitoring and Diet Assessment

Food is a key element of our life; it is socially and culturally important and plays a vital role in the definition of health. Preventing the onset and progression of diet-related acute and chronic diseases (e.g., diabetes, obesity, kidney disease) requires reliable and intuitive systems that can translate food intake into nutrient intake. To this end, systems based on innovative technologies are being introduced to exploit recent advances in computer vision, machine learning, wearable sensors, and smartphone technologies. Since 2008, AIHN has been developing technologies for monitoring nutrient intake and assessing diet by analyzing food multimedia data with AI. We have introduced the first fully operative system that estimates the carbohydrate content of meals consumed by individuals with type 1 diabetes. The first prototype was developed within the framework of the GoCARB project and has been successfully validated in a number of preclinical and clinical trials.

We are addressing the entire pipeline - from food identification and recognition to food volume and nutrient content estimation. A broad spectrum of different mobile technologies is being investigated to meet the diverse needs of people of different ages, health status, and environment. Currently, the system is being optimised and extended to meet the needs of people with diet-related diseases to help →

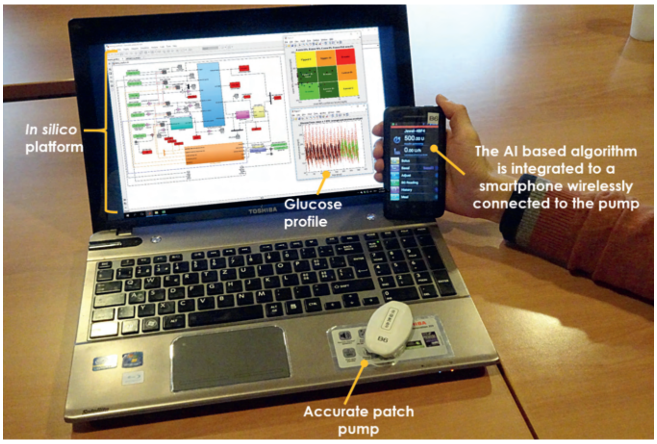

Fig. 2: The AI-based algorithm, integrated into a highly secured Android smartphone, takes input from either a blood glucose meter or continuous glucose monitors, and outputs the daily insulin treatment. The algorithm learns while being used by the patient and is able to provide personalised advice on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

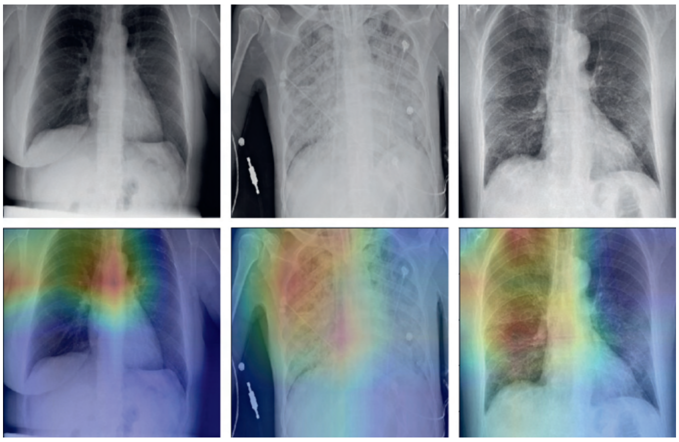

Fig. 3: Top row: three sample CRX (left: sample for healthy class, middle: sample for other types of pneumonia, right: COVID-19 pneumonia), bottom row: overlaid class activation maps.

them manage their dietary and nutrient intake and fulfil the needs of healthcare professionals in assessing the nutrient intake of both outpatients and hospitalised patients. Several validation studies are ongoing (http://go-food.tech/).

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, physical activity) trackers provide input to the algorithm, which outputs basal daily insulin and boluses for the case of pump users or suggestions regarding the daily adjustment of long-acting (basal) and rapid-acting (bolus) insulin for the case of users under multiple daily injections (MDI). The algorithm is based on reinforcement learning, a type of AI that teaches systems to learn. Our self-learning approach is adaptable and personalises daily insulin values to ensure glucose control, despite the inter- and intra-patient variabilities. The approach is data-driven, real-time, and of low computational cost. The US FDA-approved diabetes simulator was used to validate the newly introduced algorithm. The algorithm was able to achieve glucose control over the course of four virtual trials that lasted three months, under extreme scenarios of disturbances, uncertainties, and variabilities. After the in silico clinical trials, the algorithm was implemented on a mobile application. A feasibility study will start within the next months.

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, and other disease-related data 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.

During the last two 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) based on the AI-powered analysis of imaging, clinical/laboratory, and patient's history data.

Selected Publications

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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 with several research projects that involve research challenges in both diagnostic and interventional contexts.

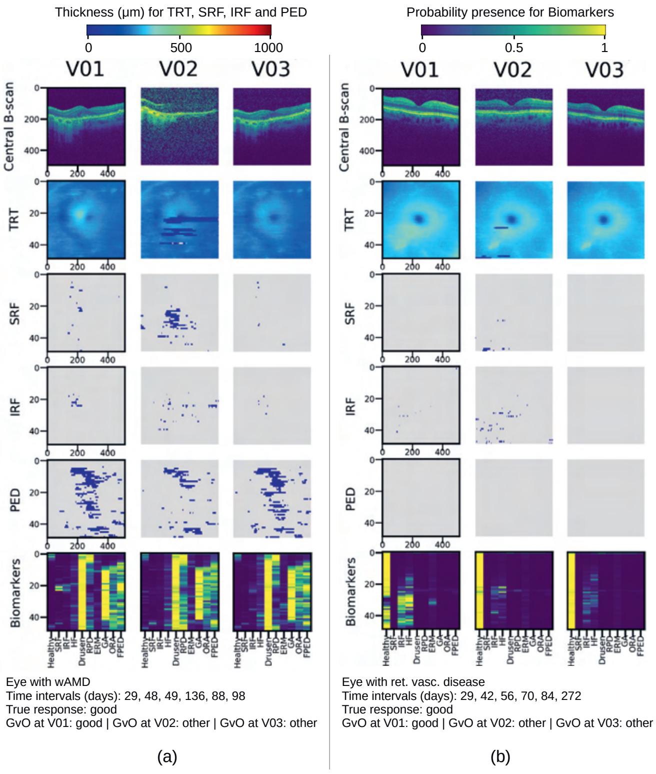

Fig. 1. Automatic detection and segmentation of surgical instrument during endoscopy.

Predicting patient responses to anti-vegf treatment for chronic retinal conditions

Assessing the potential of machine learning to predict good and poor treatment response as well as mean treatment interval in real life in patients with wAMD, RVO and DME treated according to a TRE offers great hope for managing patients in the disease mangment. To this end, we conducted a retrospective cohort study including over 500 patients, treated with anti-VEGF according to a predefined TRE protocol during 2014-2018. Eyes were grouped by disease into good, medium and poor responders, defined by the average treatment interval (good: ≥10 weeks, poor: ≤5 weeks, medium: remaining eyes). Two Random Forest models were trained to predict the probability of the long-term treatment response of a new patient. Based on the first three visits it was possible to predict a good and a poor treatment response in eyes with similar accuracy. In conclusion, machine learning classifiers are able to predict treatment response and may assist in establishing patient specific treatment plans in the near future.

Consistency-preserving Visual Question Answering in Medical Imaging

Visual Question Answering (VQA) models take an image and a natural-language question as input and infer the answer to →

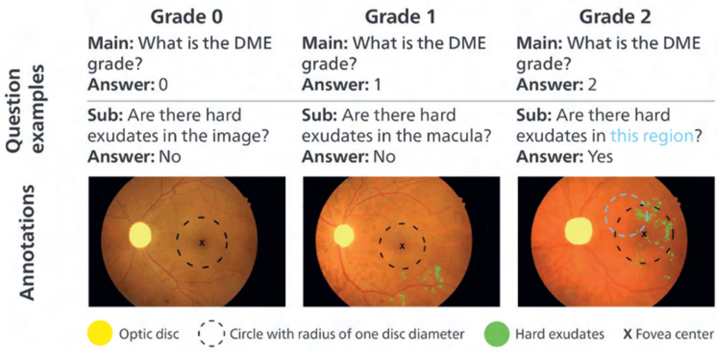

Fig. 2: DME risk grading Grade 0 is assigned if there are no hard exudates present in the whole image. Grade 1 is assigned if there are hard exudates, but only located outside a circle centered at the fovea with radius of one optic disc diameter. Grade 2 is assigned if there are hard exudates located within the circle. Examples of main and sub-questions are provided for each grade.

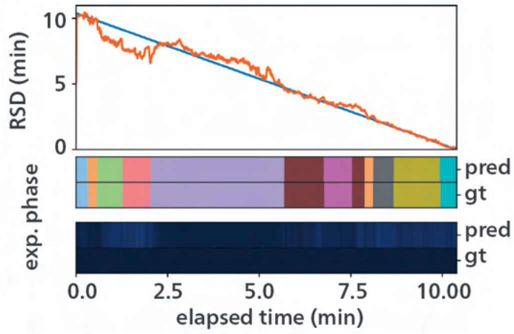

Fig. 3: CataNet: (top) the concordance between ground-truth and predicted RSD, (middle) the ground-truth and predicted surgical phases over time, and (bottom) the ground-truth and predicted probability of the surgeon's experience level.

the question. Recently, VQA systems in medical imaging have gained popularity thanks to potential advantages such as patient engagement and second opinions for clinicians. While most research efforts have been focused on improving architectures and overcoming data-related limitations, answer consistency has been overlooked even though it plays a critical role in establishing trustworthy models. In this work, we propose a novel loss function and corresponding training procedure that allows the inclusion of relations between questions into the training process. Specifically, we consider the case where implications between perception and reasoning questions are known a-priori. To show the benefits of our approach, we evaluate it on the clinically relevant task of Diabetic Macular Edema (DME) staging from fundus imaging. Our experiments show that our method outperforms state-of-the-art baselines, not only by improving model consistency, but also in terms of overall model accuracy.

CataNet: Predicting remaining cataract surgery duration

Cataract surgery is a sight saving surgery that is performed over 10 million times each year around the world. With such a large demand, the ability to organize surgical wards and operating rooms efficiently is critical to delivery this therapy in routine clinical care. In this context, estimating the remaining surgical duration (RSD) during procedures is one way to help streamline patient throughput and workflows. To this end, we propose CataNet, a method for cataract surgeries that predicts in real time the RSD jointly with two influential elements: the surgeon's experience, and the current phase of the surgery. We compare CataNet to state-of-the-art RSD estimation methods, showing that it outperforms them even when phase and experience are not considered. We investigate this improvement reviewed{ and show that a significant contributor is the way we integrate the elapsed time into CataNet's feature extractor.

A Positive/Unlabeled Approach for the Segmentation of Medical Sequences using Point-Wise Supervision

The ability to quickly annotate medical imaging data plays a critical role in training deep learning frameworks for segmentation. Doing so for image volumes or video sequences is even more pressing as annotating these is particularly burdensome. To alleviate this problem, this work proposes a new method to efficiently segment medical imaging volumes or videos using point-wise annotations only. This allows annotations to be collected extremely quickly and remains applicable to numerous segmentation tasks. Our approach trains a deep learning model using an appropriate Positive/Unlabeled objective function using sparse point-wise annotations. While most methods of this kind assume that the proportion of positive samples in the data is known a-priori, we introduce a novel self-supervised method to estimate this prior efficiently by combining a Bayesian estimation framework and new stopping criteria. Our method iteratively estimates appropriate class priors and yields high segmentation quality for a variety of object types and imaging modalities. In addition, by leveraging a spatio-temporal tracking framework, we regularize our predictions by leveraging the complete data volume. We show experimentally that our approach outperforms state-of-the-art methods tailored to the same problem.

Selected Publications

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4. Lejeune, L. and Sznitman, R., "A Positive/Unlabeled Approach for the Segmentation of Medical Sequences using Point-Wise Supervision", Medical Image Analysis, 2021

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: Optical flow quantification 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 more 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 optical measurement technology for quantifying complex three-dimensional blood flow fields (Fig. 1). Our experimental approach is complemented by high-fidelity flow solvers for transitional to 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 (Fig. 2).

Our research infrastructure enables us to perform ex vivo, in vitro, and in silico tests of different valve designs, and patient-specific modelling provides a tool for identifying the optimal personalized valve replacement therapy.

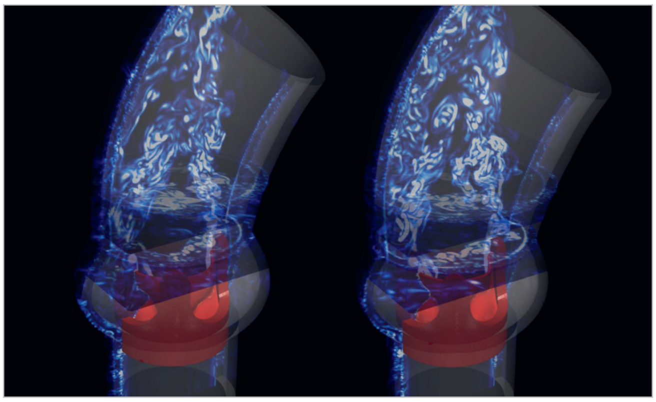

Fig 2: Turbulent blood flow after bioprostehtic aortic valve in a normal (left) and enlarged (right) ascending aorta.

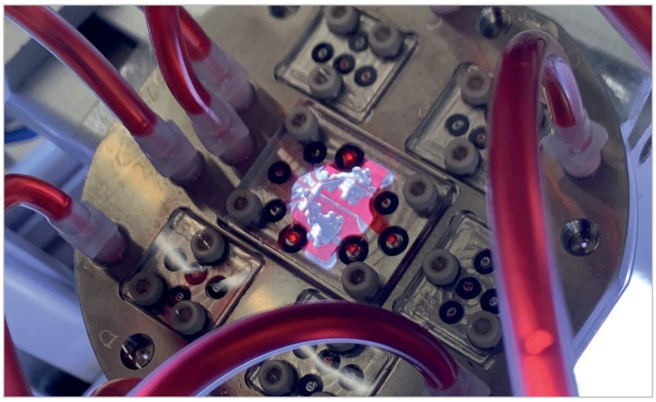

Fig 3: Microfluidic chip to model the blood flow in the heart muscle.

Myocardial Infarction

The heart muscle is supplied with oxygen and nutrients through the coronary circulation whose complex network topology at different spatial scales (epicardial vessels, collaterals, coronary microcirculation) is a central factor in the outcome of myocardial infarctions (heart attacks).

Microvascular obstruction (MVO) of the myocardium is an underdiagnosed condition caused by heart attack, which may delay or even prohibit full recovery. In MVO, blood flow at the level of the cardiac microcirculation is partially blocked such that affected regions of the heart are insufficiently perfused.

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. 3). It is used to study transport of substances (e.g. pharmaceutical agents) in the myocardium and to optimize infusion protocols for catheter-based treatment of MVO.

Dielectric Elastomer Augmented Aorta

Together with the Center for Artificial Muscles (CAM) 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), the Dielectric Elastomer Augmented Aorta compresses and dilates a section of the aorta. This supports the function of the heart by reducing the afterload (aortic blood pressure) and by increasing the coronary perfusion. The device makes use of a dielectric elastomer that actuates the pump.

We are using an in vitro benchtop model and in vivo trials to optimize the design and actuation pattern of the device. Analysis of the experimental data and theoretical models of aortic pulse propagation provide novel insight into the mechanics of the beating heart.

Capillary Blood Flow

Capillary vessels of the microcirculation are the smallest blood vessels (diameter 5 micrometer). Oxygen and nutrient exchange with the surrounding tissue takes place in the capillary networks. In contrast to blood flow in larger blood vessels, capillary blood flow follows different physical laws, which is related to the fact that capillaries are so small that red blood cells must squeeze through these vessels such that 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. We investigate how the network topology affects the heterogeneous distribution of red blood cells in the network and how the system reacts to local obstructions (e.g., micro-strokes). To study blood flow regulation mechanisms at the smallest scales, we have developed microfluidic valves to model pericyte cells that wrap around capillaries to locally dilate and constrict the vessels.

Selected Publications

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Computational Bioengineering

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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.

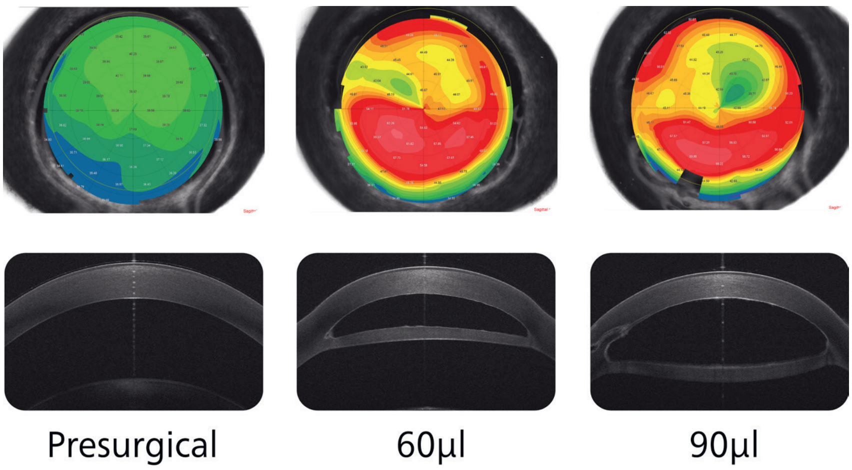

Fig. 1: Hyperoptia correction of more than ten diopters is achieved by injection of hydrogel in a pocket inside a porcine cornea (refractive maps, top row). The injected hydrogel is visible in the OCT images (bottom row).

Filler-driven hyperopia correction

Laser refractive surgery is a popular treatment for the correction of myopia, hyperopia and astigmatism. In this procedure, the cornea is permanently reshaped with a laser to restore the patient's visual acuity. The effect of laser surgery is achieved by removing corneal tissue with an excimer laser, which weakens the corneal structures.

In the past year, we have investigated an alternative treatment approach that involves precise hydrogel injections in a central pocket to reshape the corneal surface and correct hyperopia (Fig. 1). In addition, this augmentation procedure improves corneal stability rather than weakening the tissue. Our results have shown that significant refractive corrections of more than ten diopters can be achieved. Several factors play a role in the amount of refractive error corrected, such as the injected volume and the proper alignment of the patient.

This treatment, based on corneal augmentation, could provide an alternative for patients who are not candidates for current laser surgery due to the technical limitations of laser ablation. New treatment options are particularly important given the increasing prevalence of high myopia in the population.

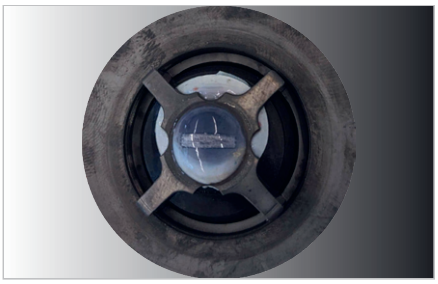

Fig. 2: Corneal strips were extracted from animal and human specimens with a femtosecond laser for mechanical characterization.

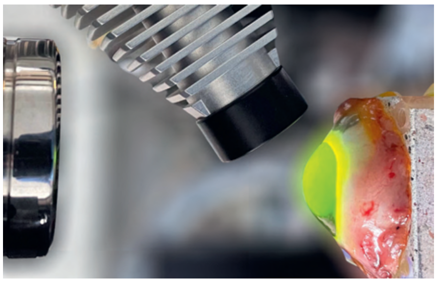

Fig. 3: Change in corneal axial deformations induced by corneal crosslinking measured by optical coherence elastography.

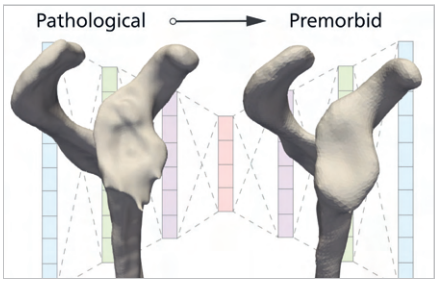

Fig. 4: Deep learning prediction of the premorbid "healthy" shape of the scapula from the current pathological bone anatomy.

Biomechanical simulation platform for personalized refractive interventions

The cornea is responsible for about 2/3 of the optical power of the visual system. Therefore, small changes in corneal shape or curvature have a significant impact on the patient's vision. Because the morphology and biomechanics of the cornea are different for each patient, generic surgical planning models are not suitable for accurately predicting the outcomes of refractive surgery. In fact, current refractive surgeries are still associated with 10-15% under- or over-correction. Patient-specific numerical models can improve the planning of refractive surgery. Still, they require accurate characterization and mathematical description of the biomechanics of the human cornea.

Since it is difficult to obtain human corneas, we developed a biomechanical characterization based on surgical waste: unused corneal grafts after partial transplantation and tissue harvested during refractive procedures. Samples at different depths of the cornea were prepared with a femtosecond laser (Fig. 2). Uniaxial tests showed that the anterior cornea behaves isotropically and that the stiffness of the tissue decreases as one moves from the anterior to the posterior surface. Using these experimental data, mechanical models of the cornea are being developed to integrate numerical simulations of refractive surgery.

Our results showed that OCT-based numerical models have great potential to guide clinicians regarding the optimal treatment approach.

Local corneal stiffening for refractive correction

Corneal crosslinking (CXL) is a treatment that can halt the progression of keratoconus, a condition caused by a localized weakening of the cornea. This treatment uses riboflavin drops and ultraviolet light to significantly increase corneal stiffness. Based on this clinical success, this procedure could be extended to also correct mild to moderate refractive errors in otherwise healthy individuals. By carefully planning the shape of the crosslinking pattern on the patient's cornea, controlled spatial variations in the biomechanical stiffness of the cornea are induced, altering its curvature and therfore the patient's vision.

Preliminary studies have shown that different crosslinking patterns (e.g., bow-tie, central spot, trefoil) lead to quantifiable changes in the axial deformation of the cornea, as measured by optical coherence elastography (Fig. 3). Importantly, the change in axial deformation measured with elastography corresponds to changes in anterior corneal curvature. Biomechanical models of the proposed approach are developed to allow accurate predictions of postoperative outcomes and optimize the CXL patterns to achieve the desired optical changes.

Deep learning to quantify the premorbid shape of shoulder bones

Total shoulder arthroplasty (TSA) is an increasingly common surgical procedure to relieve pain and disability associated with glenohumeral osteoarthritis (OA). This procedure involves replacing the degenerated glenohumeral joint with a prosthesis. Accurate positioning of the glenoid component of the implant is critical to the long-term success of TSA, as improper positioning can lead to glenoid implant failure or joint dislocation. However, determining proper glenoid implant positioning is challenging because OA significantly alters the anatomy and orientation of the bone in the area of joint contact. In addition, because OA usually affects both shoulders, it is impossible to rely on contralateral morphology.

Therefore, we developed an autoencoder-based approach to objectively predict the premorbid anatomy of the scapula. Our initial results show that the premorbid prediction reflects the healthier anatomy and restores the alignment of the joint contact surface (Fig. 4). This technique has the potential to reconstruct the premorbid shape of the glenoid cavity as it was before degeneration and thus guide the positioning of glenoid implants according to the patient's natural anatomy during shoulder joint replacement.

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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 disorders both in the hospital and at home. Core methodologies include telemonitoring, telerehabilitation, and virtual reality (VR) technology.

The research group partnered with the department of neurology (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 disorders influence daily life.

Fig. 1: Setup in an intensive care unit with physiological data recording and behavioral data recording (e.g. movement) for the early prediction of delirium. Once detected, a VR-based cognitive stimulation is used to comfort the patient and to reduce delirium.

Virtual reality stimulation for critically ill patients to reduce delirium

The aim of intensive care medicine is to treat the life-threatening conditions of critically ill patients, giving them the opportunity to continue their lives post-discharge. Unfortunately, the literature suggests that up to 50-75% of all critically ill patients experience short- and long- term cognitive impairment after a prolonged stay in the intensive care unit (ICU). It has been suggested that the cognitive impairment is a result of the noisy and stressful environment of the ICU. Therefore, one method of addressing this problem is coming up with solutions to help these critical care patients get some sensory reprieve. A promising new approach developed in our group is the use of virtual reality technology within the ICU. Virtual reality (VR) nature stimulation via a head-mounted display (HMD) moves the patient away from the ICU into a calming and pleasant environment (Fig. 1). Therefore, VR is a promising unexplored avenue to improve attentional-cognitive functions and to reduce chronic stress during an ICU stay.

Following a series of studies conducted by our group, we can conclude that first, VR stimulation by using a HDM is safe to use within the intensive care unit, did not evoke any negative side effects, and was highly accepted by clinicians and patients. Moreover, the findings provided evidence that VR nature stimulation comforts critically ill patients. Second, it was found that the VR stimulation had a relaxing →

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).

effect in the participants, as shown in vital markers of physical stress. Therefore, this work highlighted great potential to prevent and reduce cognitive impairment in critically ill patients. Future studies will continue to build on this work with a focus targeted toward delirium within the intensive care unit.

Virtual reality training for brain injured patients

Cognitive impairments are a frequent problem after right-hemispheric stroke. One kind of cognitive impairment is an attention disorder called spatial neglect, where subject cannot detect or respond properly to visual stimuli coming from the left side. Neglect results in a reduction in quality of life and performance in activities of daily living. In our work, we aim to develop a tool to assess and rehabilitate this neglect using virtual reality. The main idea for the rehabilitation is to guide the patients' attention back to the left side using different kind of stimuli. In a first pilot study with a simple visual search task, a high usability and acceptance of the virtual reality system was shown in stroke patients as well as in young and elderly healthy participants. A second study in healthy participants revealed that the combination of auditory and tactile cues is the best combination (compared to audio or tactile only) to guide the attention toward a certain target.

Another ongoing study regarding assessment is about to show the behavior of neglect patients in a dynamic search task compared to healthy participants and its correlation with the impairments in daily living due to their neglect.

Tele-monitoring for neurodegenerative diseases – the advancement of pervasive computing

Due to the advancements in technology in the past few years, pervasive technology has become more widely available. Small wearable sensors, such as smart watches, can track movement reliably through accelerometers and gyroscopes over extended periods of time, without disturbing the wearer. With the addition of photophletysmogram (PPG) sensors, heartbeat and all derivative values can be monitored without the need for a full ECG. Sensors placed on or around objects, such as ferro-electric mats for under the mattress, can monitor heart rate and breathing patterns during the night without the need for any contact sensors. And finally, ambient sensors placed permanently, yet unobtrusively in participants' homes, can track location and behavioral patterns throughout the home. Technology used for this include passive infrared (PIR) sensors, magnetic door sensors, and radar-technology based sensors.

Unobtrusive, but continuous monitoring of health-related indicators has been shown to be both feasible as well as accepted by the target groups. Those groups include both the oldest as well as patients with neurodegenerative diseases, such as Parkinson's disease.

In a study with people with Parkinson's disease (PD), the acceptance and adherence to a set of ambient and wearable sensors was tested with very good feedback. The usage of wearable sensors is especially crucial for the monitoring of PD patients, as both the symptoms and the disease progress are highly individual in their manifestations. It's imperative for the treating doctors and therapists to adjust medication and therapy to the needs of the patients. Current state of the art are self-reporting methods.

Their accuracy is often limited by the patients' recall bias when filling in. Wearable sensors, worn on the movement-dominant body parts can track typical PD-related motor symptoms, such as slowness of movement, tremors, rigidity, or the typical medication side effect – dyskinesias. Through a series of signal processing-based feature extractions and machine-learning-based symptom classification, we are working toward a more reliable symptom tracking system. This not only helps the doctors and therapists, but also increases quality of life for the patients by removing the burden of keeping a symptom diary.

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Hearing Research Laboratory

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Research Profile

The Hearing Research Laboratory is a research collaboration between the ARTORG Center and the Department of Otorhinolaryngology, Inselspital (Bern University Hospital). Our multidisciplinary team combines the expertise of engineers, audiologists, surgeons, and physicists. Our goal is to develop new medical devices and technologies that help hearing-impaired people and assist clinicians in the diagnosis and treatment of inner ear disorders. The range of research activities in our group includes psychoacoustic experiments, anatomical and electrophysiological studies, development and implementation of clinically applicable software and devices, and observational studies and clinical trials. To achieve sustainable research progress, our team members actively collaborate with leading medical, academic, and industrial partners in hearing research.

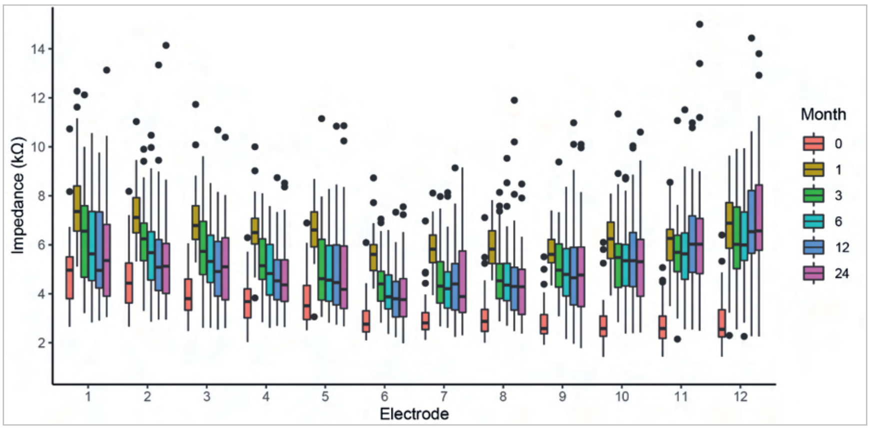

Fig. 1: Course of the electrical impedance of individual cochlear implant electrodes over a period of 2 years.

Personalized Tinnitus Diagnostics and Relief
(Innosuisse Grant No. 44423.1)

Tinnitus is the perception of noise or ringing in the ears without an external stimulus. Tinnitus can lead to severe psychological complaints and can substantially impair quality of life. The high prevalence (about 10% of the general population) and the lack of generally applicable therapies are driving the demand for care solutions for tinnitus patients. In this project, we develop a new hearing aid feature that allows personalized acoustic stimulation for tinnitus relief (PASTOR). PASTOR utilizes the possibility of temporary tinnitus suppression after an acoustic stimulus (residual inhibition), a phenomenon frequently observable in tinnitus patients. It can be used according to the current personal situation, e.g., at night as an aid to fall asleep or in times of high emotional and psychological stress. As more than 80% of tinnitus cases are associated with hearing loss, hearing aids are the ideal platform for an implementation. Moreover, as a secondary outcome of the project, we expect innovative diagnostics, contributing to a better understanding of tinnitus.

Physiological Role of the Spiral Shape of the Cochlea
(SNSF Grant No. 205321_200850)

Many believe that the spiral shape of the cochlearesults from spatial constraints and that the coiling offers no particular

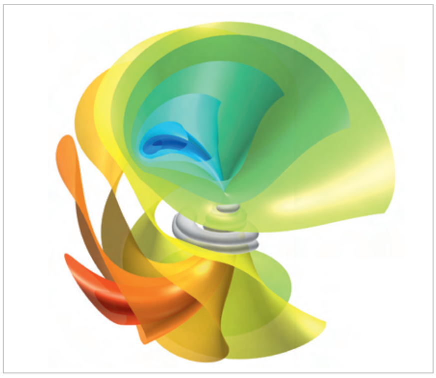

Fig. 2: Visualization of isosurfaces indicating the degree of curling of a non-linear vector field for geometric description of the human cochlea.

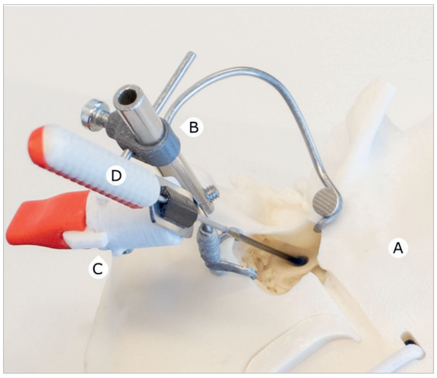

Fig. 3: Temporal bone model (A), with the insertion tool mount (B), magnetic fixation (C) and insertion tool (D) installed. Invasive cochlear implantation.

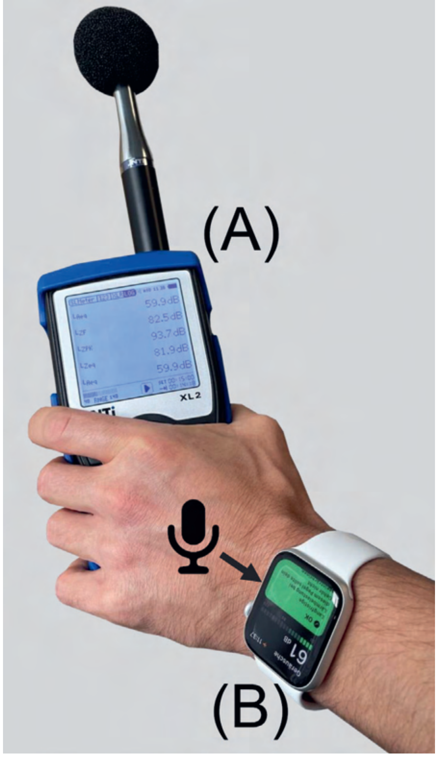

Fig. 4: Noise monitoring using a sound level meter (A) and a smartwatch (B).

advantages for hearing. However, this conclusion is based on studies that mainly focused on geometric curvature and neglected possible effects of torsion on sound propagation within the cochlea, especially secondary flow phenomena. This project aims to systematically investigate the role of geometric torsion on fluidmechanical processes in the cochlea. As part of the project, we are developing a shape-parameterization method based on kinematic surface fitting that will enable unbiased classification of cochlear morphology. In addition, computational fluid dynamic simulations are performed to estimate secondary flow profiles.

Finally, we will conduct an observational study to correlate individual cochlear shape parameters obtained from high-resolution magnetic resonance imaging with the subject hearing performance.

Cochlear Implant Technology

We are working on the advancement of cochlear implants and implantation technology. Cochlear implants are hearing prostheses with an electrode array that is inserted into the inner ear to enable deaf people to hear again. Our group is developing new instrumentation for minimally invasive insertion of electrode arrays into the cochlea.

Cochlear implants can also be used as a measurement device. The technique is called telemetry and allows measurement of electrode impedances and responses of the sensory epithelium (e.g. ECochG) as well as nerve responses (e.g. ECAP). Our group has developed promising approaches to use telemetry data for clinical purposes. For example, telemetry-based impedance data can be used to estimate the position of electrode contacts in the cochlea or to monitor the degree of hearing preservation after surgery. Algorithms developed in our group can assist surgeons in inserting electrodes and provide them with feedback on the functional and structural integrity of the inner ear (Fig.1).

Smartwatches in Audiology

Loud noise at work or during leisure time can cause hearing loss or tinnitus. However, monitoring by professional sound level meters is not practical in everyday life. We are, therefore, evaluating smartwatch-based applications for monitoring noise exposure. We believe that smartwatches will play an important role in the assessment of personal noise exposure and should be used as widely available and cost-effective means of hearing protection for clinical research. Ongoing work of our group is further focused on the use of smartwatches for clinical diagnostic purposes in tinnitus, hearing loss, and vertigo.

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Research Profile

Simulation and modelling, imaging and sensing, visualisation and robotics have reached sufficient quality and resilience to be introduced into clinical care. Research led by the Chair for Image-Guided Therapy leverages these developments to research technological innovations that could supersede the human operator inside the clinical environment. The investigations seek to i) challenge current clinical procedures and ii) conceive new procedures that provide treatment to the untreated, by setting the limits of novel clinical interventions according to technological capabilities, and not the limitations of human faculties. Translational aims for projects mean close relationships with partners, through both clinical and academic collaborations.

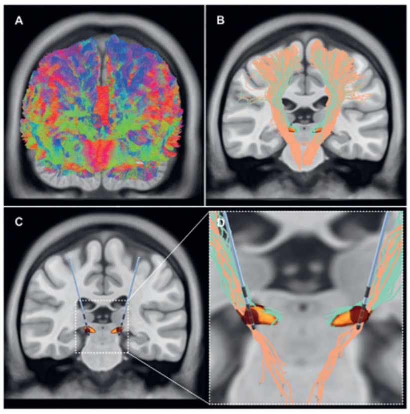

Fig. 1: Pathway activation by DBS. A: Whole-brain tractogram. B: Streamlines of pathways of interest (green: hyperdirect pathway; salmon: corticospinal tract; orange: subthalamic nucleus). C: DBS leads localization

Mapping and Modelling of Deep Brain Stimulation

(SNSF Ambizione 186142)

TBrain Neuromodulation focuses on developing computer-assisted programming for deep brain stimulation (DBS). Finding therapeutic stimulation settings has become more complex with directional DBS and may take several hours of testing. In one approach, stimulation maps that highlight effective stimulation regions are computed. In another approach, patient-specific tractography that highlight effective tracts in the brain are used. Both approaches can guide DBS programming. For DBS to treat Parkinson's disease, the optimal stimulation level or contact are suggested with about 60 % accuracy. For DBS to treat psychiatric diseases such as treatment-resistant depression, preliminary work was performed to identify effective tracts. (Fig. 1).

Fighting Liver Cancer

(H2020 MSCA-ITN 722068
Innosuisse 37855.1 IP-LS)

For patients that suffer from non-spherical, larger, or critically located tumors, the success of thermal ablation treatment is not guaranteed, as the lesions potentially →

result being over-ablated, and the surrounding structures might be at risk. The aim is to remove these limitations, by providing an automated thermal ablation treatment model, using image-based planning and robotically assisted ablation, through synchronous probe retraction and ablation energy modulation. An experimental prototype was built and a proof-of-concept regarding its feasibility was conducted in a controlled environment using tissue mimicking specimen (Fig. 2).

Virtual Histopathology of the Inner Ear by MicroCT

Anatomical investigations of the human cochlear architecture are challenging due to the organ's helical shape and encasement in the petrous bone. The limitation of histopathological studies is that they do not allow for realistic isotropic perception or reconstructions. Novel 3D imaging techniques can improve the morphological assessment of cochlear structures before and after therapeutic procedures. With the aid of geometric enlargements, angular scanning, and noise reduction, micro-CT systems can provide focal spot sizes down to 200–500 nm (Fig. 3).

Robotic Cochlear Implantation
(SNF Project Number 176007)

In recent years, the research on the procedure for robot-assisted cochlear implantation developed by our group has been translated into a medical device. Our group continues research on other aspects, such as the long-term fixation of the implant receiver-stimulator on the temporal bone and a refined planning methodology for access to the inner ear. More specifically, we proposed to use the robotic system and intraoperative planning to robotically mill a channel and an implant bed to store and protect the implant electrode and housing. Research on inner ear access focused on a refined planning strategy with automatic trajectory computation to reduce the impact of uncertainty in human decision-making on the consistency of the procedure. An experimental study in a human-ex-vivo model was designed to investigate feasibility toward a minimally invasive robotic lead channel creation both in technical phantoms as well as in ex-vivo. (Fig. 4).

Robotic Spine Surgery
(Bridge Discovery 176498, Innosuisse 29936.1 IP-ENG)

Placement of pedicle screws to fuse vertebral segments is a challenging task for surgeons. In recent years, a robotic-assisted platform to drill pilot holes was developed. To verify the accuracy of the prototype platform, multiple phantoms where conceptualized and built, each focusing on different accuracy aspects within the present workflow. The most complex phantom supports dynamic dislocation in two degrees of freedom of the vertebra as a result of drilling manipulation. Multiple accuracy experiments were conducted to determine the platform's performance (Fig. 5).

High-Fidelity Neuroendovascular Simulator
(Innosuisse 51144.1 IP-LS, Herzstifung FF20061)

Intracranial aneurysms are complex to treat. Recently, neuronavigational robots like CorPath GRX (Siemens Healthineers) have been used to treat patients found challenging to treat by accessing complex pathologies. To better prepare for the robotic endovascular interventions, neuroradiologists use the realistic 3D printed replica developed by our group and together with our spin-off SurgeonsLab AG to sufficiently prepare for the procedure. The approach assists physicians in more accurate implants choice during the planning process. In addition, the 3D replica is coupled with a high-fidelity endovascular simulator to train residents and medical students preparing for their board certification and fellowship programs.

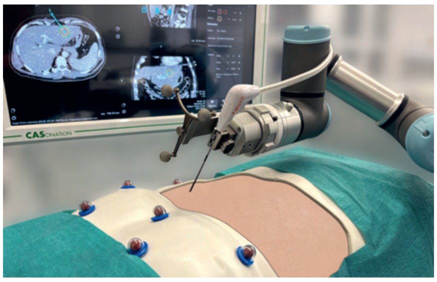

Fig. 2: Computer simulation of the intervention room setting.

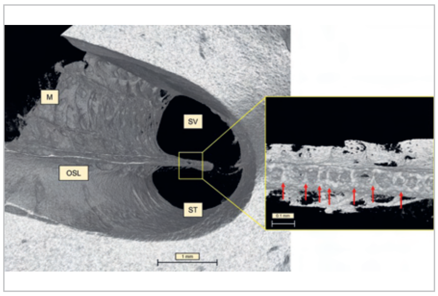

Fig. 3: Supportive pillars of the OSL coming from the cribiform wall of the modiolus (M) seen on a 2.3 µm microCT. OSL-Osseous

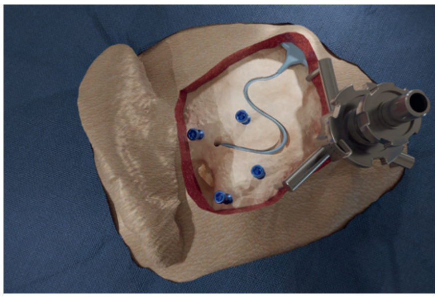

Fig. 4: Robotic milling channel and implant bed to store and protect the implant electrode and housing.

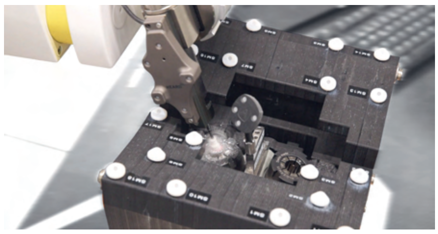

Fig. 5: Prototype platform for robotic spine surgery development.

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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. The results of these developments are aimed at advancing the fields of radiomics for 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. The developments revolve around the vision of scalable, adaptable, and time-effective machine-learning algorithms developed with a strong focus on clinical applicability.

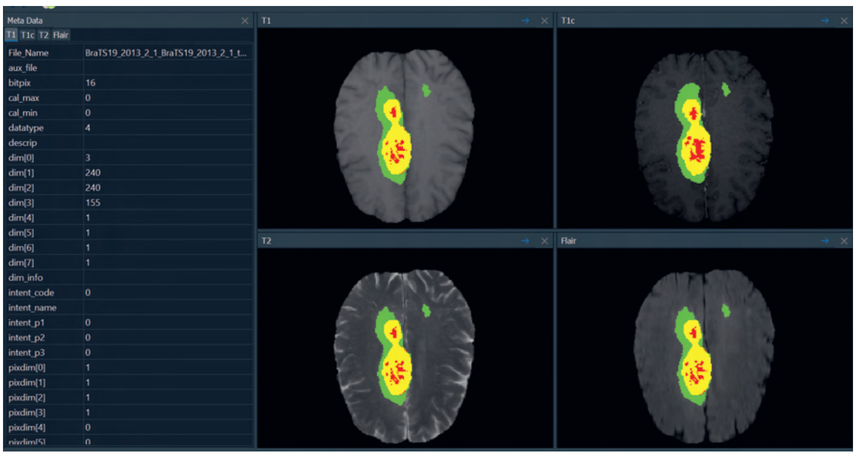

Fig. 1: Deep Learning based automated quantification and analysis of brain tumor lesions – DeepBraTumIA software. The core of this technology received during 2022 FDA approval in collaboration with the US-based start-up Neosoma.

Accurate Quantification and Radiomics Analysis for Brain Lesions

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. During 2022, in collaboration with the US-based start-up Neosoma, our group further got this technology FDA approved (510k). In this regard, a unique feature of our translational developments has been in incorporating the capability of the technology to progressively adapt to changes in imaging modalities. In addition, the developed technologies feature an inclusive model, where state-of-the-art approaches worldwide can be fused to enhance performance and robustness. Beyond lesion contouring our current research activities lie on rethinking and challenging current

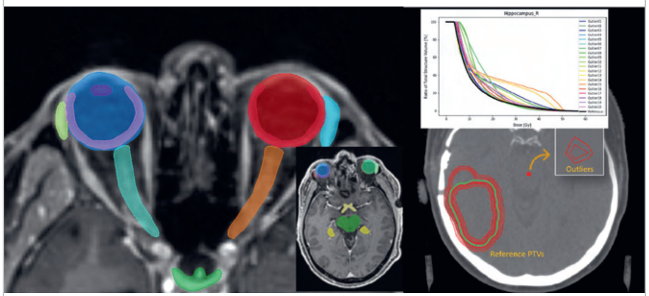

Fig. 2: Automated delineation of organs at risk for RT planning, and investigating the effect of DL-based outliers for RT planning.

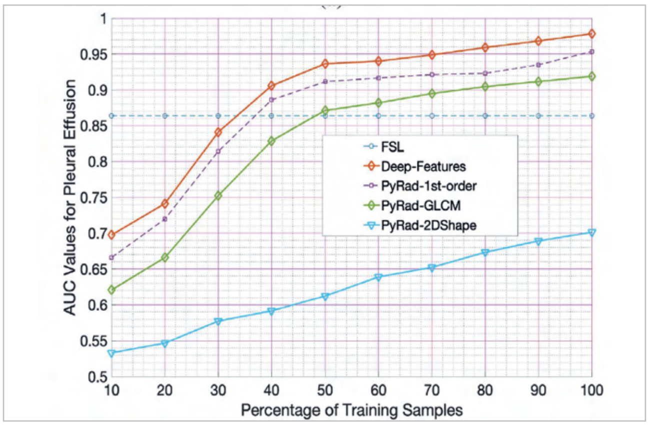

Fig. 3: Interpretability-guided medical image segmentation and classification. Our group has developed novel methodologies to employ information derived from interpretability to further boost the performance, robustness and generalization of AI systems. In this figure we exemplify how interpretability can help in improving the learning rates in active learning setups.

AI technologies such that they are optimized to the clinical end-goal. In these regards, in radiation oncology, we are investigating AI learnability approaches targeted directly towards metrics derived from the clinical-end goals, and how to train and evaluate AI-based solutions with the clinical downstream task as main focus.

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 A.I 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 developed novel methodologies to employ interpretability results of AI systems in order to improve sample selection and performance of AI systems.

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1. Poel R., Rüfenacht E., Ermis E., Müller M., Fix M., Aebersold D., Manser P., and Reyes M. Impact of random outliers in auto-segmented targets on radiotherapy treatment plans for glioblastoma. Radiation Oncology, 17, 1-18, 2022.
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Motor Learning and Neurorehabilitation Lab

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Research Profile

At the interdisciplinary Motor Learning and Neurorehabilitation laboratory, we aim to gain a better understanding of the underlying mechanisms associated with the acquisition of novel motor skills to develop innovative technology to improve the rehabilitation of neurological patients. Our research focuses on human-machine interfaces and biological learning, and, specifically, on the use of robotic assistance to help people learn motor tasks and rehabilitate after neurologic injuries. We complement the research on robotics with the use of immersive virtual reality (VR) and augmented reality (AR) to enhance patients' motivation and reduce their cognitive load during training.

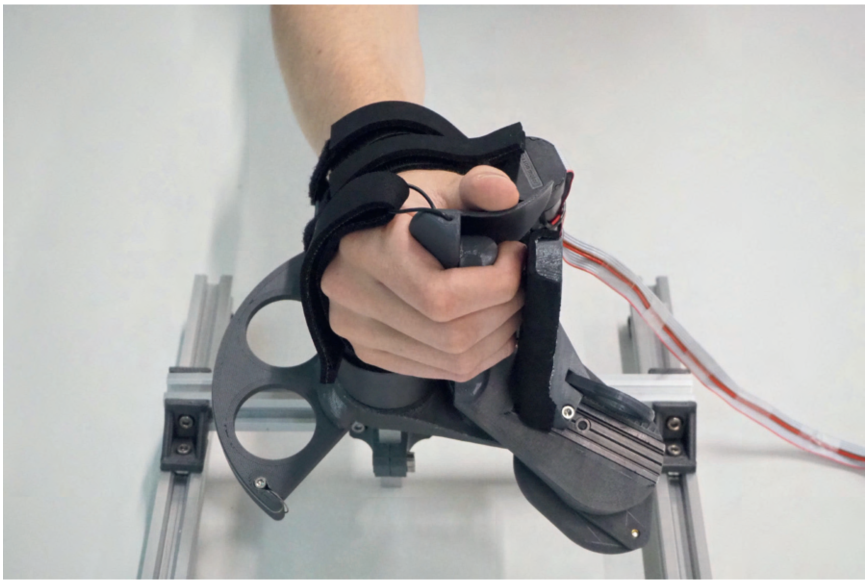

Fig. 1: Prototype of haptic hand rehabilitation device for sensorimotor training after stroke. Photo: Adrian Moser for ARTORG Center

Novel Clinical-Driven Robotic Devices for Sensorimotor Training

Every year, millions of stroke survivors lose their functional autonomy due to upper-limb impairments. To recover upper-limb functions such as reaching and grasping, stroke patients should undergo highly intense, repetitive, and long-term training. This kind of training could potentially be provided by robotic devices. However, current robotic solutions are often cumbersome to set up and too complicated to be used in clinical practice. In addition, they mostly focus on the execution of movements and neglect the training of sensory functions, such as the sense of touch, even though research emphasizes its importance for recovery. We are developing a novel upper-limb rehabilitation robot that is easy to use and capable of fine haptic rendering. Haptic rendering is the physical simulation of interaction forces with virtual tangible objects. It can be used to make patients feel if they touch and interact with objects in rehabilitation computer games. Our novel device thus allows for simultaneous sensory and motor training and has the potential to improve the recovery of upper-limb functions.

Immersive Virtual Reality to Enhance Neurorehabilitation

The addition of virtual reality during robotic training has been shown to improve patients' motivation. Yet, the virtual reality

Fig. 2: Robotic somatosensory training with haptically rendered virtual textures.

Fig. 3: Virtual inverted pendulum task with ARMin exoskeleton robot.

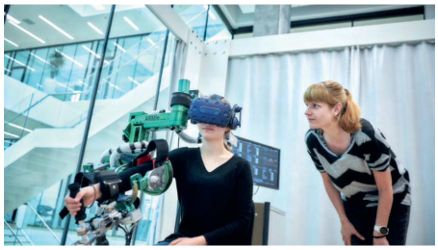

Fig. 4: Robotic motor training with ARMin exoskeleton in immersive virtual reality.

environments currently employed in rehabilitation practice are displayed on 2D screens. This transformation removes the focus of attention from the real movement and results in games that are cognitively too demanding for brain-injured patients. We explore how the use of augmented and immersive virtual reality can improve motor learning and neurorehabilitation.

Novel and commercially available head-mounted displays have great potential to realistically mimic the patient's limb in a highly immersive training environment. In this immersive training environment, the symbolic virtual representation may become a self-representation (i.e., avatar), promoting the feeling of body ownership over the virtual limb. In the brain, body ownership and motor control share neural correlates. In an experiment with 50 participants, we evaluated how body ownership and congruency of multisensory information interact with motor performance in virtual reality. Our results suggest that VR-based motor tasks providing congruent (multi)sensory feedback and enforcing body ownership via visuomotor synchronies may best support motor training.

Enhancing Touch Sensibility by Robotic Sensory Retraining

Stroke survivors are commonly affected by somatosensory impairment, hampering their ability to interpret somatosensory information, critical to support movement execution. Yet, somatosensory training - in stark contrast to motor training - does not represent standard care in neurorehabilitation.

To address this clinical need, we developed a virtual reality-based robotic texture discrimination task to assess and train touch sensibility. Our system incorporates the possibility of robotically guiding the participants' hands during texture exploration. We ran a three-day experiment with 36 healthy participants who were asked to discriminate the odd texture among three visually identical textures, haptically rendered with the robotic device. Our results showed that participants significantly improved their task performance after training. In a follow-up experiment, we evaluate the potential of providing sensory electrical stimulation to further improve the training benefits of our robotic solution.

The Impact of Somatic Feedback during Robotic Training

The absence of somatosensory information regarding the interaction with virtual objects during robot-aided training might be limiting the potential benefits of robotic training on motor (re)learning. We conducted a study with 40 healthy participants to evaluate how haptic rendering and arm weight support affect motor learning and skill transfer of a dynamic task. The task consisted of inverting a virtual pendulum whose dynamics were haptically rendered on an exoskeleton robot designed for upper-limb neurorehabilitation. We found that haptic rendering significantly increases participants' movement variability during training and the ability to synchronize their movements with the pendulum, which is correlated with better performance. Weight support also enhances participants' movement variability during training and reduces participants' physical effort. Importantly, we found that training with haptic rendering enhances motor learning and skill transfer, while training with weight support hampers learning compared to training without weight support. Further work will evaluate how to simultaneously provide robotic assistance and haptic rendering without hampering motor learning, especially in brain-injured patients.

Selected Publications

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2. K. Buetler et al., "Tricking the Brain" Using Immersive Virtual Reality: Modifying the Self-Perception Over Embodied Avatar Influences Motor Cortical Excitability and Action Initiation", Frontiers in Human Neuroscience, vol. 15, 2022.
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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 provides also 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: Members of the Musculoskeletal Biomechanics group in 2022.

Multiscale Mechanical Properties of Bone Extracellular Matrix *(Swiss Federal Excellence Postdoc Fellowship)*

Bone is a hierarchically structured bio-composite composed of mineralised collagen fibrils embedded in an extrafibrillar matrix and exhibits various toughening mechanisms from the nano- to the macroscale. This work enriched a former 3D unit-cell finite element model of a mineralised fibril array with cohesive interactions and plasticity, to reproduce the anisotropic post-yield behaviour measured previously in micropillar compression and micro tensile tests.

Fracture Risk Estimation of Vertebral Bodies with Metastatic Lesions *(with IS)*

Vertebral compression fractures (VCF) are a major clinical concern in the management of cancer patients with metastatic spine disease. The aim of this project is to estimate the strength of affected vertebral bodies using quantitative computed tomography (QCT)-based finite element analysis (FEA). As a first step, a reference database of QCT reconstructions of healthy spines acquired at the institute of forensic medicine is established.

Contribution of Bone Tissue Properties to Strength of the Ageing Human Hip *(SNF grant # 200365 with EMPA, MUG, PSI & VUT)*

This project aims to assess the influence of →

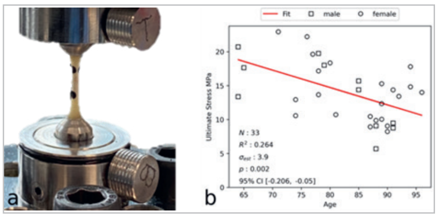

Fig. 2: The ultimate strength of demineralised bone samples tested in tension (a, left) decreases with age (b, right).

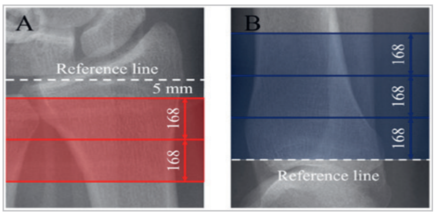

Fig. 3: Double stack and triple stack HR-pQCT scanning protocols in the radius (A, left) and tibia (B, right).

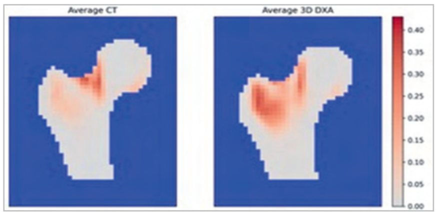

Fig. 4: Average damage derived from QCT based (left) and 3D DXA (right) based FE simulations. 0: undamaged; 1: fully damaged.

age on the mechanical integrity of both, mineral and organic phases of the human proximal femur. Using an inverse method, the hypothesis that finite element analysis (FEA) material parameters are independent of age was tested. Eighty-six human femora were scanned and QCT-based hFEA as well as µCT-based µFEA strength predictions of the femoral necks were compared with their experimental compression until failure. The errors between the simulation and the experiment for apparent modulus, yield stress, and strength were age-independent, suggesting no rationale for correcting tissue material parameters in the current FEA of the ageing femoral neck. Additionally, eighty samples were demineralized and tested in tension until failure. It has been shown that mechanical integrity of the collagen network deteriorates with increasing age and may lead to decreased post-yield properties of aged bone (Fig. 2).

Biomechanical Stability of Bone Screws in the Proximal Humerus *(with AO)*

Proximal humerus fractures (PHF) are among the third most common injuries related to osteoporosis. In this thesis, the failure mechanism of PHF treated with locking plates was investigated by testing the propagation of single screws in human bone samples under cyclic loading. With micro finite element simulations and an analytical model, it was possible to qualitatively describe the experiments. These findings might be a step towards defining the optimal treatment for patients suffering from a PHF.

HR-pQCT-Based Homogenized FEA of multiple sections of the distal radius and tibia *(with IS & MGU)*

High-resolution peripheral computed tomography (HR-pQCT)-based homogenised finite element analysis (hFEA) of distal radius and tibia becomes an effective method to assess *in vivo* bone strength. A multi-stack measurement protocol (Fig. 3) was initiated at the University Hospital in Bern and future patients might benefit from this method to detect the progression of bone diseases such as osteoporosis. A cross-sectional clinical study with the University of Basel exploiting this protocol suggested that bone strength at the tibia but not at the radius was significantly reduced in long-standing type I diabetes patients with neuropathy compared to controls after adjustment for age, gender, and BMI. From the methodological point of view, a unified image processing, calibration procedure and hFEA modelling pipeline was integrated and successfully validated with *ex vivo* mechanical compression tests of both distal radii and tibiae.

A Fragility Fracture Integrative Risk Model for CT Recycling *(SNF grant # 183584 with HES-SO, HUG, IS & UK)*

The AFFIRM-CT project aims to develop a new hip fracture risk model based on the risk of falling and integrating a CT-based femoral bone strength. During the last year, a model to predict a personalized fall rate was developed with the analysis of three different cohorts. Preliminary results showed that the number of prior falls and fear of falling are predictive for future falls. Furthermore, to estimate the energy absorbed by soft tissues during a fall, the soft tissue thickness over the hip was extracted from CT images and compared with the stiffness measured with a soft tissue indentation device at the same location.

We previously evaluated the 3D-Shaper software, which proposes to reconstruct a 3D image of the proximal femur from a 2D DXA scan and thus offers an interesting alternative when a QCT scan is not available. We extended our evaluation, which had focussed on shape and density so far, with a comparison of the bone FEA (Fig. 4).

Since March 2021, we are enrolling participants in a clinical study to validate these models. The assessment includes the risk of falling, the general health state and bone quality with HR-pQCT and DXA measurements.

Biomechanical Testing and Simulation *(with ZMK)*

Various strategies are currently debated in dental implantology to improve primary stability of dental implants, especially from the perspective of cost-effective, immediate loading procedures. The biomechanics laboratory offers an experimental protocol, but also computational models of the bone-implant interface based on µCT reconstructions, to quantify primary stability in human or bovine alveolar bone for different drilling protocols and implant

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Organs-on-Chip Technologies

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Research Profile

The Organs-on-Chip Technologies Group focuses on the development of advanced in vitro models, called organ-on-chip. 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.

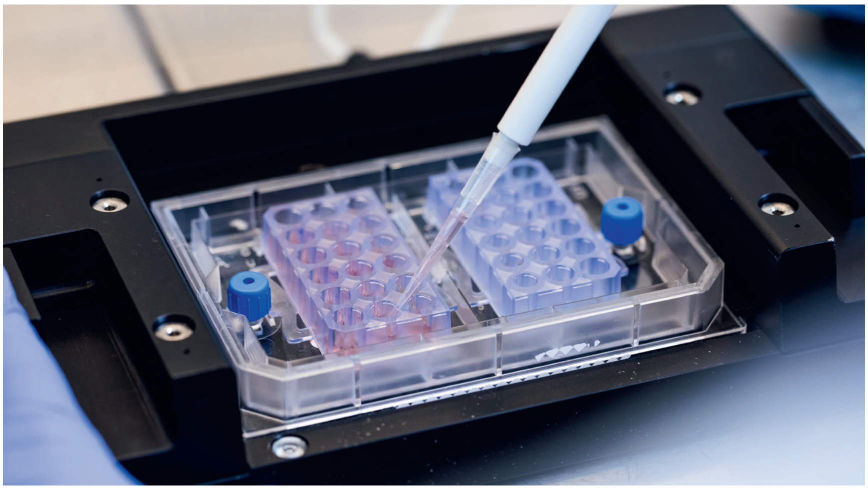

Fig. 1: Picture of a multi-well plate with two lung-on-chips. Each lung-on-chip is equipped with a 3µm-thin, porous and stretchable membrane, on which cells are cultured. (developed in collaboration with AlveoliX AG).

Breathing lung-on-chip (LOC)

The complexity of the lung can be illustrated by its delicate tree-like architecture that ends with the alveolar sacs, where the gas exchange takes place. Oxygen and carbon dioxide diffuse through an extremely thin alveolar barrier. This barrier is mainly constituted by alveolar epithelial cells, capillary endothelial cells, and the basement membrane. This whole environment is subjected to the cyclic breathing movements induced by the diaphragm, the main respiratory muscle. We developed an advanced in-vitro model of the lung alveoli, called "lung-on-chip", which mimics the human lung alveolar barrier. In that system, the barrier is made of an ultra-thin, flexible polymeric membrane, on which lung cells are cultured on opposite sides. The biocompatible silicone membrane is porous (3µm pores), which enables the lung epithelial cells - top side of the membrane - and lung endothelial cells - bottom side, in contact with blood analog - to communicate. This alveolar barrier is cyclically stretched in three dimensions as in the lung. The actuation of the barrier is created by a microdiaphragm that resembles the in-vivo diaphragm. A multi-well plate format was chosen, as it is the standard format used in the biotechnology industry (Fig.1).

To evaluate inhalation toxicity, drug safety and efficacy assessment, as well

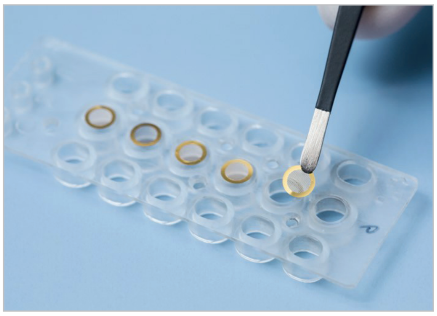

Fig. 2: Picture of the second-generation lung-on-chip with six wells with hexagonal gold grid.

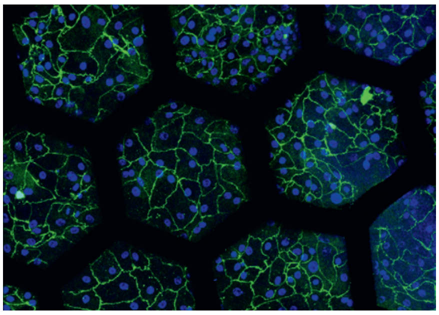

Fig. 3: Lung alveolar epithelial cells from patients cultured on the collagen-elastin membrane supported by an ultra-thin hexagonal gold grid (each hexagon is ca. 260µm wide).

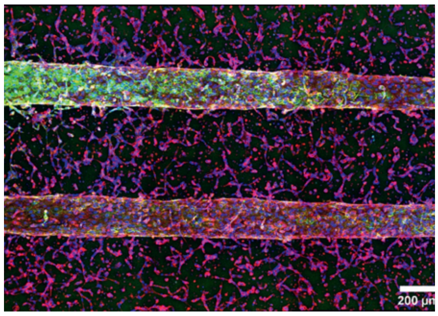

Fig. 4: Two parallel 200um-wide microvessels in fibrin hydrogel aimed at evaluating vasculogenesis exposed to cyclic stretch (day 8) (blue:DAPI, green: PECAM-1, red: F-Actin).

→ as the investigation of complex disease pathomechanisms, we developed in collaboration with AlveoliX, a new and reproducible alveolar in vitro model, that combines a human derived immortalized alveolar epithelial cell line (AXiAECs) with the lung-on-chip. The latter mimics key features of the in vivo alveolar milieu: breathing-like 3D cyclic stretch (10% linear strain, 0.2 Hz frequency). To establish a physiological model for the distal lung, AXiAECs were cultured for long-term at air-liquid interface (ALI) on-chip. Alveolar damage including inflammation (via exposure to bacterial lipopolysaccharide) and the response to a profibrotic mediator (via exposure to Transforming growth factor -1) were analyzed. In addition, the expression of relevant host cell factors involved in SARS-CoV-2 infection was investigated to evaluate its potential application for COVID-19 studies. These cells (AXiAECs) cultured on the AX lung-on-chip exhibit an enhanced in vivo-like alveolar characteristics. In breathing (dynamic) conditions, cells showed increased expression of F-actin filaments compared with cells under static culture conditions, which results from the reorganization of the cytoskeleton in response to the cyclic stretch.

Second generation lung-on-chip

Although very innovative, the ultra-thin PDMS membrane used in the first-generation lung-on-chip is an artificial material, whose intrinsic nature, properties, and size differ from the extracellular matrix (ECM) of the distal airways. The second-generation lung-on-chip with an array of in vivo like-sized alveoli and a stretchable biological and biodegradable membrane offer significant improvement over the first generation. By using a biological membrane made of collagen and elastin, it closely mimics the extracellular matrix of the lung, which makes it a more accurate model for studying lung function and pathologies (Fig. 2). The biological membrane can easily be created by pipetting a drop of ECM solution that spreads on the mesh by capillary forces. The tunable mechanical properties of the biological membrane can be easily adjusted by modifying its composition or fabrication process. This allows for long-term cell culture, as the membrane can be maintained in a dry or wet state for several months. Furthermore, this membrane allows for the creation of an air blood barrier without the need for any artificial layers between the epithelial and endothelial cells. This membrane opens the way to a new generation of lung-on-chip that enables mimicking of the biological barriers at a new level of complexity (Fig. 3). The potential applications for this model are broad, it could help to understand lung functionalities and pathologies, identify new pathways, and to discover potential new therapies.

Microvasculature-on-chip

Vascular homeostasis is the maintenance of the proper functioning of the blood vessels, which is essential for the overall health of the organs. Disruption of this balance can lead to the development of various diseases. Microvasculature-on-chip projects aim to develop functional microvasculature platforms that can be used to study the biology of the blood vessels and gain a better understanding of the mechanisms behind vascular diseases. These platforms can also be used for drug testing and the study of endothelial mechanotransduction. Two different microvasculature platforms have been developed. The first is a self-assembled complex microvascular network, while the second is a patterned vasculature exposed to cyclic forces. The three-dimensional microvasculature network is generated using a co-culture of human endothelial and mural cells within a 3D hydrogel matrix. This model is used to study the efficacy of anti-angiogenic compound (Nintedanib) and the pathogenesis of chronic obstructive pulmonary diseases (COPD). The dynamic perfusable vasculature model incorporates two patterned vessels within a hydrogel layer and is designed to investigate the effect of mechanical cyclic stretch on vasculogenesis and angiogenesis (Fig. 4). These microvasculature-on-chip platforms are valuable tools for studying the biology of the blood vessels and advancing our understanding of the mechanisms behind vascular diseases.

Selected Publications:

1. Sengupta, A., et al., A New Immortalized Human Alveolar Epithelial Cell Model to Study Lung Injury and Toxicity on a Breathing Lung-On-Chip System., Frontiers in Tox., (2022).
2. Zamprogno, P. et al. Mechanical Properties of Soft Biological Membranes for Organ-on-a-Chip Assessed by Bulge Test and AFM. ACS Biomater. Sci. Eng. 7, 2990–2997 (2021).
3. Zamprogno, P. et al. Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. Commun. Biol. 4, 168 (2021).
4. Zeinali, S., Thompson, E. K., Gerhardt, H., Geiser, T. & Guenat, O. T. Remodeling of an in vitro microvessel exposed to cyclic mechanical stretch. APL Bioeng. 5, (2021).

Urogenital Engineering

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Prof. Markus Drake, Bristol Urological Institute, University of Bristol, UK
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Angelo Locatelli
Nino Paganini
Shaokai Zheng

Research Profile

The Urogenital Engineering (UGE) group focusses on the understanding and the treatment of diseases of urinary tract (UT), many of which have a significant impact on on health and quality of life. Our translational projects address unmet clinical needs, which are identified and discussed with our clinical partners who are fully integrated in the project teams. Using innovative engineering approaches, the UGE group is developing new methods to improve the insight, diagnosis, and treatment of diseases of the urinary tract with special focus on urinary obstructions (e.g. kidney/ureteral stones), underactive bladder, overactive bladder, and incontinence. UGE and Cardiovascular Engineering (CVE) groups of ARTORG Center share experimental and computational research infrastructure/facilities. Next to computational tools and facilities, this includes our flow lab, which is equipped for bench experiments on biomedical flow systems and offers computer-controlled flow loops, pressure and flow sensors, high-speed cameras, and laser-based flow measurement systems.

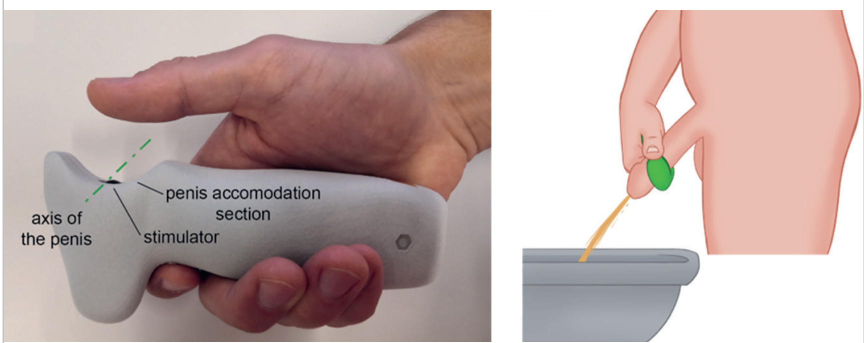

Fig. 1: Our first prototype for patients suffering from urinary retention.

Non-Invasive Solution for Urinary Retention

The UGE group is developing the world's first non-invasive solution for 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 ahead 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. 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 patients (i.e. first-in-man study). URODEA AG (www.urodea.com) is a spin-off of the ARTORG Center and is focusing on bringing this technology to the patients.

Urinary Tract Modelling

The urinary tract includes two kidneys, two ureters, a bladder, and one urethra. To achieve normal urination, all components

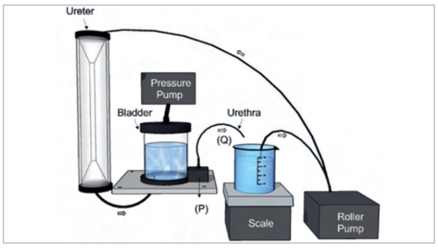

Fig. 2: In-vitro model of the urinary tract. Using a programmable pressure pump, bladder pressure waveform and flow can be controlled to mimic physiological and pathological conditions.

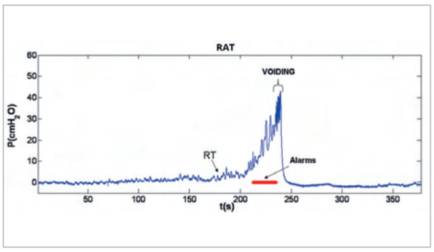

Fig. 3: Bladder pressure signal during voiding in rats.

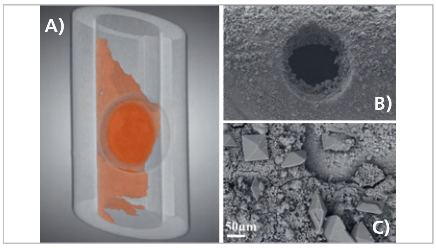

Fig. 4: A) Example of micro-computed tomography image of a stent side hole with encrustation (orange). Examples of scanning electron microscopy images of B) the stent side hole with the typical C) calcium-based encrustations.

of this system have to work in a synergic and correct way. 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) for biomechanical and fluid mechanical studies within UT. Theses platforms aim at: i) improving the insight on local fluid mechanics within UT, ii) identifying the critical aspects of current medical devices and iii) testing new solutions. In particular, our in-vitro platform has unique features as it consists of: i) a roller pump (to simulate the production of urine from kidneys) ii) a transparent ureter model, and iii) a bladder compartment whose internal pressure can be programmed to simulate the physiological and pathological bladder pressures (during the filling and emptying cycles), and iv) an outlet tube (urethra). The platform can be combined with an index matched fluid to allow particle image velocimetry (PIV) measurements for full fluid mechanical characterisation and 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 "Non-invasive Solution for Urinary Retention").

Encrustations 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 ureter length, with side holes positioned at regular intervals. Encrustation and biofilm are considered the main causes of stent failure, and it has been shown 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 dynamic 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 a deep learning model 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 characterisations 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.

Innovative Tools for Diagnosis and Treatment 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 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. We 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 patient about an impending bladder contraction (to take action against incontinence) or/and to trigger conditional sacral nerve stimulation (i.e. stimulation of bladder nerves to inhibit the bladder contraction before incontinence). Moreover, our group has pioneered the use of cardiac catheters for minimally invasive electrophysiological investigations in the urinary tract. In a proof-of-concept study, we have shown that cardiac catheters can detect and track the propagation of electrical signals in the lumen of the ureter. Further investigations will apply this technology to bladder smooth muscle.

Selected Publications

1. 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, 2022. DOI: 10.3389/fbioe. 2022.1028325
2. 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
3. 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
4. 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
5. Abou-Hassan, A., Barros, A., Buchholz, N., Carugo, D., Clavica, F., De Graaf, P., De La Cruz, J., Kram, W., Mergulhao, F., L Reis, R., Skovorodkin, I., Soria, F., Vainio, S. & Zheng, S.,Potential strategies to prevent encrustations on urinary stents and catheters – thinking outside the box: A European Network of Multidisciplinary Research to Improve Urinary Stents (ENIUS) Initiative' Expert Review of Medical Devices 2021, DOI: 10.1080/17434440.2021.1939010
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

Mechanical Design and Production

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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.

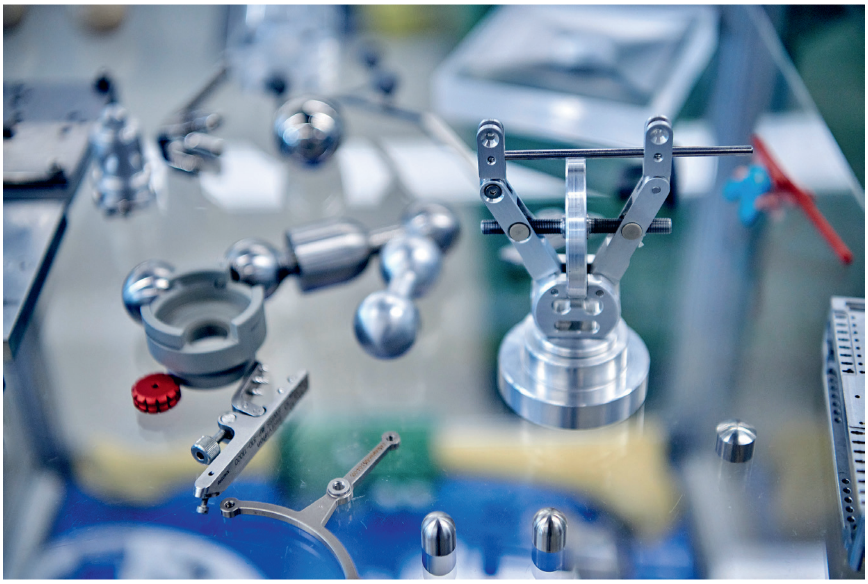

Fig. 1: Some products of the MDP group

Training and Education

The MDP group has a secondary role in training. This training encompasses the skills required to safely and proficiently operate machine shop tooling and equipment, 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. This year we conducted a total of three trial apprenticeships and decided to train Lio Ritschard as an apprentice from August 2023.

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

In April and May Meret took an extended vacation and during the two months we were able to hire Pascal Winiger as a substitute. In this short time, he settled in well and was a great support. At this point we would like to thank him for his valuable ideas from the industry which he brought into the MDP.

Research Equipment Design and Manufacturing

As expected, the requirements of a machine shop supporting research in the biomedical engineering field are as diverse

Fig. 2: Collagen Fiber Test

Fig. 3: Part of the inserzion guide tool

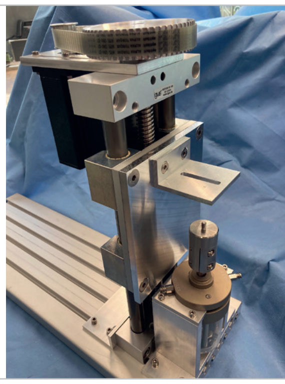

Fig. 4: Suprareactor

as the research field itself. The variety of subjects researched in the ARTORG yield a number of diverse design and production requests from prototype clinical and surgical tooling to fixtures for mechanical, biological, and kinematic testing, as well as imaging system accessories and calibration equipment. The following illustration highlights one of this year's projects.

ARTORG Musculoskeletal Biomechanics Group

In collaboration with Stefan Bracher, we produced bone specimen parts on our CNC lathe. The cortical liners from the femur were cast into prepared aluminum tubes.

On the aluminum parts, the first step was to turn the metal sleeves to the diameter of 4mm. This operation was a challenge because we had to make sure that the temperature of the metal parts did not rise above 50 C. In the second operation, we turned the now visible bone section in a defined shape. Here, the risk of fracture was the greatest risk, especially since we were not allowed to change the properties of the bone and exert too much clamping pressure on the bone section. To prevent the bone dust from getting into the machine guides, we had to install a dust extraction system that collected the dust directly at the tool. Finally, we could successfully produce 100 samples.

Inselspital, University Hospital Bern University Clinic for Cardiology Cardiovascular Center

For the insertion of a pacemaker and the pulse generator, Siro Canello has developed a tool to fix it in the heart. His idea was to join a flexible tube consisting of round titanium tube parts to form a chain. The chain should be designed so that it could be lengthened or shortened in a simple art and way.

The properties of titanium in terms of bending strength gave us a headache. With much flair and our experience to the processing have finally led to a good and usable product.

University Department of Orthopedic Surgery and Traumatology Inselspital

In this project we had the order to 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 by our apprentice Lukas Rufener as a final apprenticeship examination project. This made the conversion easier because we could use the existing documents.
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.

By the end of this year, we have also constructed the device to be able to produce the fabric samples following the tensile tests. The first jig should be ready by the end of January 2023. In a second project, it is planned to manufacture three more devices and to operate them in an incubator. We are sure that some technical and practical problems will arise which we can solve as usual.

Dissertations

Narayan Schütz
Gerontechnology and Rehabilitation
Towards Unobtrusive Sensor-Derived Digital Measures of Health in Aging

Angela Botros
Gerontechnology and Rehabilitation
Unsupervised health monitoring in home-like environments

Denis Schenk
Musculoskeletal Biomechanics
Personalized Homogenized Finite Element Analysis for the Reproducible Assessment of Bone Strength

Fabian Müller
Image Guided Therapy
Inner ear access during robotic cochlear implantation – concept and validation of a minimally traumatic approach

Leonardo Pietrasanta
Cardiovascular Engineering
Experimental Investigation of the Three-dimensional Flow Field of Novel Aortic Valve Prosthesis Designs

Philipp Aebischer
Hearing Resaerch Laboratory
SMART Insertions for Cochlear Implant Electrode Arrays: A Sleeve-based, Micromotion Avoiding, Retractable and Tear-opening Insertion Tool

Raluca Sandu
Image Guided Therapy
Quantitative assessment of ablation treatments for liver tumours – image-based efficacy analysis and predictive modelling

Michael Indermaur
Musculoskeletal Biomechanics
Osteogenesis Imperfecta does not compromise the micromechanical properties of human bone extracellular matrix

Samuel Knobel
Gerontechnology and Rehabilitation
Development and evaluation of adaptive neglect therapy tools with visual, auditive and tactile modalities using virtual reality technology

Judith van Beek
Gerontechnology and Rehabilitation
Precision Work: Innovative rehabilitation techniques for improving dexterity in neurological diseases

Fredrick Joseph Johnson
Image Guided Therapy
Mimicking brain microsurgical and endovascular procedures through additively manufactured dynamic and life-like phantoms

Joaquin Penalver
Motor Learning and Neurorehabilitation
EEG-based Imaging of Cognitive-Attentional Processes Related to Motor Performance

Eric Buffle
Cardiovascular Engineering
Opening behaviour of normal and stenotic aortic valves in low-flow situations

Research Partners

- University of Bern
- Inselspital – Universitätsspital Bern, Hopital Universitaire de Berne, Bern University Hospital
- sitem-insel
- AlveoliX – In-vitro models inspired by nature
- force dimension
- Novostia
- UKBB – University Children's Hospital Basel
- AO Foundation
- Geriatrische Klinik St.Gallen
- UCL
- Bern University of Applied Sciences
- HFR – hôpital fribourgeois freiburger spital
- Oslo University Hospital
- UEC – The University of Electro-Communications
- CASCINATION
- HIPS – Helmholtz Institute for Pharmaceutical Research Saarland
- OVIVA – Freude am Leben
- Universitat d'Alacant – Universidad de Alicante
- CHUV
- Lucerne University of Applied Sciences and Arts – Hochschule Luzern
- Paul Scherrer Institut PSI
- University of Bristol
- City of Hope
- Hocoma – a DIH brand
- PDAG – Für Ihre psychische Gesundheit
- Università degli Studi di Catania
- CorFlow Therapeutics
- HUG – Hôpitaux Universitaires Genève
- retinai
- university of groningen
- csem
- Inria – Inventeurs du monde numérique
- RMS – Testing · Research · Consulting – www.rms-foundation.ch
- University of Maryland
- Danderyds Sjukhus
- Imperial College London
- robotics – Swiss National Centre of Competence in Research
- University of Oxford
- Debiotech
- Kantonsspital Aarau
- Rutgers – The State University of New Jersey
- University of Southampton
- DLR
- Karolinska Institutet – Anno 1810
- Spital Tiefenau – Inselgruppe
- Universitäre Psychiatrische Dienste Bern
- DOMO Care
- luzerner kantonsspital
- Switzerland Innovation Park Biel/Bienne
- ulm university – universität uulm
- Empa – Materials Science & Technology
- McGill University
- Technische Universität Wien – Vienna University of Technology
- UZA
- ENIUS – European Network of Multidisciplinary Research to Improve the Urinary Stents
- MDC – Max Delbrück Center for Molecular Medicine in the Helmholtz Association
- The University of Nottingham – United Kingdom · China · Malaysia
- UniversitätsSpital Zürich
- EPFL
- MED-EL
- URODEA
- Vascular Institute Switzerland
- ETH zürich
- Newcastle University
- Università della Svizzera italiana

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