UNIVERSITÄT BERN

ARTORG CENTER
BIOMEDICAL ENGINEERING RESEARCH

# ARTORG CENTER
# ANNUAL REPORT 2021

# Foreword

Dear friends, colleagues, collaborators, and partners

This year's annual report reflects the running "restart" of activities and the return to analogue experiences of work and play.

As we begun to fill our facilities with life again, we brought together the benefits from this unintended social experiment of biomedical engineering research and teaching in the new era. We have become more efficient in the use of our time and attention, and despite the restrictions this year has been one of the most successful for awards, prizes, funding, translation investments, media engagement; not to mention the expected crop of high profile publications, theses defences, graduations, qualifications, invited talks, clinical studies, and infrastructure updates.

A major highlight of 2021 has been the search, approval, and appointment of a new ARTORG Scientific Advisory Board (SAB), only accomplished with the help of University Management and the input from our clinical partners at the Inselspital Bern/Bern University Hospital. We are therefore delighted to engage with our SAB for our first review cycle, and we look forward to hearing from this illustrious group of globally-leading researchers about how we can continue to elevate our efforts and add our contribution to biomedical engineering research.

With this restart in 2021, we look forward to receiving new members to the ARTORG, wishing well to those who leave us with plans ahead, and seeing our friends, colleagues, collaborators, and partners again to develop new ideas and bring forward solutions that benefit our most important stakeholders: the patients.

Together with the other members of the leadership team, I present this annual report as a record of our efforts, but also as the beginning step for a roadmap into a future of growth, diversity, and renewed purpose for the ARTORG.

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

**CB**
Computational Bioengineering

**CVE**
Cardiovascular Engineering

**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

**CAIM**
Center for Artificial Intelligence in Medicine

# Research Partners

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ENIUS — European Network of Multidisciplinary Research to Improve the Urinary Stents
EPFL
ETH zürich

force dimension
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HIPS — HELMHOLTZ Institute for Pharmaceutical Research Saarland
Lucerne University of Applied Sciences and Arts — HOCHSCHULE LUZERN
Hocoma — a DIH brand
HUG — Hôpitaux Universitaires Genève
Inria — INVENTEURS DU MONDE NUMÉRIQUE
Imperial College London
Kantonsspital Aarau
Karolinska Institutet — Anno 1810
luzerner kantonsspital
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MDC — MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE IN THE HELMHOLTZ ASSOCIATION
MED-EL
Newcastle University

Novostia
Optimeyes
Oslo University Hospital
OVIVA — Freude am Leben
PAUL SCHERRER INSTITUT — PSI
PDAG — Für Ihre psychische Gesundheit
retinai
RMS — Testing · Research · Consulting — www.rms-foundation.ch
robotics — Swiss National Centre of Competence in Research
RUTGERS — THE STATE UNIVERSITY OF NEW JERSEY
SPITAL TIEFENAU — INSELGRUPPE
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VASCULAR INSTITUTE SWITZERLAND

# Dissertations

**Laurent Lejeune**
*Artificial Intelligence in Medical Imaging*
Annotating Medical Sequences in the Blink of an Eye: Segmenting Video and Volumetric Medical Sequences at Frame-rate using Sparse Point-wise Supervision.

**Tim Fischer**
*Hearing Research Laboratory*
Spatial Hearing with Cochlear Implants: Development and Evaluation of Signal Processing Strategies.

**Tatiana Fountoukidou**
*Artificial Intelligence in Medical Imaging*
Towards safer machine learning for ophthalmology applications.

**Yannick Suter**
*Medical Image Analysis*
Advanced Machine Learning Technologies for Robust Longitudinal Radiomics and Response Assessment in Glioblastoma Multiforme.

**Jan Hermann**
*Image Guided Therapy*
Towards robotic micro-milling for lateral skull base surgery.

**Suyi Hu**
*Hearing Research Laboratory*
Bayesian Brain-Inspired Computational Modeling of Tinnitus and Residual Inhibition.

**Thomas Kurmann**
*Artificial Intelligence in Medical Imaging*
From Diagnosis to Surgery: Towards Artificial Intelligence based Medical Assistants.

**Ye Tang**
*Organs-on-Chip Technologies*
Nanocellulose applications in biosensing devices.

**Özhan Özen**
*Motor Learning and Neurorehabilitation*
Intelligence, Adaptation and Automation of Robotic Training for Motor Learning and Neurorehabilitation.

**Maria Vasiloglou**
*AI in Health and Nutrition*
Design and validation of a dietary monitoring and assessment system based on machine learning and computer vision.

**Nicolas Wenk**
*Motor Learning and Neurorehabilitation*
First-person immersive virtual reality to improve motor learning and neuro-rehabilitation.

Photography: Adrian Moser

# Master of Science
## Artificial Intelligence in Medicine

# Master of Science
## Biomedical Engineering

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Ioannis Papathanail

## 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

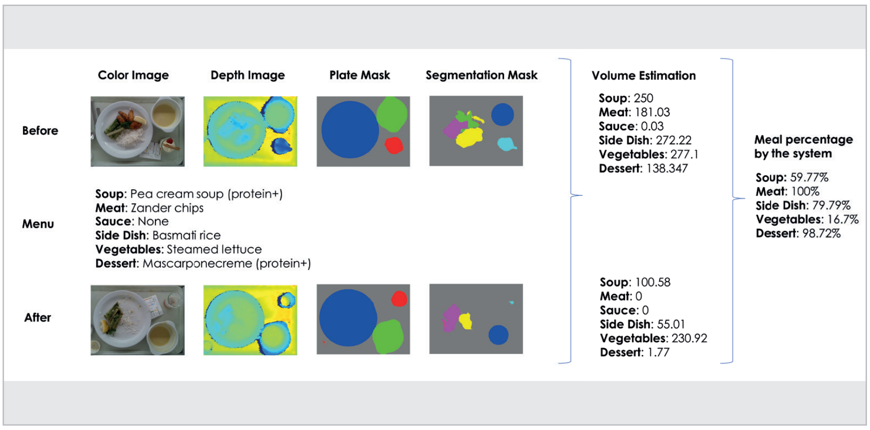


**Fig. 1:** Tackling hospitalised malnutrition: The system for hospitalised patients receives as input the daily menu and the tray images and estimates the volume of each dish before and after consumption.

### 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 them manage their dietary and nutrient intake and fulfil the needs of healthcare professionals in assessing the nutrient →

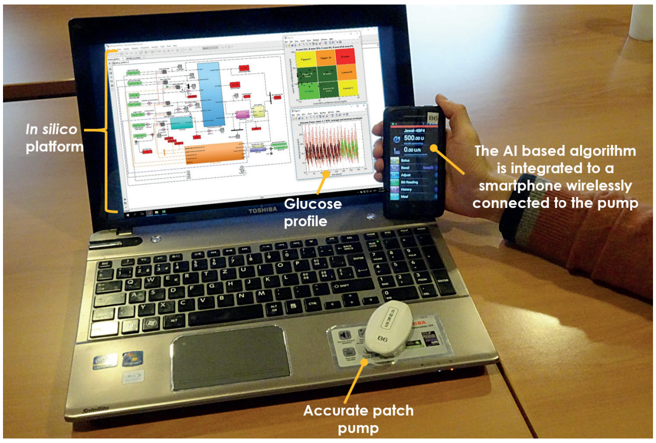


**Fig. 2:** The AI-based algorithm, integrated into a highly secured Android smartphone, takes input from either a blood glucose meter or continuous glucose monitors, and outputs the daily insulin treatment. The algorithm learns while being used by the patient and is able to provide personalised advice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

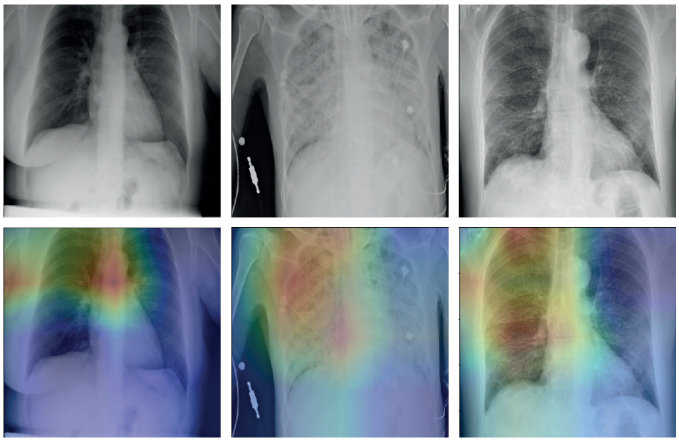

**Fig. 3:** Top row: three sample CRX (left: sample for healthy class, middle: sample for other types of pneumonia, right: COVID-19 pneumonia), bottom row: overlaid class activation maps.

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**

1. Papathanail I, Brühlmann J, Vasiloglou MF, et al. Evaluation of a Novel Artificial Intelligence System to Monitor and Assess Energy and Macronutrient Intake in Hospitalised Older Patients. Nutrients. 2021;13(12):4539. Published 2021 Dec 17. doi:10.3390/nu13124539
2. Afshar-Oromieh A, Prosch H, Schaefer-Prokop C, et al. A comprehensive review of imaging findings in COVID-19 - status in early 2021. Eur J Nucl Med Mol Imaging. 2021;48(8):2500-2524. doi:10.1007/s00259-021-05375-3
3. Fontanellaz M, Ebner L, Huber A, et al. A Deep-Learning Diagnostic Support System for the Detection of COVID-19 Using Chest Radiographs: A Multireader Validation Study. Invest Radiol. 2021;56(6):348-356. doi:10.1097/RLI.0000000000000748
4. Vasiloglou MF, Lu Y, Stathopoulou T, et al. Assessing Mediterranean Diet Adherence with the Smartphone: The Medipiatto Project. Nutrients. 2020;12(12):3763. Published 2020 Dec 7. doi:10.3390/nu12123763
5. Lu Y, Stathopoulou T, Vasiloglou MF, et al. goFOODTM: An Artificial Intelligence System for Dietary Assessment. Sensors (Basel). 2020;20(15):4283. Published 2020 Jul 31. doi:10.3390/s20154283
6. Sun Q, Jankovic MV, Mougiakakou SG. Reinforcement Learning-Based Adaptive Insulin Advisor for Individuals with Type 1 Diabetes Patients under Multiple Daily Injections Therapy. Annu Int Conf IEEE Eng Med Biol Soc. 2019; 2019:3609-3612. doi:10.1109/EMBC.2019.8857178

# Artificial Intelligence in Medical Imaging

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Prof. Aurel Perren, Institute of Pathology, University of Bern
Prof. Adrian Hüber, Dept. Diagnostic, Interventional and Pediatric Radiology, University Hospital Bern

**Raphael Sznitman**
Pablo Marquez Neila
Mathias Gallardo
Alain Jungo
Corin Otesteanu
Christopher Hahne
Negin Ghamsarian
Lukas Zbinden
Marta Colmenar
Lars Doorenbos
Michel Hayoz
Sergio Tascon-Morales
Javier Gamazo-Tejero
Maria Lopez-Antuna
Davide Scandella
Paulo Sampaio
Fei Wu

## 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.

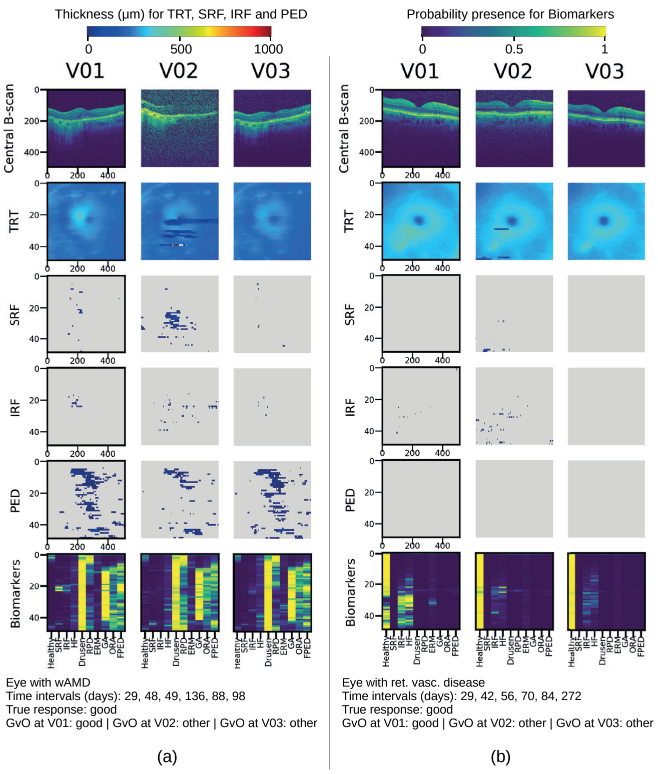


**Fig. 1.** Automatic detection and segmentation of surgical instrument during endoscopy.

### 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

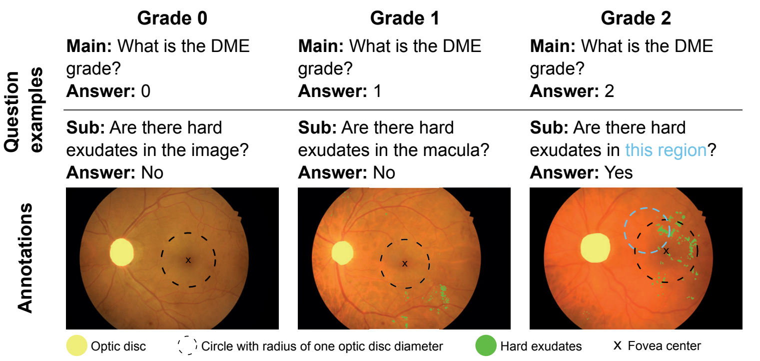


**Fig. 2:** DME risk grading Grade 0 is assigned if there are no hard exudates present in the whole image. Grade 1 is assigned if there are hard exudates, but only located outside a circle centered at the fovea with radius of one optic disc diameter. Grade 2 is assigned if there are hard exudates located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

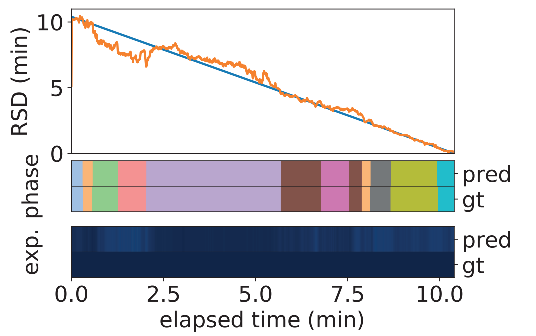


**Fig. 3:** CataNet: (top) the concordance between ground-truth and predicted RSD, (middle) the ground-truth and predicted surgical phases over time, and (bottom) the ground-truth and predicted probability of the surgeon's experience level.

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**

1. Tascon Morales, S., Marquez Neila, P., and Sznitman, R., " Consistency-preserving Visual Question Answering in Medical Imaging Show abstract". In Proceedings of the 23rd In- ternational Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), 2022.
2. Gallardo, M. Munk, M., Kurmann, T., De Zanet, S., Mosinska, A., Kutlutürk, I., Zinkernagel, M., Wolf, S. and Sznitman, R., "Machine learning can predict anti-VEGF treatment demand in a Treat-and-Extend regimen for patients with nAMD, DME and RVO associated ME". Ophthalmology Retina, 2021
3. Marafioti, A., Hayoz, M., Gallardo, M., Marquez Neila, P., Wolf, S., Zinkernagel, M. and Sznitman, R., "CataNet: Predicting remaining cataract surgery duration". In Proceedings of the 22th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), 2021.
4. Lejeune, L. and Sznitman, R., "A Positive/Unlabeled Approach for the Segmentation of Medical Sequences using Point-Wise Supervision", Medical Image Analysis, 2021

# Computational Bioengineering

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Dr. Harald Studer, Optimo Medical AG, Biel

## 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.

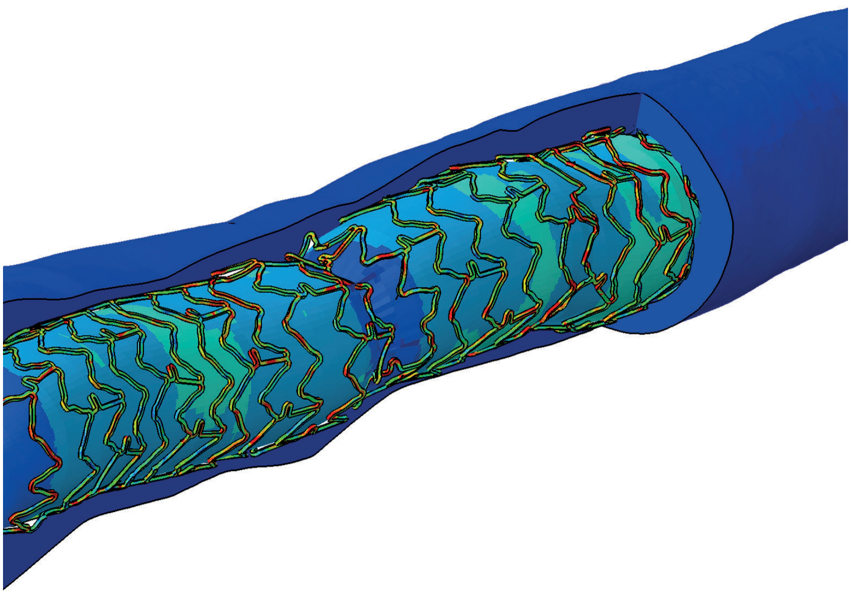

**Fig. 1:** Stent deployment with a balloon in a coronary artery of a patient simulated using the finite element method.

### Personalized prediction of percutaneous coronary interventions

Cardiovascular disease is a global public health problem. The success of percutaneous coronary interventions (PCI) to restore blood supply in stenosed arteries may be limited in severely calcified lesions. This problem is becoming more common in routine clinical practice as the age and complexity of patients referred to PCI increase. If these calcified lesions are inadequately prepared, under-expansion of the stent and associated complications may occur. In this project, we combine intra-arterial imaging and mechanical simulations to determine the outcome of PCI in patients with calcifications (Fig. 1) and compare the simulations to post-operative data. The results showed that in regions with many calcifications, the lumen area was correctly predicted by the model. However, the simulations could not reproduce the clinical lumen gain in the highly stenosed regions where no calcifications were detected. In these sections of the artery, the simulation predicted under-expansion of the stent that was not observed after surgery, probably because of other plaque components that were not detected on the OCT images. Nevertheless, these other types of softer plaques appear to be less prone to stent under-expansion and could, therefore, be ignored to focus predictions on the calcified regions of the artery.

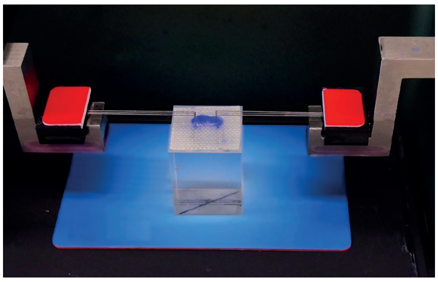

**Fig. 2:** Corneal strips 150µm thick were cut into the cornea with a femtosecond laser to quantify the depth and orientation dependence of mechanical properties measured by a uniaxial tensile test.

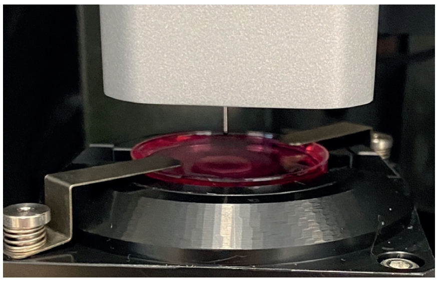

**Fig. 3:** The mechanical properties of the cornea measured using instrumented indentation.

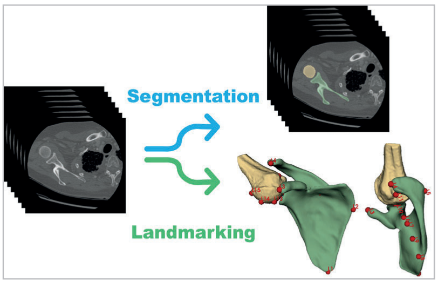


**Fig. 4:** Deep learning assessment of the degeneration of the shoulder rotator cuff muscles can automatically quantify muscle degeneration, fatty infiltration, and atrophy from CT datasets.

## Biomechanical characterization of the cornea

Refractive errors affect a large portion of the world's population. It is estimated that the number of people with myopia will increase to 4.76 billion by 2050. The shape of the cornea is a critical component of human optics. Therefore, it is important to accurately characterize its mechanical deformation in the context of surgical treatments, such as laser refractive surgery. Our goal is, therefore, to provide a complete description of the biomechanics of the cornea to understand how the tissue response changes as a function of depth and orientation. As a first step, 150µm thick porcine corneal strips were cut with a femtosecond laser at different depths of the cornea and along different orientations. Uniaxial tests (Fig. 2) were combined with numerical simulations to determine the mechanical parameters of a nonlinear mechanical model. Our results confirmed a strong dependence of material properties on depth. However, the mechanical response of porcine corneas was only slightly affected by specimen orientation, consistent with a circular arrangement of the collagen network in pigs. This measurement protocol is now being used to characterize human samples, such as unused corneal grafts and lenticules removed from patients' corneas during standard refractive procedures.

## Instrumented indentation of untreated keratoconic corneas

Keratoconus (KC) is a progressive corneal disease caused by local mechanical weakening of the cornea. It is manifested by corneal protrusion, irregular astigmatism, and severe myopia. People in the Middle East and Asia have a strikingly high incidence of KC, which is considered an epidemic in these regions. If not properly treated, KC can lead to blindness. The few methods that have been introduced to mitigate or halt the progression of KC have demonstrated poor postoperative outcomes, often requiring multiple revision surgeries. A better understanding of the biomechanical condition of these patients is necessary to improve their treatment. However, to date, no detailed mechanical characterization of the KC cornea has been presented. Our goal is to provide a spatial characterization of KC and compare the biomechanics of KC with that of normal tissue. We quantify the biomechanical properties of the tissue using state-of-the-art nanoindentation measurements (Fig. 3). Compared to other characterization techniques, nanoindentation allows us to perform multiple local measurements on the sample, which is well suited for characterizing very heterogeneous tissues such as KC. Mechanical characterization is of immediate importance for the treatment of KC patients, either for the proper selection of intracorneal ring implants or for the planning of corneal fusion by photo-chemical crosslinking.

## Automatic quantification of morphologic markers to assess total shoulder replacements

Total shoulder arthroplasty (TSA) is a common surgical procedure to relieve pain and disability associated with glenohumeral osteoarthritis. Despite satisfactory results and a relatively good long-term survival rate, there is a lack of indicators to predict the long-term success and revision risk of TSA. The biomechanical configuration of the glenohumeral joint could influence the im plant survival rate and explain possible causes of the observed complications, such as the preoperative condition of the rotator cuff muscles or the shape and orientation of the acromion. Manual quantification of these parameters is a repetitive and time-consuming process that depends on the subjective assessment and expertise of the clinicians. Therefore, we developed image analysis and deep learning-based approaches to automatically segment the bones from shoulder CT scans and locate key landmarks on the scapula to quantify multiple potential preoperative morphologic markers and provide an objective tive assessment of shoulder anatomy (Fig. 4). Our results show that automatic segmentation is consistent with manual annotation by clinicians and that automatic landmark detection even outperforms human judgement, allowing automatic and objective assessment of shoulder anatomy.

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# 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.

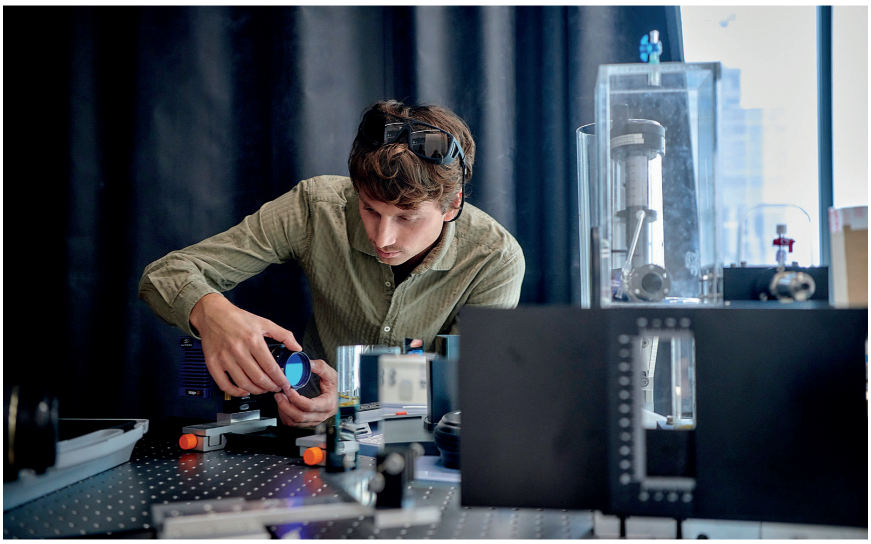

**Fig 1:** Optical flow quantification in the Cardiovascular Flow Lab.

### 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. 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.

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.

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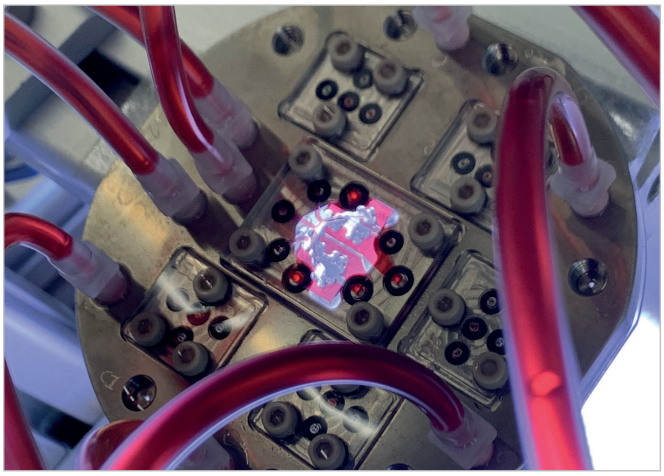

**Fig 2:** Microfluidic chip to model the blood flow in the heart muscle.

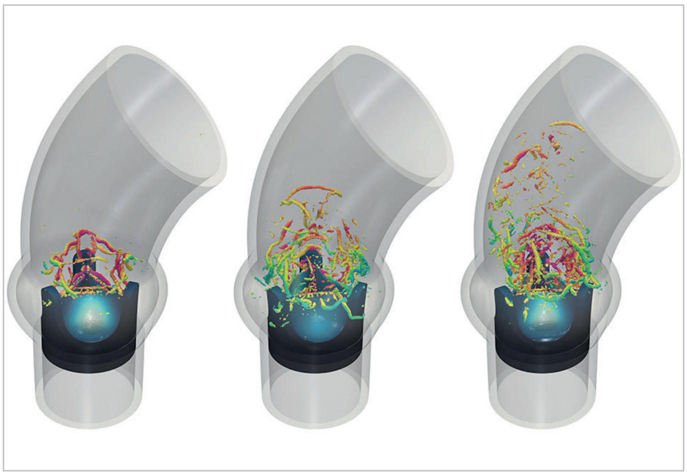

**Fig 3:** Turbulent blood flow behind a heart valve prosthesis.

## 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. 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.

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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.

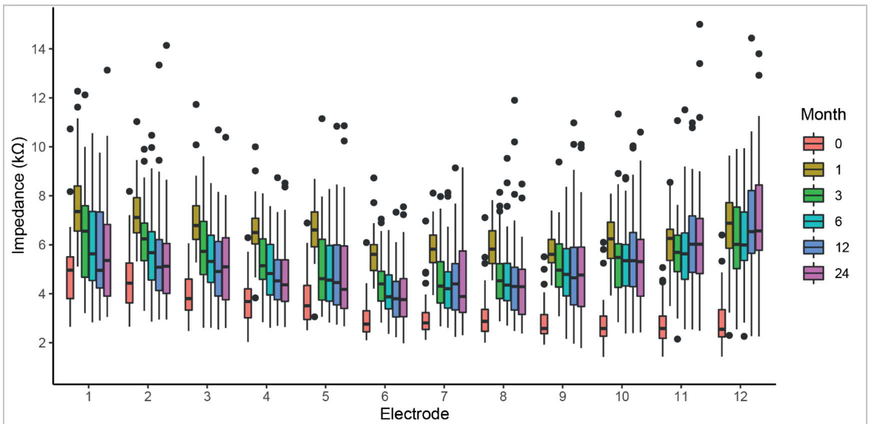


**Fig. 1:** Course of the electrical impedance of individual cochlear implant electrodes over a period of 2 years.

### 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 →

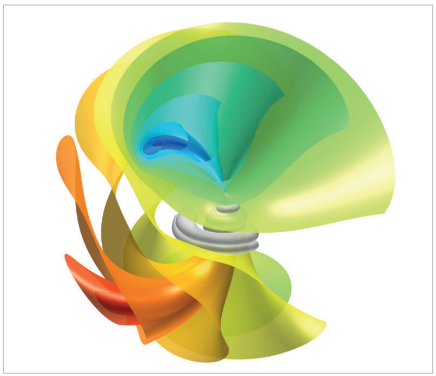

**Fig. 2:** Visualization of isosurfaces indicating the degree of curling of a non-linear vector field for geometric description of the human cochlea.

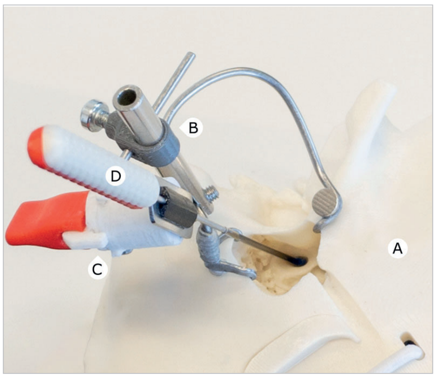


**Fig. 3:** Temporal bone model (A), with the insertion tool mount (B), magnetic fixation (C) and insertion tool (D) installed. Invasive cochlear implantation.

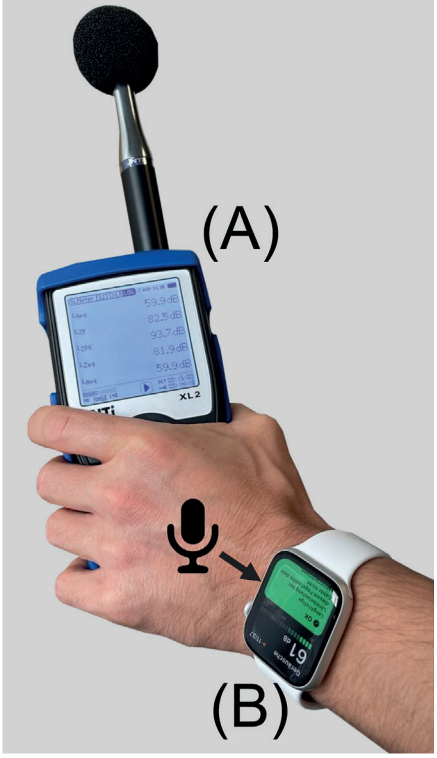


**Fig. 4:** Noise monitoring using a sound level meter (A) and a smartwatch (B).

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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# Chair for Image-Guided Therapy

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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.

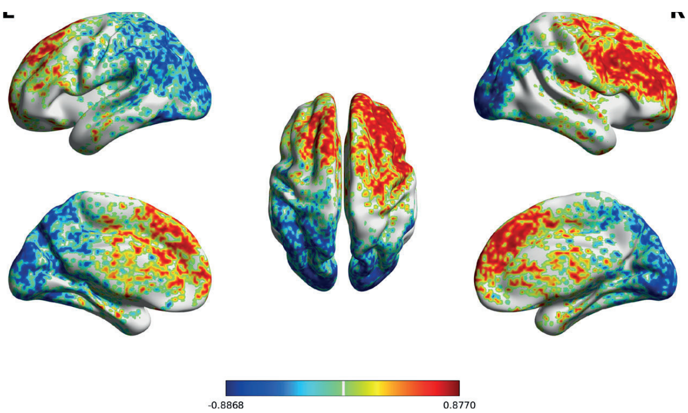


**Fig. 1:** Patient-specific map of brain areas that, when functionally connected to the DBS Volume of Tissue Activated, are statistically significantly related to depressive symptoms improvement (red) or worsening (blue) in the MADRS scale.

**Mapping and Modelling of Deep Brain Stimulation**
*(SNSF Ambizione 186142)*

The Brain Neuromodulation sub-group has continued its research on mapping and modelling of deep brain stimulation. Regarding mapping, we presented preliminary results of a multicentric European map for essential tremor. We also expanded computational methods to estimate stimulation volumes in an anisotropic medium. Finally, we have been improving stimulation maps for Parkinson's disease. Regarding modelling, we are continuing work on assisted DBS programming for Parkinson's disease based on pathway activation models. In other work on treatment-resistant depression, we have used diffusion and functional magnetic resonance images as well as patient data to better understand the effects of brain stimulation on the disease (Fig 1).

**Fighting Liver Cancer**
*(H2020 MSCA-ITN 722068*
*Innosuisse 37855.1 IP-LS)*

Clinical implementation of an ablation system able to treat tumors in a specific and standardized way draws a number of constraints. The changes introduced in →

the operating theater are often unsought and cumbersome. Therefore, to better understand and identify possible pitfalls, a computer simulation of the setting, true to the interventional suite at the hospital, was created (Fig 2). As a result, we aimed to find a solution that would bridge over the obstacles, yet without greatly adding on to the complexity of what is already in use in the clinics. Once implemented, the new "feature" will be not more than an update of the current system (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 (Figure 6) 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.

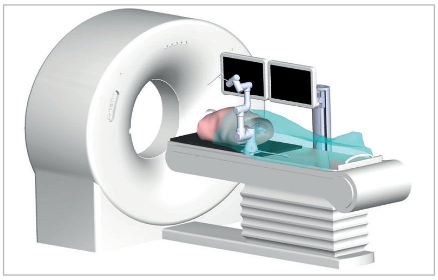

**Fig. 2:** Computer simulation of the intervention room setting.

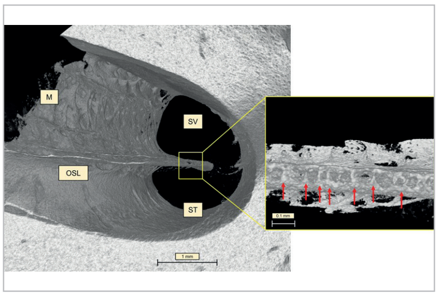


**Fig. 3**: Supportive pillars of the OSL coming from the cribiform wall of the modiolus (M) seen on a 2.3 µm microCT. OSL-Osseous

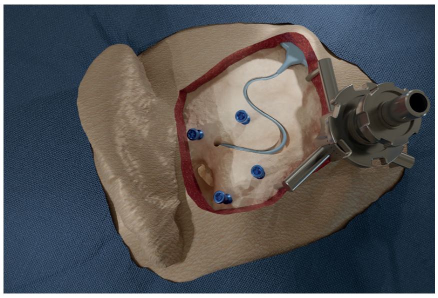

**Fig. 4:** Robotic milling channel and implant bed to store and protect the implant electrode and housing.

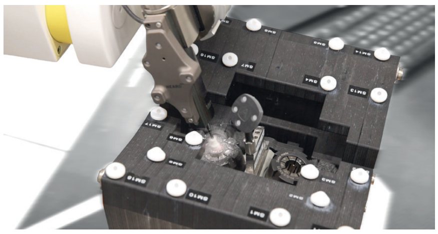

**Fig. 5:** Prototype platform for robotic spine surgery development.

**Selected Publications**
1. Bargiotas, P. et al.: Long-Term Outcome and Neuroimaging of Deep Brain Stimulation in Holmes Tremor: A Case Series. Neuromodulation: Technology at the Neural Interface 24(2), 392–399.
2. Garza, R. et al. Patient-Specific Anisotropic Volume of Tissue Activated with the Lead-DBS Toolbox. In 2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) (pp. 6285-6288). IEEE.
3. Nowacki, A et al. Probabilistic mapping reveals optimal stimulation site in essential tremor" by Annals of Neurology. (in revision).
4. Hermann J et al. In-silico assessment of safety and efficacy of screw placement for pediatric image-guided otologic surgery. Front. Surg.2021 Sep 29; 8:736217
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# Medical Image Analysis

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## Research Profile

The Medical Image Analysis group develops advanced medical image analysis technologies, and related translational biomedical engineering technologies, to quantify, diagnose, and follow-up diseases and disorders. A strong focus is given to disorders related to the central nervous system.

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.

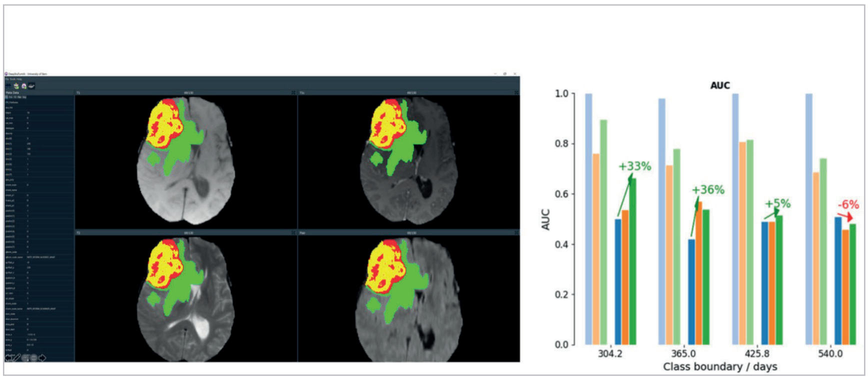


**Fig. 1:** Left: Deep learning-based automated quantification and analysis of brain tumor lesions – DeepBraTumIA software. Right: Favoring robustness in radiomics analysis can further improve overall accuracy of prediction models, demonstrated in overall survival prediction tasks.

### 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 for computer-assisted technologies.

Based on A.I technologies, our group has developed methods and produced related translational technologies to automate the delineation of brain tumors. We have made these technologies available for the research community but also further developed them for future clinical use. In 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 A.I technologies such that they are optimized to the clinical end goal. In these regards, in radiation oncology, we are →

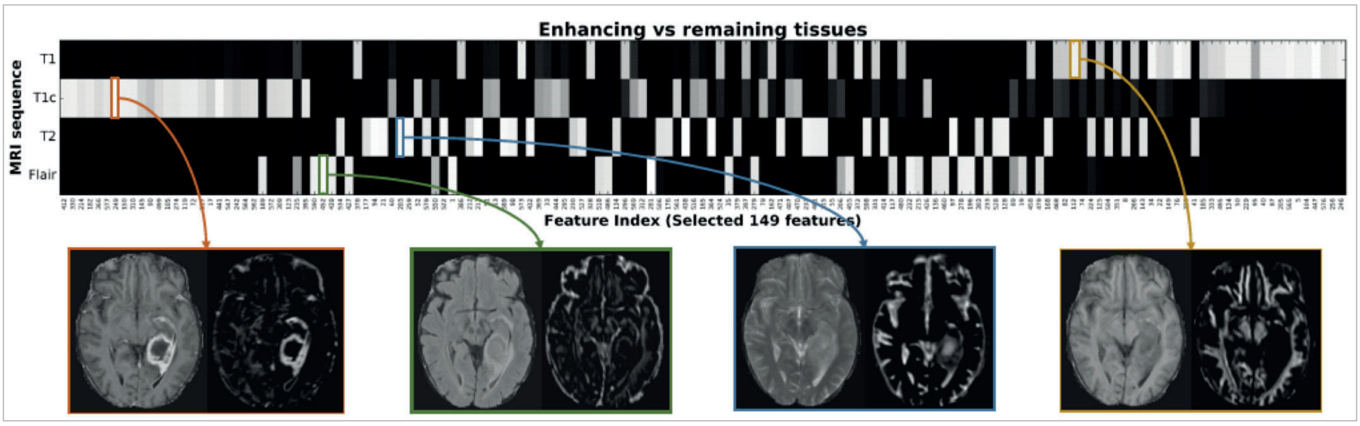


**Fig. 2:** Global interpretability of deep learning features to segment enhancing tissue. Features are sorted from most to least important (left to right). Brighter means higher squared L2-norm of the weights connecting the hidden unit of a given feature to a given MRI sequence. Bottom) examples of pairs of MRI sequences (left) and feature maps (right). Source: Pereira et al. Medical Image Analysis, 2018.

investigating A.I learnability approaches targeted directly toward metrics derived from the clinical end goals.

Radiomics is an emerging research area where image analysis methods are employed to mine imaging information to answer clinical questions. Our research in radiomics is focused in investigating patterns of robustness of radiomics-based imaging biomarkers in multi-center studies where imaging variability is inherent. We have highlighted current challenges to setup robust radiomics analysis in brain tumor imaging, and proposed methodologies to compensate these issues when models trained in single-center datasets are employed for multi-center radiomics analysis.

Due to the pandemic, our group joined efforts to investigate deep learning-based quantification and radiomics strategies for the prognosis and severity prediction of COVID-19 patients, employing a multi-omics approach relying on imaging and non-imaging information. During 2020, our group also contributed novel deep learning-based methodologies to enhance the accuracy and clinical adoption of magnetic resonance fingerprinting.

### Interpretability of Medical Image Segmentation Technologies Using Deep Learning Technologies

Our group is researching methodologies to enhance the interpretability of machine-learning models, so their decisions can be inspected (e.g. is the machine capturing the relevant relation in the data?), and interpreted by human (opening of the "black box", e.g. If a system fails, why does it fail?). Enhancing interpretability of machine-learning methods is essential in medicine to build trust with these systems, but it is also very important in line with discussions pointing to decision-making and a "right to explanation." Motivated by the current decoupling between the design of medical image sequences, and their exploitation through machine-learning algorithms. In collaboration with MRI physicists from the academic and private sectors, our group is researching machine-learning methodologies that are being applied at the image formation process stage, with the overarching goal of designing the best combination of MRI sequences and machine-learning algorithms.

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4. Silva W., Cardoso J., and Reyes M. Interpretability-guided content-based medical image retrieval. In Medical Image Computing and Computer-Assisted Intervention. MICCAI 2020, 2020.
5. Suter Y., Knecht U., Alao M., Valenzuela W., Hewer E., Schucht P., Wiest R., and Reyes M. Radiomics for glioblastoma survival analysis in pre-operative MRI: Exploring feature robustness, class boundaries, and machine learning techniques. Cancer Imaging, 20(2):1-13, June 2020.
6. Ermis E., Jungo A., Poel R., Blatti-Moreno M., Meier R., Knecht U., Aebersold D., Fix M., Manser P., Reyes M., and Herrmann E. Fully automated brain resection cavity delineation for radiation target volume definition in glioblastoma patients using deep learning. Radiation oncology, 15:1-10, 2020.

# 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.

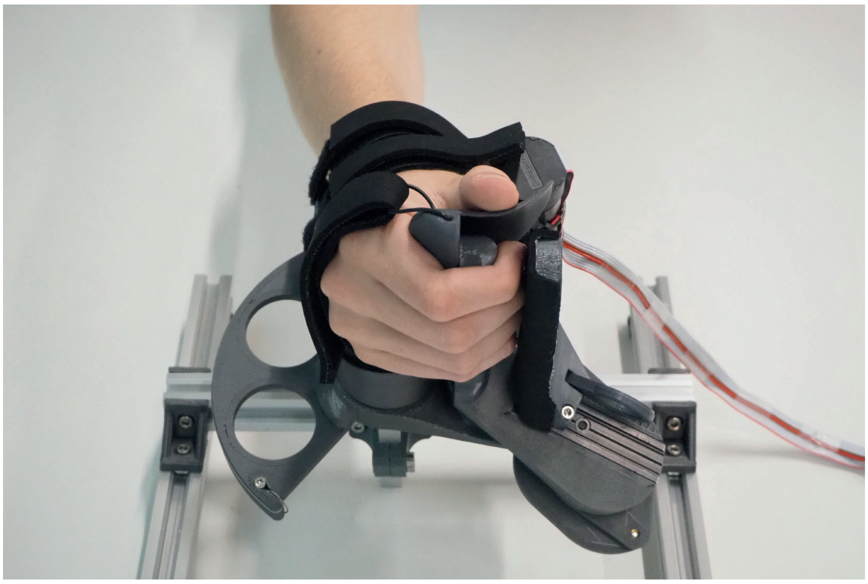

**Fig. 1:** Prototype of haptic hand rehabilitation device for sensorimotor training after stroke. Photo: Adrian Moser for ARTORG Center

### 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.

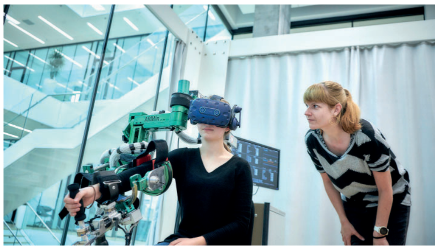
**Fig. 4:** Robotic motor training with ARMin exoskeleton in immersive virtual reality.

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**

1. Ö. Özen, K. Buetler and L. Marchal-Crespo, "Towards functional robotic training: motor learning of dynamic tasks is enhanced by haptic rendering but hampered by arm weight support", Journal of NeuroEngineering and Rehabilitation, vol. 19, no. 1, 2022.
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.
3. N. Wenk, M. V. Jordi, K. A. Buetler and L. Marchal-Crespo, "Hiding Assistive Robots During Training in Immersive VR Does Not Affect Users' Motivation, Presence, Embodiment, Performance, Nor Visual Attention," in IEEE Transactions on Neural Systems and Rehabilitation Engineering, vol. 30, pp. 390-399, 2022.
4. R. Rätz, F. Conti, R. Müri and L. Marchal-Crespo, "A Novel Clinical-Driven Design for Robotic Hand Rehabilitation: Combining Sensory Training, Effortless Setup, and Large Range of Motion in a Palmar Device", Frontiers in Neurorobotics, vol. 15, 2021.

# 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.

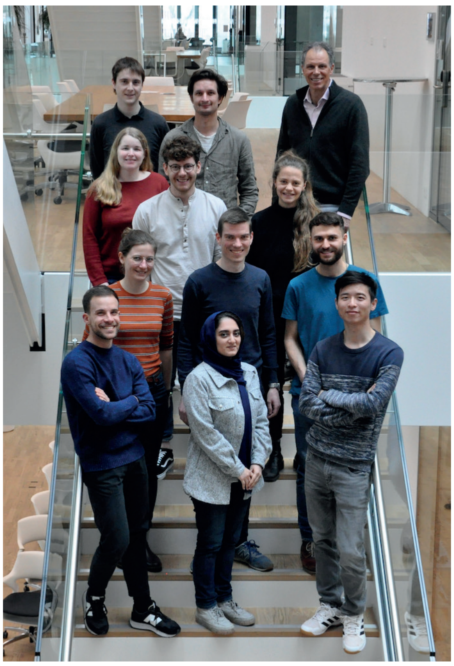

**Fig. 1:** Members of the Musculoskeletal Biomechanics group in 2021.

### Multiscale Mechanical Properties of Bone

*(SNF grant #165510 with EMPA, MGU and HWU, ESKAS fellowship)*

Bone is a complex material characterized by high strength and different toughening mechanism at various length scale. A key in understanding its postyield behaviour is the mineralized collagen fibre embedded in an extrafibrillar matrix. Combined micropillar compression and synchrotron X-Ray scattering were used to verify a 1D elasto-plastic model, and the experimental data was used to develop a 3D computational model of a unit cell to gain further insight into the influence of composition and architecture on the elastic and post-yield properties. Further microtensile and nanoindentation experiments were conducted to investigate the bone extracellular matrix properties in Osteogenesis Imperfecta (OI).

### Fabric-elasticity Relationships of Tibial Trabecular Bone in OI and healthy individuals

*(SNF grant #200365 with MGU)*

OI is an inherited form of bone fragility characterised by altered trabecular bone architecture and reduced bone mass. High resolution peripheral computed tomography (HR-pQCT) is a powerful method to investigate bone morphology at peripheral sites. In this project, trabecular morphology of distal tibiae with OI were compared to healthy controls with HR-pQCT.→

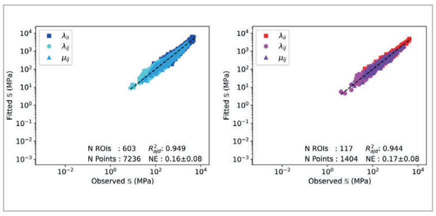

**Fig. 2:** Linear regression between observed trabecular stiffness and predicted stiffness. Left: healthy controls. Right: OI.

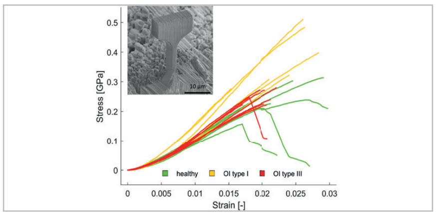


**Fig. 3:** Stress-strain curve of micro-tensile specimen of OI and healthy control bone.

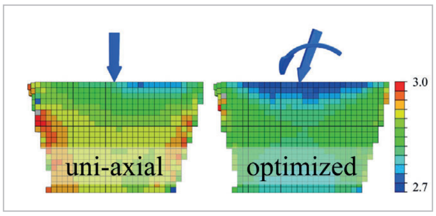


**Fig. 4:** Standard uni-axial loading boundary conditions (left) and an optimized loading boundary condition (right).

→ Mathieu Simon found the OI samples to have significantly lower bone volume fraction and trabecular number but no differences in trabecular thickness compared to control. After age and sex matching, relationships between trabecular architecture and stiffness on common regions of interest were compared between healthy controls and OI, showing that these relationships were similar for the two groups. With this work, Mathieu obtained the Student Award of the Swiss Society of Biomedical Engineering.

### Experimental and Computational Approach to Investigate the Biomechanics of the Aging Human Femoral Neck

*(with VUT)*

Aging of the population induces a higher number of fractures due to a loss of bone mass and an increasing falling risk. As the influence of ageing on bone quality is unclear, micro finite element analysis (µFE) was used to assess the influence of aging on the mechanical properties of the femoral neck. Human femoral necks were prepared and loaded in compression to measure stiffness and strength. In parallel, µFE non-linear analyses based on microCT images were run on these neck samples. The µFE simulation was able to predict the experiment's stiffness and strength, and the error did not reveal an age dependency.

### Personalized HR-pQCT-Based Homogenized FEA

*(with IS and UniBa)*

Personalised *in vivo* assessment of bone strength estimated by finite element analysis (FEA) based on HR-pQCT becomes successful in identifying people at high risk of fractures. This year we published a unified pipeline, calibrated, and validated with experimental data sets of radius and tibia samples for the clinical use. Furthermore, we developed a method for personalising the loading conditions using Wolff's law in trabecular bone adaptation and a simplified hFE method. A clinical study applying HR-pQCT-based FEA on long-term type I diabetes is ongoing with our clinical partners.

### AFFIRM-CT and Clinical Study

*(SNF grant #183584 with HUG and IS)*

Most hip fractures are caused by falls resulting in an impact force that exceeds the femoral bone strength. The AFFIRM-CT project aims to develop a new hip fracture risk model integrating a CT-based femoral bone strength. For model validation, a clinical study was conducted, starting with patient recruitment in March 2021. After the baseline visit assessing the risk of falling, the general health state and bone quality with HR-pQCT and DXA measurements, participants will be followed-up to record falls and fractures.

For the femoral bone strength estimate, a pipeline was developed that builds finite element models based on CT images. The pipeline was tested and validated using experimental data collected in an earlier study. It is now used to analyse different data sets to compare FE-based bone strength to other bone strength estimates and serves as a baseline for the development of personalized load cases. Additionally, CT scanner stability was investigated. Using an existing dataset, the sources of intensity variations were examined, identifying potential parameters affecting calibration accuracy. Results showed that CT intensities were mostly affected by body volume and table height and should therefore be corrected for these parameters. In addition, a personalized fall rate estimate model was developed. Preliminary results show that prior experienced falls are a good predictor for future falls.

### Biomechanical Testing and Simulation

*(with ZMK)*

Several projects could be conducted in the biomechanics laboratory. In a thesis aiming to test dental implants ex vivo, human mandibular and maxilla bone samples were cut, embedded, and scanned with the laboratory's µCT system for morphological assessment. The primary stability of two dental implant sizes was quantified using an in-house testing protocol and the key morphological predictors were identified. On the simulation side, an explicit finite element methodology was applied to quantify insertion torque as well as stiffness and strength of distinct implant models in various loading configurations.

**Selected Publications**

1. Hess Silvan, Bürki Alexander, Moor Beat K., Bolliger Lilianna, Zysset Philippe, Zumstein Matthias A. „A biomechanical study comparing the mean load to failure of two different osteosynthesis techniques for the step-cut olecranon osteotomy", JSES Reviews, Reports, and Techniques, 1:414-420, 2021.
2. Groetsch Alexander, Zysset Philippe, Varga Peter, Pacureanu Alexandra, Peyrin Françoise, Wolfram Uwe, "An experimentally informed statistical elasto-plastic mineralised collagen fibre model at the micrometre and nanometre lengthscale", Scientific Reports, 11-15539, 2021.
3. Casari Daniele, Kochetkova Tatiana, Michler Johann, Zysset Philippe, Schwiedrzik Jakob, "Crack nucleation in bone lamellae: influence of pores, interfaces and hydration", Acta Biomaterialia 120:135-145, 2021.
4. Indermaur Michael, Casari Daniele, Kochetkova Tatiana, Cinzia Peruzzi, Zimmermann Elizabeth, Rauch Frank, Willie Bettina, Michler Johann, Schwiedrzik Jakob and Zysset Philippe, "Compressive strength of iliac bone ECM is not reduced in Osteogenesis Imperfecta and increases with mineralization", J Bone Miner Res, 36(7):1364-1375, 2021.
5. Stipsitz Monica, Zysset Philippe and Pahr Dieter, "Prediction of the inelastic behaviour of radius segments: damage-based nonlinear micro finite element simulation vs Pistoia criterion", J Biomech 116:110205, 2021.
6. Panagiotopoulou Vasiliki, Marzieh Ovesy, Gueorguiev Boyko, Richards Geoff, Zysset Philippe and Varga Peter, „Experimental and numerical investigation of secondary screw perforation in the human proximal humerus", J Mech Behav Biomed Mater 116:104344, 2021.

# 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.

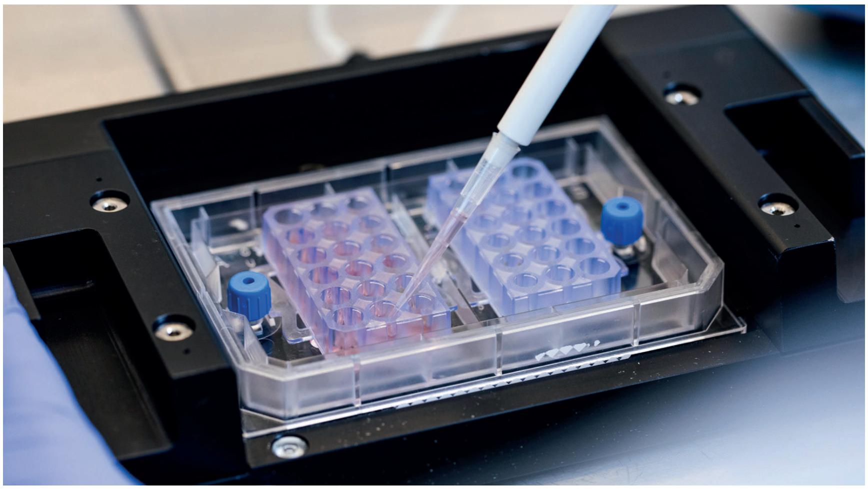

**Fig. 1:** Picture of a multi-well plate with two lung-on-chips. Each lung-on-chip is equipped with a 3µm-thin, porous and stretchable membrane (inset), on which cells are cultured. (developed in collaboration with AlveoliX AG).

### Breathing lung-on-chip (LOC)

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 polydimethylsiloxane (PDMS) 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. The actuation of the barrier is created by a microdiaphragm that resembles the in vivo diaphragm. This lung-on-chip (Fig. 1) is one of the two systems worldwide able to reproduce the breathing motions of the alveolar barrier. The toxicity of aero¬solised nanoparticles is currently assessed with this system.

### 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. To circumvent these drawbacks, we developed a second-generation lung-on-chip with an array of in vivo like-sized alveoli and a stretchable biological membrane. The membrane is made of

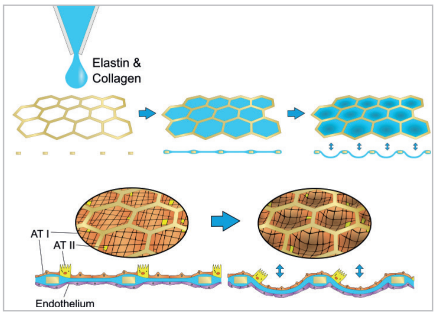


**Fig. 2:** Concept of the second-generation lung-on-chip: a drop of collagen and elastin is pipetted on a thin hexagonal gold grid. The stretchable membrane is formed by surface tension forces and evaporation[1].

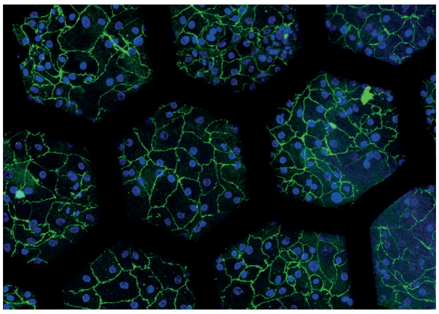

**Fig. 3:** Lung alveolar epithelial cells from patients cultured on the collagen-elastin membrane supported by an ultra-thin hexagonal gold grid (each hexagon is ca. 260µm wide).

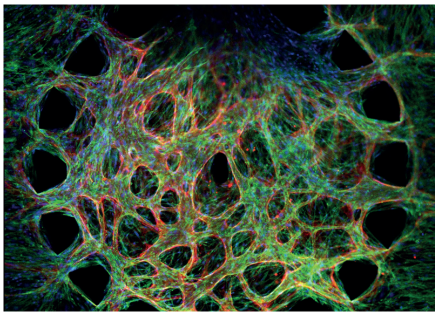

**Fig. 4:** Self-assembly of a 3D perfusable lung blood vessels network in the central chamber of the microvasculature-on-chip.

two proteins found in the lung ECM: collagen and elastin. Its fabrication process is very simple (Fig.2). The mechanical properties of the biological membrane could be easily adapted by modifying its composition or its fabrication process. It allows recreating an air-blood barrier without any artificial layer between the epithelial and the 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).

### Microvasculature-on-chip

Vascular homeostasis is important to maintain the proper functioning of the organs, and interruption of this balance plays an initial role in many diseases. Engineered models of the blood vessels can contribute significantly to mimicking the pathology of vascular disease and proceed to drug development. We developed functional microvasculature platforms to study the biology of the blood vessel and answer mechanistic questions behind the pathology of vascular disease, drug testing, and endothelial mechanotransduction. Two different microvasculature platforms have been developed. The first is a self-assembled complex microvascular network and the other is a single microvessel exposed to cyclic forces. A three-dimensional microvasculature network was generated using a co-culture of human endothelial and mural cells within a 3D matrix of hydrogel (Fig.4). A dynamic perfusable microvasculature model incorporating a single/multiple vasculature/s within a hydrogel layer was designed and developed to investigate the effect of mechanical cyclic stretch on vascular remodeling (Fig. 5).

### Nanocellulose in biosensing devices

Lateral flow immunoassays (LFIA) are progressively important Point-of-Car devices in medical diagnostics. Standard LFIA strips are restricted due to the analysis of a limited sample volume, short reaction time, and a weak optical signal. In this project, we incorporated a novel cellulose nanofiber (CNF) aerogel material into LFIA strips to increase the sample flow time. The binding interactions between the analyte and the detection antibody increase and which in return improves the limit of detection (LOD) (Fig.6). The presented optimization method offers a unique potential to transform lateral flow assays into highly sensitive, fully quantitative point-of-care diagnostics.

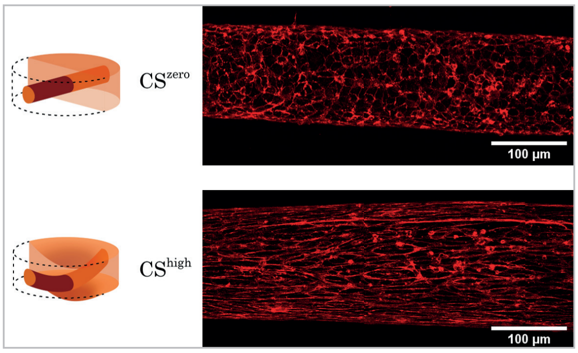


**Fig. 5:** Schematic of a blood vessel in static mode (top left) and cyclically stretched (bottom left). Endothelial cells respond to the mechanical stretch, align, and create a tight vascular barrier (right bottom)[3].

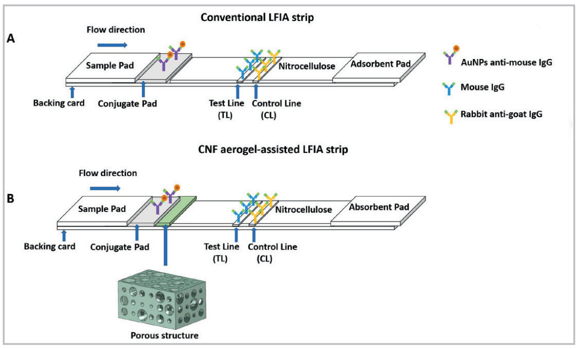


**Fig. 6:** Illustrative comparison between a conventional LFIA strip design (A) and a aerogel-assisted LFIA strip design (B)4. This study was a joint project of the ARTORG Center and CSEM.

**Selected Publications:**

1. 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).
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. 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).
4. Tang, Y. et al. Nanocellulose aerogel inserts for quantitative lateral flow immunoassays. Biosens. Bioelectron. 192, 113491 (2021).

# Urogenital Engineering

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URODEA AG, Biel, CH

## 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 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.

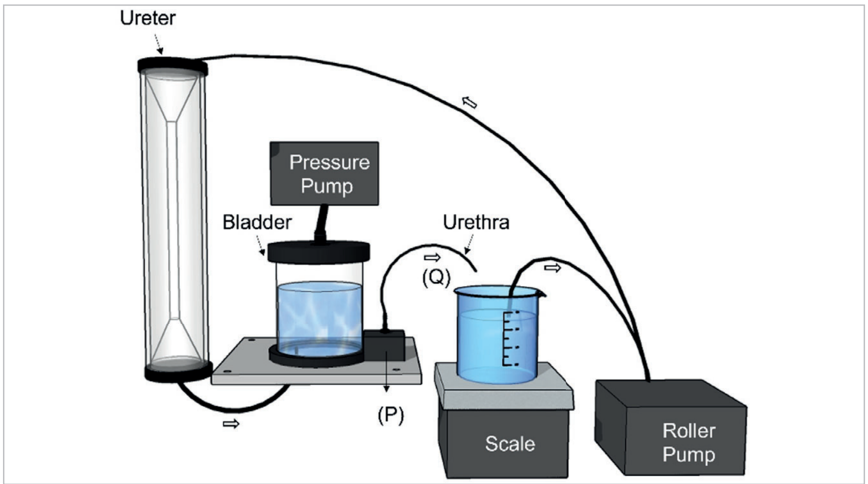


**Fig. 1:** In-vitro model of the urinary tract. Using a programmable pressure pump, bladder pressure waveform and flow can be controlled to mimic physiological and pathological conditions.

## Urinary Tract Modelling

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

**Fig. 2:** Our first prototype for patients suffering from urinary retention.

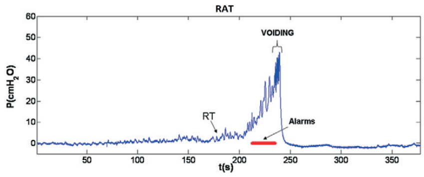


**Fig. 3:** Bladder pressure signal during voiding in rats.

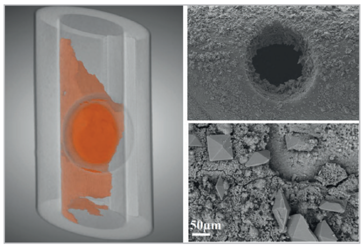


**Fig. 4:** A) Example of micro-computed tomography image of a stent's side hole with encrustation (orange). Examples of scanning electron microscopy images of B) the stent's side hole with the typical C) calcium-based encrustations.

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 chemical (bacteria, crystals) environments. Location and extent of encrustation 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 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.

### 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 an external and handheld prototype. URODEA AG is a spin-off of the ARTORG Center and is focusing on bringing this technology to the patients.

### 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., 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
2. 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
3. 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
4. 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
5. Niederhauser, T., Gafner, E., Cantieni, T., Grämiger, M., Haeberlin, A., Obrist, D., Burkhard, F., Clavica, F. 'Detection and quantification of overactive bladder activity in patients: Can we make it better and automatic?' Neurourology and Urodynamics, 1-9, 2018. DOI: 10.1002/nau.23357
6. Clavica, F., Choudhary, M. S., van Asselt, E., van Mastrigt, R., 'Frequency analysis of urinary bladder pre-voiding activity in normal and overactive rat detrusor.' Neurourology and Urodynamics, vol. 34, pp. 794-9, 2015. DOI: 10.1002/nau.22664

# 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:** Test device for the mitral valve. Photo: Adrian Moser for ARTORG Center

## 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 have had many changes in the staff. Fabio Spena left our workshop at the end of January to realize his career as a mountain bike cross country pro. We wish him much success and thank him for his excellent work and support in the MDP team in the last almost six years.

We welcomed new employee Meret Ruch as a polymechanic with a workload of 60% on February .

For students of the department for machine engineering at ETH Zurich, it's mandatory to have an industrial practical training for at least five weeks. This year, Clara Wittig performed her practical training during six weeks in our machine shop. The training was very instructive and successful. We wish her a lot of success with her studies.

Due to a high demand and heavy workload, we recruited a polytechnician, Sebastian Aellig, as an 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.

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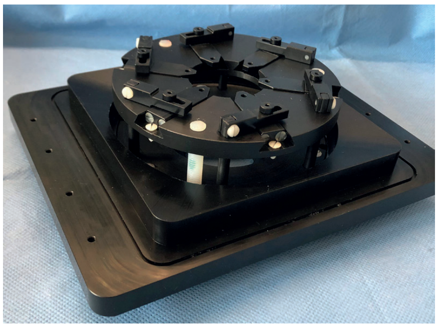

**Fig. 2:** Test device for the mitral valve.

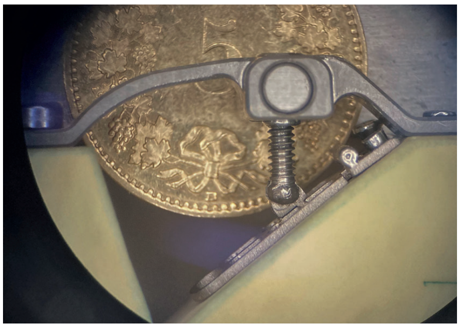

**Fig. 3:** Dental plate vertical.

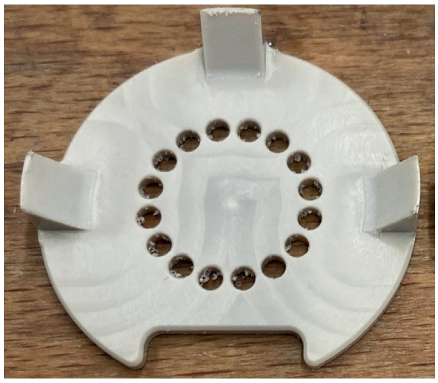

**Fig. 4:** Cornea three finger plate.

→ In 2020, we selected Piravin Jeyendran as our new apprentice, and he started his basic training on August 1, 2021 in the workshop of the physics institute of the University of Bern and will join us in the workshop in spring 2022.

Our apprentice Janosch Schär completed his basic training exam at the end of the second year with a grade of 5.4 and we congratulate him. In the coming two years, his training will focus more on CAD-CAM technologies and manufacturing more ambitious parts.

Simon Lüthi completed his four-year apprenticeship with a grade of 5.5 and achieved the third best result in the Bern- Biel Mittelland district, and we congratulate him on this huge success. We employed him in our machine shop as a poly-mechanic until the end of this year. We appreciate him as an independent and responsible worker, and wish him all the best in his future endeavors.

### Research Equipment Design and Manufacturing

As expected, the requirements of a machine shop supporting research in the biomedical engineering field are as diverse 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 Cardiovascular Engineering Group: Test device for the exploration of the mitral valve

Simon Lüthi produced this device as a practical part of his exam. The device is suitable for clamping a mitral valve and then moving it radially as well as axially. The mitral valve functions as a check valve and connects the left atrium with the left ventricle of the heart. The entire device must be made of plastic and must not contain any metal components, so that the use of ultrasound can take place without interference during the examination of the function. The design was created by Michael Stucki (CVE Group).

### Cranio-Maxillofacial Surgery Groupe DBMR, Dental Plate Vertical

Since 2007, we have had a close collaboration with Nikola Saulacic from DBMR at the University of Bern to develop devices for bone growth studies. In 2018, we developed a horizontally functioning dental plate. This year we redesigned this device so that the function can be used in a vertical position. Again, the big challenge was to fabricate all of these very small parts and assemble them under the microscope. Some parts were cut out with a laser beam and welded together by an innovative partner company.

### ARTORG Organ-on-Chip Group Chip Plate

This year, in collaboration with Rrahim Gashi as a technical employee in the ARTORG-OOC group, we were able to produce various chip plates. Thanks to the new acquisition of the Fehlmann machining center in 2020, we were able to produce these plates in many different designs. During the production we had two challenges at the same time. On one hand, the special plastic with a low melting point from which the plates are made and, on the other hand, the smallest hole to be produced was Ø 0.2mm "big."

Such projects help us in the workshop to get to know the limits of our machine park and also increase our special know-how.

### ARTORG Computational Bioengineering Group Cornea Three Finger Plates

Together with Shima Bahramizadeh Sajadi we have developed plates that are needed in the research of the cornea of the eye. With the help of these three finger plates, she can easily determine the cornea's properties on a microhardness testing machine and later perform laser tests with the cornea on the same plate on another machine. In this project seven versions have been developed with different materials. In the end, we made all the required plates from the high-temperature-resistant thermoplastic PEEK (polyether-etherketone). The machining of PEEK is a challenge for tools to keep the tolerances because the abrasion of the tools is very high.

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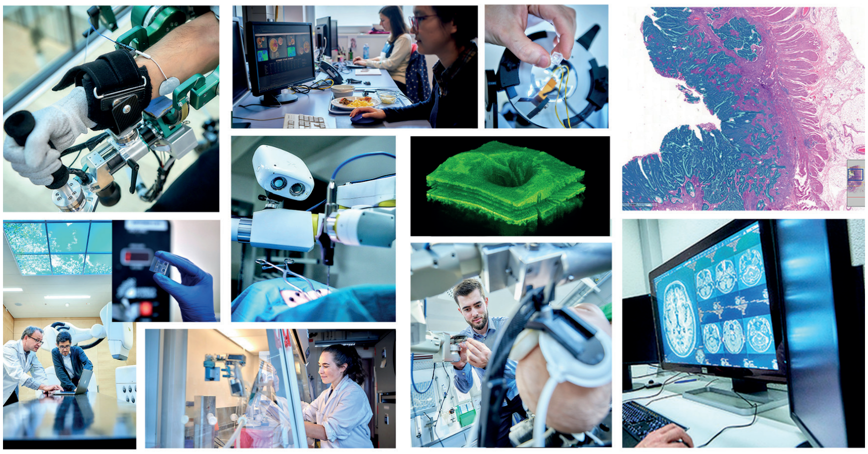
## Technology for better patient care

To take leadership in the direction of research and development of AI in medicine, the University of Bern and the Inselspital, Bern University Hospital, together with partners from sitem-insel, the Swiss Institute for Translational and Entrepreneurial Medicine, and the University Psychiatry Services (UPD) have founded the Center for AI in Medicine (CAIM).

Bringing together world-class scientists and clinicians to join with collaborators in industry, patient advocacy, and medical ethics, researchers will enable the investigation and translation of advanced digital and robotic technologies to deliver a new generation of diagnostics, treatments, and interventions. CAIM started operations in January 2021 driven by the existing expertise in AI in medical research, engineering, and healthcare digitalization education within the Bern network to bring forward AI in medicine solutions with a positive impact for patients everywhere. During its first year, CAIM was nominated for the best 2022 AI in medicine center by the Alliance of Centers of Artificial Intelligence in Medicine (ACAIM).



## Profile

The Center for Artificial Intelligence in Medicine is a research, teaching, and translation platform that investigates AI medical technologies that can faciltate the work of doctors and nurses and bring better care to patients. CAIM capitalizes on the significant presence of scientific, healthcare, and medical technology indutry players in the capital of Switzerland. It is a virtual Center of the University of Bern's medical faculty and the Inselspital, Bern University Hospital in partnership with the University Psychiatry Services (UPD) and the Swiss Institute for Translational and Entrepreneurial Medicine, sitem-insel. The University of Bern, the Inselspital, Bern University Hospital ("Digital Hospital"), and the Canton of Bern ("Engagement 2030") have major, strategic digitalization in healthcare goals. CAIM plays a key part in these efforts and connects engineers, physicians, and scientists in the area of AI in medicine, providing them with resoures and access to infrastructure so they can innovate AI and robotic technologies that are fit to make it into the clinic. As the newest member of the Bern Biomedical Engineering Network, CAIM will also gain access to industry and local resources and networks. CAIM will foster commercialization of AI technology innovation, support start-up incubation, and create sustained value and economic growth through best-in-class research and translation.

## Organization

CAIM's activities are organized on four pillars:

### Pillar I: Digitalization & AI Education

EDUCATION

CAIM provides tailored AI in Medicine education for medical doctors and engineers through a portfolio of competitive and purposefully designed post-graduate programs to equip participants for Healthcare 4.0.

### Pillar II: Network & Dissemination

DISSEMINATION

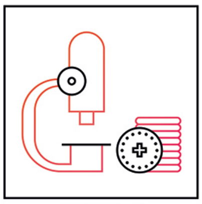
CAIM transmits trustworthy knowldege on AI in Medicine. This supports policy makers, educators and the general public by shaping the current debates on AI in Medicine with evidence-based information.

### Pillar III: Computational Facilities

INFRASTRUCTURE

CAIM facilitates access and availability to computer infrastructure, computational and data resources to support advanced digitalization and AI research within the Bern Medical Hub.

### Pillar IV: Research Project Fund



RESEARCH FUND

CAIM promotes technological innovation by funding projects with strong potential to be ground-breaking clinical approaches and a realistic pathway towards patient benefit.

## AI in Medicine – Fields of Research and Education

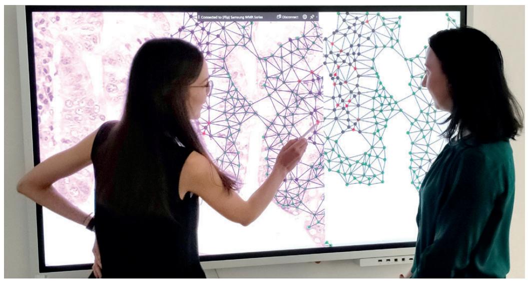
In the age of digitalization and data-based healthcare, Artificial Intelligence (AI) is an indispensable tool for analyzing large amounts of health data and rendering it into easy-to-use form to support diagnosis, treatment decision and disease management.

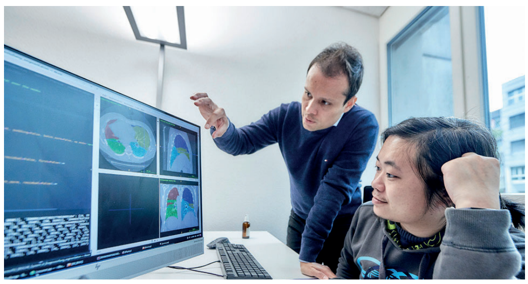
Various fields of AI in Medicine are currently being explored in Bern. Some examples include:

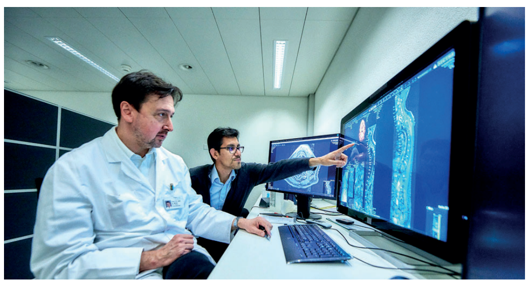
- Quantitative biosignal processing
- Biomarker identification in medical imaging
- Clinical data exploration with deep learning
- Monitoring of chronic disease progression
- Precision medicine (e.g. oncology)
- Real-time surgical navigation
- Surgical and rehabilitation robotics

CAIM provides important insights, evaluation and perspective for introducing novel AI technologies into clinicalcare by translating state-of-the-art research into tools for clinicians and healthcare professionals.

Targeted educational programs and courses of the University of Bern provide AI researchers and clinicians with cutting-edge know-how and qualifications in the field. This includes courses in "Digitilization and AI" for medical students, a dedicated Master's programme for AI in Medicine for engineers (starting fall 2021) and AI in healthcare-related postgraduate training and further education offers.







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