# Bern Biomedical Engineering Network

Annual Report 2020/21

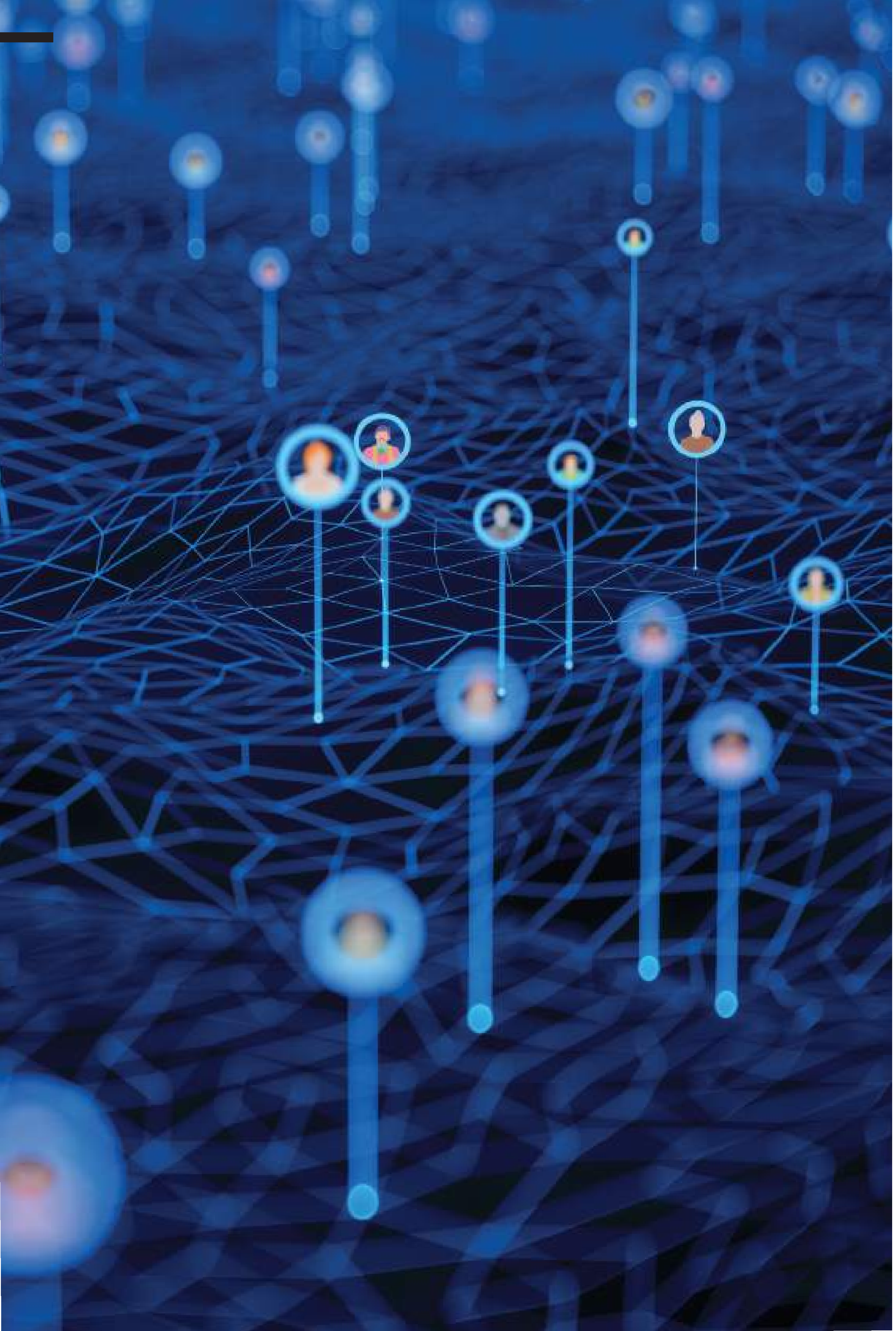

competence center for medical technology ccmt

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

UNIVERSITÄT BERN

Berner Fachhochschule
Haute école spécialisée bernoise

siteminsel





# Content




# Editorial

## Bern Biomedical Engineering Network

The years 2020/2021 were characterized by radical change both in the way we work together and in environmental circumstances guiding research and development of medical technology. The pandemic has challenged us to develop new ways to innovate, capitalizing on digitalization and flexibility and opening our horizons across national borders. Stronger regulation through the MDR and Switzerland's non-associative status in Europe have further pushed us to orientate our energies to both local and international markets.

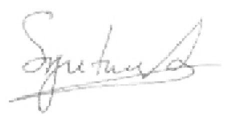
Even in these turbulent times and as we emerge into a new era of renewed personal encounters, the Bern Biomedical Engineering Network continues to leverage its assets with strong partners in research, industry, and clinic. Our network has prevailed in bringing a great number of successful start-ups forward and has made a difference to patient care and pushed the boundaries of what doctors and nurses are capable of doing.

It is through this spirit of collaboration, entrepreneurship, and the diversity of our expertise that we form an unparalleled biomedical engineering hub at the heart of Switzerland. Inspired by past pioneers and capitalizing on the unique Bernese constellation for disruptive medtech development and translation we never lose sight of patient benefit as our primary driver and goal.

The Bern Biomedical Engineering Network continues its important role in the medtech research and industry cluster of Switzerland's capital region. We have come forward with new ideas and energies and educate the next generation of experts with unabated enthusiasm. Our network offers top-quality master courses with cutting-edge specialization choices. With their academic excellence and practical expertise in the clinics, our graduates are prepared to shape the medtech landscape on an international scale, and to effectively transform medicine and healthcare through technology.

The BBEN partners remain committed to promoting shared interests, generating synergies in resources and infrastructure, and leveraging the location advantage of the medical technology sector of the Canton of Bern to foster:

- Translation of medical technology for patient benefit.
- World-class research and discovery through multi-disciplinary collaboration.
- Globally leading biomedical engineering graduate and post-graduate education and training.



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# Institutional Overview

**Swiss Institute for Translational and Entrepreneurial Medicine**
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**Empa**
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**ARTORG Center for Biomedical Engineering Research**
Murtenstrasse 50, 3008 Bern

**Inselspital, Bern University Hospital**
Freiburgstrasse, 3010 Bern

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Neubrückstrasse 10, 3012 Bern

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Mittelstrasse 43, 3012 Bern

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Murtenstrasse 35, 3008 Bern

**Institute of Applied Physics**
Sidlerstrasse 5, 3012 Bern

**BFH Centre for Health Technologies**
Aarbergstrasse 46, 2503 Biel/Bienne

**BFH Institute for Medical Informatics I4MI**
Höheweg 80, 2502 Biel/Bienne

**BFH Institut for Human Centered Engineering HuCE**
Quellgasse 2, 2501 Biel/Bienne


**BFH Bern Movement Lab**
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# sitem-insel


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**Bringing innovation to the patient – by connecting people**
The medical technology and pharmaceutical industries are cornerstones of the Swiss economy. Their product development relies on collaborations with university hospitals. Translational medicine should therefore be understood as a process-oriented and actor-centered discipline that necessarily involves numerous stakeholders from industry, academia, clinics, and authorities.

Such close and diverse collaboration among authorities, research, the start-up scene, and industry is thus only made possible by institutions such as the Swiss Institute for Translational and Entrepreneurial Medicine: sitem-insel.

sitem-insel has set itself the goal of establishing, operating, and continuously developing a national center of excellence for translational and entrepreneurial medicine, which professionalizes translational research for the benefit of patients, society, and science.

sitem-insel is located at the Insel Campus Bern and benefits from its proximity to the University Hospital (Inselspital) and the University of Bern. In sitem-insel, a wide variety of representatives from clinics, industry, research, and education are networked to innovate for the benefit of the patient. As a business, medical, and research campus, sitem-insel promotes innovation and collaboration among all partners and stakeholders. sitem-insel opens its doors to all disciplines of translational medicine as a non-profit corporation and public-private partnership (PPP).

**Three pillars**
sitem-insel strongly believes in an entrepreneurial team approach as a solution to speed up the leap from innovation in industrial development and basic research into clinical applications.

sitem-insel's operational strategy is based on three pillars:
Connecting minds: sitem-insel School (with the University of Bern) promotes professionalization by educating researchers and training executives in the field of translational medicine and biomedical entrepreneurship from a holistic perspective. The school teaches students practice-oriented high-quality knowledge, provides a strong network between people involved in the translational process, and offers training recognized by the University of Bern.

Our programs cover the most up-to-date thinking in translational science:
- Translational Medicine and Biomedical Entrepreneurship
- Artificial Intelligence in Medical Imaging
- Medical Device Regulatory Affairs and Quality Assurance (MDRQ)

Delivering impact: sitem-insel Enabling Facilities provide infrastructure for researching and developing medical device technologies, biomedical technologies, as well as combination products and diagnostics. Taking disruptive developments into account, the infrastructural design of sitem-insel's new building guarantees flexibility.

Our new building was opened in 2019—a great success in terms of costs, time, and quality. Run by public partners from university and university hospital as well as private industry partners, the premises comprise, among others, the first biosafety laboratory (BSL 3) available to external renters on a project basis, 7 Tesla MRI, a diabetes research center, a clinical anatomy training and research unit, and an open space for start-ups and spinoffs, with more planned for the future.

Delivering insight: sitem-insel Promoting Services respond to the major challenge of demanding and constantly changing regulatory requirements for translational projects. With the help of its partners, sitem-insel Promoting Services support companies in accelerating their process from invention to commercialization. 1

1

Sitem-insel Promoting Services operate a network of manufacturers, associations, scientists, and other healthcare institutions to support companies, clinics, and academia in regulatory and administrative matters.

Overall, sitem-insel Promoting Services reduce silo-building between industries, between disciplines, and, in terms of educational inputs, within individual people.

The three operational units, School, Enabling Facilities, and Promoting Services, together with the supporting units Centralized Services and Network & Communication, build sitem-insel's core organization.

Clinical Anatomy Training and Research Unit (CATR): The development of innovative diagnostic-therapeutic medtech products and learning how to use them correctly requires access to a highly equipped operation room (OR)-environment. The training can involve the use of animal or human specimens, simulation, or robotics. High ethical standards and specific infrastructure are required to work with cadaveric components. This infrastructure has been set up in the sitem-insel building as a CATR and is supported in its development and operation by, among others, the anatomy of the University of Bern and Prof. Michael D. Mueller, Co-Director of the University Clinic for Gynecology. The CATR has received generous financial support from the companies Storz and Anklin. CATR received GESEA-certification in 2021. The platform with its state-of-the-art infrastructure is extremely attractive for a variety of training courses, not only for physicians from the Inselspital, but also from the canton, Switzerland, and abroad.

Biosafety Level 3 (BSL-3) laboratory: The BSL3 laboratory, already mentioned in the last report, was successfully commissioned on schedule in 2020 despite the COVID-19 pandemic and the first lockdown phase. The Institute for Infectious Diseases of the University of Bern (ifik) operates the Biosafety Lab and the Biosafety Center. Twenty percent of the laboratory space is financed by sitem-insel and made available for external projects. First tenants for the two BSL3 spaces of sitem-insel were found quickly. In both cases the tenants work on SARS-CoV-2 projects.

Next to its own units, the sitem-insel community includes a wide variety of about 30 units from clinics, industry, research, and education to service-providers. All are joined together under one roof and drive innovation for the benefit of the patient. 2


The illustration (top down) shows sitem-insel's own units, followed by units from the University of Bern, and the Inselspital, and finally units from private companies as well as start-ups and service providers.

**Shaping the future of translational medicine – some high-lights**

NeuroTec Opening

NeuroTec, the newly opened research unit within sitem-insel, accelerates innovation and explores novel medical technology to improve diagnostics and the treatment of neurological diseases. The aim is to shift diagnosis and therapy from the hospital to the patient's home.

At the core of NeuroTec is the "Living Suite" - a smart home where human behavior is monitored and researched to understand how neurological disorders affect daily life. Areas of interest include the analysis of physiological and pathological body movements, cognitive performance, and sleep-wake patterns in both health and disease. Overall, NeuroTec promises to address problems of our aging society and thereby improve the cost-effectiveness and quality of healthcare for patients with neurological disorders.

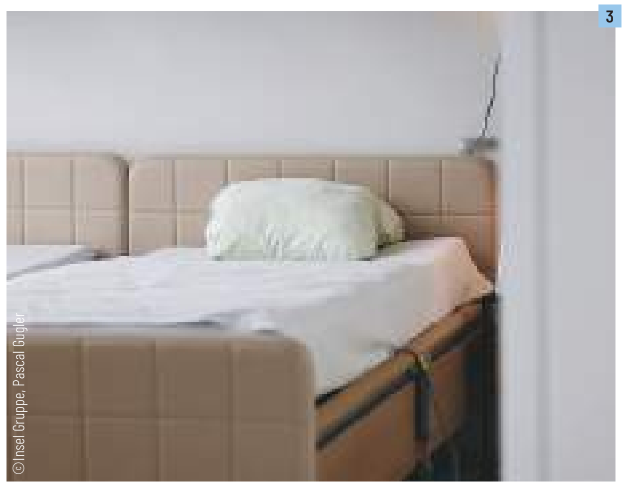
NeuroTec pools the clinical knowledge of Inselspital, University Hospital Bern, and the expertise in medical technology of the University of Bern and the medtech scene in Bern. The facilities at sitem-insel enable an active exchange with researchers in the field.

NeuroTec is run by the Department of Neurology of Inselspital, University Hospital Bern in close collaboration with the ARTORG Center for Biomedical Engineering Research of the University of Bern, with project-specific partners from academia, non-profit research institutions, and industrial partners in public-private partnerships. 3

Covasc Consortium within sitem-insel's BSL-3 laboratory

Shortly after its opening, one of the rooms of the biosafety level-3 laboratory (BSL-3) within sitem-insel, was rented out to the CoVasc consortium. The CoVasc consortium is a group of four research project leaders and 10 project partners that connects experts in heart research, vascular biology, and neuroimmunology as well as in virology. Together they investigate how and if heart and vascular cells are prone to be infected by the SARS-CoV-2 and potential consequences thereafter. The National Research Program 78 initiated by the Swiss National Foundation finances this project. 4

Screen 4 Care: An international public-private consortium of 35 partners, including sitem-insel and the University of Bern, launched Screen4Care – a research project that aims to significantly shorten the time required for




NeuroTec Loft


The entry to sitem-insel's BSL-3 laboratory


Discussion between researchers at sitem-insel

rare disease diagnosis and efficient intervention by utilizing genetic newborn screening and advanced analysis methods such as machine learning. The project will run for a period of five years with a total budget of EUR 25 million provided by the Innovative Medicines Initiative (IMI 2 JU), a joint undertaking of the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). 5

Education at the CATR: Cutting-edge education is an important part of the translational process. The Clinical Anatomy Training and Research Unit (CATR) at sitem-insel has picked up speed and has been hosting international and national surgical training courses in 2021 in its state-of-the-art infrastructure.

- 30.09 – 2.10: First GESEA course and certification in Switzerland
- 23 – 25.09: European Endometriosis League Masterclass
- 30.08 – 03.09: 5th Swiss Endoscopic Ear Surgery Course SEES and the 17th Endoscopic Paranasal Sinus & Skull Base Hands-on Course PSSB

25 – 26.06: AO Spine Master Level Specimen Course—Improving Technical and Non-Technical Skills for Complication Prevention in Complex Situations. 6

New Units: Towards the end of 2021, sitem-insel welcomed the Bern University of Applied Sciences (Berner Fachhochschule BFH) with a lease agreement for two offices into its building and is looking forward to fruitful collaborations.

Furthermore, a new collaborative project has been successfully launched by the Inselspital Bern and Empa Dübendorf. Across from the Translational Imaging Center on sitem-insel's second ground floor, where we host one of the two nationwide 7 tesla MRI machines, the instalment of the new "Dynamic Imaging Center" is taking shape. What is its aim?

The aim of the new center is to establish a novel, state-of-the-art musculoskeletal biodynamics laboratory to conduct fundamental and translational research in the area of musculoskeletal movement biomechanics, with a high-speed Dynamic Biplane Radiographic Imaging (DBRI) system at the heart of the setup.

The modern, high-speed (>150 Hz) imaging system is capable of directly capturing bony motion of various musculoskeletal joints. This allows direct in vivo imaging of bones during functional activities with sub-millimeter accuracy. The system comprises high-speed video cameras, x-ray, and large-sized image intensifiers suitable for dynamic imaging of various musculoskeletal joints, including shoulder, knee, ankle, hip, and spine.


Training in sitem-insel's CATR

The technology has progressed to a point where it is now feasible to pose- and obtain answers to – specific questions regarding joint arthro-kinematics, particularly with respect to differences between healthy and diseased joints.

This endeavour, which includes management of the DBRI system as well as the area of musculoskeletal research in general, is necessarily interdisciplinary, requiring expertise from orthopaedics, radiology, surgery, physiotherapy, and engineering. The consortium comprising the Inselspital and Empa, along with the project partners and prospective principal investigators of planned research topics, brings together a broad network of Swiss scientists, clinicians, clinician-scientists, and engineers to conduct cutting-edge research and development work.

sitem-insel's projects and collaborations, brand strategies, and its corporate governance guidelines are all characterized by a long-term perspective. The sitem-insel team is driven by innovation and strives to make sitem-insel a pioneer and operational center of excellence in translational research.

Editorial

# EMPA – Swiss Federal Laboratories

**For Materials Science and Technology**

**The Swiss Federal Laboratories for Materials Science and Technology is an interdisciplinary Swiss research institute for materials sciences and technology. As part of the Swiss Federal Institutes of Technology Domain, it is an institution of the Swiss federation. Empa's task is to support advanced material research technological innovations needed for the growing population in the areas of energy, environment, and health. At the heart of this are approximately 1'000 scientists, engineers, technicians, and general staff, the asset that makes Empa a world-renowned research institute for materials science and technology.**

In the Health and Performance Research Focus Area, we focus on material-based health care innovations addressing the growing needs of our ageing society. Together with our partners from research, hospitals, industry, and the public sector, we are pushing the limits in science and technology for a healthy future.

We develop novel materials for medical applications in and on the human body and carry out research on new materials and systems that support and protect the human body and its function under different environmental conditions and health states.

We need to understand materials-biology (proteins, bacteria, cells, etc.) interactions down to the nanoscale, using cutting-edge and specifically designed analytical equipment. Based on improved understanding, we produce systems that provide enhanced properties and performance using state-of-the art fabrication tools and working in teams of interdisciplinary scientists and engineers devoted to excellence. Striving to understand the interaction of living systems and materials, we develop and apply a wide range of models, including primary cells, multi- cellular organoids, biophysical models, and numerical simulations.

This enables us to assess biological responses already at an early stage in the development of materials and devices, to align pre-clinical and clinical research, and to accelerate the development cycles.

In short: We combine our expertise in materials science, materials processing, computational modeling, life science, and technology to generate innovative solutions.

Empa as part of the ETH domain also supports teaching at universities and universities of applied sciences (UAS) and is active in organizing scientific conferences and advanced training courses through the Empa-Academy. Conferences, lecture series, seminars, and courses are aimed at scientists, professionals from industry and the private sector, and also the general public.

Alex Do

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Head of Department



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**Research Profile**

Our research laboratory develops X-ray methodologies for understanding materials structure in life and materials science. We combine the expertise of X-ray-based imaging technology (nano- and micro-X-CT: 2D, 3D to 4D), X-ray diffraction (XRD, HRXRD), and wide- and small-angle scattering methods (WAXS, SAXS, XPCI). The gap between X-ray methods is bridged by their combination and/or fusion. Studies of dynamical processes on surfaces, at interfaces, and in fluids have a central part. Models for the understanding of complex systems such as low-density and low-contrast materials like bio-systems and polymers are established, especially for the biomedical domain and in collaboration with partners from research institutions, Swiss hospitals, and industry.

The X-ray team concentrates on life-sciences research (Health and Performance: support medical diagnostics), Nanostructured Materials (model development for system understanding: systems between order and disorder), Materials for Energy Technologies and Sustainable Built Environment (phase contrast CT, e.g. imaging of liquid transport through porous building and energy materials).

Today, new research domains can be addressed that could not be covered before: high spatial resolution imaging of biological materials; dynamical studies in bio-systems, partially ordered materials (polymers, lipids).

**Characterizing the Intravascular Clot in Acute Stroke with Multi-parametric Imaging (SNF grant 32003B_182382)**

Stroke is the first cause of acquired deficit and the second cause of death in the industrialized world. Due to the aging population, stroke incidence and the corresponding medical and economic burden imposed on society are expected to increase. Detailed volumetric information on the composition of the blood clot of the stroke patient is very valuable to understand the mechanical properties, like stiffness, of clots, which are crucial in selecting the most efficient mechanical thrombectomy (MTB) method for clot extraction. This research combines multi-modal and high-resolution imaging and analytical methods like phase-contrast micro CT, electron microscopy, and X-ray diffraction. Different clot types retrieved by mechanical thrombectomy from patients of acute ischemic stroke were evaluated through propagation-based phase-contrast microCT. The results were correlated with high-resolution scanning electron microscopy (SEM) images, confirming detected cellular and fibrillary structures. X-ray diffraction was used to identify potential endogenous calcifications. Calcifications appeared as glassy opacity areas with a moderately intense signal on microCT images, also proved by energy-dispersive spectroscopy and X-ray diffraction. Further development of automated post-processing techniques, also based on machine learning algorithms, for X-ray PB micro/nanoCT will enable high-throughput analysis of blood clot composition and their 3D histological features on large sample cohorts. This can provide statistically significant infor-mation about the biological and mechanical properties of clot types, and then, implications on the relation between clot composition and MTB outcome. This is beyond reach for state-of-the- art clinical 2D histology methods. Furthermore, comparison and correlation of ex-vivo microCT with clinical imaging methods (CT, MRI) and application of data science approaches will enable more efficient data mining and processing algorithms for the clinical imaging. 1

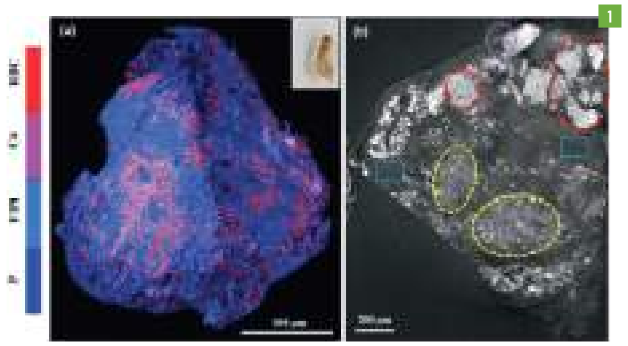
### Structural in-situ Investigations for Particle Systems and Their Early Event Dynamics in Bio-logical Environments (SNF grant 205321_173012)

Today, nanoparticles (NPs) applications in biomedical fields and medicine are increasingly important. However, after transferring NPs to a biological environment, their interactions are complex and poorly understood. Different parameters such as ionic strength and pH conditions, and the presence of biomolecules such as proteins initiate alterations in NPs' structure and therefore influence their colloidal stability.

For applications in nanomedicine, the NPs' colloidal stability in a biological environment is a crucial property as it strongly influences the product safety and efficiency. Therefore, we are espeically interested in a detailed investigations on NPs' interactions and their structural changes in early events in a biological environement. In our lab, we developed a characterization method based on small-angle X-ray scattering (SAXS) for in-situ, label-free, and dynamic studies on the early and advanced stages of NPs' interactions after exposure to a biological environment. A micromixer system is designed and fabricated, which is combinable with SAXS instruments in the laboratory and at synchrotron facilities. Silica NPs are selected to individually investigate the effect of changes in IS, pH, and the presence of protein in the environment on NPs for their colloidal stability. It is concluded that the presence of the protein reduces silica NPs' colloidal stability drastically. 2

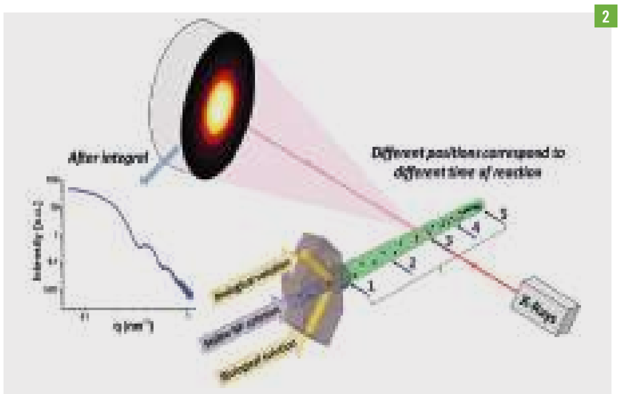
NPs' interactions in the presence of different protein concentrations are studied with respect to effects of NPs' size and surface modification. Gold NPs with 5 and 40 nm in diameter, and two surface modifications such as citrate and polyethylene glycol (PEG) are investigated. Each surface modification shows distinct stabilization mechanisms. Citrate NPs in appropriate protein concentrations stabilize by protein adsorption on their surfaces. In contrast, 5 nm PEGylated NPs show stabilization by generating self-assembled 3D ordered domains in different protein concentrations. which can be followed in detail using the designed micromixer-SAXS setup. 3

1



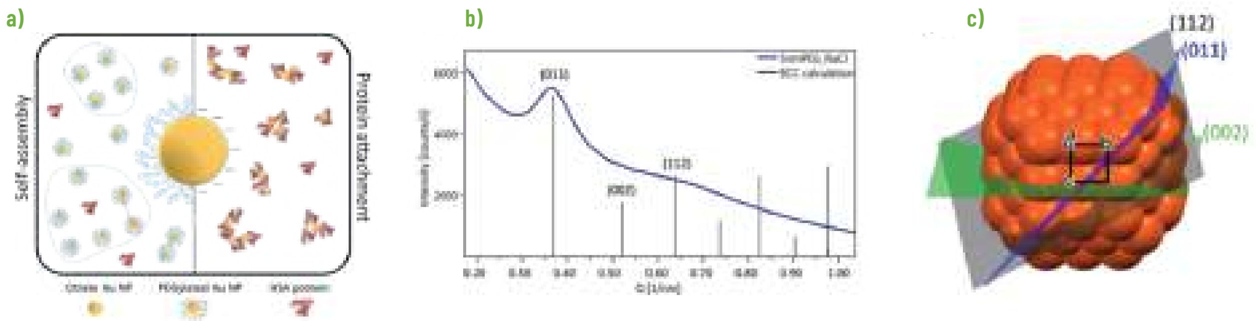
a) 3D rendering and digital histopathology by X-ray micro-CT of a blood clot segment showing different areas dominated by different constituents like red blood cells (RBC) endogenous calcifications (Ca), mixed fibrin and platelets (F/Pl), and platelets (P) The inset shows the photo of the full clot.
b) the same details shown on a virtual micro CT cut through the clot (RBC-red, blue fibrin/platelets, calcification-yellow).

2




Scheme of the micro-fluidics SAXS setup for the in-situ investigation of early events in NPs' interations in a biological environment.

3




a) two different stabilization mechanisms for gold NPs in biological environments containing human serum albumin (HSA).
b) ordering (diffraction) peak indexing for the BCC structure for the 5 nm_PEG sample.
c) schematic view on the 3D NPs assembly visualizing the diffraction planes (011), (002), (112) of the applied BCC structural model.

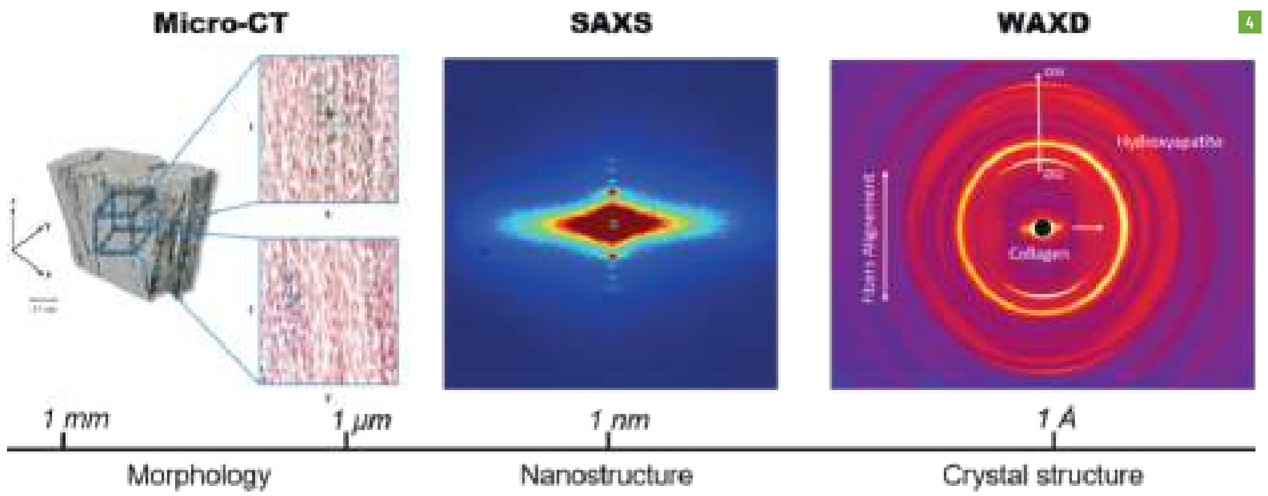


A related topic in our lab is the study of drug delivery systems where the support structures, namely electrospun fibers, influence the drug release kinetics. Ongoing work involves the fabrication of fibrous membranes with tailored architectures for the design of advanced drug delivery systems.

### Quantifying Phase Orientation and Morphology of Mineralized Turkey Leg Tendons: A Multiscale and Multimodal X-ray Analysis

Hierarchical arrangements, observed in fibrous biocomposites like bone and tendons, range from the macroscale down to the molecular level. The multiscale complex morphology, based to a large extent on correlated orientation of their constituents, contributes significantly to the outstanding mechanical properties of these biomaterials. We established a road map to quantify the hierarchical structure of a mineralized turkey leg tendon (MTLT) in a holistic multiscale evaluation by combining micro-Computed Tomography (micro-CT), small-angle X-ray scattering (SAXS), and wide-angle X-ray diffraction (WAXD). The interplay of the main MTLT components is analyzed with respect to highly ordered organic parts such as fibrous collagen and integrated inorganic components like hydroxyapatite (HA). The microscale fibrous morphology revealing different types of porous features and their orientation was quantified using micro-CT. The quantitative analysis of the alignment of collagen fibrils and HA crystallites was established from SAXS using the Ruland approach and the broadening of azimuthal profiles of the small- and wide-angle diffraction peaks. We observe a relatively lower degree of orientation of HA crystallites compared to the collagen fibrils. 4

4




Holistic approach in the analysis of hierarchical structures: from morphology (mm-µm) over nanostructure (nm) to molecular structure (Å) using X-ray based methods.

### Selected Publications


[1] Saghamanesh S., Dumitriu LaGrange D., Reymond P., Wanke I., Lövblad K-O., Neels A., Zboray R., (2022). Non contrast enhanced volumetric histology of blood clots through high resolution propagation-based X-ray microtomography. Sci Rep 12, 2022, 2778. DOI 10.1038/s41598-022-06623-8.

[2] Iranpour N, Liebi M, Ong Q, Blanchet C, Maurya A K, Stellacci F, Salentinig S, Wick P, Neels A. (2021). In-situ Investigations on Gold Nanoparticle Stabilization Mechanisms in Biological Envi-ronment Containing HSA. Advanced Functional Materials, 2021. 2110253, 1-14, DOI 10.1002/adfm.202110253.

[3] Iranpour N A, Sadeghpour A, Iranshahi K, Toncelli C, Cendrowska U, Stellacci F, Dommann A, Wick P, Neels A. (2020). A new approach for time-resolved and dynamic investigations on nano-particles agglomeration. Nano Research 13(10), 2847-2856. DOI 10.1007/s12274-020-2940-4.

[4] Kochetkova T, Peruzzi C, Braun O, Overbeck J, Maurya A K, Neels A, Calame M, Michler J, Zysset P, Schwiedrzik J. (2021). Combining polarized Raman spectroscopy and micropillar compression to study microscale structure-property relationships in mineralized tissues. Acta Biomaterialia, 2021, 119, 390-404, DOI 10.1016/j.actbio.2020.10.034.

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[6] Tien N D, Maurya A K, Fortunato G, Rottmar M, Zboray R, Erni R, Dommann A, Rossi R M, Neels A, Sadeghpour A. (2020). Responsive Nanofibers with Embedded Hierarchical Lipid Self-Assemblies. Langmuir 2020, 36, 11787–11797. DOI. 10.1021/acs.langmuir.0c01487.

[7] Maurya A K, Mias E, Schoeller J, Collings I, Rossi R M, Dommann A, Neels A. (2021). Multiscale structure properties in electrospun nanofiber scaffolds: process understanding to steer mechanical behaviors. Nanoscale Advances, 2021, 4, 491-502. DOI: 10.1039/D1NA00503K.

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**Gustav Nyström,** Cellulose and Wood Materials, Empa

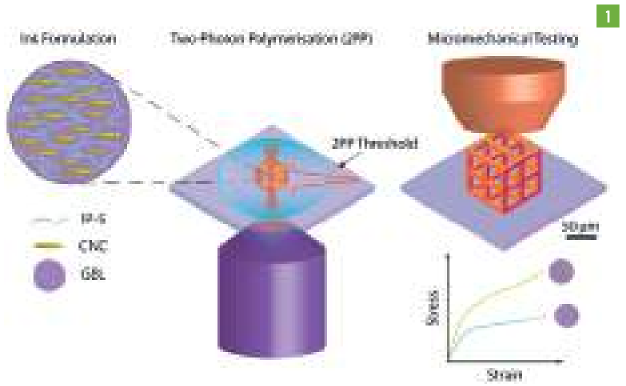
### Research Profile

Our mission is to enable materials innovation in major Swiss manufacturing areas, such as medical technologies, miniature and precision mechanics, and surface engineering. We synthesize novel materials via atomic layer deposition, physical vapour deposition, or electrochemical methods exploiting both research and industrial scale deposition equipment. We develop microfabrication methods such as 3D microprinting techniques and cleanroom-based conventional lithography processes to engineer surfaces and miniature devices. In particular, we investigate mechanical properties of inorganic and biological materials at the nano- to the millimeter-scale under extreme conditions of humidity, strain rate, and temperature and develop novel nano-mechanical and microanalysis instrumentation.

### Microscale 3D Printing and Characterization of Cellulose Nanocrystal Reinforced Composites

Metamaterials have gained importance across nearly all fields of engineering. They are an interesting alternative to classical engineering materials due to the possibility of tuning their behavior over a wide range in the material property space by a careful design of their nanostructure. Such materials are thus of special interest for biomedical implants and scaffolds for tissue engineering where specific structure-mechanical characteristics are desired. One main objective is to enhance the mechanical performance of these scaffolds that serve as a structural support for cell attachments and the subsequent tissue development. However, the fabrication of such enhanced materials at the micro- and nanoscale, remains a challenge and using reinforcement phases makes their synthesis even more problematic. In this study, we report the formulation of a novel methacrylate-based bio-compatible nanocomposite ink that is reinforced by cellulose nanocrystals (CNC). With this ink, we can create random complex 3D microarchitectures by means of two-photon lithography using our Nanoscribe GT machine in the cleanroom. The intriguing aspect of CNC is that it is an abundant resource and, thus, very attractive in developing materials for a sustainable future. Our study showed that by adding only 4.5 wt% CNC, we can increase the mechanical performance of cellular structures by 100%. Furthermore, we reach a very high polymer matrix quality, and observe that, especially with 4.5 wt% CNC, the reinforcement effect outweighs the slightly lower matrix polymerization as a result of laser shielding from the nanocrystals. Our new insights into the 3D printing of complex microstructures with a CNC-reinforced nanocomposite ink demonstrate the potential of the method to print and tune arbitrary geometries at this length scale. This allows us to optimise the design and structure-property relationships of these promising architectured materials. 1

1



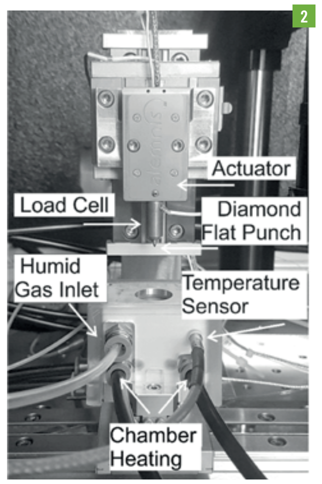

Overview of the 3D printing of microscale cellulose nanocrystal-reinforced nanocomposites by two-photon polymerisation (2PP) and their micromechanical characterisation. Inks of GBL, CNC, and IP-S (left) were manufactured where three different CNC concentrations are used for the 3D micro-fabrication (middle). Their structure-mechanical properties were determined by means of micro-compression (right) and Raman measurements.

### Instrumentation for Micromechanical Analysis of Biomaterials and Tissues

To assess biomaterials at physiologically relevant conditions, an in-house micromechanical testing platform was extended with a newly developed environmental chamber. It allows for controlling tightly the relative humidity and temperature around the sample. The chamber is heated using a heat exchanger at the base that is fed with flowing water of a set temperature. As the chamber is fabricated of aluminum and insulated from outside influences, this approach yields a constant temperature within the chamber. With this new setup we can vary the strain rates (0.0001-1000/s), temperature (20–60°C), and relative humidity (30–95%) during the experiments. This allows performing micromechanical experiments at an environment that mimics physiological conditions.

Using the novel setup, we conducted micropillar compression on ovine cortical bone at strain rates highly relevant for fracture (0.1–100/s) and at different temperatures (24–60°C) including body temperature (37°C). Determining the yield strength at varying strain rates and temperatures not only permits us to observe the strain rate dependency of cortical bone but also to identify the governing deformation mechanisms at the nanoscale based on thermal activation analysis. 2

2

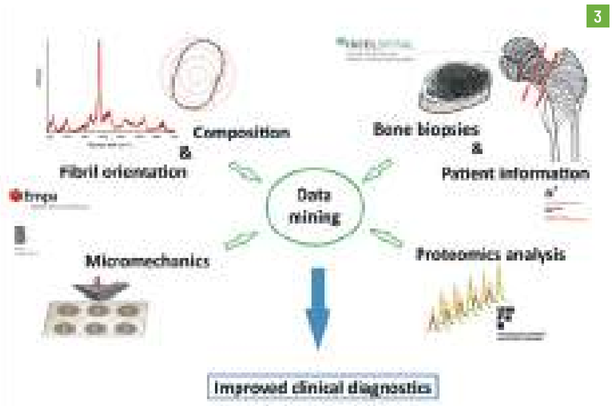



Micromechanical testing platform with the high strain rate and the temperature-controlling setup. The experiment chamber is heated with a heat exchanger that is fed with flowing water at a set temperature at the base of the chamber. The desired relative humidity is achieved by feeding a gas (usually air) with a controlled relative humidity into the chamber.

### Microscale Properties of Human Bone

Bone fractures pose a significant challenge for healthcare systems all over the world. The number of fragility fractures is increasing yearly, so are the associated healthcare costs. The most severe fractures (ex. hip, vertebra) lead to a full or partial immobilization of the patients and consequently reduced life quality. The current clinical methods for fracture risk prediction rely on bone mineral density, which only partially explains the variation seen in patients. It is therefore of high importance to investigate additional bone parameters responsible for the bone quality and to develop accessible and accurate methods of measurement of such parameters.

3




The schematic of the study on combining bone proteotype and multiscale extracellular matrix properties for improved clinical fracture risk prediction.

Within the Special Focus Area Personalized Health and Related Technologies of the ETH Board, this study aims to translate recent advances in microscale mechanical and tissue characterization techniques into clinical practice to improve current diagnostic tools by the knowledge of extracellular matrix (ECM) composition, proteotype, and micromechanical properties of individual patient biopsies. The femoral neck slices are collected during total hip arthroplasty together with the anonymized patient information from the Inselspital and Spital Tiefenau in Bern. The mesoscale morphology and mineral density of the biopsies are measured using micro-CT. Tissue quality is evaluated from the structure-mechanical property relationships on the microscale, which are assessed via site-matched polarized Raman spectroscopy and micromechanical compression experiments following previously developed methodology (Kochetkova et al., Acta Biomater. 2021). Moreover, a novel laser ablation protocol for the micropillar fabrication is developed in collaboration with ALPS Institute at the Berner Fachhochschule, allowing us to perform high throughput micropillar compression analysis. The data on the mesoscale morphology and tissue quality is then complemented by proteomic analysis, which is carried out in the Metabolomics and Proteomics Platform at the University of Fribourg. The proteomics is used for the detection of cortical bone ECM proteins and their comparison between the cohorts of patients. It will be assessed by machine learning approaches if knowledge of proteotype and microscale structure-property relationships may help to estimate the femoral strength of individual patients at higher accuracy. 3

**Selected Publications**

[1] C. Peruzzi et al., (2021). Microscale compressive behaviour of hydrated lamellar bone at high strain rates. Acta Biomaterialia 131, 403-414, DOI: 10.1016/j.actbio.2021.07.005.

[2] T. Kochetkova, C. Peruzzi et al., (2021). Combining polarized Raman spectroscopy and micropillar compression to study m icroscale structure-property relationships in mineralized tissues Acta Biomaterialia 119, 390-404, DOI:10.1016/j.actbio.2020.10.034.

## Editorial

# ARTORG

### CENTER FOR BIOMEDICAL ENGINEERING RESEARCH

The ARTORG Center at the University of Bern is a multidisciplinary MedTech Center of Excellence joining engineers, computer, material- and life scientists, clinicians, and biologists in a mission to develop innovative and clinically-proven healthcare technology for diagnosis, monitoring, treatment, and rehabilitation for patient benefit.

Through technical expertise in data science, flow mechanics, computational biomechanics, medical image analysis, microfabrication, organs-on-chip and robotics in surgery and rehabilitation, ARTORG with its twelve independent research groups co-headed by technical and clinical group heads is a strong partner of the Bern Biomedical Engineering Network.

With the foundation of the Center for Artificial Intelligence in Medicine (CAIM) as our overreaching sister organization for innovation in digitalized medicine in 2021 we are launching a strong focus in AI technologies for data-driven medical approaches, imaging, precision medicine and autonomous surgical robotics. Together with clinical experts from the Inselspital and the University Psychiatry Services, CAIM sets out to deliberately shape the digitalized healthcare future, including ethical issues of medical AI implementation with the CAIM Embedded Ethics Lab.

ARTORG's entrepreneurial spirit has enabled it to innovate biomedical technologies directly into clinical routines. The ARTORG stands for highly successful startup incubation with three MedTech Award wins within the last decade. With five of our research groups located at the Swiss Institute for Translational and Entrepreneurial Medicine, sitem-insel since mid-2019, we further strengthen our ability for a fast and successful translation of ARTORG innovations.

The ARTORG is committed to excellence in academic education and delivers globally leading master's and doctoral programs in biomedical engineering, specialist courses for clinicians and networking events with industry partners. Always starting from a clinical perspective, it has newly launched a master's program "AI in Medicine", introducing young data science engineers to AI fundamentals, and enabling them to translate skills and academic experiences at the forefront of healthcare.

**Raphael Sznitman**
Director ARTORG Center



# AI in Health and Nutrition

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**Research Profile**

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

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

**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

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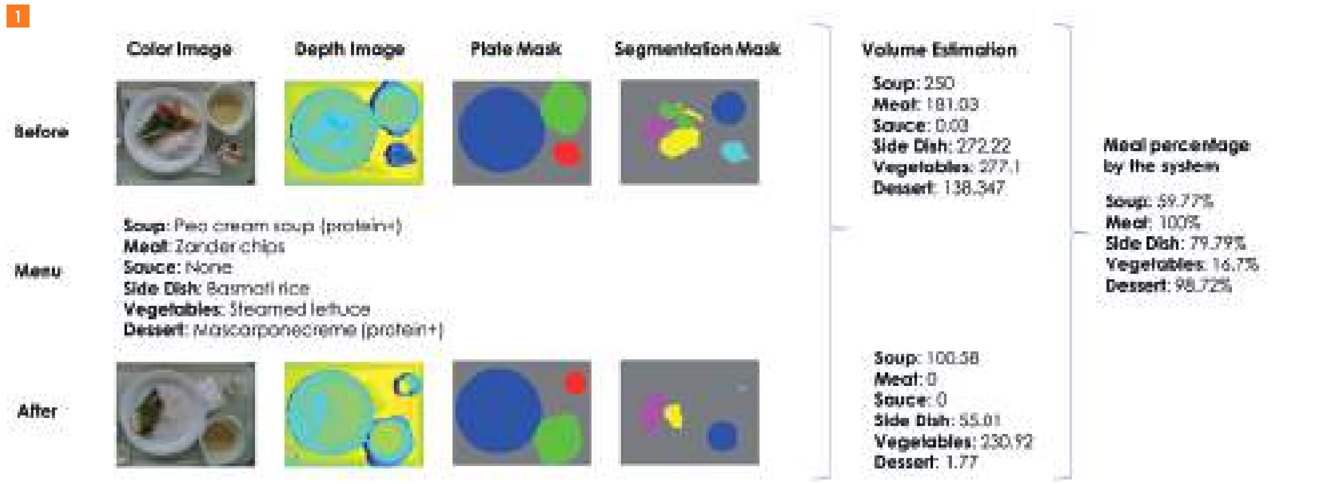



Tackling hospitalised malnutrition: The system for hospitalised patients receives as input the daily menu and the tray images and estimates the volume of each dish before and after consumption.

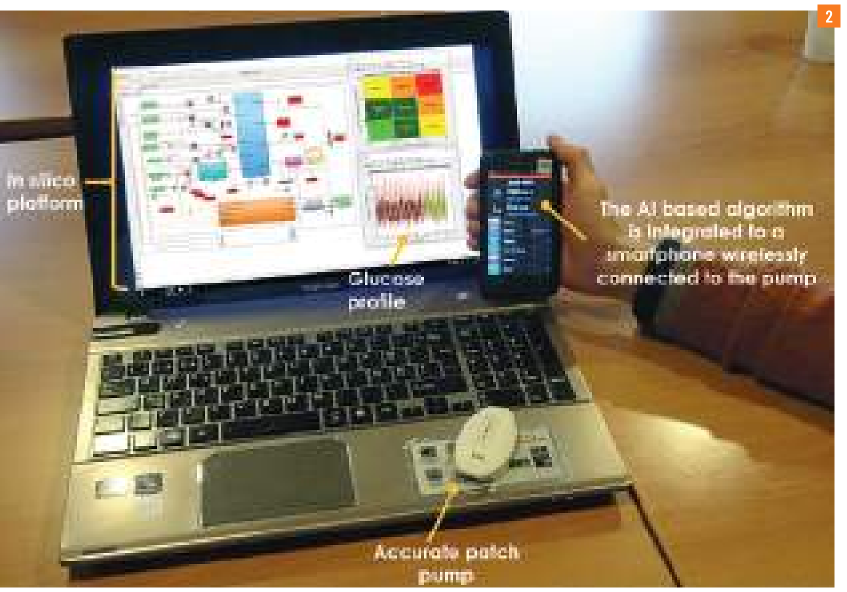
carbohydrate content of meals consumed by individuals with type 1 diabetes. The first prototype was developed within the framework of the GoCARB project and has been successfully validated in a number of preclinical and clinical trials.

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 intake of both outpatients and hospitalised patients. Several validation studies are ongoing (http://go-food.tech/). [1]

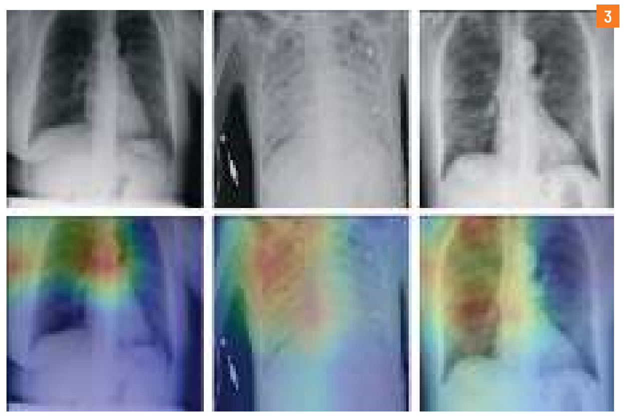
**Diabetes Management and Personalisation of Insulin Treatment**

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




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.




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

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. [2]

**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. [3]



**Selected Publications**

[1] Papathanail I, Brühlmann J, Vasiloglou MF, Stathopoulou T, et al. (2021). Evaluation of a Novel Artificial Intelligence System to Monitor and Assess Energy and Macronutrient Intake in Hospitalised Older Patients. Nutrients, 13(12) Molecular Diversity Preservation International MDPI 10.3390/nu13124539.

[2] Afshar-Oromieh A, Prosch H, Schaefer-Prokop C, et al. (2021). A comprehensive review of imaging findings in COVID-19 - status in early 2021. Eur J Nucl Med Mol Imaging 48(8):2500-2524, doi:10.1007/s00259-021-05375-3.

[3] Fontanellaz M, Ebner L, Huber A, et al. (2021). A Deep-Learning Diagnostic Support System for the Detection of COVID-19 Using Chest Radiographs: A Multireader Validation Study. Invest Radiol 56(6):348-356, doi:10.1097/RLI.0000000000000748.

[4] Vasiloglou MF, Lu Y, Stathopoulou T, et al. (2020). Assessing Mediterranean Diet Adherence with the Smartphone: The Medipiatto Project. Nutrients 12(12):3763, doi:10.3390/nu12123763.

[5] Lu Y, Stathopoulou T, Vasiloglou MF, et al. (2020). goFOODTM: An Artificial Intelligence System for Dietary Assessment. Sensors (Basel) 20(15):4283, doi:10.3390/s20154283.

[6] Sun Q, Jankovic MV, Mougiakakou SG (2019). 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. 2019:3609-3612, doi:10.1109/EMBC.2019.8857178.

# Artificial Intelligence in Medical Imaging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**Research Profile**

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

**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. 1

**Consistency-preserving Visual Question Answering in Medical Imaging**

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 meth- ods, 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. 2



**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 pointwise 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. 3

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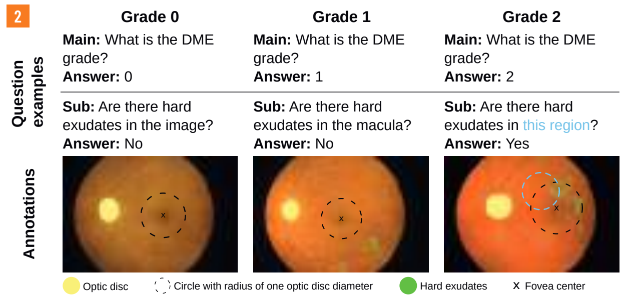
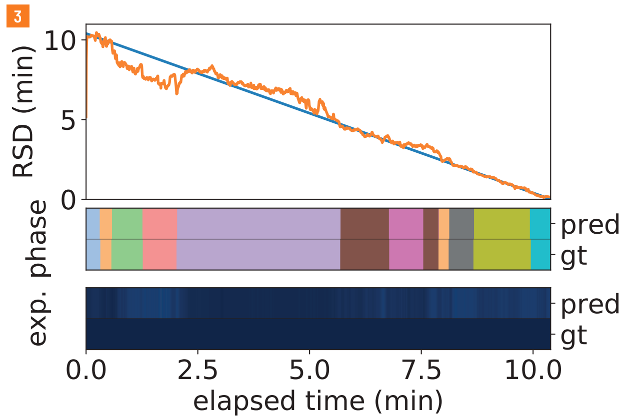



DME risk grading Grade 0 is assigned if there are no hard exudates present in the whole image. Grade 1 is assigned if there are hard exudates, but only located outside a circle centered at the fovea with radius of one optic disc diameter. Grade 2 is assigned if there are hard exudates located within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

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.

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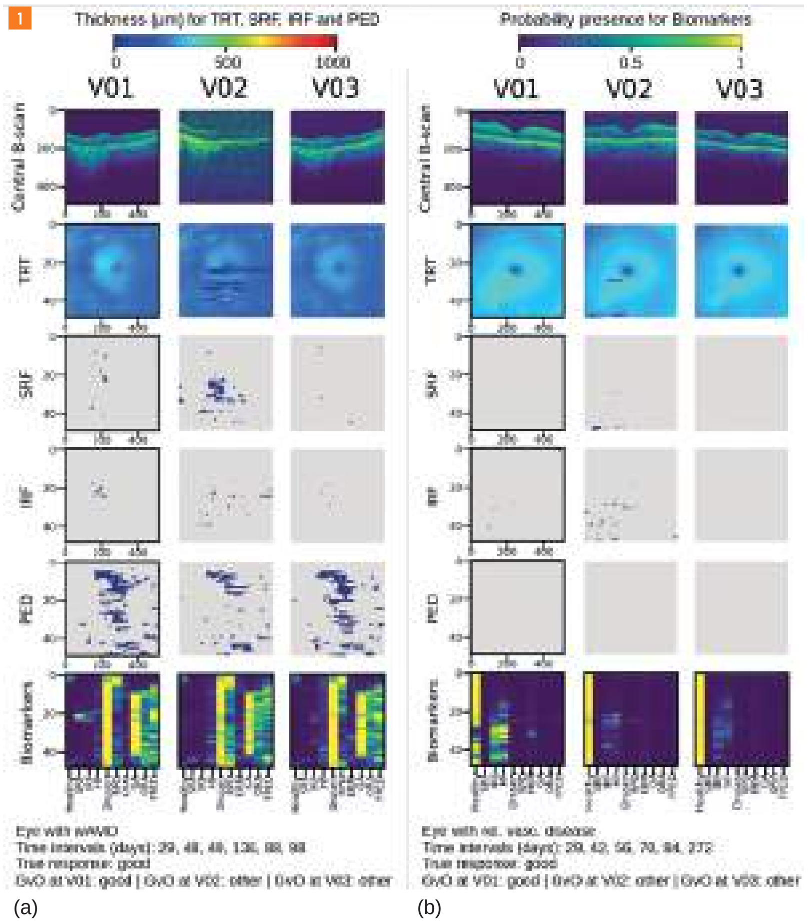


Predictions of patient responses to anti-vegf treatment using OCT imaging.


**Selected Publications**

[1] Gallardo, M. Munk, M., Kurmann, T., De Zanet, S., Mosinska, A., Kutlturk, 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

[2] 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.

[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

# 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.

**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. 1

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. 2

**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. 3

**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.

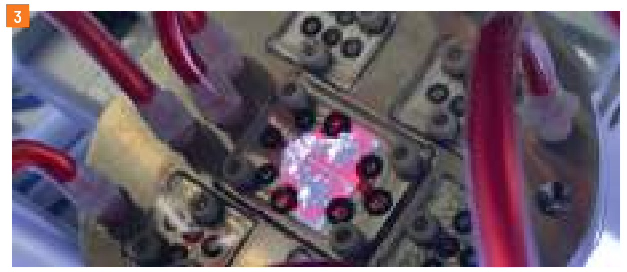
We study blood flow in complex capillary networks as they may be found, for instance, in the brain. We investigate how the network topology affects the heterogeneous distribution of red blood cells in the network and how the system reacts to local obstructions (e.g., micro-strokes). To study blood flow 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.

1


Turbulent blood flow behind a heart valve prosthesis.

2


Optical flow quantification in the Cardiovascular Flow Lab.

3


Microfluidic chip to model the blood flow in the heart muscle.



**Selected Publications**

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# Chair for Image-Guided Therapy

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**CASCINATION AG,** Bern, Switzerland
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**EMPA,** Dubendorf, Switzerland

### 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 clinical, academic and industrial collaborations.

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

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



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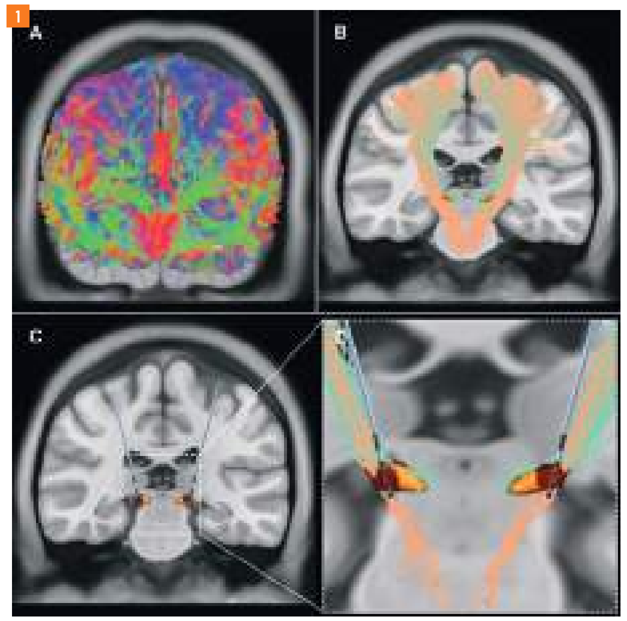

Pathway activation by DBS. *A:* Whole-brain tractogram. *B:* Streamlines of pathways of interest (green: hyperdirect pathway; salmon: corticospinal tract; orange: subthalamic nucleus). *C:* DBS leads localization and estimation of volumes of tissue activated. *D:* Streamlines activated by DBS.

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

For patients that suffer from non-spherical, larger, or critically located tumors, the success of thermal ablation treatment is not guaranteed, as the lesions potentially result being over-ablated, and the surrounding structures might be at risk. The aim is to remove these limitations, by providing an automated thermal ablation treatment model, using image-based planning and robotically assisted ablation, through synchronous probe retraction and ablation energy modulation. An experimental prototype was built and a proof-of-concept regarding its feasibility was conducted in a controlled environment using tissue mimicking specimen. 2

2

Prototype of a robotic system for thermal ablation.

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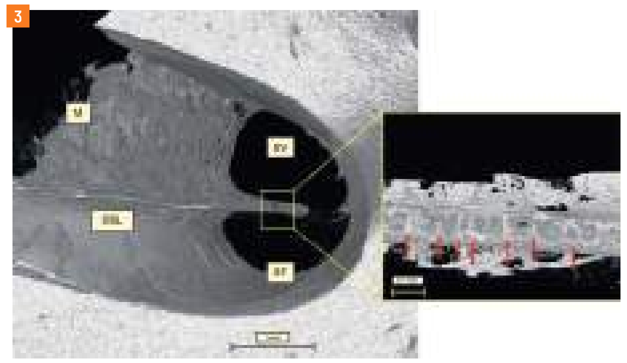
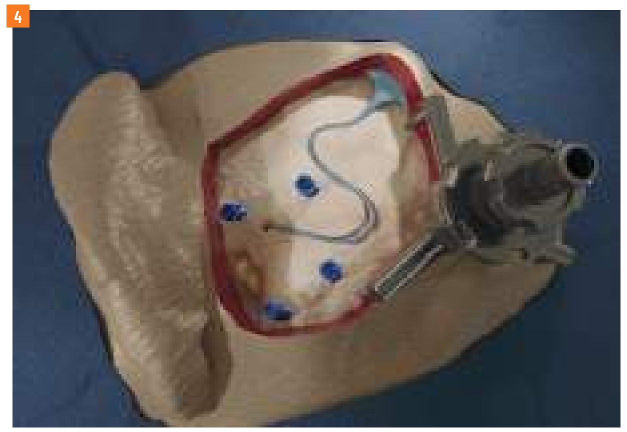


Supportive pillars of the OSL coming from the cribiform wall of the modiolus (M) seen on a 2.3 µm microCT. OSL-Osseous spiral lamina; SV- scala vestibuli; ST- scala tympani; SG- spiral ganglion; Red arrows-Habenula Openings lateral end of the OSL.

4



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

### 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. 3

### Robotic Cochlear Implantation (SNF Project Number 176007)

The research from the recent years focused on robot-assisted cochlear implantation procedure was translated into a medical device. The investigation now continues in 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. Particularly, for long-term fixation, the robotic system is proposed to be used along with intraoperative planning to mill a channel and an implant bed to store and protect the implant electrode and housing. An experimental study in a human ex-vivo model was conducted to investigate its safety and efficacy. Regarding inner ear access, the focus is 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. 4

**Selected Publications**

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[2] Bargiotas, P. et al. Long-Term Outcome and Neuroimaging of Deep Brain Stimulation in Holmes Tremor: A Case Series. Neuromodulation. 2021 Feb. 1; 24(2): 392–399.

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[9] Mueller, F. et al. Image-based planning of minimally traumatic inner ear access for robotic cochlear implantation. Front. Surg. 2021 Nov 25; 8:761217.

[10] Nowacki, A. et al. Probabilistic mapping reveals optimal stimulation site in essential tremor. Ann. Neurol. 2022 Feb 12; 91(5), 602–612.

5

Prototype platform for robotic spine surgery development.

6

Realistic, accurate scale 3D printed replica of intracranial aneurysm for pre-operative patient-specific interventional training. The image on the right shows a flow-diverter deployed in the 3D printed model that allows the radiologists to pre-select the implant specific to a patient (© SurgeonsLab AG).

**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 were 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. 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. 6

# Computational Bioengineering

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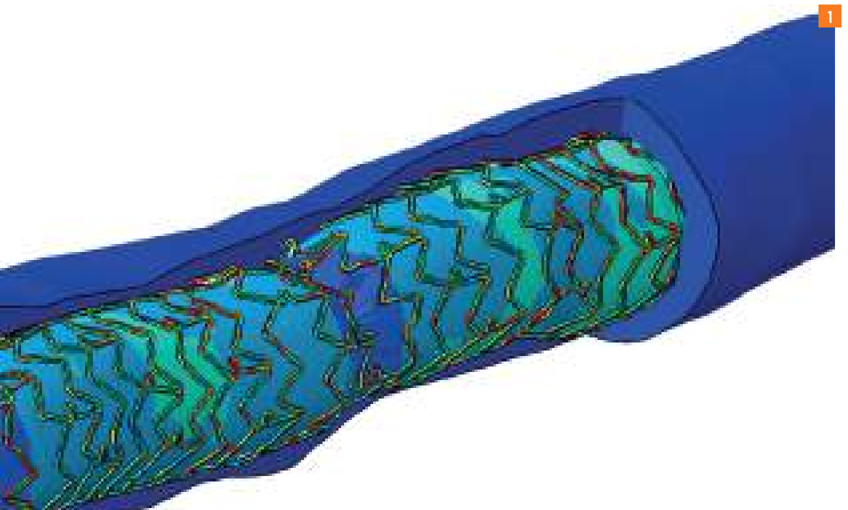

Stent deployment with a balloon in a coronary artery of a patient simulated using the finite element method.

### 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.

### 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 postoperative 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. 1



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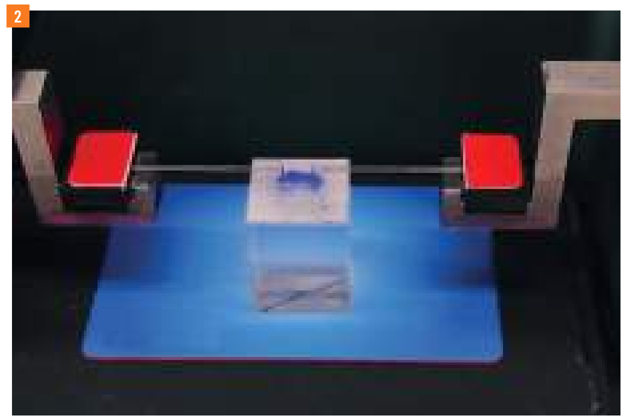
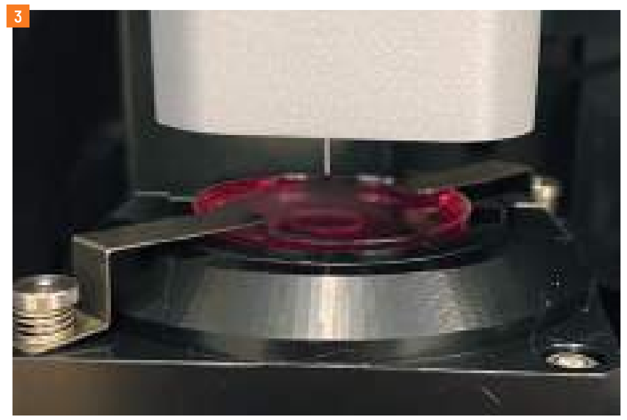


Corneal strips 150µm thick were cut into the cornea with a femtosecond laser to quantify the depth and orientation dependence of mechanical properties measured by a uniaxial tensile test.

3



The mechanical properties of the cornea measured using instrumented indentation.

### 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. 2

### 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. 3

### 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 implant 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. 4

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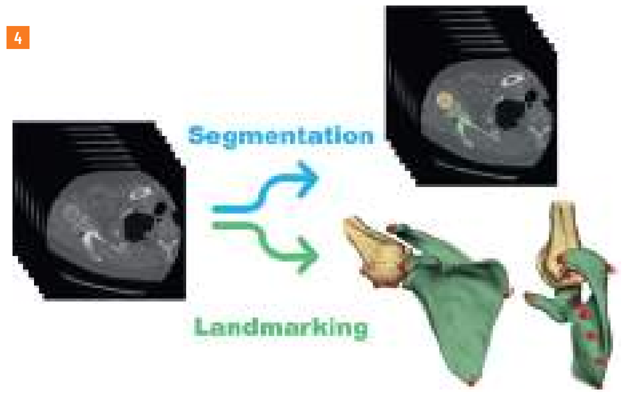


Quantification of morphologic markers was automated and worked well in both normal and pathologic shoulders, allowing their relative influence on the outcome of total shoulder arthroplasty to be evaluated.

### Selected Publications


[1] C Gökgöl, Y Ueki, D Abler, N Diehm, R - Engelberger, T Otsuka, L Räber, P Büchler (2021). Towards a better understanding of the posttreatment hemodynamic behaviors in femoropopliteal arteries through personalized computational models based on OCT images, Scientific Reports 11.

[2] Elham Taghizadeh, Oskar Truffer, Fabio Becce, Sylvain Eminian, Stacey Gidoin, Alexandre Terrier, Alain Farron, Philippe Büchler (2021). Deep learning for the rapid automatic quantification and characterization of rotator cuff muscle degeneration from shoulder CT datasets. European radiology 31:1.181-190.

[3] Romain Bagnol, Christoph Sprecher, Marianna Peroglio, Jerome Chevalier, Redouan Mahou, Philippe Büchler, Geoff Richards, David Eglin (2021). Coaxial micro-extrusion of a calcium phosphate ink with aqueous solvents improves printing stability, structure fidelity and mechanical properties, Acta Biomaterialia 125:322-332.

[4] Philippe Büchler, Jonas Räber, Benjamin Voumard, Steve Berger, Brett Bell, Nino Sutter, Stefan Funariu, Carol Hasler, Daniel Studer (2021). The Spinebot – A Robotic Device to Intraoperatively Quantify Spinal Stiffness ASME Journal of Medical Devices 15:1.03.


# Gerontechnology and Rehabilitation

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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.

**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.

**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. 1



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Living room in the instrumented apartment (SITEM Neurotec Loft).

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 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. 2

**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 ferroelectric 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.

**Selected Publications**

[1] Schütz N., Saner H., Botros A., Buluschek P., Urwyler P., Müri R.M., Nef T.(2021). Wearable Based Calibration of Contactless In-home Motion Sensors for Physical Activity Monitoring in Community-Dwelling Older Adults. Frontiers in Digital Health, 2, S. 566595. 10.3389/fdgth.2020.566595.

[2] Gerber S.M., Single M., Knobel S.E.J., Schütz N., Bruhin L.C., Botros A., Naef A.C., Schindler K.A., Nef T. (2022). An Instrumented Apartment to Monitor Human Behavior: A Pilot Case Study in the NeuroTec Loft. Sensors, 22(4), S. 1657. Molecular Diversity Preservation International MDPI 10.3390/s22041657.

[3] Knobel S.E.J., Kaufmann B.C., Geiser N., Gerber S.M., Müri R.M., Nef T., Nyffeler T., Cazzoli D. (2022). Effects of Virtual Reality-Based Multimodal Audio-Tactile Cueing in Patients with Spatial Attention Deficits: Pilot Usability Study. JMIR Serious Games, 10(2), e34884. JMIR Publications 10.2196/34884.

[4] Schutz N., Botros A., Hassen S.B., Saner H., Buluschek P., Urwyler P., Pais B., Santschi V., Gatica-Perez D., Muri R.M., Nef T. (2022). A Sensor-Driven Visit Detection System in Older Adults' Homes: Towards Digital Late-Life Depression Marker Extraction. IEEE J Biomed Health Inform., 26(4):1560-1569. doi: 10.1109/JBHI.2021.3114595. Epub 2022 Apr 14. PMID: 34550895.


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. 3 4

3


Kitchen with a number of contact-free sensors (SITEM Neurotec Loft).



4

Bedroom with integrated sensors (SITEM Neurotec Loft).

# Hearing Research Laboratory

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Stephan Schraivogel


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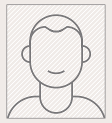
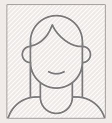

David Sprecher


Esther Gnahoré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### Research Profile

The Hearing Research Laboratory is a research collaboration between the ARTORG Center and the Department of Otolaryngology, 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.

### 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.

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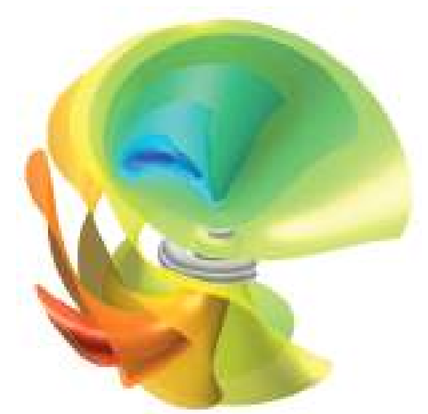
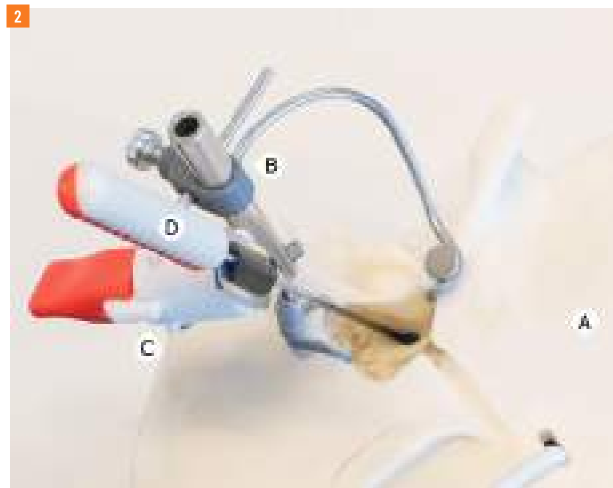


Visualization of isosurfaces indicating the degree of curling of a non-linear vector field for geometric description of the human cochlea.

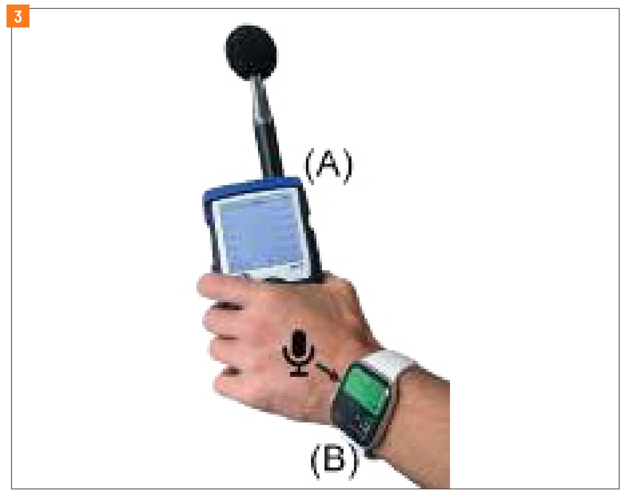


2




Insertion tool prototype for minimally invasive cochlear implantation.

3




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

### 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 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. 1

### 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. 2

### 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. 3

### Selected Publications


[1] Aebischer P, Mantokoudis G, Weder S, Anschuetz L, Caversaccio M, Wimmer W. (2022). In-Vitro Study of Speed and Alignment Angle in Cochlear Implant Electrode Array Insertions. IEEE TBME 69:129-137.

[2] Hu S, Hall D, Zubler F, Sznitman R, Anschuetz L, Caversaccio M, Wimmer W. (2021) Bayesian brain in tinnitus: Computational modeling of three perceptual phenomena using a modified Hierarchical Gaussian Filter. Hear Res 410:108338.

[3] Talon E, Visini M, Wagner F, Caversaccio M, Wimmer W. (2021). Quantitative analysis of temporal bone density and thickness for robotic ear surgery. Frontiers Surg., 10.3389/fsurg.2021.740008.

[4] Aebischer P, Caversaccio M, Wimmer W. (2021).Fabrication of Human Anatomy-Based Scala Tympani Models with a Hydrophilic Coating for Cochlear Implant Insertion Experiments. Hear Res 10.1016/j.heares.2021.108205.

[5] Hu S, Anschuetz L, Hall D, Caversaccio M, Wimmer W. (2021). Susceptibility to Residual Inhibition Is Associated With Hearing Loss and Tinnitus Chronicity. Trends Hear 10.1016/j.heares.2021.108294.

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[7] Fischer T, Schmid C, Kompis M, Mantokoudis G, Caversaccio M, Wimmer W. (2021). Effects of temporal fine structure preservation on spatial hearing in bilateral cochlear implant users. J Acoust Soc Am 150:673-686.

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[10] Fischer T, Schmid C, Kompis M, Mantokoudis G, Caversaccio M, Wimmer W. (2020). Pinna-Imitating Microphone Directionality Improves Sound Localization and Discrimination in Bilateral Cochlear Implant Users. Ear Hear 42:214-222.


# Mechanical Design and Production

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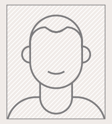
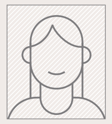

Sebastian Aellig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**Inselspital Bern**
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**Research Profile**

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. [1]

1

MDP General view

**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.

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). [2]

**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. [3]

**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. [4]

2

Test device for the mitral valve

3

Dental plate vertical

4

Cornea three finger plate

# 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.

**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 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.



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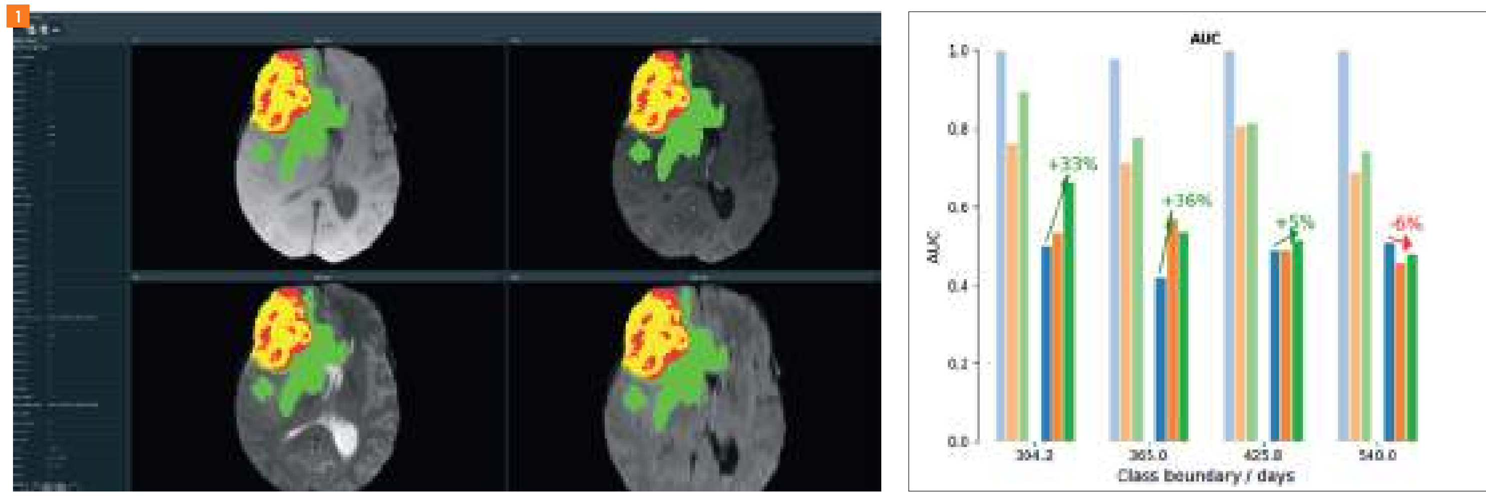
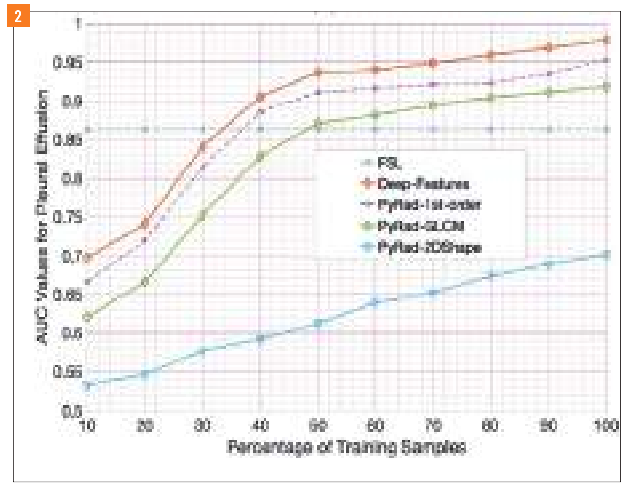



*Left:* Deep learning-based automated quantification and analysis of brain tumor lesions – DeepBraTumIA software.
*Right:* Favoring robustness in radiomics analysis can further improve overall accuracy of prediction models, demonstrated in overall survival prediction tasks.

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. During 2022, our group tested the proposed AI solution on a multi-center study, with results superior to human performance. 1

**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." During 2022 our group moved beyond explanations to develop AI systems that employ interpretability information to gain accuracy and robustness. 2

2




Interpretability-guided active learning, data mining saliency maps forimproved learning rates of trained deep learning models.
"Source: Mahapatra et al. IEEE TMI 2021"

**Selected Publications**


[1] Poel R., Rufenacht E., Herrmann E., Scheib S., Manser P., Aebersold D., and Reyes M. The predictive value of segmentation metrics on dosimetry in organs at risk of the brain. Medical Image Analysis, 73, 102161, 2021.

[2] Mahapatra D., Pollinger A., Shao L., and Reyes M. Interpretability-Driven Sample Selection Using Self Supervised Learning For Disease Classification And Segmentation. IEEE Trans. Med. Imaging, PP, 2021.

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[6] Jungo A., Scheidegger O., Reyes M., and Balsiger F. pymia: A Python package for data handling and evaluation in deep learning-based medical image analysis. Computer Methods and Programs in Biomedicine, 198, 105796, 2021.

# 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.

Prototype of haptic hand rehabilitation device for sensorimotor training after stroke

**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. 1

**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 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.



Robotic motor training with ARMin exoskeleton in immersive virtual reality

Robotic somatosensory training with haptically rendered virtual textures

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. 2

**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. 3

**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. 4

Virtual inverted pendulum task with ARMin exoskeleton robot

Selected Publications


[1] Ö. Özen, K. Buetler and L. Marchal-Crespo (2022). 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.

[2] K. Buetler et al. (2022). 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.

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# Musculoskeletal Biomechanics

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**Research Profile**

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

**Multiscale Mechanical Properties of Bone**
**(SNF grant #165510 with EMPA, MGU and HWU, ESKAS fellowship)**

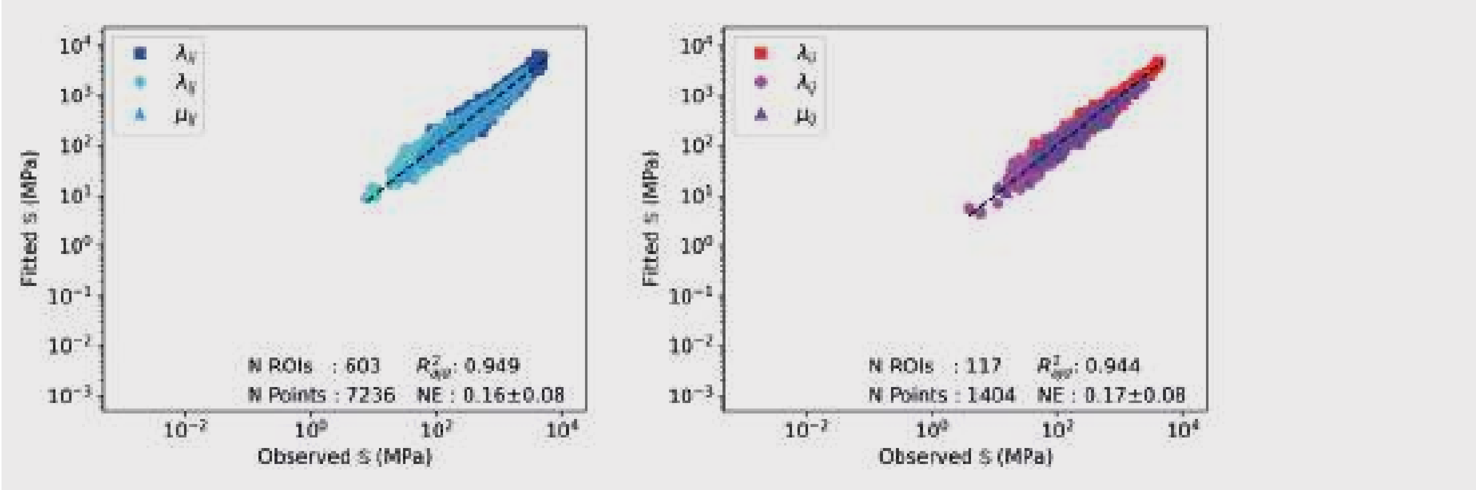
Bone is a complex material characterized by high strength and different toughening mechanism at various length scale. A key in understanding its postyield behaviour is the mineralized collagen fibre embedded in an extrafibrillar matrix. Combined micropillar compression and synchrotron X-Ray scattering 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 postyield properties. Further microtensile and nanoindentation experiments were conducted to investigate the bone extracellular matrix properties in Osteogenesis Imperfecta (OI). 1

**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. Mathieu Simon found the OI samples to have significantly lower bone volume fraction and trabecular number but no differences in trabecular thickness compared to controls. 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.



1




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

**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. 2

**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. 3

**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.

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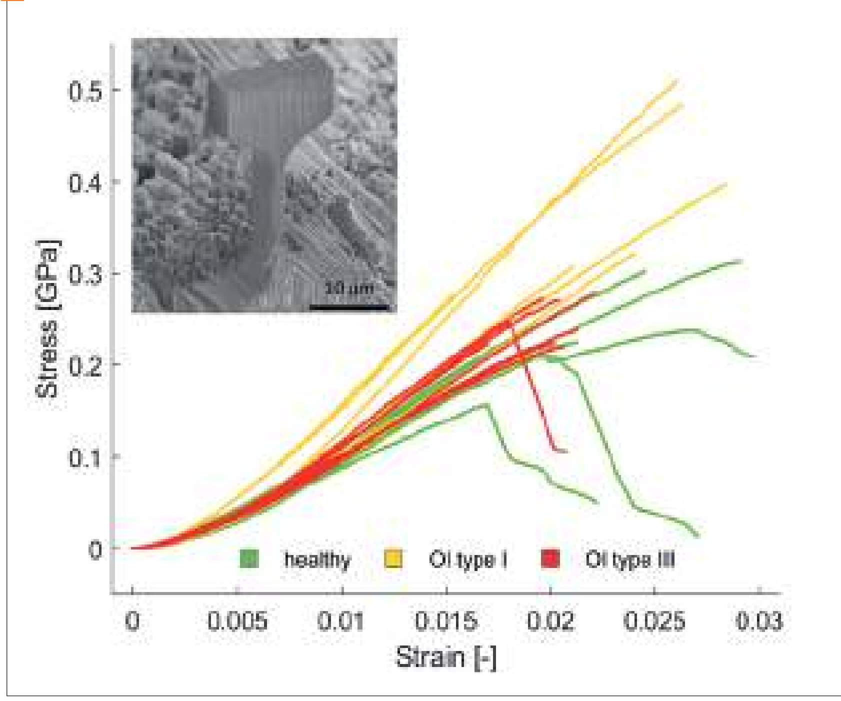


Stress-strain curve of micro-tensile specimen of OI and healthy control bone.

**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.


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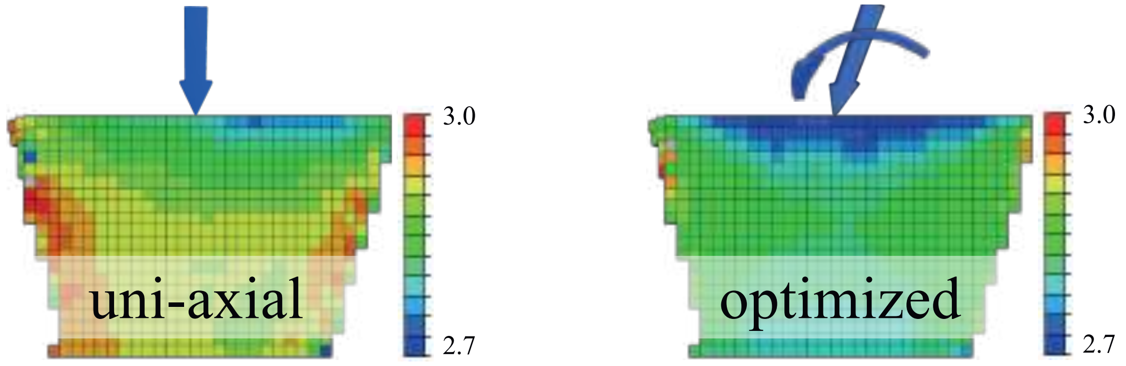
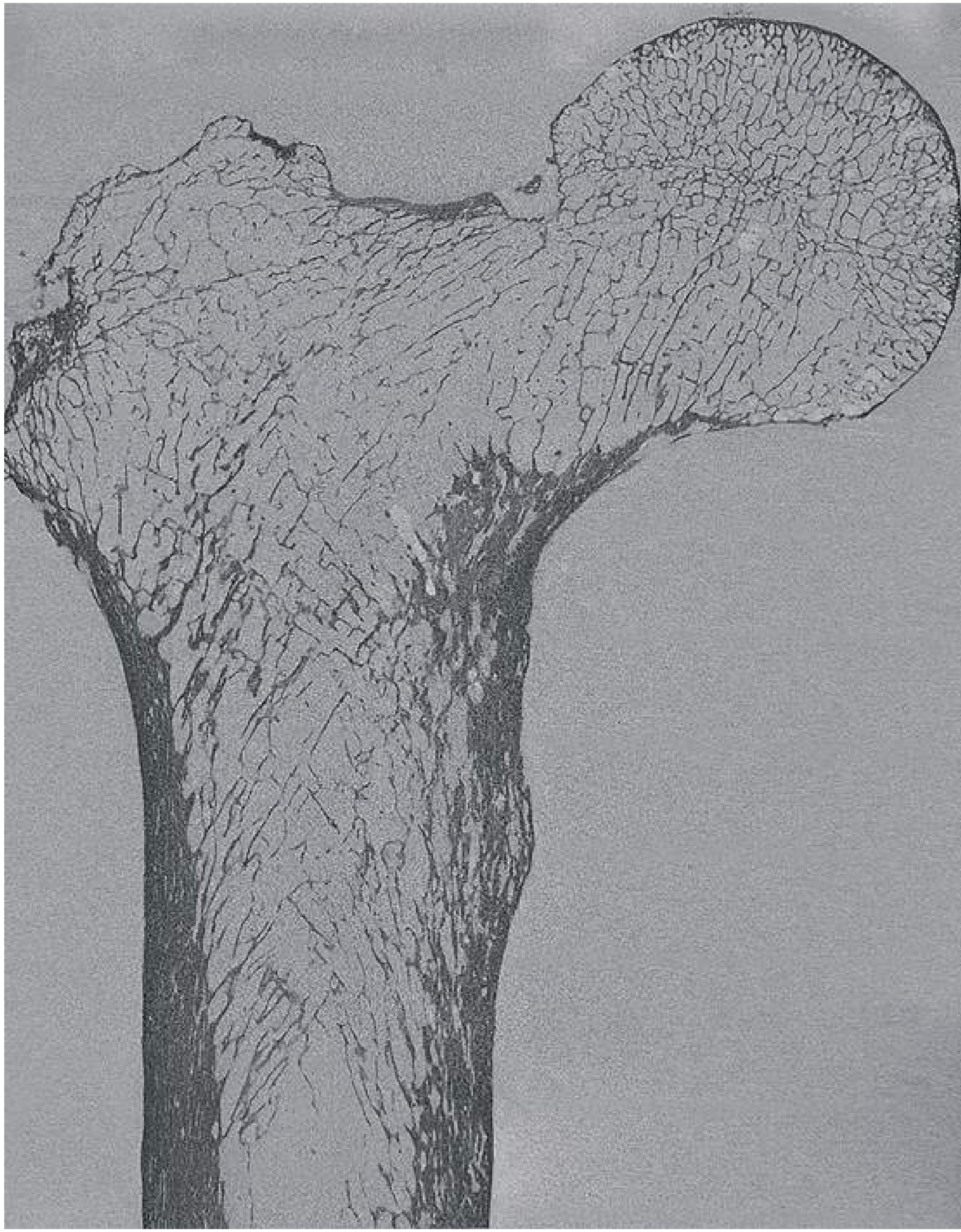



Standard uni-axial loading boundary conditions (left) and an optimized loading boundary condition (right).

**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.



# Organs-on-Chip Technologies

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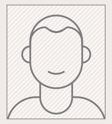
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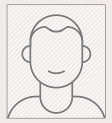
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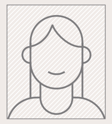
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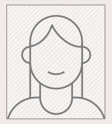
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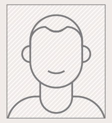
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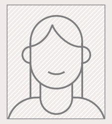
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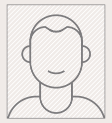
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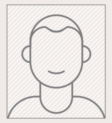
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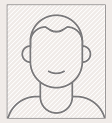
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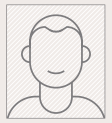
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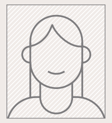
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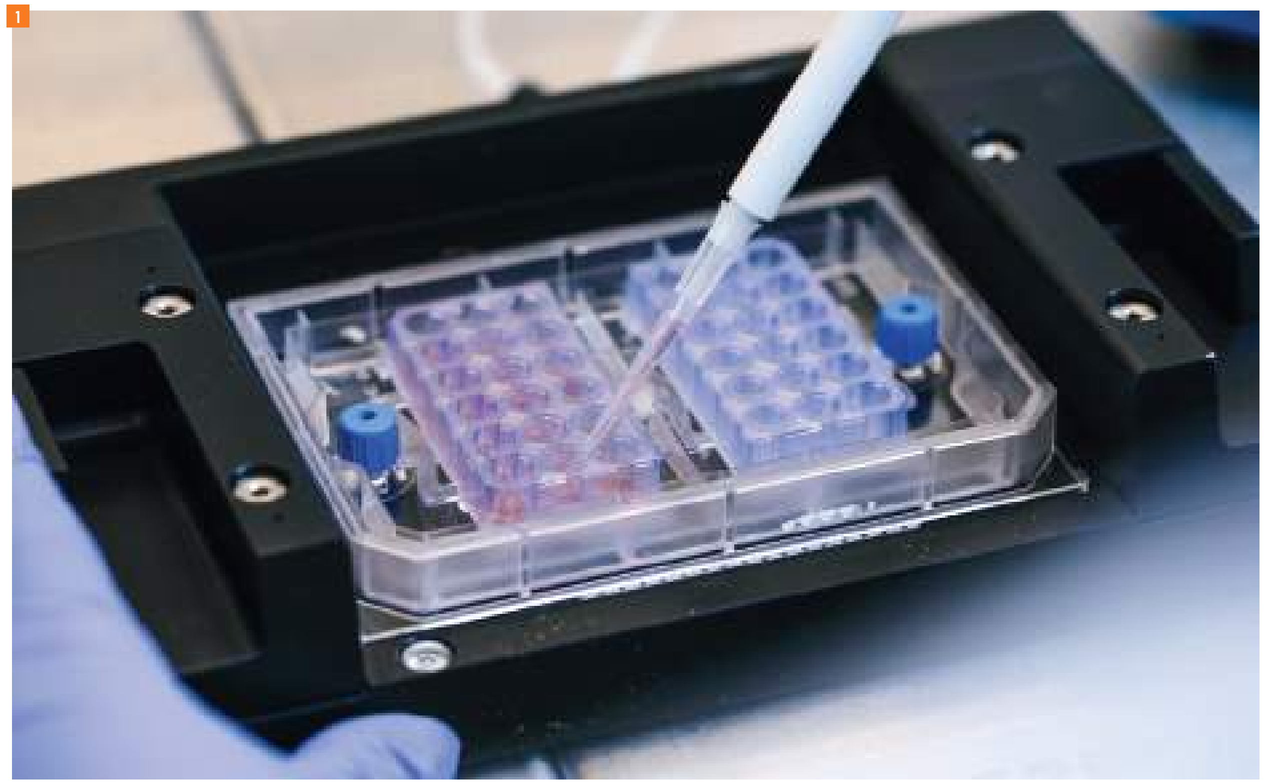
**Research Profile**
The Organs-on-Chip Technologies Group focuses on the development of advanced in vitro models, called organ-on-chip. Such devices aim at reproducing the smallest functional unit of an organ, by mimicking the cellular composition and the cellular microenvironment. The group particularly 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.

**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 aerosolised nanoparticles is currently assessed with this system. 1

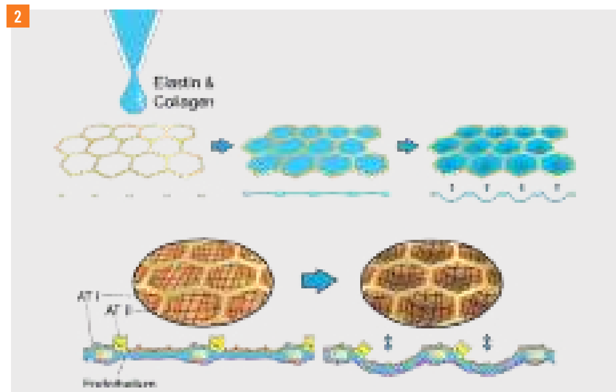
1



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).

**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 two proteins found in the lung ECM: collagen and elastin. Its fabrication process is very simple 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. 3

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.

**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 hy-

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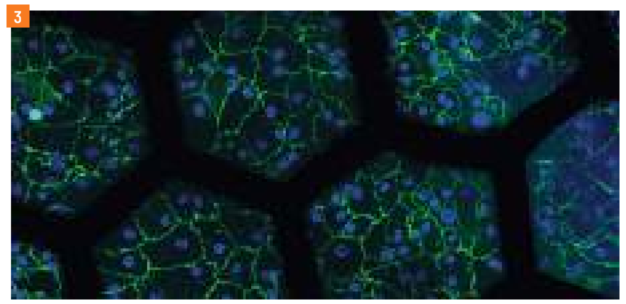
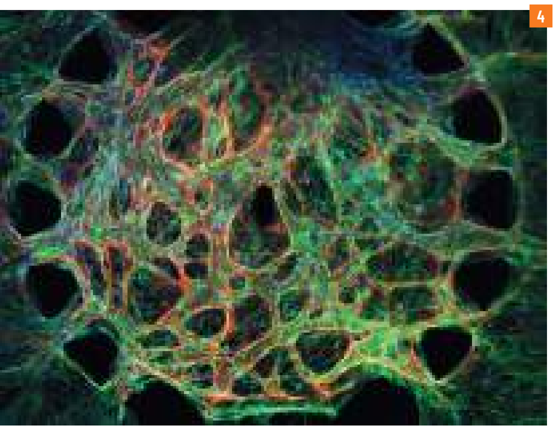


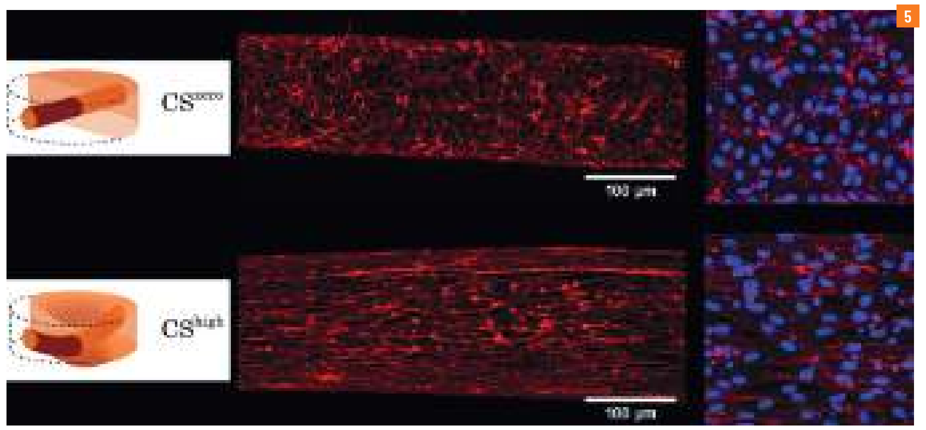
Lung alveolar epithelial cells from patients cultured on the collagen-elastin membrane supported by an ultra-thin hexagonal gold grid (each hexagon is ca. 260µm wide).

4



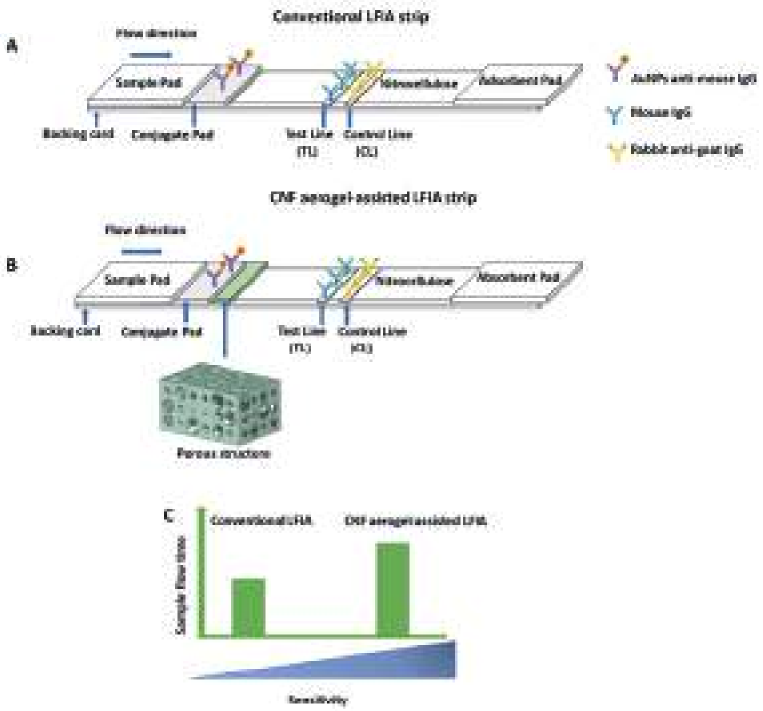
Self-assembly of a 3D perfusable lung blood vessels network in the central chamber of the microvasculature-on-chip.

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).

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.

drogel 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. 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) 6. The presented optimization method offers a unique potential to transform lateral flow assays into highly sensitive, fully quantitative point-of-care diagnostics.

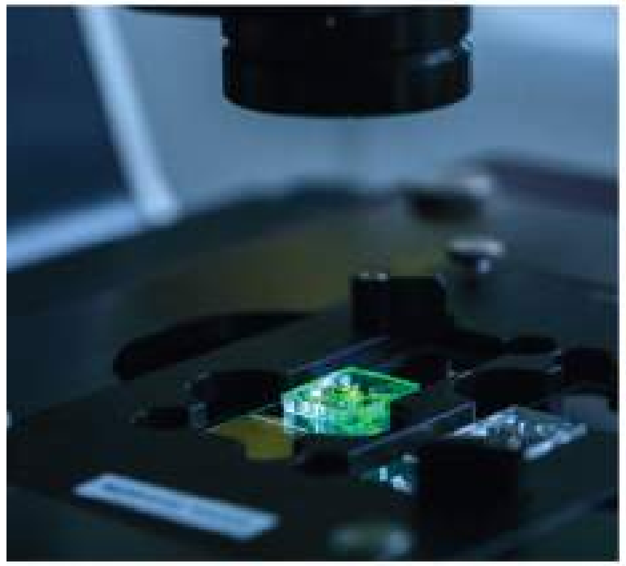
### Selected Publications

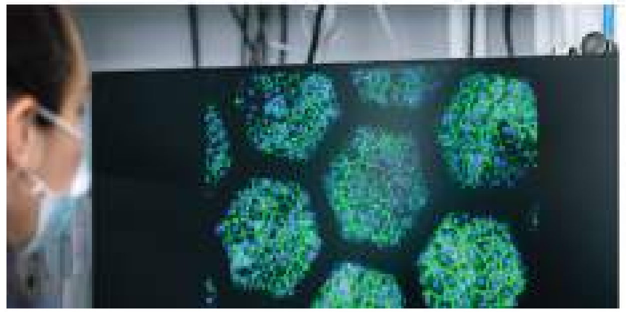
[1] Zamprogno, P. et al. Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. Commun. Biol. 4, 168 (2021).

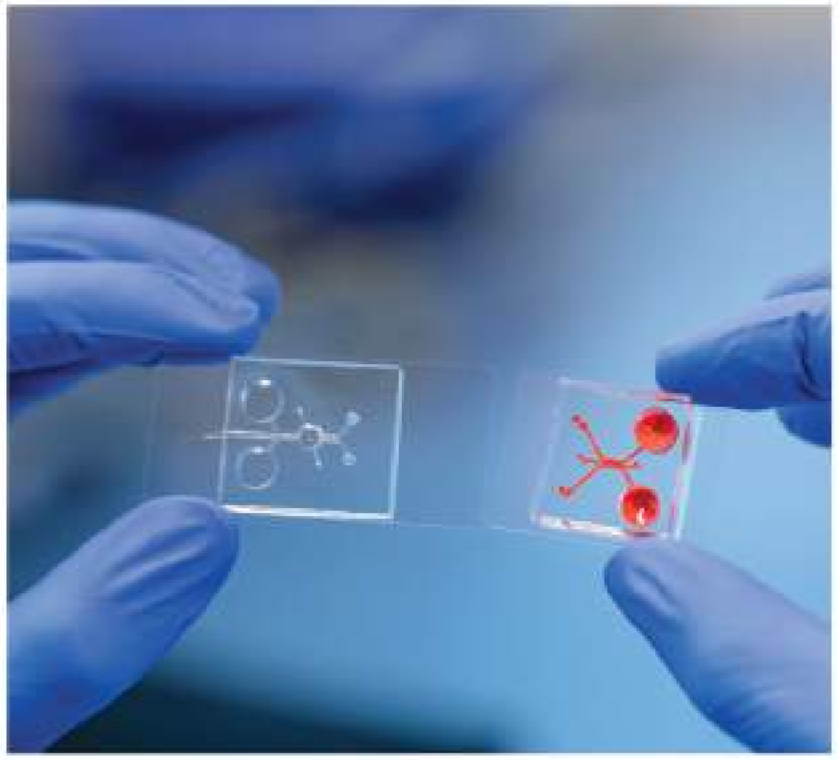
[2] Zamprogno, P. et al. Mechanical Properties of Soft Biological Membranes for Organ-on-a-Chip Assessed by Bulge Test and AFM. ACS Biomater. Sci. Eng. 7, 2990–2997 (2021).

[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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### 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.

### 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 into 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"). 1

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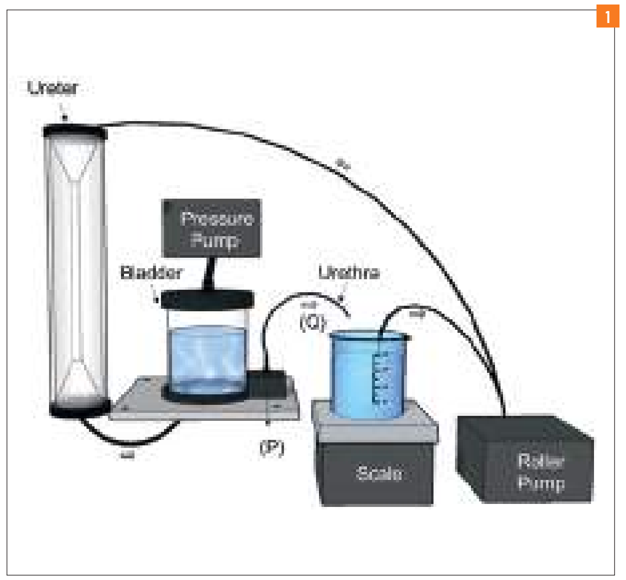
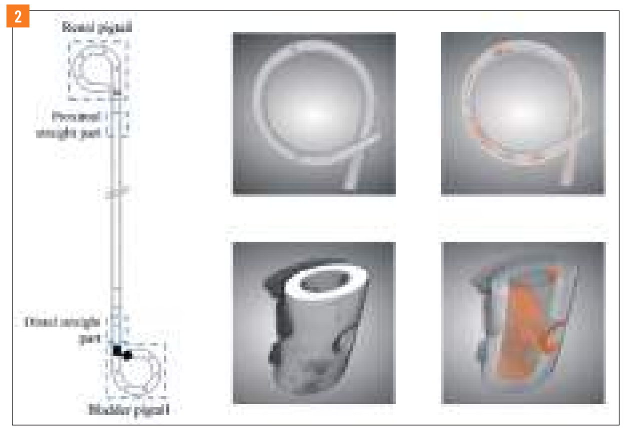



In-vitro model of the urinary tract. Using a programmable pressure pump, bladder pressure waveform and flow can be controlled to mimic physiological and pathological conditions.



2



Schematic of the four analysed sections of ureteral stent retrieved from patient (left): renal pigtail, proximal straight part, distal straight part and bladder pigtail. Three dimensional μ-CT images of the renal pigtail and proximal straight part before (center images) and after (images on the right) segmentation, respectively. Luminal encrustations from the segmentation results are shown in orange. Stents are rendered semi-transparent for better visualization.

### Encrustations in Ureteral Stents

Ureteral stents are frequently used in clinical settings to maintain the drainage of urine in the presence of ureteral obstructions (e.g. stones, tumours). Once in place, ureteral stents extend along the whole ureter length, with side holes positioned at regular intervals. Encrustation and biofilm are considered the main causes of stent failure, and it has been shown that their development in stented ureters is strongly influenced by local fluid mechanics (e.g. shear stresses). Ureteral stents, once implanted in patients, are exposed to complex fluid dynamic and 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. 2

### Non-invasive Solution for Urinary Retention

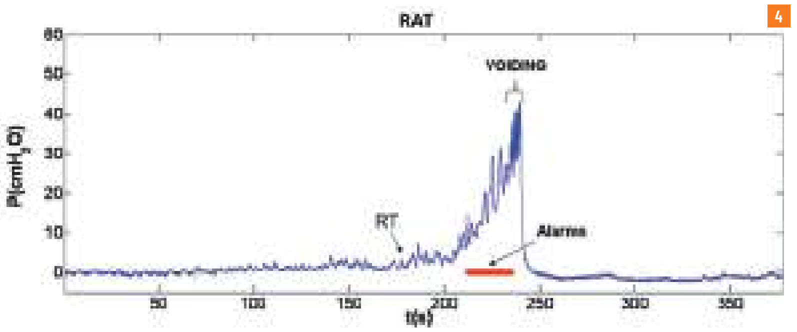
The UGE group is developing the world's first non-invasive solution for urinary retention. Patients suffering from urinary retention are unable to empty their bladder because of either a weak bladder muscle or/and a bladder outlet obstruction (e.g. enlarged prostate in men). The main complaints from 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 an unmet clinical need. 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. 3

### Innovative Tools for the Diagnosis and the Treatment of Overactive Bladder and Incontinence

Patients suffering from overactive bladder (OAB) live with a continuous urge to urinate even at low bladder 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

3


Our first prototype for patients suffering from urinary retention.

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Bladder pressure signal during voiding in rats. RT indicates the onset of rapid transients before the voiding contraction.

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. 4

## Selected Publications

**[1]** Zheng S, Amado P, Obrist D, Burkhard F, Clavica F., An in vitro bladder model with physiological dynamics: Vesicoureteral reflux alters stent encrustation pattern' Frontiers in Bioengineering and Biotechnology, 2022. DOI: 10.3389/fbioe. 2022.1028325

**[2]** Zheng S., Obrist D., Burkhard F., Clavica F. , Fluid mechanical performance of ureteral stents: The role of side hole and lumen size' Bioengineering & translational medicine Wiley, 2022. DOI: 10.1002/btm2.10407

**[3]** Zheng, S., Amado, P., Kiss, B., Stangl, F., Haeberlin, A., Sidler, D., Obrist, D., Burkhard, F., Clavica, F. 'Quantitative Evaluation of Encrustations in Double-J Ureteral Stents With Micro-Computed Tomography and Semantic Segmentation' Front. Urol. 2:836563, 2022. DOI: 10.3389/fruro.2022.836563

**[4]** Zheng, S., Carugo, D., Mosayyebi, A., Turney, B., Burkhard, F., Lange, D., Obrist, D., Waters, S., Clavica F. 'Fluid mechanical modelling of the upper urinary system' WIRES Mechanisms of Disease, 2021. DOI: 10.1002/wsbm.1523

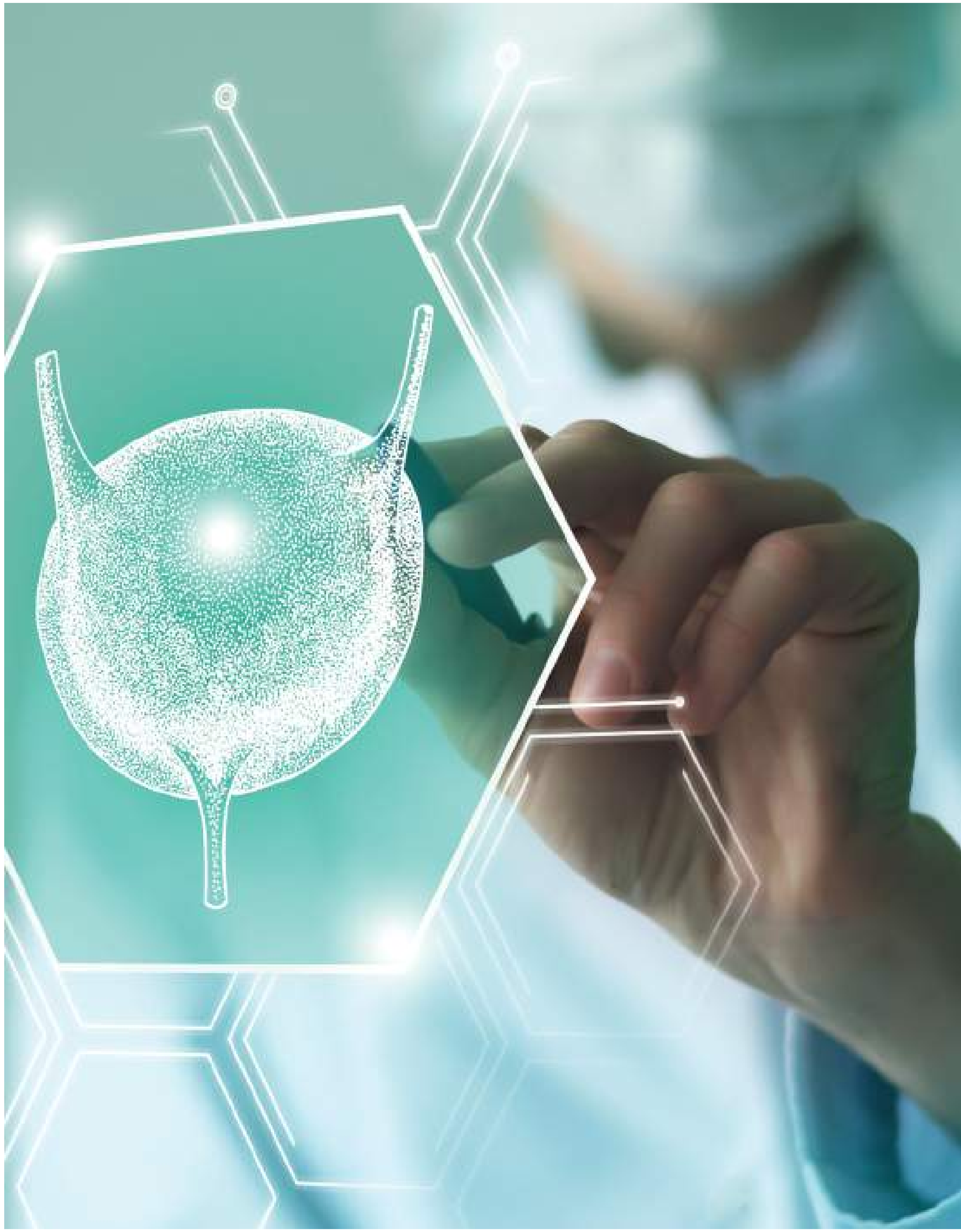
**[5]** Abou-Hassan, A., Barros, A., Buchholz, N., Carugo, D., Clavica, F., De Graaf, P., De La Cruz, J., Kram, W., Mergulhao, F., L Reis, R., Skovorodkin, I., Soria, F., Vainio, S. & Zheng, S., Potential strategies to prevent encrustations on urinary stents and catheters – thinking outside the box: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

**[6]** Häberlin A., Schürch K., Niederhauser T.; Sweda R., Schneider M. P.; Obrist D., Burkhard F. C.; Clavica F. (2018). Cardiac electrophysiology catheters for electrophysiological assessments of the lower urinary tract-A proof of concept ex vivo study in viable ureters. Neurourology and Urodynamics 87-96, 2019. doi:10.1002/nau.23816

**[7]** Niederhauser, T., Gafner, E., Cantieni, T., Grämiger, M., Haeberlin, A., Obrist, D., Burkhard, F., Clavica, F. 'Detection and quantification of overactive bladder activity in patients: Can we make it better and automatic?' Neurourology and Urodynamics, 1-9, 2018. DOI: 10.1002/nau.23357

**[8]** 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





## Editorial

# Inselspital, Bern University Hospital

Trans-professional research in the domain of biomedical engineering is firmly anchored at Inselspital, Bern University Hospital. Its interdisciplinary research aspirations connect clinicians, engineers, computer scientists, as well as data scientists in the largest University Hospital setting in Switzerland. At an institutional level, Inselspital maintains close ties to individual members of the Bern Biomedical Engineering Network (BBEN).

The links between Inselspital and biomedical engineering research institutes at the University of Bern foster strong and innovative multidisciplinary research activities. The majority of the departments presented in the following report work in close cooperation with the faculty of Medicine at University of Bern. They play a key role in supporting tertiary research and educational ambitions in their respective fields as well as taking part in different research clusters presided by the University of Bern.

As the founding partner of the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel), Inselspital provides essential resources for translational activities. It hosts the Institute on site and therefore supplies enabling facilities such as the Translational Imaging Center Bern.

Within a clinical environment, biomedical engineering research at Inselspital focuses on both long-term and short-term research objectives. Joint research platforms and core infrastructure, enabled through support of the Inselspital, provide the means for effective fundamental and translational biomedical engineering research applicable to different academic research groups and industrial partners in the canton of Bern.

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**Main Research Partners**
- Clinical Trials Unit, University of Bern
- University Hospitals Zurich, Basel, Lausanne, and Geneva
- ETH, CSEM, industry partners

**Group Members**
For a complete list see: http://www.herzgefaesszentrum.insel.ch/

**Research Profile**
The Cardiovascular Center at Bern University Hospital consists of the Departments of Angiology, Cardiology, Cardiac Surgery, and Vascular Surgery and maintains a broad range of clinical and translational research activities. The teams are involved in multicenter, randomized clinical trials as well as first-in-man human studies using innovative medical devices and pharmacological interventions. Some examples are listed below:

- Investigations of devices for the minimal-invasive treatment of coronary artery diseases, thromboembolic diseases, valvular heart diseases, vascular pathologies, novel surgical approaches (including congenital and pediatric procedures as well as extracorporeal circulation), and heart failure;
- Pharmacological therapies in the field of antithrombotic and lipid lowering drugs;
- Studies for the treatment of electrophysiological disorders and in the field of preventive cardiology;
- Novel imaging methodologies in the field of cardiovascular medicine.

Translational and preclinical research activities involve emerging technologies such as ex-situ heart perfusion systems, novel cardiovascular imaging sequences, and innovative ablation therapy and cardiac pacing solutions.

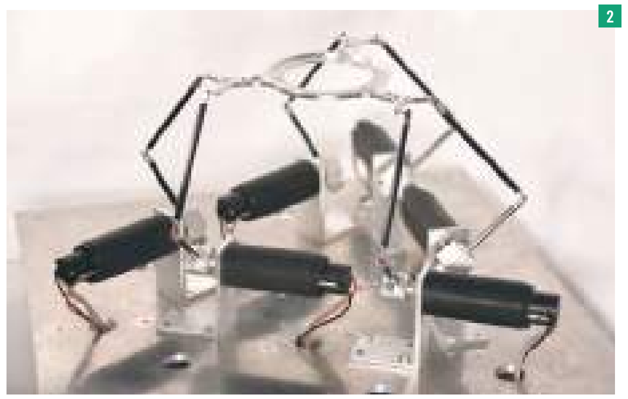
The Cardiovascular Center is an active member of the Cardiovascular Research Cluster (www.cvrc.unibe.ch).

**Optimizing the duration of antiplatelet drug therapy after stent implantation in patients at high risk for bleeding**
The appropriate duration of dual antiplatelet therapy in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent remains unclear. One month after they had undergone implantation of a stent, high- bleeding-risk patients were randomly assigned to either discontinue dual antiplatelet therapy immediately (abbreviated therapy) or to continue it for at least two additional months (standard therapy). One month of dual antiplatelet therapy was non-inferior to the continuation of therapy for at least two additional months with regard to the occurrence of net adverse clinical events and major adverse cardiac or cerebral events. Abbreviated therapy also resulted in a lower incidence of major or clinically relevant non-major bleeding. 1

1

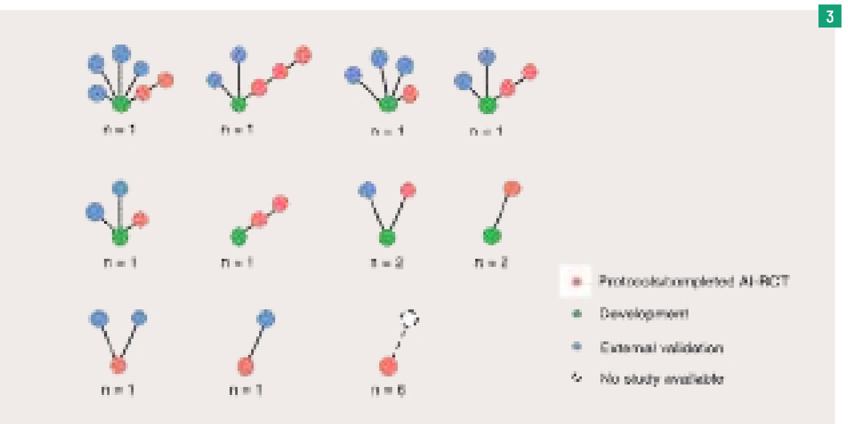

MASTER DAPT A multicenter, randomized, open-label trial comparing one month of dual antiplatelet therapy with longer treatment after the placement of a drug-eluting stent in patients at high risk for bleeding.[11]

2



Robot with the end effector platform connected to six motors via legs.[12]

3



Patterns of pathways of development (training, validation and/or testing), external validation, and clinical evaluation of artificial intelligence tools in ongoing and completed clinical trials. In network level, each circle corresponds to an individual study (green, blue, and red for development, external validation and AI-RCTs, respectively).[13]

**A robotic approach to reproducing physiological heart motions**

We developed a novel robotic approach to reproduce physiological heart motions with high accuracy and repeatability to study their effect on implantable cardiac devices. This may benefit the device development process and offer the potential to increase safety and quality of next-generation implantable cardiac devices. This approach re-uses heart motion data repeatedly without sacrificing the life of animals, thereby promoting the 3R principles. 2

**AI in medicine: AI tool development patterns and clinical evaluation**

Artificial intelligence (AI) methods are playing an increasingly important role in the era of digital healthcare transformation and precision medicine. In a recent analysis, we identified significant variations in the patterns of AI tool development (training, validation, testing) and external (independent) validation leading up to their clinical evaluation in dedicated AI randomized controlled trials (AI-RCTs). In this early phase of novel AI-RCTs, trials are characterized by heterogeneous design and reporting. Data that would allow independent replication and implementation of AI tools were not available. Of note, most AI-RCTs do not test the AI tools in geographical areas outside of those where the tools were developed; therefore, generalizability remains largely unaddressed. As AI applications are increasingly reported throughout medicine, there is a clear need for structured evaluation of their impact on patients with a focus on effectiveness and safety outcomes, but also costs and patient-centered care before their large-scale deployment. 3

### Selected Publications


**[1]** Castiglione A., Hornyik T., Wülfers E.M., Giammarino L., Edler I., Jowais J.J., Rieder M., Perez-Feliz S., Koren G., Bősze Z., Varró A., Zehender M., Brunner M., Bode C., Liin S.I., Larsson H.P., Baczkó I., Odening K.E. (2021). Docosahexaenoic acid normalizes QT interval in long QT type 2 transgenic rabbit models in a genotype-specific fashion. Europace. 2021 Oct 3:euab228.

**[2]** Valgimigli M., Frigoli E., Heg D., Tijssen J., Jüni P., Vranckx P., Ozaki Y., Morice M.C., Chevalier B., Onuma Y., Windecker S., Tonino P.A.L., Roffi M., Lesiak M., Mahfoud F., Bartunek J., Hildick-Smith D., Colombo A., Stanković G., Iñiguez A., Schultz C., Kornowski R., Ong P.J.L., Alasnag M., Rodriguez A.E., Moschovitis A., Laanmets P., Donahue M., Leonardi S., Smits P.C. (2021). MASTER DAPT Investigators. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med., 385(18):1643–1655.

**[3]** Pilgrim T., Vollenbroich R., Deckarm S., Gräni C., Dobner S., Stark A.W., Erne S.A., Babongo Bosombo F., Fischer K., Stortecky S., Reusser N., Fürholz M., Siontis G.C.M., Heg D., Hunziker L., Windecker S., Lanz J. (2021). Effect of Paroxetine-Mediated G-Protein Receptor Kinase 2 Inhibition vs Placebo in Patients with Anterior Myocardial Infarction: A Randomized Clinical Trial. JAMA Cardiol., 6(10):1171–1176.

**[4]** Karki P., Uranw S., Bastola S., Mahato R., Shrestha N.R., Sherpa K., Dhungana S., Odutayo A., Gurung K., Pandey N., Agrawal K., Shah P., Rothenbühler M., Jüni P., Pilgrim T. (2021). Effectiveness of Systematic Echocardiographic Screening for Rheumatic Heart Disease in Nepalese Schoolchildren: A Cluster Randomized Clinical Trial. JAMA Cardiol., 6(4):420–426.

**[5]** Ueki Y., Otsuka T., Bär S., Koskinas K.C., Heg D., Häner J., Siontis G.C.M., Praz F., Hunziker L., Lanz J., Stortecky S., Pilgrim T., Losdat S., Windecker S., Räber L. (2021). Frequency and Outcomes of Periprocedural MI in Patients with Chronic Coronary Syndromes Undergoing PCI. J Am Coll Cardiol., 79(6):513–526.

**[6]** Bona, Martina; Wyss, Rahel K.; Arnold, Maria; Méndez-Carmona, Natalia; Sanz, Maria N.; Günsch, Dominik; Barile, Lucio; Carrel, Thierry P.; Longnus, Sarah L. (2021). Cardiac Graft Assessment in the Era of Machine Perfusion: Current and Future Biomarkers. Journal of the American Heart Association, 10(4), e018966. American Heart Association 10.1161/JAHA.120.018966.

**[7]** Heinisch P.P., Nucera M., Bartkevics M., Erdoes G., Hutter D., Gloeckler M., Kadner A. Early-experience with a novel suture device for sternal closure in pediatric cardiac surgery. Ann Thorac Surg. 2021 Oct 2:S0003-4975(21)01584-2.

**[8]** Tomii D., Okuno T., Heg D., Gräni C., Lanz J., Praz F., Stortecky S., Windecker S., Pilgrim T., Reineke D. (2021). Sinus of Valsalva Dimension and Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation: SOV dilatation in TAVI patients. Am Heart J., S0002-8703(21)00447-6.

**[9]** Weiss, Salome; Bachofen, Bernadette; Widmer, Matthias K.; Makaloski, Vladimir; Schmidli, Jürg; Wyss, Thomas R. (2021). Long-term results of cryopreserved allografts in aorto-iliac graft infections. Journal of vascular surgery, 74(1), S. 268–275.

**[10]** Neugebauer F., Noti F., van Gool S., Roten L., Baldinger S.H., Seiler J., Madaffari A., Servatius H., Ryser A., Tanner H., Reichlin T., Haeberlin A. (2021). Leadless atrioventricular synchronous pacing in an outpatient setting: Early lessons learned on factors affecting atrioventricular synchrony. Heart Rhythm., S1547-5271(21)02517-0.

**[11]** Valgimigli M., Frigoli E., Heg D., Tijssen J., Jüni P., Vranckx P., Ozaki Y., Morice M.C., Chevalier B., Onuma Y., Windecker S., Tonino P.A.L., Roffi M., Lesiak M., Mahfoud F., Bartunek J., Hildick-Smith D., Colombo A., Stanković G., Iñiguez A., Schultz C., Kornowski R., Ong P.J.L., Alasnag M., Rodriguez A.E., Moschovitis A., Laanmets P., Donahue M., Leonardi S., Smits P.C.; MASTER DAPT Investigators. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med. 2021 Oct 28;385(18):1643–1655.

**[12]** Zurbuchen A., Pfenniger A,, Omari S., Reichlin T., Vogel R., Haeberlin A. A Robot Mimicking Heart Motions: An Ex-Vivo Test Approach for Cardiac Devices. Cardiovasc Eng Technol. 2022 Apr;13(2):207–218. doi: 10.1007/s13239-021-00566-3.

**[13]** Siontis G.C.M., Sweda R., Noseworthy P.A., Friedman P.A., Siontis K.C., Patel C.J. Development and validation pathways of artificial intelligence tools evaluated in randomised clinical trials. BMJ Health Care Inform. 2021 Dec;28(1):e100466.

**[14]** Vuillemin N., Bernhard S., Haine A., Schindewolf M., Häberli D., Hügel U., Obrist D., Baumgartner I., Capillary-venule malformation is a microfistulous variant of arteriovenous malformation, Journal of Vascular Surgery: Venous and Lymphatic Disorders, Volume 9, Issue 1, 2021, Pages 220-225

**[15]** Thakur M., Evans B., Schindewolf M., Baumgartner I., Döring Y., Neutrophil Extracellular Traps Affecting Cardiovascular Health in Infectious and Inflammatory Diseases. Cells. 2021; 10(7):1689.

# Insel Data Science Center

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**Research Profile**
The Insel Data Science Center (IDSC) is Insel Group's interdepartmental entity for digital data management. The IDSC's mission is to organize all digital data from Insel Group and make it accessible and usable. We play a facilitating role at the interface between the University Hospital of Bern and the medical faculty of the University of Bern. Our main tasks include the development and operation of a data platform as well as of applications and data science activities building thereon. In this context, we provide access to data from different sources, representing both patient-related administration as well as clinical documentation of all sorts, including literally all data types associated with the patient's journey, in compliance with the legal framework (human research act, data protection).

The activities of the IDSC are bundled in three product lines representing the specific target groups and bundling domain expertise: research, medicine, and management. Our interdisciplinary team is comprised of medical experts, data engineers, data scientists, imaging specialists, data warehouse specialists, and software developers.

**Research Products**
Our specialized tools designed for researchers support the research strategy of the Insel Group . We enable research to enhance patients' diagnostics and treatment. SearchBox – our cohort explorer for unstructured data that works like an internet search engine. The medical information from an electronic health record (EHR) can be extracted and used for research. All patient identifying data like first name, last name, address are replaced with random values to ensure anonymity. SearchBox is the primary tool to conduct a feasibility study and assemble a relevant cohort. The cohort definition can then be shared with IDSC to access further data needed for research.

i2b2 – our cohort explorer for structured data is based on open source software. It enables researchers to conduct feasibility studies on our wide set of structured data in compliance with the Human Research Act. Providing intuitive drag-and-drop interaction, researchers can quickly run simple and more complex queries. The cohort definition can then be shared with IDSC to access further data needed for research.

**Swiss Personalized Health Network**
Swiss Personalized Health Network (SPHN) is a strategic program by the Swiss government that accelerates the digitalization, co-operation, and interoperability within the federal structures of the nation's health network. One outstanding example of SPHN's success is the Federated Query System (FQS). It enables researchers to search all five university hospitals for cohorts. The clinical data are fully anonymized and the hospitals remain in full control of their provided data. The system enables researchers to find out the number of patients in the university hospitals that may be relevant for a specific research question. The available include demographic data (age class, gender), diagnosis (ICD-10), procedures (CHOP), medication (ATC), and lab results (LOINC).

SPHN has co-ordinated and financed a network of high-performance computer nodes for easy data exchange and computation power to run nationwide studies. This unique infrastructure is kept in line with the latest security standards and sophisticated research algorithms.

SPHN fosters the establishment of personalized medicine in the hospitals. Milestones for the development are defined in a so called "collaboration agreement" that sets goals to be met. The cohort explorer provided by the IDSC are two examples of SPHN-funded tools that are now in everyday use.

**Medicine**
The product line medicine focuses on patients' needs and aims for three main goals: increase quality of treatment, support physicians in their daily decision making, and enhance transparency of data points relevant to patients.

A complete picture of a single patient is accomplished by linking the various data sources that contain person-specific data. The analysis of all patient data leads to an improved quality of assessment and treatment. Using intelligent algorithms on frequently updated data decision processes are supported. From quick overviews to in-depth representation of relevant indicators and a full range of tools for physicians is provided.



**Selected Publications**

[1] Atkinson, A.; Ellenberger, B.; Piezzi, V.; Kaspar, T.; Endrich, O.; Leichtle, A.B.; Zwahlen, M.; Marschall, J. A. (2022). Bayesian Spatial-Temporal Model for Prevalence Estimation of a VRE Outbreak in a Tertiary Care Hospital. J Hosp Infect 2022, doi:10.1016/j.jhin.2021.12.024.

[2] Triep, K.; Leichtle, A.B.; Meister, M.; Fiedler, G.M.; Endrich, O. (2022). Real-World Health Data and Precision for the Diagnosis of Acute Kidney Injury, Acute-on-Chronic Kidney Disease, and Chronic Kidney Disease: Observational Study. Jmir Medical Informatics 2022, 10, e31356, doi:10.2196/31356.

[3] Musy, S.N.; Endrich, O.; Leichtle, A.B.; Griffiths, P.; Nakas, C.T.; Simon, M. (2021). The Association between Nurse Staffing and Inpatient Mortality: A Shift-Level Retrospective Longitudinal Study. Int J Nurs Stud 2021, 103950, doi:10.1016/j.ijnurstu.2021.103950.

[4] Triep, K.; Torbica, N.; Raio, L.; Surbek, D.; Endrich, O. (2020). The Robson Classification for Caesarean Section-A Proposed Method Based on Routinely Collected Health Data. Plos One 2020, 15, e0242736, doi:10.1371/journal.pone.0242736.

[5] Reyes, M.; Meier, R.; Pereira, S.; Silva, C.A.; Dahlweid, F.-M.; Tengg-Kobligk, H. von; Summers, R.M.; Wiest, R. (2020) On the Interpretability of Artificial Intelligence in Radiology: Challenges and Opportunities. Radiology Artif Intell 2020, 2, e190043, doi:10.1148/ryai.2020190043.

The IDSC was actively involved in several publications, including, among others ,e.g. VRE outbreak surveillance using hospital data and machine-learning techniques [1], the assessment and evaluation of acute and chronic kidney failure [2], the impact of nurse staffing on adverse outcomes [3] as well as classification propositions for cesarean section [4]. Also the interpretability of AI algorithms has been addressed in a comprehensive review [5].

**Management**
The product line management develops structured applications that support management decision processes. Based on key performance indicators and blended with operational data, they ensure a 360 degree view on to Insel Gruppe's business activities. The tools foster transparency across the entire organization and show the management on all levels the trends and the development of the specific data within their domain of responsibility. The relevant data are updated daily to support the decision processes with a variety of charts and figures.

# Interventional Neurovascular Research Group

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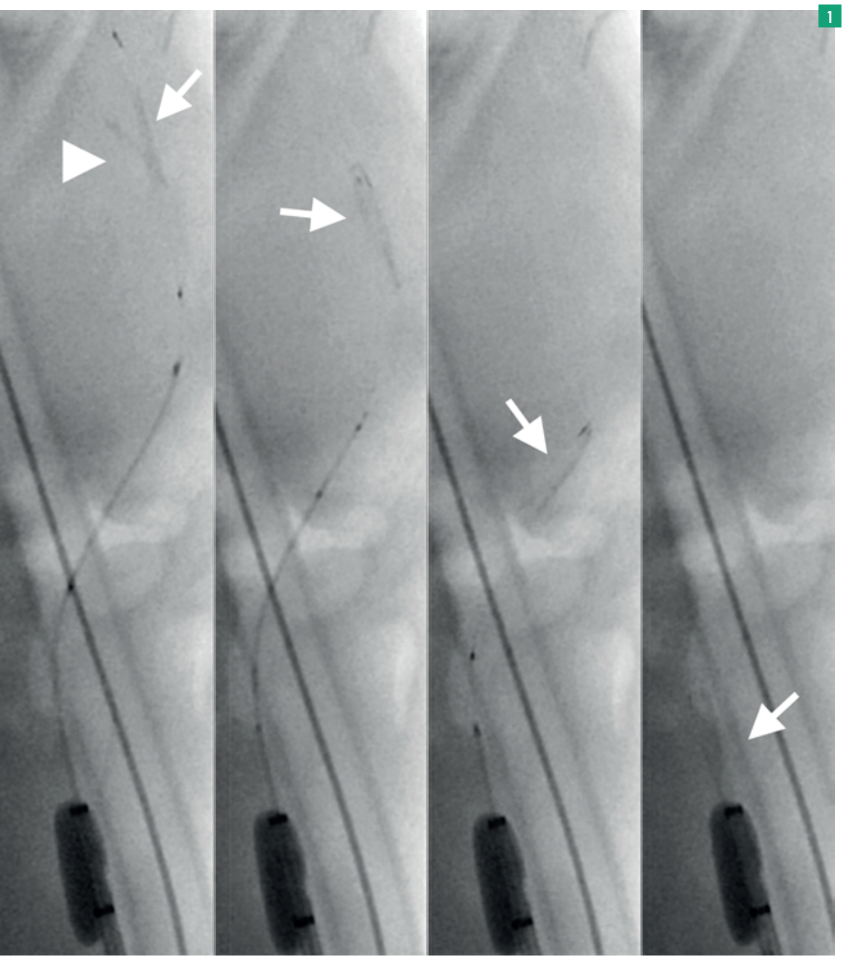


1 Successful retrieval attempt of a bifurcation thrombus in the animal model using opacified thrombi and a stent retriever device. Note retrieval of the side branch portion (arrowhead) and the straight position of the thrombus during mobilization and retrieval (arrow).

### Research Profile

In recent years, endovascular neurointerventional techniques have evolved significantly with an increasing spectrum of indications. This includes minimally invasive endovascular treatment procedures for acute ischemic stroke, intracranial aneurysms, and other cerebrovascular diseases such as arterio-venous malformations and fistulas as well as stenosis of brain supplying vessels. The Interventional Neurovascular Research Group is focusing on the pre-clinical experimental evaluation of novel treatment approaches and the development of devices for endovascular treatment of neurovascular diseases. Furthermore, the improvement and development of pre-interventional neuroimaging and imaging-guided treatment monitoring are crucial components in the management of complex cerebrovascular diseases.

### Acute Stroke Treatment

Acute ischemic stroke is a major cause of death and disability in industrialized countries. The management, diagnosis, and treatment approaches for acute ischemic stroke have enormously changed in the past decades. Initially, stroke management consisted solely of prevention, treatment of medical complications and symptoms, and rehabilitation, whereas nowadays endovascular treatment using mechanical thrombectomy has become the mainstay of stroke treatment due to large cerebral vessel occlusion. The most significant modifiable factors influencing the clinical outcome of patients are time span between symptom onset and revascularization, recanalization and reperfusion rate, and the occurrence of secondary complications such as symptomatic intracranial hemorrhage. Of those, recanalization has been shown to be the most crucial modifiable prognostic factor for favorable patient outcome. The Interventional Neurovascular Research Group has developed an in-vivo animal model for the pre-clinical evaluation and development of mechanical thrombectomy devices for the treatment of acute ischemic stroke. This model allows for a reliable evaluation of efficacy and safety as well as improvement of thrombectomy devices prior to their introduction into clinical use. Numerous experimental studies of the Interventional Neurovascular Research Group regarding mechanical thrombectomy for acute ischemic stroke treatment have been published in high-ranking journals and have paved the way for the transfer of the latest generation of mechanical thrombectomy devices, so-called stent retrievers, into clinical practice locally, but also on an international level. Furthermore, the model has gained international acceptance as an educational training model for mechanical thrombectomy device handling. Each year, the Institute of Diagnostic and Interventional Neuroradiology of the Inselspital Bern, in collaboration with the major neurological and neuroradiological European societies, organizes several distinguished international training courses dedicated to acute ischemic stroke treatment using this animal model (ESO-ESMINT-ESNR Stroke Winter School). [1] [2]

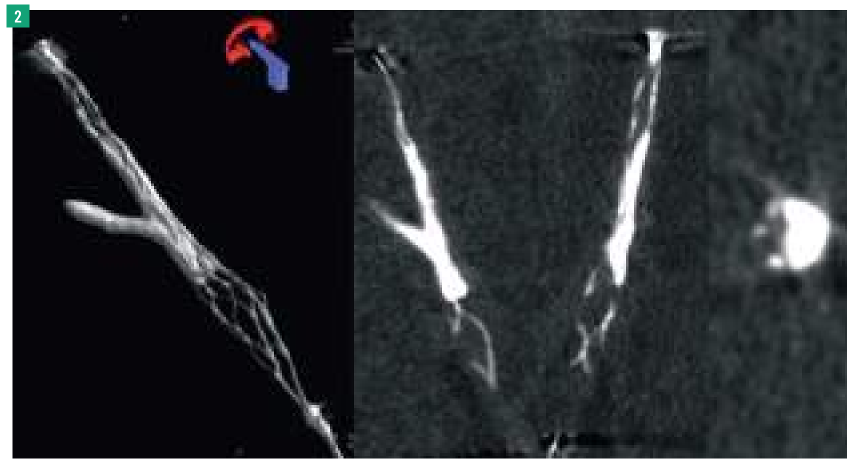
### Aneurysm Treatment

#### 1. Device and material testing

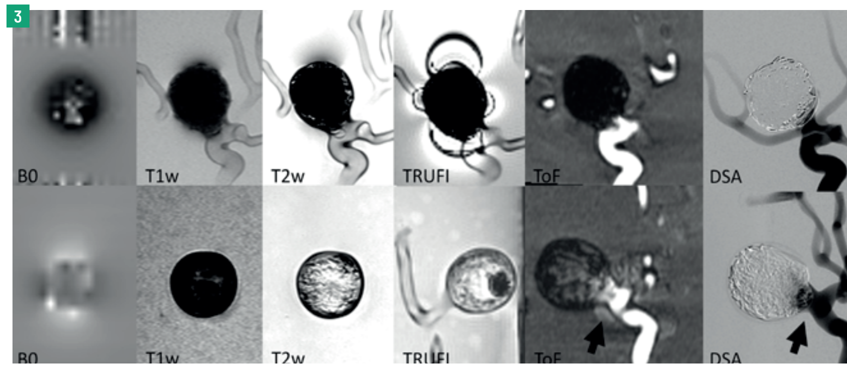
A common indication for endovascular intervention is the treatment of unruptured and ruptured intracranial aneurysms. Since the ISAT-Trial (International Subarachnoid Aneurysm Trial), the majority of these aneurysms, around 50'000 annually worldwide, are treated endovascularly. Endovascular standard treatment is the occlusion of the aneurysms by deployment of platinum coils. New polymer-based endovascular devices (polymer strands, "plastic coils") are currently under development as an adjunctive tool to platinum-based standard coils for endovascular aneurysm treatment. Conventional platinum coils cause imaging artifacts, reducing imaging quality and therefore impairing imaging interpretation on intra-procedural or non-invasive follow-up imaging. The results of the Interventional Neurovascular Research Group of in-vitro and in-vivo evaluation at different packing densities of these polymer strands showed significant reduction of imaging artifacts in fluoroscopy, CT, and MRI due to the lack of platinum compared to standard platinum coils. This might be advantageous for improved intra-procedural imaging for the detection of complications and post-treatment non-invasive follow-up imaging. Furthermore, applicability of the device under fluoroscopic guidance has been demonstrated in-vivo in a dedicated aneurysm model in rabbits which has been developed in collaboration with the Department of Neurosurgery. [3] [4]

#### 2. Development of aneurysm models using additive manufacturing techniques (3D printing)

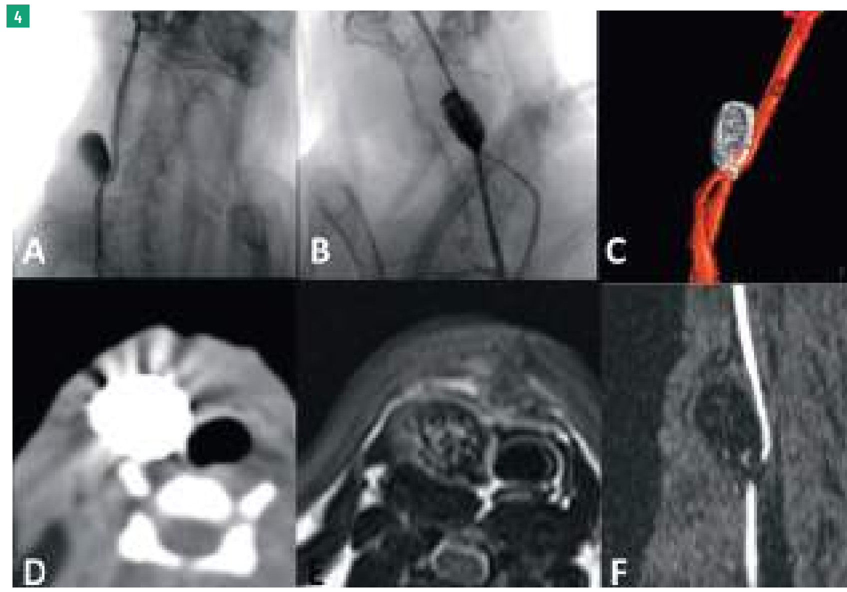
A further field of research is the development of in-vitro cerebral aneurysm models in collaboration with the ARTORG Center for Biomedical Engineering using different additive manufacturing techniques (3D printing). Patient-specific aneurysm models offer the possibility for pre-interventional planning of endovascular treatment procedures, especially for complex cerebral aneurysms using different treatment techniques. Pre-interventional in-vitro testing is helpful to determine the optimal treatment strategy and choice of devices in a specific patient to facilitate the treatment itself, to maximize treatment efficacy, and to minimize procedural risks. This approach has already been translated into clinical practice and is used on regular bases for interventional treatment planning. In addition, aneurysm models have been successfully introduced for hands-on training for complex endovascular aneurysm treatment and educational purposes. Furthermore, aneurysm models are used for the development, testing, and evaluation of novel endovascular devices and treatment approaches such as neurovascular robotics, as well as a model for measurements of different aspects of flow dynamics and their role in aneurysm formation and growth. [5]



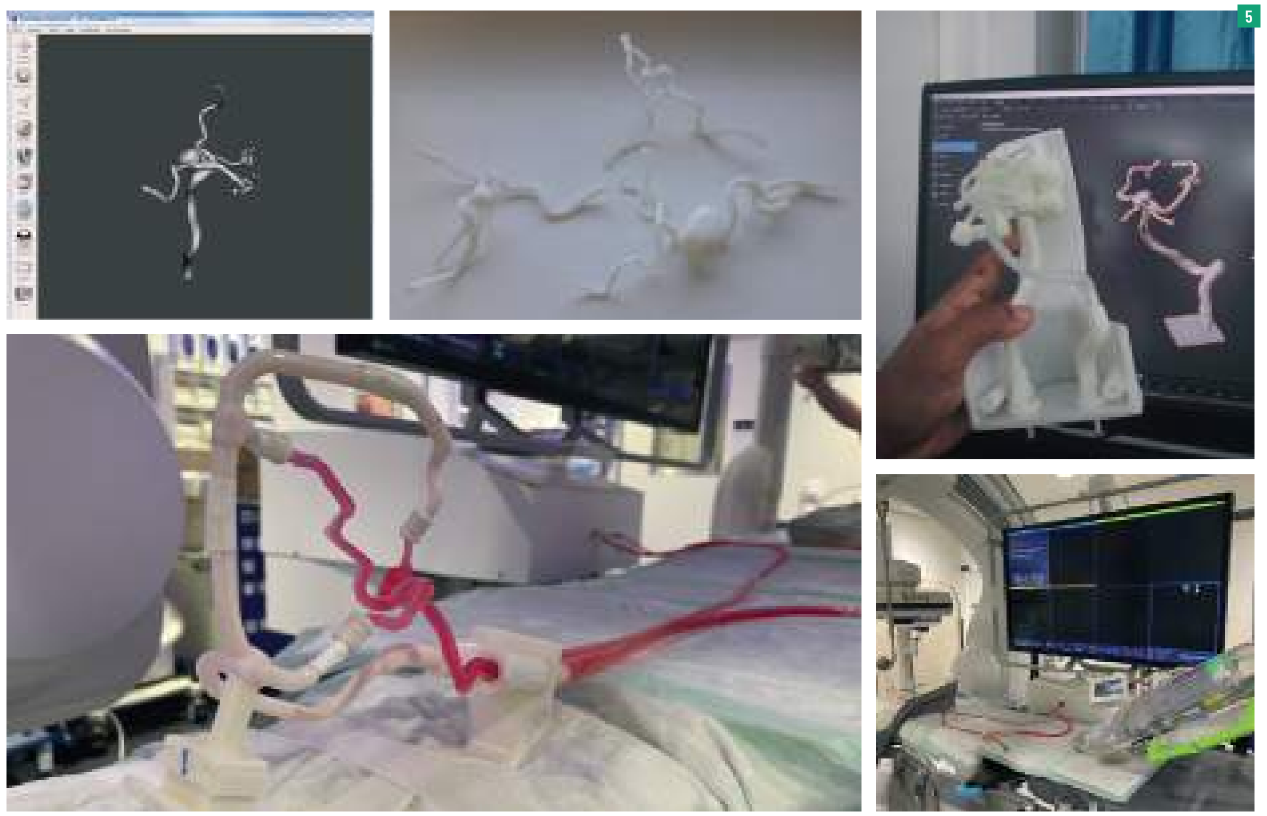
2 Flat panel CT 3D volume reconstruction, maximum intensity projection (MIP), and multiplanar reconstruction of the same thrombus. Note the typical appearance of the opacified thrombus with thrombus material inside and outside in relation to the stent struts.




3 MR images and corresponding DSA of standard platinum coils (upper row) and polymeric coils (lower row) in-vitro. Less magnetic field distortion and artefact production are seen with polymeric coils.




4 DSA demonstrating the aneurysm model in the rabbit (A). Post-treatment DSA and 3D rotational angiography (B, C) showing complete occlusion of the aneurysm. Note the persisting beam hardening artefact on CT (D). MR images demonstrating visibility of individual coil loops (E) and lack of intra-aneurysmal flow (F).



Developmental process of cerebral aneurysm models using additive manufacturing techniques (3D printing) based on patient-specific 3D imaging data sets for robotic-assisted neurointerventional procedures.

**Selected Publications**

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# Magnetic Resonance Methodology / DIN-DBMR


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### Research Profile

Magnetic resonance imaging (MRI) and spectroscopy (MRS) are powerful and extremely versatile methods for non-invasive studies and diagnostic examinations in humans. Our group is using MRI and MRS methods in close collaboration with clinical partners primarily in prospective studies of different organs. We also develop novel methods to suit pertinent needs to study physiology and pathology, together with the underlying mechanisms, in situ. Currently most MRI and MRS studies are performed in brain, kidney, muscle, liver, and heart, where the 3T and the high-field 7T scanners of the translational imaging center at sitem-insel are used. In addition, high-resolution NMR studies are performed on biopsies, cell cultures, and body fluids in close collaboration with the Clinical Chemistry of the Inselspital and with numerous clinical and pre-clinical partners. The studies aim to detect metabolic disease biomarkers and improved physiological comprehension.

### Methodology for MR spectroscopy

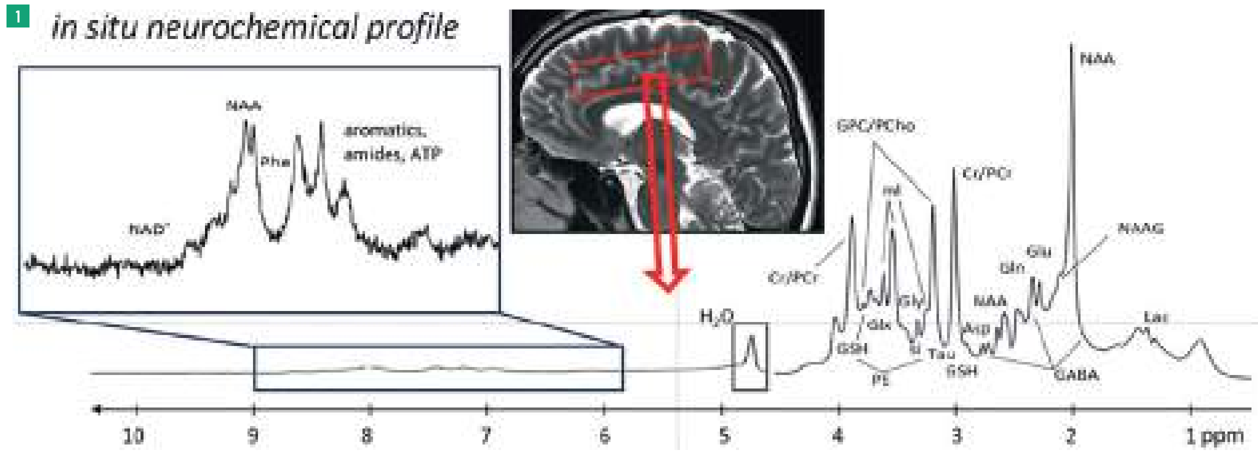
In the framework of SNF grants and a European Innovative Training network (inspire-med), MR spectroscopy methods and synergistic post-processing tools are developed that are tailored to the observation of brain metabolism, yet are also transferable to other organs. In collaboration with other Swiss and European centers, novel methods are developed, e.g. to study exchange processes between amide protons and water in human brain. Diffusion properties of brain metabolites are investigated with dedicated methodology to investigate brain, muscle, and prostate microstructure. For post-processing and quantification, traditional modeling and novel machine learning methods, including neural networks, are developed, where quantification and limits in terms of accuracy and robustness are at the center of attention. Among the directly targeted applications are metabolic diseases, like phenylketonuria, but also physiologic phenomena, such as metabolic alterations occurring in the normal course of a day or in sleep. 1

### Metabolic imaging to study glucose and lipid metabolism

Further work is aimed at the methodology for metabolic imaging of glucose metabolism in the liver and lipid storage and turnover in muscle, heart, liver, and kidney. Glucose turnover and integration into glycogen is studied at 7T, using the novel tool of deuterium metabolic imaging in combination with carbon spectroscopy. 2



1




### Renal function and potassium homeostasis

Renal function in native and transplanted kidneys has been investigated by multi-modal MRI and MRS. The functional MR modalities such as diffusion weighted imaging, arterial spin labelling, and oxygen- dependent MRI differ in terms of sensitivity for cortical or medullary renal tissue and in their assessed determinants. In collaboration with the Nephrology Department, we aim at a better perception of the physiologic basis behind functional MR parameters and why they may be changed in renal disease. Recently, in collaboration with Siemens, an improved method for respiratory-triggered diffusion has been developed and evaluated. In clinical studies fMRI measurements were performed for the Bernese renal biopsy registry, and the impact of functional kinking of iliac arteries on perfusion and oxygenation was investigated.

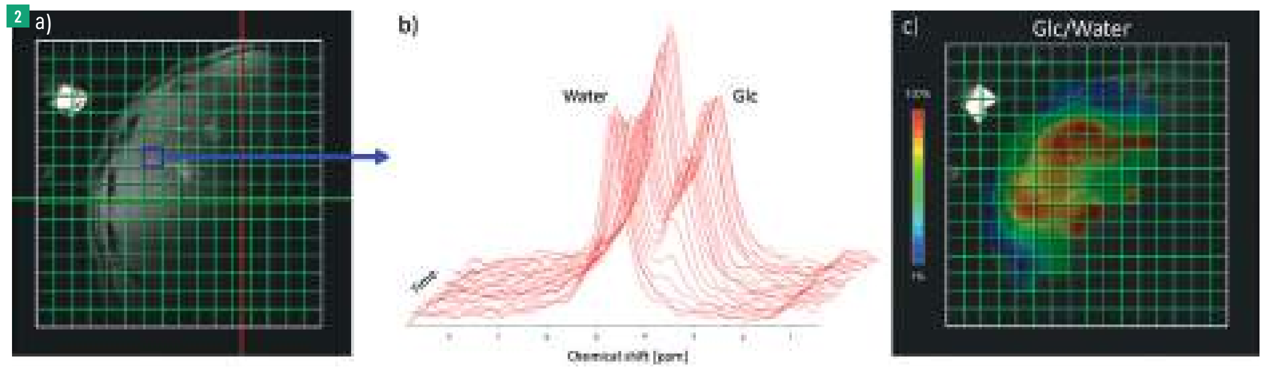
Funded by a sitem-insel Support Fund and in collaboration with the Nephrology we are currently setting up studies for localized non-invasive in vivo determination of potassium by $^{39}$K MRI and MRS on the 7T MR Scanner. Low potassium intake associates with cardiovascular disease and mortality, while beneficial effects of higher potassium intake have been demonstrated. By using $^{39}$K MRI for the first time, a non-invasive method for investigating K+ ion homeostasis in humans becomes possible.

### High-Resolution Magic Angle Spinning NMR

High-resolution magic angle spinning (HR-MAS) NMR techniques were applied to correlate in vivo and in vitro NMR spectra of tissues but also from cell cultures and body fluids.

Several HR-MAS studies have been performed on biopsies as well as on cell cultures and analyzed by "metabonomical" methods. Funded by an SNF Grant, special emphasis is on investigation of OXPHOS deficient fibroblasts for separating different defect subgroups. In collaboration with the vendor Bruker, we established a perfused bioreactor system within the NMR spectrometer and performed feasibility measurements of living 3D cell cultures inside the NMR with changing conditions monitoring consequent metabolic and oxygenation cell responses. 3

2




Spectra and liver maps of deuterated glucose and water when evaluating hepatic glucose metabolism after oral intake of deuterated glucose (Glc)

3

Bioreactor for online Metabolomics of living cells inside the NMR.

### Selected Publications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**[2]** Dziadosz M., et al. (2020). Non-water-excitation MR spectroscopy techniques to explore exchanging protons in human brain at 3 T. Magn Reson Med 84:235.

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# Medical Radiation Physics

## Division of Medical Radiation Physics within Department of Radiation Oncology


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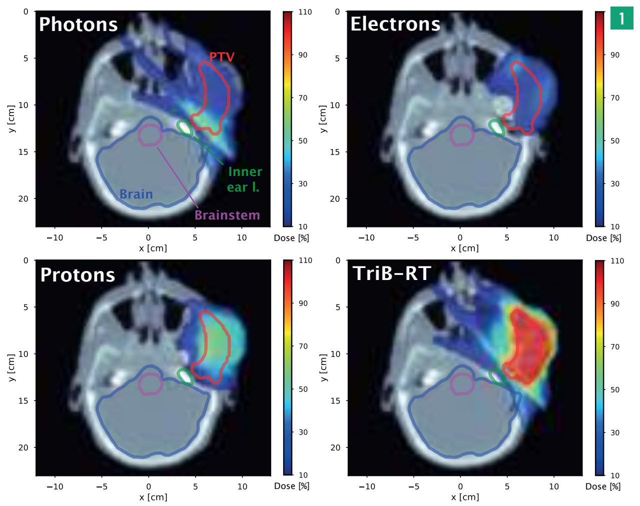



Dose contributions of photons, electrons, and protons resulting in the total TriB-RT dose distribution.

### Research Profile

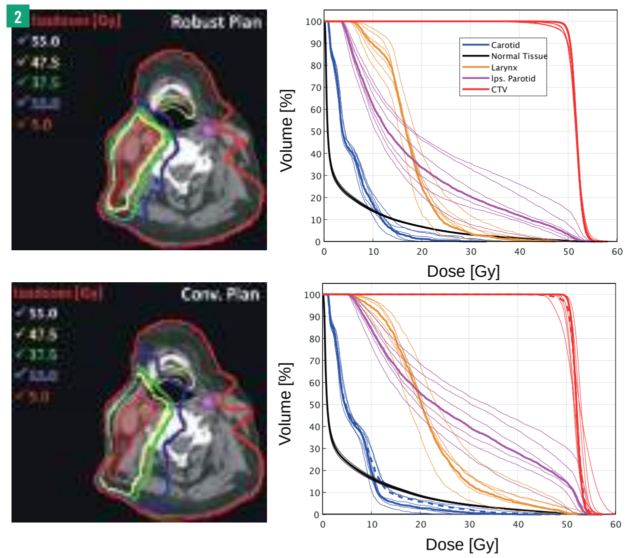
The Division of Medical Radiation Physics is part of the Department of Radiation Oncology and is active in clinical services as well as research projects and education. Medical physics is an interdisciplinary field that combines physics with medicine. Traditionally, medical physics is related to medical radiation physics and addresses aspects like dosimetry, treatment planning, quality assurance, and radiation protection. In addition to the implementation of new methods in radiation therapy, the research activities are covering more fundamental research in medical radiation physics. To accomplish the high accuracy needed in radiation therapy, sophisticated methods must be established and validated before use in clinical routine. The research performed at our division has not only proven to be of interest on a national and international level, but has also been applied to commercial products and clinical applications.

### Triple Beam Radiotherapy (TriB-RT)

Recently, our group developed a novel treatment planning process enabling the simultaneous optimization of modulated photon, electron, and proton beams for improved treatment plan quality in radiotherapy by means of benefitting from the different dosimetric characteristics of the three particle types. The framework is based on highly accurate dose calculation using Monte Carlo simulations. Dosimetric comparisons to currently available treatment techniques reveal the potential of TriB-RT. It is especially promising for cost-effective, single-room proton solutions with a fixed beamline in combination with a conventional linac delivering photon and electron fields. 1

### Robustness Assessment and Robust Optimization

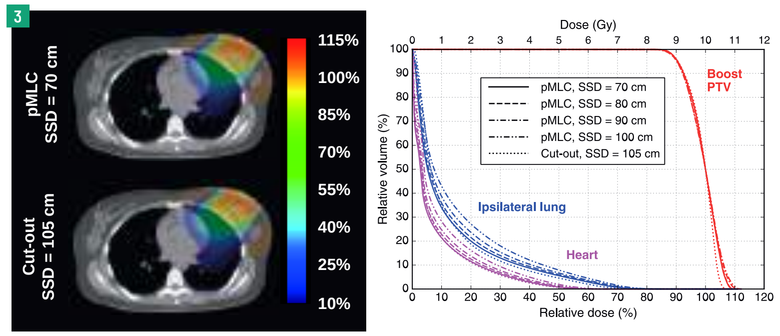
Robust assessment and robust optimization are important aspects in radiotherapy treatment planning as, for example, for mixed beam radiotherapy. This technique combines intensity-modulated photon beams with intensity- and energy-modulated electron beams. A robust optimization method was developed and experimentally verified. Robust optimized treatment plans were compared with conventional generated plans demonstrating that robust optimization is a promising alternative approach for mixed beam radiotherapy. 2




Isodose distributions for a robust and conventional treatment plan with dose volume histograms for different setup scenarios.

### Photon Multi Leaf Collimator (MLC) Based Electron Beam Treatment Techniques

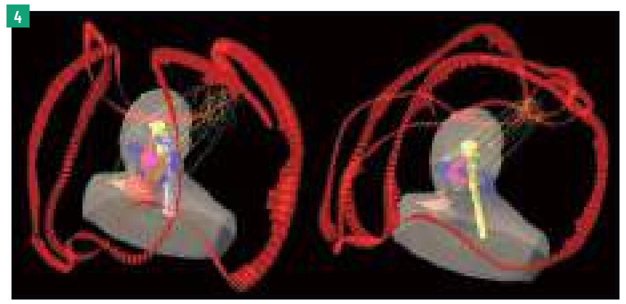
Currently, electron beam treatments are delivered using dedicated applicators with standard or patient-specific cut-outs. This is associated with several disadvantages such as time-consuming fabrication of cut-outs involving toxic materials or a cumbersome and inefficient workflow regarding treatment planning as well as delivery. Over the last few years, our research activities aimed to overcome these limitations by replacing the applicator and cut-outs by the photon multileaf collimator to shape the electron beam. This leads to a more efficient delivery for standard electron beams and prepares the floor for more advanced mixed photon and electron treatment techniques. 3




Dose distribution (left) and Dose Volume Histograms (right) of a 18 MeV electron treatment plan created for a left breast boost case.

### Dynamic Trajectory Radiotherapy (DTRT)

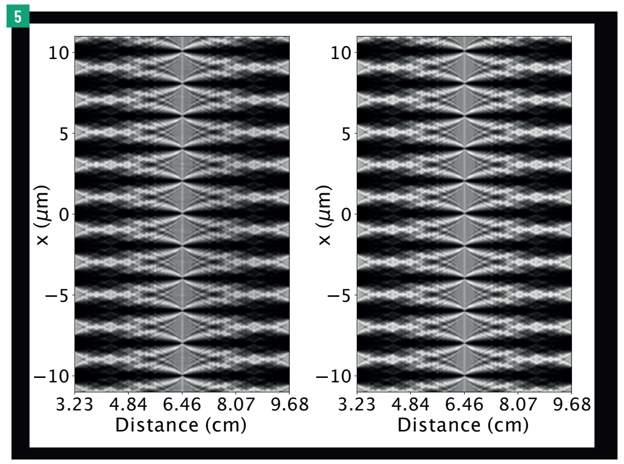
One of our main research activities addresses the potential benefit of non-coplanar beam arrangements compared to volumetric modulated arc therapy (VMAT) for various treatment sites. Dynamic trajectory radiotherapy (DTRT) is an approach that extends VMAT with collimator rotation as well as dynamic table translations and rotation for selecting beam incidences along a continuous path. For such non-isocentric DTRT techniques, a treatment planning process was developed. A potential application of these DTRT techniques could be the treatment of head and neck cancer patients for which many organs at risk have to be considered. 4




Visualization of the highly non-coplanar dynamic trajectories for two different head and neck cases.

### Monte Carlo Simulation of X-ray Grating Interferometry

Phase-sensitive X-ray imaging techniques provide complementary contrasts in addition to absorption contrast used in conventional X-ray imaging. To understand the principles and limitations of this new imaging modality, it is important to establish virtual simulation frameworks. However, traditional simulation techniques such as wave optics methods and Monte Carlo particle transport fail to model both interference and inelastic scattering phenomena simultaneously. Therefore, we developed a new semi-classical Monte Carlo algorithm for efficient and simultaneous modelling of scattering and interference processes. 5




Talbot carpets obtained with Monte Carlo (left) and wave propagator (right) on the detector position x as a function of distance to the grating.

### Selected Publications

[1] R. Kueng, S. Mueller, H.A. Loebner, D. Frei, W. Volken, D.M. Aebersold, M.F.M. Stampanoni, M.K. Fix, P. Manser (2021). TriB-RT: Simultaneous optimization of photon, electron and proton beams. Phys. Med. Biol. 66:045006, 16pp.

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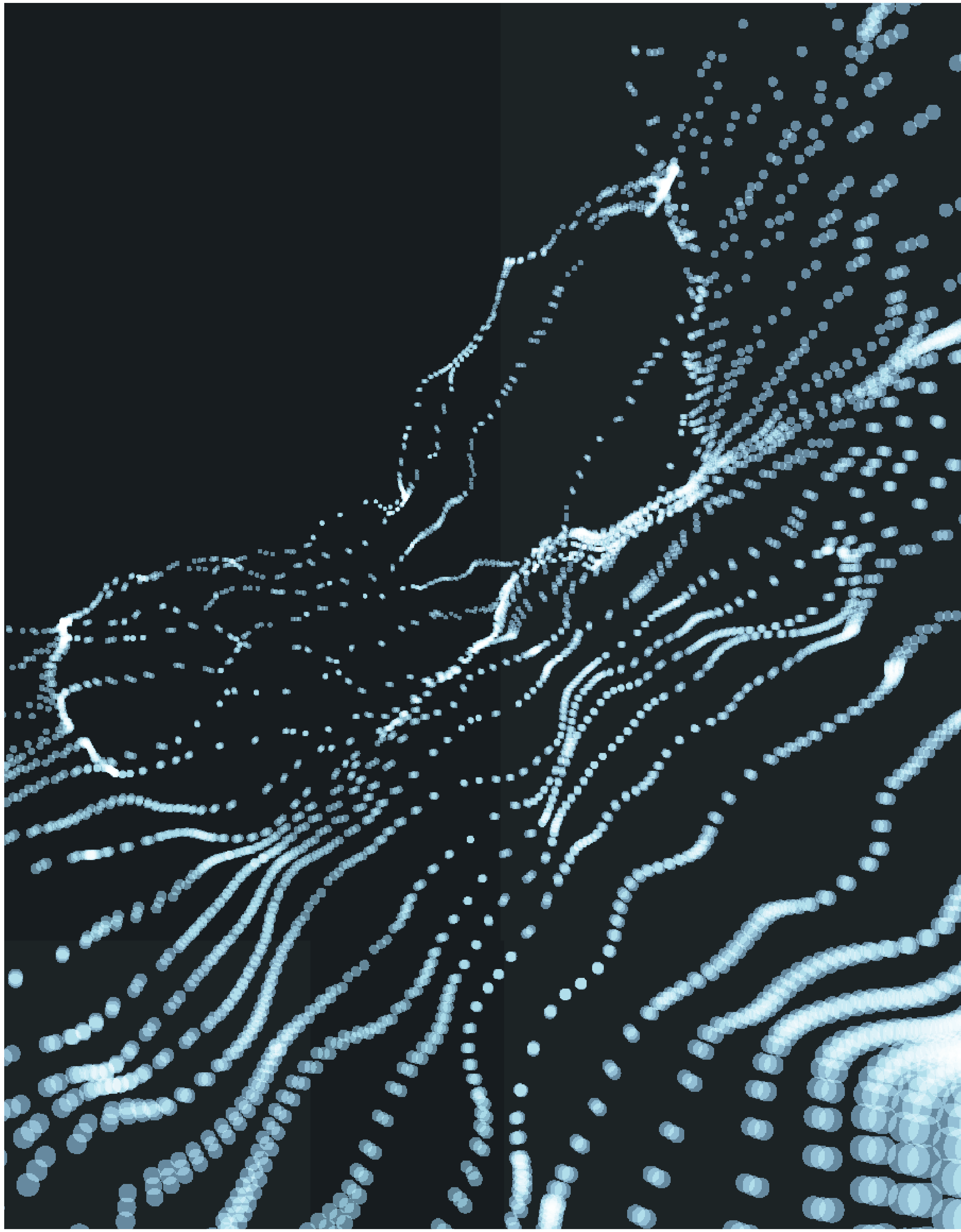
[5] S. Tessarini, M.K. Fix, P. Manser, W. Volken, D. Frei, L. Mercolli, M. Stampanoni (2022). Semi-classical Monte Carlo algorithm for the simulation of X-ray grating interferometry. Sci. Rep. 12(1):2485.



# Department of Neurosurgery

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**Research Profile**

Our aim is the improvement of our patients` quality of life and survival. Our research focus is the improvement of surgical procedures, with special attention to highly translational or clinical problems. We collaborate intensively with medical technologies partners, both regionally and internationally. Our main research areas include deep brain stimulation, tumor resection, function monitoring, robotics, and an academic software suite.

**Ability Academic Software Suite**

Another main research project is the development of a personal learning environment. This new software will help physicians master the vast amount of medical information into valuable medical knowledge. It will enable users to search, find, catalog, process, and study documents that are of long-term interest. In clinical practice, it is common to encounter a range of valuable medical information from different sources, such as textbooks, images, PDFs, journal articles, etc. The software will allow users to cope with any such source. Medical knowledge is built-up layer by layer over the course of a career, beginning in the medical course, through residency and subspecialty training, and even as a consultant the knowledge is ever expanding. In most subjects, this knowledge needs to be available long term. In current practice, physicians either create a physical library of textbooks, hardcopy journals, and printed PDFs or increasingly build a digital archive. Both, however, fail with time because of an ever-increasing volume of documents. There is also a need to share documents and comments between colleagues within such a system. Our aim is to provide a solution that is suitable for most medical subspecialties. Further applications may be found in life sciences and researchers in general.

**Towards Intelligent Sensor-enhanced Neurosurgery**

The malpositioning of pedicle screws is a common problem that can cause neurologic and vascular damage or result in non-fusion of the instrumented spine segment. A malpositioning rate of up to 15% is known from the literature. Using intraoperative navigation, the rate of misplaced screws could be lowered but remains a problem in spinal fusion surgery. Together with the ARTORG, we are addressing this challenge by an intelligent robotic system. By using the complexity of vertebral anatomy like a "sensor map," the robotic drill is able to "feel" across the bone terrain and together with so-called electromyography (EMG) neuro monitoring can avoid obstacles, including nerves and boundaries of the bone. Thicker bone, thinner bone, and nerves are sensed with super-human, robotic perception and verified at high speed with the relevant information from the CT-imaging information that was established before the procedure. This way the surgical robotic technology potentially allows the neurosurgeon to place pedicle screws perfectly and with precision in every patient, every time. The aim of this project is to introduce this augmented, robotic technology into the clinic and begin the process of clinical adoption of the next generation of neurosurgical interventions. Another field of application will be the self-sensed robotic implantation of epilepsy electrodes for SEEG. 1



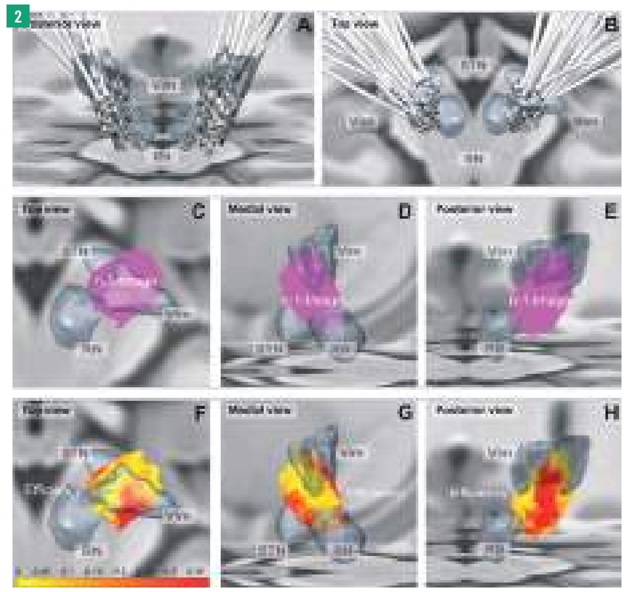
1

Laboratory set-up of spine model and robotic arm with attached high-speed drill for high-precision drilling through the pedicle of the targeted vertebral body.

**HORAO – Intra-operative Visualisation of Cerebral Fibre Tracts**

The two major challenges in neuro-oncological surgery are the differentiation between tumorous and healthy tissue and the identification and localization of specific neurological functions during surgery. In search of a new, innovative approach to overcome these challenges, neurosurgeons at Inselspital explored new ways of science. The HORAO project started with a crowdfunding challenge followed by a subsequent crowdsourcing global competition in search of an out-of-the-box innovation. The competition led to a series of new ideas, and ultimately to a collaboration with the Laboratoire de physique des interfaces et couches minces at the Ecole Polytéchnique of Paris. The new conjoint research team successfully tested a solution based on Mueller Polarimetrie in a series of experiments and was awarded a research prize by an industry leader in medical technology, as well as an extensive four-year SINERGIA Grant by the Swiss National Science Foundation (SNSF). The HORAO consortium – led by Prof. Schucht (Neurosurgery) and consisting of the LPICM in Paris as well as the Departments of Neurosurgery and Neuropathology and the SCAN Lab at Inselspital – is currently performing experiments on a new prototype in the near-in-vivo Translational Lab at Inselspital, followed by advanced neuropathology analyses and machine-learning post-processing of polarimetric data. The ultimate goal is the full integration of MP-based real-time tractography and tumor identification into the microsurgical workflow. 2

2

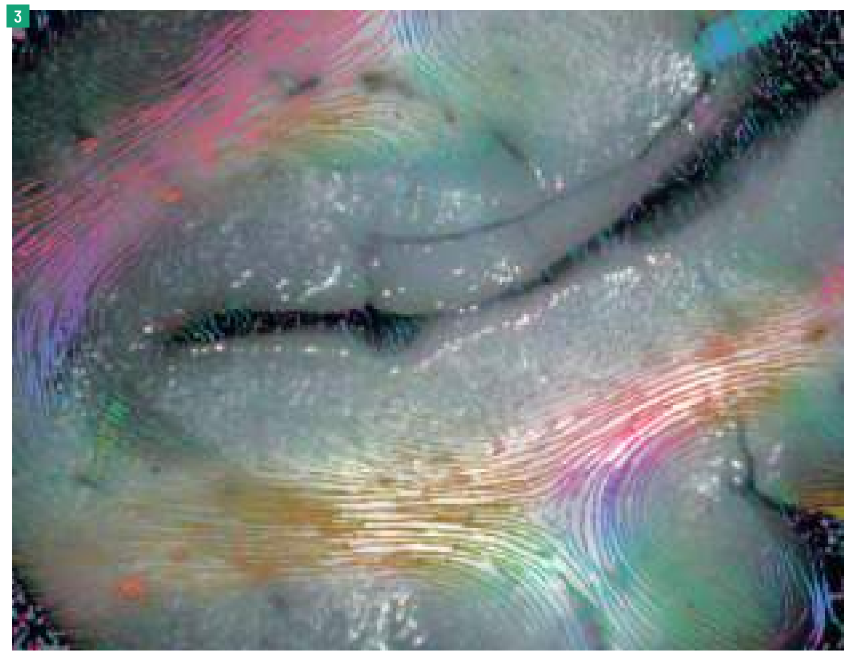


Group representation of 236 implanted DBS electrodes in the area of the motor thalamus (A), the modeled stimulated nerve tissue (pink) of the entire reconstructed patient cohort from different views (B,C,E), as well as the corresponding clinically weighted stimulation area, with areas marked in red with are associated with a better clinical effect than areas marked in yellow (F,G,H).

**Probabilistic Mapping in Deep Brain Stimulation for Movement Disorders**

The Department of Neurosurgery (Prof. Claudio Pollo, Dr Andreas Nowacki), the ARTORG Center for Biomedical Engineering Research (Dr Khoa Nguyen, Alba Segura Amil), and the Center for Movement Disorders (Prof. Paul Krack) are pooling their expertise in neurosurgery, machine-learning, and neurology to improve and facilitate the application of deep brain stimulation (DBS) as a therapy for movement disorders and neuro-psychiatric diseases. One current focus of our department is the development of probabilistic stimulation maps. These maps identify effective stimulation regions, which help the surgeons place segmented DBS leads. The neurologist can then leverage these maps to steer stimulation specifically towards effective regions, while avoiding regions that are likely to evoke side effects. This concept was first established and published in Parkinson`s disease and later applied to essential tremor. These maps are based on large clinical datasets from different European centers. Stimulation parameters and the corresponding clinical efficacy are combined with the anatomical information about the position of the stimulating electrodes and with computer simulations of the activated tissue. Large data-sets are analysed group-wise by applying complex voxel-wise statistics to yield a probabilistic stimulation map with a stimulation "sweet spot" as illustrated below. Cross-validation of the data confirms the principal predictive value of such a map to predict effective stimulation parameters and the degree of postoperative stimulation success in individual patients. 3

3



Intra-operative Mueller Polarimetry in reflection configuration reveals fibre tracts on a human brain specimen non-invasively.

#### 4D-Simulator Breakthrough in Brain Surgery

Aneurysm operations in the brain rank among the most delicate procedures in neurosurgery. The highest demands are placed on surgeons when choosing the type of intervention, planning the route, and carrying out extremely delicate procedures on the blood vessel.

A team of specialists from both the Departments of Neurosurgery at Inselspital (led by PD Dr. med. David Bervini) and the ARTORG Center of the University of Bern has developed an award-winning 4D simulator technology dedicated to the training of neurosurgical clipping (clamping the aneurysm). The simulator reproduces the visual and haptic experience of the procedure based on three-dimensional realistic replicas of skull, brain, and blood vessels of the patient's anatomy. In the simulator, the specialists find the precise 1:1 situation that will arise later in the real surgery. This extension to 4D physical simulation is unique worldwide. It accurately models the blood vessels, pulse, blood flow, and the temporal aspects of the procedure. Due to the enhanced planning and pre-op practice, risks of complications should be reduced rigorously. The 4D simulator also offers new dimensions in the education and training of neurosurgical and neuroradiological specialists, providing valuable experience by training on the 4D simulator both during their residency training for the specialist title and during subsequent in-depth courses for specialists. 4

The 4D simulator project has been supported by Innosuisse- Schweizerische Agentur für Innovationsförderung, the Swiss Heart Foundation and was awarded with the Ypsomed Innovation prize (1st prize 2021).

#### Neurophysiological Warning Criteria in Supratentorial Surgery

The resection of supratentorial tumors may be associated with functional morbidity. Postoperative functional deficits might be caused by different patterns of injury. During surgery involving the insula, deficits are frequently caused by ischemic insult rather than mechanical injuries of the fiber tracts. During surgery in the paracentral region and close to the posterior limb of the internal capsule direct mechanical injury to the motor cortex (M1) and the corticospinal tract (CST) may be of major concern. Subcortical mapping techniques may allow for estimating the distance to the CST, thus providing functional guidance during tumor resection. Therefore, motor preservation requires both mapping of the M1 and the CST and continuous monitoring by motor evoked potential (MEP) recordings.

Neurophysiological warning criteria are essential to provide surgical guidance. In this project, the intra-operative electrophysiology team at Inselspital, led by Prof. Dr. med. Kathleen Seidel, sought to provide a comprehensive overview of the available evidence on MEP warning criteria in supratentorial surgery. To this, we used the emerging framework of a scoping review and visualized the data extracted from 68 heterogeneous studies. Collectively, MEPs perform well as diagnostic and surrogate biomarkers.

A rigorous quantitative evidence synthesis in the future necessitates consensus for definitions and a standardized terminology. This will facilitate training machine-learning models and applying artificial intelligence algorithms. A future strong collaboration between the department of Neurosurgery and the Bern Biomedical Engineering Network is essential. 5

4

4D patient-specific neurosurgical simulator platform.



#### Selected Publications

**[1]** Nowacki, Andreas; Barlatey, Sabry; Al-Fatly, Bassam; Dembek, Till; Bot, Maarten; Green, Alexander L; Kübler, Dorothee; Lachenmayer, M. Lenard; Debove, Ines; Segura-Amil, Alba; Horn, Andreas; Visser-Vandewalle, Veerle; Schuurman, Rick; Barbe, Michael; Aziz, Tipu Z; Kühn, Andrea A; Nguyen, T A Khoa; Pollo, Claudio (2022). Probabilistic mapping reveals optimal stimulation site in essential tremor. (Im Druck). Annals of neurology Wiley-Blackwell 10.1002/ana.26324.

**[2]** Schucht, Philippe; Lee, Hee Ryung; Mezouar, Mohammed Hachem; Hewer, Ekkehard; Raabe, Andreas; Murek, Michael; Zubak, Irena; Goldberg, Johannes; Kovari, Eniko; Pierangelo, Angelo; Novikova, Tatiana (2020). Visualization of White Matter Fiber Tracts of Brain Tissue Sections with Wide-field Imaging Mueller Polarimetry. IEEE transactions on medical imaging, 39(12), S. 4376–4382. Institute of Electrical and Electronics Engineers IEEE 10.1109/TMI.2020.3018439.

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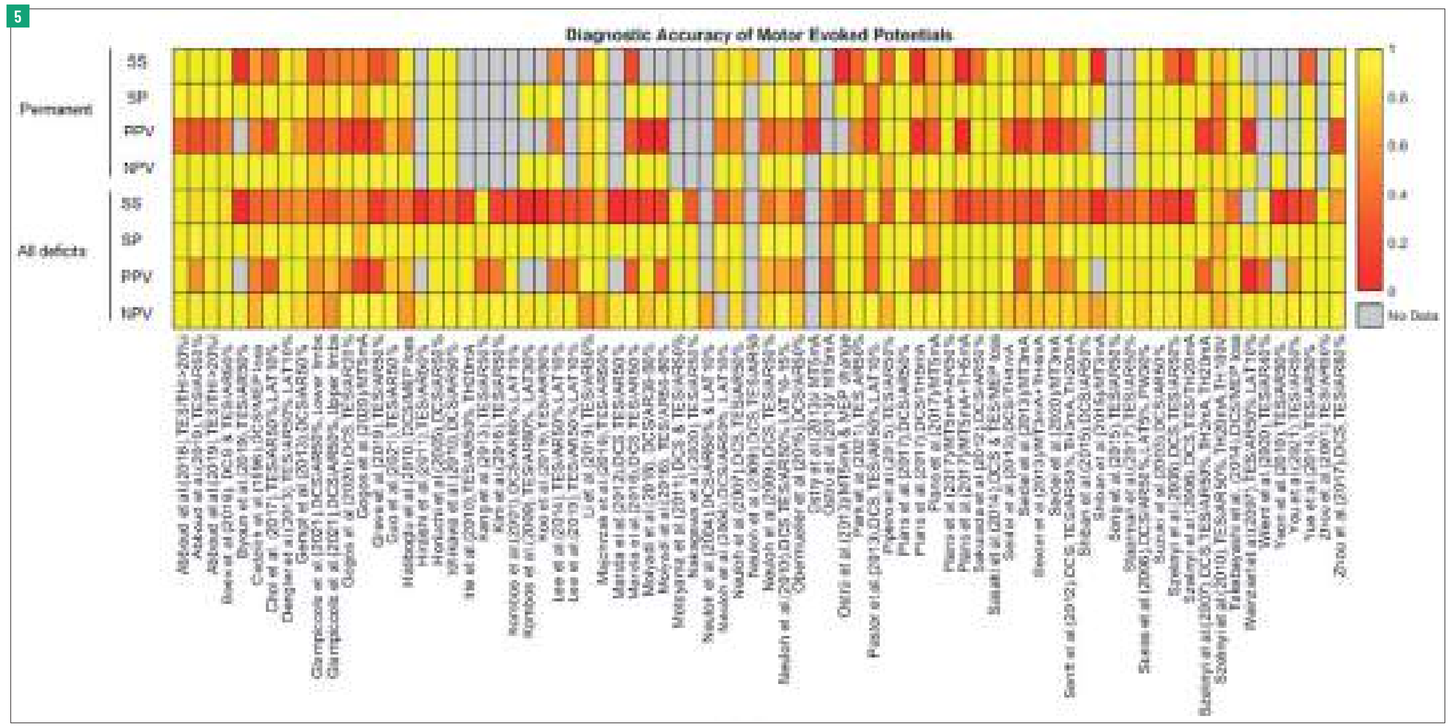


Heat map. Diagnostic accuracy analysis of the 68 included studies. In general, specificity and NPV among various studies were high. That indicates that MEPs can reliably identify the true negative cases. Sensitivity and PPV varied across studies. However, the low and modest values are impacted by the low prevalence of reported motor deficits.

# Department of Nuclear Medicine

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### Research Profile

The nuclear medicine group aims to develop novel techniques to improve diagnosis and therapy in the setting of nuclear medicine. This theme encompasses several research focuses, including instrumentation, reconstruction, quantitative analysis, computer-aided diagnosis, dosimetry, and treatment planning. As artificial intelligence (AI) becomes increasingly valuable in different medical applications, achieving equal or even superior performance compared to human experts, its integration in clinical practice is desirable and one of the group's goals. The development of new image analysis methods employing artificial intelligence, simulation, or modelling and optimization, promises to unify imaging, physiology, and therapy for the personalized practice of nuclear medicine. The group's research portfolio has two main points of focus. The first is to optimize the nuclear medicine imaging for support of patient management at several clinics, including neurology, surgery, urology, and radiation oncology. The second is to improve treatment outcomes of targeted radionuclide therapy in several diseases, including neuroendocrine cancer and prostate cancer. The group cooperates with local, national, and international partners in medicine, neuroscience, and biomedical engineering and is intensively developing artificial intelligence methods for applications such as the early differential diagnosis of parkinsonism, pancreatic cancer, and lung lymph nodes. Oncology efforts target tumor lesion detection and segmentation, radiotherapy dose reduction, cross-protocol harmonization, image synthesis, and dosimetry prediction.

### Early Parkinson's Disease Diagnosis

Differential Diagnosis of Parkinsonism Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by a



triad of motor symptoms: rigidity, tremor, and bradykinesia. Very similar clinical signs can appear in atypical parkinsonian syndromes, including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). The early differential diagnosis is essential for selection of disease-modifying treatment strategies and to achieve the best possible outcome for these patients. The research group has a long history in molecular imaging of PD and has developed deep learning methods for differential diagnosis of parkinsonian syndromes. In collaboration with PET Center of Huashan Hospital, we established a 3D convolutional neural network (CNN) developed on FDG PET images of more than a 1,000 patient with parkinsonism and more that 800 without parkinsonism, for parkinsonism differential diagnosis. The network achieved sensitivities of 98.1 %, 88.5 %, and 84.5 %, and specificities of 90.0 %, 99.2%, and 97.8% for the early diagnosis of PD, MSA, and PSP in a blind test.

As the final goal is to achieve a differential diagnosis as soon as possible, we are currently trying to extrapolate the potential of this network to early stages. As rapid eye movement (REM) sleep behavior disorder (RBD) is considered a prodromal stage of synucleinopathies such as PD and MSA, a longitudinal RBD FDG PET imaging database was established to study the potential of deep learning in predicting disease conversion in these patients. For this purpose, the previous network was adapted to derive deep metabolic imaging (DMI) indices, which were used to determine predictive scores of longitudinal RBD data. Differences in baseline DMI indices of converted and non-converted RBD patients were assessed. The preliminary results show feasibility of the development of AI technologies for early RBD phenotype conversion. Further network improvements will be attempted with a larger RBD database. 1

### Trajectory Inference of Tau Pathology in Alzheimer's Disease

Neurofbrillary tangles (NFTs) are one of the key pathophysiologic features of Alzheimer's disease (AD). NFTs are formed by the hyperphosphorylation and abnormal aggregation of tau protein. The abnormal tau pathology is related to cognitive dysfunction, and it predicts longitudinal change in neuronal loss. Therefore, the degree of tau pathology is important to understanding disease progression and may be reflective of clinical severity. Studies revealed that abnormal deposition of tau spreads in a specific spatial pattern, namely Braak stage. However, Braak staging is based on post mortem brains, each of which represents the cross section of the tau trajectory in disease progression, and numerous studies were reported that do not conform to that model. This study thus aimed to identify the tau trajectory and quantify the tau progression in a data-driven approach with the continuous latent space learned by variational autoencoder (VAE). [18F]Flortaucipir PET images were collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. VAE was built to compress the hidden features from tau images in latent space. Hierarchical agglomerative clustering and minimum spanning tree (MST) were applied to organize the features and calibrate them to the tau progression, thus deriving pseudo-time.

The image-level tau trajectory was inferred by continuously sampling across the calibrated latent features. We assessed the pseudo-time with regard to tau standardized uptake value ratio (SUVr) in AD-vulnerable regions, amyloid deposit, glucose metabolism, cognitive scores, and clinical diagnosis. The spatiotemporal trajectory of tau progression inferred in this study was consistent with Braak staging. According to the derived pseudo-time, tau first deposits in the parahippocampal and amygdala, and then spreads to the fusiform, inferior temporal lobe, and posterior cingulate. The profile of other biomarkers in disease progression agreed well with previous findings. We addressed that this approach additionally has the potential to quantify tau progression as a continuous variable by taking a whole-brain tau image into account. 2

### Treatment Planning for Targeted Radionuclide Therapy

The emerging technique of targeted radionuclide therapy (RLT) offers an effective treatment strategy for several advanced cancers, including metastatic castration-resistant prostate cancer (mCRPC) and neuroendocrine tumor. However, concerns of dose effects and risks have also been raised. The individualization of the internal radiation dose is becoming a growing interest for novel radiotracers in nuclear medicine research. Meanwhile, the European council mandates that treatments should be planned according to the radiation doses delivered to individual patients. The lack

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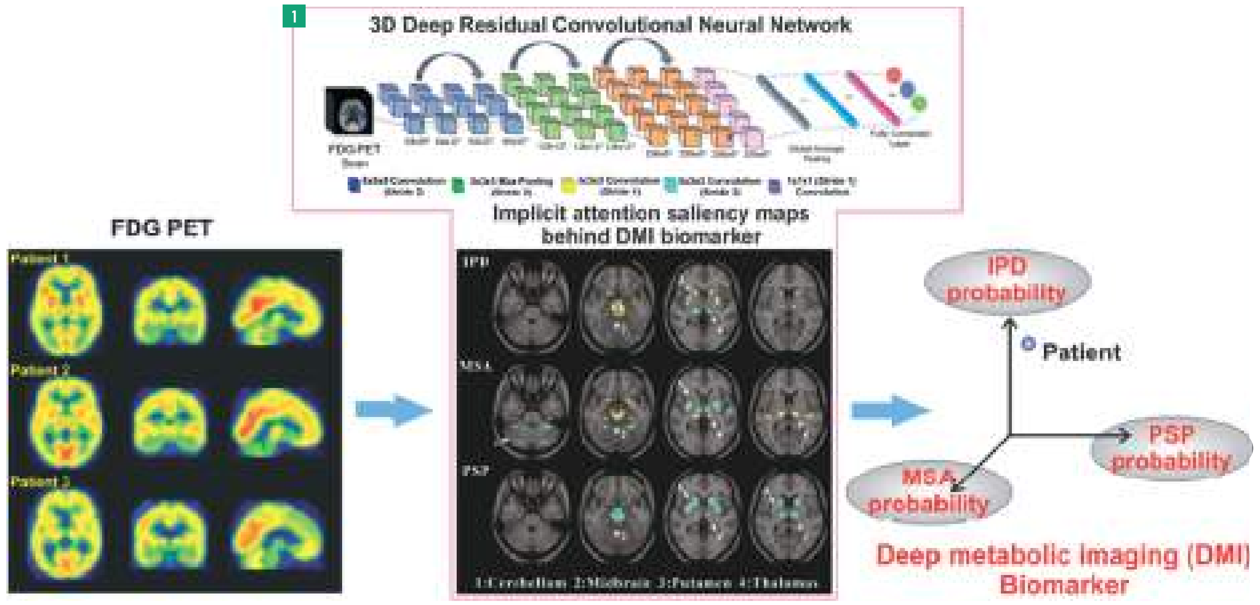
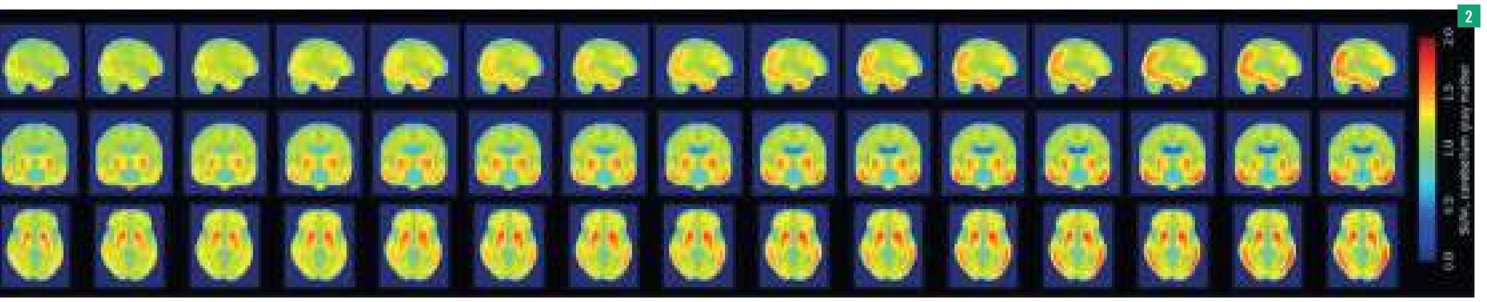



A database including parkinsonian patients and non-parkinsonian subjects with 18F-FDG PET images was established to support development of a 3D deep convolutional neural network for extraction of a deep metabolic imaging (DMI) biomarker



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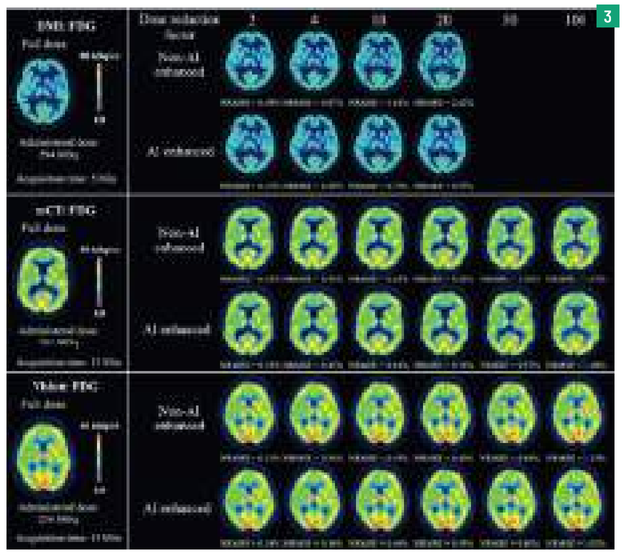


Example of test results of [18F] FDG imaging from DMI (GE Discovery MI), mCT (Siemens, Biograph mCT), and Vision (Siemens, Biograph Vision)

of accepted methods to characterize the tumor burden and predict the dosimetry before RLT hampers the realization of treatment planning. For the first time, we have developed a deep learning method, so called deep supervised residual U-Net, to detect and segment automatically prostate cancer lesions on PSMA imaging. This enables the characterization of a high number of lesions of heterogeneous size and uptake distributing in a variety of anatomical contexts with different background radioactivity. Furthermore, the group proposed a deep learning method for voxel-wise prediction of post-therapy dosimetry from pre-therapy PET images. As the accuracy is still less satisfactory due to limited data, a physiologically based pharmacokinetic (PBPK) model was integrated in the pretraining of the deep learning methods to improve the prediction.

A second research focus is to study the feasibility of individual estimation of post-therapy dosimetry for 177Lu-PSMA I&T therapy. It is still debatable whether individualized dose should be applied for the emerging PSMA-targeted RLT. A critical consideration in this debate is the necessity and feasibility of individual estimation of post-therapy dosimetry before the treatment. With this project, the group proved the concept of individual dosimetry prediction based on pre-therapy imaging and laboratory measurements.

These developments provide the potential to individualize the treatment and to maximize the theranostic benefit for targeted radionuclide therapy.

**Imaging Dose Optimization in Nuclear Medicine**

One of the group's interests is to develop tools to achieve CT-free PET imaging. AI has been proposed to replace CT-based PET attenuation correction, although concerns regarding the robustness of AI methods have been raised. The group employed a simple way to integrate domain knowledge in deep learning for CT-free PET imaging. One final topic is to develop a cross-scanner and cross-tracer deep learning method for the recovery of standard-dose imaging quality from low-dose PET. A critical bottleneck for the credibility of AI is replicating the results in the diversity of clinical practice. Thus, the group developed an AI method that can be independently applied to recover high-quality imaging from low-dose scans on different scanners and tracers. 3

**Cellular Nuclear Medicine Imaging System**

The group is also active in the development of cellular nuclear medicine imaging systems. Conventional molecular imaging measures tracer uptake in living organs. As an alternative, we have built a continuously infused microfluidic radioassay (CIMR) system, which enables real-time measurement of the dynamic cellular uptake of tracers, with the estimation of cellular pharmacokinetics. The CIMR system consists of a high-sensitivity positron emission detector positioned about the chamber holding the microfluidic slides. Perfusion medium containing tracer flows continuously into the cell chamber, while simultaneous measurement of a reference medium chamber avoids the calibration errors. By employing valid cellular compartmental models, the cellular pharmacokinetics of the tracer is robustly estimated from high-quality, real-time measurements. Our instrument was tested relative to mRNA expression of relevant enzymes using RT-PCR. Estimated ex-vivo kinetic parameters were also consistent with literature values of kinetic parameters in vivo for cancer patients. The reproducibility, stability, and capability of the CIMR system for capturing pharmacokinetic parameters constitute a valuable tool for theranostic research.

**Development of an On-Chip PET System**

Organs-on-Chips (OOCs) are micro devices mimicking in-vivo organs that find growing applications in disease modeling and drug discovery. With the growing number of uses comes a strong demand for imaging capabilities of OOCs as monitoring physiologic processes within OOCs is vital for the continuous improvement of this technology. PET would be ideal for OOC imaging due to its ability to retrieve in-vivo information about metabolism and molecular pathways. However, current imaging devices for measuring PET tracer uptake in either small animals or cell cultures are inadequate for the task of OOC imaging due to their limited spatial resolution. The group is currently developing an On-Chip PET system to make functional imaging of OOCs possible. We have optimized the design of the proposed system with a Monte Carlo simulation (MCS) and achieved a spatial resolution of 0.55 mm using a convolutional neural network (CNN) based scintillation-position prediction and SART reconstruction. The group is currently building the first prototype of the system and will perform first measurement with OOCs later this year. 4




On-Chip PET system development.

**Pharmacokinetic Modelling**

Our group is also actively developing new technologies to improve the quantitative analysis of PET molecular imaging based on pharmacokinetic modelling. We have developed physiological ground truth to improve the model selection and parametric image reconstruction. We have also developed a direct parametric image reconstruction (DPIR) method for estimating kinetic parameters and recovering single tracer information from rapid multi-tracer PET measurements. This approach has applications for dual acquisitions of different tracers. This entails integrating a multi-tracer model in a reduced parameter space (RPS) into dynamic image reconstruction along with introduction of an expectation-maximization surrogate function to incorporate a multi-tracer model for the optimization of the penalized log-likelihood. Furthermore, we have developed a new hierarchical pharmacokinetic modelling algorithm to improve the parametric image estimation by refining the setting of initial values as well as fitting boundaries hierarchically to reduce the local minima of nonlinear fitting. The methods were validated by both computational simulations and real data. The improved estimation of pharmacokinetic modelling can enhance the potential of PET imaging in diagnosis and therapy management.

**Radiotracer Development and Preclinical Imaging**

In keeping with the broader objectives of the department, aspirations for preclinical molecular imaging are the most recent topic of focus in the group. The research is centered around preclinical studies of neurodegenerative disease models such as PD and Alzheimer's disease. This should be enabled by establishment of a facility for radiotracer development through concerted use of the on-chip/small animal PET, autoradiography in vitro, and radiochromatographic measurement of tracer metabolites formed in vivo.

**Selected Publications**

**[1]** Hong, J., Kang, S., Alberts, I., Lu, J., Sznitman, R., Lee, J. S. Rominger, A., Choi, H., Shi, K. (2021). Image-level trajectory inference of tau pathology using variational autoencoder for Flortaucipir PET. 10.21203/rs.3.rs-880967/v1.

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**[9]** Han, X., Wu, P., Alberts, I., Zhou, H., Yu, H., Bargiotas, P., Yakushev, I., Wang, J., Höglinger, G., Förster, S., Bassetti, C., Oertel, W., Schwaiger, M., Huang, S.C., Cumming, P., Rominger, A., Jiang, J., Zuo, C., Shi, K. Characterizing the heterogeneous metabolic progression in idiopathic REM sleep behavior disorder. Neuroimage Clin. 2020;27:102294.

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**Research Profile**

The translational imaging center (TIC) within sitem-insel is one of the central imaging labs on campus. Biomedical imaging plays an essential role in leading research and rapid development in healthcare. Using state-of-the-art infrastructure, our in-house medical physics team supports the translation of non-invasive imaging biomarkers to perform quantitative image analysis, enhancing, therefore, interdisciplinary research and collaboration efforts. Artificial intelligence allows the analysis of a massive amount of imaging data extraction to be merged with "omics" from clinical, biological, and genetic data pools. Novel deep "algorithmic approaches" open the road toward big data analysis being performed with national and international partners. Collaborations, like the one with the ARTORG Center, strengthen the role of biomedical imaging and intervention within a motivated multi-disciplinary team. Personalized medicine requires advanced tissue diagnosis involving diagnostic radiology, as well as image-guided intervention. The BCPM as well as industry cooperation are therefore ideal partners to bring different fields of medical experts together to gain a more precise picture of individualized patient care.

**Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study**

Group Members: Catherine Aubry-Beigelman, Lukas Ebner, Manuela Funke-Chambour, Christophe von Garnier, Christian Garzoni, Thomas K Geiser, Sabina Guler

Background: The infectious coronavirus disease 2019 (COVID-19) pandemic is an ongoing global healthcare challenge. Up to one-third of hospitalized patients develop severe pulmonary complications and acute respiratory distress syndrome. Pulmonary outcomes following COVID-19 are unknown.

Methods : The Swiss COVID-19 lung study is a multicentre prospective cohort investigating pulmonary sequelae of COVID-19. We report on initial follow-up four months after mild/moderate or severe/critical COVID-19 according to the World Health Organization severity classification.
113 COVID-19 survivors were included (mild/moderate n=47, severe/critical n=66).

Conclusion: Four months after severe acute respiratory syndrome coronavirus 2 infection, severe/critical COVID-19 was associated with significant functional and radiological abnormalities, potentially due to small-airway and lung parenchymal disease. A systematic follow-up for survivors needs to be evaluated to optimise care for patients recovering from COVID-19. 1



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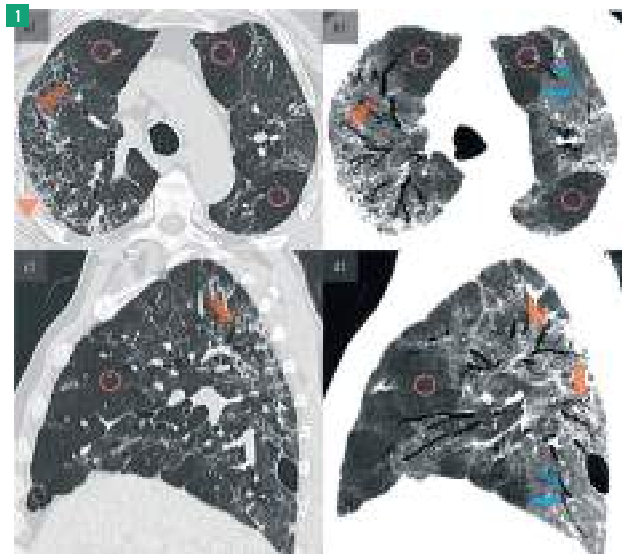

Characteristic radiological changes of a patient with severe sequelae three months after coronavirus disease 2019 (COVID-19) pneumonia. Extensive involvement of both lungs is present in a patient three months after severe COVID-19 pneumonia. Diffuse mosaic attenuation pattern in all lung lobes seen on a) axial 1-mm-thick computed tomography (CT) scan and b) 10-mm-thick minimum intensity projection (mIP) slices, c) 1-mm-thick CT and d) 10-mm-thick mIP sagittal reformats in lung windowing. This combines classical features of lung fibrosis with architectural distortion, reticulations, honeycombing (arrowhead in a), and traction bronchiectasis (straight arrows in a–d), as well as sharply demarcated areas of low attenuation in both lungs (circles in a–d). Clusters of contiguous hypoattenuating lobules and traction bronchiectasis are better visualised on mIP images with narrow window settings (b and d). Note the bulging of the interlobular septae (b and d, curved arrows) as well as the subpleural pneumatocele in c and d.

**AI-Powered Diagnosis and Management of Acute and Chronic Lung Diseases**

Group Members: Andreas Christe; Lukas Ebner; Stavroula Mougiakakou

For almost 10 years, our department, in close collaboration with the Artificial Intelligence (AI) in Health and Nutrition laboratory of the ARTORG Center, has focused on the diagnosis and management of interstitial lung diseases (ILD) using state-of-the-art AI and computer vision technologies, while the last year we translated the research finding against COVID-19.

ILD are a heterogeneous group of more than 200 chronic, overlapping lung disorders, characterized by fibrosis and/or inflammation of the lung tissue. ILD accounts for 15% of all cases seen by pulmonologists and can be caused by autoimmune disease, genetic abnormalities, infections, drugs, or long-term exposure to hazardous materials. Although ILD are a heterogeneous group of histologically distinct diseases, most of these exhibit similar clinical presentations and their diagnosis often presents a diagnostic dilemma. However, early diagnosis is crucial for making treatment decisions, while misdiagnosis may lead to life-threatening complications.

The scope of our research is to develop a framework that allows the detection and diagnosis of the pathology, its prognosis, and finally the treatment personalisation based on the AI-powered analysis of imaging, clinical/laboratory, and patient's history data as shown in Figure 2. Within this framework we introduce algorithmic approaches and a diagnosis support system able to i) fully automatically segment the lung and the anatomical structures of the lung cavity and ii) identify, characterise, and quantify different types of pathological lung tissues. The image analysis results along with the additional disease-related information are further analysed to not only support the faster diagnosis, but also for the more efficient disease management in the sense of treatment selections and disease progression. The newly introduced algorithmic approaches are continuously validated within the framework of feasibility and clinical trials, while the integrated diagnosis support system was able to detect ILD with similar accuracy to a human reader.

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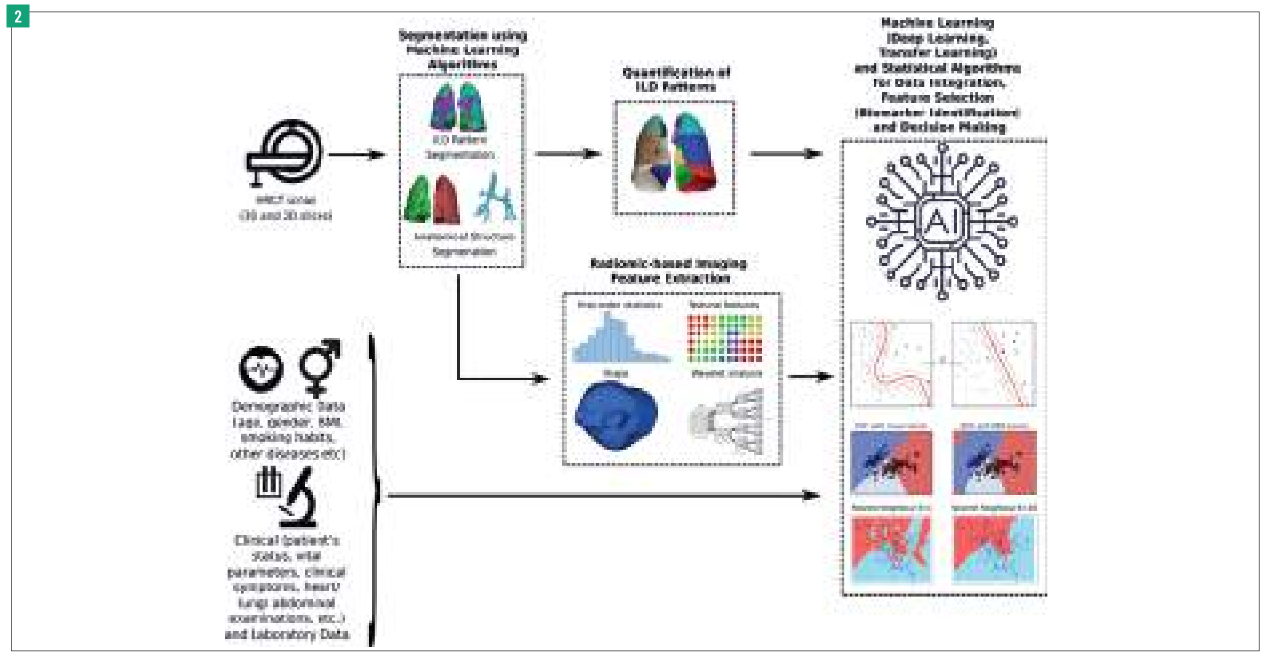



Outline of the framework for diagnosis and management of ILD

During the last two years, our research has also been extended to meet the challenges related to diagnosis and prognosis of COVID-19. COVID-19 and ILD share many similarities due to their diffuse pathological manifestations, such as ground glass opacities, band consolidations, and reticulations. To this end, the knowledge acquired over the last years was translated in the field of triage and prognosis of COVID-19 patients on the basis of imagining data and AI. The primary aims are to deploy a decision support system for COVID-19 pneumonia detection, severity assessment (acute COVID-19), and prognosis (including long COVID-19) based on the AI analysis of imaging, clinical/laboratory, and patient's history data. The system also supports the differential diagnosis of COVID-19 pneumonia from other pulmonary infections (i.e., bacterial).

Our group receives funding from the Swiss National Science Foundation, and both the Hasler and Lindenhof Foundations.

**Aortic stress imaging with new MR ergometer design**

Group members: Adrian Auderset, Anil Aksöz, Dario Haeberli, Vladimir Makaloski, Laura Marchal-Crespo, Dominik Obrist, Hendrik von Tengg-Kobligk, Matthias Wilhelm.

The research project SmartLyf involves the ARTORG Center Bern, Swiss Innovation and Translational Park Biel/Bienne (SIPBB), as well as various clinical partners from vascular medicine (Angiology, Cardiology, Vascular Surgery). After initial evaluation of the hardware, it became obvious that the original design of the MR-compatible ergometer – MAgnetic Resonance COmpatible Stepper (MARCOS) had to be adapted before it could be used for dedicated patients selected for stress analysis of the abdominal aorta and its aneurysmatic pathology 3. The original ergometer was adapted to allow abdominal MR imaging 4.

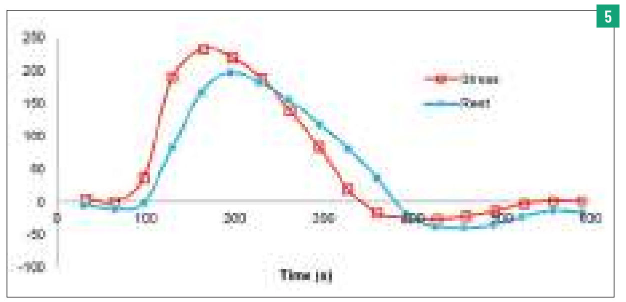
The project also enabled the development of a digital system architecture for physiology data capturing and required a check for safe and reliable vital sign data gathering and transfer by off- the-shelf wearables and mobile phones in the MR environment.

Further milestones included the development of a system to synchronize Photoplethysmography (PPG) raw data of multiple independent working wearables and the development and implementation of algorithms to filter PPG raw data, to assess the data quality and to derive vital signs that can be used to estimate the rupture risk.

Ergometer before start of Smartlyf
(design by Prof. L. Marchal-Crespo, ARTORG Center)

Ergometer after study adaptation
(design by Prof. L. Marchal-Crespo, ARTORG Center)

A pilot data workflow was established to gain rupture risk information on 2D+time and 4D MR imaging for calculating mechanical strength analysis of abdominal aneurysm and to enable a workflow to correlate MRI-based data with vital sign data from wearables to identify features in the vital sign data that correlate with pathological changes of the aorta, specifically aortic aneurysm. Preliminary data of the clinical study show that the pulse wave velocity might be a good biomarker for aneurysm assessment. 5




Comparison of the flow rates (ml/s) under rest vs. stress during located at the infrarenal aorta

**Noninvasive assessment of clinically significant portal hypertension using ΔT1 of the liver and spleen and ECV of the spleen on routine Gd-EOB-DTPA liver MRI**

Group Members: Annalisa Berzigotti, Damiano Catucci, Andreas Christe, Lukas Ebner, Kady Fischer, Christoph Gräni, Dominik Guensch, Johannes Heverhagen, Adrian Huber, Verena Obmann

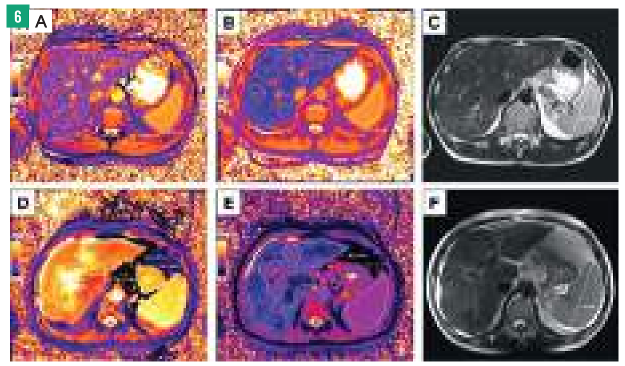
Purpose: To analyze the predictive value of ΔT1 of the liver and spleen as well as the extracellular volume fraction (ECV) of the spleen as noninvasive biomarkers for the determination of clinically significant portal hypertension (CSPH) on routine Gd-EOB-DTPA liver MRI.

Method: 195 consecutive patients with known or suspected chronic liver disease from 9/2018 to 7/2019 with Gd-EOB-DTPA liver MRI and abdominal T1 mapping were retrospectively included. Based on the presence of splenomegaly with thrombocytopenia, ascites and portosystemic collaterals, the patients were divided into noCSPH ($n = 113$), compensated CSPH (cCSPH, ≥1 finding without ascites; $n = 55$) and decompensated CSPH (dCSPH, ascites ± other findings; $n = 27$). T1 times were measured in the liver, spleen, and abdominal aorta in the unenhanced and contrast-enhanced T1 maps. Native T1 times and ΔT1 of the liver and spleen as well as ECV of the spleen were compared between groups using the Kruskal-Wallis test with Dunn's post hoc test. Furthermore, cutoff values for group differentiation were calculated using ROC analysis with Youden's index.



Results: ΔT1 of the liver was significantly lower in patients with cCSPH and dCSPH ($p < 0.001$) compared to patients with noCSPH. In the ROC analyses for differentiation between noCSPH and CSPH (cCSPH + dCSPH), a cutoff of < 0.67 for ΔT1 of the liver (AUC = 0.79) performed better than ΔT1 (AUC = 0.69) and ECV (AUC = 0.63) of the spleen with cutoffs of > 0.29 and > 41.9, respectively.

Conclusion: ΔT1 of the liver and spleen in addition to ECV of the spleen allow for determination of CSPH on routine Gd-EOB-DTPA liver MRI. 6



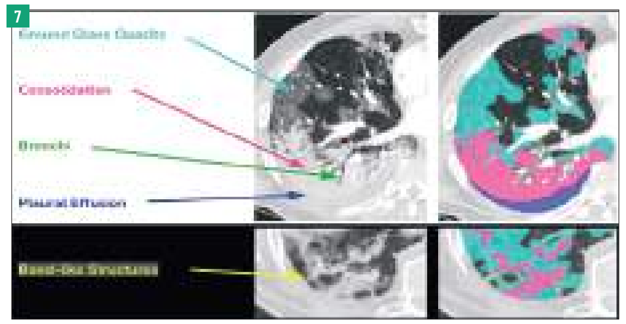

Measurements of T1 relaxation time and spleen size. In images A to C, the assessment of a 36-year-old male patient without chronic liver disease and no clinically significant portal hypertension (noCSPH) is shown. In images D to F, the same assessment is shown for a 60-year-old female patient with alcoholic liver cirrhosis (Child B) and decompensated clinically significant portal hypertension (dCSPH). In A and D, ROIs are placed in the liver, abdominal aorta, and spleen on the native T1 map. In B and E, ROIs are placed in the liver, abdominal aorta, and spleen on the T1 map 20 min after the administration of Gd-EOB-DTPA. In C and F, measurement of the spleen is shown on a T2-weighted half-Fourier acquisition single-shot turbo spin echo (HASTE) sequence. For the 36-year-old patient with noCSPH, we calculated a ΔT1 of the liver of 0.75, a ΔT1 of the spleen of 0.23 and an ECV of the spleen of 30.8. For the 60-year-old patient with dCSPH, we calculated a ΔT1 of the liver of 0.59, a ΔT1 of the spleen of 0.53 and an ECV of the spleen of 48.2.

**AI-multi-omics-based Prognostic Stratification of COVID-19 Patients in Acute and Chronic State**

Group Members: Harald Bonél, James Duncan, John Garcia Henao, Alexander Pöllinger, Mauricio Reyes, Nicola Sverzellati)

Assessing severity and predicting a patient's acute and chronic course are urgently needed in a pandemic like COVID-19. This helps physicians provide optimal care to patients and plan and allocate resources such as ICU beds. In this project funded by the SNSF, we establish an AI-multi-omics-based system for automated severity assessment and prognosis based on medical imaging and clinical/laboratory data. This study composed a high-quality dataset using CT scans from three centers and evaluated the radiological benefit of a multi-class lesion segmentation for severity classification in COVID-19 Patients. In addition, this study has developed an AI method titled AssessNet-19 to automate the clinical severity prediction of COVID-19 patients using the WHO clinical progression scale.

Material and Methods: A multi-center dataset of one hundred forty CT scans of COVID-19 positive patients was composed using the University Hospital of Bern, Parma, and Yale-New Haven Hospital. For each CT scan, 10 equidistant slices were manually segmented. As a result, four separate lesion classes were established, namely ground-glass opacity (GGO), consolidation (CON), pleural effusion (PLE), and band-like structures (BAN), as shown in Figure 7.



Manual segmentation and segmentation of five different lesion classes.

The first stage of the AssessNet-19 method inputs the multi-center CT scans to train two neural networks, one for multi-class lesion segmentation and the other for lung segmentation. Next, 107 radiomic features related to intensity histogram, 2D shape, and grey texture level were extracted on a voxel basis from all imaging scans for each lesion class. In contrast, the pixel surface area of the lung classes is used to normalize each type of lesion with the total lung area. Finally, a LASSO trade-off for feature importance and eXtreme Gradient Boosting (XGBoot) algorithm is trained for severity classification in COVID-19 patients.

A systematic method was developed to implement the WHO clinical progression scale to label the train and test data. The criteria to calculate the WHO score was that all the 140 patients have the clinical data less than 24 hours after the CT scan. Table 1 presents the three classes grouped as high-level WHO scores to assess the daily severity of the COVID-19 patients.

The similarity between manual and AI-aided lesion segmentation was evaluated using the Sørensen-Dice coefficient (DC). In addition, the AssessNet-19 prediction performance is measured by the F1-score and the confusion matrix.

Experiments Procedures and Results: The first stage of the AssessNet-19 automates the lung and multi-class lesions using a 2D U-Net neural network. The first model was trained using a 2D U-Net neural network with 93 patients and 681 axial slices and 18 patients with 852 axial slices for testing. The qualitative results are shown in Figure 8.

The second stage of the AssessNet-19 predicts the disease severity in COVID-19 patients using the high-level WHO score. One hundred five patients were used to train the XGBoost model, and 35 patients were selected for testing the model. Two approaches to extracting the radiomics features from the CT scans are compared to analyze the radiological benefit of using a multi-class lesion segmentation compared to a single class to predict the severity in patients with COVID-19. Figure 9 shows the comparison results to predict the severity classification using the high-level WHO score.

Conclusion: Our study shows that the multi-class lesion segmentation allows extracting specialized radiomic features to represent the patients' status and provides accurate severity predictions. The AssessNet-19 model works for mild, moderate, and severe COVID-19 patients, with CTs from all three centers and contrast and non-contrast scans.

Limitations: Radiomic features can classify the severity of COVID-19 patients at the high-level WHO score. However, the clinical data is necessary to predict clinical severity at the fine-grained WHO score.

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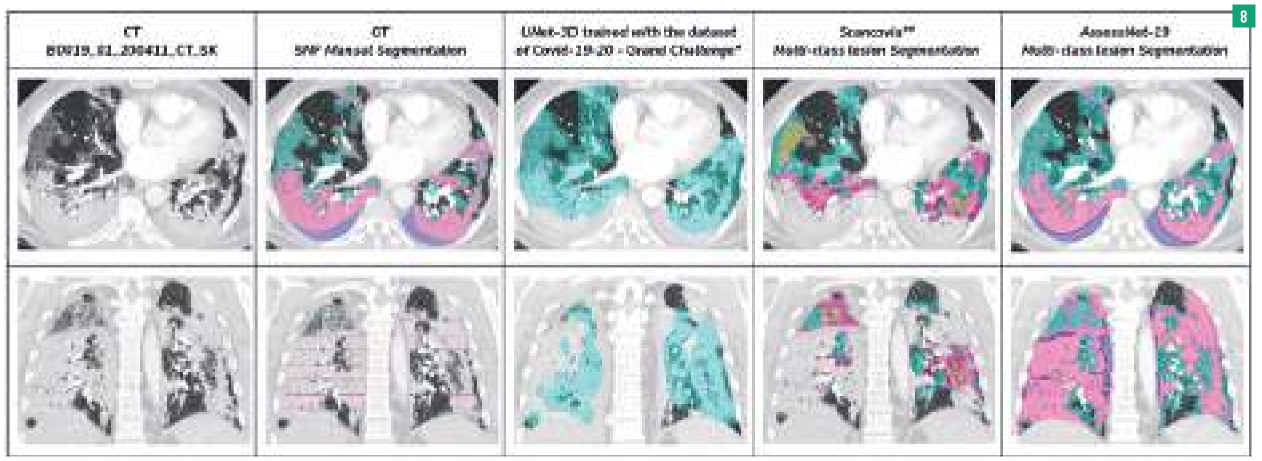

Comparison among UNet 3D, Scancovia model, and AssessNet-19 for lesion segmentation in COVID-19 patients. The AssessNet-19 method yielded a mean DC of 0.71 for GGO, 0.64 for CON, 0.57 for PLE, and 0.29 for BAN, compared to manual segmentation. A qualitative comparison among the AssessNet-19, a 3D-UNet model* trained with the grand challenge dataset, and scancovia** model for lesion segmentation in COVID-19 patients is also present. These two models fail in the segmentation of very dense lesions such as consolidation and pleural effusion, which occur in very severe COVID-19 patients.

* Source: Holger Roth. Rapid Artificial Intelligence Solutions in a Pandemic – The COVID-19-20 Lung CT Lesion Segmentation Challenge. MICCAI, Grand Challenge. 2021.

** Source: Lassau et al. AI-severity model presented in Integrating deep learning CT-scan model, biological and clinical variables to predict severity of COVID-19 patients. Nature Communications. 2021

Table 1. The WHO clinical progression scale and the three classes (high-level WHO score) were used to predict the severity of the COVID-19 patients.

| WHO clinical descriptor | Score | High-level WHO score |
|---|---|---|
| Uninfected; no viral RNA detected | 0 | – |
| Asymptomatic; viral RNA detected | 1 | |
| Symptomatic; independent | 2 | Ambulatory Mild |
| Symptomatic; assistance needed | 3 | |
| Hospitalised; no oxygen therapy* | 4 | Hospitalised Moderate |
| Hospitalised; oxygen by mask or nasal prongs | 5 | |
| Hospitalised; oxygen by NIV or high flow | 6 | |
| Intubation and mechanical ventilation: p02/Fi02 ≥150 or Sp02/Fi02 ≥200 | 7 | |
| Mechanical ventilation:p02/FI02 <150 (Sp02/FI02 <200) or vasopressors | 8 | |
| Mechanical ventilation:p02/FI02 <150 and vasopressors, dialysis, or ECMO | 9 | |
| Dead | 10 | – |

* Adapted from WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020 Aug; 20(8):e192-e197. doi: 10.1016/S1473-3099(20)30483-7. Epub 2020 Jun 12.

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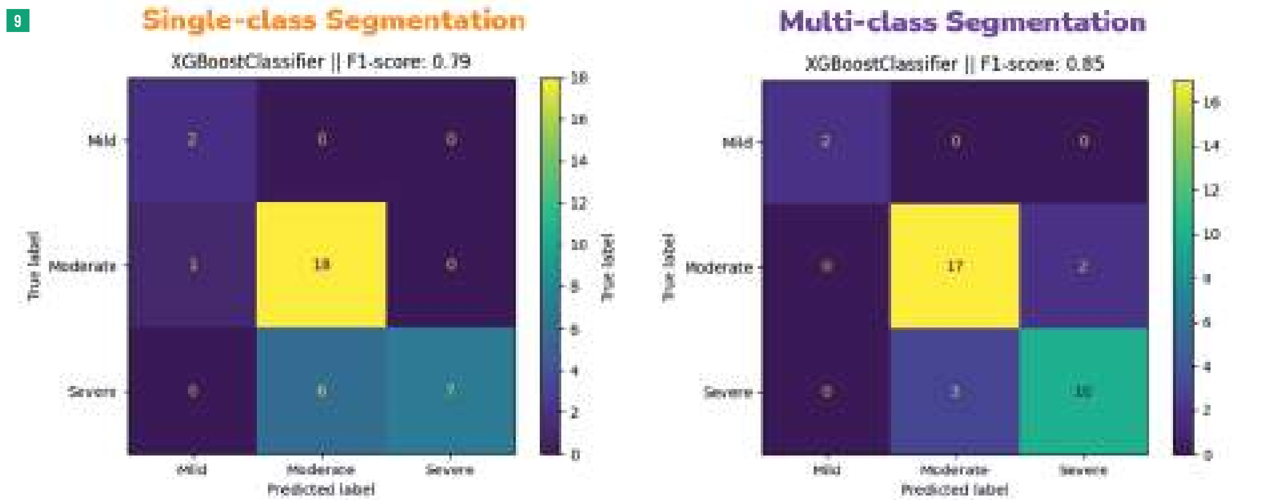


Comparing single- versus multi-class lesion segmentation for severity assessment in COVID-19 patients. *Left:* The single-class lesion model overlaps the four classes of lung lesion segmentation into one segmentation class; then, the radiomics features are extracted and the relevant features selected to feed the classifier algorithm and get an F1 score of 0.79. *Right:* The multi-class lesion model extracts the radiomics features for each lesion class segmentation. The relevant features per class are selected and integrated into one vector per patient to train the classifier algorithm achieving an F1 score of 0.85.

## Selected Publications

**[1]** Afshar-Oromieh, A., Prosch, H., Schaefer-Prokop, C., Bohn, K. P., Alberts, I., Mingels, C., Thurnher, M., Cumming, P., Shi, K., Peters, A., Geleff, S., Lan, X., Wang, F., Huber, A., Gräni, C., Heverhagen, J. T., Rominger, A., Fontanellaz, M., Schöder, H., Christe, A., Ebner, L. (2021). A comprehensive review of imaging findings in COVID-19 - status in early 2021. European journal of nuclear medicine and molecular imaging, 48(8), 2500–2524. https://doi.org/10.1007/s00259-021-05375-3

**[2]** Catucci D., Obmann V.C., Berzigotti A., Gräni C., Guensch D.P., Fischer K., Ebner L., Heverhagen J.T., Christe A., Huber A.T. Noninvasive assessment of clinically significant portal hypertension using ΔT1 of the liver and spleen and ECV of the spleen on routine Gd-EOB-DTPA liver MRI. Eur J Radiol. 2021 Nov;144:109958. doi: 10.1016/j.ejrad.2021.109958. Epub 2021 Sep 20. PMID: 34571458.

**[3]** Christe, A., Peters, A. A., Drakopoulos, D., Heverhagen, J. T., Geiser, T., Stathopoulou, T., Christodoulidis, S., Anthimopoulos, M., Mougiakakou, S. G., & Ebner, L. (2019). Computer-Aided Diagnosis of Pulmonary Fibrosis Using Deep Learning and CT Images. Investigative radiology, 54(10), 627–632. https://doi.org/10.1097/RLI.0000000000000574

**[4]** Correa Londoño, Martina; Trussardi, Nino; Obmann, Verena C.; Piccini, Davide; Ith, Michael; von Tengg-Kobligk, Hendrik; Jung, Bernd (2021). Radial self-navigated native magnetic resonance angiography in comparison to navigator-gated contrast-enhanced MRA of the entire thoracic aorta in an aortic patient collective. Journal of cardiovascular magnetic resonance, 23(1), p. 94. BioMed Central 10.1186/s12968-021-00774-9

**[5]** Ebner, L., Christodoulidis, S., Stathopoulou, T., Geiser, T., Stalder, O., Limacher, A., Heverhagen, J. T., Mougiakakou, S. G., & Christe, A. (2020). Meta-analysis of the radiological and clinical features of Usual Interstitial Pneumonia (UIP) and Nonspecific Interstitial Pneumonia (NSIP). PloS one, 15(1), e0226084. https://doi.org/10.1371/journal.pone.0226084

**[6]** Ebner, Lukas; Funke-Chambour, Manuela; von Garnier, Christophe; Ferretti, Gilbert; Ghaye, Benoit; Beigelman-Aubry, Catherine (2021). Imaging in the aftermath of COVID-19: what to expect. European radiology, 31(6), pp. 4390-4392. Springer-Verlag 10.1007/s00330-020-07465-6

**[7]** Fontanellaz, M., Ebner, L., Huber, A., Peters, A., Löbelenz, L., Hourscht, C., Klaus, J., Munz, J., Ruder, T., Drakopoulos, D., Sieron, D., Primetis, E., Heverhagen, J. T., Mougiakakou, S., & Christe, A. (2021). A Deep-Learning Diagnostic Support System for the Detection of COVID-19 Using Chest Radiographs: A Multireader Validation Study. Investigative radiology, 56(6), 348–356. https://doi.org/10.1097/RLI.0000000000000748

**[8]** Guler S.A., Ebner L., Aubry-Beigelman C., Bridevaux P.O., Brutsche M., Clarenbach C., Garzoni C., Geiser T.K., Lenoir A., Mancinetti M., Naccini B., Ott S.R., Piquilloud L., Prella M., Que Y.A., Soccal P.M., von Garnier C., Funke-Chambour M. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J. 2021 Apr 29;57(4):2003690. doi: 10.1183/13993003.03690-2020. PMID: 33419891; PMCID: PMC8082329.

**[9]** Obmann, V. C.; Marx, C.; Hrycyk, J.; Berzigotti, A.; Ebner, L.; Mertineit, N.; Gräni, Ch.; Heverhagen, J. T.; Christe, A.; Huber, A. T. (2021). Liver segmental volume and attenuation ratio (LSVAR) on portal venous CT scans improves the detection of clinically significant liver fibrosis compared to liver segmental volume ratio (LSVR). Abdominal radiology, 46(5), pp. 1912-1921. Springer 10.1007/s00261-020-02834-7

**[10]** Schmaranzer, Florian; Afacan, Onur; Lerch, Till; Kim, Young-Jo; Siebenrock, Klaus-Arno; Ith, Michael; Cullmann, Jennifer; Kober, Tobias; Klarhoefer, Markus; Tannast, Moritz; Bixby, Sarah D; Novais, Eduardo N; Jung, Bernd (2021). Magnetization-prepared 2 Rapid Gradient-Echo MRI for B1 Insensitive 3D T1 Mapping of Hip Cartilage: An Experimental and Clinical Validation. Radiology, 299(1), pp. 150-158. Radiological Society of North America 10.1148/radiol.2021200085

# Support Center for Advanced Neuroimaging (SCAN)

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**Research Partners**

**Neurology Department,** Inselspital, Bern University Hospital
**Neurosurgery Department,** Inselspital, Bern University Hospital
**Data Science Center,** University of Bern
**Neuropediatrics,** Inselspital, Bern University Hospital
**Clinical Psychiatry,** University Hospital of Psychiatry, University of Bern
**Department of Psychology,** University of Bern
**Department of Neurology,** UCLA, USA
**Department of Informatics,** Technical University of Munich, Germany
**Department of Electronics and Information Systems,** Gent, Belgium
**University of Miami School of Medicine,** Miami, Florida, USA
**Yale University Radiology & Biomedical Imaging,** New Haven, USA

**Research Profile**

The Support Center for Advanced Neuroimaging (SCAN) is a multidisciplinary imaging laboratory, where MR-physicists, computer engineers, neuroradiologists, neurologists, and psychologists investigate new applications for advanced neuroimaging together with specialized radiographers and technicians.

**Ultra-High Field MRI**

In 2019, the Translational Imaging Center (TIC) was established at the Campus of the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel AG). The TIC hosts a clinically certified 7 Tesla MRI system for basic and translational research and clinical investigation. In this context the research focus of the SCAN is the translation of 7T neuroimaging into patient care (Radojewski et al. 2021). We investigate the diagnostic yield of high-resolution clinical UHF imaging in neuromedicine (neurovascular disorders, presurgical epileptology, neuroimmunology and degenerative disorders). 1

Applying machine learning to solve problems in brain image analysis, our research group works at the intersection of machine learning and neuroradiology. Using deep learning and other techniques, we focus on model interpretability, uncertainty quantification, and model validation. In two recent projects, we implemented federated learning, a method that describes the training of machine learning models in a distributed fashion, across multiple data silos, without explicit sharing of information. 2

We provided data and segmentation architectures to the FETs project, a world-wide initiative to train models for glioblastoma delineation from the data of 6,314 glioblastoma patients from 71 geographically distinct sites. In the context of the Innosuisse project "Advanced Stroke Analytics Platform" we are exploring the potential of this technology to tools for acute stroke data analytics.



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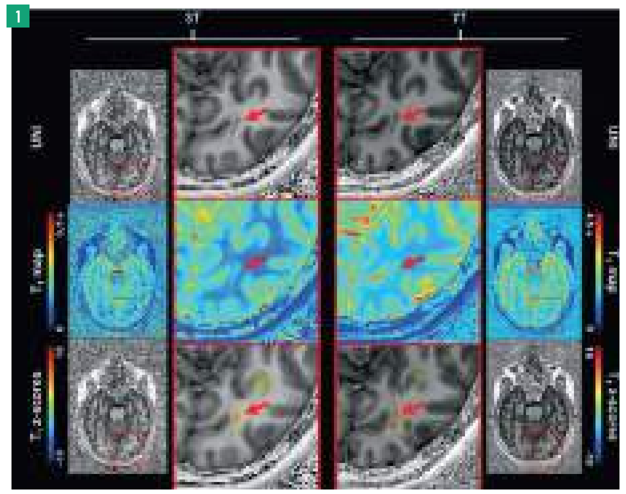

Personalized detection and characterization of brain T1 signal abnormalities with UHF MRI. Single-subject comparison against population – derived norms overlaid on a representative axial slice. An epileptogenic structural lesion exhibiting long T1 reflected by positive z-scores is indicated by a red arrow.

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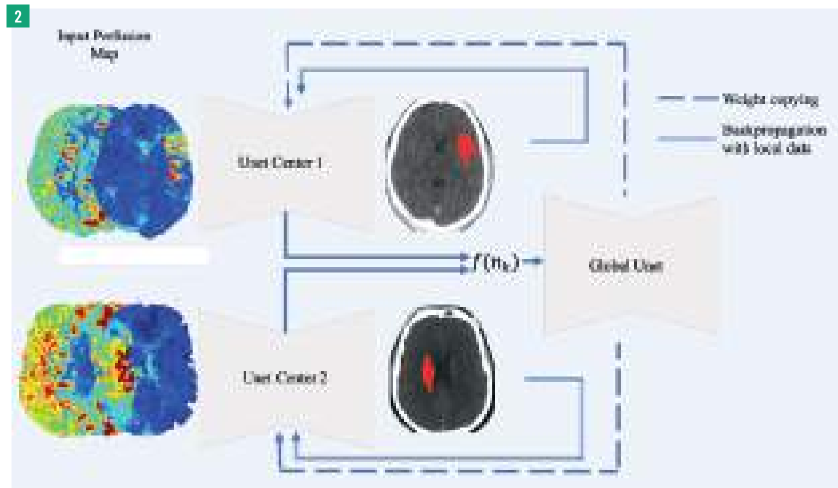



Federated learning enables training or local diffusion and perfusion models models of acute stroke on data samples in multiple institutions. Parameters (weights and biases of a deep neural network) are exchanged between centers to generate a global stroke model shared by all centers.

**The Swiss-First Study**

In an SNF-funded international SINERGIA project (https://www.swissfirst-project.com), we are currently monitoring approximately 500 patients who have experienced a first epileptic seizure. We analyse data at seven epilepsy centers in Switzerland. At the SCAN we make use of advances in MRI sequence development and signal analysis to quantitatively investigate abnormalities reflecting preexisting epileptogenesis and an increased risk for seizure recurrence. The development of new diagnostic tools based on EEG and MRI in combination with machine learning is expected to directly improve patient care. (Rebsamen et al., 2020, 2020, 2022).

**Selected Publications**

[1] Radojewski, P., Slotboom, J., Joseph, A., Wiest, R., & Mordasini, P. Clinical implementation of 7T MRI for the identification of incidental intracranial aneurysms versus anatomic variants. (2021). American Journal of Neuroradiology, 42(12), 2172-2174. doi:10.3174/ajnr.A7331

[2] Rebsamen, M., Radojewski, P., McKinley, R., Reyes, M., Wiest, R., & Rummel, C. (2022). A quantitative imaging biomarker supporting radiological assessment of hippocampal sclerosis derived from deep learning-based segmentation of T1w-MRI. Frontiers in Neurology, 13 doi:10.3389/fneur.2022.812432

[3] Rebsamen, M., Rummel, C., Reyes, M., Wiest, R., McKinley, R. (2020). Direct cortical thickness estimation using deep learning-based anatomy segmentation and cortex parcellation (2020) Human Brain Mapping, 41 (17), pp. 4804-4814. DOI: 10.1002/hbm.25159

[4] Rebsamen, M., Suter, Y., Wiest, R., Reyes, M., Rummel, C. (2020). Brain Morphometry Estimation: From Hours to Seconds Using Deep Learning. Frontiers in Neurology, 11, art. no. 244,. DOI: 10.3389/fneur.2020.00244

[5] Weng G., Radojewski P., Sheriff S., Kiefer C., Schucht P., Wiest R, Maudsley A and Slotboom J (2022); SLOW: A novel spectral editing method for whole-brain MRSI at ultra high magnetic field, https://doi.org/10.1002/mrm.29220

Editorial

# Biomedical Engineering Research at other Institutes of the University of Bern

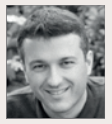
At the University of Bern, along with the beforehand listed institutions specialized in biomedical engineering research, a variety of additional research institutions from different scientific angles also engage in targeted research activities in the field of biomedical engineering.

These additional viewpoints from diverse domains contribute to a productive research environment in Bern, owing to the very interdisciplinary nature of biomedical engineering research that greatly benefits from the specific expertise these technological and scientific institutes provide.





# Computer Vision Group



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**Group Members**

Adam Bielski, Abdelhak Lemkhenter, Luigi Fiorillo, Llukman Cerkezi, Aram Davtyan, Sepehr Sameni, Alp Eren Sari, Viktor Shipitsin, Hamadi Chihaoui

**Research Profile**

The Computer Vision group conducts research on the broad areas of machine learning, computer vision, image processing, and imaging and sensor design by employing models, algorithms, and analysis tools from optimization theory, probability theory, and applied mathematics. Our general aim is to extract high-level information from images by using digital processing. Such high-level information can be in the form of geometric or photometric quantities about objects in the scene, or semantic attributes such as their category, function, etc. to achieve this aim, we develop algorithms based on modeling and/or data-driven principles. Our model-based approaches describe the identification of unknown parameters of sensors and distortions of their measured signals, such as optical aberrations (defocus and motion blur), noise, spatial loss of resolution and quantization, as optimization problems. We also introduce novel optimization techniques, with a focus on computational and accuracy performance. In this domain, our efforts have been devoted to problems in: inverse imaging (deblurring, blind deconvolution, super resolution), 3D estimation (multi-view stereo, photometric stereo, coded aperture photography), motion estimation (structure from motion, tracking). Our data-driven solutions use large datasets to learn a model. Our focus is on unsupervised learning, i.e., on identifying key learning principles that allow a machine to learn without supervision/manual annotation. Manual annotation of data samples is quite costly, error-prone, time-consuming, in some cases ill-defined, and may introduce undesired bias into the training. Moreover, we look at machine-learning methods that map data samples to simpler representations that can be used effectively on tasks we have not trained on before. As shown recently, self-supervised learning methods, which avoid human annotation, can successfully build effective representations. The idea is to exploit the structure of the data as a form of annotation to define artificial learning tasks. These methods allow one to train models on data with very little labeling by first pre-training them on large datasets without labels.

**Self-supervised Learning**

Self-supervised learning is a novel paradigm in machine learning, where one can learn features without manual annotation. The main principle is to take the available data samples, split each sample into two parts, and learn to predict one part given the other as input. This principle allows a model to learn structure in the data. We have proposed a method that learns how to solve puzzles. We split images into a set of nine tiles (input) and the corresponding pixel coordinates of the center of each tile (output). By learning to arrange the tiles in the correct order, the model learns to distinguish object parts and how these object parts are typically arranged. 1

**Disentangling Factors of Variation**

We assume that visual data can be described by a finite set of attributes, or factors, such as the object identities, 3d shape, pose, viewpoint, and the global illumination. Computer graphics rendering engines are an example of how these factors can be used to generate images. We are thus interested in the inverse process, where we obtain these factors given an image. The collection of such factors is a feature vector that can be used efficiently for object classification, detection, and segmentation. We explore completely unsupervised methods as well as partly supervised methods, where only some factors (e.g., the object category) are specified. 2

**Deblurring**

If either the camera or objects in a scene move during the exposure, images will be degraded by an artifact known as motion blur. To remove this degradation we consider explicit models of blur (shift-invariant, camera shake, non uniform) and design energy minimization methods or

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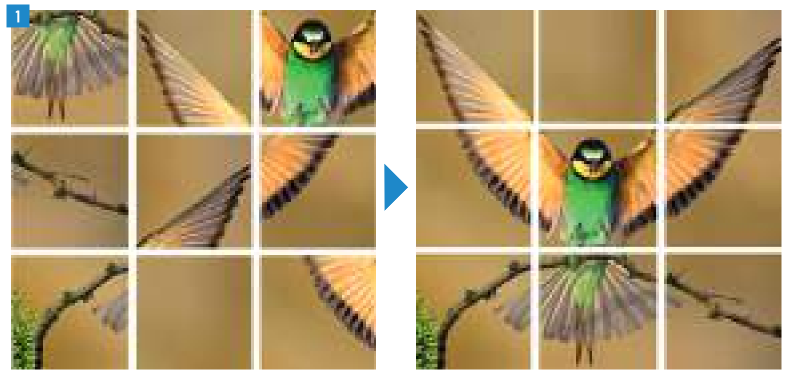
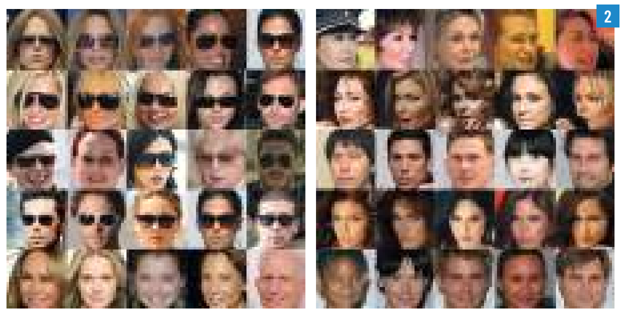


Solving a puzzle requires a machine to learn about objects and their parts and how they fit together. After successful training on this task, one can transfer the learned representation and use it to solve other visual tasks that require understanding the composition of objects.



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data-driven methods (e.g., via deep learning) to retrieve the latent sharp image. Our approaches introduce priors for sharp images and models of the blurry image noise in an energy formulation. We then build novel iterative algorithms to solve the minimization task. In one of our recent works on deblurring, we presented a method to extract a video sequence from a single motion-blurred image. 3

Motion-blurred images are the result of an averaging process, where instant frames are accumulated over time during the exposure of the sensor. Unfortunately, reversing this process is nontrivial. First, averaging destroys the temporal ordering of the frames. Second, the recovery of a single frame is a blind deconvolution task, which is highly ill-posed. We present a deep-learning scheme that gradually reconstructs a temporal ordering by sequentially extracting pairs of frames. Our main contribution is to introduce loss functions invariant to the temporal order. This lets a neural network choose during training what frame to output among the possible combinations. We also address the ill-posedness of deblurring by designing a network with a large receptive field and implemented via resampling to achieve a higher computational efficiency. Our proposed method can successfully retrieve sharp image sequences from a single motion-blurred image and can generalize well on synthetic and real datasets captured with different cameras.

### Selected Publications

**[1]** P. Vizcaino, Z. Wang, P. Symvoulidis, P. Favaro, B. Guner-Ataman, E. S. Boyden, and T. Lasse (2021). Real-Time Light Field 3D Microscopy via Sparsity-Driven Learned Deconvolution. International Conference on Computational Photography (ICCP)

**[2]** T. Watanabe and P. Favaro (2021). A Unified Generative Adversarial Network Training via Self-Labeling and Self-Attention. International Conference on Machine Learning (ICML)

**[3]** J. P. Vizcaíno, F. Saltarin, Y. Belyaev, R. Lyck, T. Lasser, and P. Favaro, (2021). Learning to Reconstruct Confocal Microscopy Stacks from Single Light Field Images. IEEE Transactions on Computational Imaging

**[4]** A. Tejankar, S. A. Koohpayegani, V. Pillai, P. Favaro, H. Pirsiavash (2021). ISD: Self-Supervised Learning by Iterative Similarity Distillation. International Conference on Computer Vision (ICCV)

**[5]** L. Fiorillo, P. Favaro, and F. D. Faraci (2021). DeepSleepNet-Lite: A Simplified Automatic Sleep Stage Scoring Model with Uncertainty Estimates. IEEE Transactions on Neural Systems and Rehabilitation

**[6]** G. Meishvili, A. Szabo, S. Jenni, and P. Favaro (2021). Learning to Deblur and Rotate Motion-Blurred Faces. British Machine Vision Conference (BMVC)

**[7]** A. Davtyan, S. Sameni, L. Cerkezi, G. Meishvili, A. Bielski, and P. Favaro (2022). KOALA: A Kalman Optimization Algorithm with Loss Adaptivity. AAAI Conference in Artificial Intelligence

**[8]** Z. Zhang, P. Favaro, Y. Tian, and J. Li (2022). Learn to Zoom in Single Image Super-resolution. IEEE Signal Processing Letters

**[9]** A. Davtyan and P. Favaro (2022). Controllable Video Generation through Global and Motion Dynamics. European Conference on Computer Vision (ECCV)

**[10]** A. Bielski and P. Favaro (2022). MOVE: Unsupervised Movable Object Segmentation and Detection. Neural Information Processing Systems (NeurIPS)

# Department of Clinical Research

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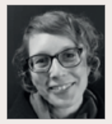
Christina Huf


Carmen Jörg


Martin Jünger


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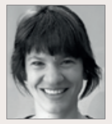
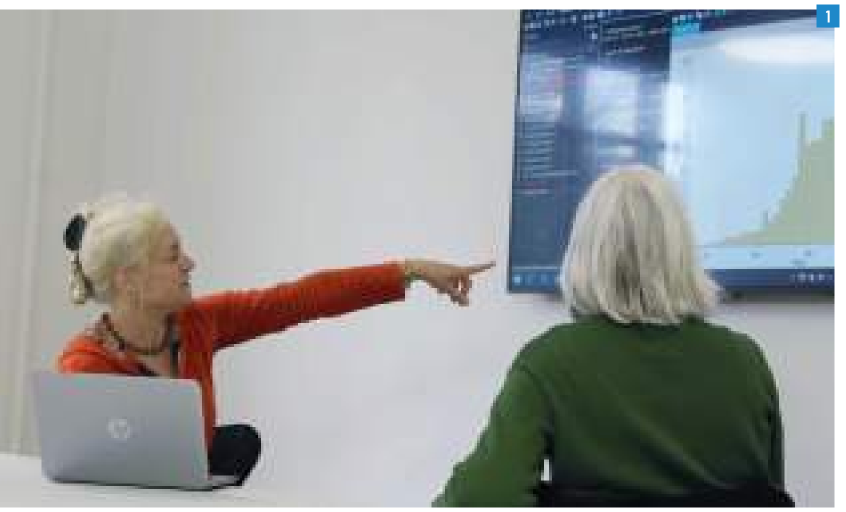

Miriam Wegmann

**Research Partners**
All clinical departments of Inselspital Bern and institutes of the medical faculty of Bern as well as other Swiss hospitals and small- to medium-sized companies.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**Research Profile**
Complexity of clinical research has been growing steadily. The Department of Clinical Research provides an umbrella organization for facilities supporting clinical researchers both at the Faculty of Medicine and at Inselspital as well as small- to medium-sized companies. The department is currently comprised of CTU Bern and the Clinical Investigation Unit. While CTU Bern has its offices at Mittelstrasse 43, Clinical Investigation operates an outpatient clinic for clinical and observational research projects in the sitem-insel building on the Inselspital campus. A full professor of clinical research will lead the department eventually.

**Statistics and Methodology**
The Statistics and Methodology division at CTU Bern offers free consultancy services in research design and statistical analysis, supports Central Data Monitoring activities, and performs statistical analyses. The overarching aim of our consultancy work is to promote the use of appropriate study designs to address the question at hand, as well as methods of data analysis that provide coherent and relevant information while realistically acknowledging the uncertainty in the results. Services include consulting on designing and analyzing clinical trials and observational studies, sample size calculation, contribution to statistical parts of the study protocol, setting-up statistical analysis plans (SAP), performing statistical analysis, preparing statistical reports, and support with manuscript writing. Ideally, our statisticians are involved early in the planning of a clinical study. Although not optimal, we also support investigators after data collection is completed. In any case, successful work means that there is a close collaboration. 1

**Data Management**
CTU Bern provides and maintains a secure and up-to-date IT infrastructure. The servers hosting the study databases are stored in dedicated server facilities. CTU Bern Data Management ensures that all software required to run the servers is regularly updated. Backups of all study- and meta-data are made regularly according to a detailed back-up plan. The plan defines internal back-ups several times per day and daily back-ups on external disks. Our security measures have been checked by the "Datenschutzaufsichtsstelle des Kantons Bern." The data management division (DM) at CTU Bern offers two different models of services and support during the setup of a clinical study database or register: 2

Entire Setup of a Study Database Done by CTU Bern
Based on paper case report forms (CRFs) or on study specifications (list of CRFs, variables etc.), CTU Bern will do the complete setup of the database (eCRFs, edit-checks, visit structure) using one of its two web-based Electronic Data Capturing (EDC) solutions.

Collaborative Setup
If an investigator wants to set up the study database mostly by her-/himself, we can introduce her/him to our EDC system REDCap, where studies can be set up independently (eCRFs, edit-checks, visit structure). CTU Bern will give as much support as requested. At the end, CTU Bern will review the implementation and set it productive, so that data-entry can start.



2


Electronic Data Capturing (EDC) Solutions
All EDC systems used at CTU Bern are web-based i.e. authorized users can access the study database via any computer with internet connection (and web-browser installed). Secure Sockets Layer (SSL) encryption is used to ensure a secure internet connection. Depending on the complexity of the study design and the needs of the investigator, CTU Bern offers different GCP-compliant EDC solutions.

**Clinical Study Management**
Clinical Study Managers at CTU Bern oversee and coordinate the overall study and ensure that every aspect of planning and execution is taken proper care of, from study conception to close-out. We make sure that milestones are reached within pre-set deadlines and budget as well as personnel constraints, while complying with Good Clinical Practice, applicable national and international regulations, scientific guidelines and standards, standard operating procedures, and not the least the study schedule and protocol requirements.

By fostering an open and effective communication between stakeholders (e.g., teams at study sites, sponsor, and other CTU divisions), we ensure that everyone is up-to-date and motivated to allow a steady and flawless conduct of the project through all its phases.

**Quality Assurance and Monitoring**
CTU Bern offers quality control and assurance services (monitoring) to sponsors including sponsor-investigators working at Inselspital Bern or other interested parties for single-center or multi-center clinical studies. Our approach takes into account the risk of the individual study and that the monitoring strategy is risk adapted. We offer two interrelated services to support you in ensuring a high-quality study conduct:

On-site Monitoring
The on-site monitor provides support for clinical studies in terms of quality control and quality assurance. He or she visits study sites at regular intervals during the study to ensure that the study is conducted in accordance with the protocol, applicable Standard Operating Procedures (SOPs), International Council for Harmonization Good Clinical Practice (ICH-GCP) guidelines, and regulatory requirements. For multi-center studies, the monitor is also an important point of contact between the sponsor and the coordination center.

Central and Statistical Data Monitoring
Central data monitoring is concerned with centralized checks of the accumulating study data. These checks are usually done on a regular basis during study conduct and include range, plausibility, and consistency checks. Because some of these measures are based on statistical techniques, there is a close collaboration between the quality assurance and monitoring division and the statistics and methodology division. There is also a close link to on-site monitoring because findings identified during central data monitoring might trigger on-site visits and vice versa.

**Quality Management**
CTU Bern's quality department, is responsible for the internal quality management of the institute. Well-defined and documented processes ensure that the legal foundations of conducting clinical research projects are met, while ensuring efficient, effective, and transparent processes are followed and continuously developed. In addition to managing the internal structures, the quality management division also offers its expertise to external customers and partners by providing consulting or support services to implement local quality assurance measures, develop procedures, or to establish comprehensive quality management structures. In addition, the quality management division can provide active support in the preparation for inspections, the writing of inspection reports, corrective and preventive action development and offers its auditing services to conduct an independent audit on your study or internal process structures.

**Clinical Investigation Unit**
Clinical Investigation is a service unit that offers professional services to investigators working at Inselspital Bern or to other interested parties engaged in single-center or multi-center clinical studies. These services

include logistic support, planning, coordination, and execution of clinical studies from phases I to IV as well as observational studies.

The Clinical Investigation Unit is situated at University Hospital Bern in the sitem-insel building and runs a fully equipped outpatient clinic. Our facilities include:

- Fully equipped treatment rooms for outpatient study visits of patients and volunteers
- Access to the certified laboratories of the Inselspital Bern, including chemistry, hematology, microbiology, therapeutic drug monitoring, and other specialized investigations. Shipping to central study laboratories, if required
- Rapid access to emergency treatment via our own life support equipment and the University Hospital's 24 h emergency center and resuscitation team
- Sample processing and controlled storage according to GCP guidelines (-20°C and -70°C)
- Controlled storage and handling of study medication, according to GCP and study guidelines
- Storage of study files (hardcopy and electronic data) for 15 years
- Working facilities for visiting study monitors 3

### Selected Publications


[1] Günthert A et al. (2022). Efficacy of topical progesterone versus topical clobetasol propionate in patients with vulvar Lichen Sclerosus - A double-blind randomized phase II pilot study. European Journal of Obstetrics & Gynecology and Reproductive Biology, 272: 88-95.

[2] Moser A et al. (2022). Mortality prediction in intensive care units including premorbid functional status improved performance and internal validity. Journal of Clinical Epidemiology,142: 230-241.

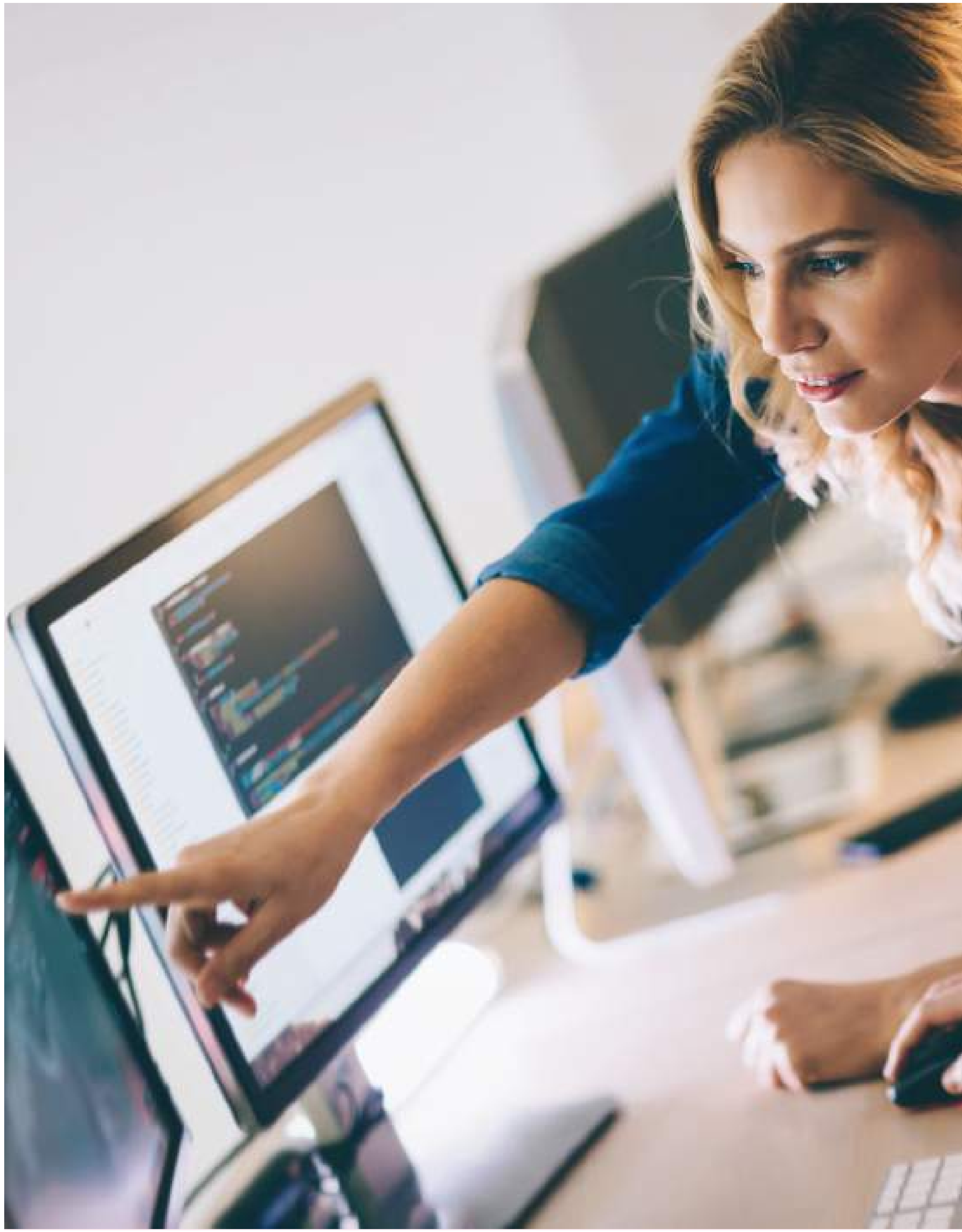
[3] Ueki Y et al. (2022). Frequency and outcomes of periprocedural MI in patients with chronic coronary syndromes undergoing PCI. Journal of the American College of Cardiology, 79: 513-526.

[4] Blum M et al. (2021). Optimizing Therapy to prevent avoidable hospital admissions in multimorbid older adults (OPERAM): cluster randomised controlled trial. BMJ. 374: n1585.

[5] Christ L et al. (2021). Tocilizumab monotherapy after ultra-short glucocorticoid administration in giant cell arteritis: a single-arm, open-label, proof-of-concept study. The Lancet Rheumatology, 3: e619-e626.

[6] Kim W-K et al. (2021). One-year outcomes of a randomized trial comparing a self-expanding with a balloon-expandable transcatheter aortic valve. Circulation,143: 1267-1269.

[7] Valgimigli M et al. (2021). Dual antiplatelet therapy after PCI in patients at high bleeding risk. New England Journal of Medicine, 385: 1643-1655.

# Bone & Joint Program of the Department for BioMedical Research (DBMR)

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1


Schematic view of research partners in the ongoing project iPspine.

### Research Profile

The skeletal system is subject to traumatic conditions (fractures, large bone defects) and pathology due to degeneration (osteoporosis, osteoarthritis, intervertebral disc degeneration). The demand for improved and efficient treatments are increasing as the population of the elderly grows and wants to stay physically active. Surgical procedures for the repair of large bone defects or degenerated spinal discs, however, still need tremendous improvements. The regeneration of skeletal tissues is the focus of the Bone & Joint Research Program. To this aim, strategies based on cells, materials, and growth factors are currently employed ex vivo (2D/3D cell cultures, bioreactors) and in vivo. Pioneering orthopedic surgery, which has been a long tradition in Bern, requires interactions between surgeons and scientists. The Bone & Joint Research Program will continue and extend this tradition and provide the clinicians with tools to improve the treatment of patients.

### Intervertebral Disc Regeneration in Orthopedic Research

There are currently four competitive funded research projects active in the field of intervertebral disc regeneration or in the field of improved spinal fusion. Two of these research projects are funded by the horizon H2020 framework, one in the field, one by the Swiss National Science Foundation, and one by the center of Applied science and Molecular Medicine (CABMM). The first topic is on progenitor cell research and financed by iPspine, a 16 M € research project, which was funded to the consortiums leader Prof. Marianna Tryfonidou, a leading veterinarian from the University Medical Center (UMC) Utrecht & Universiteit Utrecht (https://cordis.europa.eu/project/id/825925) [1]. The iPSpine partners, which include both universities and companies, joined together in January 2019 to begin researching a new, advanced therapy for the treatment of LBP caused by disc deterioration. The ultimate aim of this project is to investigate and develop a new advanced biological therapy using a type of cell called induced pluripotent stem cells (iPSCs) (https://ipspine.eu). These cells are created by re-programming fully mature cells, such as cells from blood or skin, into spine-specific cells. Over the next five years, the iPSpine partners want to show that iPSCs can work as a therapeutic strategy. By the end of the project, the therapy should be ready for advancement to the first clinical trial in people. Within this highly cross-disciplinary consortium, our group was able to isolate primary cells isolated from human trauma IVDs with written consent from patients. These cells were then delivered to consortium partners at the INSERM in Montpellier and Nantes, France. These partners were able to derive novel iPS cell lines. These cell lines can be used for future cell therapy to possibly cure degenerated IVDs.



2

Specialized Bioreactor to apply compression and torsion for culturing entire units of bovine-derived intervertebral disc explants in organ culture under compression and torsion. Left inside incubator, upper right: close-up view of culture chamber, lower right: Inside view of culture chamber with positioned bovine coccygeal intervertebral disc. This device is worldwide unique.

A second highlight is the investigation into engineered silk scaffolds for IVD repair. Here, a new project funded by the Swiss National Science has been started that targets regeneration of the IVD by using "cross-linked growth-factors and engineered" silk fibres and using knitting techniques developed by Dr. Michael Wöltje at the "Technische Universität Dresden, Institut für Textilmaschinen, und Textile Hochleistungswerktofftechnik", Dresden, Germany. [2]

A third key topic was started in Nov 2020, which involves artificial intelligence, statistical shape modelling and finite element modelling, and organ culture models for IVD regeneration [3]: The 4M € funded "Disc4All" project aims to tackle this issue through collaborative expertise of clinicians; computational physicists and biologists; geneticists; computer scientists; cell and molecular biologists; microbiologists; bioinformaticians; and industrial partners (https://cordis.europa.eu/project/id/955735). It provides interdisciplinary training in data curation and integration; experimental and theoretical/computational modelling; computer algorithm development; tool generation; and model and simulation platforms to transparently integrate primary data for enhanced clinical interpretations through models and simulations. The consortium is led by the biomedical engineer Prof. Jérôme Noailly from the Universitat Pompeu Fabra (UPF) in Barcelona, Spain (https://www.upf.edu/web/disc4all). The Disc4All early-stage researchers will provide a new generation of internationally mobile professionals with unique skill sets for the development of thriving careers in translational research applied to multifactorial disorders.

Finally, the fourth topic is the development of a coccygeal rat non-fusion model for the intervertebral disc. Here, in collaborative efforts with the RMS foundation (Bettlach, SO), porous ceramics implants are currently being tested in an in-vivo rat animal model for spinal fusion. This project has been awarded in Dec 2021 with the best-poster award at the German Spine Society Conference. [4]

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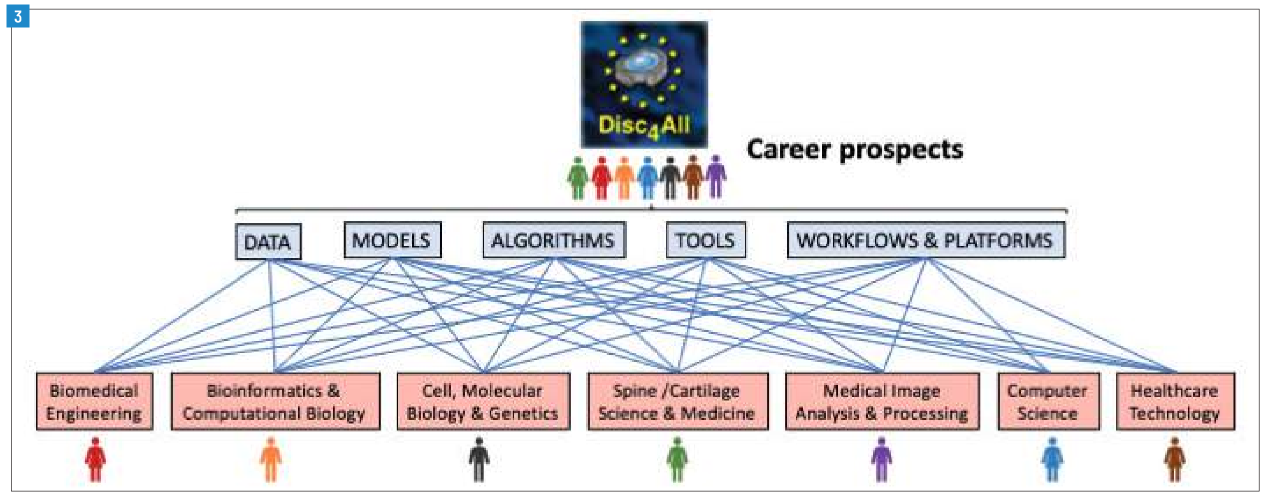
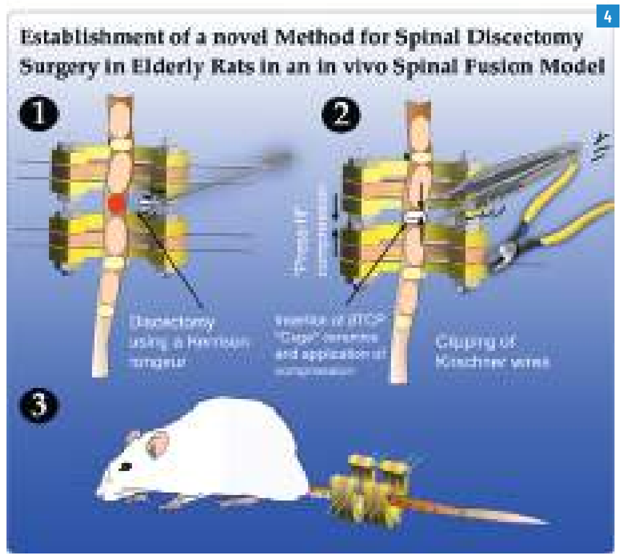
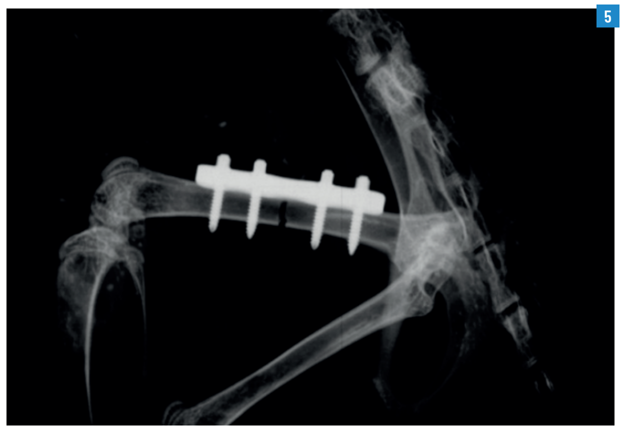



Illustration of the translational research ITN project "disc4all". It is a complex interaction of computer sciences, biologists and engineers to achieve major insights into the prevention of low back pain caused by intervertebral disc degeneration.




An overview of procedures of a newly established non-spinal fusion model. Spinal fusion in vivo animal model illustrating the concept of the procedure 1) discectomy of coccygeal intervertebral disc 2) placement of a ceramic of βTCP that was coated with cytokines 3) Schematic view of operated Wistar rat with fixator extern that applies compression to induce spinal fusion.




X-ray of a fixed bone fracture in a large bone defect model in black six mice 12-week post-operation.

**Bone Biology and Orthopedic Research**

A further topic of interest in orthopedics is the healing of osteoporotic bone treated with bisphosphonates (BP), a class of drugs inhibiting osteoclastic bone resorption. In the past year, a mouse model of OVX and ßTCP-filled femoral critical size defects was applied to investigate whether treatments with BP affect defect healing and biomaterial turnover were impaired. After harvesting all the tissue samples and preparation of the RNA, presently the outcomes are assessed by histomorphometry and 2$^{nd}$ Generation Sequencing. This work is performed by Franziska Strunz, Ph.D. student, and supported by a grant from the Alfred & Anneliese Sutter-Stöttner Foundation.

Gadolinium (Gd) is a component of contrast agents frequently used in clinical practice. Despite the frequent application, it is not clear, whether incorporation of Gd in tissues may cause negative long-term effects. In this project, the effects of ionized Gd and of complexed Gd on the development and activation of bone cell lineages are investigated. This work is performed by Franziska Strunz, Ph.D. student, in collaboration with Dr. Rainer Egli (Clinic of Diagnostic and Interventional Radiology) and supported by a grant from the Inselspital. In collaboration with Dr. Philippe Krebs (Department for Pathology, University of Bern) the effects of a deficiency in the Inositol-Polyphosphat-5-Phosphatase (SHIP1) on osteoclast development and activity is being assessed. SHIP1-deficient Styx mice are characterized by a low bone mass phenotype, and within this project, the cellular base for this phenotype is analysed in vitro and in vivo.

**Cranio Maxillo Facial (CMF) Research**

The interest of the Saulacic Research Group is focused on translational research. Key topics within the field of bone regeneration are the development of new biomaterials, assessment of the biocompatibility, and the influence of the biodegradation on guided bone regeneration.

The indication for a specific bone substitute material is related to the type and the stage of alveolar-ridge resorption. Vertical bone defects are considered the most demanding for reconstruction. The feasibility of simultaneous vertical bone augmentation using block grafts (bone ring) and implant placement was established in collaboration with Advance Research Center, The Nippon Dental University School of Life Dentistry at Niigata, Japan. In terms of osseointegration, single-stage implant placement with autogenous bone has been demonstrated as useful to shorten an overall treatment period. Different biomaterials in block form have been developed to avoid the use of the autogenous block bone grafts.

**Selected Publications**

**[1]** Croft AS, Roth Y, Oswald KAC, Ćorluka S, Bermudez-Lekerika P, Gantenbein B (2021). In Situ Cell Signalling of the Hippo-YAP/TAZ Pathway in Reaction to Complex Dynamic Loading in an Intervertebral Disc Organ Culture. International Journal of Molecular Sciences, 22, 13641.

**[2]** Gantenbein B, May RD, Bermudez-Lekerika P, Oswald KAC, Benneker LM, Albers CE (2021). EGR2, IGF1 and IL6 Expression Are Elevated in the Intervertebral Disc of Patients Suffering from Diffuse Idiopathic Skeletal Hyperostosis (DISH) Compared to Degenerative or Trauma Discs Applied Sciences, 11, 4072.

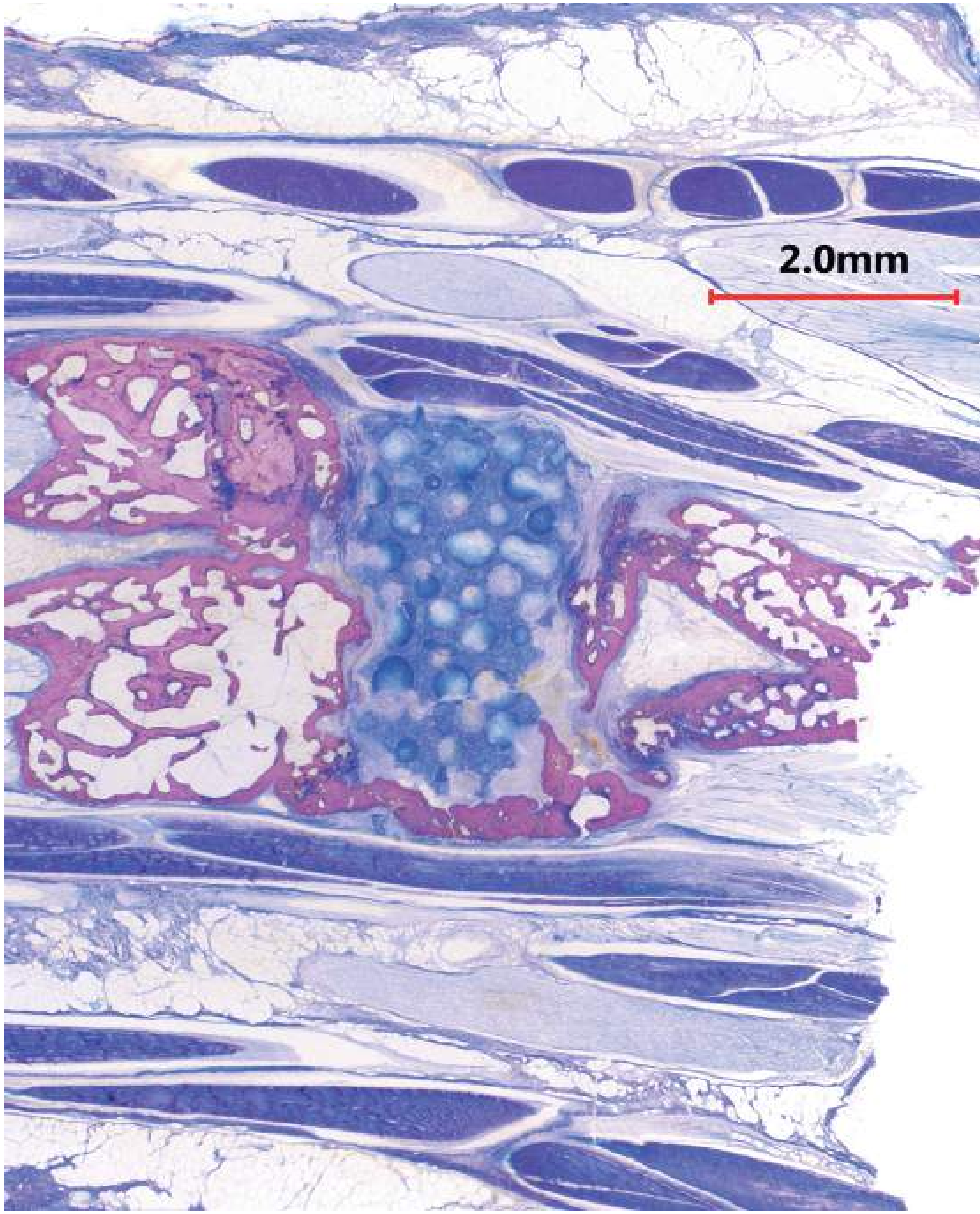
**[3]** Guerrero J, Häckel S, Croft AS, Hoppe S, Albers CE, Gantenbein B (2021). The nucleus pulposus microenvironment in the intervertebral disc: the fountain of youth? European cells & materials, 41, 707-738, 3568.

**[4]** Lazarus E, Bermudez-Lekerika P, Farchione D, Schofield T, Howard S, Mambetkadyrov I, Lamoca M, Rivero IV, Gantenbein B, Lewis CL, Wuertz-Kozak K (2021). Sulfated Hydrogels in Intervertebral Disc and Cartilage Research Cells, 10.

**[5]** Saulacic N, Muñoz F, Kobayashi E, Chappuis V, Gonzáles-Cantalapiedra A, Hofstetter W (2019). Effects of local application of alendronate on early healing of extraction socket in dogs. Clin Oral Investig, 24, 1579-1589.

**[6]** Schnyder D, Albano G, Kucharczyk P, Dolder S, Siegrist M, Anderegg M, Pathare G, Hofstetter W, Baron R, Fuster DG (2021). Deletion of the sodium/hydrogen exchanger 6 causes low bone volume in adult mice Bone, 153, 116178.






Histology of Toluidin blue/Fuchsin Red staining of Tri calcium Phosphate (TCP) carrier implanted in a rat tail animal spinal fusion model of the elderly 12 weeks post-op. The carrier was only partially resorbed by addition of 1 µg/ carrier Bone Morphogenic Protein 2 (BMP2).

# Department of Biomedical Photonics of the Institute of Applied Physics

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### Research Profile

The research of the department is focused on the investigation of various possibilities to employ pulsed infrared lasers in new medical disciplines and the optimization of the clinical outcome in fields the laser is already being used. Emphasis is placed on four interdependent fields: (1) the study of the physical processes underlying the light propagation in tissue and the interaction of laser radiation with soft and hard tissues, (2) laser-induced reversible and irreversible changes in optical properties of tissue response and the consequence of these changes on thermal and mechanical tissue damage and ablation, (3) the development of laser and fiber-delivery systems optimized for specific medical applications; and (4) the development of novel biomedical optical and ultrasound imaging techniques. In particular, we concentrate on the development of two quantitative imaging techniques: polarimetric imaging of the human brain to determine the orientation and degree of alignment of nerve fiber bundles with the goal to visualize brain tumors and optoacoustic and ultrasound imaging to image tissue structures and function. Both imaging techniques have the potential for patient-tailored tumor theranostics. Questions to be addressed are of applied and fundamental character: (i) What limits the image depth and resolution and how can both be increased? (ii) How does laser light interact with contrast agents? and (iii) How to improve multimodal imaging devices for clinical use simultaneously measuring echo and Doppler ultrasound, tissue elastography, speed of sound, and optoacoustics? Further main topics are two-photon imaging, fluorescence lifetime imaging, and interactions of ultrashort near infrared laser pulses with biological soft matter.

### Optoacoustic and Ultrasound Imaging

Optoacoustic (OA) imaging allows the display of optical contrast inside tissue based on detection of thermoelastically generated ultrasound after tissue irradiation using nanosecond pulsed lasers. In combination with pulse-echo ultrasound, OA is promising to improve diagnostic accuracy via the display of small blood vessels and the local blood oxygen saturation within the anatomical context. For this purpose we developed a hybrid real-time multi-illumination (MI) multispectral OA imaging setup with ultrasound (US) imaging capability; we trained gradient-boosting machines on MI spectrally colored absorbed energy spectra generated by generic Monte Carlo simulations, and used the trained models to estimate sO2 on real OA measurements. These studies proved highly accurate and showed consistently good estimates on sO2 values in humans. This proves that our OA imaging method has the potential to be a robust tool enabling quantitative OA oximetry imaging in humans.

On the other hand, sound speed as a diagnostic marker has been of interest for many years due to the fact that sound speed can reveal changes in the structure of tissues coming along with diseases such as cancer, cirrhosis, fibrosis, and fatty liver disease. In addition, knowledge of the spatial distribution of sound speed benefits ultrasound imaging in general. Image reconstruction conventionally assumes a homogeneous sound speed, which leads to blurring and inaccurate display of tissue anatomy in the presence of acoustic aberrations. We are developing a technique that allows for a spatially resolved quantitative detection of sound speed using conventional pulse-echo ultrasound. Within a clinical study the SoS imaging technique proved to be highly sensitive showing a lower SoS in the liver due to steatosis. Our reserach is directed towards the developemnt of a multimodal diagnostic imaging system combining classical echo and Doppler ultasound with elastography, optoacoustic and speed-of-sound measurements. 1

### Polarimetry

With more than 120 various tumor types, malignant brain tumors are a particularly difficult disease to diagnose often because their exact border is hard to precisely determine. The interaction of polarized light with matter can reveal features that are invisible to ordinary imaging techniques i. e. orientation of tissue structures. We are developing a polarimetric microscope that can measure cross- and auto-correlations between arbitrarily polarized incident and backscattered light (these correlations being commonly coded in the 4x4 Perrin-Mueller matrix). Our research shows that polarimetry allows for sensitively defining the different degrees of alignment in healthy brain tissue in-vivo without prior tissue preparation. On one hand, it can be used to help accurate delineation of cancer tissue during resection. On the other hand, given the promising sensitivity of distinguishing nuances in degree of alignment inside white matter, it could also be used to guide resections by identifying vital nerve fiber trajectories by performing tractography of nerve fiber pathways in the brain. In addition to applications in the brain, the presented method has the potential to identify pathologies in other tissue types consisting of fibrous structures, such as the skin for diagnosing skin cancer or for monitoring the healing process after skin injuries. Recently, we added a 2D single-photon counting camera that allows us to perform time-resolved measurements resulting in additional depth information and providing quantitative information about optical tissue properties. Our goal is to develop an instrument able to clinically differentiate tumorous from healthy brain tissues to clearly determine tumour boundaries. In parallel, we want to thoroughly study the fundamentals of polarized light propagation in random media. 2

### Respiratory Ciliary Clearance

Our research is directed on one hand towards a better understanding of the processes underlying the ciliary motion. For example, we would like to understand how the characteristic motion pattern of individual cilia is related to the collective ciliary motion pattern and how this can be influenced by medications. On the other hand, we would like to provide the physicians a tool to clearly diagnose primary ciliary dyskinesia (PCD). To this end, we developed a high- speed video reflection microscope and a software package for data analysis that allows us to characterize mucociliary function in vitro by means of quantitative observables, such as the ciliary beating frequency, the velocity and wavelength of the metachronal wave, and the mucociliary transport. This system has the potential to become the gold standard for clinical diagnosis of PCD allowing for patient-tailored therapies. To this end we developed a high-speed video reflection microscope and a software package for data analysis that allows us to quantitatively determine ciliary beating frequency, the velocity and wavelength of the metachronal wave, and the mucociliary transport.

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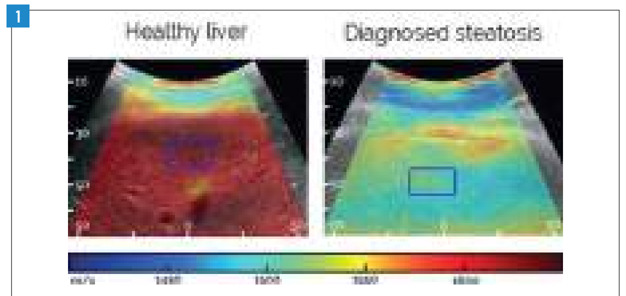
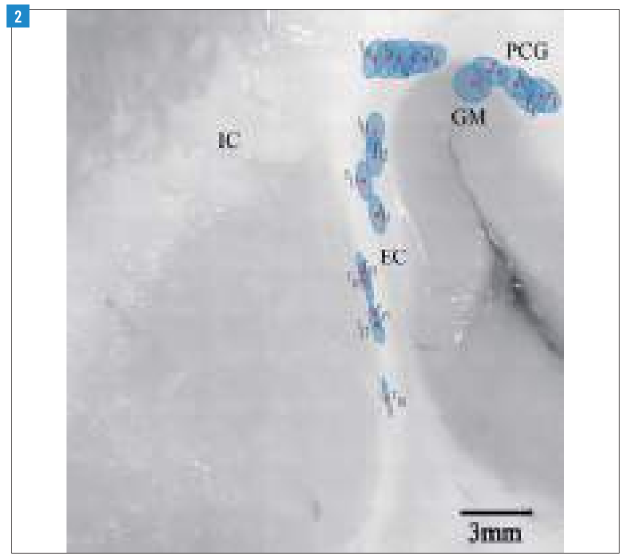



Overlayed US (gray image) and speed-of-sound (color) imaging in echo mode of a healthy and steatosis diagnosed subject.

2




Ellipse-encoded visualization of mean alignment direction and degree of alignment for different measurement points. The ellipses are superimposed on the white light image of the brain sample. The red circles represent the position of the probing beam. The orientation of the ellipses encodes the estimated mean alignment direction and the aspect ratio encodes the degree of alignment. For high degree of alignment the ellipse approaches a line, while for zero degree of alignment it becomes a circle. (EC: External Capsule, IC: Internal Capsule and PCG: Pre-Central Gyrus)

**Selected Publications**

**[1]** Pavel Subochev et al. (2022). Toward real-time giga-voxel optoacoustic/photoacoustic microscopy: GPU-accelerated Fourier reconstruction with quasi-3D implementation, Photonics, 9(1), pp.: 15

**[2]** Andy Burn et al. (2022). A quantitative interspecies comparison of the respiratory mucociliary clearance mechanism, European Biophysics Journal, 51, pp.: 51-65

**[3]** Patrick Stähli et al. (2021) Bayesian approach for a robust speed-of-sound reconstruction using pulse-echo ultrasound, IEEE Transactions on Medical Imaging, 40(2), pp.: 457-467

**[4]** Thomas Kirchner, Martin Frenz (2021). Multiple illumination learned spectral decoloring for quantitative optoacoustic oximetry imaging, Journal of Biomedical Optics, 26(8), pp.: 085001

**[5]** Arushi Jain et al. (2021). Backscattering polarimetric imaging of the human brain to determine the orientation and degree of alignment of nerve fiber bundles, Biomedical Optics Express, 12(7), pp.: 4452

**[6]** Christian Burri et al. (2021). Selective Large-Area Retinal Pigment Epithelial Removal by Microsecond Laser in Preparation for Cell Therapy, Translational Vision Science & Technology, 10(10), pp.: 17

# Center for Artificial Intelligence in Medicine

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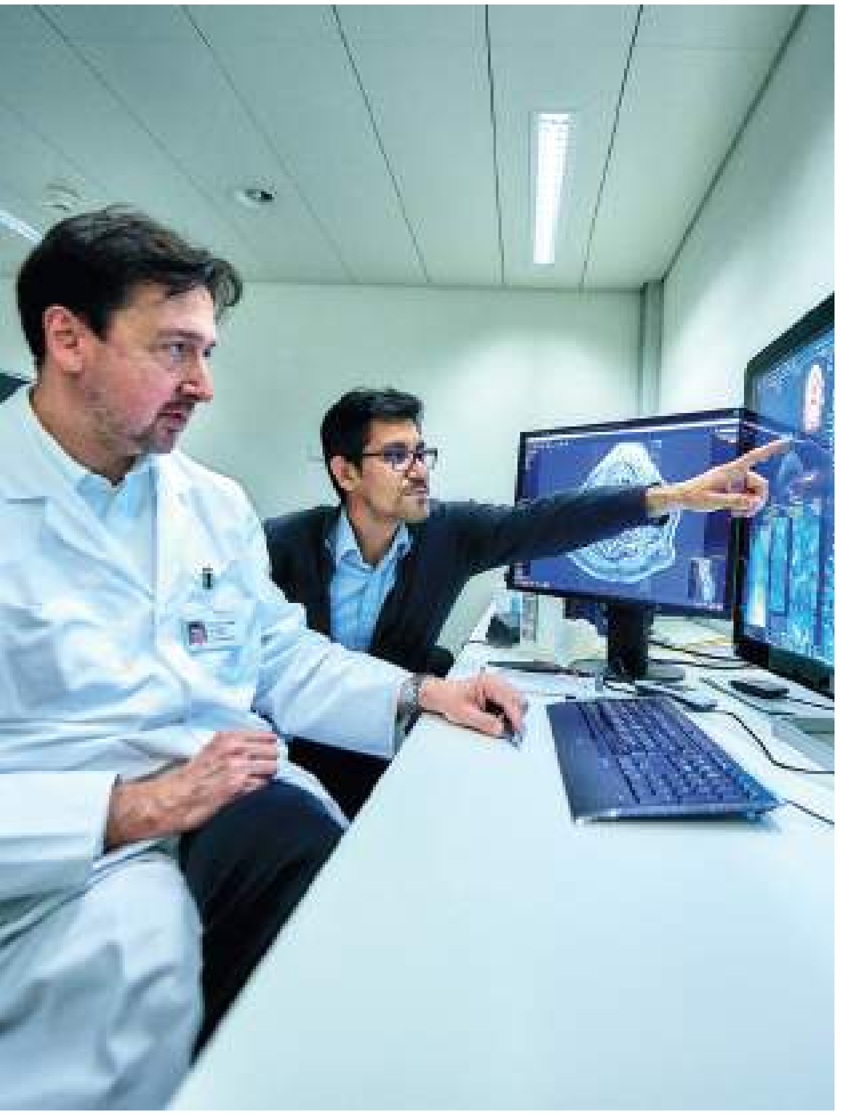


AI in medical imaging is playing a pivotal role in providing improved tools to medical experts.

**Research Profile**

To take leadership in the direction of research and development of Artificial Intelligence (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).

The CAIM is a research, teaching, and translation platform that investigates AI medical technologies that can facilitate the work of doctors and nurses and bring better care to patients. CAIM capitalizes on the significant presence of scientific, healthcare, and medical technology industry 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 resources 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 startup incubation, and create sustained value and economic growth through best-in-class research and translation.



**CAIM's activities are organized on four pillars**

Pillar I: Digitalization & AI 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

CAIM transmits trustworthy knowledge 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

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

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

**AI in Medicine – Fields of Research and Education**

In the age of digitalization and data-based healthcare, 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:

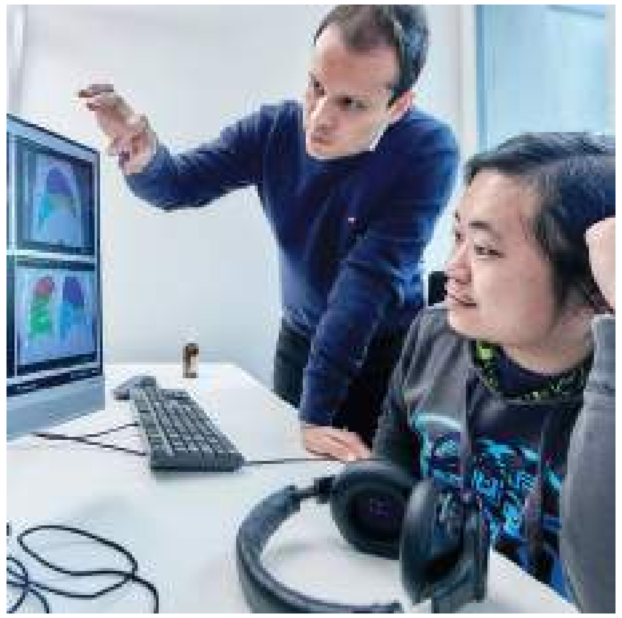
- Quantitative biosignal processing
- Biomarker identification in medical imaging
- Clinical data exploration with deep learning
- Monitoring of chronic disease progression
- Precision medicine (e. g. oncology)
- Real-time surgical navigation
- Surgical and rehabilitation robotics

CAIM provides important insights, evaluation, and perspective for introducing novel AI technologies into clinical care 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 program for AI in Medicine (started fall 2021), and AI in healthcare-related postgraduate training and further education offerings.

**MSc Artificial Intelligence in Medicine**

Our newly established master's program welcomed its first students in September 2021. The primary aim of the master's program is to train the next generation of workforce and entrepreneurs with both theory and practical experiences in AI in health and medicine. The whole concept is based not only on the provision of insight information and knowledge about the algorithms and technologies, as offered by most of the AI postgraduate programs, but to complement them with first-hand experience from healthcare providers. The program is composed of 120 ECTS points over a period of 4 semesters. The entire program is taught in English. The program is designed for students with a bachelor's degree in computer science, biomedical or electrical or mechanical engineering, physics, mathematics, or a related field. The program is built heavily on AI and healthcare including the following modules: AI, medicine, foundation and applied modules. There are also elective options, and a master's thesis to be completed towards the end of the program. The uniqueness of the master's program is that it is completely embedded in the faculty of medicine providing both theory and applications of AI courses, as well as an introduction by healthcare professionals into the medical content. Students are given the opportunity to visit various departments and university clinics, allowing them to dive deeply into clinical procedures and medical routines and apply their knowledge to identify those processes and procedures that can benefit from AI.



CAIM has been active in researching AI solutions for COVID-19 patients.

The vast amount of information in digital pathology is harnessing promising solutions to better mine disease patterns at multiple scales.

Editorial

# Bern University of Applied Sciences BFH

**Bringing specialists together, linking research and teaching, and providing the industry with well-trained professionals and close cooperation in the field of research and development: three ways that the Bern University of Applied Sciences BFH assumes responsibility and supports the medical hub of Bern.**

With the aim of promoting healthy living and well-being, the BFH is committed to addressing societal challenges in healthcare in various locations and departments. Thus, the BFH Centre Health Technologies combines competences across three departments along the entire value chain, from medical technology and medical informatics to healthcare and sport.

In addition to bringing together experts, linking research and education is an important goal of the BFH. Many of the lecturers are simultaneously engaged in research, and the latest discoveries and methods are incorporated and actively implemented in teaching – especially in the context of semester papers and projects. Thus, students often contribute to the development of marketable products, particularly in cooperation with business partners and spin-off companies. This practice-oriented education prepares students both at the bachelor's and master's levels to become outstandingly qualified specialists and executives in the industry.

Medtech is an important branch of industry for Switzerland and has been able to grow steadily in recent years. The BFH is ready to further contribute to this positive development by providing the industry with well-trained professionals and close cooperation in the field of research and development. The BFH is well connected as a member of the Medical Cluster and the Competence Centre for Medical Technology – and a valuable partner in the Mittelland region, as well as throughout Switzerland and internationally.

**Sebastian Wörwag, President**
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**Research Profile**
The BFH Centre Health Technologies as an interdepartmental collaboration between the School of Engineering and Computer Science, the School of Health Professions, and the Swiss Federal Institute of Sport Magglingen SFISM combines areas of expertise (see below) across the entire value-creation chain from medical technology and medical informatics to healthcare and sports. 1

Various research institutes jointly foster technologies that improve the quality of life of patients and the health of society and enhance the performance of people who participate in sports. Applied interdepartmental research and development projects across the entire process chain from idea generation to innovative products or services as well as impact analysis are aimed – in a user-centric and participative way, incorporating relevant stakeholders in the fields of healthcare and sports.

**Esophageal ECG System for 3D Pacemaker Lead Localization**
The increase in cardiovascular diseases has led to a corresponding increase in pacemaker implantations worldwide. One of the risks that may occur during this procedure is the misplacement of stimulating pacemaker electrode leads. To overcome the limitations of state-of-the-art pacemaker lead localization methodologies, we are developing an innovative system

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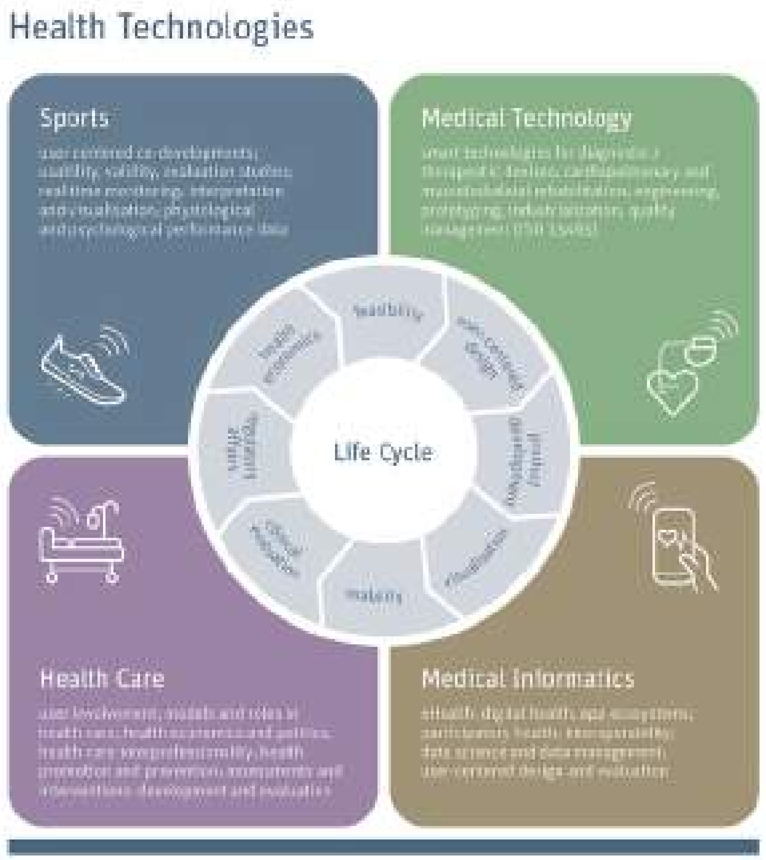

for three-dimensional, minimally invasive, real-time pacemaker lead localization using esophageal ECG. The esophageal ECG system (esoECG), consisting of the esoECG-3D catheter and esoLive analysis software, has been investigated for atrial arrhythmia applications and has demonstrated the ability to localize stimulations from various locations on the heart epicardium. Preliminary data analysis has shown the system can be applied to ventricle pathologies as well, a novel concept for esophageal ECG, which is historically considered limited to atrial applications. Innovative localization in the ventricle region makes the esoECG system available for use in a wider range of applications, such as localizing pacemaker leads during implantation surgery. The ability to locate leads in three dimensions in real-time should result in fewer misplacements, which would in turn improve the quality of life of patients and help save hospital resources.

The current research is highly interdisciplinary, including work on improved catheter designs, data acquisition device development, signal processing, and finally software development of the visualization tool. Overall, we aim to provide a fully integrated esoECG system as a surgical tool for pacemaker lead localization and other minimally invasive, real-time cardiac localization tasks using esophageal ECG.

This project is in close collaboration with the Department of Cardiology at the Bürgerspital in Solothurn and is currently funded by the BRIDGE program, jointly offered by SNSF and Innosuisse.

### Tibial Translation

Injury to the anterior cruciate ligament (ACL) occurs frequently in physically active people. A rupture of the ACL results in joint instability and can eventually lead to knee osteoarthritis. For clinical decision-making about treatment modalities or to assess the rehabilitation progress, mechanical knee stability is evaluated during clinical examination by manually testing the passive knee displacement (Lachman Test, Drawer Test, Pivot Shift test), also described as anterior tibial translation. Mechanical knee stability during functional tasks, like standing or walking, is of utmost importance since knee stability is challenged in exactly these situations. The mentioned clinical knee stability tests are limited to passive situations and cannot directly be applied to weight-bearing situations. Therefore, a prototype of a measurement system to assess anterior tibial translation was recently developed in cooperation between the Biomedical Engineering Laboratory of the Institute of Human Centered Engineering at the BFH School of Engineering and Computer Science and the Bern Movement Lab at the BFH School of Health Professions.

The measurement systems consists of a device with linear transducers on the tibia and patella and a data acquisition software with a graphical user interface that allows physiotherapists to measure the anterior tibial translation. On one hand, it currently covers the passive clinical testing condition for validation against the state-of-the art. On the other hand, it supports a weight-bearing testing situation where the tibia is artificially perturbed and pulled forward by a distinct impulse while a test subject is standing in a regular pose. Validity and reliability have recently been evaluated in a cross-sectional study with 20 healthy test subjects. The evaluation has demonstrated a valid and clinically relevant measurement instrument to assess anterior tibial translation, which has the ability to detect the cutoff value of 3 mm described in the literature for the diagnosis of ACL-deficient knees. Further research is required to investigate ACL-deficient or hypermobile knees to gain more insight into the variability of the anterior tibial translation in different cohorts. The long-term goal is to measure the anterior tibial translation under dynamic loading like stair climbing, which is currently pursued within another bachelor's thesis project.

### Sprechende Bilder

Language barriers are the most common obstacles to emergency care for migrant children and young people, seriously impacting patient safety. Understandable communication in care is therefore essential for safe, high-quality, and equitable healthcare. The project "Sprechende Bilder" (Talking images) aims to address these challenges. A digital image-based tool was developed to support non-verbal communication in pediatric emergencies. The tool was developed in a participatory design process involving potential users (pediatric emergency nurses, migrant children, and parents) and an interdisciplinary team of BFH researchers from communication design, nursing research, and medical informatics. Requirements were collected through interviews and questionnaires shared with nurses. Besides requirement collection, the development process includes mockup testing, prototype development, usability testing, and user studies. During the entire development process, feedback from future users was collected. Key research questions were: How to design a communication aid for pediatric emergency? How to design images that are understandable for people with diverse cultural backgrounds? Which features are useful for the daily practice? 2

2

The digital image-based tool can support non-verbal communication in pediatric emergencies.

### Findings

The participatory design process enabled us to design images that are understandable for migrant parents and nurses. Participants confirmed that the images – even though kept simple – are extremely representative. Communicating visually is considered to be clear. However, we also learned that only image-based communication is insufficient for an empathic interaction in emergency situations. The interactions between parents and nurses also included mimicking and gestures to support the communication. There is great potential to extend the tool, for example regarding the follow-up procedures and regarding documentation facilities.

**Selected Publications**

**[1]** Beatrice Kaufmann, Anouk Haldemann, Christopher Lueg, Loraine Olalia, Friederike Thilo, Kerstin Denecke (2021). Can we do better than gesturing? Requirements for a digital communication aid to support non-verbal communication in paediatric emergency care, Proc. of Medinfo Conference.

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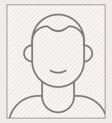
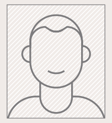

Murat Sariyar


François von Kaenel


Alexander Kreutz

**Research Profile**

Knowledge management

We focus on activities in the field of decision-making support (clinical decision support), expert systems and terminology, semantics, and ontologies closely associated with them for applications in the field of pharmaceutical treatment safety and data management, for example, clinical studies or e-learning.

Evaluation of medical IT applications

We possess expertise in the evaluation of medical IT applications – for example, clinical IT systems, decision-support systems, and active and assisted living (AAL) installations – as well as in the assessment of quality initiatives and e-health infrastructure.

E-Health and telemedicine

We lead and support a variety of initiatives in the field of e-health and telemedicine, dealing with the development of the Swiss Electronic Health Record, Mobile Health, the establishment of integrated care processes, and telemedicine applications. We analyse aspects of technical and semantic interoperability, the integration of Active and Assisted Living (AAL) into healthcare, and the secondary use of data and Big Data.

Patient-centred applications

A key area of our research activities is patient-centred applications, such as personal mobile applications (mHealth), studies on patient empowerment and self-management, and compliance support activities. We also focus on personalised medicine as an area of application. Informed patient privacy consent plays a significant role here. An example of application is the development of a pollen allergy app (Ally Science) for a major pollen study, supported by the citizen science approach, based on the MIDATA personal data and consent-management platform.

Information management and economic analysis of processes in the healthcare sector

Finally, another area we focus on is information management and the economic analysis of processes in the healthcare sector. We possess expertise in this environment for the analysis of treatment processes, the optimisation of treatment chains, the design of clinical pathways, including pathway cost calculations, and the working procedures for electronic order communication (Computerised Physician Order Entry (CPOE)).

**Digitalisation and transmission of clinical information in nursing (digi-care)**

Situation

According to an analysis by eHealth Suisse, the use of information and communication technologies (ICT) in healthcare is essential, and nursing staff are increasingly confronted with the digitization of work processes. This will also radically change the way clinical patient information is communicated by nurses and other healthcare professionals. It is therefore essential to promote the teaching of the relevant competencies in education and training, the exchange of good practice, and the development of effective teaching and learning methods.

Course of action

In the first phase, we will conduct an ethnographic study in six hospital units (general care, acute care, or rehabilitation wards) in Italian-speaking Switzerland (n = 2) and German-speaking Switzerland (n = 4) to identify situations in which clinical patient information is shared and that are perceived as significant by the study participants. In the second phase, we will select and validate a set of typical significant situations, working closely with study participants and experts. In the third phase, we will use the selected situations to develop two types of prototypes: a) prototypes of video-based multimedia learning situations that can be used in vocational schools and in the workplace for education and training, and b) prototypes



Digitisation of examination and reporting processes in radiology

of solutions that can be used to mitigate the situations judged to be critical from a technological point of view. In the fourth phase, we will validate the developed prototypes (learning situations and technological solutions) together with the study participants and with experts and disseminate the results. We will follow an ethnographic approach with targeted observations of the activities through job shadowing and auto-confrontation interviews. Data analysis and processing follows semiological principles and aims to identify the subjective meaning of the situations.

Results

The 37-month project successfully launched in October 2020, with 16 context analysis interviews conducted at four hospitals through October 2021. 320 hours of job shadowing were captured with video and 16 self-confrontation interviews were conducted. By this time, 140 information sharing situations and 76 IT-related incidents could be selected and documented from the first four hospitals. In the meantime, data collection has been successfully completed in all six hospitals. Currently, the data analysis is being carried out in order to discuss the results step by step with the hospitals concerned and with experts from the field of continuing education in a multi-stage process starting in the second quarter of 2022 and to select particularly interesting situations and incidents for which training videos, process illustrations, and mockups for a better IT design will then be developed.

**"SMARAGD": Supporting Radiology Reporting using Natural Language Processing**

Radiology is a high-throughput medical discipline that serves different customer groups (referring physicians and patients). The high work pressure and economic constraints necessitate compromises in service. For example, referring physicians receive medical reports in prose, but would prefer a standardized and digitized form. Personal contact of physicians (radiologists) with their patients is only possible in exceptional cases for logistical reasons. The SMARAGD project aims to support the radiological reporting process using Natural Language Processing (NLP).

On one hand, the project will develop methods for automatically structuring radiology reports. Using a combination of an NLP pipeline and a novel template, reports written in German prose can be output in a structured, standardized, and completeness-checked form. On the other hand, an anamnesis chatbot will be developed to give patients an option of an anamnesis conversation using a chatbot before the examination. The content, also processed via NLP, is fed to the radiologists during the reporting process.

The project will apply user-centered design methods to ensure an adequate user experience of the developed technologies. It will also help to understand the usual working method of radiologists resulting in technologies that support, not hamper, the daily work.

The entire software development cycle will be covered in the project. Starting with collecting requirements, the needs from physicians and patients will be collected. Building upon technologies from industry partners, the project will extend the existing methods and bring technologies together to create new products. Software development will be accompanied by comprehensive technical testing as well as user and usability testing. In addition, research will investigate the regulatory compliance of this AI-based medical device software.

Project partner

- Inselspital Bern, SITEM, ID Suisse AG, SIPBB, mimacom, wemedoo, BFH
- Funding organization: Innosuisse

**Selected Publications**

**[1]** Tippenhauer, Kevin; Philips, Marwin; Largiadèr, Carlo R.; Sariyar, Murat; Bürkle, Thomas (2020). Integrating Pharmacogenetic Decision Support into a Clinical Information System; Stud Health Technol Inform. 2020 Jun 16;270:618-622.

**[2]** Zbinden, Chantal; Strickler, Moritz; Sariyar, Murat; Bürkle Thomas; Seidel, Kathleen (2021). Digitizing Data Management for Intraoperative Neuromonitoring.; Stud Health Technol Inform. 24;278:211-216.

# Institute for Human Centered Engineering HuCE

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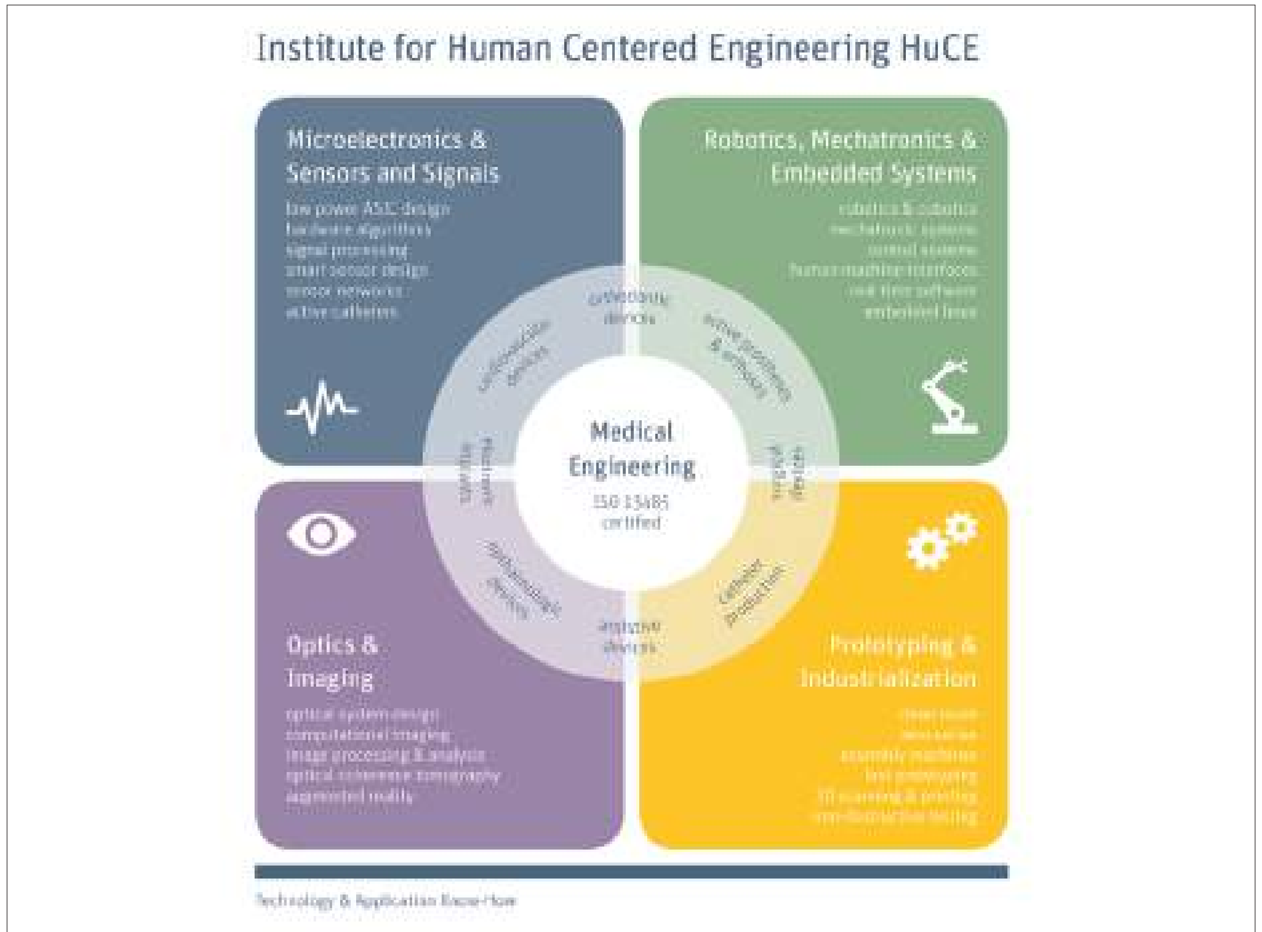
**Research Profile**
The Institute for Human Centered Engineering HuCE is a collaboration of six applied research and development laboratories, which provide a broad spectrum of engineering competencies focused on medical technology and industrial automation (see below). We aim to develop research-based technologies and foster their transfer into marketable products and services in close collaboration with industrial enterprises and hospitals.

The six laboratories presented on the subsequent pages, are:
- Microelectronics Laboratory
- Optics Laboratory
- Biomedical Engineering Laboratory
- Laboratory for Computer Perception and Virtual Reality
- Robotics Laboratory
- Laboratory for Sensor Technology






# Microelectronics Laboratory

## Institute for Human Centered Engineering

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**Julien Zimmermann,** Head of Manufacturing, Endress+Hauser Flowtec AG



### The HuCE-microLab in a nutshell

We provide broad technology know-how in various disciplines ranging from microelectronics, signal processing, feedback control, high-speed hardware algorithms to microstructures and surfaces, which are tailored to novel smart medical devices. Our engineering competences are complemented by micro-assembly and packaging technologies as well as validation know-how of manufacturing processes in our in-house clean room, optimally equipped for medical device manufacturing enabling the bridge from research to small series production.

### Windowed State Space Filters for Peak Interference Suppression in Neural Spike Sorting

In neural tissues, each firing neuron cell generates action potentials, which are observed as electric spikes on microelectrodes of a neural probe placed on the cortex. Multiple such spikes generated by a single neuron typically have a signature waveform due to the neuron cell geometry and orientation. For real-time neural decoding in brain implants, each detected spike must be linked back to the corresponding neuron, a process called spike sorting. Neural signals often originate from high-density, multi-channel probes with high data rates. Especially for recent neural probes with hundreds of channels, the computational effort of template matching with matched filters becomes substantial, as it scales linearly with the number of filter taps, channels, and patterns. Therefore, there is an urgent need to reduce the complexity of such filters.

In our approach, we use computationally attractive Autonomous Linear State Space Model (ALSSM) filters to substitute linear finite impulse response (FIR) filters. We approximate the impulse response of peak interference suppression filters by low-order ALSSMs and perform the signal convolution in the new, low-dimensional ALSSM feature space. We demonstrate our method on real neural recordings from array probes and conclude that our ALSSM substitution has an order of magnitude lower computational complexity and outperforms standard SNR-matched filters in detection quality. 1

### Neonatal Esophageal Observation (NEO)

Preterm infants, who account for more than 10% of all births worldwide, very often require cardiorespiratory monitoring on a neonatal intensive care unit due to autonomic dysregulation. Surveillance of the heart rhythm and respiratory rate, however, is cumbersome since surface ECG and EMG registrations suffer from relevant motion artifacts. The resulting high number of false positive alarms impedes care prioritization and optimal support of these neonates. Furthermore, accurate diagnostic tools that objectively assess and monitor precisely the level of maturation of neonates are lacking. Discharge of preterm infants from the hospital is only indicated once autonomic dysregulation is completely dissolved.

To overcome the limitations of state-of-the art technology, we aim to develop a novel monitoring system for preterm infants. The neonatal esophageal observation (NEO) system bases on esophageal signal recording, a technique that is widely known to provide high-quality electrocardiography and diaphragm electromyography. Based on recent technical advances in diagnostic catheter design and manufacturing, and achieved insights of esophageal signals, the NEO project proposes that vital signs and autonomic dysregulation may be monitored with a single esophageal catheter. The new catheter will integrate multiple sensors that, in combination with model-based signal and data processing based on machine learning, may provide accurate and robust measurements of heart rate, respiratory rate, swallowing-breathing coordination, temperature, and SpO2. In addition, the multilumen catheter allows simultaneous enteral feeding.

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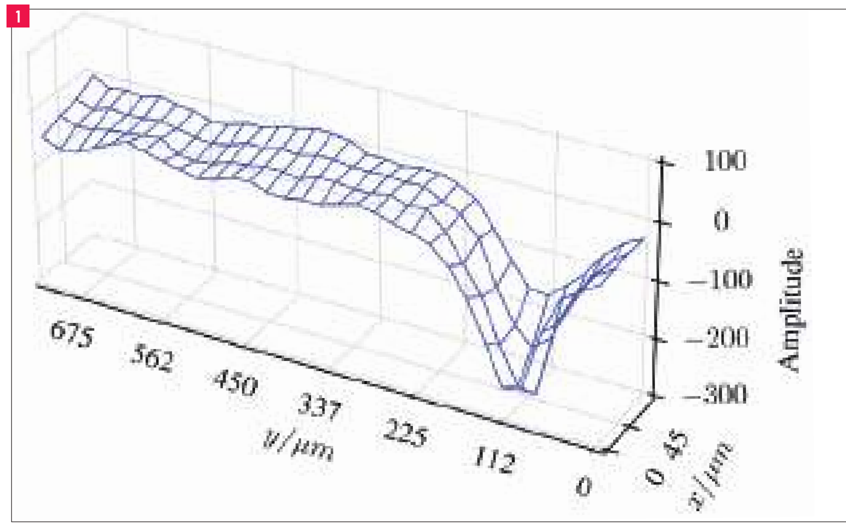


Spatial plot of a single neuron spike from a micro-electrode array probe on a mouse cortex. The probe spans an area of 67 x 720 µm.

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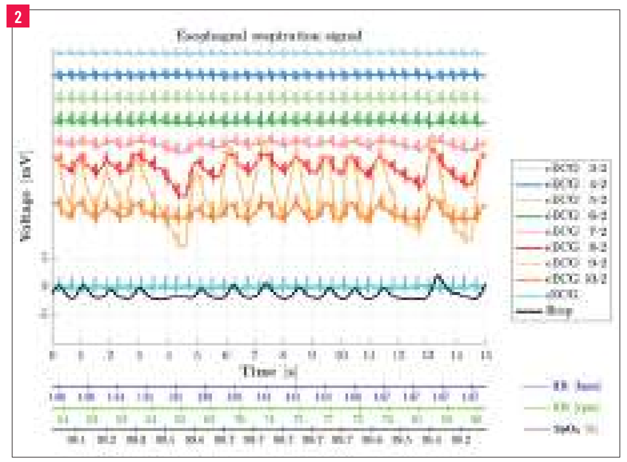

Multichannel esophageal signals providing reliable estimates of the neonate's heart rate and respiratory rate based on model-based processing

The NEO approach is a scalable solution dedicated to low-income and highly developed countries. Basic and cost-effective cardiorespiratory monitoring may be achieved with a low-cost catheter version in combination with telemetric data exchange to remote hospitals serving as monitoring unit. On the other hand, a multisensory catheter in combination with advanced monitoring of perceived level of maturation and achievement states, personalized care may be possible in more advanced hospitals. However, both solutions are expected to drastically reduce the number of false alarms in NICU monitoring and concurrently lower the monitoring burden as the result of lower resource allocation by the NICU and optimized NICU stay of preterm infants. 2

### Smart Catheter Design and Manufacturing

The objective of the novel platform is to foster sustainable innovation in the development and production of smart diagnostic and therapeutic catheters through the patented design and manufacturing process. The design concentrates on thin-film, flexible printed electronic circuits (FPCB) with liquid crystal polymer (LCP) as biocompatible substrate, which integrates the multichannel and/or multimodal sensors or actuators as well as miniaturized amplifier or driving circuitries. Analog-to-digital conversion placed shortest to the sensor or multiple MEMS transducers are potential new features integrated into the next generation of active catheters. The

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3D CAD design of a smart catheter with active transducers embedded (left) and prototype of a smart catheter with FEM-optimized LCP design for multiple passive electrodes

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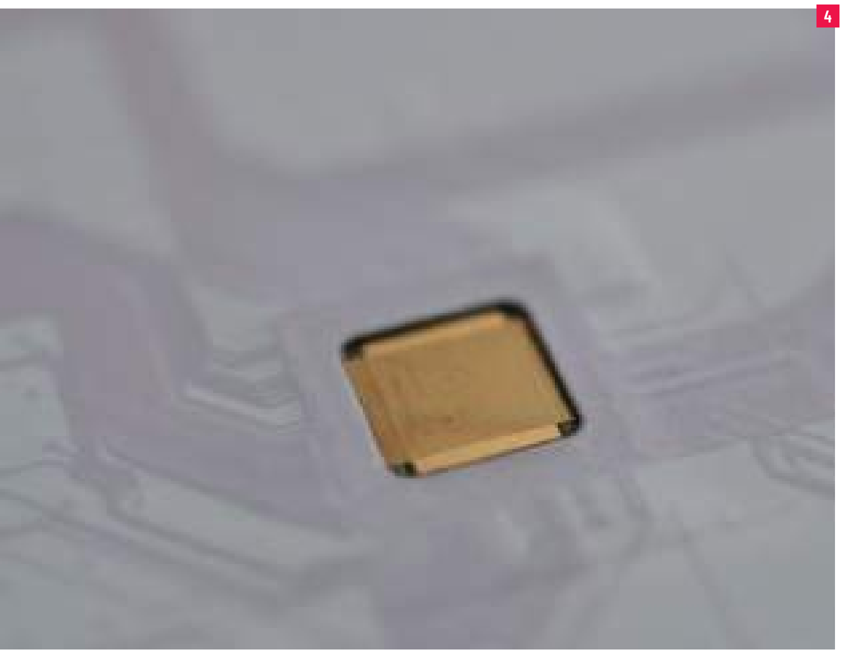

Microchip embedded in LCP

smart catheters will provide the interventionalist with new instruments that benefit from improved performance, higher resolution, and novel sensing and imaging capabilities. On the other side, the manufacturing process is based on a versatile thermobonding process that combines the LCP with the catheter tube. Complete encapsulation is possible with widely used medical-grade tube polymers, such as thermoplastic polyurethane or Pebax. Furthermore, the thermobonding process has been shown to allow a higher degree of automation compared to conventional catheter manufacturing, which will lower the production costs and consequently increase the rentability for legal or OEM catheter manufacturers, i.e. the principal customers of the LCP platform.

The goal of this research project is to extend the novel catheter platform with an enhanced LCP design process based on tailored FEM and CAD models, to increase the maturity of the thermobonding processes and consequently the manufacturing automation, and to announce the innovation in the research community and Medtech industry. A focus is also on the integration of catheters with active transducers into the platform as well as to the design and manufacturing of catheter demonstrators for representative clinical applications. 3

### Packaging for a Microchip-based Multiwell System

Available instruments for cell-based studies are not suited to exploit the potential offered by promising and recently introduced biotechnologies like human stem cells and 3D tissues, such as brain organoids, i.e. lab-grown miniature organs.

The goal of this project as research collaboration with 3Brain and CSEM is to develop a new platform that delivers unrivalled brain-on-chip phenotypic assays in 24-well format. Thanks to >1000 electrodes integrated per well and the BioSignal Processing Unit, the multiwell device features 24k simultaneous read-out sensors. The aspired packaging based on Liquid Crystal Polymer (LCP) will fuse the microchip with the readout circuits and the well frames in a semi-automatic process that may reduce both electrical and leakage failures. While the environment will be controlled by the readout instrument (T, humidity, $CO_2$), new plate inserts will ensure precise sample positioning during both manual and automated operations.

The platform aims at revolutionizing preclinical drug discovery with a high-throughput microchip-based multiwell system. By integrating state-of-the-art microchips into each of the wells that make up a multiwell plate, the system will deliver in situ processing power and data intelligence. Integrated intelligence is a remarkable distinction from other products in the preclinical market, which are purely based on plastic passive plates. The new packaging based on LCP has the potential to reduce failure rates and consequently improve yield and cut production costs. 4

### Capillary Driven Image Flow Cytometry for Blood Cell Analysis

Conventional flow cytometry is routinely used in clinical practice for counting total blood cells and in particular white blood cell sub-types to gain insight into the health of patients. We work on a point-of-care-based solution for image-based flow cytometry method to determine the complete blood cell count. A capillary-driven microfluidic chip is used, which has the advantage over conventional flow cytometry systems in terms of its small size, mechanical simplicity, and robustness, making it suitable for use in portable point-of-care devices. 5

Our approach measures WBCs without lysing the RBCs, enabling a differential WBC count in whole blood, while investigating the RBC as well. To distinguish WBCs in the large bulk of RBCs, fluorescence microscopy methods typically applied to blood smears are used. Having algorithmically identified the individual WBCs, they are classified into three target WBC subgroups based on the difference in their fluorescent spectra and the different ratio of average red to green intensities, as can be done with the specific fluorescent acridine-orange staining that has been used. A scatterplot of the average red-green channel values for the detected cells of 2 µL of blood is shown. Three clusters can be seen, corresponding to the three WBC classes. The contours of the calculated three-component gaussian mixture model are superimposed. By fitting a gaussian mixture model, the likelihood of a given cell belonging to each of the given classes can be calculated and robust class ratios determined even if the clusters are not perfectly separable, as is the case here. For this sample, the relative number of lymphocytes, monocytes, and granulocytes are 26.0%, 5.7% and 68.3%, respectively, which are within the expected range of a healthy individual. Tests for analysing red blood cells more in depth as well as reference tests at the Insel hospital in Bern are planned. 6



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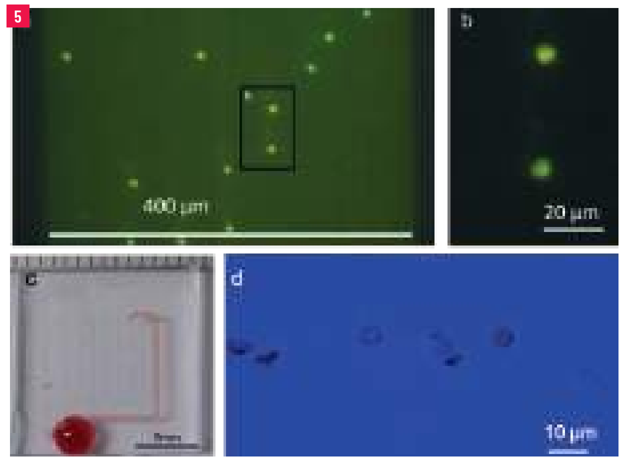


(A) Large microfluidic channel for WBC fluorescent imaging (B) Zoom of two flowing granulocytes (C) Microfluidic chip with hydrophilic surfaces for capillary action (D) Small microfluidic channel for RBC imaging

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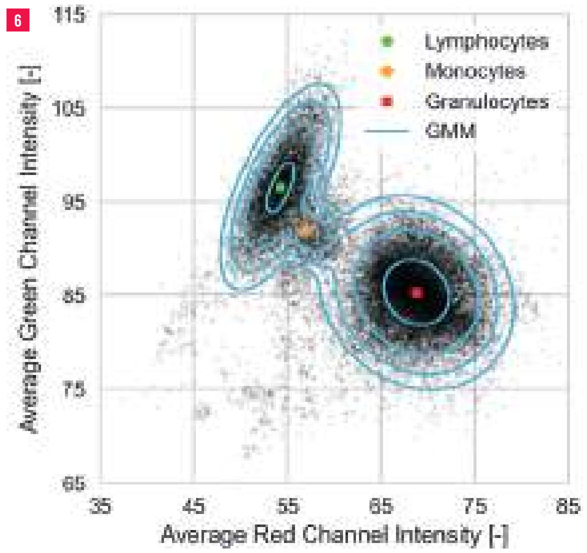


Scatterplot of cell-averaged red and green values of all WBC detected in 2 µL of blood that has flown through the microfluidic channel. Contour lines represent a three-component gaussian mixture model that are superimposed to determine the three major sub-types of WBC.

## Selected Publications

[1] Bürgin, Corine, Patrizia Simmen, Nishant Gupta, Lilian Suter, Samuel Kreuzer, Andreas Haeberlin, Sven M. Schulzke, Daniel Trachsel, Thomas Niederhauser, and Kerstin Jost. "Multichannel Esophageal Signals to Monitor Respiratory Rate in Preterm Infants." Pediatric Research, October 2, 2021, 1–9.

[2] Simmen, Patrizia, Samuel Kreuzer, Manuel Thomet, Lilian Suter, Barbara Jesacher, Phuong-Anh Tran, Andreas Haeberlin, Sven Schulzke, Kerstin Jost, and Thomas Niederhauser. "Multichannel Esophageal Heart Rate Monitoring of Preterm Infants." IEEE Transactions on Biomedical Engineering 68, no. 6 (June 2021): 1903–12.

# Optics Laboratory

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**Research Profile**

Optical Coherence Tomography and Laser Tissue Interaction

The Optics Laboratory of the HuCE Institute focuses on optical coherence tomography (OCT) and laser tissue interaction. The laboratory equipment includes various OCT devices as well as a complete set of optoelectronic measuring equipment and opto-mechanical basic materials. Both spectral-domain (SD-OCT) and swept source (SS-OCT) systems at all common wavelengths are available. Due to the long-term focus of the R&D activities in the field of OCT as well as continued cooperation with various industrial and clinical partners, the Optics Laboratory has acquired significant expertise in the development of OCT systems for specific applications.
Examples are the development of a dedicated OCT for anterior chamber imaging for refractive surgery in combination with a femtosecond treatment laser, the implementation of OCT-based dosimetry control for selective retina therapy with a microsecond treatment laser, and the development of polarization-sensitive OCT for collagen fiber orientation determination in the cornea. Ongoing projects focus on laser tissue interaction in the ultraviolet as well as visible range for applications in the cornea, respectively the retina of the human eye.

Microsecond Large-Area Removal of Retinal Pigment Epithelium in Preparation for Cell Therapy

In recent years, regenerative medicine has become a very promising and advanced scientific research topic. This is also the case for retinal degenerative diseases, such as age-related macular degeneration (AMD). Although there are already promising results regarding retinal pigment epithelium (RPE) stem cell therapy in AMD, a methodology with minimum impact on surrounding tissues for the desirable removal of the diseased host RPE cells preceding the recolonization is still missing. Attempts for selective RPE excision have been made with various surgical tools or chemically. However, these methods are unsatisfactory due to handling complications and unintentional side effects, such as proliferative vitreoretinopathy or retinal toxicity. Therefore, as a novel approach, selective microsecond laser irradiation targeting RPE cells was used for minimally invasive, large-area RPE removal in preparation for delivery of retinal cell therapeutics.



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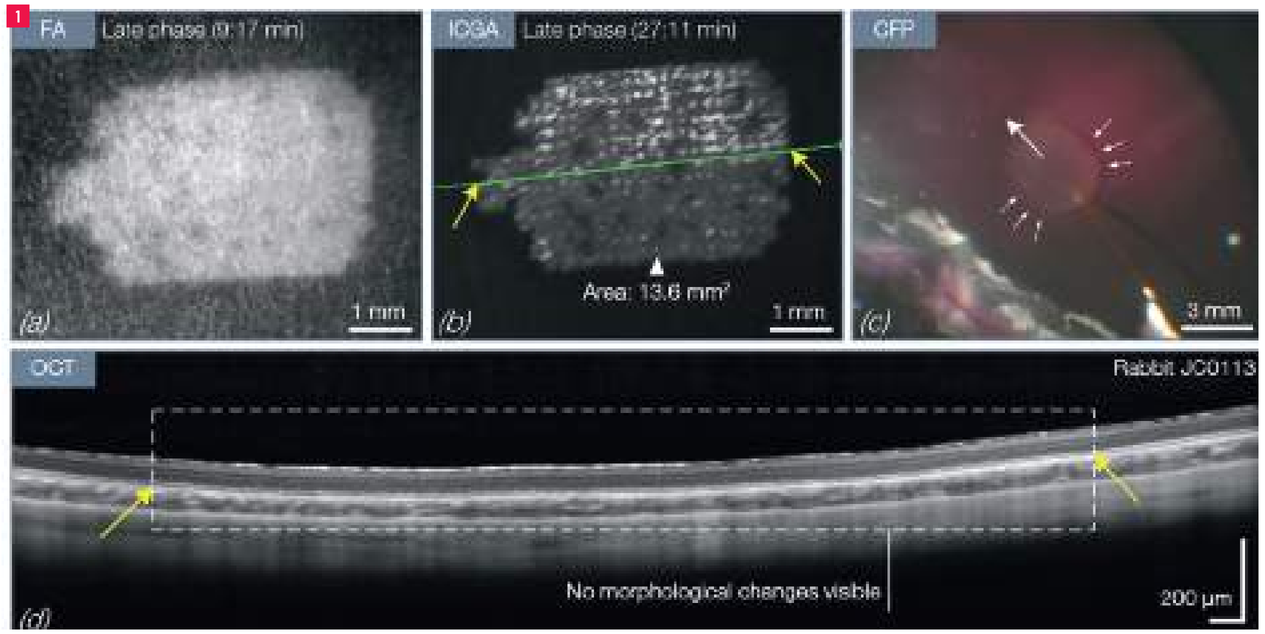



Multimodal imaging of large-area RPE removal after microsecond laser exposure. (a) Late-phase FA showed hyperreflectivity over the treated area. (c) For late-phase ICGA, the treatment pattern was clearly visible. The laser-irradiated area was 13.6 mm2. (c) During subretinal injection, the fluid followed the laser-irradiated area in a controlled manner, away from the cannula. (d) The green line in (b) demarcates the displayed cross-section in the corresponding SD-OCT B-scan image, which shows no visible morphological changes.

Together with a team headed by Boris Stanzel (Eye Clinic Sulzbach, DE), this approach was tested for the first time in an in vivo rabbit model. Ten rabbit eyes were exposed to laser pulses of 8 µs in duration (wavelength, 532 nm; top-hat beam profile, 223 × 223 µm2). A device called SPECTRALIS CENTAURUS was used, which was developed in the Optics Laboratory together with the industrial partners Meridian (Thun, CH) and Heidelberg Engineering (Heidelberg, DE). Post-irradiation retinal changes were assessed with fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCT. Following vitrectomy, a subretinal injection of balanced salt solution was performed over a lasered (maximum 13.6 mm2) and untreated control area. 1

The results of this experiment show that large-area, laser-based removal of host RPE without visible photoreceptor damage is possible and facilitates surgical retinal detachment (Fig. 1). Therefore, the method of selective microsecond laser-based, large-area RPE removal prior to retinal cell therapy may reduce iatrogenic trauma and appears to facilitate superior integration of RPE suspension grafts, compared to subretinal injection alone.

The same device is currently being tested at the Inselspital Bern in a clinical trial regarding selective retina therapy (SRT) with automated real-time OCT laser control.

**Measuring Corneal Collagen Fibre Distribution Using Polarisation-Sensitive OCT**

Today's operation planning for arcuate keratotomy to correct astigmatism during cataract surgery depends on nomograms, statistical diagrams, and the assessment of the surgeon. Unfortunately, the patients are often not satisfied with the visual outcome and still require distance glasses. To overcome this issue, Optimo Medical AG developed the software Optimeyes for the patient-specific simulation, optimisation and planning of cornea surgeries based on a mechanical FEM model and unique algorithms.

The biomechanical properties of the cornea, such as the shape and the strength, arise largely from the precisely organized corneal collagen fibrils structure. The exact knowledge of collagen distribution in the cornea is crucial for accurate patient-specific modeling and surgery planning. Polarization Sensitive Optical Coherence Tomography, on the other hand, may have the capability to indirectly reveal the underlying highly organized collagen structure by detecting its birefringent properties. This information may serve as valuable patient-specific input for surgery planning.

Our research infrastructure and expertise enable us to develop dedicated measuring devices to perform initial ex vivo experiments and to provide proof of concept.

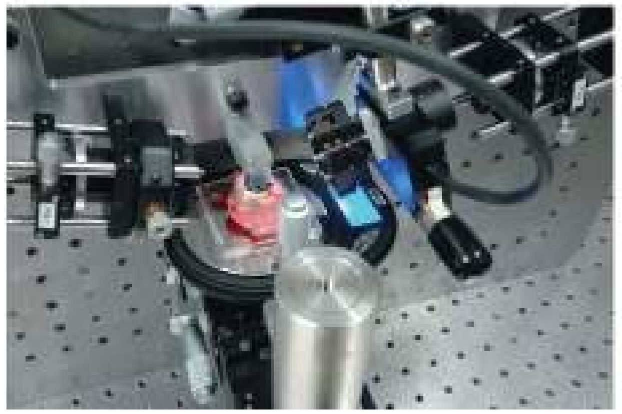
Pulsed Laser for Corneal Tissue Ablation

In ophthalmology, pulsed ArF (193 nm) or up-converted solid-state (210 nm and 213 nm) lasers are used for refractive surgery because the absorption coefficient of corneal tissue in the deep ultraviolet is very high.

For this project, the main objectives are 1) to develop a beneficial UV ablation laser based on different laser technologies then meanwhile establish for, and 2) to investigate the impact of the temporal pulse shape on the ablation result.

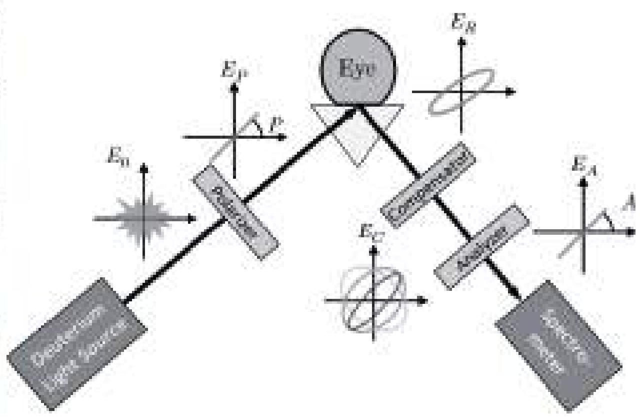
2

(a)



Rotating Compensator Ellipsometry Setup (a)

(b)




Rotating Compensator Ellipsometry Setup (b)

Using different laser technologies allows also for achieving different laser wavelengths than the above mentioned. However, this implies that the optical properties at potential wavelengths are known, especially the corneal absorption coefficient, which is fundamental for the ablation processes. In the past, several groups have published measured absorption coefficients, yet the reported values vary by an order of magnitude. In order to 1) identify reasons for such large variations and 2) to provide the absorption coefficient at other than the three commonly used wavelengths, we first performed ellipsometry on porcine cornea in the wavelength range between 185 nm and 250 nm (Fig. 1). Specifically, we studied the temporal evolution of the absorption coefficient after enucleation for different storing and preparation conditions. We found that tissue degradation leads to a decreasing absorption coefficient irrespective of storage or preparation protocol. The almost linear decrease during the first nine hours post mortem allowed us to extrapolate the absorption coefficient to the time of death and to establish the in vivo absorption coefficient of porcine cornea between 185 nm and 250 nm. The findings will be published in the next issue of the Journal of Biomedical Optics. 2

For precise tissue ablation, a wavelength possessing a small optical penetration depth is required to confine the energy deposition to a small volume. However, to maximize the temperature, it is also required that thermal diffusion during the irradiation time is minimal (thermal confinement). Further, the ablation threshold will be decreased for minimal stress propagation during the irradiation time (stress confinement). Current ablation laser systems use a pulse duration of 10-20 ns. Accordingly, stress confinement for ablation lasers in the deep UV range is off by a factor of >20, while thermal confinement is undercut by a factor or >150. The impact of the UV pulse duration to the ablation result was never investigated for corneal tissue in the ns region, and an impact of the temporal pulse shape is expected as well, as demonstrated in literature for temporal Airy pulses in the ps region [N. Götte et al., Optica, 3(4), 389 (2016)].

The development of the UV ablation laser that allows for investigating these dependencies is in progress. The temporal pulse width and shape will be tuneable within 1 ns to 500 ns and a UV pulse energy >0.5 mJ is anticipated.

**Selected Publications**

**[1]** Burri Christian et al. (2021). Selective large-area retinal pigment epithelial removal by microsecond laser in preparation for cell therapy, Transl Vis Sci Technol.;10(10):17.

**[2]** Burri Christian et al. (2021). Dynamic OCT signal loss for determining PRE radiant exposure damage thresholds in microsecond laser microsurgery, Appl Sci.;11:5535.

# Biomedical Engineering Laboratory

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### The HuCE Biomedical Engineering Lab in a Nutshell

We have knowledge and experience in various engineering disciplines to develop specific solutions to challenges arising in medicine and biology. We concentrate our development and research activities on system integration and development of functional prototypes (mechanics and construction, electronics, software).

### Orthosis System MOWA (modular walking)

#### Introduction

People suffering from foot drop have an increased risk of falling. Often, limited movement in one joint is compensated for by excessive movement in other body parts. This can result in further complications due to overuse. As a treatement, the foot is stabilized with a rigid orthosis at the cost of range of motion. The novel MOWA orthosis (Fig. 1) is less rigid and allows more freedom of movement while still providing enough support to the user for a smoother gait. The goal of this Innosuisse project is to standardize the selection of user-specific combinations of MOWA modules. Therefore, applied research is conducted in sensor-based gait analysis (task of the HuCE-Biomedical Engineering Lab) and a data-driven orthosis selection algorithm. This approach allows for balance between stability and freedom of movement, while replacing the previously lengthy and costy trial-and-error process to fit a conventional orthosis to the user.

#### Gait Analysis Tool

The gait analysis tool (GAT) is a compound of inertial measurement units (IMU) and a processor, and it outputs spatio-temporal gait features. One IMU is placed on each segment of the legs and on the pelvis. The orientation of each sensor is estimated with a Kalman filter, commonly used in navigation tasks. From there, the gait features are calculated, and the time series are segmented into individual strides. The strides are then passed to the selection algorithm.

#### Outlook

The accuracy of the GAT will be compared clinically against the gold standard (optical motion capture). The GAT and the selection algorithm will then be implemented in the MOWA supply chain for fast and user-specific supply. [1]

### 4D-Spine

#### Introduction

Scoliosis is a complex deformity of the spine that affects 0.5–5.0% of the global population of which 80–90% belong to Adolescent Idiopathic Scoliosis (AIS). AIS type of scoliosis is developed by an unknown etiology and occurs mainly during preadolescence or before skeletal growth and maturation and mostly affects females. AIS is mainly manifested as a frontal and lateral distortion and deformity of the spine, which includes 3D axial rotation of vertebrae that affects the shape of rib cage (thorax) as well as the position of the scapulae and pelvis and consequently the aesthetic appearance of the patient's body and posture.



#### Surface Topography Measurements

The current gold standard for the clinical assessment of scoliosis, known as EOS imaging, involves X-ray imaging in the sagittal and frontal plane while the patient is upright standing. To monitor the progression of the pathology and to assess treatments or surgery outcome, patients often undergo repeated X-ray imaging, resulting in repeated exposure to potentially harmful ionizing radiation. A novel 3D optical method, for example rasterstereography (RST), is a less expensive, non-ionizing technique that estimates deformity-related changes of the patient's back using only light as a medium and thus allowing the investigation of the external shape and insights to the deformity of the spine. Figure 2 shows the assessment of the spine based on 3D surface measurements using the ScolioSIM tool, which outputs the spatial position and rotation of each vertebrae. [2] [3]

Today, however, there is no system available allowing for radiation-free, simple, fast, affordable, and dynamic (4D) measurements. Therefore, in this Innosuisse project, the BFH researches the possible 3D scanning methodologies that can be used in such a device and develops a low-cost prototype for capturing 3D body images of the human back. In Figure 3, an evaluation test setup is shown in which different 3D measurement technologies are investigated for their suitability to scan the human back.

### Moving Spine

#### Introduction

Musculoskeletal disorders in the spine are the main cause of age-related loss of autonomy and generate very high healthcare cost. The Moving Spine device is an intelligent and portable rehabilitation and diagnostic device on which the patient lies. It can then replicate the movements of walking in the spine and treat and document its rotational capacity. Based on its diagnostic function, it collects and analyses data, self-regulates in real time, and thus digitizes and personalizes the rehabilitation of the spine, leading to an increase in autonomy and a decrease in healthcare costs.

#### Methods

We monitor and process several device-specific parameters in order to automate, personalize, and individualize the treatment with Moving Spine. We further develop and implement a novel pressure sensor matrix, which enables an additional monitoring of the pressure distribution in real time to draw valuable diagnostic conclusions and adapt the treatment accordingly.

#### Outlook

The novel hardware and software will be implemented in a new prototype. A number of trials will follow to test and optimize the treatment further. [4] [5]

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The modular MOWA orthosis for patient-specific care

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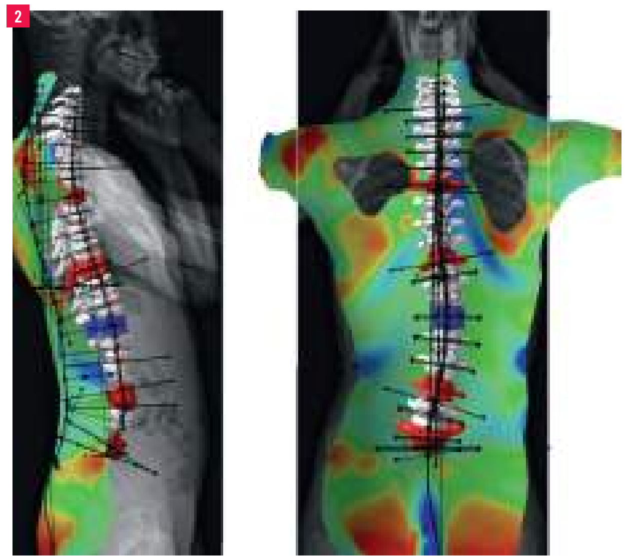
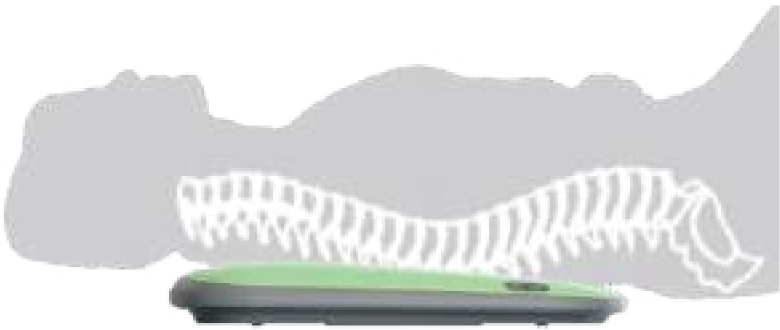


Human spine assessed by ScolioSIM based on 3D surface measurements

3

Test setup of different 3D measurement technologies and devices for the measurement of the human back

4



5

Illustration of a patient lying on the device

Illustration of pressure data acquired by a novel sensor matrix

**Selected Publications**

**[1]** Daniel Kaufmann, Christian Burri, Patrik Arnold, Volker M. Koch, Christoph Meier, Boris Považay, Joern Justiz (2017). Dosimetry Control and Monitoring of Selective Retina Therapy using Optical Coherence Tomography. Presented at OSA's 2017 European Conference on Biomedical Optics (ECBO), Published in SPIE Proceedings Vol. 10416.

**[2]** P.O. Gaggero, A. Adler, A. D. Waldmann, Y. Mamatjan, J. Justiz, V. M. Koch (2015). Automated robust test framework for electrical impedance tomography. Physiological Measurement, (IOP Publishing), vol. 36, issue 6, pp. 1227-1244.

**[3]** Y. Mamatjan, B. Grychtol, P. Gaggero, J. Justiz, V. M. Koch, and A. Adler (2013). Evaluation and Real-Time Monitoring of Data Quality in Electrical Impedance Tomography. IEEE Transactions on Medical Imaging, vol. 32, issue 11, pp. 1998-2007.



# Laboratory for Computer Perception and Virtual Reality

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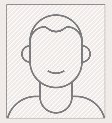
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### The HuCE-microLab in a nutshell

In the Computer Perception and Virtual Reality Lab, we deal with the analysis and synthesis of 2D and 3D digital images and their use in robotics and human-machine interaction. Our research lab focuses its applied research and development on image and video data analysis as well as 3D data visualisation and interaction in virtual space. With the latest visualisation techniques, complex data can be processed in a novel way and made intuitively accessible. Among other things, we use these methods to simplify human-machine interactions.

### Agile Robotic System for High-Mix Low-Volume Production

Traditional automation is not profitable for high-mix low-volume production. The project's goal is to develop an intuitive yet flexible automation system that allows companies to develop their own automation solutions in a profitable way.

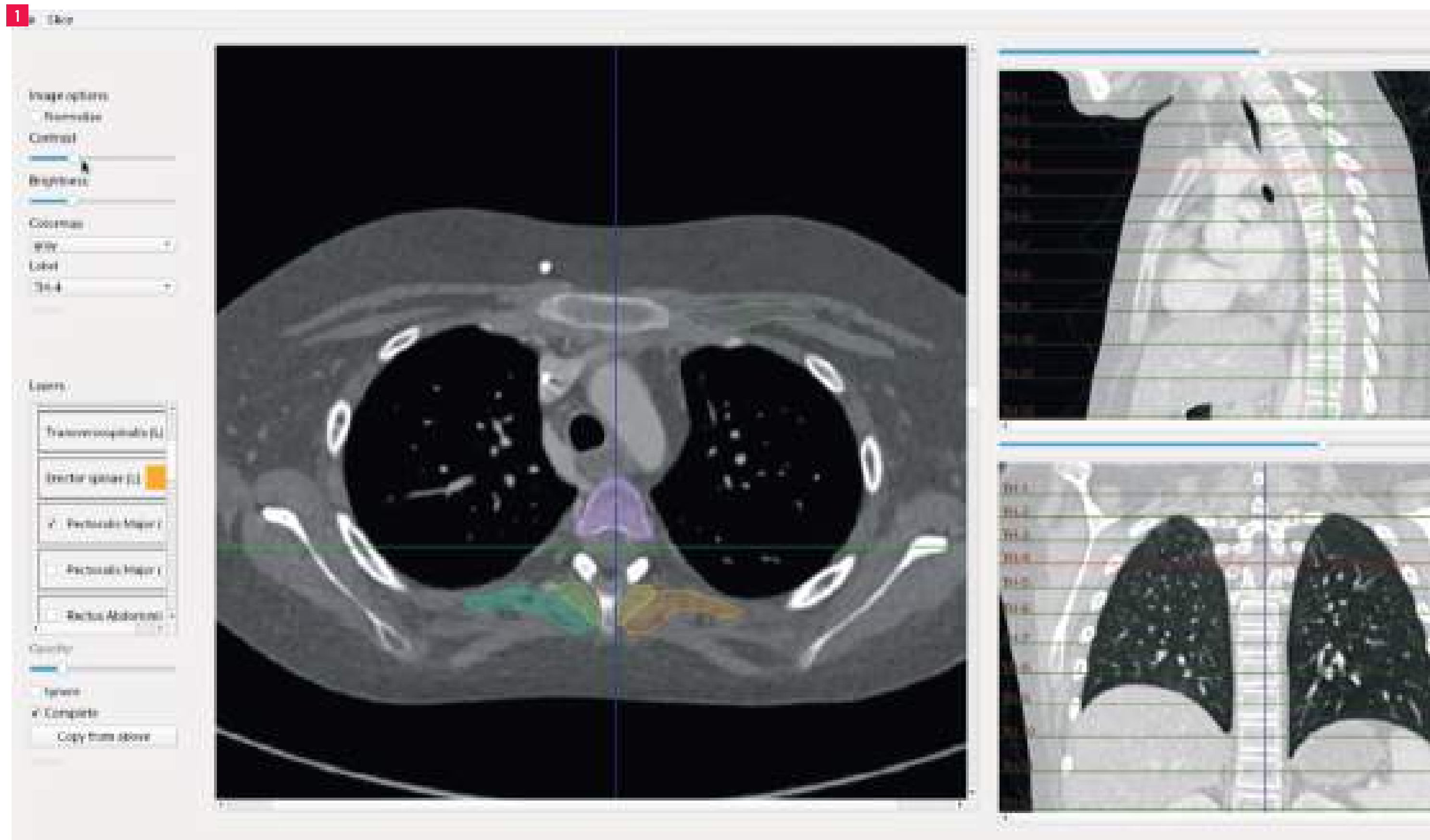
#### Situation

In Switzerland, a lot of work is still done manually. In many cases, automating these tasks would decrease production costs and align prices with the competition. However, although technically possible, traditional, fixed automation solutions for assembly tasks are not economically viable for companies with a high-mix low-volume production, meaning the lot sizes are small, with a large product diversity and high-quality requirements. In addition, the system needs to be rapidly reallocated to new tasks according to production needs and flexible enough to allow for the integration of new products. Instead of relying on these traditional high-end solutions requiring external expertise, the company involved in the research project wishes to develop their internal know-how to be able to develop ad-hoc, flexible automation solutions.

#### Course of Action

To keep the flexibility of manual work in the automation solution, a production system needs to be developed that is, in this case, a smart human-machine interface (HMI) that enables workers to efficiently use the robotic solution according to his/her needs to improve productivity. Since the worker is no robotic expert, the system needs to be smart; it needs to be able to translate human-defined goals into actual robotic trajectories. To achieve this, the researchers propose developing a digital twin of the workspace. Since the robotic system needs to be flexible, the workspace is unknown and needs to be modeled online according to sensory information and a priori knowledge. The digital twin is generated in real-time based on the fusion of sensory information (cameras and lidar) and a priori information (e.g., CAD files, process descriptions, etc.). A probability is associated with the different recognized objects, and active perception is used to improve performance. An interface allows the user to add new objects and define the parameters of a set of pre-defined algorithms for object recognition and localization. In order to simultaneously address the question of flexibility and intuitiveness, the HMI is based on a three-layer architecture. The architecture allows for programming of new tasks without coding, but also automatically creates the associated intuitive interface for operators.





1 MuscleMoDel

#### MuscleMoDel

This project led by the division of physiotherapy aims at developing an artificial intelligence-based approach for the automated extraction of patient-specific information on spinal muscle morphology from medical images. The successful treatment of spinal pathologies depends on well-founded knowledge of the disease mechanisms. Unfortunately, many spinal pathologies are not sufficiently well understood, and treatment effects are controversial. This is partially due to the fact that relevant biomechanical parameters such as segmental compressive forces can only be measured in vivo using highly invasive approaches. Due to the technical advances in the past two decades, this can now be achieved using complex digital technologies such as musculoskeletal (MSK) modeling.

However, MSK modeling is only accurate if the models are patient-specific, particularly in terms of muscle properties. To adjust such parameters, we usually rely on manually segmented CT scans, but these processes are highly time-consuming and therefore not applicable for research on larger samples or for everyday clinical practice.

One possible way to speed up these processes might be to use an artificial intelligence (AI) approach such as deep learning, which uses biologically inspired neural networks that enable computers to learn from observational data. A well-trained neural network could reduce the time needed for image segmentation from several hours to a couple of seconds per patient.

To be able to train the neural network appropriately, we will establish a training dataset consisting of approximately 200 trunk CT/MRI scans of healthy children and adolescents. To extract the required training data, scans will be manually segmented, including the assessment of trunk muscle morphology, by determining muscle cross-sectional area (CSA) and relative location for each horizontal vertebral mid-plane using a custom-built image processing software. Using our training dataset, we will then retrain a ready trained convolutional neural network (CNN) for the recognition of vertebral body as well as erector spinae and multifidi muscle contours. The process of retraining a ready trained network is called transfer learning and takes far fewer epochs and results in better accuracy. Finally, muscle morphology data will be implemented into our MSK models using a previously established MATLAB-pipeline. 1

# Robotics Laboratory

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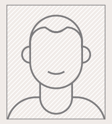
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### The HuCE Robotics Lab in a Nutshell

We have knowledge and experience in robotics and mechatronics to develop specific solutions to challenges arising in medicine, rehabilitation, everyday life with disabilities, and manual industrial production. We concentrate our development and research activities on system integration and development of functional prototypes, in particular in the area of collaborative robotics.

### Body Motion Analysis with 6D Tags and 2D Cameras

Three-dimensional Motion Capture (MoCap) can be useful in various stages of the rehabilitation process, as well as in diagnostics, sport sciences, and ergonomic analysis. Gait assessment is the most widely used application. MoCap also allows for objective, more informed decision-making. High costs are the primary factor preventing a broader application in clinical routine. Therefore, it is desirable to develop more affordable alternatives. In this project phase, an affordable application was developed based on printable tags and regular 2D cameras. The application is capable of analysing a squat knee flexion and a hop-test and was evaluated against a state-of-the-art 3D MoCap system from Vicon. Further development will enable the application to run on hand-held tablets and smartphones and be extended to general gait analysis and arm motions. [1] [2]

### A Hand Exoskeleton for Somatosensory and Motor Training

A hand exoskeleton was built that provides enough range of motion and force to move the fingers and execute common hand gestures, such as grasping an object or tapping the fingers on a flat surface. It provides finger position tracking to analyse the finger movements and recreate the hand in a 3D environment, where the patient could grasp virtual objects and feel them pushing back. The device may be used in combination with electrical stimulation and is hence made to be electrically noise-proof. The weight and volume of the device are minimized to provide a seamless experience to the patient and is quick to equip and remove it. Finally, the device covers as little surface of the hand's palmar side as possible to maximize natural somatosensory feedback. The focus was set on building a functional prototype with mechanical, electronical, data processing, and comfort aspects that could be improved upon. [3]

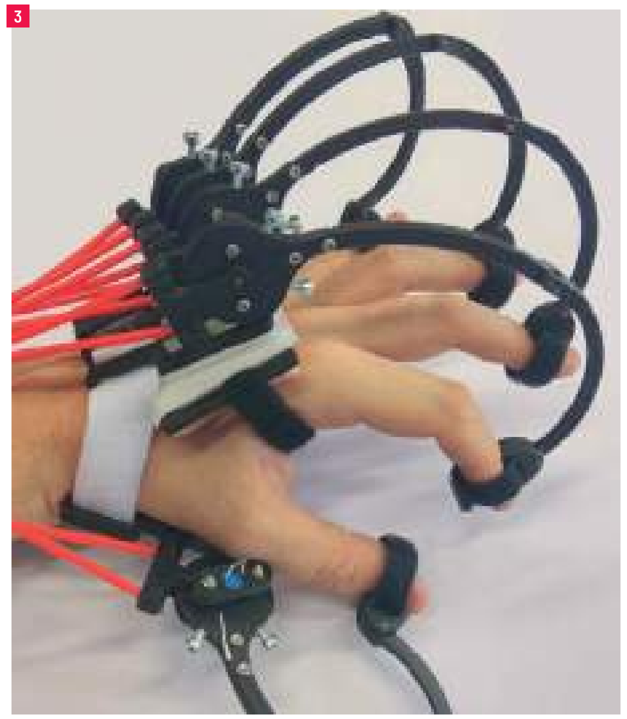


1

Body Motion Analysis

2

Analysing a squat knee flexion

3

A hand exoskeleton for somatosensory and motor training

**Selected Publications**

**[1] Lara Piers (Master Thesis, BME)**
Towards Gait Analysis with 6D Tags and 2D Cameras:
Setup and Analysis of a Hop Test
Supervisors: Gabriel Gruener, Patric Eichelberger, Heiner Baur
Institutions: Bern University of Applied Sciences,
Institute for Human Centered Engineering,
Examiners: Patric Eichelberger, Gabriel Gruener

**[2] Caley Temple (Bachelor Thesis, BFH)**
Development of a Hand Exoskeleton for Somatosensory and Motor Training
Supervisors: Gabriel Gruener,
Laura Marchal-Crespo
Institutions: Bern University of Applied Sciences,
Institute for Human Centered Engineering,
Examiners: Gabriel Gruener, Laura Marchal-Crespo

# Laboratory for Sensor Technology

## Institute for Human Centered Engineering

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### The HuCE Sensors Lab in a nutshell (150–200)

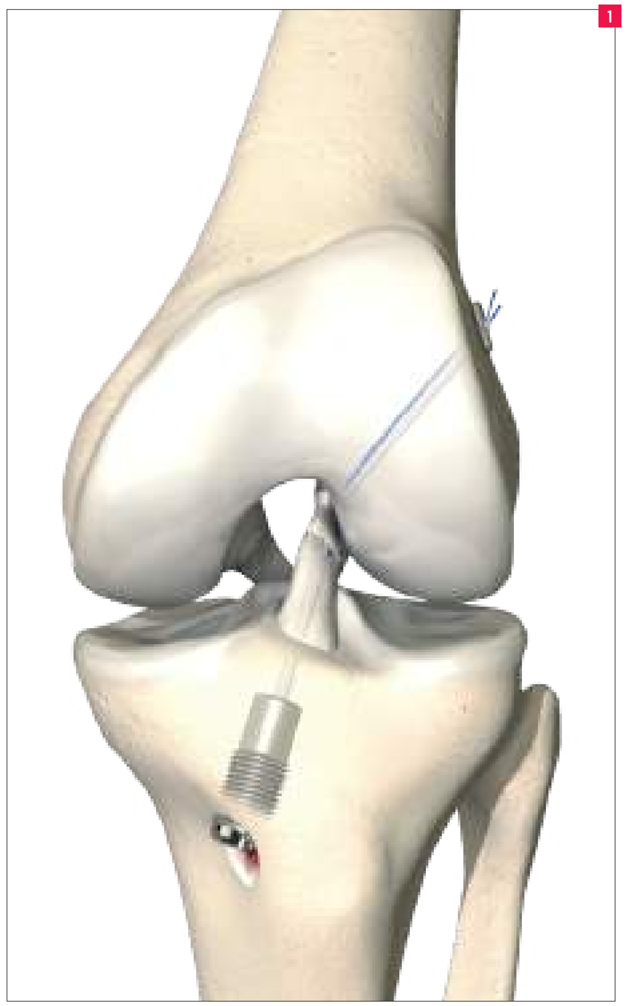
Our laboratory develops sensor systems in the medical, sports, and industrial fields. We can integrate existing sensors into your application. In some cases, when no industrial sensor is available, we design sensors to best suit your application. We focus on mechanical sensors, i.e., force, pressure, tactile, and distance sensors, accelerometer, gyroscope, magnetic sensors, or IMU sensors. We also perform critical measurement for quality control or production monitoring, for example with a 2D laser Doppler vibrometer.

The group also has a strong expertise in applied mathematics, for example hyperspectral imaging, deep learning, machine learning, partial differential equations, or inverse problems.

### Load Sensor for in vivo Data Acquisition

The Ligamys implant used for anterior cruciate ligament (ACL) rupture healing was successfully introduced in the medical device market by Mathys Ltd. in 2012. Despite the clinical success, a growing need for a smaller implant is reported from the market. To further decrease implant size and optimize the rehabilitation process, in vivo data of the healing process is needed. Therefore, the goal of the QuaLiHeal project (Innosuisse 28867.1 IP-LS) was to find the right sensor principle to be integrated into an instrumented Ligamys. The Sensors Laboratory together with the Switzerland Innovation Park Biel/Bienne and the research group Biomechanical Engineering (BME) at ZHAW were involved in the development of various innovative solutions in the minimal space available within the implant. The developed sensor system is now ready to be integrated within an ACL-healing implant and will be capable of measuring in vivo loads wirelessly. Once the verification and validation are completed, it can be used in a clinical study to generate the necessary data to better understand and improve the ACL healing and rehabilitation processes, as well as minimize the implant size. 1

1


Sensor system capable of measuring in vivo loads wirelessly



3


Laser Doppler Interferometer

### 2D Hand Grip Sensor

A cylindrical sensor has been developed to accurately measure position and pressure of all fingers of a complete hand. Very detailed studies about the biomechanics of the hand are now possible. This hand grip sensor can be used for diagnostics as well as a control tool after a hand operation to measure the rehabilitation process. It provides a much more detailed picture of the biomechanical activity and of the hand and all fingers than the actual devices on the market. A high-resolution tactile sensor and a dedicated readout electronic have been developed, allowing 3,000 pixels representing a hand imprint to be delivered in real time. This wireless device transmits data to a smartphone or other smart device for direct analysis. It can also be shared or stored. Data analysis algorithms have also been developed to facilitate the diagnosis. This project has been performed with EoSwiss Ldt. in Geneva. A patent application for this device has been submitted, and a clinical study is ongoing. 2

### Laser Doppler Interferometer

The Laboratory for Sensor Technology and Applied Mathematics has a high-end PSV-500 Scanning Vibrometer that allows non-contact vibration mapping and analysis of vibrating structures. This laser Doppler vibrometer allows for determination of vibrating velocity or displacement over areas ranging from $mm^2$ to $m^2$. It has applications in acoustics, structural dynamics, and ultrasound measurement, for example. 3

2


Hand grip sensor

# Institute for Rehabilitation and Performance Technology IRPT

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### Research Profile

The Institute for Rehabilitation and Performance Technology IRPT uses methods and technologies from sports and exercise physiology to improve rehabilitation outcomes for people after they've experienced accidents or illness. The IRPT specialises in the areas of cardiopulmonary and neurological rehabilitation after stroke or spinal cord injury, feedback control for physiological systems, as well as automation and control of training equipment. The IRPT collaborates closely with Swiss companies and rehabilitation clinics, thus ensuring that research results can be quickly and directly applied for the benefit of patients. A growing number of projects funded by the Swiss National Science Foundation (SNSF) and Innosuisse support basic research, transfer of knowledge into industry, and the development of innovative products. The IRPT team consists of research assistants, Ph.D. students, postdocs, and a group of bachelor's and master's project students. The team members have varied backgrounds in electrical, mechanical and bio-mechanical engineering, human movement sciences, physiotherapy, and rehabilitation medicine. The IRPT is located within the School of Engineering and Computer Science of Bern University of Applied Sciences BFH.

1

IRPT rehabilitation robotics lab

### Rehabilitation Engineering

The interdisciplinary research of the Rehabilitation Engineering Group focuses on neural control of movement in clinical populations with neurological deficits resulting from spinal cord injury, stroke, or other pathologies. By combining rehabilitation technology and cognitive performance feedback, the group's goal is to reinforce the patient's volitional drive and to exploit the central nervous system's lifelong capacity for plasticity, regeneration, and repair. This approach promotes cardiopulmonary and musculoskeletal health and supports an environment in which positive neurological adaptations can occur. The work harnesses multidisciplinary expertise in engineering, neurosciences, sports and exercise science, and medicine. This allows professionals to address prevention and management of the progressive secondary complications of spinal cord injury, stroke, and a wide range of further neurological conditions. This approach promotes neurological recovery for improved motor control, sensation, and autonomic function. 1

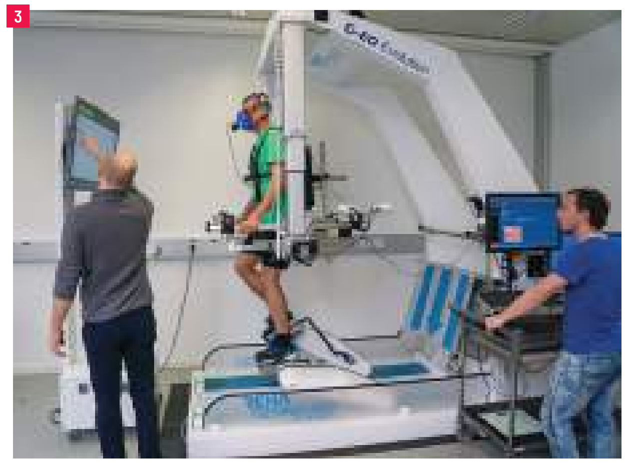
The Rehabilitation Engineering Group develops new technical devices and extends the functionality of existing products. Recent developments include novel rehabilitation devices for adults and children with neurological impairment, involving close collaboration with the BFH SCI-Mobility Lab and the company GBY AG. The group develops recumbent cycling systems for people with complete lower-limb paralysis. These systems use functional electrical stimulation (FES) of the paralysed muscle groups. The IRPT participated in the FES Bike Race at Cybathlon 2016 (bronze medal winner) and 2020 (fourth place). 2



2


IRPT team at the FES Bike Race, Cybathlon 2016

3



Cardiopulmonary rehabilitation with the G-EO System end-effector gait-rehabilitation robot

The functionality of existing robotics-assisted rehabilitation devices, including gait-rehabilitation robots and tilt tables, has been extended to facilitate application for cardiopulmonary rehabilitation. This involves biofeedback of patient effort, volitional control of mechanical work rate, together with automatic feedback control of physiological outcome variables, including heart rate, oxygen uptake, and metabolic work rate. A key feature of the group's work is the employment of methods from sports and exercise physiology and the adaptation of these protocols to the rehabilitation setting. Working closely with key clinical collaborators, these approaches are applied in the clinic for rehabilitation of people with various neurological problems including stroke and spinal cord injury. 3

The IRPT has an excellent infrastructure for research including a dedicated research lab within the Reha Rheinfelden. Robotics-assisted devices include exoskeleton (Lokomat, Hocoma AG) and end-effector (G-EO System, Reha Technology AG; Lyra, medica Medizintechnik GmbH) gait rehabilitation robots, a robotics-assisted tilt table (Erigo, Hocoma), and an adaptive leg robot (Allegro, Dynamic Devices AG). The institute also has modern cardio-respiratory monitoring systems.

### Sports Engineering

The Sports Engineering Group focuses on interdisciplinary research on advanced feedback control methods for treadmill and cycle-ergometer automation and on basic research in the area of physiological heart rate variability (HRV). The work builds on multidisciplinary expertise in engineering and sports and exercise science. This research deals mainly with high-end performance, but many of the methods have also been translated successfully into activities of the Rehabilitation Engineering Group for application in patients with neurological deficits. 4

The group has developed feedback control algorithms that allow exercise intensity to be specified for training and testing via automatic regulation of heart rate, oxygen uptake, or metabolic work rate. In each case, a target profile for the controlled variable is selected. During the exercise, treadmill speed and slope, or cycle work rate, are automatically adjusted so that the target response is achieved. High-precision, automatic positioning algorithms for the treadmill have also been developed. This allows users to select their own walking or running speed, while the feedback control continuously adjusts treadmill speed to maintain a reference position.

The following selection of research and development projects gives an overview of the spectrum of research activities of the Sports Engineering Group:

- Investigation of the characteristics of heart rate variability, dynamics, and control during exercise, currently funded by the Swiss National Science Foundation (SNSF)
- Feedback control of heart rate, oxygen uptake, or metabolic work rate during treadmill and cycle-ergometer exercise
- Automatic position control for walking and running on a treadmill

The IRPT labs are equipped with high-performance treadmills (Venus and Pulsar, h/p/cosmos sports and medical gmbh) and cycle ergometer (LC7, Monark Exercise AB) technology. Various position monitoring sensors, including ultrasound and laser, and a real-time communication protocol give complete control over the treadmill/ergometer through a computer. The institute also has modern cardio-respiratory monitoring systems for online breath-by-breath monitoring, ECG recording, and HRV analysis.

4

IRPT human performance testing lab

### Selected Publications


**[1]** J. Fang and K. J. Hunt (2021). Mechanical design and control system development of a rehabilitation robotic system for walking with arm swing. Frontiers in Rehabilitation Sciences, vol. 2, no. 720182, pp. 1–14, https://doi.org/10.3389/fresc.2021.720182.

**[2]** H. Wang and K. J. Hunt (2021). Heart rate control using first- and second-order models during treadmill exercise. Systems Science & Control Engineering, vol. 9, no. 1, pp. 651–662, https://doi.org/10.1080/21642583.2021.1976304.

**[3]** H. Wang and K. J. Hunt (2021). Identification of heart rate dynamics during treadmill exercise: comparison of first- and second-order models. BioMedical Engineering OnLine, vol. 20:37, pp. 1–10, https://doi.org/10.1186/s12938-021-00875-7.

**[4]** J. Fang, M. Haldimann, L. Marchal-Crespo, and K. J. Hunt (2021). Development of an active cable driven, force-controlled robotic system for walking rehabilitation. Front. Neurorobot., vol. 15, no. 651177, pp. 1–16, https://doi.org/10.3389/fnbot.2021.651177.

**[5]** K. J. Hunt and C. Hurni (2019). Robust control of heart rate for cycle ergometer exercise. Med. Biol. Eng. Comput., vol. 57, no. 11, pp. 2471–2482, https://doi.org/10.1007/s11517-019-02034-6.

**[6]** K. J. Hunt, A. Zahnd, and R. Grunder (2019). A unified heart rate control approach for cycle ergometer and treadmill exercise. Biomed. Signal Process. Control, vol. 54, https://doi.org/10.1016/j.bspc.2019.101601.

**[7]** M. Laubacher, E. A. Aksöz, A. Brust, M. Baumberger, R. Riener, S. A. Binder-Macleod, and K. J. Hunt (2019). Stimulation of paralysed quadriceps muscles with sequentially and spatially distributed electrodes during dynamic knee extension. J. Neuroeng. Rehabil., vol. 16:5, https://doi.org/10.1186/s12984-018-0471-y.

**[8]** K. J. Hunt and J. Saengsuwan (2018). Changes in heart rate variability with respect to exercise intensity and time during treadmill running. BioMedical Engineering OnLine, vol. 17:128, https://doi.org/10.1186/s12938-018-0561-x.

**[9]** O. Stoller, M. Schindelholz, and K. J. Hunt (2016). Robot-assisted end-effector-based stair climbing for cardiopulmonary exercise testing: feasibility, reliability and repeatability. PloS ONE, vol. 11(2): e0148932, https://doi.org/10.1371/journal.pone.0148932.

**[10]** J. Saengsuwan, C. Huber, J. Schreiber, C. Schuster-Amft, T. Nef, and K. J. Hunt (2015). Feasibility of cardiopulmonary exercise testing using a robotics-assisted tilt table in dependent-ambulatory stroke patients. J. Neuroeng. Rehabil., vol. 12:88, https://doi.org/10.1186/s12984-015-0078-5.

**[11]** O. Stoller, E. D. de Bruin, M. Schindelholz, C. Schuster-Amft, R. A. de Bie, and K. J. Hunt (2015). Efficacy of feedback-controlled robotics-assisted treadmill exercise to improve cardiovascular fitness early after stroke: a randomised controlled pilot trial. J. Neurol. Phys. Ther., vol. 39, pp. 156–165, https://doi.org/10.1097/NPT.0000000000000095.


# Movement Biomechanics and Physiotherapy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### Research Profile

The Applied Research and Development Physiotherapy of the School of Health Professions at the Bern University of Applied Sciences focusses on movement biomechanics in a physiotherapy context. We analyse human movement in relevant daily life activities and situations. The Bern Movement Lab is equipped with essential kinematic, kinetic, and neuromuscular analysis methods to provide an excellent environment for movement science research. We are engaged in teaching physiotherapy (BSc, MSc, PhD) as well as biomedical engineering (MSc) students. The aR&D Physiotherapy runs several research groups that focus on neuromuscular control, spinal movement biomechanics, foot biomechanics and technology, pelvic floor and continence, public health and physiotherapy-related health economics, work disability prevention, higher education research in health professions, and healthy ageing and wellbeing.

### Neuromuscular Control (Heiner Baur)

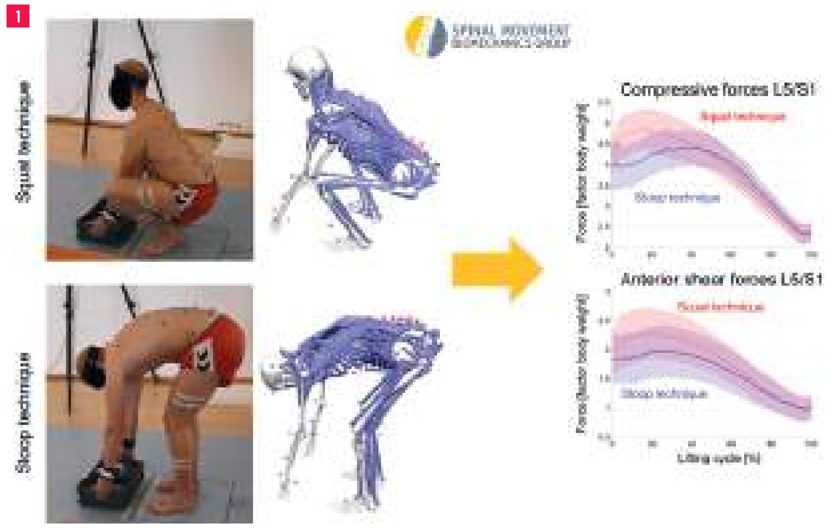
The lower extremity is involved in all movements of daily life and physical activity. We focus on the influence of internal (age, gender, etc.) and external factors like training parameters or pathologic conditions on dynamic movement patterns. The general methodological paradigm combines the pure biomechanical view with a focus on the organization and adaptation of the neuromuscular system. Currently, the group is working on the acute and long-term influence of anterior cruciate ligament (ACL) injury on knee stability and knee function in general to develop rehabilitation strategies and preventive measures. Beside mechanical stability, adequate neuromuscular control secures necessary joint stability and protection. The evaluation of sensorimotor control in functionally relevant situations may therefore serve as a key element in functional diagnostics. The extraction of objective outcomes can help to rate rehabilitation progress or return-to-sport decisions after rehabilitation. The methodological setup can potentially be used to check the effects of orthotic devices or to investigate the effects of different surgical reconstruction techniques.



### Spinal Movement Biomechanics (Stefan Schmid)

The Spinal Movement Biomechanics Group focuses on the identification of biomechanical parameters that help clinicians better understand musculoskeletal spine disorders and develop new or more effective prevention and treatment strategies. Using optical motion capture, surface electromyography, and personalized musculoskeletal modelling techniques, we are conducting laboratory-based experimental research to investigate kinematics, segmental loading, and individual muscle forces of the spine during functional activities in different patient populations. Our current focus lies on spinal deformities and non-specific chronic low back pain (CLBP). 1

1

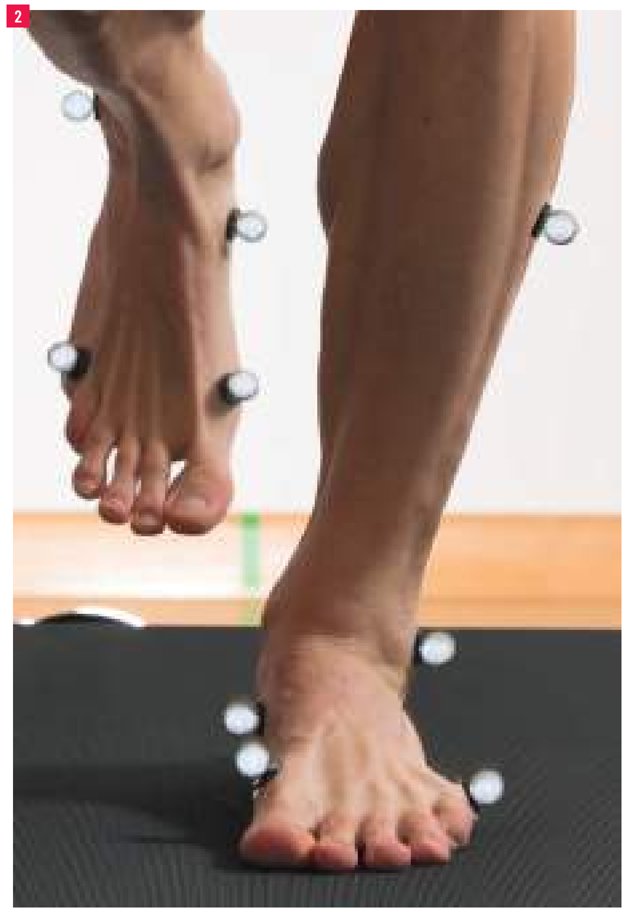



Simulating spinal loading using motion capture-driven musculoskeletal modelling

### Foot Biomechanics and Technology (Patric Eichelberger)

The Foot Biomechanics and Technology Group is concerned with gaining a better understanding of foot biomechanics and related complaints and evaluating or developing therapy options with a focus on applying current technology to the assessment and therapy of the locomotor system and orthotics. It's part of our mission to bring the lab to patients, physiotherapists, clinicians, or orthopaedic technicians. We aim to apply the latest technological developments to transfer objective assessment of movement biomechanics and neuromuscular control from the laboratory into the clinical routine to further build evidence in physical therapy. Currently, the group is working on the topic of relationships between plantar pressure, foot, and lower extremity kinematics and associated complaints with the overall goal of optimizing foot orthoses and physiotherapeutic interventions. 2

2



Clinically oriented measurement of foot kinematics by quantifying navicular bone motion using four reflective markers and 3D motion capture

### Pelvic Floor and Continence (Irene König)

The mean prevalence of stress urinary incontinence (SUI) in women is 37 %. SUI is clearly underestimated by public opinion, mainly because it is a taboo subject. Two thirds of women suffering from SUI reported a negative impact on quality of life since the involuntary urine leakage affects their physical and psychosocial well-being while putting a burden on their economic situation. Even young women are affected, often in sports, but especially after delivery. From a scientific point of view, physiotherapy is the first-line treatment in this field, as its effectiveness has been thoroughly evaluated. In our Pelvic Floor and Continence Group we want to further improve and optimize physiotherapy related to SUI. We investigate diagnostic techniques, interventions, and therapy plans regarding patient information, perception, and movement as well as strengthening of the pelvic floor muscles (PFMs) in isolated contractions and complex whole-body movements. Specifically, we focus on the neuromechanical aspects of PFMs, i.e., the activation and contraction behavior during voluntary and involuntary, reflexive contractions, which are essentially important to guarantee continence.

### Public Health and Physiotherapy-Related Health Economics (Jan Taeymans)

The group currently focuses on a joint collaboration (SNF-WEAVE) with the University of Applied Sciences and Arts of Southern Switzerland (SUPSI) and the Vrije Universiteit Brussel (Belgium) where the project's focus is on rehabilitation sciences of overweight or obese patients with chronic low back pain. Chronic low back pain (CLBP) is the most expensive cause of work-related disability. It causes the highest number of years lived with disability. The most severe and debilitated CLBP patients often have co-morbidities such as overweight and obesity. Despite the growing body of scientific literature pointing toward the close relationship between overweight/obesity and CLBP, few treatment programs for people with CLBP take overweight into account. Therefore, we propose studying the added value of a behavioral weight reduction program (changes in diet, behavior, and physical exercise) to current best evidence rehabilitation (pain neuroscience education plus cognition-targeted exercise therapy) for overweight or obese people with CLBP. An international, multi-center randomized controlled trial comparing a behavioral weight reduction program combined with pain neuroscience education and cognition-targeted exercise therapy versus pain neuroscience education and cognition-targeted exercise therapy alone will be conducted. The primary outcome is pain and the primary endpoint was chosen at 12 months follow-up; secondary outcomes include healthcare use and daily functioning. More specifically, it includes innovative research targeting chronic low back pain rehabilitation as well as a health economic evaluation. The results of this study will apply to rehabilitation practice, public health, and health economics.

**Work Disability Prevention (Maurizio Trippolini)**

This group's research focuses on disability prevention strategies, enhancing recovery in musculoskeletal disorders, healthcare effectiveness, work disability, and methods to achieve safe and sustained return to work. Specific topics include healthcare for workers with musculoskeletal injury in compensable settings, development and evaluation of self-reported assessments, and performance-based tests that measure physical functioning and psychosocial factors. Research methods include quantitative, qualitative, and mixed-methods of observational studies in primary care or rehabilitation. Implementation of findings from clinical research into practice and continuing professional education are at the core of our motivation.

**Selected Publications**


**[1]** Blasimann A, Koenig I, Baert I, Baur H, Vissers D. (2021). Which assessments are used to analyze neuromuscular control by electromyography after an anterior cruciate ligament injury to determine readiness to return to sports? A systematic review. BMC Sports Sci Med Rehabil. 13(1):142.

**[2]** Busch A, Blasimann A, Mayer F, Baur H. (2021). Alterations in sensorimotor function after ACL reconstruction during active joint position sense testing. A systematic review. PLoS One 16(6):e0253503.

**[3]** Clijsen R, Brunner A, Barbero M, Clarys P, Taeymans J. (2017). Effects of low-level laser therapy on pain in patients with musculoskeletal disorders: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 53(4):603-610.

**[4]** Galliker G, Scherer DE, Trippolini MA, Rasmussen-Barr E, LoMartire R, Wertli MM.(2020). Low Back Pain in the Emergency Department: Prevalence of Serious Spinal Pathologies and Diagnostic Accuracy of Red Flags. Am J Med. 133(1):60-72.e14.

**[5]** Knechtle D, Schmid S, Suter M, Riner F, Moschini G, Senteler M, Schweinhardt P, Meier ML (2021). Fear avoidance beliefs are associated with less lumbar spine flexion during object lifting in pain-free adults. Pain, 162(6), 1621-1631.

**[6]** Koenig I, Eichelberger P, Luginbuehl H, Kuhn A, Lehmann C, Taeymans J, Radlinger L. (2021). Activation patterns of pelvic floor muscles in women with incontinence while running: a randomized controlled trial. Int Urogynecol J. 32(2):335-43.

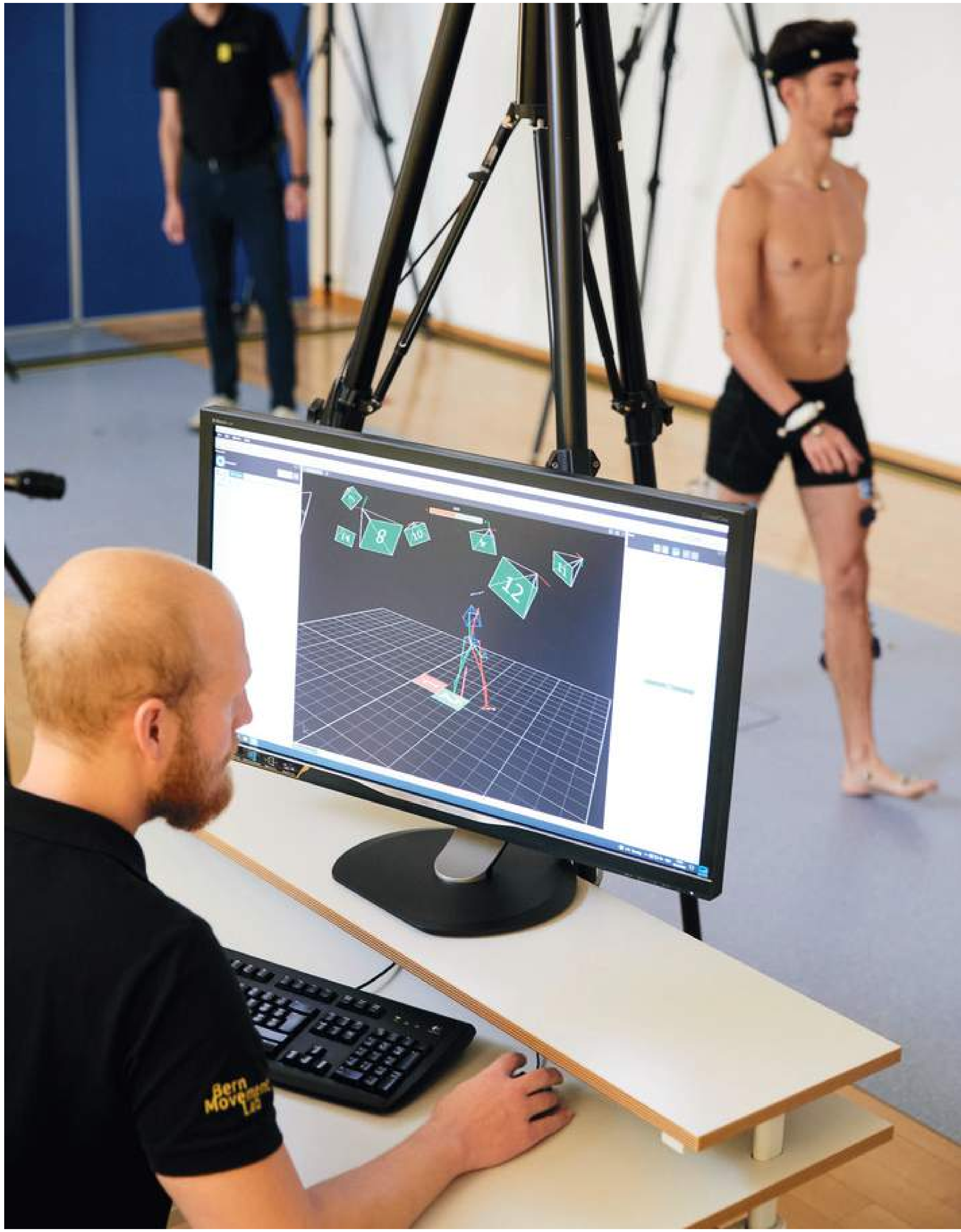
**[7]** Lutz N, Taeymans J, Ballmer C, Verhaeghe N, Clarys P, Deliens T. (2019). Cost-effectiveness and cost-benefit of worksite health promotion programs in Europe: a systematic review. Eur J Public Health, 29(3):540-546, doi: 10.1093/eurpub/cky269, Erratum in: Eur J Public Health. 29(2):380.

**[8]** Schmid S, Burkhart KA, Allaire BT, Grindle D, Bassani T, Galbusera F, Anderson DE (2020). Spinal compressive forces in adolescent idiopathic scoliosis with and without carrying loads: a musculoskeletal modeling study. Frontiers in Bioengineering and Biotechnology (Biomechanics), 8, 159.

**[9]** Luginbuehl H, Lehmann C, Koenig I, Kuhn A, Buergin R, Radlinger L. (2021). Involuntary reflexive pelvic floor muscle training in addition to standard training versus standard training alone for women with stress urinary incontinence: a randomized controlled trial. Int Urogynecol J., 16:524.

**[10]** Trippolini MA, Young AE, Pransky G, Elbers NA, Lockwood K, Cameron ID (2019). Beyond symptom resolution: insurance case manager's perspective on predicting recovery after motor vehicle crash. Disabil Rehabil. 1:1-9.

**[11]** von Arx M, Liechti M, Connolly L, Bangerter C, Meier ML, Schmid S (2021). From Stoop to Squat: A comprehensive analysis of lumbar loading among different lifting styles. Frontiers in Bioengineering and Biotechnology (Biomechanics), 9, 769117.

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## Editorial

# Master Biomedical Engineering

**What a relief! After a year and a half of the coronavirus pandemic and online education, we were allowed to return to the lecture halls in the fall. Finally, we were able to benefit from face-to-face interactions again and explore the relevance of hybrid and fully virtual solutions in a more detached mindset. In all options, our students appreciated the possibility of reviewing the lectures' contents, watching the available podcasts.**

From a personnel point of view, Mrs Ulla Jakob was promoted head of the study coordination team. This is a highly deserved career step and I wish to acknowledge here her exceptional dedication to ensure optimal learning conditions, complete information, and fair treatment to all students of the program. My thanks extend to all members of the study coordination who support Mrs Jakob, especially for the additional tasks generated by the pandemic.

This year, a resized biomedical engineering day was organized online for the first time. After the display of the new master's program in artificial intelligence in medicine, eight companies presented themselves and a live surgery was retransmitted from the department of thoracic surgery. I would like to thank Gregor Kocher and Patrick Dorn for presenting an impressive intervention that generated a broad flow of questions. My special thanks go to Julia Spyra for the seamless organization and the MSB team for technical support.

At this same occasion, the RMS award for the best average grade during the entire program was attributed to Adrian Ruckli, while the best master thesis awards were decerned to Mrs Giuditta Thoma for basic science and Mr Maxime Chiarelli for innovation. The best PhD thesis was attributed to Serife Kucur for her work „Exploration and Exploitation of Visual Fields: from Acquisition to Prediction of Glaucoma". Congratulations to all of them.

Despite the reduced number of events, the master's program exhibits a healthy condition with 38 alumni and 70 new students. The list of courses was revised, and a new study plan was endorsed by the medical faculty for the upcoming academic years. The degree of our students' satisfaction, as reflected in the independent evaluation of the University of Bern, remains stable despite the frequent alternation of teaching and examination modes.

Once again, I wish to express my appreciation to the lecturers for their constant involvement in the program and their personal efforts to deliver the best possible education to our graduate students. With this recognition in mind, I am very glad to present our yearly report in the next pages. I wish you an enjoyable reading.

**Prof. Philippe Zysset**



# Structure of Courses

**Structure of Courses in the Master's Program**

Since the start of the master's program Biomedical Engineering in March 2006, the constant effort to improve the quality of our curriculum has resulted in substantial changes of the course structure. The first curriculum consisted of a number of individual courses that were either mandatory or elective, but their coherence with regards to content was in most cases not expressed by a defined structure. However, two major modules (formerly called "focus areas") already existed.
As of fall semester 2009, all courses were grouped in a strictly modular way to enhance both the clarity and flexibility of the curricular structure. The main idea was to guide the students through their studies in a better way by adding an elective part to the major modules, which formerly had consisted exclusively of mandatory courses. Besides, the curriculum was expanded by a number of new specialized courses as well as an additional major module called "Image-Guided Therapy."

Adaptations in the legal framework of the master's program now offer more flexibility in the design of courses and modules, thus providing the basis for a second fundamental restructuration of the curriculum as of fall semester 2013. In particular, a module called "Complementary Skills" was introduced. In addition, the list of mandatory courses in both basic and major modules was revised. More recently, in fall semester 2017, a module "Preparation Courses" was created. The courses in this module are intended to fill gaps regarding prerequisites for basic and advanced courses in the master's program Biomedical Engineering.
After intensive preparation, the curriculum was again restructured as of fall semester 2021. The focus is now on a more practice-oriented education, which is achieved primarily through the newly created "BME Laboratories." These will be conducted in the second semester in the research groups of the University of Bern, the Bern University of Applied Sciences (BFH), as well as our partner institutions Bern University Hospital (Inselspital) and Empa, the Swiss Laboratories for Materials Science and Technology . In addition, thanks to the great commitment of the Institute of Biochemistry and Molecular Medicine, practical laboratories are now included in the course "Biological Principles of Human Medicine," which illustrate and complement the theoretical lectures.

**The Curriculum**

### Duration of Studies and Part-Time Professional Occupation

The full-time study program takes four semesters, which corresponds to 120 ECTS credits, one ECTS credit being defined as 25-30 hours of student workload. It can be extended to a maximum of six semesters. When a student decides to complete the studies in parallel to a part-time professional occupation, further extension is possible on request. To support regular part-time work, mandatory courses take place (with rare exceptions) on only three days per week.

### Preparation Courses

Owing to the interdisciplinary nature of the BME master's program, our students come from various fields of study. Especially students with a non-engineering background – for example in medicine – do not fulfill all prerequisites for the courses of the master's program. Therefore, introductory courses in MATLAB, C++ programming, Electrical Engineering, Engineering Mechanics, and Material Science as well as the tutorial-based course "Selected Chapters in Mathematics" were introduced and allow us to create a tailor-made curriculum for these students. Students with a background in engineering, on the other hand, can select these courses freely if they feel the need to refresh some of the knowledge provided.

### Basic Modules

The basic modules provide students with the necessary background to be able to fully understand the complex subject matter in the specialized courses. All students have to complete all courses in the Basic Modules Human Medicine, Applied Mathematics, and Biomedical Engineering. In the first semester, all mandatory courses belong to this group, whereas in the second semester, the courses from the basic modules make up approximately 20%.

### Major Modules

The choice of one of three major modules Biomechanics, Electronic Implants, or Image-Guided Therapy after the first semester constitutes the first opportunity for specialization.
Approximately one third of the major modules consist of mandatory courses. In the elective part of the major module, the student is allowed to select every course from the list of courses in the master's program, giving rise to a high degree of diversity and flexibility and allowing for numerous course combinations. However, this freedom makes it somewhat difficult for the student to make reasonable choices regarding professional prospects.
This is why the responsible lecturers developed a recommended study plan to guide the students through the course selection process and to avoid organizational problems such as overlapping courses. If a student follows the recommended path, he or she can be sure to establish a sound professional profile.

### Module "Complementary Skills"

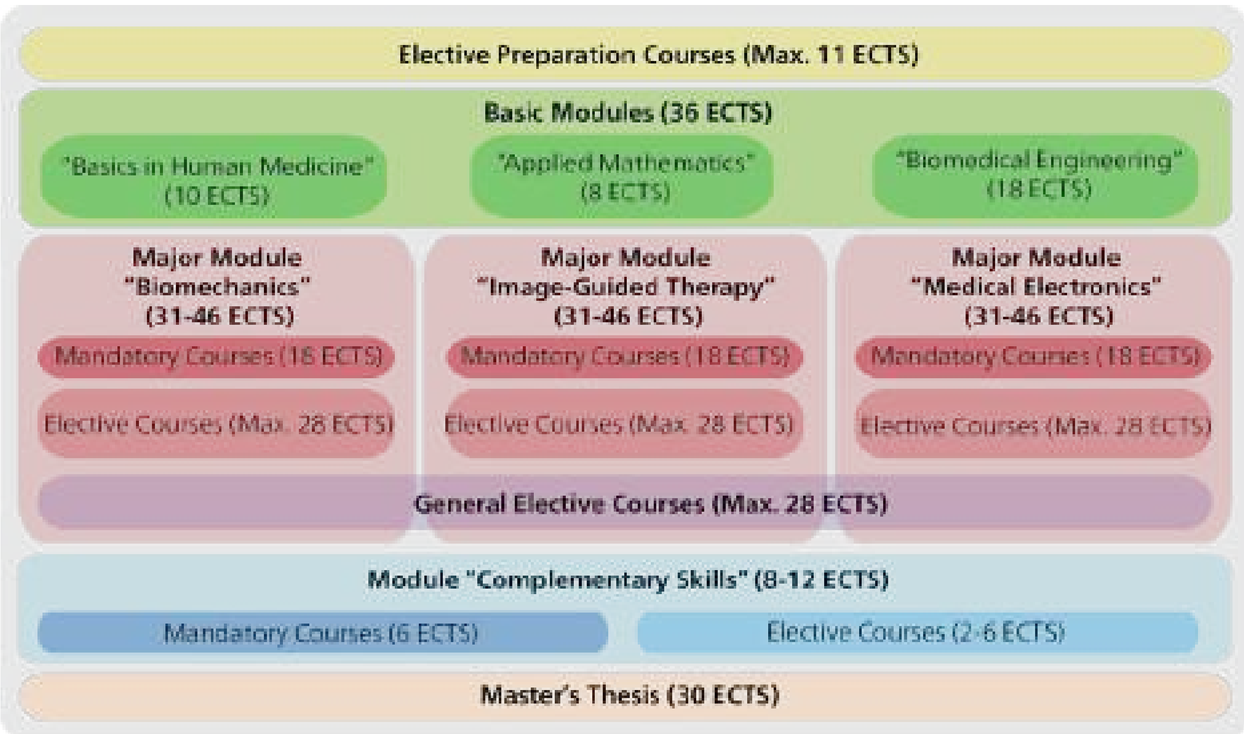
Apart from the rapid development of technology itself, today's biomedical engineers are increasingly challenged by complementary issues like ethical aspects, project planning, quality assurance and product safety, legal regulations and intellectual property rights, as well as marketing aspects. Language competence in English is of paramount importance both in an industrial and academic environment. This situation has been accounted for by the module called "Complementary Skills" where students are required to complete two mandatory courses (Innovation Management; Fundamentals of Quality Management and Regulatory Affairs) as well as 2-6 ECTS from the electives courses (Ethics in Biomedical Engineering; Scientific Writing in Biomedical Engineering; Clinical Epidemiology and Health Technology Assessment).

### Master's Thesis

The last semester is dedicated to a master's thesis project on an individually suited topic in an academic research group at the University of Bern or the Bern University of Applied Sciences or, for particular cases, in an industrial research and development environment. As a rule, all 90 ECTS credits from the course program have to be completed, thus ensuring that the student is able to fully concentrate on the challenges imposed by exciting research activities. The master's thesis includes the thesis paper, a thesis presentation and defense, as well as a one-page abstract for publication in the Annual Report of the master's program.

### List of Courses

- Advanced Topics in Machine Learning
- Applied Biomaterials
- Basics in Physiology for Biomedical Engineering
- Biological Principles of Human Medicine
- (Bio)Materials
- Biomedical Acoustics and Audiology
- Biomedical Instrumentation
- Biomedical Laser Applications
- Biomedical Sensors
- Biomedical Signal Processing and Analysis
- BioMicrofluidics
- C++ Programming I
- C++ Programming II
- Cardiovascular Technology
- Clinical Applications of Image-Guided Therapy
- Clinical Epidemiology and Health Technology Assessment
- Computer-Assisted Surgery
- Computer Graphics
- Computer Vision
- Continuum Mechanics
- Design of Biomechanical Systems
- Dynamical Models: Analysis, Conception and Simulation
- Ethics in Biomedical Engineering
- Finite Element Analysis I
- Finite Element Analysis II
- Fluid Mechanics
- Functional Anatomy of the Locomotor Apparatus
- Fundamentals of Quality Management and Regulatory Affairs
- Image-Guided Therapy Lab
- Innovation Management
- Intelligent Implants and Surgical Instruments
- Introduction to Artificial Intelligence
- Introduction to Biomechanics
- Introduction to Digital Logic
- Introduction to Digital Signal Processing
- Introduction to Electrical Engineering
- Introduction to Engineering Mechanics
- Introduction to Engineering Mechanics
- Introduction to Material Science
- Introduction to Programming
- ntroduction to Signal and Image Processing
- ntroductory Anatomy and Histology for Biomedical Engineers
- Lecture Series on Advanced Microscopy
- Low Power Microelectronics
- Machine Learning
- Medical Image Analysis
- Medical Image Analysis Lab
- Medical Informatics
- Medical Robotics
- Microsystems Engineering
- Numerical Methods
- Ophthalmic Technologies
- Osteology
- Principles of Medical Imaging
- Programming of Microcontrollers
- Regenerative Dentistry for Biomedical Engineering
- Rehabilitation Technology I
- Rehabilitation Technology II
- Scientific Writing in Biomedical Engineering
- Selected Chapters in Mathematics
- Short Introduction to MATLAB
- Technology and Diabetes Management
- Tissue Biomechanics
- Tissue Biomechanics Lab
- Tissue Engineering
- Wireless Communication for Medical Devices






# Major Module

## Biomechanics

**Head of Module**
**Prof. Dr. Philippe Zysset**
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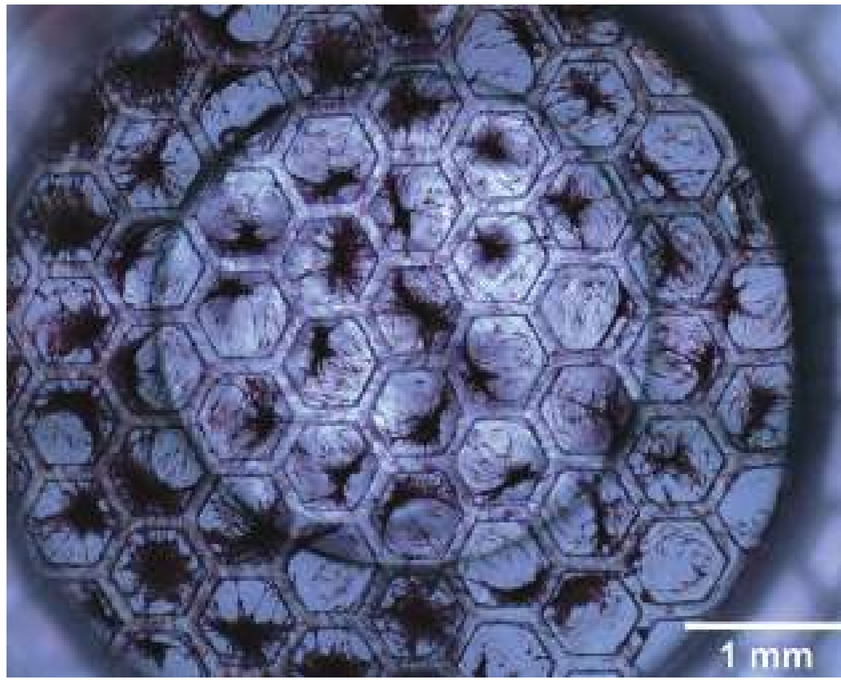
The respiratory, cardiovascular, and musculoskeletal systems are the transport and structural bases for our physical activities, and their health have a profound influence on our quality of life. Lung diseases, cardiovascular diseases, musculoskeletal injuries, and pathologies are costly ailments facing our healthcare systems, both in terms of direct medical costs and compensation payments related to loss of work.

In this module, students will gain a comprehensive understanding of the multi-scale organisation of the respiratory, cardiovascular, and musculoskeletal systems, combining knowledge from the cell, tissue, organ, to the body level. They will learn how to apply engineering, biological, and medical theory and methods to resolve complex problems in biomechanics and mechano-biology. Students will learn to draw connections between tissue morphology and mechanical response, and vice versa. Students will also gain the required expertise to apply their knowledge in relevant, practice-oriented problem solving in the fields of pneumology, cardiology, cardiovascular surgery, orthopaedics, dentistry, rehabilitation, and sports sciences.

The mandatory courses in this module provide the student with fundamental knowledge of fluid and solid mechanics, tissue engineering, tissue biomechanics, and finite element analysis. This provides an overview of the functional adaptation of the respiratory, cardiovascular, or musculoskeletal system to the demands of daily living and the necessary conditions for its repair and regeneration. This major module requires a prior knowledge of mechanics, numerical methods, and related engineering sciences, as many of the mandatory and elective courses build upon these foundations. Elective courses allow the students to extend their competence in a chosen direction, gaining knowledge in analytical methodologies, medical device design, minimally invasive surgery, or rehabilitation.

Knowledge gained during the coursework highlights the multidisciplinary nature of this study focus area, encompassing the cell to body, the idea to application, and the lab benchtop to the hospital bedside. This knowledge is applied during the final thesis project, a project often with a link to a final diagnostic or therapeutic application. Examples of recent master thesis projects include lung alveoli array on chip, development of an in-vitro model of the lower urinary tract, personalized prediction of percutaneous coronary interventions, setup and analysis of a hop test, and development of a device for sensorimotor hand training.

Career prospects are numerous. Many students proceed to further post-graduate education and research, pursuing doctoral research in the fields of biomechanics, tissue engineering, lab-on-chip, or development of biomaterials. Most of the major companies in the fields of cardiovascular technology, orthopaedics, dentistry, rehabilitation engineering, and pharmaceuticals are strongly represented within the Swiss medtech industry and have an ongoing demand for graduates of this major module. At the interface between biomedical engineering and clinical applications, graduates may also pursue careers related to the evaluation and validation of contemporary health technology, a cornerstone for future policies on the adoption of these new methods in the highly competitive healthcare domain.




Normal human lung fibroblasts are cultured on a bilayer built of a hypersoft thin polydimethylsiloxane (PDMS) membrane and a hexagonal PDMS mesh (Photo: C. Kündig).

# Major Module

## Electronic Implants

**Head of Module**
Prof. Dr. Volker M. Koch
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Electronic implants are devices such as cardiac pacemakers and cochlear implants. Due to miniaturization and other developments, many new applications have become feasible, and this exciting area is growing rapidly. For example, cochlear implants provide people a sense of sound. These people were previously profoundly deaf or severely hard of hearing. Recently, researchers demonstrated that electronic retinal implants allow the blind to read large words.

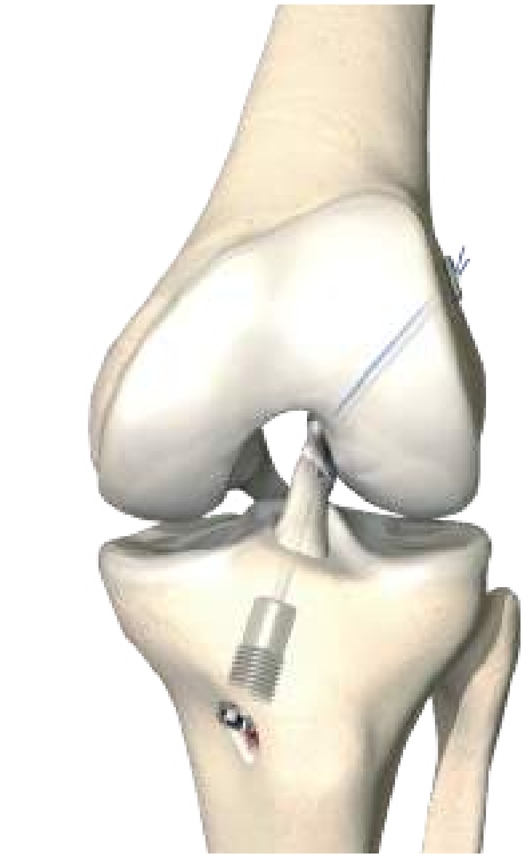
There are many more applications for electronic implants beyond treating heart problems, hearing loss, or blindness. For example, there are electronic implants that treat Parkinson's disease, obesity, depression, incontinence, hydrocephalus, pain, paraplegia, and joint diseases.

In this module, students will gain a comprehensive technical and application-oriented understanding that will allow them to select, use, design, and optimize electronic implants and similar biomedical systems. Since the work on such complex systems is usually done in interdisciplinary groups, another important goal is that graduates are able to work and communicate in teams consisting of, for example, engineers, scientists, and medical doctors.

Specifically, students will learn about technology basics including intelligent implants and surgical instruments, biomedical signal processing and analysis, low-power microelectronics, wireless communications for medical devices, biomedical sensors, and microsystems engineering including MEMS technology. Application-oriented elective courses are also taught, e.g., cardiovascular technology, biomedical acoustics, biomedical laser applications, ophthalmic technologies, and diabetes management.

Students may already apply their knowledge as a part- time assistant in an institute and/or during their master's projects. After finishing the degree program, a wide variety of career paths is available, ranging from research and development to project and product management. Many companies in Switzerland work in this field, and "traditional" implants manufacturers have recently become interested in electronic implants, for example, to measure forces in knee implants.

This major is open to all students in our master's program. However, typically, students have an engineering-related background such as electrical engineering, microtechnology engineering, systems engineering, mechatronics engineering, mechanical engineering, or computer science.



The Ligamys implant used for anterior cruciate ligament (ACL) rupture healing has been instrumented to be able to measure in-vivo loads wirelessly. This work was part of an Innosuisse project. The BFH (HUCE-SensorLab) together with the Swiss Innovation Park Biel and the HAFL were involved in the development of this innovative solution.



# Major Module

## Image-Guided Therapy

**Head of Module**
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Phone: +41 31 632 75 75

Image-gGuided tTherapy refers to the concept of guiding medical procedures and interventions through perceiving and viewing of medical image data, possibly extended by using stereotactic tracking systems. Medical imaging typically relates to a great variety of modalities ranging from 2D fluoroscopy and ultrasound to 3D computed tomography and magnet-resonance imaging, possibly extended to complex 4D time series and enhanced with functional information (PET, SPECT). Guidance is realized by determination of the spatial instrument-to-patient relationship and by suitable visualization of tracking and medical image data. Image guidance is very often accompanied by other surgical technologies such as surgical robotics, sensor- enhanced instrument systems, as well as information and communication technology.

Students of the IGT module will study the clinical and technical fundamentals of image-guided therapy systems. They will develop an understanding of currently applied clinical standards as well as an overview of the latest advancements in research. Successful students will be enabled to develop novel clinic-technological applications for complex medical procedures as well as improve existing approaches. This will be the foundationbasement for successful careers both in the industrial and academic sector.

Mandatory courses of this module are concerned with the fundamentals of sSignal and iImage pProcessing and mMedical iImage aAnalysis. Furthermore, fundamental aspects of stereotactic image guidance, tracking, patient-to-image registration, and basic clinical applications are taught in the course Computer-Assisted Surgery. Recent trends and fundamental aspects in surgical robot technology, minimally invasive procedures and its applications within IGT are introduced in the course Medical Robotics. Additional elective courses extend students' competencies in related areas such as computer graphics, pattern recognition, machine learning, and regulatory affairs.

Demonstrator for robotic spinal surgery (© ARTORG Center, 2021)

# Faculty

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Roland Wiest, Prof. Dr.

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Bertrand Dutoit, Prof. Dr.
Juan Fang, Dr.
Stéphane Felix, Prof. Dr.
Gabriel Gruener, Prof. Dr.
Horst Heck, Prof. Dr.
Andreas Habegger, Prof.
Kenneth James Hunt, Prof. Dr.
Inniger Dominik
Jörn Justiz, Prof. Dr.
Volker M. Koch, Prof. Dr.
Martin Kucera, Prof.
Sylvain Le Coultre, Prof.
André Lisibach, Prof. Dr.
Alexander Mack, Dr.
Christoph Meier, Prof.
Fabio Modica
Thomas Niederhauser, Prof. Dr.
Patrick Schwaller, Prof. Dr.
Andreas Stahel, Prof. Dr.
Jasmin Wandel, Prof. Dr.
Thomas Wyss Balmer, Dr.

### Partner Institutions and Industry

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Markus Auly
Alessandro Bertolo, Dr.
Marc Bohner, Prof. Dr.
Nicolas Bouduban
Emmanuel de Haller, Dr.
Nicolas Alexander Diehm, Prof. Dr.
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Reto Luginbühl, Dr.
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Simon Milligan, Dr.
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Birgit Schäfer, PD Dr.
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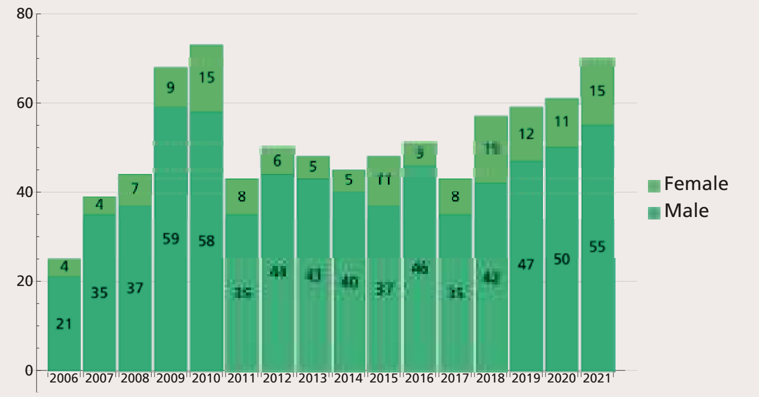
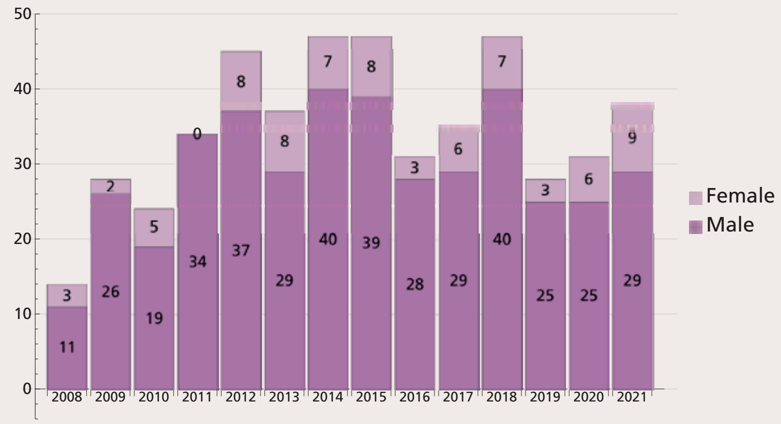
Benjamin Simona, Dr.
Jivko Stoyanov, Prof. Dr.
Prabitha Urwyler, PD Dr.
Tim Vanbellingen, PD Dr.
Peter Varga, Dr.
Peter Wahl, Dr. med.
André Weber, Dr.
Burak Yilmaz, Dr.
Guodong Zeng, Dr.
Andreas Zumbühl, Prof. Dr.

# Number of New Students and Graduates

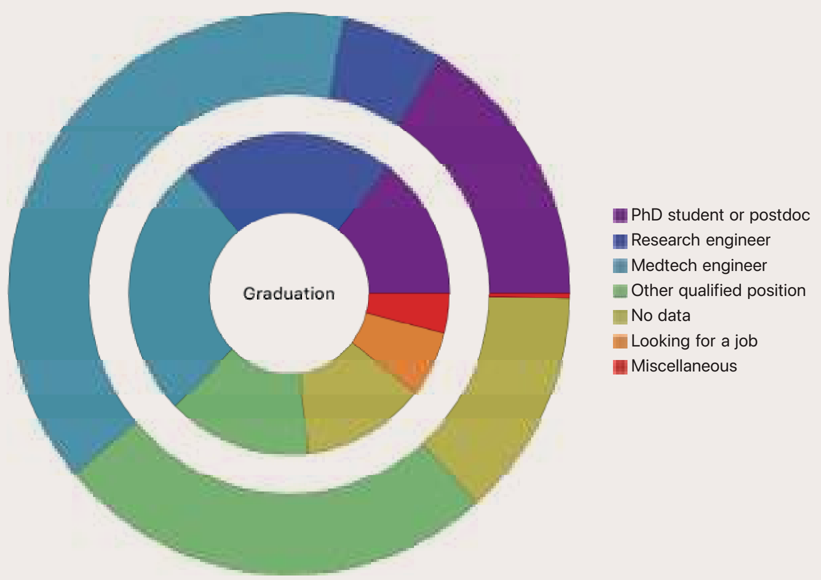
**Number of New Students**




**Number of Graduates**




**Profession after Graduation: Activity after 1 (inner circle) and 5 years**





# Completed Master's Theses in 2021

**Eylem Akalp**
Modality Dependent Accuracy Analysis of Patient-Specific 3D Anatomy Modelling
Supervisors: Dr. Kate Gerber, MSc Hanspeter Hess
Institutions: University of Bern, Sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: Dr. Kate Gerber, Dr. Guodong Zeng

**Cyril Albrecht**
Trajectory Planning for Robotic Thermal Ablation with overlapping Volumes
Supervisors: Milica Bulatović, Dr. Iwan Paolucci
Institution: ARTORG Center for Biomedical Engineering Research, University of Bern
Examiners: Milica Bulatović, Prof. Dr.-Ing. Stefan Weber

**Raphael Andonie**
Time-Adaptive Algorithms for Low-Power Medical Devices
Supervisors: Prof. Dr. sc. ETH, Dr. med. Reto Wildhaber, MSc Christof Baeriswyl
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering HuCE
Examiners: Prof. Dr. Marcel Jacomet, Prof. Dr. sc. ETH, Dr. med. Reto Wildhaber

**Martin Bertsch**
Targeted Drug Delivery in Glioblastoma Mouse Models
Supervisors: Prof. Dr. Roch-Philippe Charles, MSc Javier Pareja
Institution: University of Bern, Institute for Biochemistry and Molecular Medicine
Examiners: Prof. Dr. Roch-Philippe Charles, MSc Javier Pareja

**Benjamin Bircher**
Middle Ear Laser Doppler Vibrometry Assessment for improved Electrocochleography
Supervisors: Prof. Dr. Bertrand Dutoit, Klaus Schürch
Institutions: Bern University of Applied Sciences, HuCE-ScienceLab, BFH-TI
University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: PD Dr. Wilhelm Wimmer, Prof. Dr. Bertrand Dutoit

**Muriel Bischof**
Effect of Angiopoietin-1 and Angiopoietin-2 on Human IVD Progenitor Cells
Supervisors: Prof. Dr. Benjamin Gantenbein, Dr. Julien Guerrero
Institution: University of Bern, Department for Biomedical Research
Examiners: Prof. Dr. Benjamin Gantenbein, Dr. Julien Guerrero

**Pavel Bouduban**
Ex Vivo Validation of an Implantable Continuous Cardiac Monitor
Supervisors: Prof. Dr. Thomas Niederhauser, Sven Krause
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering HuCE
Examiners: PD. Dr. Thomas Niederhauser, PD. Dr. med. Dr. phil. Andreas Häberlin

**Thomas Buchegger**
Speech Recognition for Parkinson Patients in an Instrumented Apartment
Supervisors: Dr. Stephan Gerber, Pascal Reuse
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Tobias Nef, Dr. Stephan Gerber

**Linard Büchler**
Assessment of Cell Viability and Metabolic State using Autofluorescence Spectroscopy inside Cell Bulk
Supervisors: Karl-Heinz Selbmann, Prof. Christopher Meier, Prof. Dr. Torsten Ochsenreiter
Institutions: Bern University of Applied Sciences, Institute for Printing Technology
Bern University of Applied Sciences, Institute for Human Centered Engineering
University of Bern, Institute of Cell Biology
Examiners: Karl-Heinz Selbmann, Prof. Christopher Meier

**Nina Chatelain**
Mechanical and Biological Validation of a Novel Microvasculature-on-Chip Device
Supervisors: Prof. Dr. Olivier T. Guenat, MSc Dario Ferrari
Institution: University of Bern, ARTORG Center for Biomedical Research
Examiners: Prof. Dr. Olivier T. Guenat, MSc Dario Ferrari

**Carolina Duran**
Confounder-Free Deep Learning Training for Brain Tumour Segmentation
Supervisor: Prof. Dr. Mauricio Reyes
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Mauricio Reyes, PD John Anderson Garcia Henao

**Lukas Geisshüsler**
In Vitro Setup for Temporal Interference Stimulation
Supervisors: Prof. Dr. Thomas Niederhauser, MSc Elisa Maira Kaufmann
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering HuCE
Examiners: Prof. Dr. Thomas Niederhauser, PD Dr. Dr. med. Andreas Häberlin

**Katrin Gfeller**
Design of an End-Effector Based Arm-Swing-Device for Gait Training
Supervisors: Dr. Juan Fang, Prof. Dr. Kenneth Hunt
Institution: Bern University of Applied Sciences, Institute for Rehabilitation and Performance Technology
Examiners: Prof. Dr. Kenneth Hunt, Dr. Juan Fang

**Rafael Gfeller**
A Bioactive Transplantation Device for Reduction of Complications after Pressure Injury Surgery
Supervisors: Prof. Dr. Jivko Stoyanov Ph.D, Dr. Alessandro Bertolo Ph.D.
Institution: Swiss Paraplegic Research, Nottwil
Examiners: Prof. Dr. Jivko Stoyanov Ph.D., Prof. Dr. Benjamin Gantenbein Ph.D.

**Michael Herren**
Deep Learning based Segmentation and Fat Fraction Analysis of the Shoulder Muscles using quantitative MRI
Supervisors: Dr. Nicolas Gerber, MSc Hanspeter Hess
Institution: University Bern, sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: Dr. Kate Gerber, Dr. Nicolas Gerber

**Ece Su Ildiz**
Lack of Endothelial PECAM-1 Enhances Extravasation of Brain Seeking Melanoma Cells Across the Blood-Brain Barrier in vitro
Supervisor: Prof. Dr. Ruth Lyck
Institution: University of Bern, Theodor Kocher Institute
Examiners: Prof. Dr. Ruth Lyck, Dr. Giuseppe Locatelli

**Marc** Ilic
Devlopment of Stenosed Coronary Arterial Phantom for a Coronary Artery bench Simulator
Supervisors: MSc Cornelia Amstutz, PD Dr. med. Dr. phil. Andreas Häberlin
Institution: University of Bern, sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: MSc Cornelia Amstutz, Prof. Dr. Jürgen Burger

**Camille Kaufmann**
Development of an Ultrasonic Scaler for Dental Calculus Removal
Supervisor: Martin Hofmann
Institution: University of Bern, sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: Prof. Dr. Jürgen Burger, Martin Hofmann

**Simon Krebs**
A Novel Device to Measure Applied Forces During Minimal Invasive Coronary Interventions
Supervisors: Dr. Adrian Zurbuchen, MSc. Cornelia Amstutz, PD Dr. med. Dr. phil. Andreas Haeberlin
Institutions: University of Bern, sitem Center for Translational Medicine and Biomedical Entrprenuership
University Hospital Bern (Inselspital), Department of Cardiology
Examiners: Dr. Adrian Zurbuchen, Prof. Dr. med. et phil. nat. Rolf Vogel

**Christian Kündig**
Lung Alveoli Array on Chip: Reproduction of Alveolar Structure with in Vivo Stiffness Gradient
Supervisors: Prof. Dr. Olivier Guenat, MSc Dario Ferrari
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier T. Guenat, MSc Dario Ferrari

**Caleb Leichty**
Development of High-Throughput Platform for IPF-on-Chip Model
Supervisors: Prof. Dr. Olivier Guenat, Dr. Pauline Zamprogno
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier Guenat, Dr. Pauline Zamprogno

**Ajith Manimala**
Development of an In-Vitro Model of the Lower Urinary Tract with Physiological Mechanical Properties
Supervisors: Dr. Lukas Bereuter, PD Dr. Francesco Clavica
Institutions: University of Bern, ARTORG Center for Biomedical Engineering Research
University Hospital Bern (Inselspital), Department of Urology
Examiners: Dr. Lukas Bereuter, PD Dr. Francesco Clavica

**Nalet Julian Meinen**
Motion Classification in Video Recordings
Supervisors: Aileen Naef, Dr. Stephan Gerber
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. sc. Tobias Nef, Aileen Naef

**Killian Monnin**
Detection of Disease and Conditions in Optomap imaging
Supervisors: Prof. Dr. Raphael Snitzman, Dr. Andrés Marafioti
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila

**Rafael Philippe Morand**
Denoising Inertial Measurement Units with Deep Learning for Human Gait Analysis
Supervisors: Prof. Dr. Volker M. Koch, Dr. Pascal Leimer
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering
Switzerland Innovation Park Biel/Bienne AG
Examiners: Prof. Dr. Volker M. Koch, MSc Thomas Wren

**Robert A. Münger**
Evaluation and Application of Alternative Segmentation using Gaussian Process and Deep-Learning models
Supervisor: Prof. Dr. Mauricio Reyes
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Mauricio Reyes, Prof. Dr. med Nicolaus Andraschtke

**Remo Pascal Muri**
Personalized Prediction of the Outcome of Percutaneous Coronary Interventions
Supervisors: Prof. Dr. Philippe Büchler, Dr. Can Gökgöl
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Philippe Büchler, Dr. Can Gökgöl

**Rémy Minh-An Nguyen**
Development of a Hybrid Bone Conduction Implant Demonstrator
Supervisors: PD Dr. Wilhelm Wimmer, Emile Talon
Institution: ARTORG Center for Biomedical Engineering Research
Examiners: PD Dr. Wilhelm Wimmer, Emile Talon

**Basil Peterhans**
Multi-Angle Optical Coherence Tomography Data Reconstruction
Supervisor: Prof. Dr. Patrik Arnold
Institution: University of Applied Sciences Bern, Institute for Human Centered Engineering
Examiners: Prof. Dr. Patrik Arnold, Dr. Silvano Balemi

**Lara Piers**
Towards Gait Analysis with 6D Tags and 2D Cameras: Setup and Analysis of a Hop Test
Supervisors: Prof. Dr. Gabriel Gruener, Dr. Patric Eichelberger, Prof. Dr. Heiner Baur
Institutions: Bern University of Applied Sciences, School of Health Professions
Bern University of Applied Sciences, Institute for Human Centered Engineering
Examiners: Dr. Patric Eichelberger, Prof. Dr. Gabriel Gruener

**Christian Piguet**
Positive-Unlabeled Learning for Segmentation from Sparse Annotations
Supervisors: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila

**Adrian Rechsteiner**
Positional Accuracy Evaluation of a Robotic System for Spinal Surgery
Supervisors: Prof. Dr. Stefan Weber, Marcel Schoch
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Stefan Weber, MSc Fabian Müller

**Ralph Rechsteiner**
High-Level Synthesis of an Edge Detector Using Windowed State Space Filters in 180nm CMOS
Supervisors: Prof. Dr. Reto Wildhaber, MSc Christof Baeriswyl
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering HuCE
Examiners: Prof. Dr. Marcel Jacomet, Prof Dr. Reto Wildhaber

**Simon Salzmann**
Optical Coherence Tomography Assisted Laser Treatment of Retinal Detachments
Supervisors: Prof. Christoph Meier, Dr. med. Sami Al-Nawaiseh, Dr. med. Philip Wakili
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering
University Hospital Münster, Department of Ophthalmology
Knappschaftsklinikum Saar, Eye Clinic Sulzbach
Examiners: Prof. Christoph Meier, MSc Christian Burri

**Leonardo Pietro Emanuele Sartori**
Interpretability-Driven Failure Modes Investigation of Deep Learning Segmentation Models
Supervisor: Prof. Dr. Mauricio Reyes
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Mauricio Reyes, Dr. Alain Jungo

**Barbara Schläpfer**
Quantification of the Energy Loss through Turbulence in an Aortic Stenosis Model using Particle Tracking Velocimetry and Doppler Echocardiography in a Silicone Ascending Aorta Phantom
Supervisor: Dr. med. Eric Buffle
Institution: University of Bern, ARTORG Centre for Biomedical Engineering Research
University Hospital Bern (Inselspital), Department of Cardiology
Examiners: Prof. Dr. Dominik Obrist, Dr. med. Eric Buffle

**Jana Stárková**
Retinal Images and Meta-Data Verification to Ensure Data Consistency and Anonymity
Supervisors: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila, Dr. Mathias Gallardo
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila

**Stefan Weber**
Deep Learning based Fully Automatic Quantification of Rotator Cuff Tears from MRI
Supervisors: PD Dr. Kate Gerber, MSc Hanspeter Hess, Dr. Guodong Zeng
Institution: University of Bern, sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: PD Dr. Kate Gerber, Dr. Nicolas Gerber

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Editorial

# Networking

**Our innovative capacity is only as strong as our network. For this reason the BBEN supports networking of members right from the start.**

The annual Biomedical Engineering Day (BME Day) provides an irreplaceable hub for prospective and current students, alumni and industry partners to connect. It offers students the opportunity to make valuable contacts and become actively involved in the Biomedical Engineering Club to lay the corner stones for their future careers. Participants can explore the potentials of academic-commercial collaborations via industry-driven project proposals, also leveraging on the skills and knowledge of the research community. New partnerships and commercial networking of medtech and life science companies in our region have more than once arisen from this occasion. Even in a virtual format, the event has succeeded in forging new collaborations.



# The Biomedical Engineering Club

## The BME Club and Its Mission

**The BME Club executive Board members in 2020**

Samuel Knobel
Email: info@bmeclub.ch

**Group Members**

Adel Tekari
Alumni

Mark Keller
Corporate

Tobias Imfeld

Tamara Melle

Fredrick Joseph

Arina Shvetsova

The Biomedical Engineering (BME) Club is a non-profit Alumni organisation from the University of Bern that aims to provide and promote networking events among its interdisciplinary members. We are a constantly growing group of biomedical engineers, scientists, past and present students and medical technology corporate eager to bring together the fields of engineering, biology, and clinical medicine. The BME-Club accomplishes these goals by networking and hosting events, in particular, information sessions to learn about cutting-edge research fields of bioengineering, attendance of national/international conferences, and visit plans to industries and laboratories. The BME Club has been recognized as an official Alumni association of the University of Bern under the umbrella organization – Alumni UniBE. A dedicated executive committee within the BME-Club follows the principles of our constitution. We are an enthusiastic and versatile group that performs diverse activities including:

- Regular visits to Swiss medical and engineering companies
- Organization of the annual MEDICA trip
- Information on career opportunities for Masters levels
- Organization of the annual Welcome event for new students of the BME Master program
- Organization of an annual Alumni gathering for networking purposes
- Sponsorship of the best, Master thesis award at the annual BME day
- Sponsorship of 2 Travel Grants to International conferences
- Joint membership for former students of the University of Bern
- Offering (optional) joint membership with Swiss Society for Biomedical Engineering

Taken together, the BME club represents a unique platform for professional, lifelong communication and networking events.

Further details on the BME-Club are available on our website:
> http://www.bmeclub.ch
… our LinkedIn appearance
> https://www.linkedin.com/company/biomedical-engineering-club/
… and frequently added posts of the Instagram profile of the BME-Master course > https://www.instagram.com/bme_unibe/

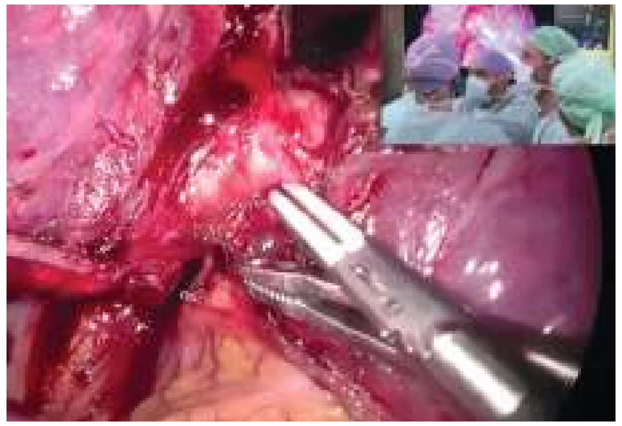
**How to Join**

Becoming a BME member is easy! Simply join at any BME Club event or sign in at our website. We are looking forward to seeing you.

# Biomedical Engineering Day 2021

## The first virtual BME Day was a great success

The surgical team at the operating table



Live surgery (lung resection due to cancer)

On May 7, 2021, the first virtual Biomedical Engineering Day in 13 years was held. The master's program in Biomedical Engineering of the University of Bern organized this event for the 12th time.

The event is an efficient platform in Switzerland for networking of master's and Ph.D. graduates and Swiss and international medical technology companies. This year's companies introduced themselves through oral presentations in a Zoom webinar and gave insight into their commercial activities and their company philosophies as well as showed their demands on junior employees. Students had the opportunity to get to know potential employers and contact them directly during the virtual coffee break organized in the virtual town "gather city."

The BME Day offered great opportunities for the Bernese biomedical researchers, too. The ARTORG Center for Biomedical Engineering Research and the Bern University of Applied Sciences, a partner within the master's program, used the opportunity to present current research projects to more than 200 virtual participants. Interestingly, master's and Ph.D. students play an important role in many of these projects. Thereby, this event was a demonstration of scientific achievements, too. In addition to company representatives, scientists, researchers, and young academics, medical doctors participated in this year's event as well.

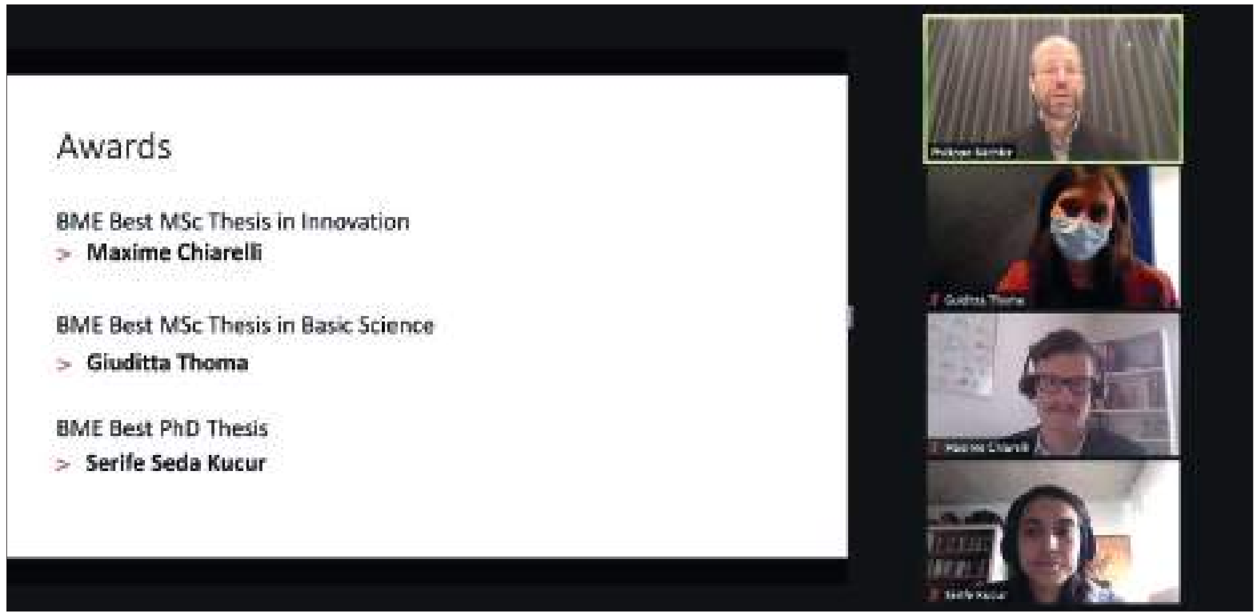
For the first time, young researchers presented their projects in a humorous way during a "my thesis in 180 seconds" session. One highlight of the morning was definitely the successful live surgery by Gregor Kocher and Patrick Dorn, Department of Thorarcic Surgery, University Hospital Bern (Inselspital). Many students asked questions in the live chat during the lung surgery.

**Awards**

The following awards for excellent academic achievements in the field of Biomedical Engineering at the University of Bern were presented:

- Swiss Engineering Award for the best master's thesis (innovation): Maxime Chiarelli (Estimation of the Energy Loss through Turbulence in an Aortic Stenosis Model Using Backlight Particle Tracking Velocimetry in a Silicone Ascending Aorta Phantom)
- Swiss Engineering Award for the best master's thesis (basic science): Giuditta Thoma (Lung-Alveoli-on-Chip: Mechanical Characterization of a New Biological Membrane)
- CCMT Award for the best Ph.D. thesis: Serife Kucur (Exploration and Exploitation of Visual Fields: from Acquisition to Prediction of Glaucoma)
- BME Club Awards for the best master's thesis abstract:
  1st place: Simone Poncioni (Optomechanical Simulations of Laser Refractive Surgeries)
  2nd place: Nathan Gyger (Contactless Detection of Gait and Gait Abnormalities)
  3rd place: Martin Bertsch (Targeted Drug Delivery in Glioblastoma Mouse Models)
- RMS Award for the best GPA in the MSc Biomedical Engineering: Adrian Ruckli (GPA 5.77)

The award winners from left to right: Maxime Chiarelli, Giuditta Thoma, Serife Kucur, Simone Poncioni, Adrian Ruckli




Chairman Philippe Büchler (top) awards the prizes to Giuditta Thoma, Maxime Chiarelli and Serife Kucur


The virtual industrial exhibition in Gather City

**We thank our sponsors and exhibitors**



# Acknowlegdments

The BBEN would like to express its gratitude to the many supporters from academia, industry and government without whose invaluable contributions its operations would be impossible. We are grateful for our visionary partners, stakeholder, and funders who believe in the uniqueness of the BBEN innovative power. The number of our technologies that have sprouted from their infancy in our labs and are today employed in routine clinical practice are testimony to the success of our collaboration model and we are especially proud of our spin-outs who demonstrate their appreciation for their incubation and birth here by actively supporting our network.

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WIR BEWEGEN MEHR

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schweiz suisse svizzera

PASC
Platform for Advanced Scientific Computing

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