# Bern Biomedical Engineering Network

Annual Report 2018/19

sitem-insel

Berner Fachhochschule
Haute école spécialisée bernoise

Universität Bern

Inselspital
Universitätsspital Bern
Hopital Universitaire de Berne
Bern University Hospital

competence center for medical technology ccmt

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



## Bern University of Applied Sciences



## Academic Education and Teaching



## Networking

# EDITORIAL

The 2018/19 Bern Biomedical Engineering Network (BBN) Report showcases the ongoing importance of the network's role in the medtech research and industry cluster of the Bern region.

The BBN partners continue to collaborate in research, educate the next generation of biomedical engineers, and pioneer the introduction of medtech products into the clinic and the marketplace.

The establishment of the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel AG) is progressing with élan. sitem-insel AG will continue to be a central partner of the Bern Biomedical Engineering Network. The three operational divisions of sitem-insel AG have taken up their work on translation in 2018. It will offer support to streamline the way from prototype to commercialisation of medical products. An important accelerator to enable translation is the establishment of an innovation culture and the strengthening of interdisciplinary and interprofessional cooperation. Another critical success factor is the availability of state-of-the-art facilities and resources. Planning and construction of the laboratories and workshops of the sitem-insel Enabling Facilities are almost complete. One of the highlights of this year was the successful installation of the 7-Tesla MRI. The sitem-insel Promoting Services division covers regulatory areas for medical product approval. In addition courses to prepare the medical technology industry for the transition to Medical Device Regulation (MDR) were offered and many smaller companies were individually mentored. In 2017, the first cohort of the sitem-insel School of the Masters of Advanced Studies in Translational Medicine (MAS) took up their studies and project work and the class of 2019 graduated. Many of the MAS projects originated in the Bern Biomedical Engineering Network and were further developed decisively by the students within the framework of the sitem-insel School. With their knowledge gained in sitem-insel, these graduates contribute effectively to the professionalization of translation throughout Switzerland.

Several members of the BBN have been successful in the highly competitive Swiss National Science Foundation and Innosuisse - Swiss Innovation Agency BRIDGE Program in 2018 - 2019. The program funds projects that accelerate basic science discovery into innovative products. For medical technology this means a translation remit to address an unmet clinical need. The first BRIDGE Proof-of-Concept project at the Berner Fachhochschule called "Thermobonding Process for the Automatic Manufacturing of Advanced Diagnostic Catheters" commenced in 2019. The first BRIDGE Discovery project at the ARTORG Image Guided Therapy group in cooperation with the Inselspital and the Swiss Center for Electronics and Microtechnology entitled "Towards Intelligent Sensor-enhanced Robotic Neurosurgery" has been launched in 2018. The BRIDGE Proof-of-Concept project "ALLY: AI-Enabled Mobile Perimetry" was awarded to the ARTORG Opthalmic Technology Laboratory. In Biel, work for the new Berner Fachhochschule campus and the Switzerland Innovation Park has started to merge its technical disciplines, including the biomedical engineering and rehabilitation institutes, in the new campus. Along with the developments on the Insel campus, the Berner Fachhochschule campus and the Switzerland Innovation Park will proactively strengthen the already very successful joint Master's program in Biomedical Engineering.

The BBN was founded to encourage cooperation by highlighting common interests, share available resources and leverage the location advantage of partners nearby. This report reflects the success of this continued effort to build a strong and transparent network that benefits the medical technology sector of the Canton of Bern.

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Bern University of Applied Sciences
Engineering and Information Technology

Raniero Pittini
Head of Swiss Medtech Center
Head of Research Medtech
Switzerland Innovation Park
Biel/Bienne AG

Simon Rothen
CEO
sitem-insel AG

# INSTITUTIONAL OVERVIEW

Inselspital, Bern University Hospital
Freiburgstrasse, 3010 Bern

Swiss Institute for Translational and Entrepreneurial Medicine
Freiburgstrasse 18, 3010 Bern

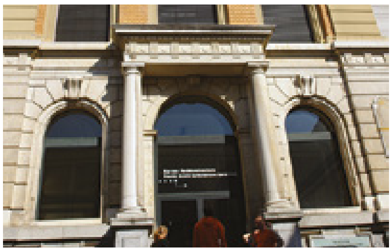
ARTORG Center for Biomedical Engineering Research
Murtenstrasse 50, 3010 Bern

Institute of Social and Preventive Medicine
Mittelstrasse 43, 3012 Bern

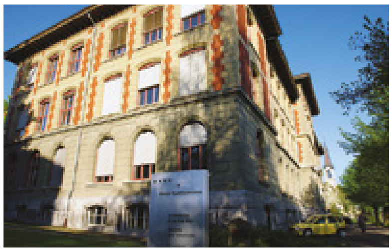
Clinical Trials Unit Bern
Mittelstrasse 43, 3012 Bern

Institute of Applied Physics
Sidlerstrasse 5, 3012 Bern

University of Bern
School of Dental Medicine
Freiburgstrasse 7, 3010 Bern



Institute for Human Centered Engineering
Quellgasse 21, 2501 Biel



Institute for Rehabilitation and Performance Technology
Pestalozzistrasse 20, 3400 Burgdorf

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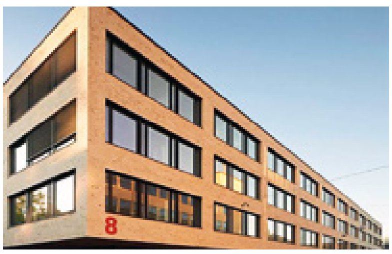
Institute for ICT-Based Management
Höheweg 80, 2502 Biel

Switzerland Innovation Park Biel/Bienne AG
Aarbergstrasse 5, 2560 Nidau-Biel

Institute of Computer Science
Neubrückstrasse 10, 3012 Bern

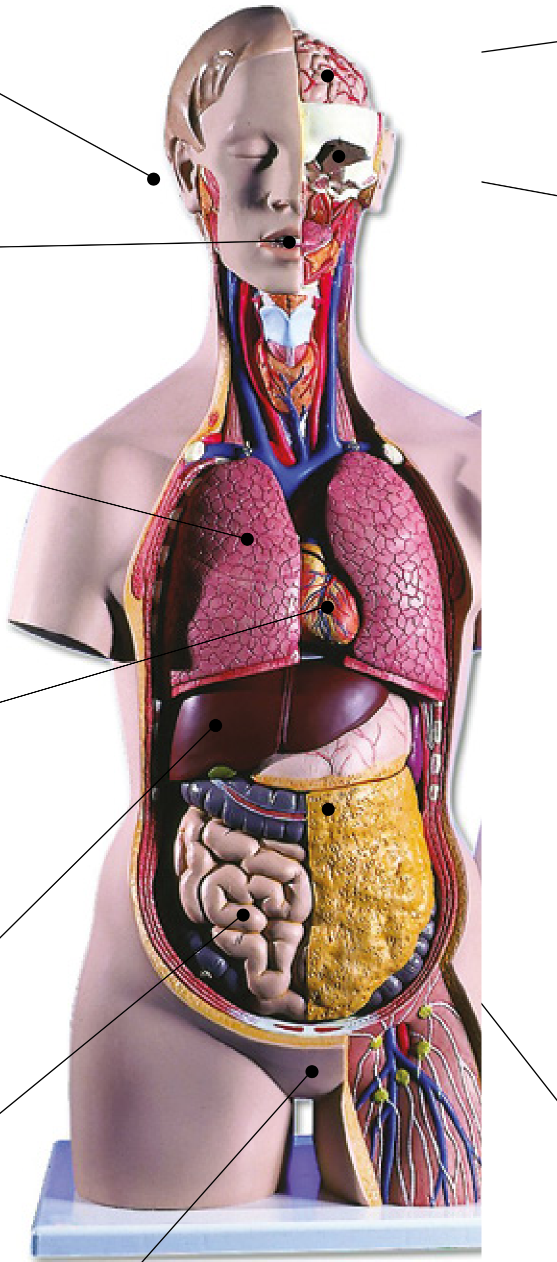


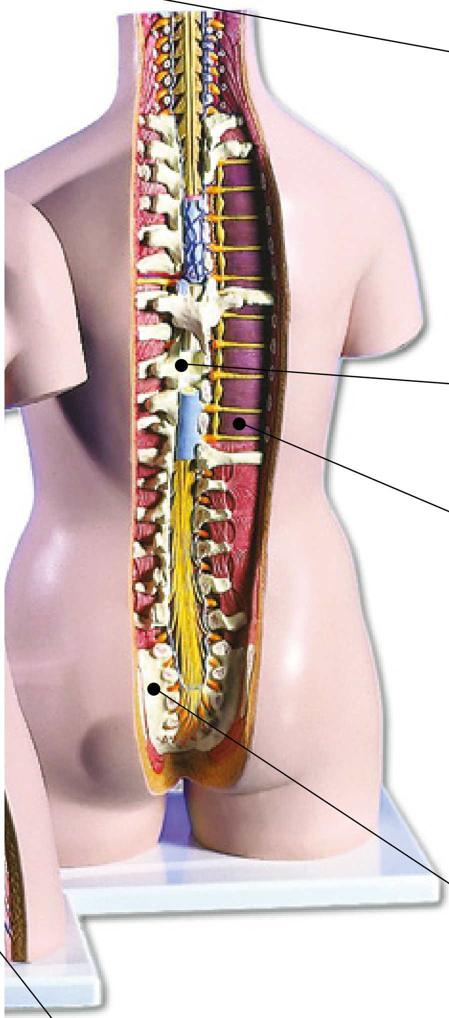
Institute of Psychology
Fabrikstrasse 8, 3012 Bern

EMPA
Feuerwerkstrasse 39, 3602 Thun

# OVERVIEW OF CLINICAL SPECIALITIES








sitem insel

# Swiss Institute for Translational and Entrepreneurial Medicine sitem-insel

Simon Rothen, Head of sitem-insel
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### Clinical and Research Partners

All clinical institutions from the University Hospital of Bern

**Research Profile**

sitem-insel AG – The Swiss Institute for Translational and Entrepreneurial Medicine in Bern – operates and develops a National Center of Excellence that assists in the transition from research findings and prototypes to marketable products.

sitem-insel's strategy is to create and foster an enhanced environment for translational medicine in Switzerland. The strategy is based on three pillars:

- **sitem-insel School** offers university education to professionals in medical devices and life science industry. The school's Continuing Professional Development (CPD) courses are taught by university faculty and private-sector lecturers.
- **sitem-insel Enabling Facilities** provides infrastructure and personnel at the interface between the private sector and university hospitals for R&D and clinical trials of innovative products.
- **sitem-insel Promoting Services** promotes innovation and optimizes administrative and regulatory effort from bench to bedside.

### Translational Medicine

Translational medicine deals with the transition from new findings and products from industrial development and basic research to clinical application.This process-oriented discipline professionalizes the interaction between industry, universities, clinicians, regulatory bodies and investors.

**Organization**

sitem-insel is an independent, non-profit public private partnership with the legal form of a public limited company. Current income is primarily generated through rent of the tenants from industry, clinic, and research. In addition, funding of CHF 50m has been approved for the start-up phase (2017-2020) from the Canton of Bern and the Federal Government. Substantial funding was also received from private industry and foundations.

**Location**

Starting in May 2019, sitem-insel will operate from its new building on the campus of the university hospital (Inselspital).

sitem-insel's location facilitates and promotes sustainable medical innovation through efficient interaction between clinicians, researchers, the private sector, regulatory authorities, and other stakeholders. The location is close to the highway, the central station, the University of Bern, and the city center.

**Translational Research at sitem-insel**

Projects at sitem-insel emerge from the bottom up, based on the initiative of investigators from private companies, hospitals, basic research institutions, and start-ups. As sitem-insel aims to account for disruptive developments, the new building's infrastructural design guarantees flexibility. Several platforms have been designed to facilitate translational projects with specific novel technologies. Operated by industry partners, institutes from the university of Bern, the Inselspital, and other stakeholders these platforms are open for national and international projects from investigators independent of their origin. Among the platforms are:

*Diabetes Center Berne*

The Diabetes Center Berne (DCB), together with the Department of Diabetes, Endocrinology, Clinical Nutrition and Metabolism of the University of Bern (UDEM), is researching new therapeutic approaches for diabetes and developing innovative technologies. The research institute is located in the sitem-insel building on the campus of the Inselspital Bern. Dr. h. c. Willy Michel, Chairman of the Board of Directors of the Ypsomed Group, allocates CHF 50 million privately for this project.

*CSL Behring Research Center*

The biopharmaceutical company CSL Behring will operate the CSL Biologics Research Center (CBRB) within sitem-insel's premises with the aim to identify and characterize innovative novel drug candidates. Close cooperation between clinicians and industrial R&D is essential for purposefully bringing new biologics to patients. The proximity to the university hospital is thus a major advantage for the development of novel patient-oriented products.

*Biosafety Laboratory*

The Biosafety Laboratory will be directed by the Institute for Infectious Diseases of the University of Bern. The development of new diagnostic-therapeutic products for infections suffers from a lack of both laboratories complying with biosafety regulations and cooperation between the various partners in the field. This is why the Biosafety Laboratory (BSL2 and BSL3) will be established at sitem-insel as a central platform for cooperation between public and private stakeholders. Project proposals are highly welcome.

*Dental Research Center*
The research laboratories of the School of Dental Medicine (SDM) at the University of Bern, with their first-class track record in translational research over more than 40 years, will be integrated into the Dental Research Center at sitem-insel. They have been successfully cooperating with medtech companies such as Straumann (Basel) and Geistlich (Wolhusen) for decades, and they will gain access to a first-class infrastructure and benefit from the existing expertise of other research groups.

*ARTORG Center for Biomedical Engineering Research*
The ARTORG Center for Biomedical Engineering Research is the medical technology research hub of the University of Bern. A multidisciplinary team of clinicians, engineers, life scientists, allied health professionals, social and management scientists, commercial partners and patient stakeholders are fully-embedded in the medical faculty and in alliance with the Insel Group. Translation research that addresses unmet clinical needs in major disease areas transforms basic research findings in microfluidics, fluid mechanics, rapid prototyping, image processing, robotics and artificial intelligence into clinical solutions in neurology, respiratory, ENT, ophthalmology, hepatobiliary, metabolic, orthopedic and cardiovascular medicine. In the last decade, a sustained translation pipeline at the ARTORG has supplied projects for successful commercial ventures that have attracted investment, approved devices and launched products into clinical care.

*Clinical Anatomy Training and Research Unit*
In cooperation with KARL STORZ – the leading endoscope manufacturer – the Clinical Anatomy Training and Research Unit at sitem-insel offers an infrastructure adapted to ethical requirements to promote product development, advanced training courses, and networking with other platforms within sitem-insel's new building and beyond.

*Decomplix*
• Decomplix simplifies market access for medical devices and in-vitro diagnostics. Decomplix goes beyond consulting as a legal manufacturer. Developers and manufacturers are guided through the CE certification by proven experts. Decomplix' customers gain legal protection, reduced risks and faster time-to-market.

*Translational Imaging Center*
• The Translational Imaging Center builds upon a cooperation between Siemens Healthcare AG, the Inselspital, and sitem-insel. Siemens' innovative clinical 7 Tesla MRI scanner is the heart of the Translational Imaging Center, which will be installed in combination with a high-end 3 Tesla MRI device. Placing the Translational Imaging Center in sitem-insel and thus close to the Inselspital is ideal. The Insel Group, together with the University of Bern, possesses outstanding international scientific and clinical expertise to take translational MR innovations to the next level.

Further platforms – the Cardiovascular Test and Innovation Center, the Clinical Trials Unit, the Metabolomics Unit, the NeuroTec Center, among others – are currently in planning in cooperation with the Inselspital and other partners.

# Swiss School for Translational Medicine and Biomedical Entrepreneurship

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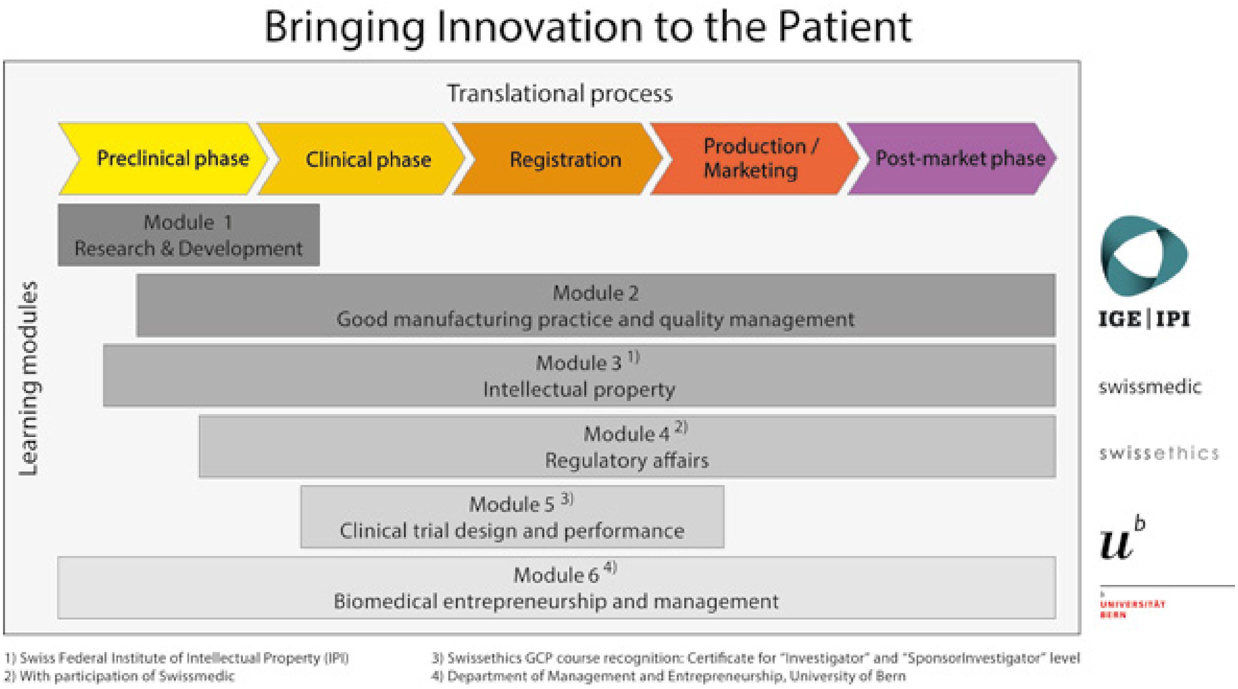
**The Curriculum**
The program aims to offer continuing education to specialists in industry, hospitals and in academia in the field of translational medicine and entrepreneurship, who are highly needed in both industry and universities. Participants will acquire the know-how to initiate and implement the translation process of products from the stage of development in industrial or basic science institutions to clinical applications with the goal of their commercialisation. The focus will be on both diagnostic and therapeutic medical devices and medicinal products.

A Master of Advanced Studies (MAS), a Diploma of Advanced Studies (DAS), or a Certificate of Advanced Studies (CAS) is awarded by the University of Bern upon successful completion of the program. The curriculum consists of a prerequisites section (e-learning) and six independent modules of various sizes. The modules comprise case studies, quizzes, article based learning and concept lectures. The faculty includes teachers and supervisors from research and development oriented private companies, scientists from Federal Institutes of Technology (ETHZ, EPFL), Universities and Universities of Applied Sciences, collaborators from regulatory agencies, financial experts and clinicians.

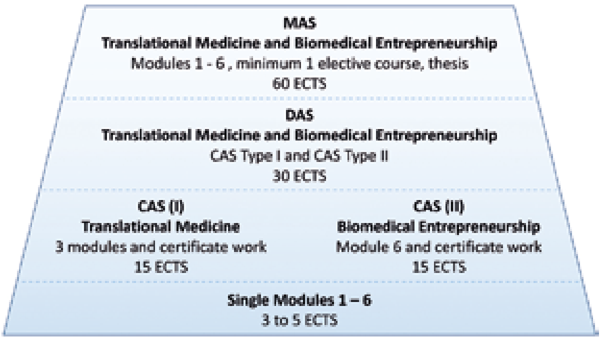



Program Overview MAS in Translational Medicine and Biomedical Entrepreneurship (60 ECTS)

**Compatibility between Studies and Professional Occupation**
The MAS, DAS and CAS courses are modular study programs that include blended learning which means that distance e-learning will be supplemented by concept lectures, peer learning and interactive discussions with specialists. Having only a limited number of face-to-face sessions allows for large flexibility while at the same time permitting participants to profit from the specialists' expertise. All study programs (MAS, DAS, CAS and individual modules) are conceptualized as extra-occupational programs that can be reconciled with the usual professional work.

**Prerequisites and Modules**
The program consists of a prerequisites section (e-learning) and six modules (blended learning). The admission requirements are those of the University of Bern. While the program is open to all academic disciplines, participants without a background in natural science, engineering or medicine may need additional time to meet the prerequisites. To meet the prerequisites, participants are offered the possibility to refresh their knowledge according to their individual needs. A collection of quizzes on basics of biopharmacy, pharmaceutical technologies, medical technologies, OMICS technologies, biostatistics and epidemiology associated with online content are offered to review topics that need refreshing.

In Module 1 "Research & Development" basic heuristic principles related to the discovery and development of medical devices and medicinal products are revised. Module 2 "Good Manufacturing Practice and Quality Management" focusses on how to ensure that all activities linked with a translational process maintain the desired level of excellence required by regulatory agencies. Module 3 "Intellectual Property" is dedicated to different types of Intellectual Property and legal aspects for biomedical products that are crucial for the successful commercialization of medical devices and medicinal products. Module 4 "Regulatory Affairs" sheds light on the role of public and government agencies, regulatory agencies and notified bodies along the translational pathway. In Module 5 "Clinical Trial Design and Performance" key characteristics of clinical trial design and conduct will be considered. Participants will learn about the prerequisites for such scientific studies, the understanding of the pathophysiology of the underlying diseases, the definition of quantifiable endpoints by clinicians and the analyses of statistical data. Finally, Module 6 "Biomedical Entrepreneurship and Management" is concentrated on various aspects of entrepreneurship such as leadership in large multidisciplinary teams, product management, business administration, and the successful commercialisation of medical devices and medicinal products.




Modular Curriculum for MAS / DAS / CAS courses and single modules

Depending on the certificate selected, different numbers of ECTS points are required.

- CAS "Translational Medicine"
  Three modules of choice from modules 1 to 5
  (min. 13 ECTS) and certificate work (2 ECTS)
- CAS "Biomedical Entrepreneurship"
  Module 6 and certificate work (2 ECTS)
- DAS: Both CAS programs
- MAS: All six modules and master thesis

**Additional Information**

The course language is English. In-class courses are held at sitem-insel, E-learning courses may be performed anywhere. The participants of the CAS, DAS and MAS programs are enrolled at the University of Bern.

The fee for the MAS is CHF 31'500.-, for the DAS CHF 23'100.- and for each CAS CHF 12'600.-. The fee for single modules is between CHF 3'150.- and CHF 6300.-, depending on the size. For more information please contact Juergen Burger (juergen.burger@sitem-insel.ch) or Pascale Anderle (pascale.anderle@sitem-insel.ch) and visit www.sitem-insel.ch.

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SWITZERLAND INNOVATION
PARK BIEL/BIENNE

# Switzerland Innovation Park Biel/Bienne - Swiss Medtech Center

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Jürg Grossenbacher, psy-bern AG
C. Della Giacoma, Clienia AG
Barbara Hochstrasse, private clinic Meiringen

**Research Profile**
Switzerland Innovation Park Biel/Bienne (SIP BB) is part of the new Swiss organization Switzerland Innovation. The park promotes innovation and pushes the translation of edge technologies into marketable products nationally and internationally. One of its research group is the Swiss Medtech Center – a point of contact for research, medicine, and industry. It is a place for interdisciplinary work and innovative projects in the field of medicine and health technology. Specialists of national and international partner networks complement internal research and engineering resources for building optimally adapted teams for each project.
The focus of our research is implementation of technology in the medical field to find new applications and the investigation of their effects on patients, health care professionals, medical environment, and the health care system. We position ourselves deliberately in the interface between humans, technology, and environment to complement technology-driven research partners. The Swiss Medtech Center works on projects involving multidisciplinary fields in the medical sector, in particular: biomechanical systems, data-oriented health care, and medical 3D technologies.

**Biomechanical Systems**
*Research Overview*
This research area concentrates on the application of sensors and actuators in biomechanical systems to address clinical and health care problems. In addition to development of multimodal sensor systems and integration of actuators in biomechanical systems, the focus lies on investigating the interaction between the biomechanical systems, the patient, and the medical environment. The aim of the research is the application of sensor- and actuator-based systems and the identification of the benefit for patients, users, medical professionals, and different stakeholders in the health care system (clinic, insurance, public authority, and others).

*Project Example: QuaLiHeal - Quantification of Ligament Healing*
The Ligamys implant used for anterior cruciate ligement (ACL) rupture healing was successfully introduced in the medical device market by Mathys in 2012 with more than 6,000 implantations to date. However, there are still issues that slow down its success story as the rather large implant size is limiting faster sales growth. 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 (CTI 28867.1) is to assess sensor priciples to be integrated in an instrumented Ligamys implant that will later be used in a clincal study to generate the necessary data. SIP BB is involved in the assessment of various mechanical and electronical sensor technologies as well as in the integration of the technology in the minimal space available in the implant respecting all user, safety, and requlatory requirements.
Project partners: Mathys Ltd Bettlach, BFH Center, ZHAW, Switzerland Innovation Park Biel/Bienne AG

**Medical 3D Technologies**
*Research Overview*
This research area concentrates on the integration of 3D technologies in medtech and healthtech applications. The focus lies on the complete digital-process chain using cutting-edge 3D technolgies, from medical imaging (3D scanning, ultrasound, x-ray, CT, MRT) over data processing, simulation, and visualisation techniques using appopriate soft and hardware (Segmentation, Rendering, CAD, FEA/CFD, VR/AR) all the way to direct automated-manufacturing methods using 3D data (CAM, SLM, SLA, FDM, SLS).
On one hand, the goal is finding new applications for 3D technologies, for example in the field of patient-specific products or new innovative surgical techniques. For this the 3D techologies are adapted to the application in order to explore and enlarge their potential. On the other hand, the research is focussed on the interaction between the techologies and the medical environment during the application to optimize the benefit for the medical professionals and the patients.

*Project Example: MOWA - Modular Walking Orthosis for an Effective Treatment of Patients with Weak Foot Dorsiflexion*
In today's state of the art for patient- specific ankle-foot orthoses, the final configuration has to be defined even before fabrication and cannot be modified afterwards. An optimal setup of the orthosis can therefore not be tested by the patient and often leads to unsatisfying results. The

goal of the MOWA project (CTI 25393.1) is the development and evaluation of a new modular patient-specific orthosis system using advanced manufacturing methods and sensor technology. The MOWA orthosis will be the first of its kind to allow testing of different configurations that can be adapted to the pathology of the patient for optimal results. In this project we investigated the integration of a digital- manufacturing process chain with modern 3D technologies like 3D scanning and 3D printing. Additionally, we were responsible for exploration of the component interfaces of the modular system to ensure adequate usability for the orthopedition and patient.

Currently the MOWA project is in the evaluation phase and ends in March 2019. A spin-off company called MOWA HealthCare AG was founded in October 2018 by the industry partner for further product development and commercialization of the MOWA orthosis system.
Project partners: orthopunkt AG, BFH Centre, HSR, UKBB, Switzerland Innovation Park Biel/Bienne.

**Data Oriented HealthTech**

*Research Overview*

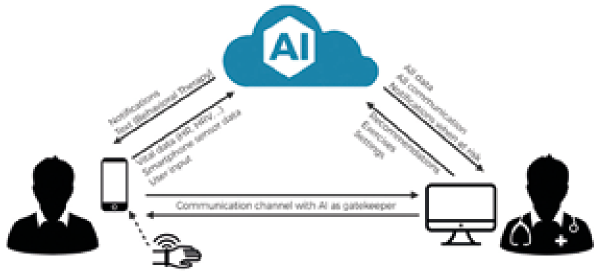
This research concentrates on application of machine-learning algorithms and data-mining methods on medical data. The goal is to validate known mechanisms and discover new patterns. Thanks to these findings, insights, treatments, diagnosis, and prognosis can be improved.
We focus

- on adequate ontologies in collaboration with patients and medical specialists
- on objective and subjective data collection in a user-friendly manner in everyday routines
- analysis and visualization of data

On the technological side, we cover the entire data process. From data acquisition by means of wearables and sensor integration over data handling and processing to visualization. On the application side, we work on personalized medicine, hospital information systems, eHealth, mHealth, and telemedicine especially in the field of ageing society and chronical diseases.

*Project Example: Resilience Training Robot*

We investigate an intelligent mobile assistant in the project RestArt (CTI 26046.1) for burnout-patient after stationary stay in clinic. It complements ambulatory treatment and supports the patient in everyday life. RestArt is measuring stress and recovery by means of a wearable connected to a mobile device. The data is collected in the cloud and is analyzed. This structure adds an additional dimension to todays established relation between clinician and patient. The clinician gets a complete overview about the patient's condition at any time, not only during the weekly therapy sessions. He gets automatic evaluation of the stress curve and gets warned when necessary. On the patient's side, data is not only collected by means of a wearable, but interactively by a chatbot. Based on the patient's condition, automatic situational interventions are proposed so that the patient does not relapse into unhealthy stress patterns.




Project partners: resilient llc, psy Bern AG, Clienia AG, Privatklinik Meiringen, Hochschule Luzern iHomeLab, Switzerland Innovation Park Biel/Bienne AG

**Events and Workshops Run by Switzerland Innovation Park Biel/Bienne**

*Regulatory affairs support program: "Basiswissen Medtech Regulatory"*

For an idea to become a medical product, all involved persons need at least basic knowledge about regulatory affairs. Therefore, SIP BB offers half-day courses in regulatory affairs called "Basiswissen Medtech Regulatory" in collaboration with the regulatory expert Andrea Schütz-Frikart.

The course is designed to give the participants solid basic knowledge about the regulatory aspects that are so important for the process of bringing medical products to the market. Originally developed to support start-up companies entering the medical field, the course started in 2017 has since then become a well-established introduction course for all personnel related to the medtech field. The goal is to give participants an easy-to-understand overview of the strongly regulated world of medical product manufacturing without the need for them to become a regulatory specialist. The course helps them to get access to the regulatory affairs specialist network and makes it possible for them to discuss with the specialists on a certain level of expertise.

Workshops in 2019:
- 29. January 2019
- 23. April 2019
- 17. September 2019

For more information and registration: www.sipbb.ch/workshop/basis-medtech-regulatory/

*Medtech Innovation Event*

In 2018, the Medtech Innovation Event (MIE) was held for the fourth time. Organized by Swiss Medtech, be-advanced and Switzerland Innovation Park Biel / Bienne, the Medtech Innovation Event brings together companies, investors, and science.

The whole event is focused on pitches by startups/industrial innovators and solution providers. Additionally, there is also a tabletop exhibition and a 1-to-1 partnering service.

As an innovator/startup you get direct access to our members of the CTO Medtech Club. The CTO Medtech Club brings together technology and innovation managers of the major medtech companies. The club members meet on a regular basis for an open exchange among themselves to discuss the continuous development of Switzerland as an industrial location for medtech companies. They strongly support pooling synergies of players in innovation from research, development, support organisations, and the industry. And moreover, members make their knowledge, experiences, and connections available for innovators during the Medtech Innovation Event.

Medtech Innovation Event 2019:
- 2. September 2019

For more information and registration:
https://www.sipbb.ch/mie

# 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 applied 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 with advanced material research technological innovations needed for the growing population in the areas of energy, environment and personal health. At the very heart of all of this are the 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 Research Focus Area "Health and Performance", we focus on material-based health care innovations addressing the growing needs of our ageing society. Together with our partners from research, industry, hospitals or the public sector we are pushing the limits in science and technology for a prosperous tomorrow.

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.

For this, 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 the improved understanding we produce systems providing 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, bio-physical models or 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 Dommann
Head of Department

# Laboratory for Advanced Materials Processing

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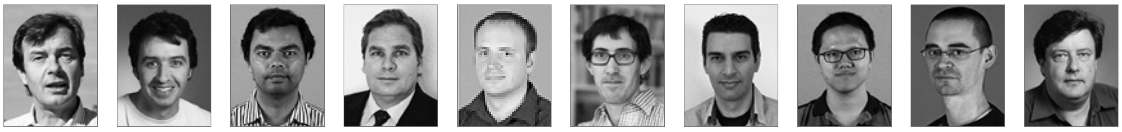

**Patrik Hoffmann** | Marc Leparoux | Antaryami Mohanta | Kilian Wasmer | Sergey A. Shevchik | Bastian Meylan | Georgios Violakis | Tri Quang-Le | Matthias Leister | Bernhard von Gunten

## Research Partners

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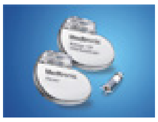
Dr. F. Vakili Farahani, Coherent Switzerland, Belp, Switzerland



Medtronic pacemakers: AzureTM, AdvisaTM DR MRITM SureScanTM and MicraTM Transcatheter Pacing System


### Research Profile

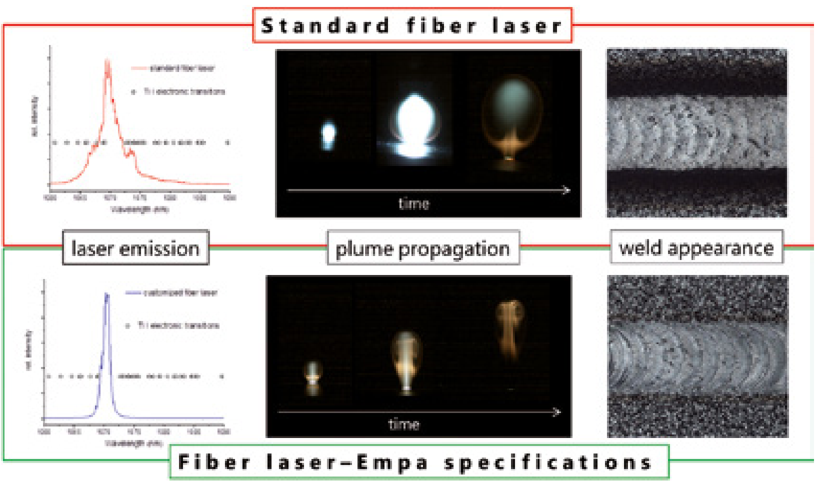
Our mission is the innovative consolidation and functional modification of materials by studying, monitoring, and understanding beam and plasma induced processing. We offer to the society and industry methods for the creation of novel nanostructured materials, their shape-forming and integration into devices.
Our competences in materials interactions with microwaves-IR-NIR-vis-UV-DUV waves as well as with electrons; laser processing technologies (additive manufacturing, welding, ablative micro- and nano-structuring); safe production and handling of powders, including nanoparticles; functional modification of small particle diameter powders (40 µm to 0.02 µm); design of new high-performance materials such as metal alloys and composites; optical and acoustical real-time observation and monitoring of processes; data analysis by machine learning and artificial intelligence; are a unique combination that offers us and our academic and industrial partners from various business fields (e.g. biomedical technology, power generation, watch making) prosperous competitiveness.

### Powder and Nanocomposites Processing

The core activity of this group has been nanoparticles fabrication by an evaporation-condensation plasma process. To optimize the synthesis and the material properties, optical in-situ characterization techniques were investigated and developed. For instance, the plasma properties (temperature, thermal equilibrium state, electron density) were assessed by optical emission spectroscopy while the evaporation of coarse particles, plasma fluctuations and flow turbulences were characterized by high speed imaging. These in-situ monitoring methods are used to investigate the fundamental interactions between different lasers and materials in bulk or powder form. Indeed a hot vapour plume is emitted during laser welding of metals or during laser additive manufacturing from powders.

### Laser welding of titanium

The replacement of solid state lasers by new generation of low maintenance fibre lasers was investigated to weld titanium housings of pacemakers. Indeed first tests performed at Medtronic in Tolochenaz revealed a black deposition around the weld zone when using the fibre laser despite the use of similar processing conditions as for the Nd:YAG lasers. A simulation chamber allowing the use of different lasers and the control of the environment has then been built at Empa for reproducing the industrial processing conditions while allowing a better understanding of the laser-material interaction through the use of process diagnostic tools. It was then demonstrated that the fibre laser wavelength is interacting with the titanium vapour leading




High speed camera side views, SEM weld pictures to a confinement of the plume above the welding zone and consequently a redeposition of nanoparticles formed by condensation through mixing with the colder environment. A customization of the new laser wavelength avoids this interaction and a clean weld could then been achieved.

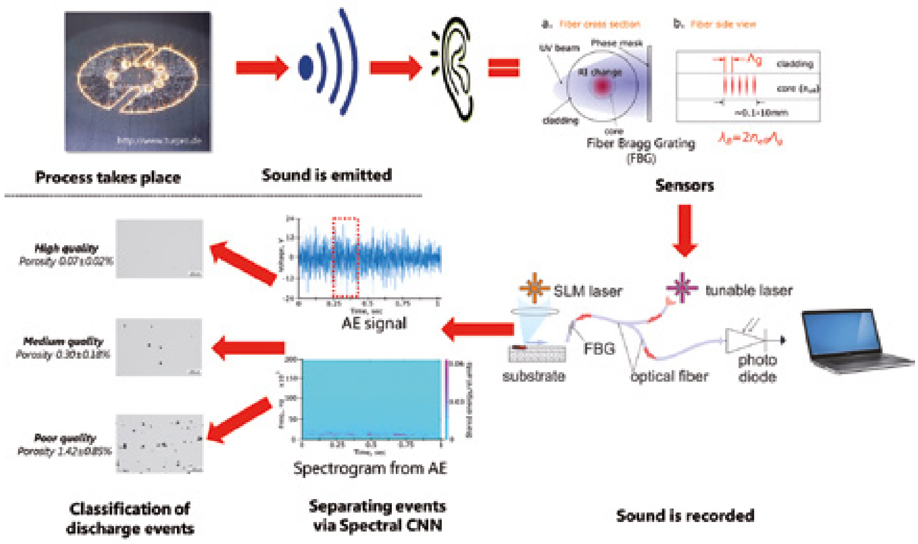
**Dynamical processes**

The core activity of the dynamical processes group is to develop monitoring and control of dynamical and complex processes via a fundamental understanding. It includes four main fields which are tribology (the study of friction and wear; the science of interacting surfaces in relative motion), fracture mechanics (field of mechanics concerned with the study of the propagation of cracks in materials), laser processes (laser machining including ablation of bone and muscle, laser surface texturation, laser polishing, additive manufacturing, etc..) and predicative maintenance (technique to predict the future failure point of a machine component, so that the component can be replaced, based on a plan, just before it fails) .

To achieve both goals, each process is investigated by combining specific, various but complementary in-situ methods. It includes high-speed camera, acoustic emission, fibre Bragg gratings and interferometry systems. The results are analysed using high level signal and image processing.
The combination of specific knowledge of the group members with the different technics allows us to answer question to a wide range of industrial processes where there is an interaction between any kind of material and any kind of tools such as grinding, laser, electrical discharge, etc.

**In situ and real-time monitoring of additive manufacturing (Project MoCont)**

Additive manufacturing (AM) is considered as a revolution in manufacturing. This is also the case for the medical sector. However, the high expectations face sometimes technical difficulties that prevent even more industrial applications. The main reason is the lack of process reproducibility and the absence of a reliable and cost-effective process monitoring. To overcome this difficulty, we proposed a very innovative approach which combines acoustic emission (AE) with artificial intelligence (AI) for in situ and real-time monitoring of AM processes.
The works performed so far demonstrate that the proposed approach has high potential to be implemented in industry for several reasons. The approach is fast; the classification of the process is made within milliseconds. The system is cost effective. It can be adapted on most industrial machine. Finally, it is the only solution to stop the process before the complete piece is produced for quality testing and so it can help save a lot of raw material and machining time.




Scheme of detection and data treatment for process monitoring


## Selected Publications

Kenhagho H.N., Shevchik S.A. Saeidi F., Neige F., Meylan B., Rauter G., Guzman R., Cattin P., Wasmer K., Zam A., (2019): Characterization of Ablated Bone and Muscle for Long-Pulsed Laser Ablation in Dry and Wet Conditions, Materials, Vol. 12, Issue (8), paper ID: 1338, pp: 1-16, https://doi.org/10.3390/ma12081338

Wasmer K., Le-Quang T., Meylan B., Vakili-Farahani F., Olbinado M.P., Rack A., and Shevchik S.A., (2018): Laser Processing Quality Monitoring by Combining Acoustic Emission and Machine Learning: A High-Speed X-Ray Imaging Approach, Procedia CIRP, Vol. 74, Issue 2018, pp: 654–658, https://doi.org/10.1016/j.procir.2018.08.054

Le-Quang T., Shevchik S.A., Meylan B., Vakili-Farahani F., Olbinado M.P., Rack A., and Wasmer K., (2018): Why Is In Situ Quality Control of Laser Keyhole Welding a Real Challenge? Procedia CIRP, Vol. 74, Issue 2018, pp: 649–653, https://doi.org/10.1016/j.procir.2018.08.055

Shevchik S.A., Kenel C., Leinenbach C. and Wasmer K., (2018): Acoustic Emission for In Situ Quality Monitoring in Additive Manufacturing Using Spectral Convolutional Neural Networks, Additive Manufacturing, Vol. 21, Issue May 2018, pp: 598-604, https://doi.org/10.1016/j.addma.2017.11.012

# Laboratory for Mechanics of Materials and Nanostructures

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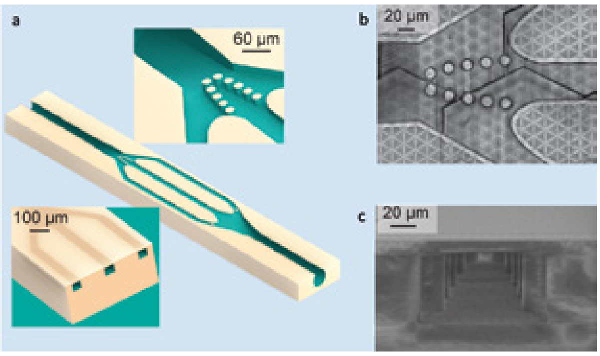
Olivier Guenat, ARTORG Center for Biomedical Engineering Research
Beat Neuenschwander, Berner Fachhochschule
Klaus-Arno Siebenrock, Inselspital

### Research Profile

We focus on 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 condition of humidity, strain rate and temperature and develop novel nano-mechanical and microanalysis instrumentation.

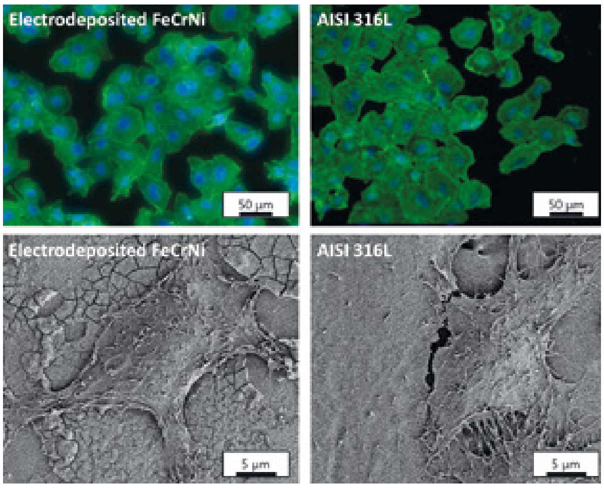
### Additive manufacturing at the micron scale

We develop a number of micro-additive manufacturing technologies ranging from UV-lithography and galvanoforming of biocompatible materials to 3D microprinting exploiting 2 Photon Polymerisation (2PP). 2PP in combination with the printing workflow of standard additive manufacturing processes enables the manufacturing of micro- and mesoscale parts with complex designs and high shape accuracy in an additive way. Nuclear magnetic resonance (NMR) allows for non-invasive studies of intact living entities. NMR experiments at the volume scale of single microorganisms and single cells are hindered by the limited sensitivity of the detector. Many interesting biological entities (e.g., the human ovum and those of other mammalians) have typical volumes below 1 nL. NMR probes for such small volumes require high resolution 3D printed microfluidic structures for confinement of samples. The adopted 2PP printing approach allows to develop complex microfluidic devices tailored to position and feed biological samples in the most sensitive region of the NMR probes.




(a) Schematic CAD visualization of the microchannel used to trap a single C. elegans worm. (b) Optical microscope image and (c) SEM image of a 3D printed section of the trapping system inside the microchannel. Collaboration with Prof. J. Brugger, EPFL.

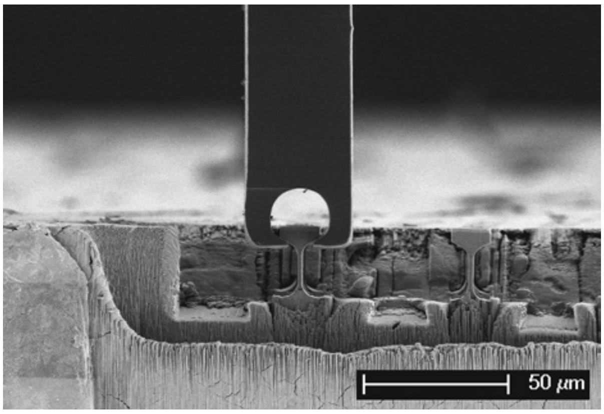
The LiGA process (Lithography & Galvanoforming) allows for precision manufacturing of high aspect ratio components and devices and Nickel-based components that are already extensively exploited in the watch industry. For biomedical applications a range of biocompatible alloys needs to be developed. We develop stainless steel microcomponents with high corrosion resistance and high biocompatibility. Stainless steel with varying Chromium contents were prepared by adjusting the current density during electrodeposition. Cell compatibility demonstrated that electrodeposited materials exhibit low cyto-toxicity comparable to 316L stainless steel.




Cytotoxicity tests: A comparison of cell adhesion (top pictures) and morphology (bottom pictures) on electrodeposited Fe-Cr-Ni and AISI 316L stainless steel.

**Instrumentation for micromechanical analysis of soft and hard tissues**

At Empa, new scientific instruments are developed and validated that allow measuring material properties at the length scale of a few micrometres. As part of a running Ambizione grant of Dr. Jakob Schwiedrzik (SNF grant #174192), a micromechanical testing platform was successfully developed in collaboration with Alemnis AG (Thun, Switzerland) that allows performing experiments under controlled environmental conditions in a large range of strain rates from 0.0001 to 1000/s. Temperature and relative humidity in the experimental chamber can be tightly controlled. Furthermore, a micromechanical setup was developed that allows measuring tensile properties of materials at the microscale. This is especially important in complex nanocomposite materials like bone or wood, as they feature very different properties in tension and compression. The new setup features a self-aligning gripper that compensates small errors in placement as well as an optimized sample geometry and is now used to assess microtensile properties of biological materials like bone or teeth.

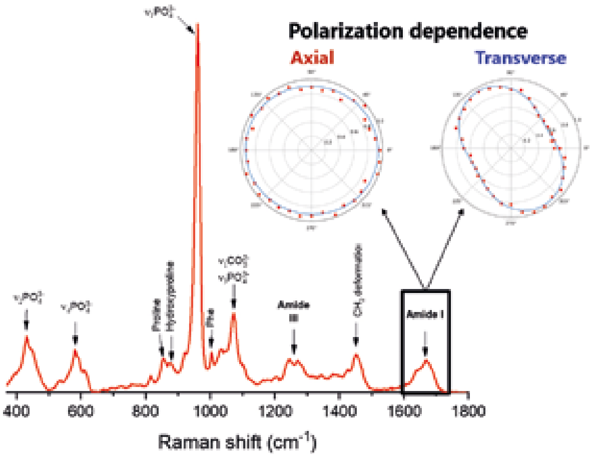



Microtensile experiment on bone tissue. Performing tensile experiments on the length scale of a few µm provides important insights into the properties of nanocomposites such as the bone extracellular matrix.

**Microscale Properties of Human Bone**

As modern societies age, the increasing number of fractures poses a challenge for health care systems worldwide. Hip fractures are especially deleterious, as they lead to a loss of mobility and show an increased mortality. Whole bone strength depends on bone mineral density measured by clinical densitometry, but also on the tissue quality resulting from a continuous remodelling of the bone extracellular matrix. It is therefore important to study structure-property relationships in bone on several length scales and to combine this with complementary proteomics information in order to identify changes in tissue quality with age and in the presence of diseases such as osteoporosis or osteoarthritis.

Within the Special Focus Area Personalized Health and Related Technologies of the ETH Board, Empa is mainly collaborating with the ARTORG Center of the University of Bern and the Orthopaedic Department of the Inselspital to translate recent advances in microscale material characterization into clinical practice. Biopsies of patients who underwent total hip replacement surgery are scanned using Micro-Computed Tomography to assess their morphology and estimate whole bone strength based on numerical simulations. Tissue quality is evaluated by identifying structure-mechanical property relationships on the microscale based on site-matched polarized Raman spectroscopy and micropillar compression experiments, which will be utilized for an improved personalized prediction of bone strength and fracture risk.




Typical Raman spectrum of bone tissue. The amide I peak is highly polarization dependent, which allows tracking local fibril orientation in 3D. Collaboration with Prof. M. Calame, Empa.

**Selected Publications**


E. Montinaro et al., (2018) "3D printed microchannels for sub-nL NMR spectroscopy," PLoS One 2018, 13(5), e0192780. DOI: 10.1371/journal.pone.0192780

E. Bertero et al. (2018) "Electrodeposition of amorphous Fe-Cr-Ni stainless steel alloy with high corrosion resistance, low cytotoxicity and soft magnetic properties", Surf Coat Techn. 349, 745, DOI: 10.1016/j.surfcoat.2018.06.003

J.J. Schwiedrzik et al., (2017) "Nanoscale deformation mechanisms and yield properties of hydrated bone extracellular matrix", Acta Biomaterialia 60, 302-314, DOI: 10.1016/j.actbio.2017.07.030

D. Casari et al., (2019) "A self-aligning microtensile setup: Application to single-crystal GaAs microscale tension–compression asymmetry", Journal of Materials Research, DOI: 10.1557/jmr.2019.183

# Center for X-ray Analytics

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Dr. Peter Wahl, Division of Orthopaedics and Traumatology, KSW, Winterthur
Prof. Karl-Olof Lövblad, Neurointerventionnel services, HUG, Geneva
Prof. Brigitte von Rechenberg, Musculoskeletal Research, UniZH, Zurich
Dr. Jakob Schwiedrzik and Dr. Johann Michler, Empa, Thun
Dr. Peter Wick and Prof. Inge Herrmann, 'Particles-Biology Interactions' Lab, Empa, St. Gallen
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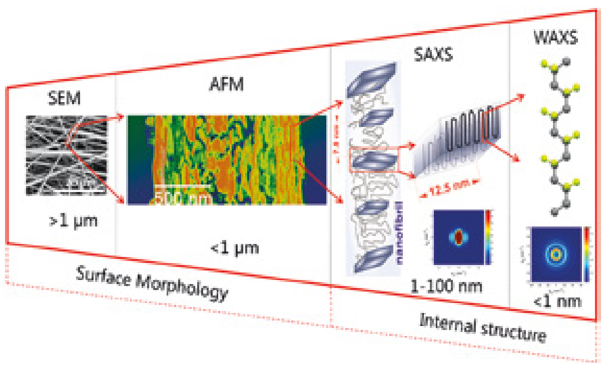
Dr. Bruno Koller, Scanco Medical AG, Brüttisellen

**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: new 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 which could not be covered before: high spatial resolution imaging of biological materials; dynamical studies in bio-systems, partially ordered materials (polymers, lipids).

**Structural in-situ studies for particle system synthesis and their early event dynamics in biological environments: Particle systems between order and disorder (SNF grant 173012)**

The research is related to model establishment for nano-objects and partially ordered systems through in-situ studies for system dynamics on bio-systems such as polymers, nano-particles and their interactions with the bio environment. Fibers are used for tissue engineering, as sensors or drug carrier systems. The nano-fiber functionality is influenced by the fabrication process, post treatments and the conditions under operation. For the systems understanding, a full and detailed structurally characterization is needed, which has been achieved by the development of new X-ray based analytical methodology based on SAXS and WAXS. Particular emphasis was placed on anisotropic morphologies being developed during the nanofiber fabrication process. Global analysis was performed on SAXS data to derive the nanofibrillar structure of repeating lamella crystalline domains with average dimensions of 12.5 nm thickness and 7.8 nm spacing along with associated tie-molecules. The varying surface roughness of the nanofiber was evaluated by extracting the Porod exponent in parallel and perpendicular direction to the nanofiber axis, which was further validated by AFM. Additionally, the presence of a mixture of the monoclinic *alpha* and the orthorhombic *beta* PVDFhfp phases was derived from WAXD. The current study shows a generic approach in detailed understanding of internal structures and surface morphology for nanofibers. For potential applications in the biomedical domain, we developed a comprehensive roadmap towards structural hierarchy and anisotropy in fiber systems based on scattering and diffraction studies.




Schematic representation of the multimodal and multidimensional analytical approach for electrospun PVDFhfp fibers: from nanofiber morphology to the atomic structure.

Nanoparticle systems are in focus for drug delivery. Therefore, nanoparticle formation, agglomeration and first events in biological environments are studied using novel in-situ fluidic cells on the SAXS instrument combined with simulation tools.

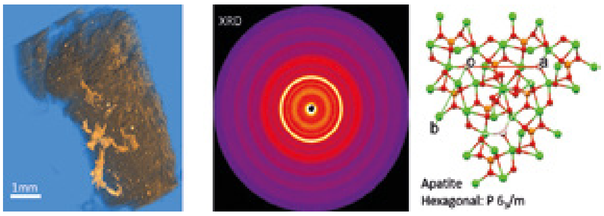
**Synergistic studies to optimize local antibiotic delivery systems for the treatment of musculoskeletal infections: in-situ dynamical structural and functional understanding (with KSW)**

Multifunctional and adaptive material concepts are envisioned for medical application, and consequently create new requirements for research. Better understanding of the interactions of the materials with the living organism is necessary. Functional materials might be brought in contact with the body either through direct application, or indirectly by means of drug delivery vehicles. This research focusses on the understanding of drug release from carrier systems to the surrounding biological environment. More precisely, the release mechanisms of antibiotics from inorganic support structures into a body-like environment is studied, together with the biological effect of the mentioned release, with the aim of establishing a predictive drug release model. Before new drug release systems can be implemented in medical applications, preclinical research work is required to obtain fundamental data about the interaction of the drug with the carrier and about the release kinetics of the drug from the carrier.

**Exploring the Origins, Characteristics and Implications of Placental Calcification - A Materials Science Approach (SNF Grant 173077)**

Calcification is a phenomenon that has been known for decades, but yet remains poorly understood. In placenta research, calcium phosphate-based minerals have been identified in placental tissues but actual composition, ultrastructure and characteristics of these mineral deposits remain largely unclear, prompting questions to whether they serve physiological purpose or be part of a pathological mineralization process.

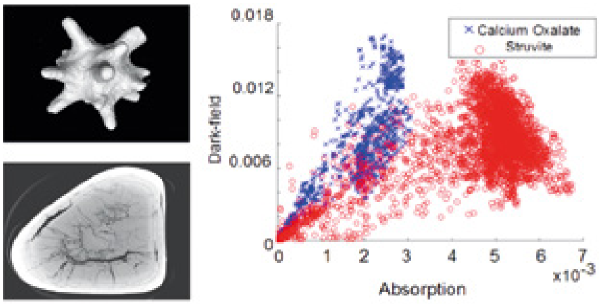
The localization and the nanostructural characteristics of the mineral deposits in placental tissues are studied at unprecedented resolution using cutting-edge materials science techniques, including X-ray microtomography, density-dependent colour scanning electron microscopy (DDC-SEM), nanotomography (Focused Ion Beam (FIB)-SEM) and spectroscopy and X-ray diffraction methods.




3D rendering based on X-ray microtomography of placenta tissue showing significant calcifications (leftmost), X-ray diffraction pattern of an isolated mineral fraction giving also the structural information.

**Quantification of kidney stones based on multimodal X-ray imaging methods**

Quantification of mixed-type kidney stones using X-ray dark-field tomography is investigated. We use a weighted total-variation regularized reconstruction method to compute the ratio of dark-field over absorption signal (DA Ratio) from noisy projections. Experiments show that this approach can distinguish between a struvite and a calcium oxalate stone.




3D rendering of different types of kidney stones (left). Scatter plot of dark-field versus absorption of one representative slice from the struvite stone (red circle) and the calcium oxalate stone (blue cross) (right).

## Selected Publications

Maurya A K, Weidenbacher L, Spano F, Fortunato G, Rossi R M, Frenz M, Dommann A, Neels A, Sadeghpour A. (2019) Structural insights into semicrystalline states of electrospun nanofibers: a multiscale analytical approach. Nanoscale, 2019, 11(15), 7176-7187. DOI: 10.1039/C9NR00446G

Thamsen B, Plamondon M, Granegger M, Schmid Daners M, Kaufmann R, Neels A, Meboldt M (2018) Investigation of the axial gap clearance in a hydrodynamic-passive magnetically levitated rotary blood pump using X-ray radiography. Artificial Organs, 2018, 42(5):510–515. DOI: 10.1111/aor.13074

Buhmann M T, Abt D, Nolte O, Albrich W, Strempel S, Neu T R, Betschart P, Zumstein V, Neels A, Maniura-Weber K, Ren Q (2019) Quantitative analysis of Biofilms on Ureteral Stents reveals Dis-tinct Microbial Communities and Low Bacterial Load for Patients without Urinary Tract Infection. Microbiome, 7(1), 60

Carrel M, Morales V L, Beltran M A, Derlon N, Kaufmann R, Morgenroth E, Holzner M (2018) Bio-films in 3D porous media: delineating the influence of the pore network geometry, flow and mass transfer on biofilm development. Water Research, 134, 280-291. http://doi.org/10.1016/j.watres.2018.01.059

Hu S, Yang F, Griffa M, Kaufmann R, Anton G, Maier A, Rieß C (2017) Towards quantification of kidney stones using X-ray dark-field tomography. IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017), 1112-1115

Merriam T, Kaufmann R, Ebert L, Figi R, Erni R, Pauer R, Sieberth T (2018) Differentiation of dental restorative materials combining energy-dispersive X-ray fluorescence spectroscopy and post-mortem CT. Forensic Science, Medicine, and Pathology, 14(2), 163-173

# ARTORG CENTER FOR BIOMEDICAL ENGINEERING RESEARCH

In 2018-19 the ARTORG has been delivering a decade of ambitious biomedical engineering research and development across a wide variety of clinical areas. Together with the Institute of Surgical Technology and Biomechanics (ISTB) the ARTORG has formed the medical technology hub of the University of Bern and the Bern University Hospital, Inselspital. So with the retirement of the Director of the ISTB Prof. Dr.-Ing. Lutz-Peter Nolte following outstanding leadership of the institute since 2002, the fusion of the ISTB and the ARTORG under the ARTORG banner was agreed to strengthen biomedical research and teaching in the Faculty of Medicine of the University of Bern. Some groups of the merged ARTORG will take advantage of the facilities of the Swiss Institute for Translational and Entrepreneurial Medicine (SITEM) and relocate into the SITEM building upon completion in late spring 2019. The principles of the research activities at the ARTORG Center in the however will be unchanged, like co-leadership of the groups by technical and clinical group heads. The proximity to SITEM will provide excellent access to the additional technical facilities of the SITEM. These will expand the ARTORG's infrastructure and resources of to benefit all BBN members in collaborative projects.

Over the last two years the ARTORG groups have moved forward projects in all core clinical areas. This has resulted in high-profile publications, a significant number of completed clinical trials and wins at the Ypsomed Innovation Awards and the Bernese Business Creation Competition.

The enlarged ARTORG will remain an active member of the BBN and the wider medical technology community at cantonal, national and international level. The technologies and companies that have launched products and services into clinics are established businesses in their own right now and have paved the way for new ideas and solutions to unresolved clinical challenges. The pipeline of the ARTORG is strong and sustained, with projects in urology, ophthalmology and medical models moving along the development pathway and attracting funding and partners.

Considering ways to address to unmet clinical needs is the motivation of all those working at the ARTORG. A key part of the ARTORG's ability to produce clinical solutions is the membership in the BBN, as evidenced by the many collaborations and connections to all other partners in the network showcased in this report. And it is the access to this diversity of scientific, technological and clinical expertise that enables projects in the BBN to be translated into credible, clinical solutions while maintaining high standards of biomedical research.

We look forward to our continued and successful cooperation with our partners in the BBN.

The ARTORG consists of 12 groups at two sites:
- Musculoskeletal Biomechanics (P.Zysset)
- Computational Bioengineering (P. Büchler)
- Medical Image Analysis (M. Reyes)
- Tissue and Organ Mechanobiology (B. Gantenbein)
- Hearing Research Laboratory (W. Wimmer)
- Cardiovascular Engineering (D. Obrist)
- Image-Guided Therapy (S. Weber)
- Diabetes Technology (S. Mougiakakou)
- Gerontechnology and Rehabilitation (L. Marchal-Crespo & T. Nef)
- Organs-on-Chip Technologies (O. Guenat)
- Ophthalmic Technology Laboratory (R. Sznitman)
- Information Processing in Medical Interventions (G. Zheng)

Stefan Weber
Director

# Hearing Research Laboratory

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Suyi Hu


Markus Huth


Yves Kompis


Murielle Lerch


Eric Lochmatter


Georgios Mantokoudis


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Christoph Schmid


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Cendres+Métaux SA/Diavantis, Biel, Switzerland
Cochlear AG, Basel, Switzerland
MED-EL GmbH, Innsbruck, Austria
Oticon A/S, Smørum, Denmark

### Research Profile

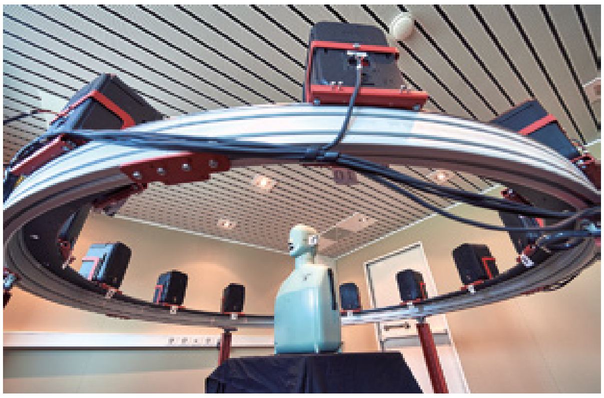
The Hearing Research Laboratory is a clinically directed research collaboration between the ARTORG Center and the Department of Otolaryngology at the Bern University Hospital (Inselspital). We primarily aim to develop innovative technology to help patients with hearing disorders and to assist clinicians in the diagnosis and treatment of inner ear diseases. Our multidisciplinary group gathers experts from the fields of audiology, medicine, physics, and engineering sciences. Our research activities include psychoacoustic experiments, anatomical studies, software and hardware development for clinical applications, and clinical evaluation studies.

### Tinnitus Assessment

Tinnitus is the perception of sound in the absence of an external acoustic stimulus. Severe forms of tinnitus can substantially impair quality of life. Although often originating from inner ear damage, most types of tinnitus are maintained in their chronic form by abnormal neuronal activity. Objective tinnitus assessment could be enabled by identification of neuronal correlates in electroencephalography (EEG). We are investigating statistical approaches and computational modelling to extract direct signatures of tinnitus in EEG data. The project aims to gain new insights into the behavior of tinnitus and to potentially improve clinical tinnitus assessment and classification. In addition, the group is developing mobile tools for tinnitus self-assessment. The patient-centered approach aims to deepen clinical assessment datasets from snapshot measurement under quiet conditions, to continuous long-term self-monitoring of the symptoms under more “life-like” conditions.

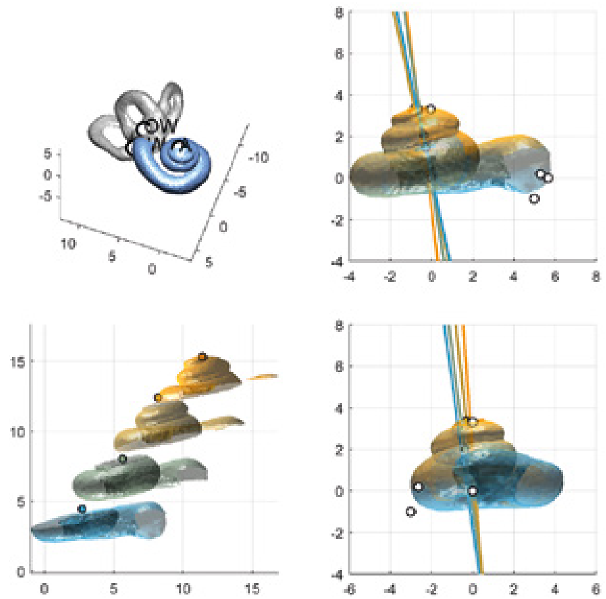
### Experimental Audiology

Sound field audiometry, in which acoustic test stimuli are delivered through loudspeakers instead of earphones, is an integral component in the evaluation of the clinical hearing-rehabilitation progress. The assessment of hearing thresholds, speech understanding in quiet and noise, and sound localization abilities provides essential outcome measures that can be directly linked to the quality of life of patients treated with hearing implants. In the area of experimental audiology, the Hearing Research Laboratory focuses on clinical studies aiming to contribute to the scientific community and clinical practitioners alike. To enable a more realistic but reproducible assessment, our group develops methods to reproduce complex sound environments and dynamic test situations that are required to capture the benefit of modern hearing implant technology.


Multi-speaker set up for sound field audiometry

### Inner Ear Morphology and Cochlear Implantation

The inner ear, the organ of hearing and balance, exhibits a remarkable structural complexity ranging over several spatial scales. To date, it remains unclear why the cochlea is shaped like a spiral. Recently, imaging modalities enable study of the anatomy of the human cochlea in more detail. At the same time, there is an increasing interest in understanding and modeling the cochlear shape, mainly motivated by the aim to improve the treatment outcomes of auditory neuroprostheses (i.e., cochlear implants) by consideration of patient-specific anatomy. Our group is investigating approaches to extract information from radiographs (i.e., patient-specific anatomy) and use it to improve implantation and implant fitting outcomes. In addition, we aim to model the electrical current spread during stimulation with cochlear implants.



Cochlear shape analysis.

### Temporal Bone Lab

To evaluate novel implantation technologies and promote surgical training, a fully equipped facility with several work spaces for anatomical dissections and otologic surgery is hosted in collaboration with the Institute of Anatomy of the University of Bern. The Temporal Bone Lab offers the opportunity for experimental and translational research and has a key function in the transfer of novel technologies prior to implementation into clinical routine. The proximity to the Bern University Hospital (Inselspital) permits concomitant radiological examination of the specimens. Currently investigated topics include cochlear implantation procedures, endoscopic approaches to the middle ear and the lateral skull base, as well as the development of suitable surgical instrumentation. In addition, the Hearing Research Laboratory supports surgical training and anatomical studies to enable the refinement of personal surgical skills and one-on-one teaching by our experienced faculty members.

### Selected Publications

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Wimmer W, von Werdt M, Mantokoudis G, Anschuetz L, Kompis M, Caversaccio M. Outcome prediction for Bonebridge candidates based on audiological indication criteria. Auris Nasus Larynx 2019; in press

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Anschuetz L, Huwendiek S, Stricker D, Yacoub A, Wimmer W, Caversaccio M. Assessment of Middle Ear Anatomy Teaching Methodologies Using Microscopy versus Endoscopy: A Randomized Comparative Study. Anat Sci Educ 2018; doi: 10.1002/ase.1837

Anschuetz L, Weder S, Mantokoudis G, Kompis M, Caversaccio M, Wimmer W. Cochlear Implant Insertion Depth Prediction: A Temporal Bone Accuracy Study. Otol Neurotol 2018; 39:e996-e1001

Gawliczek T, Munzinger F, Anschuetz L, Caversaccio M, Kompis M, Wimmer W. Unilateral and Bilateral Audiological Benefit With an Adhesively Attached, Noninvasive Bone Conduction Hearing System. Otol Neurotol 2018; 39:1025-1030

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# Cardiovascular Engineering

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## Clinical Partners

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### Research Profile

The Cardiovascular Engineering (CVE) group develops diagnostic and therapeutic technology for cardiovascular diseases, such as valvular heart disease and myocardial infarction. Our research aims to improve the durability and biocompatibility of therapeutic devices and implants and to develop novel diagnostic tools. The translational research projects address immediate clinical needs that were identified together with our clinical partners who are closely integrated in the project 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 measure relevant 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 biomedical flow systems. Efficient use of high-performance computing tools allows the integration of our computer models into clinical practice.

### Heart Valves

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 without the need for re-operation, this represents 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 sophisticated experimental and computational infrastructures for the study of heart valves. This includes pulsatile flow loops, compliant silicone phantoms, and modern optical-measurement technology for quantifying the complex three-dimensional blood flow. Our experimental approach is complemented by computer models for fluid-structure interaction between blood flow and soft tissue. We use high-order flow solvers for transitional to turbulent flow together with finite-element models for soft tissue, which are coupled 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.

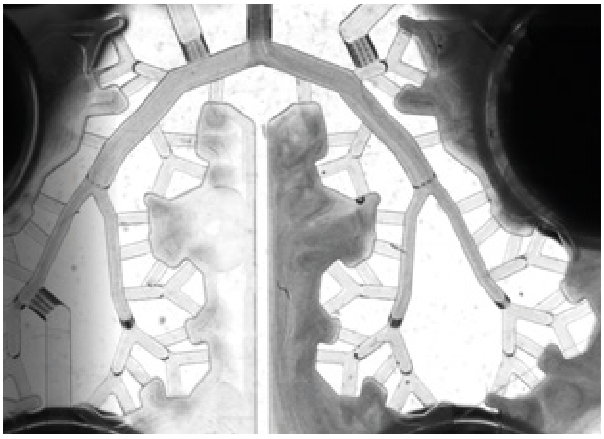
Bioprosthetic heart valve in a test cell

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.

### Myocardium

The myocardium is supplied with oxygen and nutrients through the coronary circulation. Its complex vascular network topology at different spatial scales (epicardial vessels, collaterals, coronary microcirculation) governs several physiological mechanisms and is a central factor in the outcome of myocardial infarctions (heart attacks).
Computer models of vascular trees and multi-scale benchtop circulation models allow us to study pathophysiological

processes in vascular networks. They are used to study transport of substances (e.g. pharmaceutical agents) in the myocardium to develop novel diagnostic and therapeutic approaches for heart attack patients. Microfluidic chips are used to model microcirculatory networks for the study of microvascular obstruction of the myocardium or brain tissue.



Perfused microfluidic chip for studying microvascular obstructions of the myocardium

**Translational Electrophysiology**

Heart rhythm disorders are common and may have devastating consequences. The group for Translational Electrophysiology (a collaboration between CVE and the Department of Cardiology, Bern University Hospital) aims to develop tools and devices for cardiac rhythm management. A main research focus is the development of novel technologies for cardiac pacing. Pacing leads of contemporary pacemakers are prone to dislocations and insulation defects. Recently introduced leadless pacemakers overcome these limitations. However, they do not allow for multi-chamber pacing. Ultra-low-power communication technology is used in custom-built leadless pacemakers to allow for multisite pacing. A second focus is on the development of tools for arrhythmia diagnosis where novel minimal-invasive alternatives are developed to perform precise bedside EP examinations.

Testing of an implantable solar panel

## Selected Publications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Frey, Sabrina; Cantieni, Tarcisi; Vuillemin, Nicolas; Haine, Axel; Kammer, Rafael Franz; von Tengg-Kobligk, Hendrik; Obrist, Dominik; Baumgartner, Iris (2018). Angioarchitecture and hemodynamics of microvascular arteriovenous malformations. PLoS ONE, 13(9):e0203368. doi: 10.1371/journal.pone.0203368

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# Diabetes Technology Research

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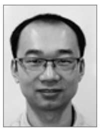

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Maria Vasiloglou

## Research Partners

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Andreas Christe, Diagnostic, Interventional and Paediatric Radiology
Christoph Stettler, Diabetes, Endocrinology, Nutritional Medicine & Metabolism
Zeno Stanga, Endocrinology, Nutritional Medicine & Metabolism

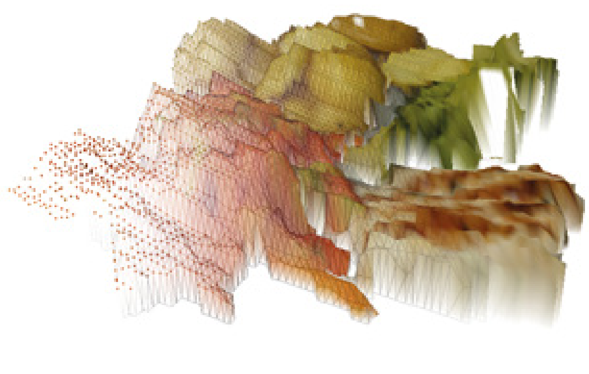
### Research Profile

The Diabetes Technology Research (DTR) group focuses primarily on the interface between machine learning, artificial intelligence and their applications in diabetes, obesity, and other non-communicable diseases. DTR creates innovation to translate "data into knowledge" and "research into clinical practice." Our ongoing research activities include:

- innovative systems for dietary monitoring and assessment based on artificial intelligence
- reinforcement learning for optimisation of insulin treatment
- artificial intelligence systems for computer-aided diagnosis

### Nutrient Intake Monitoring and Diet Assessment

Food is a key element of our life; it is of social and cultural importance, 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, DTR has been developing technologies for monitoring nutrient intake and assessing diet by analyzing food multimedia data with artificial intelligence. We have introduced the first fully operative system for estimating the carbohydrate content of meals taken 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.



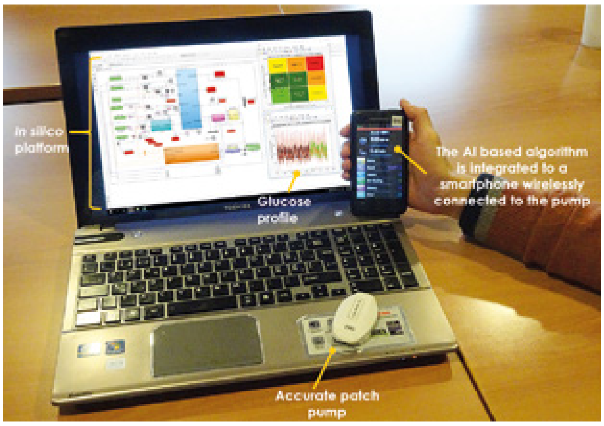
As input, the goFOOD™ system takes images of a plated meal. It then detects and classifies the different items within the plate, estimates their volume and calculates their nutrient content.

We are addressing the entire pipeline - from food identification and recognition to food volume and estimation of nutrient content. A broad spectrum of different mobile technologies is being investigated, in order to meet the diverse needs of people of different ages, health status, and environments. Currently, the system is being optimised and extended to meet the needs of people with diet-related diseases, in order to help them to manage their dietary and nutrient intake, and to fulfil the needs of healthcare professionals in assessing the nutrient intake of both outpatients and hospitalised patients (http://go-food.tech/).

### Personalisation of Insulin Treatment

Treating T1D 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 DTR that allows daily adjustment of the insulin infusion profile (basal and bolus dose) on the basis of fluctuations in the patient's glucose. Information from glucose-monitoring devices (self-monitoring of blood glucose or continuous glucose monitors) provides input to the algorithm, which outputs basal daily insulin and boluses – one value for each of the three main meals. The algorithm is based on reinforcement learning, a type of artificial intelligence that teaches systems to learn. Our self-learning approach is adaptable and personalises daily insulin values, in order to ensure glucose control, despite the inter- and intra-patient variabilities. The approach is data-driven, real-time, and of low computational cost. The U.S. 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 for disturbances, uncertainties, and variabilities. After the in silico clinical trials, the algorithm was implemented on JewelCOM™, which integrates a glucose meter and can



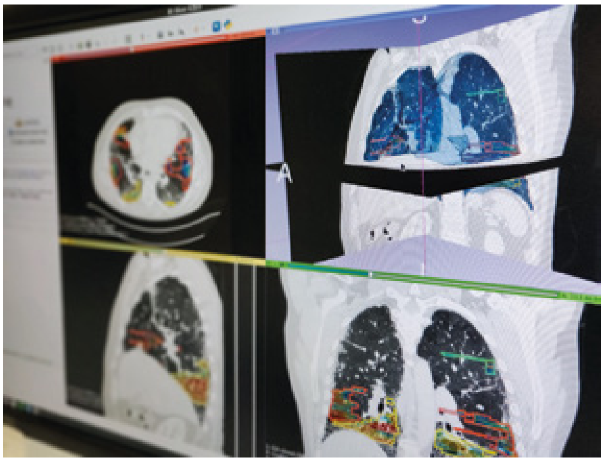

The artificial intelligence-based algorithm, integrated into a highly secured Android smartphone, takes input from either a blood glucose meter or continuous glucose monitors, and outputs the daily insulin profile. The algorithm learns while being used by the patient and is able to provide personalised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

wirelessly control the JewelPUMP™, a pump able to deliver accurate amounts of insulin. Both JewelCOM™ and JewelPUMP™ were provided by DEBIOTECH SA.

**Computer-aided Diagnosis Support**

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.

We have introduced and evaluated INTACT, an end-to-end system for the automatic classification of HRCT images into four radiological diagnostic categories. The proposed CAD system consists of a sequential pipeline in which the anatomical structures of the lung are first segmented. Then the pathological lung tissue is identified, and this information is combined to give a final radiological diagnosis. The overall pipeline is based on novel machine-learning algorithms that have been designed for the task of diffuse pathological tissue segmentation.



INTACT in action

## Selected Publications

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M. Anthimopoulos, S. Christodoulidis, L. Ebner, T. Geiser, A. Christe, S. G. Mougiakakou. Semantic Segmentation of Pathological Lung Tissue with Dilated Fully Convolutional Networks. IEEE J Biomed Health Inform. 2018 Mar 26

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Y. Lu, D. Allegra, M. Anthimopoulos, F. Stanco, G. Farinella, S. Mougiakakou. A Multi-Task Learning Approach for Meal Assessment. In Proceedings of the Joint Workshop on Multimedia for Cooking and Eating Activities and Multimedia Assisted Dietary Management (CEA/MADiMa '18). ACM, New York, NY, USA, 46-52

WO2018167727A1, System and method for improving the drug therapy management, S. Mougiakakou, Q. Sun, M. Jankovic, L.-D. Piveteau, S. Proennecke, J. Budzinski

# Gerontechnology and Rehabilitation Group

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Özhan Ozen | Rebecca Paladini | Joaquín Peñalver | Carina Röthlisberger | Hugo Saner | Nadine Schmid | Narayan Schütz | Prabitha Urwyler | Sinan Uslu | Tim Vanbellingen | René Vielgut

Eduardo Villar Ortega | Nicolas Wenk | Patric Wyss

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Kenneth Hunt, Department of Engineering and Information Technology, Bern University of Applied Sciences

### Research Profile

The interdisciplinary Gerontechnology and Rehabilitation research group is a collaborative research effort of the ARTORG Center for Biomedical Engineering Research and the Division of Cognitive and Restorative Neurology within the medical faculty at the University of Bern.
Gerontechnology is the study of age-related problems and how to address them using technology-based solutions. Rehabilitation technology aims to restore cognitive and motor functions lost as the result of illness or accidents. The relevance of these fields increases with the aging of our society. In this context, the group develops and evaluates assistive and rehabilitative technologies to support elderly and disabled people to enhance autonomy and promote independent living while reducing the risks associated with daily living. Current projects aim to promote independent living with assistive technology, ICT-based tools for training and prevention of cognitive decline and virtual reality(VR)-assisted motor rehabilitation.

### Optimize Motor Learning to Improve Neurorehabilitation

There is increasing interest in using robotic devices to deliver rehabilitation therapy following stroke. Robotic guidance is generally used in motor training to reduce performance errors during practice. However, to date, the functional gains obtained after robotic rehabilitation are limited. A possible explanation for this limited benefit is the inability of the controllers to adapt to the subjects' special needs.
Research on motor learning has emphasized that movement errors are fundamental signals that drive motor adaptation. Thereby, robotic algorithms that augment errors rather than decrease them have great potential to provoke better motor learning and neurorehabilitation outcomes, especially in initially more skilled subjects. The aim of this project is to improve robotic neurorehabilitation by developing novel robotic training strategies that augment or reduce movement errors based on subjects' skill (disability) level, age, and characteristics of the trained motor task, e.g. using machine learning algorithms.

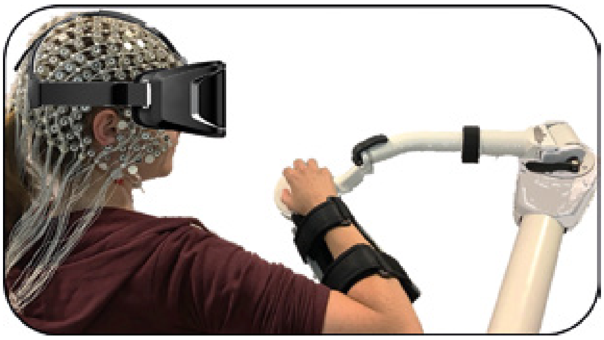
### Tricking the Human Brain

The addition of virtual reality during robotic training has been shown to provide a motivating and safe environment. Yet, the virtual reality environments currently employed in rehabilitation practice are quite simplistic and cognitively too demanding for brain-injured patients. The aim of this project is to trick the human brain through virtual reality and robotic devices and investigate 1) the effect of visualization technologies on cognitive effort, 2) how to increase body ownership over a virtual limb during robotic motor training, and 3) the relationship between the level of embodiment and motor performance. The gained knowledge

Virtual (VR) versus Augmented (AR) Reality: Interaction in virtual training environment with avatar of the subjects' real limb in VR (left) and own limb in AR (right) may help to improve therapy outcomes of already existing rehabilitation systems and could have direct implications for the recovery of activities of daily living in neurologic patients.

### EEG-based Assessment and Adaptation of Robotic Training in Neurorehabilitation

Motor learning is a complex cognitive and motor process in which environmental perception (e.g. visual) and sensorimotor information (e.g. proprioception) during practice of a motor task are integrated and consolidated as internal models in the brain. In addition, this integration of environmental stimuli is influenced by higher cognitive processes, such as task understanding and motivation. Visual and robotic feedback have been used to enhance motor learning and neurorehabilitation outcomes. However, to date, less is known about adapting robotic neurorehabilitation to patients' cognitive and motor deficits. The aim of this project is to characterize and quantify the underlying cognitive (task understanding, emotional engagement) and motor (formation of internal models) processes at the neural level using electroencephalography (EEG). These EEG markers can be used to assess the neurocognitive and motor status of the patient and to adapt the training environment (visual and robotic feedback) for task understanding, engagement, and recall of internal models associated with motor learning.



Robot-assisted arm training in virtual reality and recording of brain activity with EEG electrodes placed on the head

### Virtual Reality in Rehabilitation

*Critically ill patients*: Approximately 50-75% of patients in the intensive care unit (ICU) suffer neurocognitive late effects and reduction of quality of life after prolonged stay in the ICU. The use of visuo-acoustic Virtual-Reality (VR) nature stimulation is an unexplored avenue to reduce cognitive impairments during their stay in the ICU. Results of an ongoing study provided evidence that VR stimulation has great potential for the treatment of neurocognitive late effects, directly used in the ICU and thus improving the long-term quality of life of critically ill patients.

*Stroke patients*: Approximately 16'000 people per year suffer from stroke in Switzerland, of which 25% experience post-stroke cognitive impairment called unilateral spatial neglect. A promising new cognitive rehabilitation strategy is training visual search tasks in a 3D VR environment. The developed VR training is currently being tested in a feasibility cum proof of concept study.

### Assistive Technology

Healthy Aging: Prolonged independent living is a question of preference in today's aging society. Assistive technology provides new possibilities for real-time preventive proactive services for demanding care needs. This could help in identifying potentially adverse changes in behavior or vital signs before a life-threatening event (e.g. fall or stroke). In our study, we investigate whether multimodal sensor technology can promote healthy aging through detection and assessment of risk factors for adverse events.

Symptom Classification in Parkinson's disease (PD): PD affects more than 4.1 million patients worldwide. The cardinal PD symptoms are movement-related, including resting tremor, rigidity, bradykinesia, postural instability, and freezing of gait. There is a strong clinical need for monitoring motor performance in PD for improving therapeutic regiments and assessment in clinical trials. Existing research focuses on classifying (machine learning and signal processing) on only one of the many symptoms in a clinical setting. The aim of this project is to develop a new system for the monitoring of PD motor symptoms.

Multimodal Sensors – Emfit, Biovotion, Axivity

### Tele-rehabilitation for Language and Cognition

Aphasia is the impairment of language functions that occurs following brain damage. Affected patients undergo face-to-face speech and language therapy (SLT). Research findings particularly highlight positive effects of higher training frequency on functional outcome. A tele-rehabilitation application (Bern Aphasia App) was developed within a multidisciplinary team of speech and language therapists, neurologists, psychologists, and computer engineers. With this application, patients can train independently while the therapists have access to the patients' performance allowing them to tailor the tasks to the difficulty level. The aim of this project is to investigate the effects of high-frequency, short-duration, tablet-based SLT in chronic stroke outpatients in a clinical trial. *Cognition*: Engagement in cognitively stimulating leisure activities can help mediate cognitive impairment due to aging and brain injury. The main objective of this project is to provide a novel and enjoyable way to assess and promote cognitive health using custom-designed puzzle video games. The results of our play-test study in healthy older adults indicated that puzzle games are particularly enjoyable and easy to interact with. To adapt the game to the player's skill level, we have generated difficulty levels for the puzzle games by varying the size of the puzzle board and the number of game objects.

### Selected Publications

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# Chair for Image-Guided Therapy

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Ushasari Sarma | Daniel Schneider | Marcel Schoch | Pascale Tinguely | Hendrik von Tengg | Thomas Winklehner

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Iris Baumgartner, Director and Head of Department of Angiology
Daniel Candinas, Director and Head of Department Visceral Surgery and Medicine
Marco Caversaccio, Co-Director and Director of ENT, Head and Neck Surgery
Jan Gralla, Director Institute of Diagnostic and Interventional Neuroradiology
Johannes Heverhagen, Director and Head of Department of Diagnostic, Interventional and Pediatric Radiology
Andreas Raabe, Director and Chairman Department of Neurosurgery

## Research Partners

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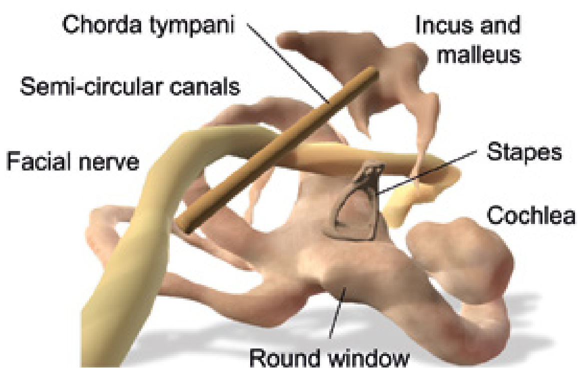
Karolinska Institutet, Stockholm, Sweden
HNO Universitätsklinikum Düsseldorf
UZA University Hospital Antwerp
CAScination AG, Bern, Switzerland
MED-EL GmbH, Innsbruck, Austria

### Research Profile

Simulation and modelling, imaging and sensing, visualisation and robotics have reached sufficient quality and resilience for use in medical technologies that can be introduced into clinical care. Research led by the Chair for Image Guided Therapy (IGT) investigates these technologies for applications that could replace the human operator in medical procedures. By considering the optimal, clinical outcome, it is conceivable for example that a partially autonomous technology could take over tasks better performed by "machines". Translational aims for projects mean close relationships with clinical co-investigators at the Inselspital and other National and International partners through clinical and academic collaborations.

### Minimally Invasive Cochlear Implantation (CI)

Surgical robot systems can work beyond the limits of human perception, dexterity and scale making them inherently suitable for use in microsurgical procedures. The robotic microsurgery group in collaboration with the ENT surgery team of the Inselspital has concluded a clinical trial on the use of the robotic cochlear implantation platform. Nine patients were operated on in total, of which six had the full procedure of robotic middle ear access as set-out by the trial design. In three patients the safety architecture of the robotic platform successfully provided the ENT surgical team with precision data, which supported the decision to convert to the conventional procedure. Research work on the robotic CI platform continues on the otology planning software, milling applications and neuromonitoring. The planning software and the robotic CI platform and are being commercially developed by CAScination AG into




Photorealistic rendering of middle and inner ear structures.

the Otoplan™ and HEARO™ products. In late 2018 the CAScination team performed its first successful robotic CI surgery with the HEARO™ system in collaboration with the ENT surgical team of Prof Paul Van de Heyning, University of Antwerp Hospital, Belgium.

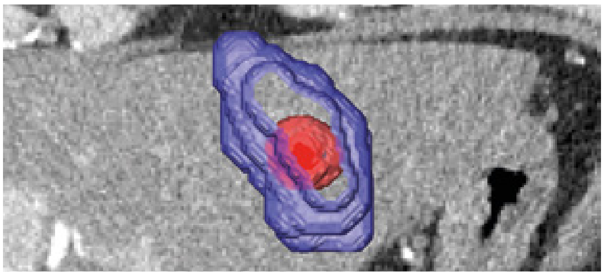
**Robotic Spine Surgery**

The most common procedure in neurosurgery of the spine is the placement of pedicle screws for the stabilisation of failing vertebrae or malformation of the vertebral column. The challenge of manual spine surgery using pedicle screws to fuse and stabilise functionally unstable vertebrae is the "uneven terrain" of vertebral bone. The functional articulation of the human vertebral spine that confers lateral and rotational mobility, static stability and compressional strength is only possible because vertebrae have a complex shape and bone density composition. Modern navigation and guidance methods have improved the screw placement accuracy, however there remains a residual of 15% of cases in which misplaced screw positioning can lead to impingement of nerves and subsequent revision surgery. By applying the principles of "true pose estimation" that were incorporated into the robotic cochlear implantation platform to develop a robotic spine surgery platform and combining it with a dedicated neuro monitoring modality, a radically different form of pedicle screw surgery will be possible. Such sensor-enabled surgical robotic drilling technology turns the variability of the vertebrae from a surgical challenge into the basis of precision surgical procedures. 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 neuro monitoring can avoid obstacles including nerves and boundaries of the bone. The IGT group together with the Department of Neurosurgery and the Swiss Center for Electronics and Microtechnology received the first Swiss National Science Foundation and the Swiss Commission for Technology and Innovation BRIDGE Discovery award given to the University of Bern for the project entitled „Towards Intelligent Sensor-enhanced Robotic Neurosurgery". The Bernese BRIDGE consortium plans to develop robotic spine surgery technology that allows the neurosurgeon to place pedicle screws perfectly and with precision in every patient, every time.

**Fighting Liver Cancer**

*Objective methods for efficacy assessment of Ablations*

The success of the image-guided, percutaneous ablation treatment of hepatocellular carcinoma (liver cancer tumors) is defined by complete tumour destruction with a safety margin of 5-10 mm around the original tumor site. At present the criteria of the radiological "all clear" of the tumor site is individual, visual inspection by the radiologist and is considered the "gold standard". However, progress in ablation techniques and more considered reflection of the clinical effect of the results, ablation will require quantitation. As part of the HORIZON 2020 Innovative Training Network "HiPerNav" a study was carried out to evaluate quantitative techniques for automatic measurement of the ablation coverage in guided percutaneous liver interventions derived from tumor and ablation segmentations.



2D CT slice of a patient with liver tumour, selected for percutaneous image-guided ablation treatment. Subsequent tumor (red) and ablation (blue transparent) segmentations displayed as volume objects at the original site of the lesion.

*Augmented reality in 3D laparoscopic liver resection*

Laparoscopic liver resection in favour of open liver surgery is becoming a credible, clinical choice. Even in major liver surgery, its use in high-volume liver units has demonstrated reduced complication rates and less perioperative morbidity. However in lower volume clinical units laparoscopic liver resections are not as readily performed, as less experienced clinicians are challenged by the lack of tactile feedback, bad depth perception and limited field of view, all major drawbacks of the technique. In collaboration with the Department of Hepatobiliary Surgery, Augmented Reality (AR) in 3D laparoscopic liver surgery with a landmark-based registration technique is being investigated. Early results indicate that use of AR is feasible with only little impact on the intraoperative workflow and applications for the detection of vanishing lesions are of particular benefit. In further work non-rigid registration algorithms will be assessed to improve registration accuracy and address intraoperative anatomical deformation.

The surgeon is using the navigated instruments to locate and remove tumors in the liver. With the 3D glasses the surgeon gets a depth perception from the virtual anatomical structures and the real-time endoscopic image.

**Selected Publications**


J. Ansó et al., (2018) "Neuromonitoring During Robotic Cochlear Implantation: Initial Clinical Experience," Ann. Biomed. Eng., vol. 46, pp. 1568–1581

I. Paolucci et al., (2018) "An augmented reality navigation system for laparoscopic liver surgery – First experiences," HPB, vol. 20, pp. S265–S266

I. Paolucci et al., (2018) "An intraoperative ultrasound-based navigation approach for laparoscopic ablation of liver tumors," HPB, vol. 20, pp. S452–S453

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# Organs-on-Chip Technologies

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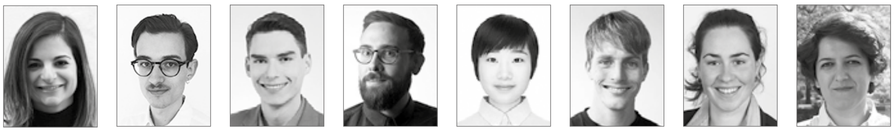

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### Research Profile

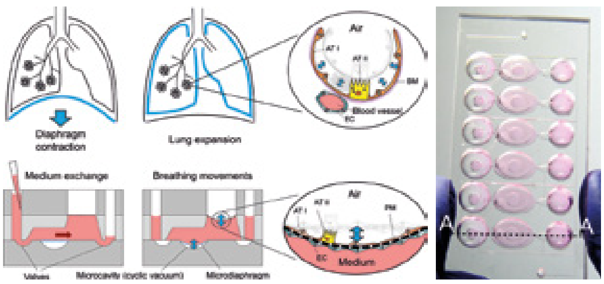
The Organs-on-Chip Technologies Group focuses on the development of advanced in-vitro models of the lung able to recreate the cellular microenvironment of the respiratory tract. To achieve these objectives, interdisciplinary research is performed at the interface of cell biology, lung mechanics, microtechnology, and microfluidics. Tiny microchannels and microwells with length scales that are comparable to the dimensions of mammalian cells can be microstructured by soft lithography and other techniques. Such microfluidic devices have the capability to accurately control the cellular microenvironment.

For the future, such bioartificial lung-on-chip systems are deemed to be extremely important for the investigation of the pathophysiology of different lung diseases and the understanding of fundamental cellular or molecular mechanisms that take place in the lung. They are also intended to be implemented for precision medicine, a new paradigm in which the treatment efficiency can be tested with the patient's own cells in order to individualize and optimize the therapy.

### Breathing Lung-on-Chip

The complexity of the lung can be illustrated by its delicate tree-like architecture that ends with the alveolar sacs, where the gas exchanges take place. Oxygen and carbon dioxide diffuse through an extremely thin alveolar barrier, whose thickness is only about 0.2 to 1µm. This barrier is mainly constituted by alveolar epithelial cells, capillary endothelial cells, and of the basement membrane. The alveolar epithelium is in contact with air, while endothelial cells that formed the small vascular capillaries are in contact with blood. This whole environment is subjected to a cyclic, mechanical constraint induced by the respiratory movements. A healthy lung is typically stretched by about 5 to 12 percent for a respiratory rate of 10-12 breaths per minute.

We developed an advanced in-vitro model of the lung alveoli, called "lung-on-a-chip". It mimics the human lung alveolar barrier in an unprecedented way. In sharp contrast to standard Petri dishes, in which cells are cultured in a static environment, human lung cells are cultured in an in-vivo-like environment that resembles that of the lung. Lung epithelial cells – in contact with air – are cultured on one side of an ultra-thin and flexible membrane, whereas lung endothelial cells – in contact with a blood analog – are seeded on its other side. This alveolar barrier is cyclically stretched in three dimensions as in the lung. The actuation of the barrier is created by a microdiaphragm that resembles the diaphragm, the main muscle responsible for breathing. In addition to mimicking the in-vivo situation, the lung-on-chip was designed to be robust and easy to use.



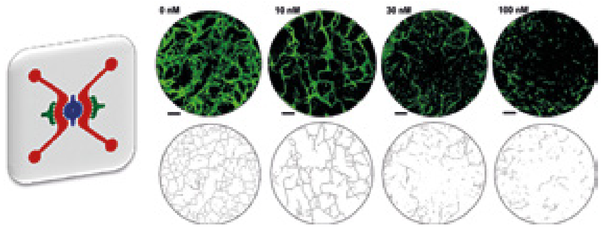

Concept of the ARTORG lung-on-a chip: Top: in-vivo, the lung expands following the contraction of the diaphragm. The breathing motions are transferred from the organ-level to the individual alveoli. The alveolar barrier consists of type I (AT I) and of type II (AT II) alveolar epithelial cells and of endothelial cells (EC) between which the basal membrane (BM) is sandwiched. Bottom: Schematic cross-sections (A-A on the picture right) of the lung-on-chip with two operation modes: i) Breathing and ii) Medium exchange modes. Right: Photograph of the lung-on-chip with 6 independent alveolar barrier systems filed with cell culture medium. (from Stucki et al. Scientific Reports 2018).

The mechanical stress induced by the breathing movements is known to play a key role in a number of cellular processes, such as alveolar stability and tissue remodeling, to name but a few. The mechanical properties of lung tissues are affected by different lung pathologies such as acute lung injury, inflammation, and fibrosis. Our model is therefore expected to better predict the drug response and thus reduce the number of drug candidates to be tested in costly clinical trials.

**Functional Lung Microvasculature-on-Chip**

Endothelial cells, in particular endothelial microvascular cells, present in the lung parenchyma, play an important role in inflammation and the initiation of fibrogenic events in lung pathologies, such as in idiopathic pulmonary fibrosis. Nevertheless, the clear mechanism on how and if these mechanisms are related is still unknown and requires novel in-vitro models allowing reproduction of the microvasculature of the lung.

In order to model the microvasculature of the lung, new in-vitro models aiming at the creation of a perfusable microvasculature that mimics the lung capillary microenvironment were developed. Endothelial cells and pericytes or fibroblasts in fibrin gel are seeded in a microfluidic compartment, where they self-assemble and create stable microvessels with diameter typically ranging from 20 to 200um and length between 100um to 2mm. The signaling of pericytes or fibroblasts located outside of this compartment enables to open the vascular lumens that can then be perfused. In addition, upon exposure to phenylephrine, a known vasoconstrictor, the vessels contract significantly as would have been expected in-vivo. The models were further developed to investigate the effects of nintedanib, a drug used to treat idiopathic pulmonary fibrosis.



Left: Microfluidic platform for the generation of three-dimensional microvessel architecture. Human lung fibroblasts in hydrogel in the two outermost chambers (green), Human endothelial cells and fibroblasts in hydrogel in the circular central chamber (blue), and cell culture media (red) in two symmetric microchannels. Right: Effect of anti-fibrotic drug component (nintedanib), an agent developed to treat idiopathic pulmonary fibrosis, on in vitro microvessel network. Nintedanib has anti-angiogenic effect and decreases microvessel density, vascular interconnectivity, and sprouting. Top row: microvessel network in untreated chips and nintedanib-treated chips. Green color reflects endothelial cells intracellular junctions and illustrates vascularized regions. Scale bar: 150 µm. Bottom row: axial thinning of the microvessel networks for better visualization of vascular interconnectivity. (from Zeinali et al., Angiogenesis, 2018).

## Selected Publications


Zeinali, Soheila; Bichsel, Colette A.; Hobi, Nina; Funke, Manuela; Marti, Thomas M.; Schmid, Ralph A.; Guenat, Olivier T.; Geiser, Thomas (2018). Human microvasculature-on-a chip: anti-neovasculogenic effect of nintedanib in vitro. Angiogenesis, 21(4), pp. 861-871

Mermoud, Yves; Felder, Marcel Christian; Stucki, Janick; Stucki, Andreas; Guenat, Olivier Thierry (2018). Microimpedance tomography system to monitor cell activity and membrane movements in a breathing lung-on-chip. Sensors and Actuators B: Chemical, 255(3), pp. 3647-3653

Guenat, Olivier Thierry; Berthiaume, François (2018). Incorporating mechanical strain in organs-on-a-chip: Lung and skin. Biomicrofluidics, 12(4), 042207

Stucki, Janick; Hobi, Nina; Galimov, Artur; Stucki, Andreas; Schneider-Daum, Nicole; Lehr, Claus-Michael; Huwer, Hanno; Frick, Manfred; Funke-Chambour, Manuela; Geiser, Thomas; Guenat, Olivier Thierry (2018). Medium throughput breathing human primary cell alveolus-on-chip model. Scientific Reports, 8(1), p. 14359

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Stucki, Andreas; Stucki, Janick Daniel; Hall, Sean; Felder, Marcel Christian; Mermoud, Yves; Schmid, Ralph; Geiser, Thomas; Guenat, Olivier Thierry (2015). A lung-on-chip array with an integrated bio-inspired respiration mechanism. Lab on a chip, 15(5), pp. 1302-1310


## Patents


O. Guenat, M. Felder, A. Stucki, J. Stucki, T. Geiser, "Device for in-vitro modelling in-vivo tissues of organs", WO2015032889A1, EP3041926A1, US10066198B2 (granted)

O. Guenat, J., Stucki, C. Léchot, M. Aeschlimann, "Modular System for in-vitro modelling tissues of organs in vivo", EU Patent Application No. 16200451.9 (2016)

O. Guenat, J., Stucki, C. Léchot, M. Aeschlimann, "Cell culturing system and method", WO2018096054A1

# Ophthalmic Technology Laboratory

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### Research Profile

The Ophthalmic Technology Laboratory works on novel methods that apply Artificial Intelligence (AI) methods to develop clinical tools for ophthalmology, interventional radiology and surgical robotics. The rise in ophthalmic patient numbers is putting increased pressure on eye clinics worldwide. The need is a combination of i) insufficient clinical personnel to manage patients for diagnosis and monitoring and the ii) time taken and lack of standardization of manual diagnostic modalities. Both are ideal opportunities for the application of high-accuracy and high-throughput ophthalmic AI tools. In close collaboration with clinicians, biologists and other health practitioners, we investigate data-driven, virtual versions of the traditional hardware tools that have constituted ophthalmic clinical care for centuries. Perimeters, Slit-Lamps and OCT image annotation have all received the AI treatment in our laboratory and we have translated a number of them into clinical care at the Inselspital and other National and International partner clinics. In a new approach to broaden the AI applications to domains like human space flight and astrophysics, the OTL group has started a collaboration with the Center for Space and Habitability (CSH) of the University of Bern to explore the use of machine learning for exoplanetary science.

### Mobile Perimetry for Glaucoma Care

Glaucoma is a pernicious retinal disease that if left unmanaged leads to blindness. Currently Glaucoma diagnostics use perimetry measurement to assess patient's visual capacity to sense light over the entire periphery of their vision. While the standard of care, the perimetry assessment takes over 8 minutes for a single eye. Faster and more patient-appropriate examinations for patients would be a major improvement to current care. The OTL group is leading research into Glaucoma diagnostics and management of a state-of-the-art solution that allows examinations in just 2 minutes per eye and can be integrated into a traditional perimeter or any virtual reality headset. Based on tailored machine deep learning methods for image enhancement, this methodology can radically improve the quality of the diagnostic readout, even when acquired in a shorter time than standard acquisition. The work has been awarded the BRIDGE SNSF and Innosuisse – Swiss Innovation Agency Proof of Concept (PoC) Award (to Ms Serife Seda Kucur) to develop the technology further and carry out a clinical trial.

### Slitlamp based video mosaicking

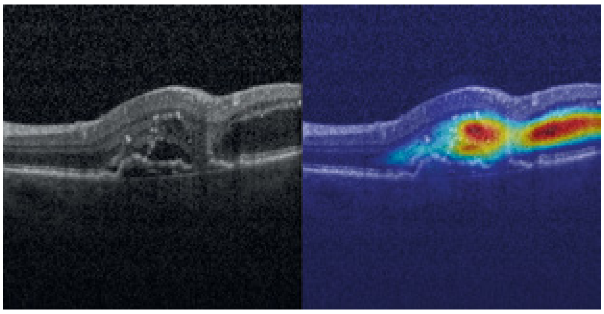
To this day, the slit lamp remains the first tool used by an ophthalmologist to examine patient eyes. Imaging of the retina poses however a variety of problems, namely, a shallow depth of focus, reflections from the optical system, a small field of view and non-uniform illumination. For ophthalmologists, the use slitlamp images for documentation and analysis purposes however remain extremely challenging due to large image artifacts. For this reason, we propose an automatic retinal slit lamp video mosaicking, which enlarges the field of view and reduces amount of noise and reflections, thus enhancing image quality. Our method is composed of three parts: i) viable content segmentation, ii) global registration and iii) image blending. Frame content is segmented using gradient boosting with custom pixel-wise features. SURF is used to find pairwise translations between frames with robust RANSAC estimation and graph-based SLAM for global bundle adjustment. Foreground-aware blending based on feathering merges video frames into comprehensive mosaic. The end result are retinal mosaicks that are by ophthalmologists as they provide a large field of view.

**Computer-Assisted Selective Retina Therapy**

In recent years, selective retina laser treatment (SRT), a sub-threshold therapy method, avoids widespread damage to all retinal layers by targeting only a few. While these methods facilitate faster healing, their lack of visual feedback during treatment represents a considerable shortcoming as induced lesions remain invisible with conventional imaging and make clinical use challenging. To overcome this, we have developed a new strategy to provide location-specific and contact-free automatic feedback of SRT laser applications. We leverage time-resolved optical coherence tomography (OCT) to provide informative feedback to clinicians on outcomes of location-specific treatment. By coupling an OCT system to SRT treatment laser, we visualize structural changes in the retinal layers as they occur via time-resolved depth images. We then propose a novel strategy for automatic assessment of such time-resolved OCT images. To achieve this, we introduced novel image features for this task, that when combined with standard machine learning classifiers yield excellent treatment outcome classification capabilities. In effect, this technique presents a much-needed strategy towards noninvasive, safe, reliable and repeatable SRT applications.

**Efficient OCT volume reconstruction from slitlamp microscopes**

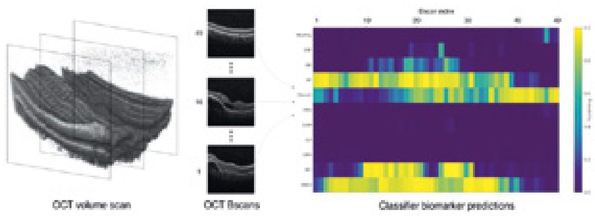
Since its introduction 25 years age, Optical Coherence Tomography (OCT) has contributed tremendously to diagnostic and monitoring capabilities of pathologies in the field of ophthalmology. Despite rapid progress in hardware and software technology however, the price of OCT devices has remained high, limiting their use in private practice and in screening examinations. To this end we have developed a slitlamp-integrated OCT device, built with off-the-shelf components, which can generate high-quality volumetric images of the posterior eye segment. To make this possible, we developed a novel strategy for 3D image reconstruction in this challenging domain that allows for state-of-the-art OCT volumes to be generated at fast speeds. The result is an OCT device that can match current systems in clinical practice, at a significantly lower cost.



Visualization of biomarker auto-detection by the AI system in an OTC cross section.

**Deep Learning for Automatic AMD identification in OCT volumetric data**

Optical Coherence Tomography (OCT) provides a unique ability to image the eye retina in 3D at micrometer resolution and gives ophthalmologist the ability to visualize retinal diseases such as Age-Related Macular Degeneration (AMD). While visual inspection of OCT volumes remains the main method for AMD identification, doing so is time consuming, as each cross-section within the volume must be inspected individually by the clinician. In much the same way, acquiring ground truth information for each cross-section is expensive and time consuming. This fact heavily limits the ability to acquire large amounts of groundtruth, which subsequently impacts the performance of learning-based methods geared at automatic pathology identification. To avoid this burden, we proposed a novel strategy for automatic analysis of OCT volumes where only volume labels are needed. That is, we train a classifier in a semi-supervised manner to conduct this task. Our approach uses a novel Convolutional Neural Network (CNN) architecture that only needs volume-level labels to be trained to automatically assess whether an OCT volume is healthy or contains AMD. Our architecture involves first learning a cross-section pathology classifier using pseudo-labels that could be corrupted and then leverage these towards a more accurate volume-level classification.




Automated analysis of OCT eye scans for numerous biomarkers.

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Kucur, Marquez-Neila, Abegg and Sznitman, "Patient Attentive Sequential Strategy for Perimetry-based Visual Field Acquisition. Medical Image Analysis", (2019)

Lejeune, Grossrieder and Sznitman, "Iterative multi-path tracking for video and volume ground truth annotation with sparse point supervision", Medical Image Analysis, 2018

Marquez Neila, Fisher, Sznitman and Heng, "Using Supervised Machine Learning to Analyze Spectra of Exoplanetary Atmospheres", Nature Astronomy, 2018

Du, Kurmann., Chang, Allan., Ourselin, Sznitman., Kelly. and Stoyanov. "Articulated Multi-Instrument 2D Pose Estimation Using Fully Convolutional Networks", IEEE Transactions on Medical Imaging, 2018

# Computational Bioengineering

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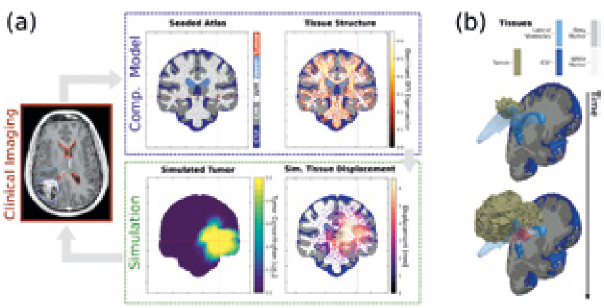
### Research Profile

The Computational Bioengineering Group tackles challenges in basic and applied medical research with modern computational simulation tools. Rather than focusing on the computational methods themselves, we are concerned with their appropriate application for the resolution of practical and fundamental clinical questions. Numerical methods are combined with experimental and clinical research in order to improve the quality and extend the validity of our models.
Together with our collaborators, we constitute a strong team covering a wide spectrum of research topics ranging from direct support of surgical patient treatment to basic bone properties. Besides our core expertise in applying finite element analysis to study skeletal biomechanics, we are seeking to improve planning of computer aided interventions by developing and applying refined numerical techniques into the field of computer aided surgery.

### Mathematical modeling of the biomechanical forces causing brain tumor mass-effect

Brain tumors present with different growth phenotypes, ranging from invasive lesions without notable 'mass effect' to strongly displacing lesions that induce mechanical stresses and result in healthy tissue deformation, midline shift or herniation. Biomechanical forces, such as those resulting from displacive tumor growth, shape the tumor environment and are known to affect tumor growth and evolution. Likewise, tumor growth drives physical changes in the micro-environment that affect tissue solid and fluid mechanics.
We develop mathematical models to study the biomechanical impact of brain tumor growth and possible treatment implications. We use these models to investigate determinants of tumor shape, such as the influence of tissue structure and growth location, and to evaluate quantitative image-based measures of tumor mass effect. Along with these models, we develop approaches for identifying patient-specific growth characteristics from clinical imaging data.

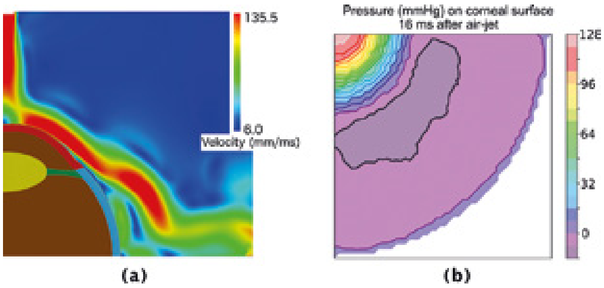



(a): Computational models are initialized from clinical imaging data. The simulation predicts tumor invasion and mechanical stresses induced by tumor growth. Simulation results are compared to imaging findings. (b): Simulated time evolution of 3D tumor growth and tissue deformation.

### Planning of refractive interventions

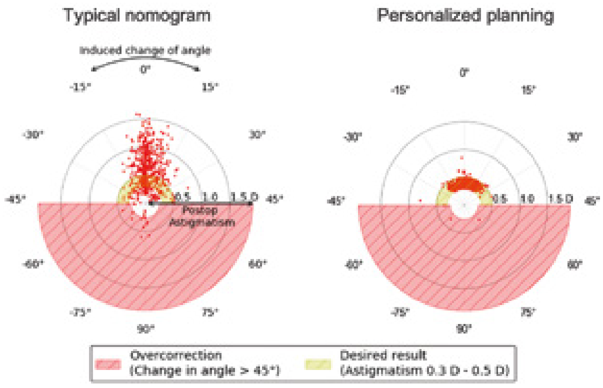
Refractive interventions are widespread techniques for vision correction such as myopia or astigmatism. The cornea of the patient is reshaped by surgical intervention like incisions and laser ablation of stromal tissue. The amount of tissue to remove is traditionally estimated based on experimental nomograms. Unfortunately, the change of corneal power is frequently over- or under-estimated.
We proposed an opto-mechanical simulation framework to quantify the optical outcome induced by alteration of the corneal biomechanics. Our models rely on the precise shape of the anterior and posterior surfaces of the cornea measured pre-operatively. However, new tools are required to characterize the biomechanics of the patient's cornea. Non-contact tonometry (NCT) represents an appealing approach for the in-vivo characterization of corneal biomechanics. This technique relies on a short air pulse to induce a deformation of the cornea. However, before being able to derive mechanical information from these measurements, the actual load applied on the cornea by the strong air-jet must be quantified. We showed that the standard approach that neglects the corneal deformation when calculating the pressure on the tissue, induces an error of up to 200%. This finding is

expected to greatly impact the mechanical characterization of the cornea in-vivo from tonometric measurements.




Fluid-structure simulation of the air-puff used to deform the cornea during non-contact tonometry. The fluid velocity on the deformed corneal surface (a) induces a complex distribution of air pressure on the cornea surface (b).

This numerical framework was used to perform personalized simulations of different surgical procedures. For example, arcuate keratotomy is a surgical technique used to correct astigmatism following cataract interventions. Our numerical simulation framework could estimate the outcome of different planning options before the surgery. Based on this numerical approach, we were also able to propose optimization algorithms to automatically determine the

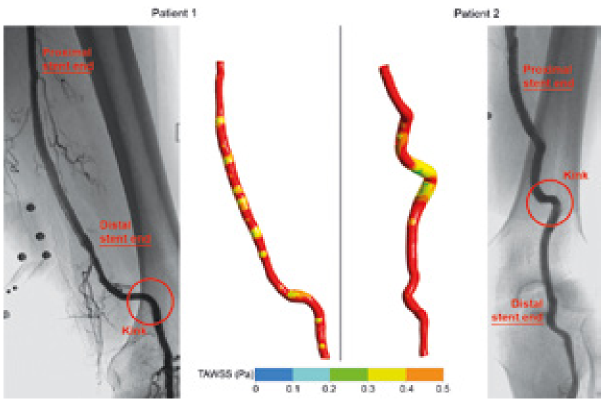



The outcome of personalized arcuate keratotomy simulations on more than 600 patients. The outcome of the intervention is shown using polar plots; the distance from the center represents the postoperative astigmatism while the polar position describes the rotation of the steep meridian induced by the surgery. The surgical procedure must reach a final astigmatism of 0.4D (yellow area) while absolutely avoid inducing overcorrection (red area). Results show that the outcome of existing nomogram exhibit a large variability across patients, while the personalized optimization of the surgical parameter leads to more reliable postoperative astigmatism, and limits the risks of overcorrection.

surgical parameters optimal for each specific patient. The patient-specific optimization of the surgery proved to better control the outcome of the intervention, leads to more reliable postoperative astigmatism, and limits the risks of overcorrection.

**Finite element analysis of peripheral arterial disease**

Endovascular therapy in patients suffering from peripheral arterial disease show high rates of restenosis. We hypothesized that restenosis following revascularization is associated with hemodynamical markers derived from blood flow during leg flexion. Therefore, we performed personalized computational fluid dynamics (CFD) analyses of patients, who underwent routine endovascular femoro-popliteal interventions. Based on restenosis rates reported at 6 months follow-up, statistical analyses were performed to quantify the relationship between hemodynamical parameters predicted by the numerical simulations and clinically-observed restenosis. Results showed that unphysiological arterial deformations induced postoperatively by the flexion of the leg led to adverse hemodynamic conditions that may trigger restenosis. Statistical models based solely on hemodynamical markers showed a prediction accuracy of more than 75%, which indicates that flow parameters are sufficient to predict restenosis. This approach, based on the immediate post-operative configuration of the artery, has the potential to identify patients at increased risk for restenosis. Based on this information, clinicians could take preventive measures and more closely follow these patients to avoid complications.




The distribution of shear stress in two stented arteries that exhibited arterial kinking during leg flexion. The location of the atheroprone areas were concentrated around the kinks. Additional areas affected by adverse flow were within the stented segments, in which leg flexion resulted in pinching of the artery along the length of the stent.

## Selected Publications

Lieger O, Schaub M, Taghizadeh E, Büchler P. How Symmetrical Are Bony Orbits in Humans? J. Oral Maxillofac. Surg. 2018;9. https://www.sciencedirect.com/science/article/pii/S0278239118309832

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# Information Processing in Medical Interventions

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### Research Profile

Information Processing during medical interventions, including medical image computing and computer assisted interventions, has been playing an increasingly important role in diagnosis and treatment of various diseases. Specifically, medical image computing ensures the derivation of optimized parameters from the acquired multimodality medical images, allows for exploitation of the image-derived parameters, and facilitates the development of anatomical and associated physiological models which can further help in understanding different disease mechanism. Recently the breakthroughs in Artificial Intelligence (AI), especially those based on deep learning, has led to medical applications which are now having a profound impact on personalized therapy. In collaboration with national and international experts from both industry and academia, IPMI group actively embrace such a technical trend, reflected by the development of medical image computing algorithms that achieved state-of-the-art performance on multimodality medical images. Another focus of the group is on translational research, aiming to improve healthcare delivery to patients.

## Current Research Areas

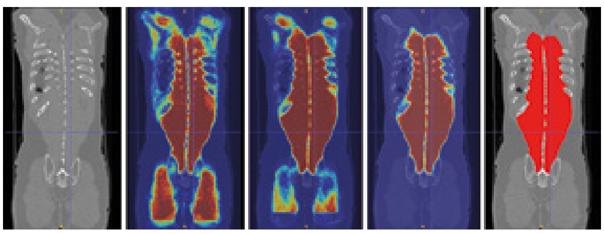
### Bayesian VoxDRN for whole heart segmentation (SNSF Grant 169239)

We proposed a probabilistic deep voxelwise dilated residual network, referred as Bayesian VoxDRN, to segment the whole heart from 3D MR images. Bayesian VoxDRN can predict voxelwise class labels with a measure of model uncertainty, which is achieved by a dropout-based Monte Carlo sampling during testing to generate a posterior distribution of the voxel class labels. Our method has three compelling advantages. First, the dropout mechanism encourages the model to learn a distribution of weights with better data-explanation ability and prevents overfitting. Second, focal loss and Dice loss are well encapsulated into a complementary learning objective to segment both hard and easy classes. Third, an iterative switch training strategy is introduced to alternatively optimize a binary segmentation task and a multi-class segmentation task for a further accuracy improvement. Experiments on the MICCAI 2017 multi-modality whole heart segmentation challenge data corroborate the effectiveness of the proposed method.

The architecture of our Bayesian VoxDRN.

### Fully automatic segmentation of paraspinal muscles from 3D Torso CT images (JSPS Fellowship)

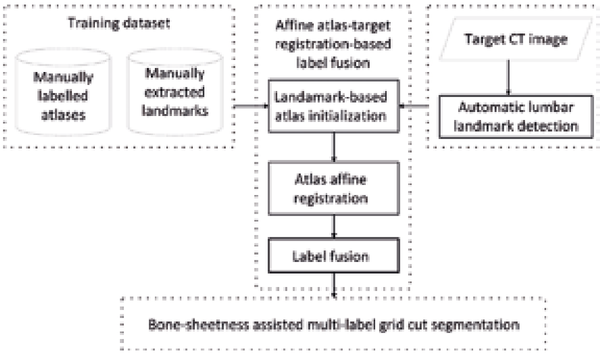
We proposed a novel learning-based method for fully automatic segmentation of paraspinal muscles from 3D torso CT images. Multi-scale iterative random forest classifications with multi-source information were employed to speed up the segmentation to improve the accuracy. Here, multi-source images include the original torso CT images and later also the iteratively estimated and refined probability maps of the paraspinal muscles. Validated on 20 torso CT images, the presented method achieved a mean Dice coefficient of 93.0%.



A segmentation example

**Fully automatic segmentation of lumbar vertebrae from CT images (SNSF grant 157207)**

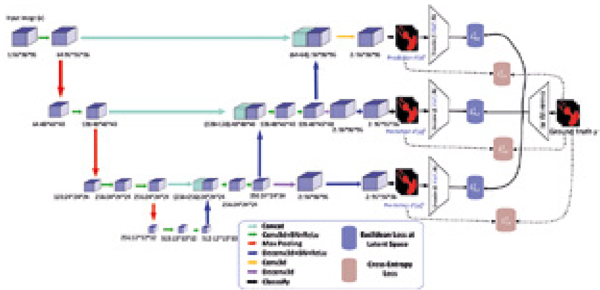
We present a method for automatic segmentation of lumbar vertebrae from a given CT image. More specifically, our automatic lumbar vertebrae segmentation method consists of two steps: affine atlas-target registration-based label fusion and bone-sheetness assisted multi-label graph cut which has the inherent advantage of automatic separation of the five lumbar vertebrae from each other. We evaluate our method on 21 clinical lumbar spinal CT images with the associate manual segmentation and conduct a leave-one-out study. Our method achieved an average Dice coefficient of 93.9 ± 1.0% and an average symmetric surface distance of 0.41 ± 0.08 mm.




A Schematic view of the fully automatic segmentation approach.

**Multi-modal image computing for computer assisted interventions (SNF grant 163224 and Insel-Ortho-IP-MI Cooperation)**

This project focuses on developing an efficient method to generate 3D anatomical models using CT-free imaging protocols that are used in clinical routine in order to support computer-assisted diagnosis and surgical planning of femoroacetabular impingement (FAI). The project aims for development of a fully automatic approach based on multi-modal images combining 2D X-ray radiograph with 3D MR images acquired with small field of view. In year 2018, we developed a multi-level latent shape space constrained 3D U-net which we named as Latent3DU-net for automatic segmentation of the proximal femur from radial MRI of the hip.



A Schematic view of the Latent3DU-net.

## Selected Publications

*Edited Books*

G Zheng, W Tian and X Zhuang (eds.): Intelligent Orthopaedics – Artificial Intelligence and Smart Image-guided Technology for Orthopaedics. Springer, 2018. ISBN: 978-981-13-1396-7

*Selected Peer-reviewed Papers*

L Maier-Hein, M Eisenmann, A Reinke, S Onogur, M Stankovic, P Scholz, T Arbel, H Bogunovic, A P. Bradley, A Carass, C Feldmann, A F Frangi, P M. Full, B van Ginneken, A Hanbury, K Honauer, M Kozubek, B A. Landman, K März, O Maier, K H Maier-Hein, B Menze, H Müller, P F. Neher, W Niessen, N Rajpoot, G Sharp, K Sirinukunwattana, S Speidel, C Stock, D Stoyanov, A Aziz Taha, F van der Sommen, C-W Wang, M-A Weber, G Zheng, P Jannin, A Kopp-Schneider. Why rankings of biomedical image analysis competitions should be interpreted with care. Nature Communications, 9(1):article5217, 2018

N Kamiya, J Li, M Kume, H Fujita, D Shen and G Zheng. Fully automatic segmentation of paraspinal muscles from 3D torso CT images via multi-scale iterative random forest classifications. International Journal of Computer Assisted Radiology and Surgery, 13(11):1697 – 1706, 2018

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# Medical Image Analysis

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### Research Profile

The Medical Image Analysis group develops advanced medical image analysis technologies, and related translational biomedical engineering technologies, to quantify, diagnose, and follow-up disorders related to the central nervous system (e.g. glioblastomas, stroke, multiple sclerosis, etc.).
The group develops novel techniques for multimodal image segmentation and analysis of brain lesions, presently including glioblastoma multiforme, multiple sclerosis, and acute ischemic stroke. The results of these developments are aimed at advancing the fields of radiomics for the discovery of innovative noninvasive 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. The group further supports these developments with dedicated techniques for super-resolution imaging, aiming at bridging information from low and high levels of image resolution, and fast and robust human-machine interfacing, designed to leverage the communication between computer algorithms and expert domain knowledge.

### Accurate Quantification and Radiomics Analysis for Brain Lesions

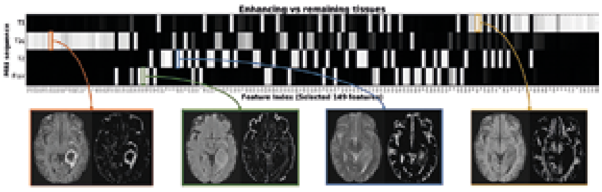
Magnetic Resonance Imaging (MRI) and its variants are a powerful imaging modality that encompasses rich anatomical and physiological information at a high resolution. In neurosciences, these modalities have become a standard in clinical practice. However, the interpretation of the images requires the combined use of different modalities, which leads to the need of computer-assisted technologies. The group has developed several methodologies to analyze MRI images with focus on multimodal image segmentation for brain image lesion analysis studies. These developments are driven by clinical requirements, such as computation speed, robustness, and use of standard clinical imaging protocols.
Accuracy is particularly paramount for an image-guided brain lesion quantification technology. Through a strong interdisciplinary collaboration with the department of neuroradiology at the University Hospital, Bern, our interdisciplinary group has developed over the years accurate and clinically-relevant (i.e. in line with clinical requirements) solutions based on machine-learning methodologies for automated brain tumor segmentation, stroke lesion segmentation, and multiple-sclerosis lesion segmentation, which have ranked among top approaches at MICCAI (Medical Image Computing and Computer-Assisted Interventions) challenges, top venue of the medical image computing field. Our seminal work on automated brain tumor volumetry was awarded the Young Scientist Publication Impact Award 2016, in recognition for being the most impactful MICCAI work of the last five years, as well as the Ypsomed Innovation Award 2016.
Automated brain lesion quantification technologies are now used for Multidimensional Response Assessment in Glioma Patients, which is an interdisciplinary effort aimed at developing longitudinal radiomics technologies and non-invasive biomarkers providing a better assessment of disease progression and patient response to therapy.

### Uncertainty and Interpretability of Medical Image Segmentation Technologies Using Deep-Learning Technologies

Next to accuracy, the robustness of computer-assisted technologies is fundamental for their effective deployment and integration in medicine. Particularly, it is crucial to develop technologies that can cope with computer errors stemming from the large heterogeneity of medical images, the complex pathophysiology of disease, among other factors. To this end, our group is developing algorithms that check the reliability of machine learning's results by yielding uncertainty estimations of computer-generated results, which can be used to change the paradigm, so medical experts are no longer executioners of the task (e.g. brain tumor delineation) but use this information to monitor and correct them in a time-effective manner. In addition, as the amount of collected medical image information is rapidly growing, it is vital to develop Human-Machine Interfacing technologies (HMI) to ensure scalability of time-effective monitoring and correction technologies of computer-generated results.

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, so to build trust with these systems, but it is also very important in line with discussions pointing to decision-making and a "right to explanation."

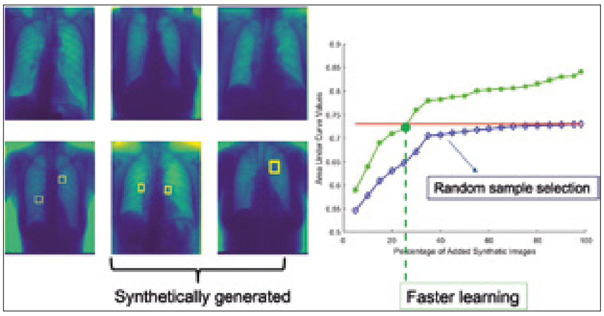
Motivated by the current decoupling between the design of medical image sequences, and their exploitation through machine learning algorithms. In collaboration with MRI physicists from the academic and private sectors, our group is researching machine-learning methodologies that are being applied at the image-formation process stage, with the overarching goal of designing the best combination of MRI sequences and machine-learning algorithms.




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

### Efficient Focused Active Learning for Evolutive Deep Learning in Medical Image Analysis

We develop techniques for focused active learning, enabling fast learning rates of deep learning technologies for image segmentation and image classification. The approach utilizes measures of uncertainty of computer-generated results to focus on difficult learning areas of an image. The focused learning is coupled with a smart data augmentation approach that synthetically generates similar data samples around the data point of current focus. Experimental results on medical images show the ability of the approach to learn at faster rates than traditional active-learning systems, while enabling a better usage of the available training set.




Focused Active Learning. Exploiting sample informativeness and synthetic data augmentation enables a faster learning (see slope of green curve) versus standard active-learning approaches (blue curve), and an improved use of the information compared to the performance obtained when training with all available data at once (red line)

### Towards Streamlined and High-throughput Data Curation Processes

Our group is establishing technologies for automatic quality assessment of curated data, as well as the reliability of the machine-learning models produced with curated medical image information. On the one hand, automatic quality assessment of curated data is essential for high-throughput data curation of a highly heterogeneous and error-prone human interaction process of medical image information in the clinical routine. On the other hand, it is crucial to research and develop technologies that can inspect the reliability of machine-learning models derived from this data. We initiated a Swiss-wide initiative to create infrastructure and technologies for a local and distributed radiomics platform, which features a data curation workflow occurring within the daily clinical routine. By leveraging the daily clinical workflow with human-machine intelligence technologies, we aim to create a rich and sustainable symbiosis between their daily clinical needs, and the data-curation process needed for biomedical research, therapy assessment (e.g. clinical trials), and in general for the improvement of data-driven biomedical engineering technologies.

### Selected Publications


Dwarikanath M., Bozorgtabar S., Thiran J.P., and Reyes M. Efficient Active Learning for Image Classification and Segmentation using a Sample Selection and Conditional Generative Adversarial Network. Medical Image Computing and Computer-Assisted Intervention -- MICCAI 2018, Lecture Notes in Computer Science, In Press, 2018

Jungo A., Meier R., Ermis E., Blatti-Moreno M., Herrmann E., Wiest R., and Reyes M. On the Effect of Inter-observer Variability for a Reliable Estimation of Uncertainty of Medical Image Segmentation. Medical Image Computing and Computer-Assisted Intervention -- MICCAI 2018, Lecture Notes in Computer Science, In Press, 2018

Chandran V., Maquer G., Gerig T., Zysset P., and Reyes M. Supervised learning for bone shape and cortical thickness estimation from CT images for finite element analysis. Medical Image Analysis, 52, 42 - 55, 2019. http://www.sciencedirect.com/science/article/pii/S1361841518308612

Pinto A., Pereira S., Meier R., Alves V., Wiest R., Silva C., and Reyes M. Enhancing clinical MRI Perfusion maps with data-driven maps of complementary nature for lesion outcome prediction. Medical Image Computing and Computer-Assisted Intervention -- MICCAI 2018, Lecture Notes in Computer Science, In Press, 2018

Barros N., Meier R., Pletscher M., Stettler S., Knecht U., Herrmann E., Schucht P., Reyes M., Gralla J., Wiest R., and Slotboom J. On the relation between MR spectroscopy features and the distance to MRI-visible solid tumor in GBM patients. Magn Reson Med, 2018. https://doi.org/10.1002/mrm.27359

Suter Y., Rummel C., Wiest R., and Reyes M. Fast and Uncertainty-Aware Cerebral Cortex Morphometry Estimation Using Random Forest Regression. ISBI 2018: Proceedings of the 2018 IEEE international conference on Biomedical imaging, In Press, 2018

# Musculoskeletal Biomechanics

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### Research Profile

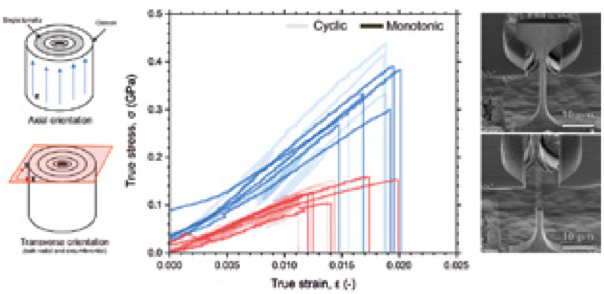
Motivated by prevention, diagnosis and treatment of degenerative diseases the research of the musculoskeletal biomechanics group focuses on multi-scale structure-function relationships of bone from the extracellular matrix to the organ level. A combined theoretical, experimental, and numerical approach is applied to model, validate and simulate the mechanical behavior of bone tissue in the course of 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.

### Micro-meso scale transition of bone strength (SNF grant 165510 with EMPA)

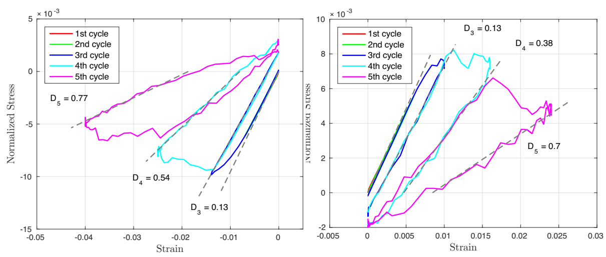
A micromechanical tensile setup was designed and optimized to test focused ion beam (FIB) fabricated samples on the length scale of a single lamellae (3-7 um) inside a scanning electron microscope (SEM). The tensile response of ovine osteonal bone was characterised in both axial and transverse orientations. The micro-tensile tests revealed a clear size effects and anisotropy of the mechanical properties at this length scale. Both axial and transverse samples revealed higher strengths than the ones measured on the macroscale by a factor of 2.5, highlighting the hierarchical organization of bone tissue. Interestingly, the anisotropy was found to be more pronounced in tension than in previous compression tests.

### An Explicit Micro-Finite Element Model of Trabecular Bone (with RMS)

The ability to simulate the post-yield behavior of trabecular bone under large deformations would help in predicting damage in osteoporotic bones and at bone-implant interfaces. For this purpose, an explicit micro finite element (μFE) approach was adopted and an isotropic, elasto-plastic model with distinct yield and ultimate strains was implemented. Element deletion was triggered after reaching the ultimate strain criterion, which produced damage in the form of a stiffness reduction. The method was applied to 3 human trabecular bone samples of different BV/TV using 13 monotonic load cases. An apparent quadric strength surface for trabecular bone was successfully fitted in a normalized stress space.



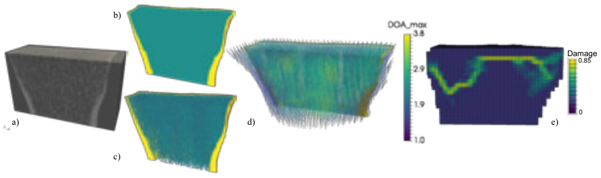

Micro-tensile stress strain behavior of ovine osteonal bone (left), high resolution secondary electron image of a micro-tensile specimen before and after loading (right)




Cyclic normalised stress-strain curves for trabecular bone in compression and tension using explicit finite element analysis

### Normative Database of HR-pQCT-Based Bone Strength Assessment by Homogenized FEA in the Healthy Swiss Population (with EUT, PO and VUT)

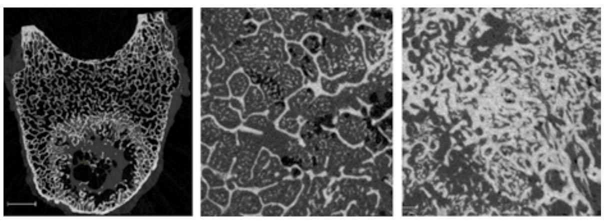
High-resolution peripheral quantitative computed tomography (HR-pQCT) reconstructions enable the application of finite element analysis (FEA) to compute bone strength, which is clearly associated with fragility fractures in postmenopausal women. Recently, a new homogenized FEA approach was developed to reduce evaluation time by improving the computation of fabric and the superposition of material properties in mixed elements. The current project aims to determine in vivo precision of the methodology using a calibration phantom, but a clinical study (NODARATIS) providing a normative database for radius and tibia strength in the healthy Swiss population is currently conducted by our clinical partner (PO).




HR-pQCT image (a) with segmentation of cortex (b) and trabeculae (c) to extract main orientation or fabric (d) and finite element analysis to estimate failure load of the wrist

### Strength of Metastatic Vertebral Bodies (SNF grant #165510 with HMS)

Metastatic bone disease can lead to pathological fractures which are, especially in the spine, a major clinical concern. Only little is known about the material properties of bone tissue in the vicinity of metastatic lesions. In addition, clinical grading scales were shown to have limited sensitivity in estimating fracture risk of metastatic vertebrae. Accordingly, the aim of this project is to analyze the mechanical properties of metastatic bones at the tissue (nanoindentation) and organ (bio-mechanical test of entire bones) level. With the insight gained from the experiments, micro-CT based finite element models are generated and validated. These models can potentially be used in the future to identify metastatic bones at risk of fracture and thus help to induce the appropriate treatment.



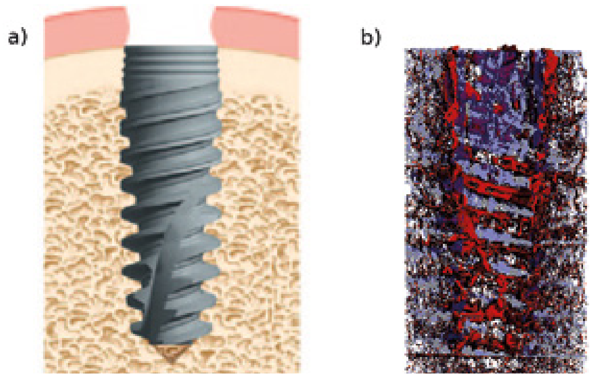
Lytic (left), normal (center) and blastic lesions (right) in metastatic vertebrae

### Non-Linear Models of Mineralized Collagen Fibril Arrays (with HWU)

Recent small-angle X-ray scattering (SAXS) and wide-angle X-ray diffraction (WAXD) experiments revealed small mineral and collagen strain ratios with respect to the apparent strain during micropillar compression of mineralized turkey leg tendon (MTLT). The aim of this starting project is to develop 1D analytical and 3D finite element models of mineralized collagen fibrils embedded in a mineralized matrix of non-collagenous proteins that deliver an apparent elastic modulus, ultimate stresses and constituent strain ratios that are compatible with experimental observations. Results aim to provide further insights for computational fracture risk prediction of bone tissue.

### Peripheral Trabecular Bone Compaction and Primary Stability of Dental Implants (with NB)

Primary stability is a key metric to decide upon immediate or postponed loading of a dental implant after surgery. To assess primary stability, understanding of the biomechanics of the bone-implant interface becomes indispensable. Different drilling protocols and various design features of a dental implant were investigated in bovine trabecular bone. The pilot holes were drilled and the implants were inserted with instrumented tools. The bone-implant systems were imaged with μCT and tested mechanically to quantify primary stability. The μCT images revealed the spatial extent of trabecular bone compaction, while both stiffness and strength were clearly dominated by the surrounding bone volume fraction (BV/TV).




Compaction of trabecular bone around a dental implant using subtractive μCT imaging

### Biomechanical Testing

Several biomechanical experiments were conducted in the laboratory for internal projects and industrial contract research. To help improve treatment of scoliosis, we tested the material of an experimental 3D printed corset with different mesh sizes in tension. This nylon PA 12 material was stiffer and reached higher ultimate forces than the standard polyethylene material. Biomechanical tests were also performed within a master's thesis with the aim to validate mutually the location and intensity of microdamage between a bone overloading experiment and its simulation by non-linear micro-finite element analysis (microFE). The results supported the hypothesis that a weak but statistically significant relation exists between them.

## Selected Publications


Panyasantisuk Jarunan, Dall'Ara Enrico, Pretterklieber Michael, Pahr Dieter, Zysset Philippe, "Mapping anisotropy improves QCT-based finite element estimation of hip strength in pooled stance and side-fall load configurations", Med Eng Phys, 59:36-42, 2018

Ovesy Marzieh, Voumard Benjamin and Zysset Philippe, "A non-linear homogenized finite element analysis of the primary stability of the bone-implant interface" Biomech Model Mechanobiol, 17(5):1471-1480, 2018

# Tissue and Organ Mechanobiology

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### Research Profile

The Tissue & Organ Mechanobiology (TOM) Group of the Institute for Surgical Technology and Biomechanics (ISTB), University of Bern, conducts translational research in the intersection of tissue engineering, biology and applied clinical research. The group's primary aim is to understand the cellular response onto biomechanical stimuli and how cellular communities are affected in situ using 3D tissue and organ culture models. Our research can be divided into two main foci: On the one hand the group investigates causes of low back pain due to intervertebral disc (IVD) degeneration and on the other hand the group focuses on the human knee where they aim to identify cell-based solutions for the non-healing or delayed ruptures of the anterior cruciate ligament (ACL). The common focus of the TOM group is to advance *in vitro* organ culture models, which match closely the human situation and where regenerative therapy strategies, such as novel biomaterials and cells, can be tested in a most authentic in vitro set-up.

### Low Back Pain and Intervertebral Disc Degeneration and Regeneration

The TOM group conducts research in two main directions: i) IVD research in the area of regeneration using biomaterials and stem cells and ii) in the area of non-successful spinal fusion and possible involvement of pseudo-arthrosis. For the first research area we use a combination of 3D tissue and organ culture approaches. The research of the second focus is the understanding of the balance between BMP agony and antagony. Besides the investigation of the exogenous stimulation of BMP antagonists on mesenchymal stem cells (MSC) and osteoblasts, the main focus lies on the observation of the interaction between IVD cells and osteoblast, by performing co-cultures.

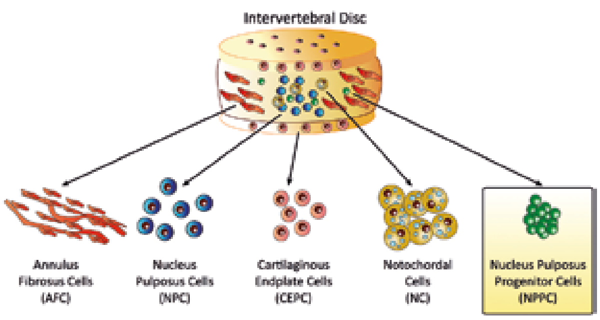
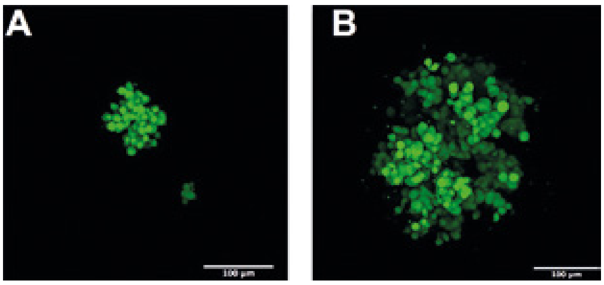



Image illustrating the four "classical" cell populations previously characterized in the intervertebral disc. In yellow on the right are the newly detected Tie2+ nucleus pulposus progenitor cells (NPPC).

In a Gebert Rüf financed project a fiber-reinforced hydrogel was tested in a physiologically clinically relevant organ culture model by cross-linking the fibrin mesh with genipin. Therefore, a healthy control, an injured IVD (2 mm biopsy punch) and the repaired IVD were tested, and histology was performed to visualize the injury and integration of the novel silk and fibrin hydrogel. These results were recently reported in the Journal of Functionalized Biomaterials and in the European Spine Journal.

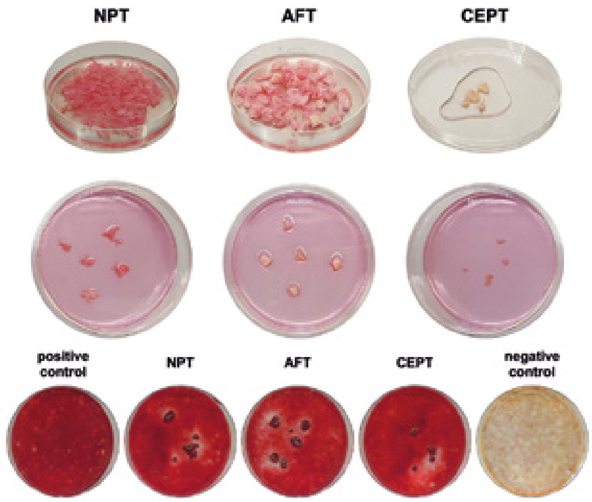



Confocal Laser Scanning Microscopy of A) nucleus pulposus progenitor cells (NPPC) and B) nucleus pulposus cells (NPC) after seven days of colony unit forming assay in a viscous medium. NPPC do result in more dense and spherical colonies whereas NPC form more lose and wider spread colonies. Cells were stained with a live dye in green. Scale bar = 100 µm.

Recently, autochthonous progenitor cells were detected in the human IVD, which could lead the path to cell therapy. Here, we concentrated on the most suitable isolation protocols to "fish" nucleus pulpous progenitor cells (NPPC) from the total population of cells in the bovine coccygeal disc. We also focused on their multipotency capacity and their application for IVD repair. Future research is to understand how these cells can be best isolated and whether these cells can be maintained in vitro to regenerate the IVD. Furthermore, it would be highly desirable to investigate how induced pluripotent stem cells (iPSC) could be used for IVD repair. This is the main aim in an upcoming Horizon 2020 Project named "iPSpine" starting in 2019 for three years in collaboration with internationally well-known scientists and experts in the field of engineering, biomaterials and biomechanics.

**Biological Repair of the ruptured Anterior Cruciate Ligament**
In Switzerland, the incidence of ACL ruptures is estimated at 32 per 100,000 in the general population and even more than double in the sports community. The current gold standard for ACL repair is reconstruction using an autograft, however, this approach has shown some limitations. Here, cell-based approaches using collagen patches or the application of platelet-derived plasma (PRP) are of interest for the clinical application.

**Reducing the Senescence in Mesenchymal Stem Cells**
Stem cell therapy faces the problem of the necessity to rely on fetal bovine serum (FBS) for cell expansion, which proved to have major disadvantages for application in the clinics. Additionally, MSC undergo senescence during expansion in vitro, which impairs their therapeutic potential. Here, alternate serum-free media formulations were investigated in terms of cell proliferation and differentiation potential, which could make their way to a GMP-compliant solution.




Human mesenchymal stromal cells (hMSC) were seeded in 100 mm Petri dishes and cultured until they reached 90% of confluency. Human intervertebral disc (IVD) explants (tissue of the nucleus pulposus (NPT), annulus fibrosus (AFT) or cartilaginous endplate (CEPT), 2-5 $mm^3$) were cultured in direct contact with the hMSC in osteogenic medium (lacking bone morphogenetic protein 2). Top row: preparation of tissue. Middle row: Contribution of human NPT, AFT and CEPT on the top of hMSC monolayer. Bottom row: Alizarin red staining of direct culture after stimulation of 21 days with osteogenic medium (except negative control) and co-cultured with NPT, AFT and CEPT. Proof-of-concept of inhibitory effects (N = 1).

## Selected Publications

Frauchiger DA, May RD, Bakirci E, Tekari A, Chan SCW, Wöltje M, Benneker LM, Gantenbein B, Frauchiger D, May R, Chan S, Benneker L (2018) Genipin-Enhanced Fibrin Hydrogel and Novel Silk for Intervertebral Disc Repair in a Loaded Bovine Organ Culture Model. J Funct Biomater 9(3):40. doi: 10.3390/jfb9030040

Frauchiger DA, Heeb SR, May RD, Wöltje M, Benneker LM, Gantenbein B. Differentiation of MSC and annulus fibrosus cells on genetically engineered silk fleece-membrane-composites enriched for GDF-6 or TGF-β3. J Orthop Res 2018; 36:1324-1333 DOI: 10.1002/jor.23778

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Sakai D, Schol J, Bach FC, Tekari A, Sagawa N, Nakamura Y, Chan SCW, Nakai T, Creemers LB, Frauchiger DA, May RD, Grad S, Tryfonidou MA, Gantenbein B (2018) Successful fishing for nucleus pulposus progenitor cells of the intervertebral disc across species. JOR Spine 2018e: doi: 10.1002/jsp2.1018

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## Selected Conference Contribution

Gantenbein B. Invited Keynote: Repair of the Intervertebral Disc using Biomaterials and Progenitor Cells, in Proceedings of Biospine Asia Pacific, 26-28 April 2018, Seoul, South Korea

## PhD theses

Daniela Frauchiger, "Engineered Silk, Reinforced Hydrogel and Progenitor Cell Therapy for Intervertebral Disc Repair", PhD in Biomedical Engineering, Medical Faculty, GCB University of Bern., February 2018

Simon Wüest, "Cartilage Tissue Engineering and Electrophysiological Recordings on Microgravity Platforms", PhD in Biomedical Engineering, Medical Faculty, GCB University of Bern, June 2018

# Mechanical Design and Production

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**Urs Rohrer**


Fabio Spena


Simon Lüthi


Danaël Gasser


Dominic Seibold


Alexander Macpherson


Dominik von Ah


Daniel Germann

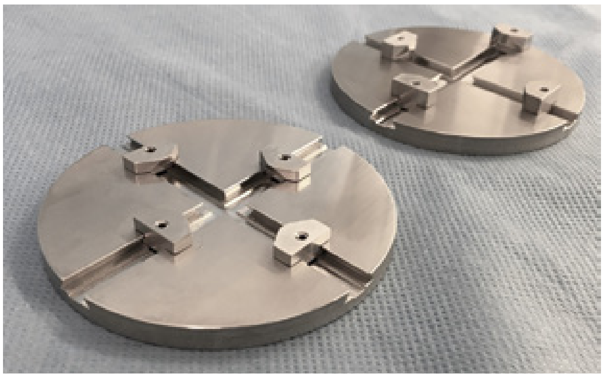

Lukas Rufener

**Group 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 ISTB and 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. We also support industrial and academic external research collaborators with their mechanical design and production needs.

**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.
In 2018, we made one trial apprenticeship and elected Janosch Schär as our new apprentice and he will begin his 4-year training next year on 1st of August as a Polymechanic EFZ apprentice.
For students at the ETH Zürich on the department for machine engineers, it's mandatory to have an industrial practical training at least for five weeks. This year we performed this training with Dominic Seibold and Alexander Macpherson. It was a very instructive and successful training and we wish them a lot of success in their studies.
Due to a high demand of workload, we recruited Dominic von Ah, Daniel Germann and our former apprentice Lukas Rufener as alternative civilian-service employees. They performed administrative tasks and increased the productivity of our team and we thank them for the work they have accomplished in our workshop.

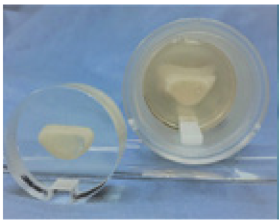
**Research Equipment Design & Manufacturing ISTB**
As expected, the requirements of a machine shop supporting research in the biomedical engineering field are as diverse as the research field itself. The variety of subjects researched in the ISTB yield a number of diverse design and production requests 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 illustrations highlight a few of this year's projects.

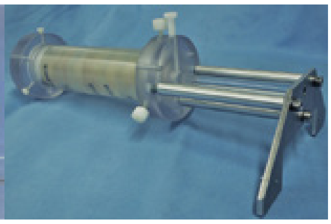
**Project: MB-Groupe, Additional Equipment for the Lap-machine**
The Musculoskeletal Biomechanics group has bought a lap-machine and they need some special additional equipment. For example this two clamping devices that make it possible to clamp different samples to the machine and to treat the surface in a very fine roughness and flatness. The device plate ground surface must have the same roughness and flatness as later the samples have, and must be plane-parallel 0.005mm (5µ), because the sample holder of the lap machine is working with a vacuum system.



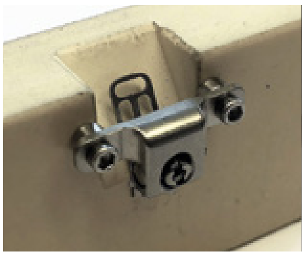
**Project: MB-Group, Calibration Phantom for Radius Bone Samples**
The calibration phantom was developed in cooperation with Denis Schenk from the musculoskeletal biomechanics group and was manufactured in our machine shop. The phantom can contain up to six samples. With the CNC milling machine, each sample got an indentation fitting

the bar fixed within the tubular sample holder to always ensure correct repositioning of the samples. The correct repositioning is important because the phantom will be sent to other centers in Switzerland or abroad to compare the results or calibrate different HR-pQCT* scanners.
*High-resolution peripheral quantitative computed tomography



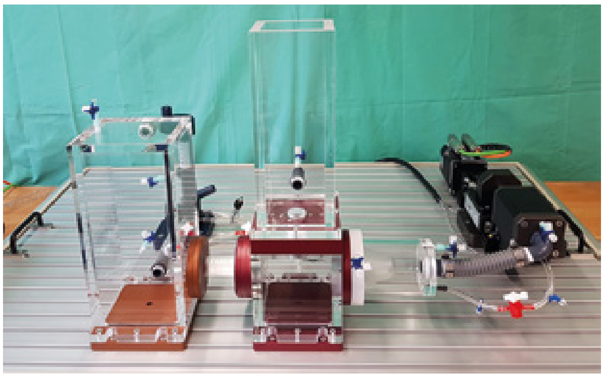


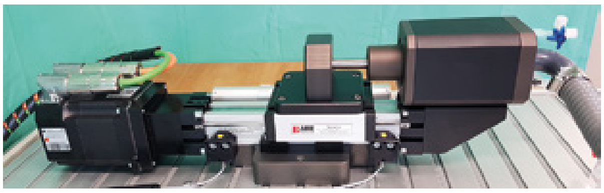
**Project: DBMR Cranio-Maxillofacial Surgery Groupe, Dental Plate**
Since 2007, we have a strong collaboration with Nikola Saulacic from the DBMR at the University of Bern, to develop devices in different shapes for studies in the field of bone growing. This year we developed some devices for the jawbone growing research. The big challenge was the manufacturing of the very small parts and also to assemble them under the microscope. Some parts were cut out with a laser beam and laser welded together in a partner company. We produced all other parts on our CNC-milling machine and CNC-lathe.

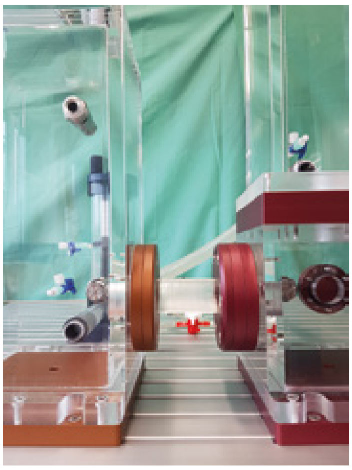


**Mechanical Design & Production ARTORG**
The workshop at the ARTORG Center was managed by Danaël Gasser as a full-time polytechnician. He manufactured some different project parts, mainly for the CVE (Cardiovascular Engineering) and IGT (Image Guided Therapy) groups.
His function was to design parts of devices himself and to manufacture these parts afterwards. The ARTORG workshop pursues many of the same aims as the MDP group at the ISTB. The partnership between the two groups has grown and strengthened as a "core facility" sharing work and knowledge.
The highlight of this year projects is shown in the following illustration.

**Project CVE: Left-heart pulse-duplicator system**
In collaboration with the EPFL (L'Ecole polytechnique fédérale de Lausanne) at Neuchatel we developed a new artificial blood flow loop system and a new pump device. The existing flow loop and its pump in our lab had some problems with the piston guidance and was leaking. For this reason, we have successfully developed a new pump piston guide concept. The whole system was mounted on a plate so that it can be transported and easily moved. A new type of tube connection for different artificial aortas allows for an easy exchange of the vessel phantoms, and the two flow chambers are longitudinally displaceable to adjust the test section to different phantom lengths.








Operationssaal, Universitätsklinik für Viszerale Chirurgie und Medizin, Inselspital
(Foto: Pascal Gugler für Insel Gruppe AG)

# INSELSPITAL, BERN UNIVERSITY HOSPITAL

The Inselspital – Bern University Hospital remains a major focal point of the activities of the BBN. The decision in 2018 by the Swiss Federal Government to approve a further 100 medical school places in the Medical Faculty of the University of Bern confirms the confidence in the quality of the medical education delivered by the Inselspital and the Medical Faculty of the University of Bern. And these new medical students will be part of a very special environment in the domain of biomedical engineering research. Biomedical engineering researchers can be found in the clinics and operating rooms of the Inselspital and junior and senior clinicians join the technical research teams in the BBN. These close and successful technical and clinical collaborations are showcased in this edition's contribution of the Inselspital to this report.

At an institutional level the Inselspital has built and maintained close ties to individual partners of the BBN. The progress and milestones of the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel AG) of the last two years are also the accomplishments of the Inselspital. As the founding partner of sitem-insel, the Inselspital is essential for all translational activities. It hosts the sitem-insel on the Inselspital campus and provides resources through the sitem-insel Enabling Facilities, for example the Translational Imaging Center Bern - home to a 7 tesla UHF MRI device.

In the area of digitization in medicine the Inselspital will be at the forefront of harnessing the power of high-quality, curated clinical data. The Insel Data Coordination Lab that manages access and governance of patient data by researchers, and the Insel Data Science Center which will be the data research hub, are building blocks for the Inselspital's data science-driven research collaborations within the BBN and beyond.

The interdisciplinary research aspirations of the Inselspital connect clinicians, engineers, computer scientists, life and physical scientists in the largest University Hospital setting in Switzerland. This unique network of stakeholders will continue to investigate and translate credible technical solutions to unmet challenges in diagnostics, therapeutics and rehabilitation.

Matthias Gugger
Director Teaching and Research

# Insel Data Science Center (IDSC)

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Andrea Wermuth

## Clinical and Research Partners

All clinics of Insel Gruppe AG, ARTORG, SITEM, SPHN

### Research Profile

The Insel Data Science Center (IDSC) is a newly formed interdepartmental entity of the Insel Group, in operation since October 2018. The IDSC's mission is to organize all INSEL data and to make it accessible and useful. 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 (data protection). We conduct research projects in the field of data science in close collaboration with the involved clinical departments or directorates. Besides research partnerships, we closely cooperate with the industrial sector to shape the development and translation of technology right at the forefront. We establish a core competency in medical data science and participate in teaching digital medicine.

The activities of the IDSC are organized in three product lines: research, medicine and management. Our interdisciplinary team comprises of medical experts, data engineers, data scientists, biomedical imaging specialists, data warehouse specialists and software developers.
Our vision is to be Europe's leading clinical data science center in artificial intelligence and mixed reality.

### Swiss BioRef: Personalized Reference Values for Precision Medicine

Reference values for laboratory tests are crucial to define pathological or disease states as well as treatment thresholds. Since they depend on many factors, including patient-related variables (e.g. sex, genetic background) and sample-related variables (e.g. mode of collection, storage), definitions of "medical norms" may vary across disciplines and contexts. With the rise of personalized medicine, the concept of "classical" reference ranges has become outdated, since comparing a patient to a more or less adequate "healthy" control population cannot take into account intra-individual thresholds of what for a specific patient might be a "normal" or "healthy" state. Especially in a population increasingly suffering from a wide range of comorbidities, normal testing results might be an exception and not even be desirable. To properly assess a patient's measurements, it is important to take the whole spectrum of potential sources of bias, comorbidities and confounders into account and to generate personalized "target values" we would expect from a healthy "digital twin" of the specific patient. Algorithms to derive subsets of such values from e.g. hospital cohorts are already in place, however, for robust statistics and reliable estimates, numbers of patients are needed that necessitate inter-institutional data collation and joint computation.

To address these issues, an Infrastructure Development Project «Swiss BioRef: Personalized Reference Values for Precision Medicine» is carried out in cooperation with the Geneva University Hospitals, the Swiss Paraplegic Research (SPF) in Nottwil, the University Children's Hospital Zurich and the University Hospital of Lausanne (CHUV). The project is headed by the Inselspital, with PD Dr. med. Alexander Leichtle, Head of the Product Line Research (Directorate of Teaching and Research) and senior physician at University Institute of Clinical Chemistry (UKC) being the Principal Investigator, and is supported during 12 months by a fund of the Swiss Personalized Health Network (SPHN).

With the Swiss BioRef we openly connect a wide spectrum of representative cohorts at the IDSC in Bern, providing HPC infrastructure, laboratory-specific knowledge and a statistical skillset for this task, utilizing the SPHN infrastructure as a service platform for anonymized data exchange. We will build an interactive web-based platform within the SPHN that allows the application of the underlying algorithms on cohort specific datasets and visualized result queries for specific patient data submissions.

### MedCo: Enabling the Secure and Privacy-Preserving Exploration of Distributed Clinical and *Omics Cohorts in the SPHN

Current tools do not provide sufficient privacy and security guarantees to allow for sharing sensitive and identifying data, such as for example *omics data, among different clinical sites. MedCo is a SPHN/PHRT (Personalized Health and Related Technologies) co-funded Infrastructure Development Project fostering the development of a distributed cohort explorer solution for SPHN care providers, which allows for sharing health-related data in a secure, ethical and transparent way. In the past two years, CHUV and EPFL have jointly developed a new open-source system named MedCo that integrates current cohort explorers and enables investigators to explore, under strong privacy and security guarantees, *omics and highly identifying clinical data stored at different clinical sites. To achieve this, MedCo uses state-of-the-art data protection techniques such as homomorphic collective encryption and differential privacy. However, despite its great potential, MedCo is still too immature for being adopted in clinical operational settings. The goal of this project is very practical: advancing MedCo from its current academic prototype version to a production-ready version to be deployed in the SPHN in order to make it the de-facto software solution for exploring sensitive and identifying medical data.

**Disease Classification**

Disease Classification through ICD-10 coding is an essential pillar of modern medicine and enhances the mutual understanding of diseases. ICD coding allows a structured collection of clinical data for therapeutic decisions, research and economic analysis. In the busy clinical routine however, physicians do not have time to complete their reports with ICD-10 codes. For inpatient hospitalizations, ICD coding is usually performed by coding professionals. In contrast, outpatient reports often lack standardized encoding, hampering not only an efficient review of past cases, but also the availability of data for research and analysis, as well as an accurate inclusion of patients in clinical trials.

Our Medical Data Analysis Team aims to facilitate the process of medical coding of outpatient cases by applying machine-learning methods that automatically analyze past human-coded discharge reports of inpatient cases and that learn to apply appropriate ranges of ICD-10 codes to an uncoded full-text report. To get an understanding of what is contained in the data, explorative data analysis takes a deep dive into the metadata available from the clinical case the discharge report belongs to. Descriptive statistics are used to visualize data types as well as metadata structure, distribution and content. The data is re-encoded into so-called features to make its most informative parts most prominent. The frequency distribution of words within one report, the so-called bag of words, is often a good fingerprint of the category of text and can be used for coarse document classification.

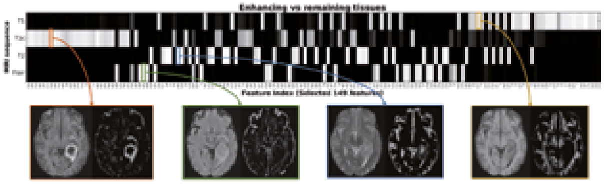
A Random Forest classification model is applied to the bag of words of the medical narrative, as well as to the respective case, patient and lab measurement data. Although this model is found to capture several codes fairly well (60% chance of predicting the correct main diagnosis; correctly predicting 25% of all report codes), it can inspect texts only on the word-frequency basis and confuses very similar diagnoses.

State-of-the-art NLP deep neural networks can help to overcome these limitations: using a novel method called word embedding, a deep neural network model can learn to predict ICD-10 codes only from the textual part of the report. High dimensional representations of single words encode their semantics and thereby allow the model to understand text meaning and to quantify word similarities. In contrast to the Random Forest model, this deep neural network model is able to capture word order and as a result, to also understand negation and – to a certain degree – medical context. Consequently, it outperforms the Random Forest model in predicting the correct main diagnosis and the overall set of diagnoses (74.1 % vs. 60 % and 48.3% vs. 25%, respectively). Since the developed model is not overly specific to the ICD-10 coding of medical reports, its conceivable scope of application is fairly broad: It can help to context-independently tag or label text components, to highlight text segments relevant to a topic and to propose topics missing from reports, and could be of help in many other medical contexts as well.

**Accurate and Robust Human+Machine Intelligence for Medical Image Analysis**

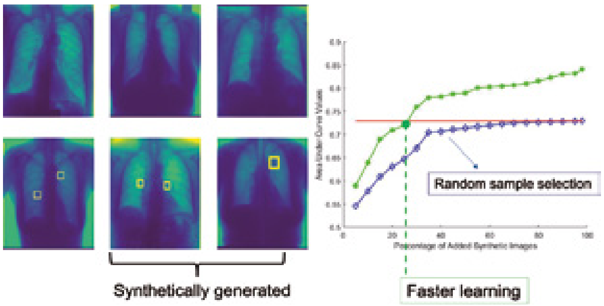
The Healthcare Imaging A.I. group has developed several methodologies to analyze MRI images with focus on multimodal image segmentation for brain image lesion analysis studies. These developments are driven by clinical requirements such as computation speed, robustness, and use of standard clinical imaging protocols. Through a strong interdisciplinary collaboration with the department of neuroradiology, at the University Hospital, Bern, our group has developed accurate and clinically-relevant solutions based on machine learning methodologies for automated brain tumor segmentation, stroke lesion segmentation, and multiple-sclerosis lesion segmentation, which have ranked among top-approaches at MICCAI (Medical Image Computing and Computer-Assisted Interventions) challenges, top-venue of the medical image computing field. Our seminal work on automated brain tumor volumetry was awarded the Young Scientist Publication Impact Award 2016, in recognition for being the most-impactful MICCAI work of the last five years, as well as the Ypsomed Innovation Award 2016.

Next to accuracy, the robustness of computer-assisted technologies is fundamental in medicine. To this end, our group is developing algorithms that check the reliability of machine learning's results by yielding uncertainty estimations of computer-generated results, which can be used so medical experts are no longer executioners of the task (e.g. brain tumor delineation) but use this information to monitor and correct them in a time-effective manner. In addition, as the amount of collected medical image information is rapidly growing, it is vital to develop Human-Machine Interfacing technologies (HMI) to ensure scalability of time-effective monitoring and correction technologies of computer-generated results. Our group is researching methodologies to enhance the interpretability of machine learning models, so their decisions can be inspected, and interpreted by a human operator.




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

We develop techniques for focused active learning, enabling fast learning rates of deep learning technologies for image segmentation and image classification. The approach utilizes measures of uncertainty of computer-generated results to focus on difficult learning areas of an image.




Focused Active Learning. Exploiting sample informativeness and synthetic data augmentation enables a faster learning (see slope of green curve) versus standard active learning approaches (blue curve), and an improved use of the information compared to the performance obtained when training with all available data at once (red line).

Our group is establishing technologies for automatic Quality Assessment (Q.A) of curated imaging data, as well as the reliability of the produced machine learning models. We initiated a Swiss-wide initiative to create infrastructure and technologies for a local and distributed radiomics platform. By leveraging the daily clinical workflow with human+machine intelligence technologies, we aim at creating a rich and sustainable symbiosis between daily clinical needs, and the data curation process needed for the development and improvement of A.I. technologies.

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# Inner Ear Research Laboratory

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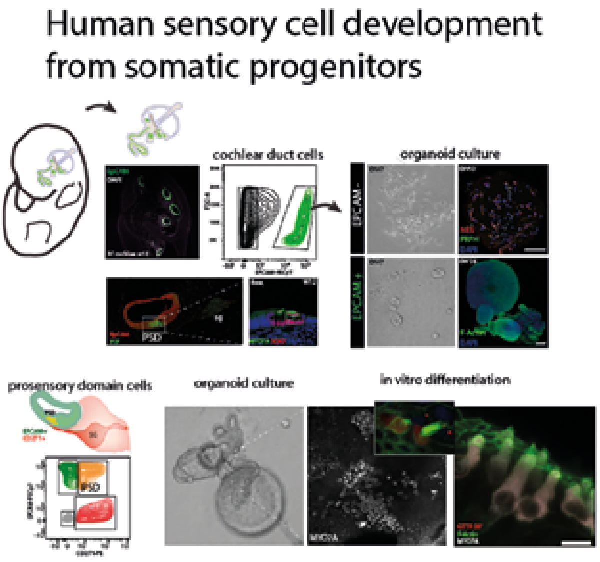
Otostem (www.otostem.org) Members: Stefan Heller, Dept. of Otolaryngology, Head & Neck Surgery and Institute for Stem Cell Biology and Regenerative Medicine Stanford University School of Medicine, CA

### Research Profile

Our group aims to understand basic mechanisms that control sensory organ development, degeneration, and regeneration in order to develop novel therapeutic strategies for hearing loss. Sound perception in mammals relies on the function of highly specialized mechano-sensitive hair cells located within the cochlear sensory epithelium. Hair cells act as primary sound receptors. In turn, they activate sensory neurons of the spiral ganglion, which relay the signal to the brain stem and further to brain centers for interpretation. Due to the lack of proliferative and regenerative capacity of the sensory organs, loss or damage of hair cells and spiral ganglion neurons results in permanent hearing impairment. Disabling hearing loss affects 360M people worldwide and has a negative impact on the quality of life of those affected and presents a high socio-economic burden. The lack of knowledge relative to human sensory cells specification and the absence of tools to study human hair cell in vitro represent a major bottleneck for the development of causal therapies for hearing loss. In order to overcome these limitations, we have developed two complementary strategies aiming at deriving sensory cells types from pluripotent stem cells (PSC) and somatic progenitors. In addition we are assessing novel strategies to trigger tissue regeneration.

### Human inner ear development and cochlear organoids cultures

We have recently characterized the molecular signature of the developing human inner ear. Moreover, we have developed novel strategies to purify cochlear progenitors and optimized 3D culture conditions that allow for their in vitro expansion and differentiation to functional hair cells (Roccio et al Nature Communications 2018). This strategy allows for the first time to probe mechanisms of sensory cell degeneration and regeneration in human native hair cells in vitro. We will continue this line of research by refining the culture conditions for expansion of somatic progenitors, as well exploit single cell sequencing for a deeper and unbiased characterization of the developing sensory organs. These data sets will be used to benchmark the sensory cell types derived from differentiation of PSCs, as above, and to optimize the current protocols.

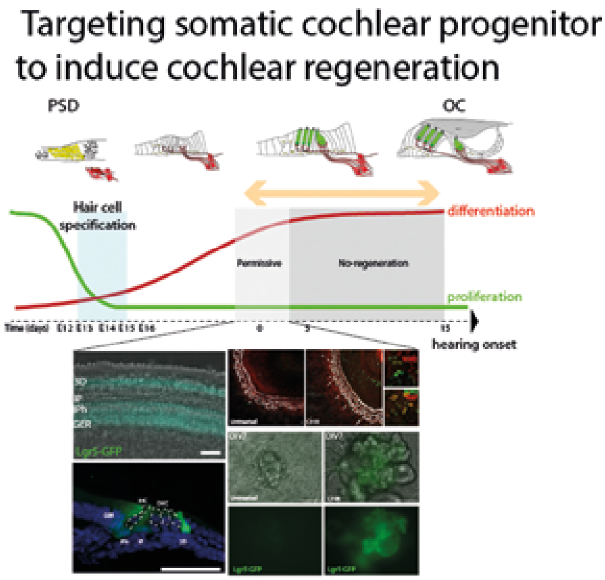



*Figures adapted from Roccio et al. Nature Communications 2018.*

### Cochlear Regeneration

Despite some recent evidence demonstrating that the early postnatal murine sensory epithelium harbors a population of progenitors that could be experimentally triggered to differentiate into hair cells, therapeutic strategies aimed at tissue regeneration are still in their infancy. We have shown that activation of Wnt signaling can induce cell cycle re-entry of supporting cells in the sensory epithelium, while Notch signaling inhibition induced trans-differentiation of supporting cells to hair cells in vitro (Roccio et al Scientific Report 2015). Small molecule inhibitors targeting Wnt and Notch signaling are currently being tested in vivo in animal models of sensorineural hearing loss. In collaboration with the institute of infectious diseases at the University of

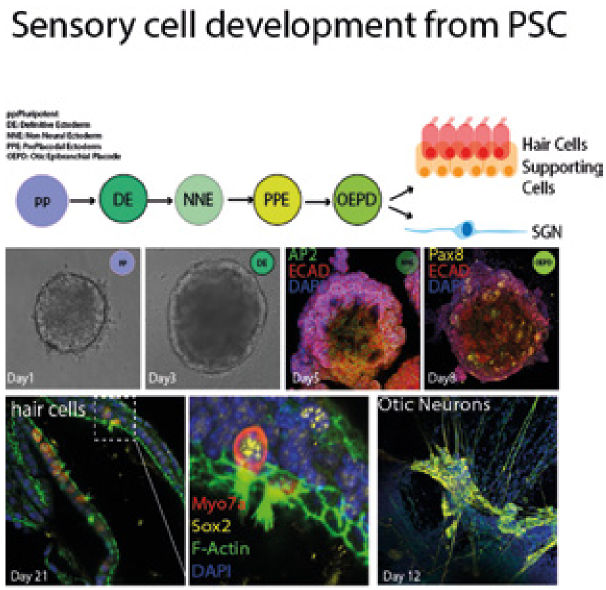
Bern (Group Leib), and the small biotech company Audion Therapeutics, we are currently assessing hair cell regeneration in an animal model of bacterial-meningitis-induced hearing loss (Perny et al. Journal of Neuroscience 2016 and Erni et al. In preparation). Future research directions include a refined molecular analysis of the mechanisms that prevent plasticity and regeneration and the assessment of novel strategies of tissue reprograming and de-differentiation to elicit a regenerative response.




*Figures adapted from Roccio et al. Scientific reports 2015. & Roccio et al. Nature Communications 2018.*

**Derivation of inner ear sensory cell types from pluripotent stem cells**

We have established culture conditions, so called "inner ear organoids," where PSC can be efficiently guided through the steps of otic development by small molecules and growth factors and differentiated to hair cells or spiral ganglion neurons in vitro (Perny et al Frontiers in Cellular Neuroscience 2017). Future research will focus on developing inner ear organoid models from human PSC to study in vitro organ development, genetic mutations causing hearing loss, drug ototoxicity, and therapeutic strategies.




*Figures adapted Perny et al Frontiers in Cellular Neuroscience 2017.*

### Selected Publications

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# Magnetic Resonance Spectroscopy and Methodology DBMR-DIPR

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### Research Profile

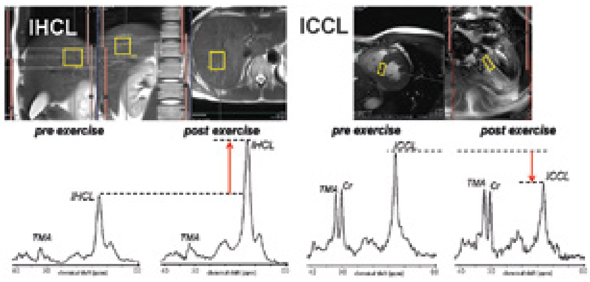
Magnetic resonance imaging (MRI) and spectroscopy (MRS) are powerful and extremely versatile methods for non-invasive studies and diagnostic examinations in humans. Our group is using these MRI and MRS methods in close collaboration with clinical partners primarily in prospective studies of different 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 (see Figure for effect of short-term exercise on ectopic lipid reservoirs in liver and muscle). In addition, high-resolution NMR studies are performed on biopsies, cell cultures, and body fluids.

### Teaching Profile

The AMSM participates in university teaching programs for students of medicine, chemistry, biochemistry, and biomedical sciences.

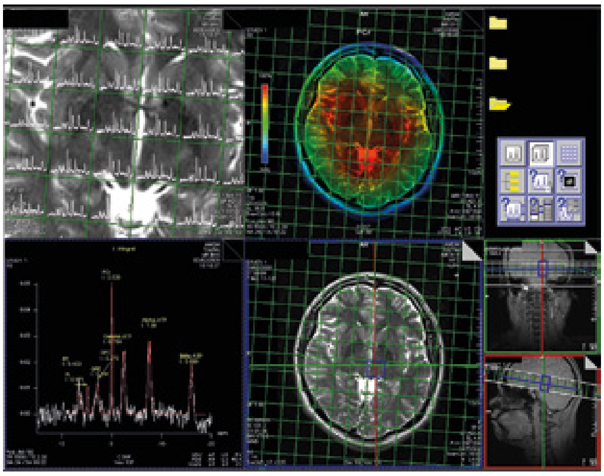
### Brain Physiology

A newly started SNF grant aims at the development of MR methods and synergistic post-processing methods that are tailored to the observation of brain metabolism, yet are also transferable to other organs. In collaboration with the ETH and University of Zurich, as well as the MPI in Tübingen, exchange processes between amide protons and water are studied in human brain at the highest field strengths available for investigation of human subjects. MRS is optimized for evaluation of systemic brain diseases and for optimal reproducibility in longitudinal studies. Diffusion properties of brain metabolites are investigated with dedicated methodology in collaboration with the Clinic for Neurology. A similar MRS sequence was also developed for the study of microstructure in brain and muscle.




### European Innovative Training networks (ITNs)

TRANSACT (TRAnsforming Magnetic Resonance Spectroscopy into A Clinical Tool) was an EU-funded Marie Curie Initial Training Network (http://www.transact-itn.eu/), which aimed at improving and automating MRS methods and post-processing tools so that the clinical use of MRS becomes more robust and widespread. The specific aim of our subproject was the definition and automatic recognition of spectral quality and clinical usability so that radiologists without specific methodological knowledge should be better able to use MRS in their routine. Machine-learning networks were shown to yield similar accuracy as human experts for quality assessment in spectra acquired for brain tumor assessments and deep learning was used for artifact detection. A follow-up ITN (Inspire-Med) was submitted and granted to focus on multi-parametric and multi-modal MRI/MRS and PET techniques in a European multicenter research and training network.

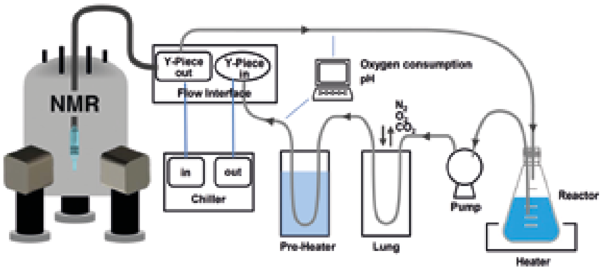


## Renal Function

Renal Function in native and transplanted kidneys has been investigated by multi-modal MRI and MRS in preparation of a Sinergia Grant. Renal function deteriorates after kidney transplantation for multiple reasons. The functional MR modalities differ in terms of sensitivity for cortical or medullary renal tissue and in their assessed determinants. We aim at a better perception of the physiologic basis behind functional MR-parameters and why they may be changed in renal disease. Reproducibility and comparability studies have been performed employing several functional MR methods, such as diffusion weighted imaging, arterial spin labelling, and oxygen-dependent MRI. In clinical studies, renal ectopic lipids were investigated by MRS and MRI, fMRI measurements were performed for the Bernese renal biopsy registry, or the impact of functional kinking of iliac arteries on perfusion and oxygenation was investigated.

## High-Resolution Magic Angle Spinning NMR

Since MR spectra in vivo have a limited spectral resolution, high-resolution magic angle spinning (HR-MAS) NMR techniques were applied to correlate spectra of tissue and body fluids in vivo and vitro. HR-MAS makes NMR spectroscopy applicable also to semi-solid materials including biological tissues or cell cultures, which under static conditions yield only poorly resolved NMR spectra providing only little information.
HR-MAS allows for metabolically characterization of tissue types like brain, muscle, prostate, breast, liver, or kidney. Several HR-MAS studies have been performed on biopsies like muscle or sheep brain as well as on cell cultures and analyzed by statistical "metabonomical" methods. Most recently, a Bioreactor was established for investigating metabolic responses of living cells inside the NMR upon challenges in real-time.




Bioreactor for online Metabolomics of living cells inside the NMR.

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Vermathen M, Müller J, Furrer J, Müller N, Vermathen P. 1H HR-MAS NMR spectroscopy to study the metabolome of the protozoan parasite Giardia lamblia. Talanta. 2018 Oct 1;188:429-441. doi: 10.1016/j.talanta.2018.06.006. Epub 2018 Jun 5

# Division of Medical Radiation Physics within Department of Radiation Oncology

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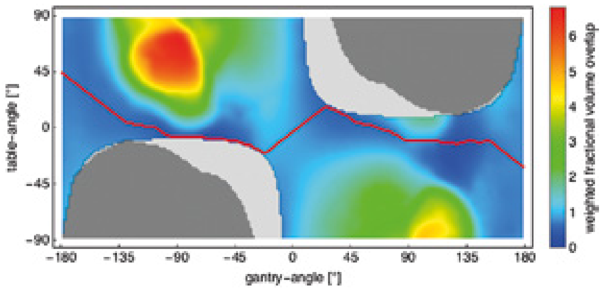
Andreas Raabe, Director and Chairman of Department of Neurosurgery, Inselspital, Bern University Hospital
Stefan Weber, Chair Image Guided therapy and Director, ARTORG Center, University of Bern

### 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 in 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 have to be established and validated before being used 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 transferred to commercial products and clinical applications.

### Dynamic Trajectory Radiotherapy (DTRT)

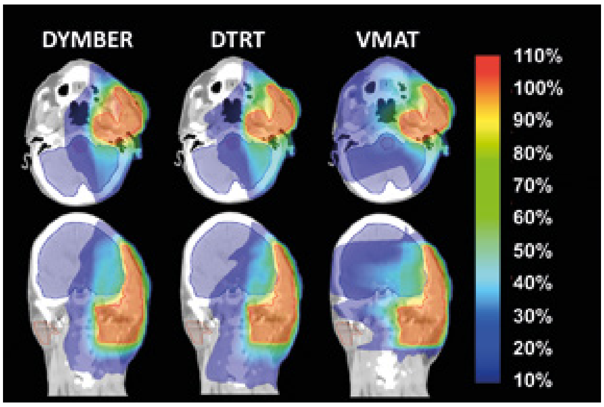
While over the last years, intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) have become the common standard, there are some dosimetric limitations associated with these techniques. One of them is based on the fact that typically these techniques are performed in a coplanar beam arrangement around the patient. Our research addressed this issue and developed optimization and verification solutions for so-called dynamic trajectory radiotherapy (DTRT). By this means, the intensity-modulated photon beams are delivered while the table as well as the linear accelerator (gantry) are rotating.




Penalty map of combinations of gantry- and table-angles, which are used to define an optimal path (trajectory) for DTRT.

### Dynamic Mixed-Beam Radiation Therapy (DYMBER)

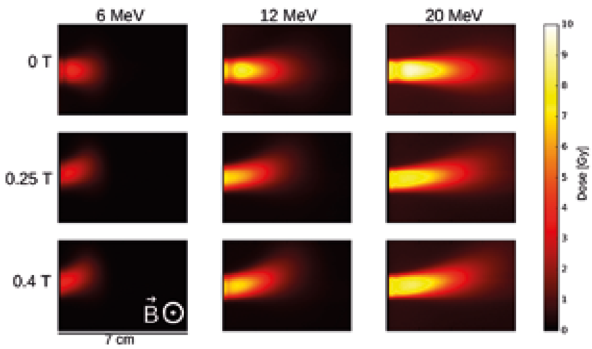
Over the last several years, our research activities aimed to optimize the dose distributions using mixed-beam radiation therapy approaches. For this purpose, photon beams and electron beams are optimized simultaneously. More recently, we combined dynamic trajectory radiation therapy (DTRT) with modulated electron radiotherapy (MERT) resulting in so-called dynamic mixed-beam radiation therapy (DYMBER). It could be shown that this approach has the potential to lead to improved dose distributions when compared to standard approaches like VMAT. Current investigations in our research group aim to bring these non-coplanar beam arrangements into clinical practice so that patients can benefit from these improved dose distributions.




Optimized dose distributions for different techniques, demonstrating the dosimetric benefit of DYMBER.

### Monte Carlo for Particle Transport Simulation in the Presence of Magnetic Fields

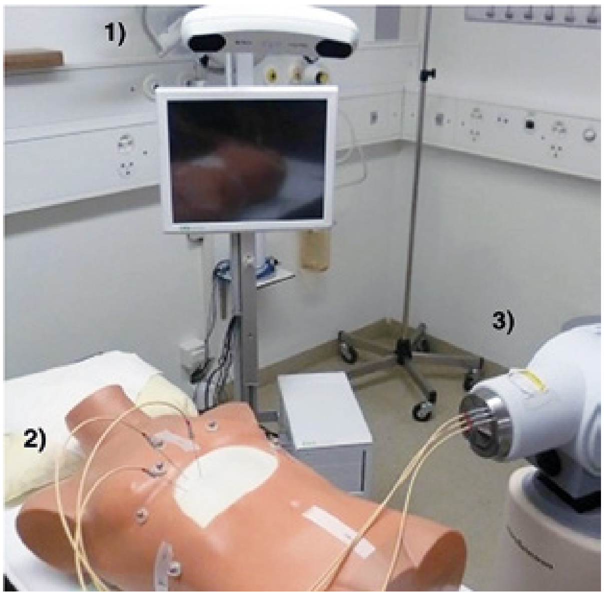
Accurate and efficient dose calculation is essential for treatment-planning purposes in radiation therapy. Monte Carlo (MC) simulations are commonly known as the most accurate method to perform this task. In recent years, linear accelerators were equipped with magnetic resonance imaging (MRI) leading to an increased complexity with respect to the task of accurate dose calculation. Our group works on this topic, and first investigations could be performed with a collaboration with University of Sidney (Australia) in the context of electron dosimetry.




Measured dose distributions for electron beams with different energies and for different magnetic field strengths.

### Improved Accuracy for Brachytherapy Applications

Accuracy is generally a key aspect in radiation therapy, and from that it is clear that the corresponding requirements are fairly strong and quality assurance plays an important role. For brachytherapy, since the inverse square law dominates the accuracy of the dose distribution, the positioning of the radioactive source is critical. In our group, we investigate several methods in order to cope with these challenges of correct positioning the sources, and we investigated a method that enables highly precise implantation of catheters into a patient using navigation guidance.




Experimental setup showing the navigation system 1), the phantom 2), and the brachytherapy system 3).

### Selected Publications

M.K. Fix, D. Frei, W. Volken, D. Terribilini, S. Mueller, O. Elicin, H. Hemmatazad, D.M. Aebersold, P. Manser, Part 1: Optimization and evaluation of dynamic trajectory radiotherapy, Med. Phys. 45(9), 4201-4212, 2018

S. Mueller, P. Manser, W. Volken, D. Frei, R. Kueng, E. Herrmann, O. Elicin, D.M. Aebersold, M.F.M. Stampanoni, M.K. Fix, Part 2: Dynamic mixed beam radiotherapy (DYMBER): Photon dynamic trajectories combined with modulated electron beams, Med. Phys. 45(9), 4213-4226, 2018

P. Manser, D. Frauchiger, D. Frei, W. Volken, D. Terribilini, M.K. Fix, Dose calculation of dynamic trajectory radiotherapy using Monte Carlo, Z. Med. Phys. 2018

E. Herrmann, D. Terribilini, P. Manser, M.K. Fix, G. Toporek, D. Candinas, S. Weber, D.M. Aebersold, K. Loessl, Accuracy assessment of a potential clinical use of navigation-guided intra-operative liver metastasis brachytherapy - a planning study, Strahlenther Onkol, 194(11), 1030-1038, 2018

# Department of Neurosurgery

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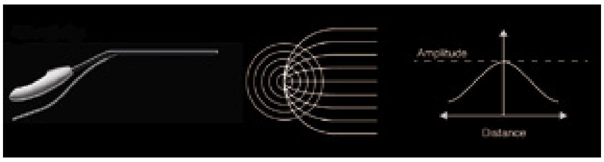
### Research Profile

Our focus is the improvement of surgical procedures, with special attention to highly translational or clinical problems. We collaborate strongly with the medical technologies partners as a main scientific and economical factor in the Kanton Bern. Areas include deep brain stimulation, tumor resection, function monitoring, robotics, and an academic software suite.

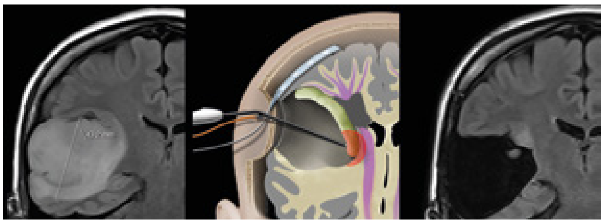
### Continuous Dynamic Mapping to Identify the Distance to Neuronal Structures

Intraoperative electrical brain mapping techniques help to preserve function but also increase the success rate of radical tumor resection by clarifying whether a region that is presumed preoperatively to be eloquent is confirmed intraoperatively to be eloquent. However, removing the last part of a tumor near an eloquent area potentially puts neurological functions at risk. Therefore, we are working on methods to estimate intraoperatively the exact distance to subcortical tracts (as the corticospinal tract) by intraoperative neurophysiological mapping.




Schematic illustration of the dynamic mapping device. The suction tip includes a monopolar mapping probe. Current can be delivered via the connector beneath the handle. The device is electrically isolated up to its tip. The stimulation current flow is directed from the probe's tip to a far reference. The equal-potential field lines are illustrated on the right as well as the current-to-distance relation curve. The suction can be used for subpial dissection and simultaneous stimulation at every site and during every step of surgical tumor resection. An acoustic alarm sound is triggered from the system when certain amplitude is reached at a predefined stimulation intensity (which might be decreased stepwise when approaching the corticospinal tract).

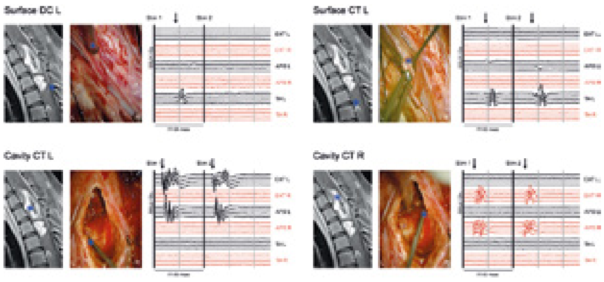
A further project focuses on identifying slectively the corticospinal tract in the spinal cord. During surgery of intramedullary spinal cord tumors, anatomical landmarks are distorted and neurophysiological identification of eloquent structures is essential as all structures are in an extremly close relationship. As part of an international team, we are working on a stimulation paradigm to slectively identify dorsal column and corticospinal tract to guide tumor removal in those high-risk surgeries.



Left: T2 coronar image of a right-sided tempero-insular tumor. Middle: The combined approach of monitoring techniques (here via a strip electrode placed on the cortex) for remote vascular injury and continuous subcortical short train stimulation via the electrified suction device) enables real-time functional feedback during tumor surgery close to the corticospinal tract. Coronar view of a right insular tumor, tumor tissue in green, corticospinal tract in violet. Right: Early postoperative image showing a small tumor remnant towards the corticospinal tract. The lowest subcortical mapping threshold during surgery was 3 mA, elicited via the strip electrode without significant changes. Postoperative the patient presented with a mild hemiparesis, which recovered completely within 14 days.

### Human Brain Stimulom Project

The Department of Neurosurgery, the ARTORG Center for Biomedical Engineering Research (Prof. Stefan Weber), and the Center for Movement Disorders (Prof. Paul Krack) are pooling their respective expertise in neurosurgery, robotic surgery, and neurology to improve deep brain stimulation (DBS) from preoperative planning, to implantation and postoperative programming. The long-term goal of this project is to move towards a more efficient DBS

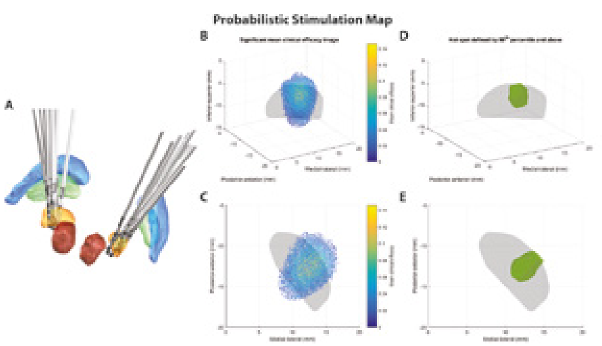



Guiding tumor resection via the double train stimulation paradigm. This is a 10-year-old patient with a ganglioglioma at level C4- T3. The figure illustrates the site of mapping in the MRI and microscopic view as well as four consecutive trials of recordings from bilateral EXT, APB and TA. The upper-left panel shows mapping of the left DC surface. The upper-right panel illustrates mapping of the left corticospinal tract (CT) of the surface after the dentate ligament is cut and the cord slightly rotated. The lower two panels illustrate low-intensity (0.2 mA) mapping in the left and right resection cavity still applying the double-stimulation paradigm. EXT=extensor digitorum, APB=abductor pollicis brevis, TA=tibialis anterior, L = Left and R = Right.

implantation as well as an automated and smart DBS with improved DBS device. This will increase the percentage of potential DBS candidates who could have access to the therapy for neuropsychiatric diseases.

One current focus of our department is the development of delivering DBS with segmented leads and provide probabilistic stimulation maps. These maps identify effective stimulation regions, which help the surgeons place stimulation 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. These maps are based on data from extensive clinical testing and artificial intelligence. For a map for Parkinson's disease, 28 patients were analysed. These patients were implanted with segmented DBS leads in the subthalamic nuclei and were systematically assessed at six months post-operation. Stimulation parameters and the corresponding clinical efficacy were combined with the position of the stimulation leads and with computer simulations of the activated tissue. The data was pooled to perform a group analysis using voxel-wise statistics. Finally, this analysis yielded a probabilistic stimulation map with a stimulation "sweet spot" as illustrated below.

Future work will expand this technique to other indications such as essential tremor or even psychiatric diseases. Furthermore, the concept will be tested in a prospective study to evaluate the utility of computer-assisted DBS programming based on these probabilistic maps.



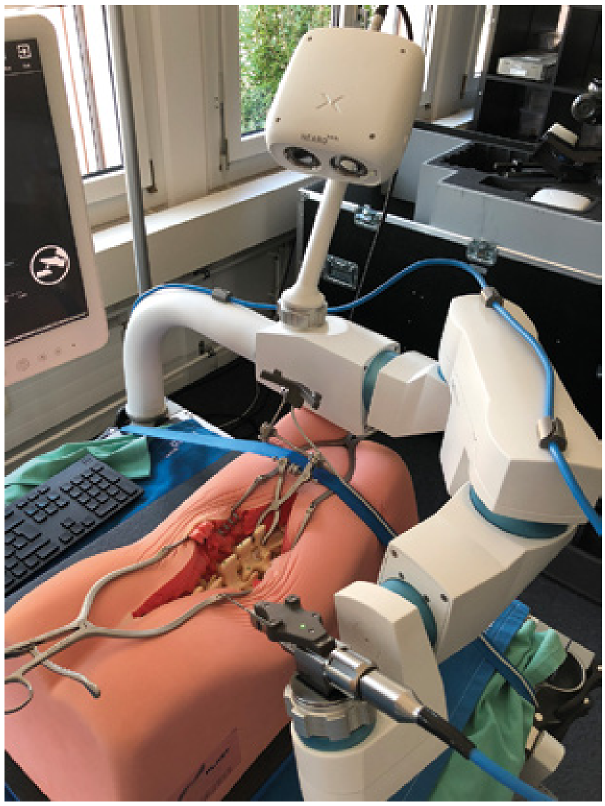

**Impedance Spectroscopy: Towards Real-time in vivo Analysis of Tissue**

Today, robotic surgery may be used to enhance the surgeon's tool kit. Robotic interventions are not free of errors, e.g. positioning of the surgical tool, and thus additional safety mechanisms are required to ensure preservation of delicate structures proximal to the tool path. To prevent inappropriate operation of the robot during surgical manipulation, in situ assessment of tissue properties proximal to the surgical tool is crucial. Electrical impedance is the passive property of a tissue and quantifies its ability to oppose flow of current. Tissue impedance is unique between different biomaterials (tissues), and this property may be used to guide surgical tools.

Tumor boundaries are non-visible for the surgeon during tumor resection. Many efforts have been made, such as introduction of fluorenscence-guided surgery (5-ALA), intraoperative magnetic resonance imaging (MRI), and ultrasound (US). Nevertheless, all these methods have important limitations, for example lack of fluorescence in low-grade gliomas. New technologies to classify tissue at tumor borders as cancerous or non-cancerous are desirable. Other teams have tried impedance spectroscopy in animal models (e.g. validation of glioma in rats). In an interdisciplinary project, we aim to explore the accuracy and reproducibility of impedance spectroscopy to classify different types of brain tumor tissue (e.g. glioma, metastasis, healthy tissue).

**Towards Intelligent Sensor-enhanced Robotic 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 robotc implantation of epilepsy electrodes for SEEG.

The current research activities of the ARTORG and Department of Neurosurgey are funded by the BRIDGE Discovery programme, which is conducted by the SNSF and the CTI. It offers new funding opportunities at the intersection of basic research and science-based innovation, thereby supplementing the funding activities of the two organizations.

**Computer-Based Algorithm for Patient-Specific Skull Implants**

Another research activity focused on improvement of conception, design, and intraoperative fabrication of patient-specific implants (PSI) for cranioplasty. Cranioplasty after decompressive hemicraniectomy or large-format craniotomies is a challenging procedure, especially in cases when a patient's own cranial flap is unavailable. Computer-aided design and 3-dimensional (3D) printing have enabled fabrication of PSI from a variety of polymer, ceramic, or metal components with satisfying postoperative cosmetic and functional results. However, computer-aided design and manufacturing of PSI requires fundamental knowledge of 3D processing software and can be difficult and time-consuming in a variety of cases. We developed a fully automated computer-based algorithm for PSI design (CAPSID) requiring no manual operation of 3D-processing software by the surgeon. With the help of CAPSID, an accurate PSI and its corresponding mold is calculated based on the patient's CT scan within 5-15 minutes. The corresponding mold is 3D printed and used for intraoperative fabrication of the PSI under sterile conditions.

Preoperative CT scan | 3-D printed mold | Postoperative result

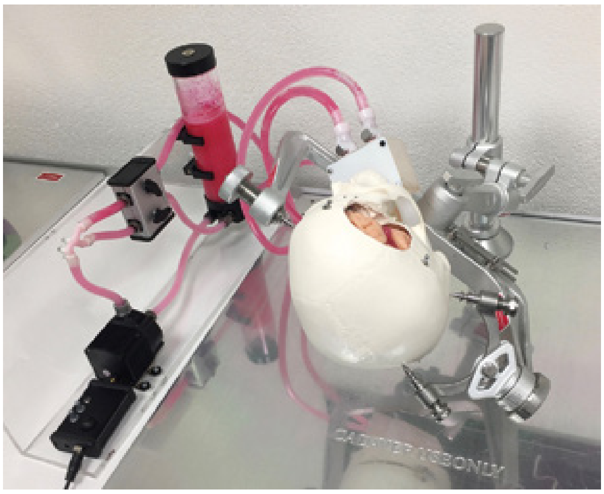
Based on our experience with the implantation of a CAPSID based PSI in the first 10 patients, our algorithm has allowed the rapid and cost-effective manufacturing of implants. CAPSID molds are highly accurate and cosmetic results are excellent. Currently, our prospective study assessing the practicability and accuracy in the clinical setting is ongoing. The study was approved by the local ethics committee. The study protocol is available on http://clinicaltrials.gov (NCT02828306).

**Intracranial Aneurysm Microsurgery Training Model**

Intracranial aneurysms are frequently diagnosed cerebral malformations of the brain and one of the main causes of intracranial haemorrhage, particularly in the young population. Microsurgery, consisting of the aneurysm dissection and occlusion by one or more small permanent clips, is a validated treatment modality for patients diagnosed with one or more intracranial aneurysms. Because of their heterogeneity, fragile structure,complex anatomy, close relation to the main arterial branches and to the surrounding brain, aneurysm dissection and clipping can be challenging. Microsurgical training, surgical simulation, and direct surgical exposure are essential to safely perform intracranial aneurysm surgical treatment. Together with ARTORG, we have been developing single-patient silicon customized brain and aneurysm models. The models are created using professional 3D printers, based on 60 individualized diagnostic segmented images. Furthermore,

these models are implemented with a realistic blood turbulence and pulsatile flow hardware, in order to reproduce and anticipate tactile properties met during surgery. The aim of this dry model is not only to train neurosurgeons to manipulate, dissect, and safely clip aneurysms, but also to reduce the morbidity of surgery by anticipating the surgical anatomy and clipping alternatives in those specific patients where a challenging surgical situation can be anticipated.

Ultra-thin silicon layered, single-patient custimized aneurysm model.



Complete single-patient customized simulation model, including a pressure-adjustable pulsatile pump and rheology fluid.

**Ability Academic Software Suite**

Another main research project is the development of a personal learning environment. This new sofware 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 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 ever increasing amounts 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.

## Selected Publications

Nowacki, A., Nguyen, T. K., Tinkhauser, G., Petermann, K., Debove, I., Wiest, R., & Pollo, C. (2018). Accuracy of different three-dimensional subcortical human brain atlases for DBS–lead localisation. NeuroImage: Clinical, 20, 868-874

Deletis V, Seidel K, Sala F, Raabe A, Chudy D, Beck J, Kothbauer KF. Intraoperative identification of the corticospinal tract and dorsal column of the spinal cord by electrical stimulation. J Neurol Neurosurg Psychiatry. 2018 July; 89(7):754-761

Seidel K, Biner MS, Zubak I, Rychen J, Beck J, Raabe A. Continuous dynamic mapping to avoid accidental injury of the facial nerve during surgery for large vestibular schwannomas. Neurosurg Rev. 2018 Oct 26. doi: 10.1007/s10143-018-1044-z

# Bone and Joint Research Cluster, Department for BioMedical Research (DBMR)

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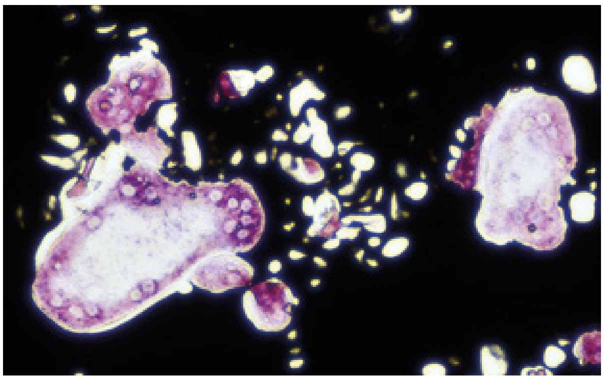
### Research Profile

The research of the Bone Biology and Orthopaedic Research Group of the Department for BioMedical Research is focused on the topics of (i) osteoimmunology, (ii) fracture repair, (iii) molecular transport in bone cells, (iv) BMP and BMP antagonists in osteoclastogenesis, and (v) Gadolinium and bone cell lineages. Some of these projects will be outlined in more detail below. (i) Osteoimmunology, the investigation of the crosstalk between inflammatory processes and bone homeostasis, is studied in close collaboration with the Department of Rheumatology, Clinical Immunology and Allergology, University Hospital, Inselspital. (ii) Fracture repair in elderly people undergoing treatment against osteoporosis is both a scientifically and a clinically relevant process. We have developed experimental models allowing the investigation of the repair of model defects in osteoporotic animals treated with anti-resorptive bisphosphonates in rigidly and non-rigidly fixed osteotomies and in CaP-filled critical size defects. (iii) Within the NCCR Platform TransCure, which aspires to identify molecular transporters as putative therapeutic targets, we focus on the effects of iron homeostasis on cells of the osteoclast lineage. (iv) BMP are growth factors inducing osteogenic responses in cells and tissues. Their activities are modulated by a family of antagonists. The question, whether the action spectra of BMP antagonists are limited to the inactivation of BMP, or whether this family of proteins exerts autonomous effects, is unanswered and is the focus of this project. (v) Recently it was observed that Gadolinium Chelates, which are used as contrast agents in MRI, accumulate in various tissues. The biological effects of long-term exposure to small doses, however, have not yet been investigated. In collaboration with the Department of Diagnostic and Interventional Radiology, University Hospital, Inselspital, the effects of Gadolinium on development and activity of bone cell lineages will be uncovered.

### Molecular Transport in Osteoclast Lineage Cells

Within the NCCR platform TransCure, which aims at the identification of transport molecules as potential therapeutic targets, the expression of molecular transporters in osteoblast (OB) and osteoclast (OC) lineage cells was investigated. In particular, our interest is focused on the role of iron homeostasis and the transporters DMT1 and ferroportin (FPN). Iron may be critically involved in OC development and activity, since the availability of energy is

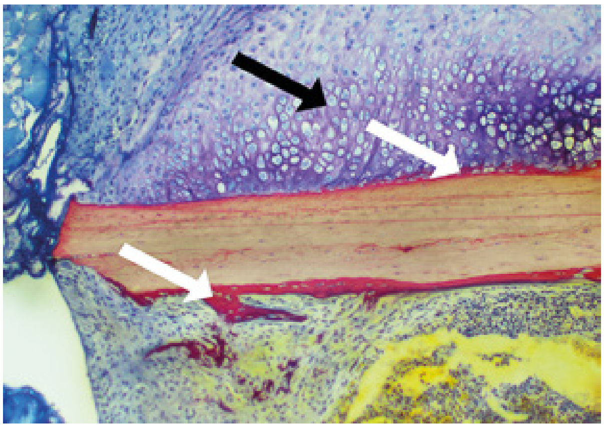


In vitro mineral dissolution by osteoclast lineage cells. Mature osteoclasts are seeded onto a layer of amorphous CaP. Within 24h, resorption pits are formed. Van Kossa staining (mineral, black) combined with staining for Tartrate resistant acid phosphatase, an in vitro marker for mature osteoclasts.

a prerequisite for both processes. Indeed, iron was found both to modulate the development and the activity of OC lineage cells, supporting the development of F4/80-positive macrophages and stimulating the resorption activity of mature OC. Generation of OC-specific DMT1 and FPN ko mice did not reveal a bone phenotype. There was, however, a transient alopecia observed in OC-spec. FPN ko mice. The phenotype suggested a leaky TRAP-promoter, which was subsequently demonstrated, rather than an OC- dependent effect. Further studies will investigate the interplay of respiration, iron homeostasis, and oxygen pressure. This project is part of the SNF-funded NCCR TransCure, with the leading house the Institute of Biochemistry and Molecular Medicine at the University of Bern.

**Bone Repair and Osseointegration**

Bone repair in elderly and osteoporotic patients who are treated with anti-resorptives has become an increasingly relevant topic in orthopaedic surgery. To address the problems that arise when treating frail bones with low bone turnover, small rodent models for osteoporosis, anti-resorptive treatment, and defect fixations of different mechanical stabilities were established. In a first study, setting small osteotomies into osteoporotic femora under treatment with alendronate (ALN), no impairment of bone repair caused by the deficiency in estrogen was visible. Treatment with ALN affected the repair process during the late remodelling phase only, but the stability of the fixation of the defect exerted profound effects on the repair process, rigid fixation leading to direct, membranous bone formation and non-rigid fixation leading to repair by endochondral bone formation.



Histological analysis of a non-rigidly fixed small osteotomy. The formation of new cartilage (black arrow) and new bone (white arrows) is visible. Cartilage represents the initial stage of callus formation to reach primary stability of the defect. Tissues were embedded in MMA and ground sections were stained using McNeal's Tetrachrome Stain.

Similar studies on critical size defects, filled with ßTCP, in rats revealed again estrogen deficiency to be of little consequence for the healing process, while treatment with ALN prevented resorption of the implant and its replacement by bone. The study revealed, as described before that an inhibitor of the antagonists of Bone Morphogenetic Proteins (BMP), the BMP2 variant L51P, increased the efficacy of endogenously synthesised and exogenously added BMP by blunting the inhibitory activity of BMP antagonists. The conclusion from these studies was that treatment with bisphosphonates may be critical in patients receiving a resorbable biomaterial (allogeneic bone transplant, resorbable CaP ceramics), since the treatment prevents turnover and osseointegration of the implant. To answer the question whether it is sufficient to stop treatment during the repair process or whether an extended drug holiday will be necessary requires further studies.

**Gadolinium – Long-term Effects on Bone Cell Lineages**

In collaboration with the Department of Diagnostic and Interventional Radiology, University Hospital, Inselsptial, the effects of Gadolinium on bone cell lineages will be investigated. Recently, attention has been brought to the fact that contrast agents based on Gadolinium (Gd) accumulate in various tissues, among them CNS and bone. The aim of this study will be to elucidate Gd effects on bone cell lineages in vitro and on bone in vivo. This work will be done together with R. Egli from Department of Diagnostic and Interventional Radiology and the RMS Foundation in Bettlach, CH.

**Research Profile Tissue and Organ Mechanobiology**

The Tissue and Organ Mechanobiology (TOM) Group of the Bone and Joint Research cluster, University of Bern, conducts translational research in the intersection of tissue engineering, biology, and applied clinical research. The group's primary aim is to understand the cellular response onbiomechanical stimuli and how cellular communities are affected in situ using 3D tissue and organ culture models. The research can be divided into two main foci: (i) On the one hand, the group investigates how intervertebral disc (IVD)-related low back pain could be reduced by investigating tissue-engineered regeneration strategies (ii) on the other hand, the group focuses on the human knee where they aim to identify cell-based solutions for the non-healing or delayed ruptures of the anterior cruciate ligament (ACL). The common focus of the TOM group is to advance in vitro organoid culture models, which match closely the human situation and where regenerative therapy strategies, such as novel biomaterials and cells, can be tested in a most physiologically authentic in vitro set-up.

**Low Back Pain and Intervertebral Disc Degeneration and Regeneration**

The TOM group conducts research in two main directions in the field of spine: i) IVD research in the area of regeneration using biomaterials and stem cells and ii) in the area of non-successful spinal fusion and possible involvement of pseudo-arthrosis. For the first research area, the group uses a combination of 3D tissue and organ culture approaches. The research of the second focus is the understanding of the balance between BMP agony and antagony. Besides the investigation of the exogenous stimulation of BMP antagonists on mesenchymal stem cells (MSC) and osteoblasts, the main focus lies on the observation of the interaction between IVD cells, MSCs, and osteoblast, by performing co-cultures.

In a Gebert Rüf financed project a fiber-reinforced hydrogel has been tested in a physiologically clinically relevant organ culture model by cross-linking the fibrin mesh with genipin, a natural cross-linker. These results were recently reported in the Journal of Functionalized Biomaterials and in the European Spine Journal. A genetically enhanced silk fleece material that contains a relevant cytokine for the IVD in combination with fibrin hydrogel has been successfully tested in the customized two degree-of-freedom bioreactor set-up.

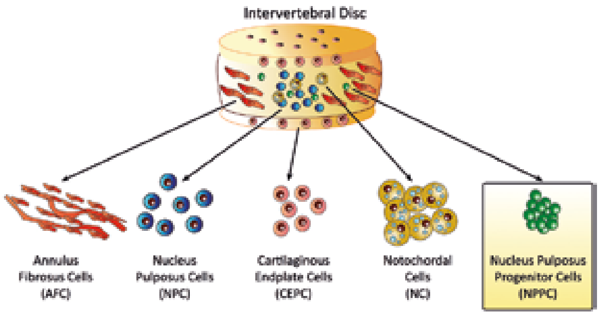



Image illustrating the four "classical" cell populations previously characterized in the intervertebral disc. In yellow on the right are the newly detected Tie2+ nucleus pulposus progenitor cells (NPPC).

Recently, particular autochthonous progenitor cells were detected in the human IVD, which could lead the path to cell therapy to retard IVD degeneration. Here, we concentrated on the most suitable isolation protocols to "fish" nucleus pulpous progenitor cells (NPPC) from the total population of cells in the bovine coccygeal disc. We also focused on their multipotency capacity and their application for IVD repair. Future research is to understand how these cells can be best isolated and whether these cells can be maintained in vitro to regenerate the IVD5. Furthermore, it would be highly desirable to investigate how induced pluripotent stem cells (iPSC) could be used for IVD repair. This is the main aim in an upcoming Horizon 2020 Project named "iPSpine" starting in 2019 for three years in collaboration with internationally well-known scientists and experts in the field of engineering, biomaterials, and biomechanics.

**Reducing the Senescence in Mesenchymal Stem Cells**

Stem cell therapy faces the problem of the necessity to rely on fetal bovine serum (FBS) for cell expansion, which proved to have major disadvantages for translation in the clinics. Additionally, MSC undergo senescence during expansion in vitro, which impairs their therapeutic potential. Here, alternate serum-free media formulations were investigated in terms of cell proliferation and differentiation potential, which could make their way to a GMP-compliant solution.

## Selected Publications

*Bone Biology and Orthopaedic Research*

Albano G, Dolder S, Siegrist M, mercier-Zuber A, Auberson M, Stoudmann C, Hofstetter W, Bonny O, Fuster DG (2017) Increased bone resorption by osteoclast-specific deletion of the sodium/calcium exchanger isoform 1 (NCX1) Pflugers Arch 469:225

Ruef N, Dolder S, Aeberli D, Seitz M, Balani D, Hofstetter W (2017) Granulocyte-macrophage colony-stimulating factor-dependent CD11c-positive cells differentiate into active osteoclasts Bone 97:267.

Schaller B, Saulacic N, Beck S, Imwinkelried T, Liu EWY, Nakahara K, Hofstetter W, Iizuka T (2017) Osteosynthesis of partial rib osteotomy in a miniature pig model using human standard-sized magnesium plate/screw systems: Effect of cyclic deformation on implant integrity and bone healing J Craniomaxillofac Surg 45:862

Uster S, Coelho FM, Aeberli D, Stein JV, Hofstetter W, Engelhardt B, Seitz M (2018) TNFalpha blockade mediates bone protection in antigen-induced arthritis by reducing osteoclast precursor supply Bone 107:56

Hauser M, Siegrist M, Keller I, Hofstetter W (2018) Healing of fractures in osteoprotic bones in mice treated with bisphosphonates – a transcriptome analysis Bone 112:107

Hauser M, Siegrist M, Denzer A, Saulacic N, Grosjean J, Bohner M, Hofstetter W (2018) Bisphosphonates reduce biomaterial turnover in healing of critical-size rat femoral defects J Orthop Surg 26:1

*Tissue and Organ Mechanobiology*

Frauchiger DA, May RD, Bakirci E, Tekari A, Chan SCW, Wöltje M, Benneker LM, Gantenbein B, Frauchiger D, May R, Chan S, Benneker L (2018) Genipin-Enhanced Fibrin Hydrogel and Novel Silk for Intervertebral Disc Repair in a Loaded Bovine Organ Culture Model. J Funct Biomater 9(3):40. doi: 10.3390/jfb9030040

Frauchiger DA, Chan SCW, Benneker LM, Gantenbein B (2018) Intervertebral disc damage models in organ culture: a comparison of annulus fibrosus cross-incision versus punch model under complex loading. Eur Spine J: doi: 10.1007/s00586-018-5638-52

Frauchiger DA, Heeb SR, May RD, Wöltje M, Benneker LM, Gantenbein B. Differentiation of MSC and annulus fibrosus cells on genetically engineered silk fleece-membrane-composites enriched for GDF-6 or TGF-β3. J Orthop Res 2018; 36:1324-1333 DOI: 10.1002/jor.23778

Sakai D, Schol J, Bach FC, Tekari A, Sagawa N, Nakamura Y, Chan SCW, Nakai T, Creemers LB, Frauchiger DA, May RD, Grad S, Tryfonidou MA, Gantenbein B (2018) Successful fishing for nucleus pulposus progenitor cells of the intervertebral disc across species. JOR Spine 2018e: doi: 10.1002/jsp2.1018

May RD, Frauchiger DA, Albers CE, Benneker LM, Kohl S, Gantenbein B (2018) Inhibitory Effects of Human Primary Intervertebral Disc Cells on Human Primary Osteoblasts in a Co-Culture System. Int J Mol Sci 19(4): doi: 10.3390/ijms19041195

Wuest SL, Caliò M, Wernas T, Tanner S, Giger-Lange C, Wyss F, Ille F, Gantenbein B, Egli M. Influence of Mechanical Unloading on Articular Chondrocyte Dedifferentiation. Int J Mol Sci 2018; 19: [DOI: 10.3390/ijms19051289

Wuest SL, Gantenbein B, Ille F, Egli M. Electrophysiological experiments in microgravity: lessons learned and future challenges. NPJ Microgravity 2018; 4:7 DOI: 10.1038/s41526-018-0042-3

# Nuclear Medicine Group

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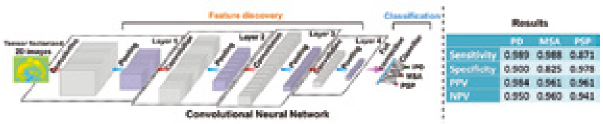
### Research Profile

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. 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 outcome 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 differential diagnosis of parkinsonism, pancreatic cancer, and lung lymph nodes. Oncology efforts target tumour lesion detection and segmentation, radiotherapy dose reduction, cross-protocol harmonization, image synthesis, and dosimetry prediction.

### Differential Diagnosis of Parkinsonism

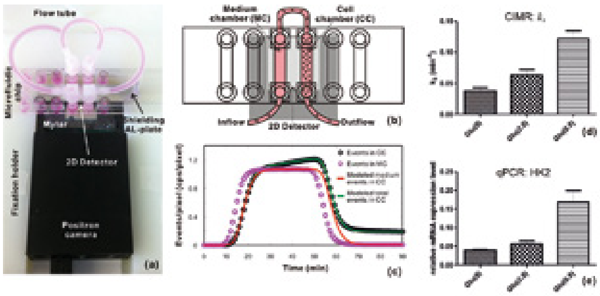
Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by a triad of motor symptoms: rigidity, tremor, and bradykinesia. Very similar clinical signs can appear in atypical parkinsonian syndromes, including multiple system atrophy (MSA) and progressive supranuclear 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. We established a four-layer convolutional neural network (CNN) on the tensor-factorized 2D images to differentiate PD, MSA, and PSP. The preliminary test on 257 patients of PD, MSA, and PSA has proven its ability to reach comparable accuracy to state-of-the-art. Furthermore, we have developed a deep projection neural network (DPNN) to directly extract the 2D pattern images using deep learning. To enable convergence with limited data, the network was pretrained with a large database of 1077 brain FDG PET datasets of diverse neurological diseases. The DPNN can further improve the accuracy of differential diagnosis by incorporating nonlinear features identified using deep learning.




A sketch of the preliminary four-layer convolutional neural network on 2D tensor factorized images, tested on 257 patients of which 136 were PD, 91 MSA, and 30 PSP. The right panel summarizes the corresponding classification results.

### Cellular Nuclear Medicine Imaging System

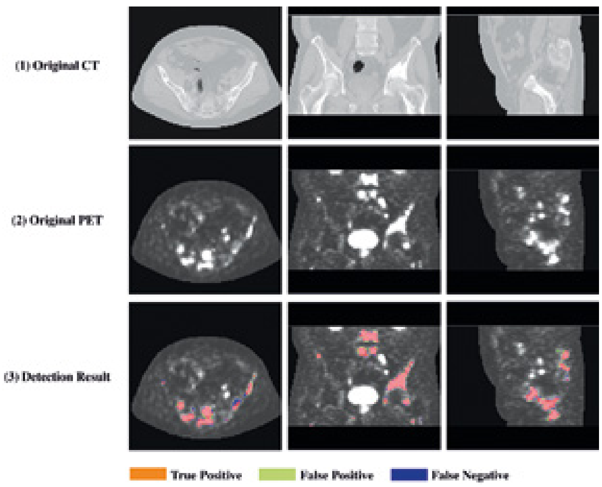
The group is also active in the development of cellular nuclear medicine imaging systems. Conventional molecular imaging measures tracer uptake in living organs. As an alternative, we have built a continuously infused microfluidic radioassay (CIMR) system, which enables real-time measurement of the dynamic 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.




The continuously infused microfluidic radioassay (CIMR) system: (a) photograph of the microfluidic chip in operation; (b) sketch of the tracer medium flow during the measurement; (c) representative cellular pharmacokinetic modelling; (d,e) comparison of cellular pharmacokinetics with relevant qPCR results for human breast cancer cell line SkBr3 cultured in media of three different glucose concentrations (0.5, 2.5, and 5 mM).

### Treatment Planning for Targeted Radionuclide Therapy

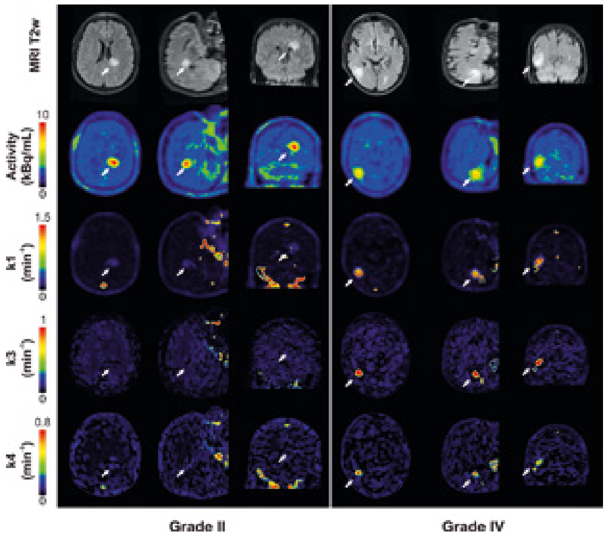
The emerging technique of targeted radionuclide therapy (RLT) offers an effective treatment strategy for several advanced cancers, including metastatic castration-resistant prostate cancer (mCRPC) and neuroendocrine tumours. However, concerns of dose effects and risks have also been raised. The European council mandates that treatments should be planned according to the radiation doses delivered to individual patients. However, the lack of accepted methods to characterize the tumour 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, we proposed the concept to employ artificial neural networks (ANNs) to predict the post-therapy dosimetry. These developments provide the potential to individualize the treatment and to maximize the theranostic benefit for targeted radionuclide therapy.




Representative bone-lesion segmentation results of the proposed network deep learning method. Row (1) depicts original CT slices, Row (2) the corresponding PET slices, and Row (3) the detection result of the proposed network. The three columns show the axial, sagittal, and coronal views.

### 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 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.




Preliminary test of hierarchical pharmacokinetic modelling on dynamic FET PET. The improved parametric images allow visual differentiation of low-grade and high-grade glioma using $^{18}$F-FET.

**Radiotracer Development and Preclinical Imaging**

The new group member, Professor Cumming, brings an extensive background in preclinical molecular imaging. His recent publications include comprehensive reviews of the status of PET imaging of neuroinflammation using tracers for the microglial marker TSPO and other targets depicting specific components of neuroinflammatory processes. Other publications arise from his international network of collaborations in basic and clinical research, i.e. EEG-based detection of internal affective state (Malaysia), preclinical studies of antipsychotic action (Erlangen, Germany), PET imaging of late sequelae of traumatic brain injury in veterans (Australia), multimodal imaging of schizophrenia (South Korea), and dopaminergic markers of schizophrenia (Mannhein, Germany).

In keeping with the broader objectives of the department, aspirations for molecular imaging are centred 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 small animal PET, autoradiography in vitro and radiochromatographic measurement of tracer metabolites formed in vivo.

### Selected Publications

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M. Brendel, A. Jaworska, F. Overhoff, T. Blume, F. Probst, F. Gildehaus, J. Carlsen, P. Bartenstein, C. Haass, J. Herms, M. Willem, A. Rominger. Efficacy of chronic BACE1 inhibition in PS2APP mice depends on the regional Aβ deposition rate and Plaque Burden at Treatment Initiation. Theranostics (2018) 9(18):4957-4968

S. Parhizkar, T. Arzberger, M. Brendel, G. Kleinberger, M. Deussing, C. Focke, B. Nuscher, M. Xiong, A. Ghazemi, N. Kazmarski, S. Krasemann, S. Lichtenthaler, S. Müller, A. Colombo, L. Monasor, S. Tahirovic, M. Willem, N. Pettkus, O. Butovsky, P. Bartenstein, D. Edbauer, A. Rominger, A. Ertürk, D. M. Holtzman, M. Meyer-Luehmann, C. Haass. Loss of TREM2 function increases amyloid seeding but reduces plaque associated ApoE. Nature Neurosci (2018) (in press)

T Grimmer*, K Shi*, J Diehl-Schmid, B Natale, A Drzezga, S Förster, H Förstl, M Schwaiger, I Yakushev, H-J Wester, A Kurz, B H Yousefi. 18F-FIBT may expand PET for β-Amyloid Imaging in Neurodegenerative Diseases. Molecular Psychiatry. 2018; in press (* Co-first author)

L. Xu, G. Tetteh, J. Lipkova, Y. Zhao, H. Li, P. Christ, M. Piraud, A. Buck, K. Shi*† and B. H. Menze†. Automated Whole-Body Bone Lesion Detection for Multiple Myeloma on 68Ga-Pentixafor PET/CT Imaging Using Deep Learning Methods. Contrast Media Mol Imaging, Epub online Jan. 2018 († Equal contribution, * Corresponding author)

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# Interventional Neurovascular Research Group

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**Pasquale Mordasini** | Tomas Dobrocky | Jan Gralla | Pascal Mosimann | Eike Piechowiak | Felix Zibold

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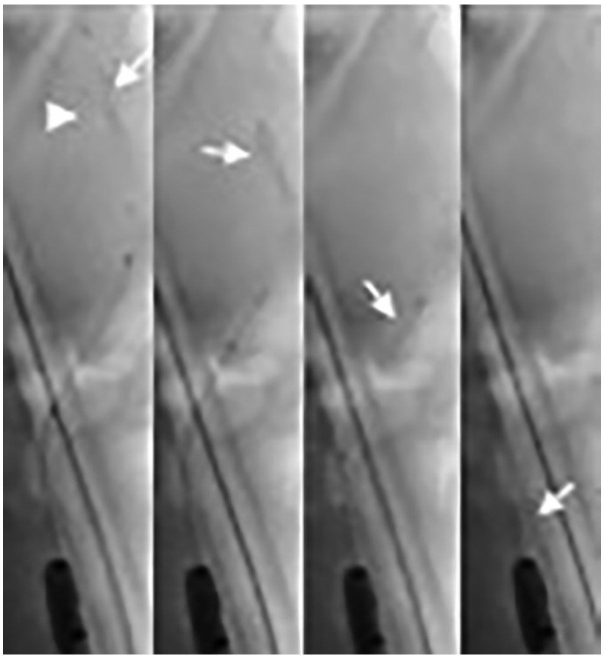
Marco Caversaccio, Chairman and Head, ENT Department
Andreas Raabe, Chairman and Head, Neurosurgery Department
Stefan Weber, Chairman and Head ARTORG Center of Biomedical Engineering Research
Hans Rudolf Widmer, Head of Research Group Neurosurgical Research Laboratory, Neurosurgery Department

### Research Profile

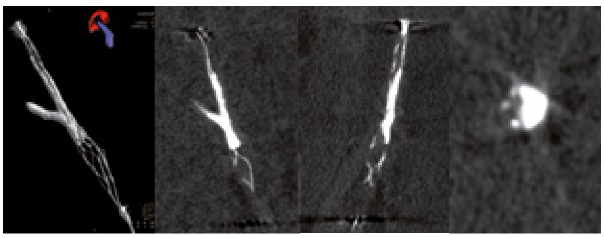
In recent years, endovascular neurointerventional techniques have evolved significantly with an increasing spectrum of indications. This includes minimally invasive endovascular treatment procedures for acute ischemic stroke, intracranial aneurysms, and other cerebrovascular diseases such as arterio-venous malformations and fistulas as well as stenosis of brain-supplying vessels. The Interventional Neurovascular Research Group focuses 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, stoke 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



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 (arrow head) and the straight position of the thrombus during mobilization and retrieval (arrow).



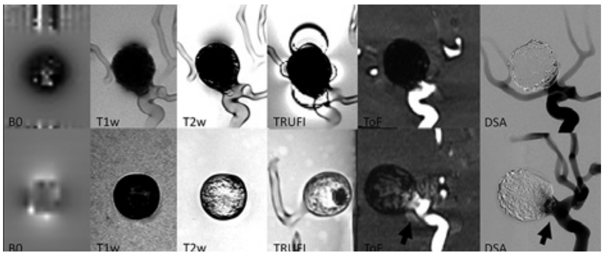
Flat-panel CT 3D volume reconstruction, maximum-intensity projection (MIP) and multiplanar reconstruction of the same thrombus. Note the typical appearance of the opacified thrombus with thrombus material inside and outside in relation to the stent struts.

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.

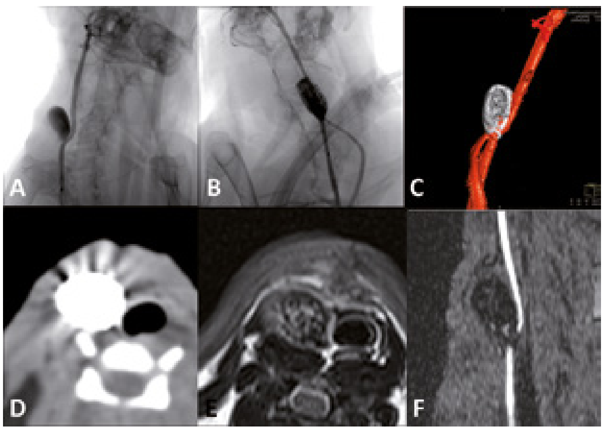
**Aneurysm Treatment**

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.



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.



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).

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 in order 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


Developmental process of cerebral aneurysm models using additive manufacturing techniques (3D printing) based on patient specific 3D imaging data sets.

and educational purposes. Furthermore, aneurysm models are used for the development, testing, and evaluation of novel endovascular devices and treatment approaches, as well as a model for measurements of different aspects of flow dynamics and their role in aneurysm formation and growth.

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Jung S, Gilgen M, Slotboom J, El-Koussy M, Zubler C, Kiefer C, Luedi R, Mono ML, Heldner MR, Weck A, Mordasini P, Schroth G, Mattle HP, Arnold M, Gralla J, Fischer U (2013) Factors that determine penumbral tissue loss in acute ischaemic stroke. Brain 136:3554-60

# Visceral Surgery

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Adrian Keogh


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Anja Lachenmayer


Dominik Obrist


Deborah Stroka


Pascale Tinguely


Stefan Weber


Joel Lavanchy


Corina Kim


Felix Baier

**Research Profile**
Visceral Surgery research covers a broad range of clinical, translational, and basic studies, on topics including computer-assisted liver surgery, regenerative medicine, liver cancers, surgical site infections and artificial intelligence (AI) in video assessment. We explore novel developments in image-guided technology into the context of computer-assisted liver surgery, to improve intraoperative navigation and augmenting accuracy in targeting intrahepatic lesions. Our specific interests within regenerative medicine include how molecular and immune regulation influence liver regeneration and in particular, how intestinal bacteria are systemically disseminated upon major liver surgery and can influence surgical outcomes. And finally, using preclinical models and translational studies we aim to better understand the pathophysiology of hepatocellular carcinoma to develop novel treatment approaches.

**Percutaneous stereotactic image-guided microwave ablation for malignant liver lesions**
Tumour ablation is a minimally invasive technique that is commonly used for the treatment of tumours in the liver and has become more widely used since the development of modern imaging tools. Thermal ablation includes radiofrequency ablation (RFA) and microwave ablation (MWA). The advantages of MWA is the potential to treat larger tumors faster, with a reduced perivascular heat sink effect. MWA is well recognized for hepatocellular carcinoma (HCC), where it has been shown to be a safe, effective and minimally-invasive treatment option, that can be repeated in case of local recurrence. Moreover, it is becoming an increasingly recognized alternative to surgery in patients with impaired liver function, associated extrahepatic disease, lesions inaccessible to surgical resection, extensive bi-lobar metastatic disease or concurrent medical conditions precluding an operation.

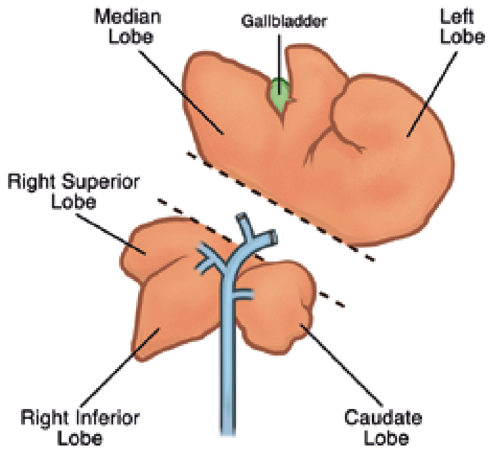
In collaboration with the ARTORG, computer-assisted navigation techniques have been introduced to increase efficacy of ablation. Computer-assisted stereotactic navigation is particularly interesting under several conditions: very small or invisible "vanishing" lesions (targeting accuracy); very large lesions requiring multiple needle placements in order to achieve complete ablation; or difficult-to-reach or treat lesions (close proximity to major vessels/bile ducts, liver dome, segment I lesions). Using computer-assisted stereotactic navigation has shown to improve the precision of the needle placement.


Navigation phase of stereotactic image-guided microwave ablation. Navigated alignment of the aiming device along the planned trajectory, with the cross-hair viewer indicating the trajectory direction.

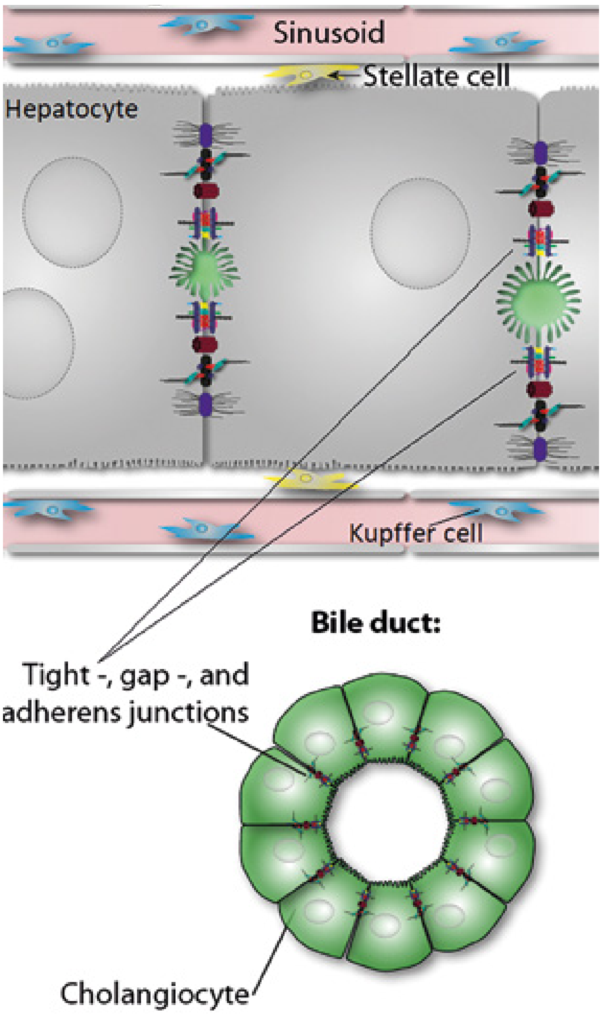
We are investigating whether stereotactic image-guided microwave ablation (SMWA) leads to an effective treatment of several kinds of malignant liver lesions and might offer a potentially curative treatment option for patients with tumors not amenable to ablation when using conventional image-guidance. In addition, we are evaluating the short-term clinical outcome of patients undergoing percutaneous SMWA for non-colorectal liver metastases. We aim to establish SMWA as a technically feasible, safe and minimally invasive treatment option for liver metastases in selected patients as offering an alternative to resection or a purely palliative treatment.

**Regenerative Medicine in the Liver**
The liver is able to sense and respond to damage to regenerate itself by the proliferation of its major parenchymal cell type, the hepatocyte. Hepatocytes re-enter cell cycle, and proliferate to restore the damaged or lost tissue mass. This ability of the liver is particularly important for patients undergoing major liver surgery in which loss of tissue is unavoidable. We are investigating the mechanisms that drive regeneration by focusing on the role of the innate immune

system, influence of the gut microbiota and the influence of extracellular signals. To study liver regeneration, we use a well-established partial hepatectomy model in mice.



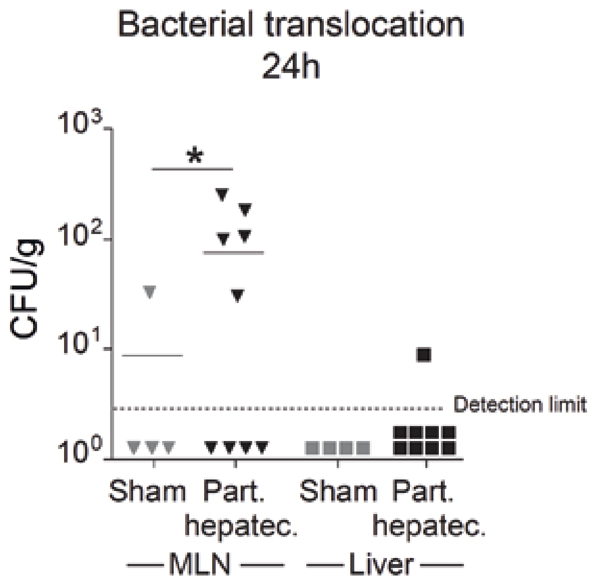

Anatomy of the mouse liver with 2/3 partial hepatectomy depicted. The median and left liver lobes are excised and the remnant liver tissue of the right and caudate lobes regrow until the original mass of the liver is reached.




Cell junctions in the hepatic plate and the bile duct. This figure schematically depicts a hepatic cord and a bile duct. The hepatic cord consists of neighbouring hepatocytes that are lined by spaces of Disse and the sinusoidal blood circulation. Bile ducts are formed by a circular arrangement of cholangiocytes. Hepatocyte and cholangiocyte membranes contain adherence junctions, gap junctions and tight junctions. Tight junctions seal of the cell membranes of adjacent cells, forming thereby the canalicular or ductular cavities that contain cytotoxic bile.

In addition, we investigate novel pathways activated in the regenerating liver, with the goal of defining new targets to promote liver function and hepatocyte proliferation during regeneration of diseased livers. Currently, we are focusing on the importance of cell-cell contact proteins located within tight junctions (TJ). TJ form para-cellular boundaries to control the passage of molecules through the liver epithelium and we believe play a vital role in liver homeostasis and regeneration.

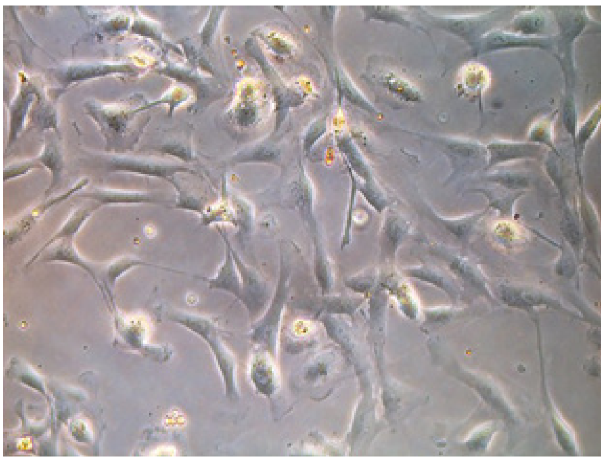
Another focus of our research is to understand how intestinal microbes can influence surgical outcomes. In particular, we aim to identify the origin and circulating pathways of microbes that may be released during major surgical procedures such as liver resections. We try to understand how microbes contribute to complications after surgery and to define host protecting mechanisms that are in place to prevent high incidence of surgical infections.




Major liver surgery (partial hepatectomy) causes an increase of bacterial titers in mesenteric lymph nodes (MLN) 24 hours post-surgery.

**Diagnostic device to monitor the stiffening of fibrotic tissue in-vitro**

Liver fibrosis is a life-threatening disease, whose hallmark is tissue stiffening and loss of liver function. Therapeutic options remain difficult to define as the drug response



Human hepatic stellate cells in culture

differs from patient to patient. In collaboration with ARTORG (Group Olivier Guenat) we are helping to develop patient-specific assay, based on organs-on-chip technologies, able to test anti-fibrotic compounds and identify the best therapeutic option for each patient. To assist with this goal, we are contributing our expertise with the isolation and characterization of human hepatic stellate cells to provide a cell source for the engineered chips. In the liver, the stellate cell is the residential fibroblast and are the primary cell responsible for collagen deposition which is the cause of increased tissue stiffness. However, disease progression is complex and involves the interplay between stellate cells and multiple other liver and immune cells types and involves genetic, metabolic and environmental factors. Together, we aim to generate a fibrosis model on a chip to individually test patient sample using in-vitro in devices that resemble the diseased organs to help design the most efficient treatment.

**Artificial intelligence in video assessment**

In surgical education, traditional in-training reports can fail to detect deficiencies because objectivity is influenced by examiner-trainee interaction. Therefore, we aim to develop a means of independent objectivity by an automated skill assessment of surgical trainees.

We are working on a training set of 500 video recordings of standardized laparoscopic interventions rated by experts to train machine-learning algorithms how to rate surgical skills. We will address the questions of 1) is automated rating of surgical skills using machine-learning algorithms comparable to expert rating and 2) can automated assessment of surgical skill predict clinical outcome? Ultimately we are aiming to address whether surgical skill, measured in postoperative complications, can be safely predicted using artificial intelligence powered rating of laparoscopic videos.

## Selected Publications

Dosch M, Zindel J, Jebbawi F, Melin N, Sanchez-Taltavull D, Stroka D, Candinas D, Beldi G. Connexin-43-dependent ATP release mediates macrophage activation during sepsis. Elife. 2019 Feb 8;8. pii: e42670. doi: 10.7554/eLife.42670. PMID: 30735126

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Studer P, Horn T, Haynes A, Candinas D, Banz VM. Quality of life after hepatic resection. Br J Surg. 2018 Feb;105(3):237-243. doi: 10.1002/bjs.10735. PMID: 29405277

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# Support Center for Advanced Neuroimaging SCAN

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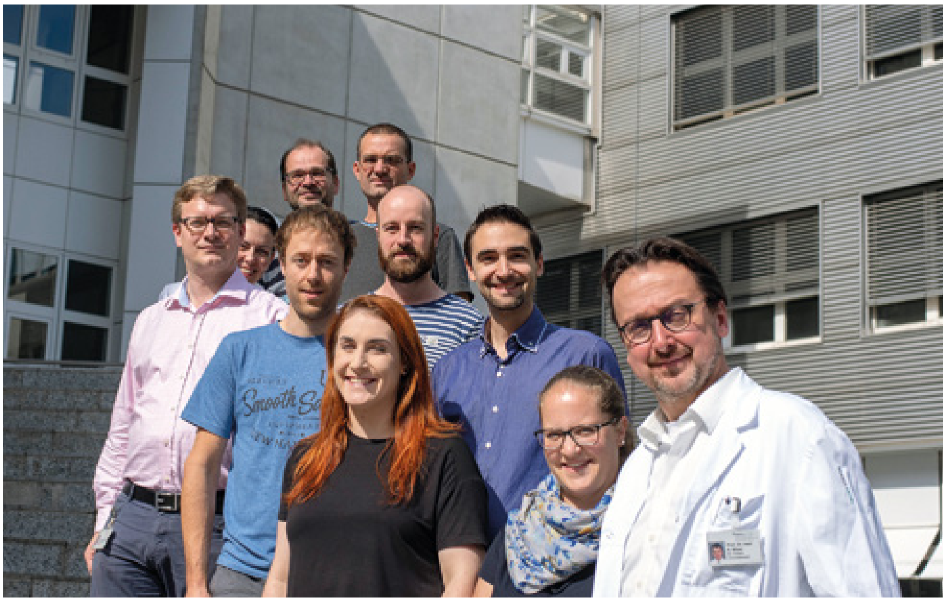

## Group Members

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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

### Research Profile

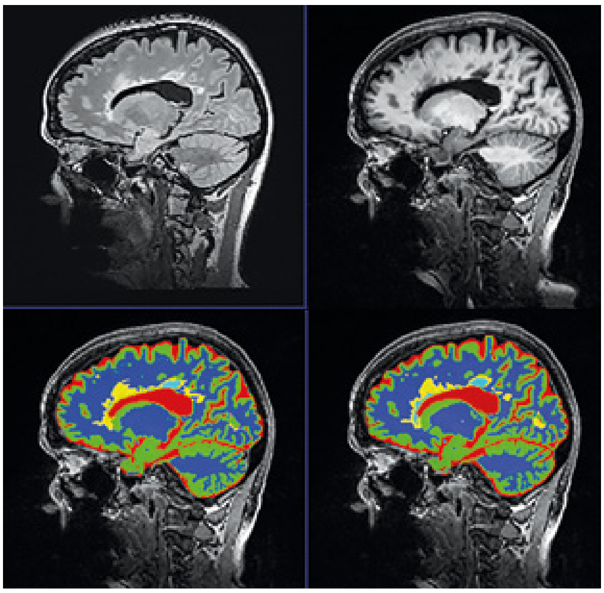
The Support Center for Advanced Neuroimaging (SCAN) is a multidisciplinary imaging laboratory hosting MR-physicists, computer engineers, neuroradiologists, neurologists, and psychologists. Our aim is the development, post-processing, and clinical validation of advanced structural and functional neuroimaging technologies to improve patient care through non-invasive neuroimaging technologies.

### Ultra High Field MRI

The SCAN has cooperated with the Excellence Center of Ultra High Field MRI at the Medical University in Vienna/Austria on a clinical study that led to the FDA approval of the first UHF system for clinical use (Springer et al. 2016). We are currently investigating the yield of UHF for direct neuronal current imaging (see below) for functional brain imaging together with our colleagues in Vienna. With the advent of a clinically approved UHF system, we will continue this line of research in Bern in 2019.

### Machine Learning

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.



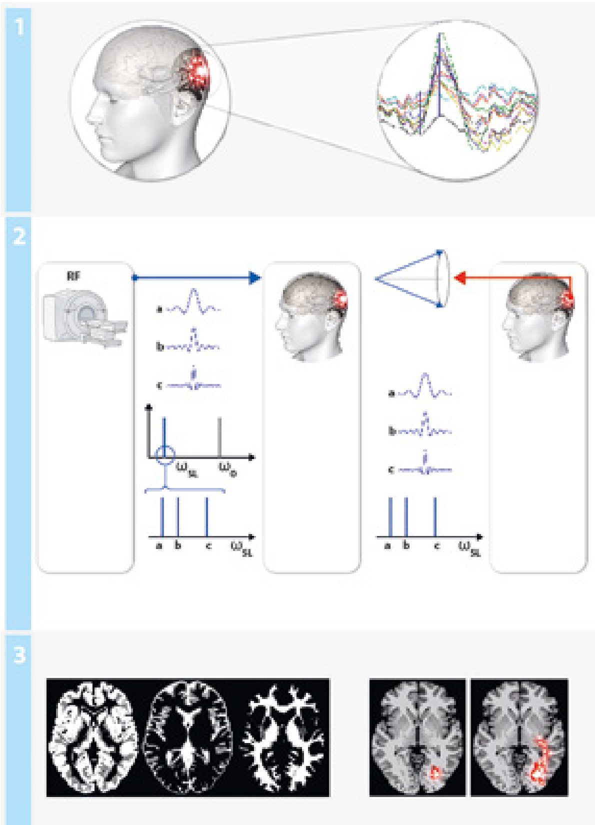
Specific fields where we develop and apply machine-learning techniques include:

- discovery of imaging biomarkers for brain tumors (Meier et al., 2016) and stroke (Pereira et al., 2018)
- image-segmentation techniques to identify lesions and neuroanatomical structures from native and contrast- enhanced T1-weighted, T2-weighted and FLAIR images (McKinley et al., 2016)
- triage patients and predict tissue damage and patient outcome in stroke (McKinley et al., 2017)

**Clinical Imaging: The Swiss-First Study**

In an SNF-funded international SINERGIA project, we collect and analyze neuroimaging (MRI) and electrophysiological (EEG) data from patients who experience a first event with transient neurological deficit or loss of consciousness at seven Centers in Switzerland. Between 10-15% of the population have a seizure or seizure-like event in their lifetime. This may remain isolated or mark the beginning of epilepsy. The development of new diagnostic tools based on easily accessible and non-invasive techniques like EEG and MRI will improve patient care.

At the SCAN we make use of recent advances in MRI sequence developments and signal analysis to investigate abnormalities reflecting preexisting epileptogenesis and/or an increased risk for seizure recurrence. We combine neural current imaging (Kiefer et al., 2016) and morphometric MRI analysis (Rummel et al., 2017, 2018). All information will be subjected to machine-learning algorithms. Preliminary studies suggest very good performance of the outlined methods in differentiating epileptogenic from non-epileptogenic activities in patients with chronic epilepsy. Within the project, we aim to extend these methods to patients admitted at the emergency department and determine their yield in differentiating early-onset epilepsy versus clinically similar events of other origins.

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# Orthopedic Surgery and Traumatology

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**Klaus A. Siebenrock** | Matthias Zumstein | Lorin M Benneker | Moritz Tannast | Frank M. Klenke | Fabian Krause | Sven Hoppe

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Willy Hofstetter, Department of Clinical Research, University of Bern
Ernst Hunziker, Department of Orthopedic Surgery, Inselspital, Bern University Hospital
Hans-Jörg Sebald, thespinecenter, Thun
Waldo Vanlenzuela, Institute for Surgical Technologies and Biomachanics, University of Bern

### Research Profile

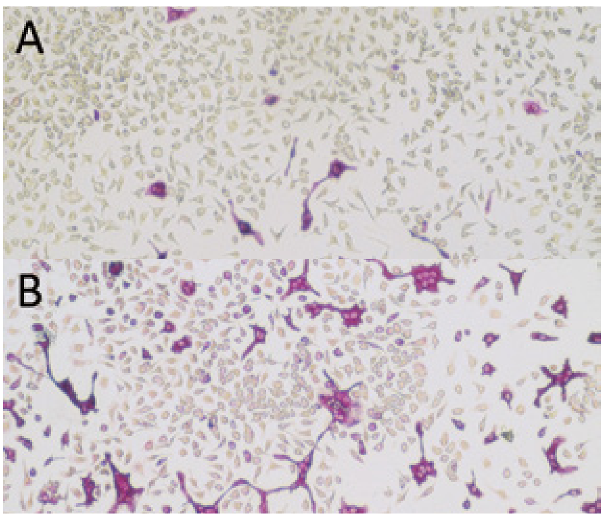
The Department of Orthopedic Surgery consists of six research groups. In each specific field, we perform clinical as wells as pre-clinical and basic research. Hip research focuses on the development of osteoarthritis and pre-arthritic deformities like femoroacetabular impingement. 3D MRI is used to simulate pre-arthritic deformities and access early stages of chondral lesions. In a sheep model, different impingement morphologies and its treatment can be simulated. Spine research is focused on disc-degeneration models and tissue-engineered disc regeneration and the treatment of osteoporotic fractures. The main focus of knee research is the regenerative treatment of the anterior cruciate ligament. Prosthetic infections and anti-infectious implants are also research topics. The shoulder and elbow team is working on statistical shape modeling of shoulder morphology, rotator cuff regeneration including stem cells, and the investigation of surgical techniques and implants. Arthrosis of the ankle joint, innovative treatment of ankle fractures, and AMIC plastic in osteochondral lesions is the main focus of foot and ankle research. Translational medicine is the latest research field which that come to focus the during the next years.

### Regulation of BMP Signalling

BMP-2 and BMP-7 have been approved for clinical use for bone regeneration. However, the growth factors are required at supraphysiological concentrations to stimulate bone healing effectively.

Endogenous antagonist induced by exogenous BMP therapy may be responsible for the limited clinical efficacy of BMPs. We, along with other researchers, have shown that BMPs induce the expression of their antagonists such as Noggin, Gremlin, and Chordin *in vitro*. To enhance the osteogenic activity of BMPs, L51P, a molecularly engineered BMP-2 variant with deficient BMP receptor binding but unchanged binding to modulator proteins, such as Noggin, Gremlin, and Chordin has been developed. The modification made L51P a BMP receptor-inactive inhibitor of BMP antagonists. *In vitro*, L51P reversed the Noggin-mediated inhibition of BMP-2-induced alkaline phosphatase expression in C2C12 promyoblasts and primary murine osteoblasts. L51P itself did not induce osteoblast differentiation directly and did not activate BMP receptor-dependent intracellular signalling due to deficient BMP type I receptor-binding.

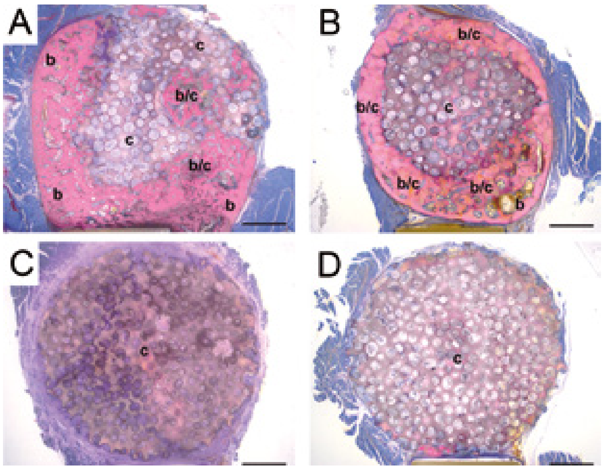
Recent data suggest that the BMP-antagonist Noggin stimulates osteoclast development of osteoclast progenitor cells (OPC) in the presence of trace levels of the osteoclast growth factor Receptor Activator of NF-κB Ligand (RANKL). The finding that the Noggin effect on osteoclast development could not be blocked by L51P, led to the hypothesis that Noggin action is not restricted to an anti-osteogenic effect by blocking BMP actions, but that Noggin supports osteoclastogenesis through a direct and eventually receptor-mediated mechanism. We have collected evidence that Noggin, by an as-yet-unknown pathway, activates TGFβ signaling. Furthermore, recently evidence was published that linked RANKL signalling to the family of lgr orphan receptors, which in turn may be activated by members of the R-spondin family and by Noggin. While lrg5 has been used as markers for adult stem cells, we have generated evidence that the members of this family of proteins are expressed in differentiating haematopoietic cells as well. Further elucidation of the effects of BMP-2 treatment on the induction of endogenous antagonists and the regulatory function of these antagonists is essential and will help to minimize BMP-therapy-associated adverse effects and improve the clinical efficacy of BMP-2 treatment.




BMP-antagonist Noggin enhances RANKL mediated OC formation. TRAP staining of OPC cultures on day 5 after addition of RANKL 2.5 ng/ml (A) and RANKL 2.5 ng/ml with Noggin 33 nM (B).

**Bone Substitute Materials**

Autologous bone is widely accepted as the standard biologic material to augment bone healing and to reconstruct bone defects. There are, however, critical limitations associated with the harvest of autologous grafts, such as donor site morbidity, prolonged surgery time, and limited supply. Calcium phosphate (CaP) ceramics such as beta-tricalcium phosphate (β-TCP) ceramics have been approved for the repair of osseous defects. However, new bone formation and the substitution of the materials by authentic bone remains incomplete. Therefore, BMP have been used to improve bone defect healing with bone substitute materials. Using animal models established together with the Group for Bone Biology and Orthopedic Research, the healing of critical size bone defects with CaP-based biomaterials has been studied extensively. Furthermore, a sustained delivery system of growth factors from CaP ceramics has been established in collaboration with Prof. E. B. Hunziker and Prof. Y. Liu (Academic Center for Dentistry Amsterdam, The Netherlands).




RANKL augments bone formation and accelerates biomaterial degradation of β-TCP cylinders implanted into rat femur defects when combined with BMP-2/L51P. Implants loaded with 25 μg/ml RANKL, 1 μg/ml BMP 2, 10 μg/ml L51P (A, B) and vehicle control (C, D), McNeal tetrachrome-stained histologies after 8 (A, C) and 16 weeks (B, D). Scale bars 1 mm.

Sustained delivery of BMP-2 was shown to promote healing of long bone critical size defects in a femur defect model in rats. More importantly, L51P loaded to β-tricalcium phosphate (β-TCP) ceramics reduced the demand of exogenous BMP-2 to induce bone healing without promoting bone formation directly when applied alone. Although bone formation was enhanced significantly, material turnover of BMP-2 and L51P loaded β-TCP ceramics remained incomplete when the materials in critical size segmental bone defects. Therefore, our group focused its research on the promotion of cell-mediated material resorption as a means to enhance β-TCP-ceramic-associated bone repair more recently. The osteoclast growth factor RANKL was incorporated into β-TCP ceramics and was shown to induce the formation of active, resorbing osteoclasts on the material surface and to stimulate the cell-mediated calcium phosphate resorption *in vitro*. *In vivo*, stimulation of osteoclast-mediated resorption may contribute to a coordinated sequence of material resorption and bone formation. Future research will investigate whether RANKL delivery is a promising tool to promote the substitution of CaP-based ceramic biomaterials by new bone *in vivo*.

**Imaging**

The complexity of lower back pain is likely to be beyond the horizon of a simple bony disease. Sarcopenia, muscle degeneration plays a more important role than yet perceived and will necessitate increased attention in the future. Factors influencing paraspinal muscle degeneration are still not well understood. Fatty infiltration is known to be one main feature of the degeneration cascade. The main interest of our research is to illustrate the cluster of paraspinal lumbar muscle degeneration on MRI. Using a novel semiautomatic technique for quantitative muscle/fat discrimination, MRI sequences can be compared on a three-dimensional basis and can be analyzed regarding the most influential factors of the degeneration cascade (collaboration with Dr. W. Valenzuela, ISTB). Another research focus lies in the classification of disc and annulus fibrosus degeneration and pathologies using quantitative MRI techniques (collaboration with ISTB, DCR and Dep. of Radiology, Inselspital).

**Regenerative Medicine for Disc Degeneration:**

Degenerative disc disease has a very large socio-economic relevance affecting a large proportion of the population. As surgical solutions are costly and have their limitations, we investigated for more than 15 years regenerative strategies using whole organ cultures (bioreactors) where the role of stem cells and therapeutic agents can be assessed in a relevant and controlled environment. Currently, the latest developments in Nucleus pulposus regeneration and Annulus fibrosus repair from the unique bioreactors are being transferred into large animal models (collaboration with Prof. B. Gantenbein ISTB, Bern and Prof. M. Alini, AO Research Institute Davos).

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# Radiology Research Group

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## Research Partners

Iris Baumgartner and Team, Department of Angiology, Inselspital, Bern University Hospital
Thierry Carrel and Team, Department of Cardiac Surgery, Inselspital, Bern University Hospital
Daniel Candinas and Team, University Clinic for Visceral Surgery and Medicine, Inselspital, Bern University Hospital
Jean-François Dufour and Team, Swissliver, University of Bern and Inselspital, Bern University Hospital
Frauenhofer MeVis, Bremen and Berlin, Germany
Thomas Geiser and Team, Pulmonary Unit at the University Hospital of Bern
Industry: ANSYS, Canonsburg, PA, USA; Cascination, Bern
Roland Kreis, AMSM, Bern
Dominik Obrist and Team, Cardiovascular Engineering, ARTORG, University of Bern
Aurel Perren and Team, Institute of Pathology, University of Bern
Jürg Schmidli and Team, Department of Vascular Surgery, Inselspital, Bern University Hospital
Stefan Weber and Team, ARTORG, University of Bern and by the University Hospital
University of Sheffield

### Research Profile

Biomedical imaging plays an essential role in leading research and rapid development in healthcare. Using state-of the-art infrastructure, non-invasive imaging biomarkers are available to perform quantitative image analysis, enhancing, therefore, translational research. Artificial intelligence and machine learning permit the analysis of a massive amount of imaging data for knowledge extraction, which may be enhanced by considering the entire spectrum of available clinical, biological, and genetic information. Novel deep "algorithmic approaches" open the road toward big data analysis. Up-to-date technology is being introduced and tested to co-develop prototypes together with our interdisciplinary partnerships. Collaborations, like the one with ARTORG, strengthen the role of biomedical imaging and intervention within a multi-disciplinary team, to nourish our healthcare system and the hospital's future joint vision. Personalized medicine requires advanced tissue diagnosis involving diagnostic radiology, as well as image-based Intervention. MR-guided intervention avoids ionizing radiation while providing real-time imaging during the procedure and methods for hot-spot targeting. Many patients may benefit from image-guided therapy by reducing intervention time and increasing minimal invasive procedures' precision.

### Machine-Learning-Based CAD System for ILD Diagnosis

Interstitial lung diseases (ILD) are a heterogeneous group of more than 200 chronic, overlapping lung disorders, characterized by fibrosis and/or inflammation of the lung tissue. The diagnosis of 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. Computer-aided diagnosis (CAD) systems could enhance the diagnostic performance of radiologists for interstitial lung diseases.

We introduced and evaluated INTACT, an end-to-end system for the automatic classification of HRCT images, into four radiological diagnostic categories. The proposed CAD system consists of a sequential pipeline, in which first the anatomical structures of the lung are segmented, then the pathological lung tissue is identified, and finally by combining this information a final radiological diagnosis is reached. The overall pipeline is based on novel machine-learning algorithms that have been designed for the task of diffuse pathological tissue segmentation.

Our group receives funding from the Swiss National Science Foundation (SNF; grant number 32003B_156511) and the Lindenhof Foundation (17-08-F).

### Flow-sensitive 4D MRI of Cardiovascular Hemodynamics

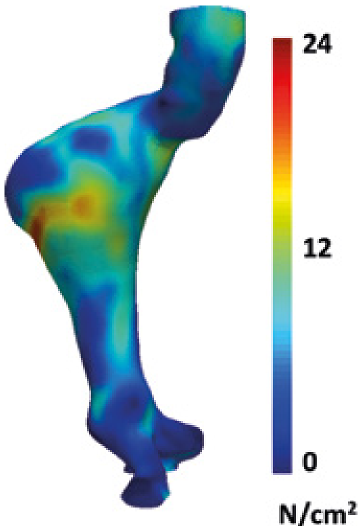
Flow-sensitive 4D magnetic resonance imaging (4D flow MRI) is a powerful tool to non-invasively assess cardiovascular hemodynamics in vivo. 4D flow

MRI allows the investigation of the impact of pathophysiological alterations in the cardiovascular system on the flow conditions as well as the determination of hemodynamic parameters such as pressure differences. Furthermore, hemodynamics can be acquired in well-controlled in-vitro model systems offering the possibility to test and predict hemodynamic consequences of alterations of the vessel geometry or using such data as a test bench for computational simulations. We are developing the entire range of applications from acquisition to post processing of hemodynamic data, including flow visualization, vessel segmentation, and quantification. Applications encompass in-vivo studies of time-resolved 3D flow patterns in normal and pathological vascular geometries as well as in-vitro studies of realistic MR-compatible models consisting of an aorta model produced by rapid prototyping and a ventricular assist device.

**Abdominal Aortic Aneurysm Rupture Risk Analysis**

After an incidental diagnosis, the threshold for abdominal aortic aneurysm (AAA) repair is based on either a maximum diameter of 5.5 cm (in males; 5 cm in females), a growth rate of ≥1 cm/year or pain, depending on whether the AAAs are symptomatic or asymptomatic. Patients who do not fall under any of these criteria are kept under surveillance and their aneurysms are imaged every three to eighteen months. Looking only at aneurysm size is limited since we know from autopsy studies that small aneurysms account for 10% to 24% of all ruptured AAAs.

Our research mainly focuses on biomechanical, geometric, clinical, and texture-based indices of AAAs to classify them based on rupture risk. The protocol for biomechanical analysis of AAAs begins from segmentation of MR/CT images to extract contours of the inner wall, outer wall, and lumen of the aorta. A resulting patient-specific 3D reconstruction of the AAA is used to generate volume and surface meshes, which are used as input to a finite element model to evaluate the distribution of first principal stress (shown in figure). Distribution of wall strength is also evaluated at the corresponding elements. The ratio of wall stress and wall strength at each element generates a distribution of rupture potential index (RPI) on the surface of the AAA.




Peak wall rupture risk index (PWRRI) is evaluated as the maximum value of RPI and represents the rupture potential of each patient-specific AAA.

**Interventional Radiology**

*a) MR Intervention*

Image-guided minimal-invasive interventional procedures are state-of-the-art diagnostic and therapeutic modalities. This enables the collection of fluids and tissue samples for diagnostic purposes as well as performance of minimal-invasive therapies e.g. focal tumour therapy. Most procedures are performed under ultrasound (US) or computed-tomography guidance (CT) with known side effects including poor visibility of deep-seated lesions (US) or radiation exposure (CT). MRI-guided procedures promise fewer side effects and improve detection of lesions, especially for soft tissue lesions. However, many technical problems must be overcome as MRI involves strong magnetic fields and radiofrequency radiation. Our group develops new devices for MRI-guided interventions, new techniques, and new applications. This project is carried out in close collaboration with Siemens Medical Systems.

*b) Soft Tissue Biopsy Optimization*

Biopsy needle systems may be commercially labelled as of the same caliber, but they differ in terms of micro-mechanical characteristics. The micro-mechanical differences between needles mainly consist of needle external diameter, needle tray height, and effective needle tray length. The purpose of our research is to assess those micro-mechanical needle system characteristics that influence the performance of needle systems in terms of tissue quantity and quality.

**Medical Imaging Computational Lab (MICAL): Radiomics and Imaging Biomarkers**

Modern image processing applications are becoming increasingly complex, and their efficient use requires adequate infrastructure and dedicated personnel. Highly standardized and innovative imaging protocols are being used for high-quality level of processing results. Our research efforts incorporate testing of new applications, as well as co-development with partners from academics and industry. We are establishing a medical imaging computational laboratory that is attractive to our participating clinical and biomedical partners. We are continuously extending our portfolio, producing surrogate parameters/radiomics to represent various functional and structural information. Our precise segmentation results are incorporated into translational and disruptive techniques, including rapid prototyping. To achieve the best benefit for all partners we are synchronizing our processing strategy with the Insel Data Science Center (IDSC) and Insel Data Coordination Lab (IDCL).

**Selected Publications**


Anthimopoulos MM, Christodoulidis S, Ebner L, Geiser T, Christe A, Mougiakakou SG. Semantic Segmentation of Pathological Lung Tissue with Dilated Fully Convolutional Networks. IEEE J Biomed Health Inform. 2018 Mar 26

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# Department of Cardiology

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|---|---|---|---|---|
| **Stephan Windecker** | Thomas Pilgrim | Lorenz Räber | Tobias Reichlin | Marco Valgimigli |

## Research Partners

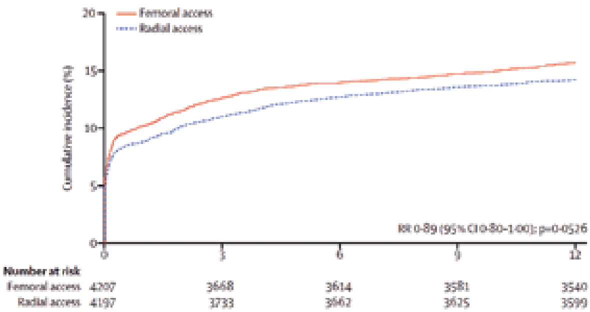
Clinical Trials Unit, University of Bern
Departments of Cardiology at the University Hospitals Zurich, Basel, Fribourg, Lausanne, and Geneva

### Research Profile

The Department of Cardiology at Bern University Hospital has a broad range of clinical research activities. They encompass investigations of devices for the percutaneous treatment of coronary artery and valvular heart disease, studies for the treatment of electrophysiological disorders of the heart, as well as clinical trials of medicinal products (for example, antithrombotic drugs to prevent thromboembolism and of lipid-modifying drugs for cardiovascular risk reduction). The teams are involved in large-scale, multicenter, international, randomized clinical trials as well as in first-in-man human studies using innovative products. The research group has well-established national and international partnerships.

### Coronary Artery Disease

Cardiovascular ischemic events commonly arise from atherosclerotic plaque rupture leading to platelet activation, thrombus formation, and reduction of blood flow to the heart or brain. Antithrombotic therapy is central to prevent blood clot formation but it increases bleeding risk. One of the main scientific activities was the balance between the risk of myocardial ischemia and bleeding prevention in patients with coronary artery disease, undergoing percutaneous coronary intervention. The final one-year results of the large-scale, randomized MATRIX trial established the superiority of radial over femoral access site for percutaneous coronary intervention.




Co-primary composite outcome of all-cause mortality, myocardial infarction, or stroke at 1 year in patients randomised to radial versus femoral access.

The GLOBAL LEADERS is an open-label, superiority randomized trial designed to challenge the current treatment paradigm of dual antiplatelet therapy (DAPT) for 12 months followed by aspirin monotherapy among patients undergoing percutaneous coronary intervention (PCI). The final two-year results of the large-scale randomized GLOBAL LEADERS trial were presented at the 2018 European Society of Cardiology congress in Munich and published in the Lancet.

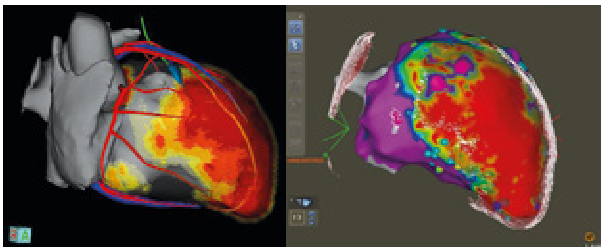
The five-year results of the randomised, single-blind, multicentre, non-inferiority BIOSCIENCE trial were published this year. Sirolimus-eluting stents with a biodegradable-polymer coating were compared to everolimus-eluting stents with a non-resorbable polymer coating. The five-year risk of target lesion failure among all-comer patients undergoing percutaneous coronary intervention was similar in both groups.

### Structural Heart Disease

Transcatheter Aortic Valve Replacement (TAVR) represents an alternative treatment for patients with severe aortic valve stenosis at increased surgical risk. Refinements in device technology, improved imaging, and streamlining of the procedure resulted in a decline in peri-procedural complications, setting the stage for TAVR expansion to intermediate- and low-risk patients. Our group compares different strategies for the treatment of valvular heart disease, investigate the importance of cardiac comorbidities on clinical outcomes, and investigates newer-generation devices for the treatment of aortic stenosis.

### Electrophysiology

The interventional treatment of cardiac arrhythmias has been the treatment in the field of cardiology with the most spectacular progress over the past decade. In 2018, the Inselspital for the first time has become the academic center with largest ablation volume in Switzerland. The interventional treatment of atrial fibrillation and ventricular tachycardias are the most complex procedures and the focus of our research activities. For the ablation of ventricular tachycardias, we are assessing the value of preprocedural imaging by means of cardiac CT or MRI for multimodality substrate assessment.



Catheter-Ablation of ventricular Tachycardia using Image Integration of pre-processed cardiac CT's for multimodality substrate assessment

**Selected Publications**


Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P; MATRIX Investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet. 2018 Sep 8;392(10150):835-848. doi: 10.1016/S0140-6736(18)31714-8. Epub 2018 Aug 25.PubMed PMID: 30153988

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METTLER TOLEDO

# BIOMEDICAL ENGINEERING RESEARCH AT OTHER INSTITUTES OF THE UNIVERSITY OF BERN

Supplementary to the previously mentioned institutions concerned with biomedical engineering research, a number of additional research institutions of the University of Bern, active in vastly different domains of science, also conduct specific research activities in biomedical engineering.

While the research interests of the institutes lie in differing domains, biomedical engineering research, with its interdisciplinary nature, benefits greatly from the specific expertise that these technological and scientific institutes provide.

# Clinical Trials Unit CTU Bern

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**Sven Trelle**

## Group Members

More than 50 staff members with different backgrounds, from statistics, biology, and informatics to quality management

## 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

### Research Profile

CTU Bern is the clinical trials unit of the Faculty of Medicine of the University of Bern and Inselspital, Bern University Hospital.

The aims of CTU are to support and collaborate in clinical trials, epidemiological studies, and meta-analyses in any clinical field to strengthen and expand the evidence base for health care nationally and internationally. CTU offers the scientific, technical, and computing expertise needed to support patient-oriented clinical research at all stages, from conception to completion and dissemination. Relevant expertise is provided within the unit itself or by facilitating and coordinating contact with outside experts. Services are provided in a modular fashion and range from advice and general support to full development of the design and conduct of clinical studies. CTU Bern works according to established scientific standards and the services offered by the unit enable clinical researchers to comply with legal and regulatory requirements.

CTU Bern is organized into five divisions: Statistics and Methodology, Data Management, Project Management, Monitoring and Regulatory Affairs, and Clinical Investigation. These divisions provide a range of services from methodological consulting, to GCP-compliant data management solutions, central/on-site monitoring, and statistical analysis. Although the primary focus of CTU Bern lies on late-phase clinical studies, it has some expertise on early- phase clinical trials, including exploratory clinical trials.

### 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.

The statistical staff at CTU Bern has wide experience in analyzing various study types such as:

- Cohort and case-control studies
- Randomized-controlled trials, including cluster-randomized trials
- Diagnostic accuracy and method comparison studies
- Meta-analyses, including meta-regression and network meta-analysis

using statistical analyses techniques such as:

- Multivariable model-building
- Multilevel/mixed-effects models
- Multivariate analysis (psychometrics)
- Survival analysis
- Bayesian statistics

CTU Bern has only limited infrastructure for large-scale data analysis such as analyzing genome-wide association studies.

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.

### Data Management

CTU Bern provides and maintains a secure and up-to-date IT infrastructure. The servers hosting the study databases are stored in a dedicated server facility. 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:

*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 setup 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 make it productive, so that data-entry can start.

*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.

**Quality Assurance and Monitoring**
CTU Bern offers quality control 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 Conference on 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.

**Clinical Investigation**
Clinical Investigation is a service unit within the CTU Bern 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.

**Selected Publications**


Pilgrim T et al. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial. Lancet. 2018; 392: 737-46

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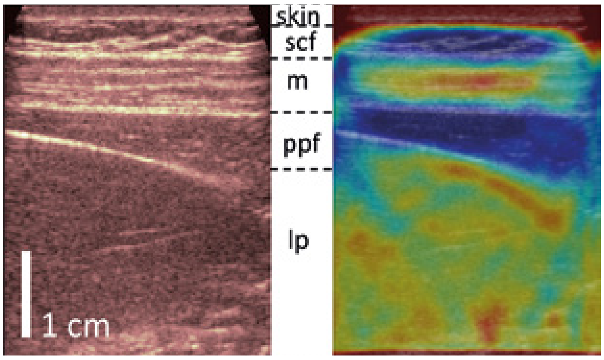
EU-Horizon 2020 Project partners "Risk assessment of plaque rupture and future cardiovascular events (CVENT) by multi-spectral photoacoustic imaging"
EU-Horizon 2020 Project partners "Photoacoustic/Ultrasound Mammoscopy for evaluating screening-detected abnormalities in the breast (PAMMOTH)"

### 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 in which lasers are 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 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 optoacoustic imaging techniques, an emerging molecular imaging modality offering to image tissue structures and function and having the potential of patient-tailored tumor nano-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 nano-sized contrast agents and how to determine their biodistribution in the body? and (iii) How to improve multimodal optoacoustic devices for clinical use simultaneously measuring echo and Doppler ultrasound, tissue elastography, speed of sound, and optoacoustics? Additional main topics are two-photon imaging and interactions of ultrashort near infrared laser pulses with biological soft matter as well as laser-induced tissue soldering using nanoparticle doped scaffolds.

### Optoacoustic Imaging

Optoacoustic (OA) imaging allows the display of optical contrast inside tissue based on detection of thermoelastically generated ultrasound after tissue irradiation using short 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 oxygenation level within the anatomical context. An important requirement for such a combination is a clinically useful OA imaging depth of several centimeters. This has been difficult to achieve in the past owing to clutter signals originating from the site of tissue irradiation. We have combined a fiber coupled tunable laser source and a research ultrasound system, which allows real-time imaging and freehand clinical scanning of humans.
Sound speed as a diagnostic marker has been of interest for many years due to the fact that sound speed can reveal structural changes of tissue that come 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 presence of acoustic aberrations. We are developing a technique where spatially resolved quantitative detection of sound speed is achieved using conventional pulse-echo ultrasound. This technique is promising as an addition to conventional ultrasound, as




Combined US (left) and speed-of-sound (right) imaging in echo mode. Blue and red show low and high speed of sound, respectively. scf: subcutaneous fat, m: muscle, ppf: post-peritoneal fat, lp: liver parenchyma.

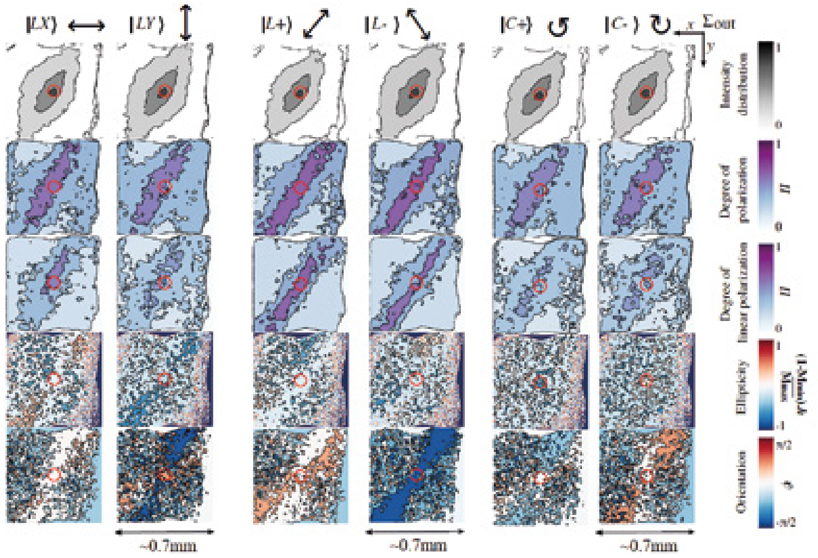
well as for improving spatial resolution and contrast of all ultrasound-based modalities including OA imaging. Our reserach is directed towards the developemnt of a multimodal diagnostic imaging system combining classical echo and Doppler ultasound with elastography, optoacoustic, and speed-of-sound measurements.

**Combined quantitative optoacoustic and near-infrared imaging**

In collaboration with the University of Zurich, we combine an OA/US system with near-infrared imaging with the goal of developing a safe bedside imaging method that can detect spatially resolved oxygenation levels deep inside the brain of preterm neonates and is able to monitor the effects of preventive and neuroprotective interventions. Cerebral ischemia is considered a key initiating factor for periventricular diffuse white matter injury (WMI), which has become the dominant brain pathology and is the major reason for persisting spastic motor deficits and cognitive abnormalities in preterm infants. Near-infrared imaging allows us to reconstruct the slow spatial variations of hemoglobin concentrations based on diffuse optical reflectivity, and complement OA imaging, which shows the blood oxygenation level of distinct vessels and capillaries at high spatial resolution. At the same time, near-infrared imaging provides the optical properties of the tissue that are required for quantitative optoacoustic imaging. Parallel to conducting phantom studies to demonstrate the feasibility of our approach and to optimize our multimodal imaging system, we are preparing our clinical trials.

**Polarimetric microscopy**

With more than 120 various tumor types, malignant brain tumors are a particularly difficult disease to diagnose. Brain surgery constitutes the first and decisive step for the treatment of such tumors and is followed by adjuvant therapy. It is extremely crucial to achieve complete tumor resection during surgery; nonetheless, this is a highly challenging task, as it is very difficult to visually differentiate tumorous cells from the surrounding healthy white matter tissue. An erroneous estimation of the tumor's borders carries heavy consequences for the patient: If the tumor is not entirely resected, there is an almost 50% risk of tumor recurrence; on the other hand, if healthy tissue is removed, this might irrevocably damage the brain, leading to irreversible disabilities. Therefore, a clear and unambiguous distinction between the tumor and its surrounding is paramount during surgery. Polarimetry is emerging as a new diagnostics tool. The interaction of polarized light with matter often reveals 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 outgoing intensities (these correlations being commonly coded in the 4x4 Perrin-Mueller matrix). The 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 bases of polarized light propagation in random media.




Stokes vector characterizing intensity, degree of polarization, degree of linear polarization ellipticity and tissue structure orientation measured at six different polarization input states.

## Selected Publications


Leonie Ulrich et al.: Spectral correction for handheld optoacoustic imaging by means of near-infrared optical tomography in reflection mode, Journal of Biophotonics, ed.: J. Popp, vol.: 12, no.: 1, pp.: e201800112, 2019

Manes Hornung, Arushi Jain, Martin Frenz, H. Günhan Akarcay: Interpretation of backscattering polarimetric images recorded from multiply scattering systems: a study on colloidal suspensions, Optcs Express, ed.: James Leger, vol.: 27, no.: 5, pp.: 621, 2019

Mariana De Niz et al.: Toolbox for in vivo imaging of host-parasite interactions at multiple scales, Trends in Parasitology, ed.: Pengfei Kong, vol.: 35, no.: 3, pp.: 193-212, 2019

Tigran Petrosyan, Maria Theodorou, Jeff Bamber, Martin Frenz, Michael Jaeger: Rapid scanning wide-field clutter elimination in epi-optoacoustic imaging using comb LOVIT, Photoacoustics, ed.: Vasilis Ntziachristos, vol.: 10, pp.: 20-30, 2018

Maju Kuriakose, Jan-Willem Muller, Patrick Stähli, Martin Frenz, Michael Jaeger : Receive beam steering and clutter reduction for imaging the speed-of-sound inside the carotid artery, Journal of Imaging, vol.: 4, no.: 12, pp.: 145, 2018

# Computer Vision Group

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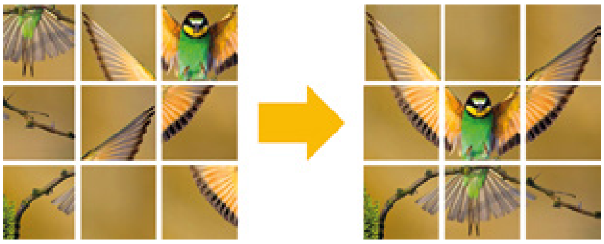
**Research Profile**

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 machinelearning 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.



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 of the composition of objects.

**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.

Disentangling the factors of variation for celebrity faces. After we obtain a disentangled representation of a face, we can select a part of it, e.g. sunglasses (left) or head pose (right), and search for nearest neighbors that match the selected feature chunk.

**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 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.

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.

Example of a motion blurred image of a moving object (left). Learned from a large database of blurred and sharp image pairs, we are able to invert the blurring process and restore the sharp texture details such as the text shown here.

### Selected Publications

M. Jin, G. Meishvili, and P. Favaro (2018) Learning to Extract a Video Sequence from a Single Motion Blurred Image. Proc. of the IEEE Conference on Computer Vision and Pattern Recognition (CVPR)

M. Jin, S. Roth, and P. Favaro (2017) Noise-blind image deblurring. Proc. of the IEEE Conference on Computer Vision and Pattern Recognition (CVPR)

M. Jin, S. Roth, P. Favaro (2018) Normalized Blind Deconvolution. European Conference on Computer Vision (ECCV)

Q. Hu, A. Szabó, T. Portenier, M. Zwicker and P. Favaro (2018) Disentangling Factors of Variation by Mixing Them. Proc. of the IEEE Conference on Computer Vision and Pattern Recognition (CVPR)

M. Noroozi, A. Vinjimoor, P. Favaro and H. Pirsiavash (2018) Boosting Self-Supervised Learning via Knowledge Transfer. Proc. of the IEEE Conference on Computer Vision and Pattern Recognition (CVPR)

M. Noroozi and P. Favaro (2016) Unsupervised Learning of Visual Representations by Solving Jigsaw Puzzles. European Conference on Computer Vision (ECCV)

S. Jenni, and P. Favaro (2018) Self-Supervised Feature Learning by Learning to Spot Artifacts. Proc. of the IEEE Conference on Computer Vision and Pattern Recognition (CVPR)

# Institute of Psychology, Cognitive Psychology

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### Research Profile

The Department of Cognitive Psychology at the Institute of Psychology investigates the basic mechanisms that underlie cognitive functions like perception, mental imagery, learning, decisions and spatial orientation. Our laboratories are equipped with virtual reality technology, a MOOG motion platform, eye-tracking facilities, EEG, GVS, and CVS. The members of the group are experienced with various psychophysical methods, advanced statistical data analysis, and computational modelling. We are responsible for introductory and advanced statistics courses in the psychology curriculum. As well as being strongly involved in basic research projects, we are keen on implementing our findings in clinical research. Promoting cognitive performance will become a primary challenge for the future of society as life expectancy has increased rapidly, while simultaneously knowledge decays faster and faster. We frequently collaborate locally with partners from ENT, neurology, psychiatry, and pathology, and we are engaged in several international collaborations. The PI currently co-leads the interfaculty research collaboration "Decoding Sleep."

### Mental Imagery: Seeing with the Mind's Eye

Mental imagery is a core cognitive ability, which aids problem solving, memory, planning, and creativity. We investigate the neuro-cognitive mechanisms that underlie mental imagery, develop tools to measure individual differences, explore new ways to use mental imagery in cognitive training, and investigate how mental images interact with sensory processing from other modalities. We were able to demonstrate that mental-imagery training improves performance in visual-perception tasks. The perceptual threshold was reduced in the same manner as expected after perceptual learning with real stimuli. Previous models on perceptual learning all require a physical stimulus whereas our experiments revealed that perceptual learning - the most basic form of learning - can result from imagery

Virtual reality set-up for immersion in realistic scenes and interaction with avatars. The head-mounted display is equipped for eye tracking.

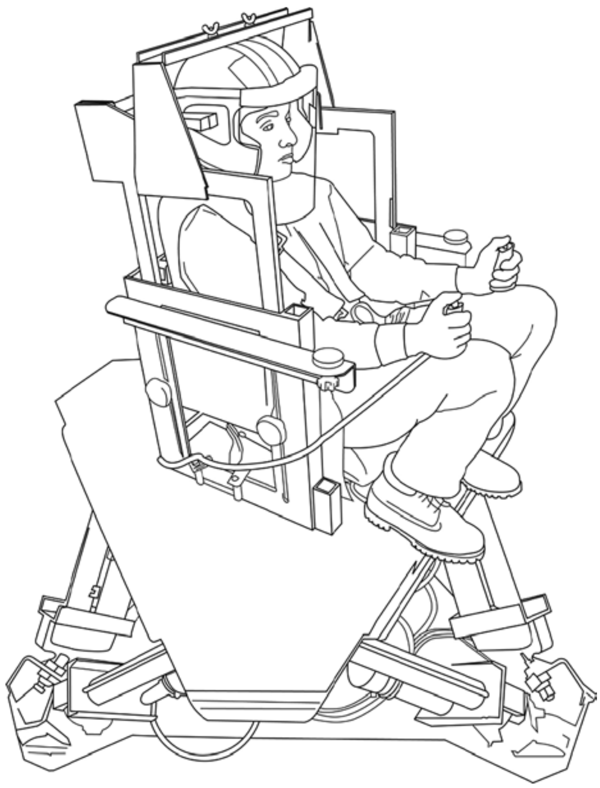
training (funded by SNF). Moreover, recent research from our group shows that there are systematic eye movements during mental imagery even though there is no perceptual input to be processed. The eyes tend to revisit the location where stimuli have been encoded when the information needs to be retrieved at a later point in time. We are currently examining in more detail the non-sensory role of eye fixations during memory retrieval, mental image construction, and mental image scanning, including patient groups and with the use of TMS and MEPs. Once we know more about the functional role of eye movements in memory and imagery, we can design interventions to promote cognitive performance.

**Decisions in Medical Diagnostics**

More recently, we started to investigate decisions in medical diagnostics. We analysed how pathologists make decisions, and how decisions are influenced by prior experience (inner ear and pathology). We investigate when biases in judgment start to emerge and what can be done to counteract the bias. This could be implemented in professional education. Cognitive psychology has a lot to offer, and its use in the clinical context is by far not exploited.

**Spatial Cognition and the Vestibular Sense**

Several projects focus on the processing of gravito-inertial information, and we use Bayesian statistics for modelling and to analysing mechanisms of perception (e.g., subjective visual vertical). In several experimental studies, we were able to demonstrate that vestibular information is involved in high-level cognitive tasks such as mental body transformations, numerical cognition, affective processes, empathy, and decisions. In collaboration with the ENT Department, we are currently developing cognitive rehabilitation tools for unilateral and bilateral vestibular patients suffering from chronic symptoms (e.g., vertigo). Using an extended training regime, we aim to activate via top-down processes cortico-fugal vestibular projections in order to counteract the asymmetry in brainstem vestibular nuclei as they result from unilateral loss (funded by SNF).



Moog motion platform (six degrees of freedom) used for psychophysics of self-motion perception.

Portraitfotos: © Luca Christen, 2019; Group members without picture: M. Ertl, A. Moye

**Selected Publications**


Martarelli CS, Mast FW (2013) Eye movements during long-term pictorial recall. Psychol Res, 77(3):303-309

Moser, I., Vibert, D., Caversaccio, M.D. & Mast, F.W. (2017). Impaired math achievement in patients with acute vestibular neuritis. Neuropsychologia, 107, 1-8

Grabherr, L., Jola, C., Berra, G., Theiler, R. & Mast, F.W. (2015). Motor imagery training improves precision of hand movement in hemiparetic patients. NeuroRehabilitation, 36, 157–166. doi:10.3233/NRE-151203

Gurtner, L., Bischof, W.F. & Mast, F.W. (2019). Recurrence quantification analysis of eye movements during mental imagery. Journal of Vision, Vol.19, 17. doi:10.1167/19.1.17

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# Translational Biomaterials Research in Implant Dentistry and Periodontology

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Various industry partners, e.g. Straumann, Basel; Geistlich Pharma AG, Wolhusen; Curaden AG, Kriens; Regedent, Zürich
Tateyuki Iizuka, Director and Head of Department of Cranio-Maxillofacial Surgery
Reyes Mauricio, Head Image Analysis, Institute for Surgical Technology & Biomechanics

### Research Profile

The research focus is primarily translational and clinical focusing on in vitro and in vivo evaluation of novel antimicrobials with potential effects for the treatment of dental related infections (e.g. caries, periodontitis and periimplantitis), novel biomaterials for hard and soft tissue regeneration around natural teeth and dental implants. It involves a strong network of basic researchers and clinicians from the various clinics from the School of Dental Medicine, medical hospital and numerous international centers.

### Highlights in research

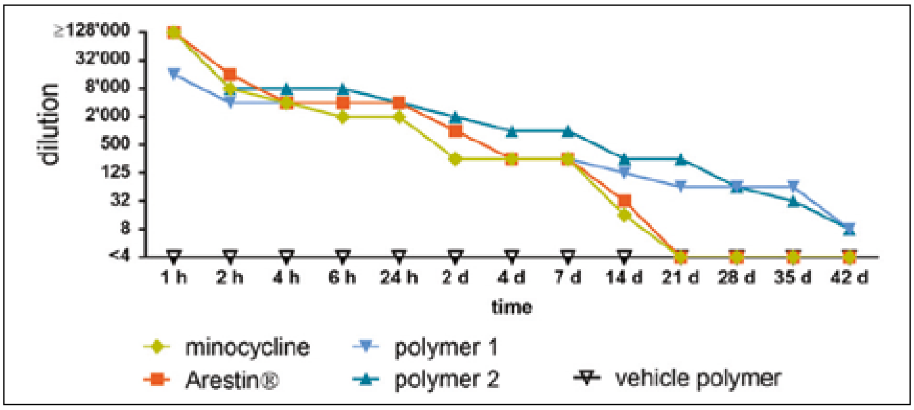
*Oral microbiology*

Novel modalities for the antimicrobial therapy of periodontitis were also evaluated in various in vitro models. New polymer formulations (developed at University Halle, FHI-IZI and FHI-IWMS Halle) have been shown to have superiority in their antimicrobial activity when compared with a commercially available product.

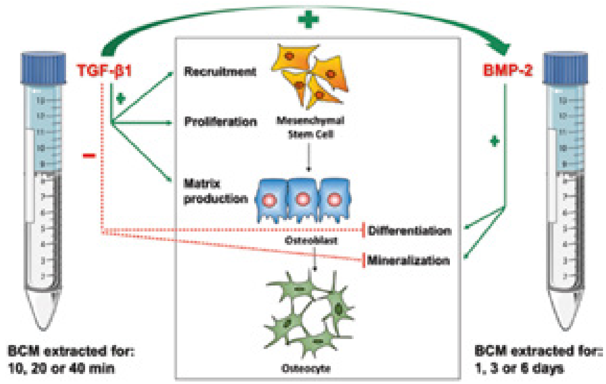
*Bone and soft tissue regeneration research at the Laboratory of Oral Cell Biology*

Recent research has investigated the composition of Bone Conditioning Media (BCM) and its activity on the osteogenic potential of mesenchymal stem cells and new bone formation. BCM extracted within minutes, corresponding to the time of the surgical procedure, is characterized with the fast release of transforming growth factor-β1 (TGF-β1). In contrast, BCM extracted over extended time periods, corresponding to the first days after the augmentation procedure took place, is enriched in bone morphogenetic protein-2 (BMP-2).

BCM obtained during surgical procedure causes increased proliferation of mesenchymal stem cells, thus expanding the pool of osteoblast progenitors and has the potential to stimulate the production of bone matrix. BCM released from the autograft in situ and respectively, the BMP-2 contained in this medium stimulates the late stages of osteoblast differentiation and mineralization, thus continuously contributing to the progression of osteogenesis (Asparuhova MB, et al. Int J Oral Sci. 2018; 10(2):20).

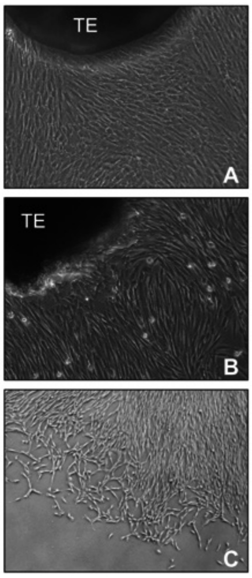



Antimicrobial activity (maximum dilution of eluate) of minocycline-containing formulations against Porphyromonas gingivalis over time. The flow of gingival crevicular fluid is simulated.




Schematic representation of the biological activity of bone-conditioned medium (BCM), derived from autologous bone grafts, on the osteogenic potential of mesenchymal stem cells. A complex interplay between two growth factors, TGF-b1 and BMP-2 contained in the BCM, is depicted.

Further research has evaluated the in vitro effects of bioactive substances such as hyaluronan (HA), enamel matrix proteins, or recombinant growth factors on the regenerative potential of primary oral fibroblasts. HA influences the cellular inflammatory response and extracellular matrix remodeling by affecting pro-inflammatory cytokine and matrix metalloproteinase gene expression, respectively (Asparuhova MB, et al. J Periodontal Res. 2018; 00:1-13).




**Cell types involved in periodontal regeneration:**

A) Human Gingival Fibroblasts
B) Human Palatal Fibroblasts
C) Periodontal Ligament Cells

treatment with HA

**Positive effects on:**

- Viability
- Proliferation
- Migration
- Wound healing potential including:
  – cellular inflammatory response
  – extracellular matrix remodeling
- Stemness

Schematic representation of the biological activity of hyaluronan (HA) on the wound healing properties of primary cell types involved in periodontal regeneration. (TE: tissue explant).

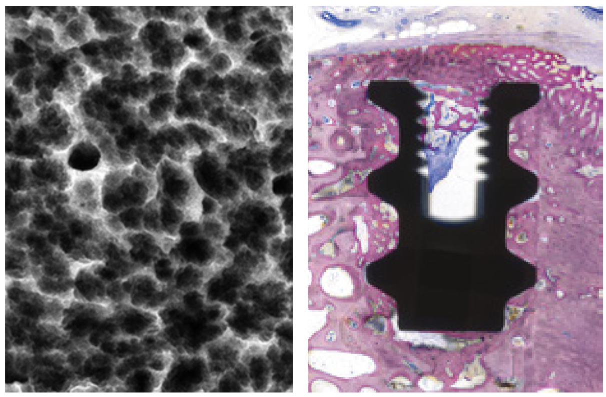
*Research on dental implants at the Robert K. Schenk Laboratory of Oral Histology*

***Osseointegration of ultrafine-grained titanium with a hydrophilic nano-patterned surface***

In a preclinical model, a new ultra-fine grained titanium (ufgTi) implant material with a hydrophilic nano-patterned surface to commercially pure titanium (cpTi). The metallographic properties of ufgTi were significantly better than those of cpTi. Histomorphometric and biomechanical torque out analysis revealed no significant differences between ufgTi and cpTi whereas high bone-to-implant contact values were obtained irrespective of both bony microarchitecture and mineral density thus suggesting that ufgTi has therapeutic potential for small diameter implants allowing less invasive treatments.

*Macrophage polarization and subsequent gingival fibroblast response on commercially available dental implant materials*

Recently results from the laboratory have shown that implant surface characteristics substantially impacted macrophage behavior. While surface composition (Titanium vs zirconia vs titanium-zirconium alloy) had little effect on macrophage polarization or gingival fibroblast response, modifications via hydrophilicity to both pure titanium and titanium-zirconium alloy favored the secretion of macrophage pro-resolution markers and subsequently resulted in a favorable gingival fibroblast cell response when cultured with macrophage-conditioned media. These findings suggest that surface hydrophilicity rather than material composition improve soft tissue integration of dental implants.



The ufgTi viewed in the laser confocal microscope (left). Excellent osseointegration after 8 weeks (right).

## Selected Publications


Asparuhova MB, Caballé-Serrano J, Buser D, Chappuis V. Bone-conditioned medium contributes to initiation and progression of osteogenesis by exhibiting synergistic TGF-b1/BMP-2 activity. Int J Oral Sci 2018; 10(2):20

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Eckert M, Mizgalska D, Sculean A, Potempa J, Stavropoulos A, Eick S. In vivo expression of proteases and protease inhibitor, a serpin, by periodontal pathogens at teeth and implants. Mol Oral Microbiol. 2018 Jun;33(3):240-248.

# SwissRDL – Medical Registries and Data Linkage

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**Research Profile**

SwissRDL is a centre of excellence for medical registries and data linkage and part of the Institute of Social and Preventive Medicine ISPM. Originally known as IEFM (Institut für Evaluative Forschung in der Medizin) the group joined forces with ISPM in 2015 and was renamed to SwissRDL (see www.SwissRDL.unibe.ch).

In collaboration with external partners, e.g. medical associations and foundations, SwissRDL develops, implements, hosts and maintains national and international medical registries and multicenter studies. The registries are hosted on our own IT infrastructure at the University of Bern and are web- and app-based Electronic Data Capturing (EDC) systems. We support our partners in medical informatics, patient safety and privacy protection. Our research focuses on health system and service research as well as health technology assessment. We focus on indication, process and outcome quality assurance in medicine in collaboration with local, national and international partners and organizations.

The second core excellence is Data Linkage. Longstanding experience in building large cohorts (for example the Swiss National Cohort www.swissnationalcohort.ch) where big data were linked using probabilistic record linkage methodology led to our outstanding expertise in linking data where no unique identifier is available and therefore simple merging is not possible. SwissRDL has been involved in several data linkage projects in Africa, e.g. linking HIV data with cancer registry data.

**Medical Registries**

Why do we need registries? While randomized clinical trials can answer the question about efficacy, registries can answer the question about effectiveness. They allow health technology assessments, reveal results of therapies applied in day-to-day routine clinical or health care setting, reflect all facets and problems of clinical reality (correct diagnosis, compliance, access...) and have a high external validity. Registry data can be used to assess indication and outcome quality, to compare effectiveness of procedures and are indispensable in post-market surveillance.

*Data entry and data transfer*

SwissRDL offers support for medical registries on different levels: we help to develop a registry, estimate the costs, create the data model, plan the electronic case report forms (eCRF) and implement them into our system. The SwissRDL registry software system is developed and maintained by our own development team. Registry data can be entered into our system in various ways: 1) direct entry via web browser, 2) first on paper and afterwards entered manually into our system by data entry clerks. 3) We have developed apps for tablets for data entry. They allow a more flexible data entry and are fully maintained by SwissRDL. 4) Finally, several clinics implemented our CRFs into their clinic information system. Using RESTful API web services, the data are transferred automatically into the registry system at SwissRDL.

*Data center and user support*

For data protection reasons, we separate for each registry or quality study the identifying information about the patients from the clinical data on physically different servers. Each registry has its own registry server with SwissRDL running more than 50 virtual servers at the moment. Detailed user profiles allow to offer customized functions for each role in each project. Data are stored at a tier 4 data center of the University, with redundant systems for network, server hardware, file storages, climate control and backup systems. All data are backed up daily in a second data center of the university.

SwissRDL offers different levels of support, depending on partners' needs. Core technical support comprises timely support for registry access issues, problems with web services or browsers, network and login and authentication issues. First level support includes user management, support of daily requests from users at the hospitals. The support team is available over the phone and by email, offers webinars and arranges on-site trainings if needed.

*Data quality, monitoring and reporting*

The enhancement of the quality of registry data is fostered at different time points and levels. a) Before data collection: Through carefully designing the eCRFs in close collaboration with the registry partners. The most crucial question about developing registries is: What do you want to find out in 3 years? As registries are set-up as long-time data collection tools, the aims and the questions to be answered have to be clearly defined at the beginning, as this defines the variables collected. b) During data entry: The rules and validation system ensure high quality of data in real-time by checking type, range, comparability with already existing data and logical correctness. c) During the maintenance of a registry: Central data monitoring uses semi-automated scripts to check the plausibility of data, detects abnormal frequencies and outliers and rises red flags for suspicious events.

On-site monitoring ensures that data are collected according to the protocol, and according to GCP guidelines and regulatory requirements. Using standardized procedures, data in the registry are compared with the original data in the hospital and short reports for the hospitals give a feedback about the quality of the data and lists potential steps for quality improvements.

SwissRDL creates different kind of reports for the registry partners, e.g. quarterly or annual reports, or reports per clinic. For suppliers we offer implant reports for specified products. Furthermore, our data managers and statisticians analyze data for scientific publications and posters.

*Implant library*

SwissRDL has built up an implant library with the support from SIRIS foundation, Swiss Medtech and the supplier companies, which sell implants in Switzerland. The library allows to identify implants easily by scanning the barcode or QR code after the operation in the hospital. The barcode is identified in the implant library and the detailed information about the used implant, e.g. brand, type, material, size is automatically stored in the registry. The catalogues of the implants are regularly updated. Currently, we have data on hip, knee, spine and shoulder implants. The library can easily be enhanced with implants from non orthopaedic surgery, e.g. cochlea implants or implants for heart surgery. At the moment, SwissRDL has more than 1.5 million implants registered.

*Examples of registries by SwissRDL*

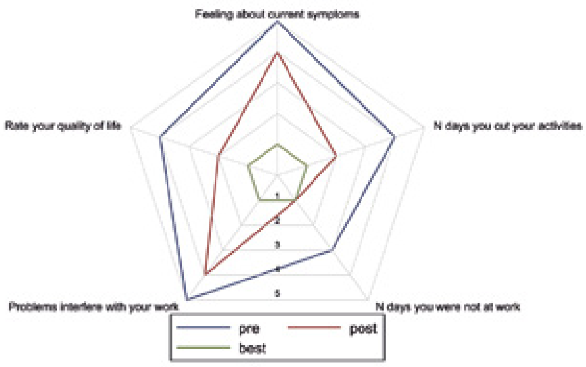
SwissRDL is in charge of the national hip and knee implant registry SIRIS. More than 40'000 hip and knee joint implants per year from over 150 hospitals have been recorded since 2012, including primary operations and revisions, see www.siris-implant.ch for details and the annual report. Another national registry is Swissnoso: surveillance of surgical site infections. Since June 2009, more than 400'000 cases have been recorded and reports show declining infection rates in some of the recorded procedures, see National Report published by Swiss National Association for Quality Development in Hospitals and Clinics, www.anq.ch. HomeCareData is the platform of Spitex Schweiz for the quality management using RAI-HC and interRAI instruments. The platform is hosted and maintained by SwissRDL, with more than 1 million forms recorded since 2013, see www.homecaredata.ch.

Additionally, SwissRDL maintains and hosts international registries, for example the German spine registry DWG, or the French hip registry SOFCOT. In total, more than 15 registries and quality studies are maintained and hosted by SwissRDL.

**Patient recorded outcome measures PROM – quality assessment**

Increasingly, the quality of medical procedures is not only measured with revision rates or complication rates, but with the quality and success of procedures and treatments assessed by the patient. This includes Patient Recorded Outcome Measures (PROMs), like the EQ5D from EuroQoL or questionnaires specific to the spine (COMI) or the hip and knee (WOMAC). SwissRDL has a plethora of questionnaires already implemented in their system.

PROMs require a different data entry method compared to standard registry information, as the patient doesn't have access to computers in the hospital. Therefore, SwissRDL offers apps, where sets of PROMs can be used by our registry partners. Tablets are used in hospitals and are given to the patients during the normal scheduled doctor's visits. For follow-up questionnaires where no visit is scheduled, links for online data entry are sent to patients. Naturally, there is always the option to fill in paper-based PROMs.




**Data Linkage**

Two main reasons have led to increased need for data linkage in research: Tight research budgets and resources stimulate the use of existing data and the development of high-performance computational power allows to use, analyse and link huge data to answer questions not possible previously. Applying error tolerant probabilistic record linkage methods, SwissRDL has been involved in many projects linking existing data. In absence of a unique identifier, we use existing discriminative information to calculate the probability of the records belonging to the same person. In case of privacy protection issues, we developed methods to link data using hashed bit arrays (Bloom filter, privacy preserving probabilistic record linkage P3RL), without revealing identifying information like names or date of birth to the linkage center. For some research projects, linking existing data is crucial: for example, to calculate the revision rate of implants in an aging population correctly, we need to know if the patients are still alive, or whether they have emigrated or are lost-to-follow-up. This is only possible with the linkage to the National mortality registry and population registry at the Federal Statistical Office.

## Selected Publications

See annual reports of large registries, e.g. www.siris-implant.ch for SIRIS, or www.anq.ch for Swissnoso.

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Bieri, Kathrin S; Goodwin, Kelly Jayne; Aghayev, Emin; Riesner, Hans-Joachim; Greiner-Perth, Ralph (2018). Dynamic Posterior Stabilization versus Posterior Lumbar Intervertebral Fusion: A Matched Cohort Study Based on the Spine Tango Registry. Journal of neurological surgery. Part A, Central European neurosurgery, 79(3), pp. 224-230. Thieme 10.1055/s-0037-1615264

Schmidlin, K., Clough-Gorr, K. M., & Spoerri, A. (2015). Privacy preserving probabilistic record linkage (P3RL): a novel method for linking existing health-related data and maintaining participant confidentiality. BMC Medical Research Methodology, 15, 46. https://doi.org/10.1186/s12874-015-0038-6

# BERN UNIVERSITY OF APPLIED SCIENCES

Today, many tasks call for interdisciplinary solutions. In order to better address these requirements, the Bern University of Applied Sciences (BFH) aims to concentrate and strengthen its competencies in specific areas based on established research groups. The BFH centres offer answers to current and future social and technological issues. They are unique in Switzerland due to their set-up and holistic approach.

For example, the BFH Centre for Technologies in Sports and Medicine combines the research and development activities of various institutions: two research institutes from the field of engineering and information technology collaborate with the Health Division and the Swiss Federal Institute of Sport. Thus, engineers can work together with medical doctors, health and physiology specialists, as well as sports coaches to achieve the common goal of sharing expertise with industrial partners and expediting innovation.

In addition to bringing together experts, linking research and education is an important concept 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 bachelor's and master's levels to become outstandingly qualified specialists and executives in the industry. People who are already working can take their careers one step further with continuing education, for example, with the new program in Digital Health.

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 Bern University of Applied Sciences is well connected as member of the Medical Cluster and the Competence Centre for Medical Technology – and a valuable partner in the region Mittelland, as well as throughout Switzerland and internationally.

L. Rohr

Lukas Rohr
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# Institute for Medical Informatics I4MI

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**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. A sample project is the audit of the Tarmed accounting system for H+, the association of Swiss hospitals.

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. A sample project is the production of an evaluation handbook for the Swiss eHealth initiative.

E-Health and telemedicine

We run and support a wide range of initiatives in the field of e-health and telemedicine concerning the development of the Swiss electronic patient records system, mobile health, the set-up of integrated care processes, and telemedical applications. In this we analyse aspects of technical and semantic interoperability, the integration of AAL environments, the secondary use of data, and big data. An example of our activities in this area is the set-up of the national test environment for the Swiss electronic patient records system.

Patient-centred applications

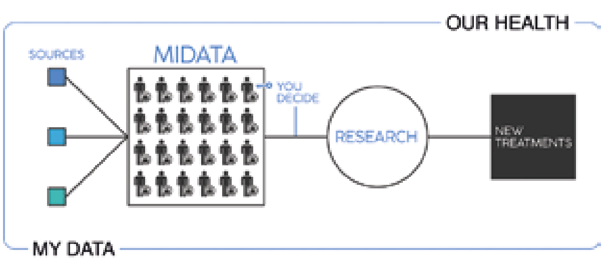
A key area of our research activities is patient-centred applications, such as personal mobile applications (apps), studies on patient empowerment and self-management, compliance support activities, and the integration of AAL with the service providers. We also focus on personalised medicine as an area 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 and our own management tools in this environment for the analysis of treatment processes, the optimisation of treatment chains, the simulation of logistics processes, the design of clinical pathways, including pathway cost calculations, and the working procedures for electronic order communication (Computerised Physician Order Entry (CPOE)). One example is the "Hospital of the Future" project in cooperation with GS1.

**MIDATA: Patient-centric Administration of Personal Health Data**

MIDATA provides a new approach to the storage, management, and secondary use of personal health data. MIDATA places the emphasis on citizens as the owners of their data and thus transforms them from passive recipients of healthcare services to key players. Both healthy and ill citizens will be able to manage their own medical and non-medical health data themselves, thus obtaining maximum value added from this data. Organised as a not-for-profit association, MIDATA is controlled by the data owners themselves and ensures that society benefits from the gains made from the secondary use of data. This citizen-controlled added value from the data, which is currently still located in silos, forms the basis for personalised medicine and more effective and sustainable healthcare provision.




The MIDATA IT architecture has a modular structure and provides a FHIR API and semantic interoperability. It is based on cloud computing technology. The data undergoes multiple encryptions and is stored with a leading Swiss cloud provider to guarantee the highest level of data security. Members can enter, manage, analyse, and visualise their data via a website and mobile apps, as well as granting healthcare providers and researchers access to particular data sets. Service providers and researchers access this shared data via their own dedicated portal.

Further services enable communication and the selection of appointments with healthcare providers. The possibilities presented by gamification and the creation of competitions between members will be introduced in the next version. MIDATA combines the attributes of an electronic patient records system and a personal data account with social networking tools and links to apps and applications of third-party providers.

Two pilot projects are currently in preparation. In the first project, the effectiveness of new treatments for chronically ill multiple sclerosis patients will be tested in a clinical study with the Department of Neurology at the University Hospital Zurich. The second project in collaboration with the University Hospital of Bern (Inselspital) focuses on after-care for obesity patients after bariatric surgery.

Project partners
- Federal Institute of Technology Zurich, Institute of Molecular Systems Biology
- University Hospital of Bern (Insel Group), Department of Visceral Surgery and Medicine, Obesity Centre
- University Hospital Zurich, Department of Neurology, Neuroimmunology and Multiple Sclerosis (NIMS)

**Hospital of the Future Live**

In the "Hospital of the Future" multi-stakeholder project, we focused on the extent to which the integration of treatment-relevant information flows can produce improvement potential at hospitals.

More than 20 organisations from the Swiss healthcare sector – including six hospitals, the IHE-Suisse and ehealthsuisse – came together for the workshops. They have thus far specifically identified over 50 future application scenarios with the focus: How can medical IT have a positive impact for people on the treatment pathway or the care network within five to seven years?

A typical treatment pathway (hip replacement) was selected from the perspective of a fictitious patient "Ms. Elisabeth Brönnimann," analysed in terms of efficiency, treatment quality, and patient safety and compared with an optimised pathway. Particular attention was often paid to the technical and cultural interfaces at the hospitals and along the outpatient/inpatient interface.

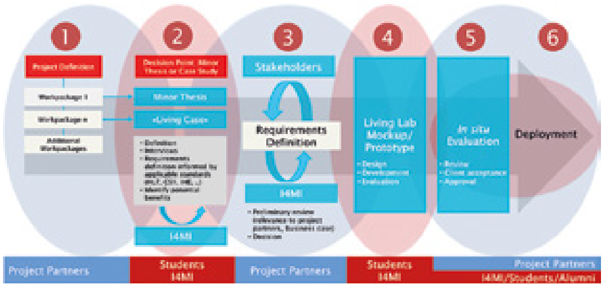
The work packages defined at the workshops were implemented as prototypes in I4MI's Living Lab. In particular, they focused on elements such as electronic patient records (EPD), the integration of mobile devices, and an active assisted living (AAL) apartment. The decisive factor was always how the situation looked from Ms Brönnimann's perspective, which means that user-centred design is a key element in the overall project.

**Findings**

Two current medical IT developments in the healthcare sector in particular – the setting-up of e-health communities and the advent of the digital transformation (Health 4.0, Internet of Things) – provide many opportunities for the effective, people-focused digitisation of the healthcare sector.

The combination of these technologies is likely to produce a major synergy effect. The challenges include:
- The implementation of regulatory provisions in the context of eHealth Suisse
- The increase in patient safety through an improved overview of the treatment processes, e.g. an improved medication process
- The traceability of medical products and pharmaceuticals
- The appropriate application of international standards
- The convergence of existing technologies, such as eHealth (networking), pHealth (personalised health data), mHealth (mobile health), and aHealth (automation) for a digitised society.

In the "Hospital of the Future" project, these conditions provided the framework for the focus on integral information flows along patient-oriented treatment paths, care networks, and the supply chains associated with them.




Project plan as an innovation process: (1) Multi-stakeholder workshops, where the work packages are defined, are held twice a year. These may be new packages or take work done in previous projects into more depth. (2) The work packages are incorporated into the following semester for the medical IT students in the form of internships, seminar projects, or bachelor theses. (3) The stakeholders support the students as experts according to their area of expertise and evaluate the results based on suitability for application. (4) Promising projects are implemented as prototypes in the Living Lab of the Medical IT Department and are integrated into the treatment process in their entirety (taking account of upstream and downstream processes and information flows). (5) The most promising developments are implemented as pilot projects with future users in collaboration with the stakeholders/project partners and (6) a business plan is drawn up and they are rolled out on the market in the event of a positive response.


**Selected Publications**

https://www.e-health-suisse.ch/gemeinschaften-umsetzung/epd-gemeinschaften.html

Widmer W., Schaffhuser K., Gesundheitswesen gestalten, careum Verlag, p. 110-134, 1st edition 2018

# Institute for Human Centered Engineering HuCE

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Rolf Vogel, Head of Cardiology, Solothurn Hospital, Solothurn
Adrian Lussi, School of Dental Medicine, University of Bern

## Research Profile

The Institute for Human Centered Engineering HuCE combines its know-how acquired from research projects in various fields with engineering technologies in an interdisciplinary way to develop new products for industry and hospitals. The focus is on strong engineering technology core competences. Our practical problem-solving approach together with our clinical partnerships provides a basis for innovative products. The engineering core competences in our six research laboratories are:

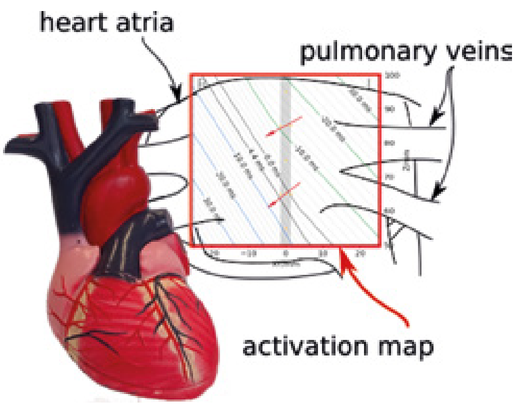
- Medical Instrumentation
- Electronic Implants
- Optical Instruments for Diagnosis
- Imaging in Medical Technology
- Optical Coherence Tomography
- Haptic Feedback Systems
- Sensors and Sensor Networks
- Signal Processing and Control
- Low-power Microelectronics
- High-speed Hardware Algorithms in Combination with Biomedical Engineering Applications

HuCE is currently involved in several SNF and more than a dozen Innosuisse/CTI-funded research projects, several medtec and industrial engineering projects, and has been the incubator for a few spin-off companies.

## Research Area: Medical Diagnostic Devices in Electrophysiology

### Semi-Invasive 3D Mapping System for Cardiac Arrhythmias Using Esophagus ECG Signals

Early detection of adverse arrhythmias is, in many cases, crucial to prevent more serious consequences. Whenever an arrhythmia is identified and an interventional therapy is indicated, the therapy planning so far usually relies on 12 lead ECG signals solely. Many common arrhythmias are localized in the heart's atria, exactly in that location that is insufficiently represented in common ECGs. Thus, our approach complements this standard ECG signals with ECG signals measured in the esophagus: The esophagus runs close to the hearts atria and, thus, provides a superior signal quality there. But we not only are interested in solely recording these signals, we use them to calculate the electrical activity on the atria surface in a three-dimensional manner, leading to a so-called activation mapping. The current research tightly links multiple disciplines: the catheter construction, signal acquisition technique, signal processing including high-speed hardware algorithm based on FPGAs and ASICs, and finally application software development, writing a diagnosis-supporting visualization tool. Overall, we aim at a bedside tool that provides clinicians with additional information and thus facilitates diagnosis in cardiology, or more specific, in rhythmology. This project is in close cooperation with the Department of Cardiology at Bern University Hospital and financed by SNF CR23I2_166030.

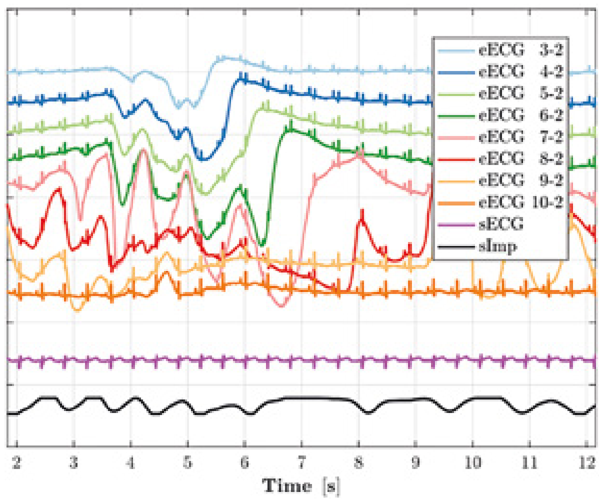



The figure shows an activation map of the left atrial posterior wall (red box), visualizing the electrical activity of the heart at each single beat. This map is the result of an algorithm performing a three-dimensional mapping based on the esophageal ECG measurements.

### Neonatal Esophageal Observation (NEO) System for Improved Preterm Infant Care

Preterm infants, who account for more than 10% of all births worldwide, very often require cardiorespiratory monitoring on a neonatal intensive care unit (NICU) due to autonomic dysregulation. Surveillance of the heart rhythm and respiratory rate, however, is cumbersome since surface ECG and impedance 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. Objective discharge from the NICU cannot be guaranteed.

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, the NEO project proposes that vital signs and autonomic dysregulation may be monitored with a single esophageal catheter. With the initial support of the Swiss Heart Foundation and Bangerter-Rhyner-Foundation a first step towards the NEO system has been realized: the visualization of peristaltic waves in preterm infants by multichannel esophageal electrodes.

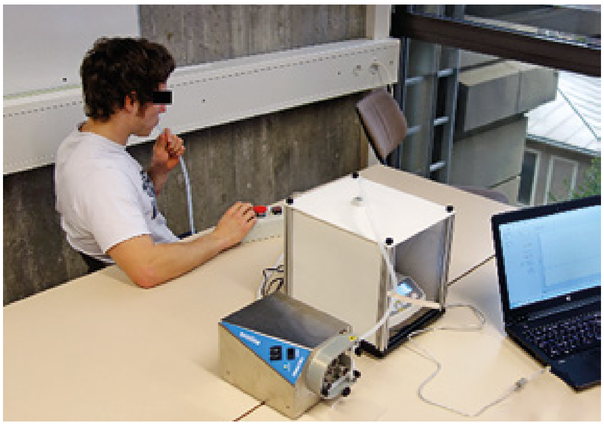



Multichannel esophageal signals recorded with a nasogastric feeding tube depicts peristaltic waves travelling from the most proximal (#2) to the most distal electrodes (#10).

## Research Area: Therapy

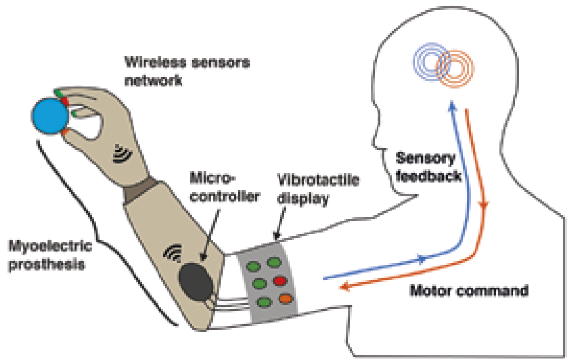
### Drinkometer

An effective treatment for morbid obese patients is the gastric bypass operation in which the size of the stomach is reduced and reconnected to bypass the first portion of the small intestine. Studies suggest that the selection and intake of foods varying in fat content and glycemic index, as well as the pattern of ingestion within and across meals, changes for patients after such an operation. We developed a device («drinkometer ») that can measure detailed aspects of ingestion over time within a meal in humans. The drinkometer records the drinking speed with 1 kHz sampling and identifies individual sucks and bursts with their respective volumes, durations, and rates. A first study proves that our novel drinkometer can detect differences in drinking behavior dependent on different motivational states, thus, adds to the technological toolbox used to explore human ingestive behavior. The project is a collaboration with the UniSpital Zurich, which also financed it.



The Drinkometer device in use with a test-person.

**WiseSkin – a Prosthesis with Sensor Skin**
Amputation of a hand or limb is a catastrophic event affecting life quality. The WiseSkin project aimed at developing a prosthesis with a sensor skin that would allow for the feeling of pressure. The project was sponsored by NanoTera and SNSF, with three partners: CSEM, EPFL, and BFH. The WiseSkin concept is based on a sensor «skin». Wireless communication is used to transfer data to the actuators. Our work involved the investigation of a non-invasive sensory-substitution system using phantom maps, system design, as well as final integration and development of a functional prototype.




Concept of the WiseSkin demonstrator (source: LSBI-EPFL).

**DrillMon - Nerve Detection while Drilling**
To restore hearing in deaf patients, Cochlear implants are widely used. During implantation, when drilling, it is important to not harm delicate anatomical structures, in particular the facial nerve. Today, there are systems that allow determining distance to nerves. Some of these require removing the drill and inserting a stimulation electrode. We are developing an improved drilling system that integrates the stimulation electrode into the drill. This allows nerve detection without changing tools while the drill is spinning with up to 80'000 rpm. The project is financed by Innosuisse and involves the industrial partners Bien-Air Surgery SA (Le Noirmont) and inomed Medizintechnik GmbH (Emmendingen, Germany).

Drilling in a custom-made phantom with nerve monitoring.

**Concept for a Low-Cost Hand Prosthesis for Children**
According to the World Health Organization, about 30 million people in Africa, Asia, and Latin America do not have access to adequate prostheses or orthotics. Commercial myoelectric prosthesis cost between 20’000 and 100’000 CHF. In developed countries, insurance companies usually limit contributions to prosthetic services to 500 to 3’000 CHF per year and 10’000 CHF to prosthetic devices during a person's lifetime. While a hand prosthesis may be a one-time investment for an adult, children and adolescents need to replace their prostheses often as they grow.

Realized prototype low-cost hand prosthesis. Size comparison between the hand of a 9-year-old child and the prosthesis. The prosthesis is controlled intuitively by reading EMG signals near the elbow.

In this project, a low-cost prosthesis for children and adolescents that is able to support daily activities was designed and built. To reduce costs, the expensive components of the prosthesis are reused as the child grows and the mechanical structure is 3D-printed. The estimated material costs are below 500 CHF for a prosthesis.

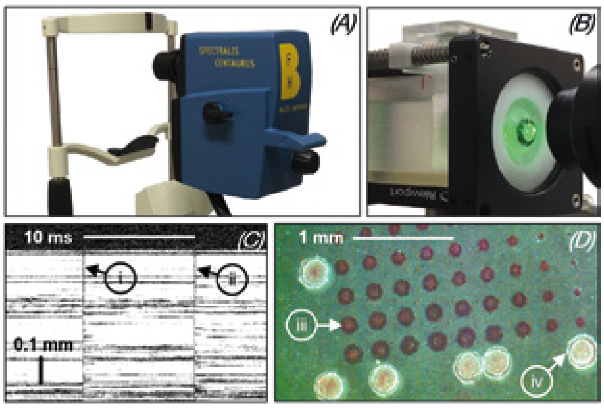
A functional prototype has been realized to prove the concepts behind the development. The prosthesis is intuitively controlled by an eight-electrodes EMG sensor placed on the forearm of the patient. Machine-learning based on a neural network acquires the sensor signal and recognizes the pattern. A controller then commands the six degrees of freedom of the prosthesis to achieve the desired hand configuration. Future work shall miniaturize the computation unit and power supply. Usability tests with patients will provide important end-user feedback. Finally, the device shall be further developed into a commercial product in developed countries and for humanitarian use in developing countries.

**Optical Coherence Tomography Controlled Selective Retina Therapy for In-vivo Treatment**

Conventional laser photocoagulation (LPC) is a common treatment method for retinal diseases that unfortunately leads to collateral damage of all retinal layers including healthy, non-regenerative photoreceptors. An alternative approach is selective retina therapy (SRT), in which finely dosed laser pulses in the sub-microsecond range cause selective cell death limited to the retinal pigment epithelium (RPE).

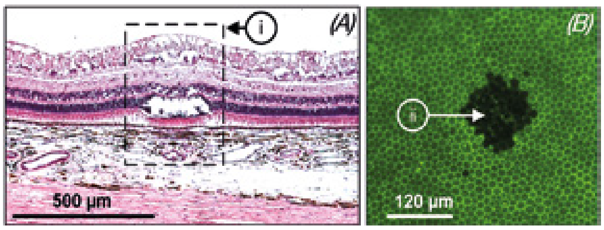
However, the complexity of radiant exposure control in variable absorbing tissue prevented wider uptake of the technology. Recent literature shows that optical coherence tomography (OCT) can provide reliable dosimetry control in parallel with SRT because RPE lesions can be predicted indirectly as a change of OCT signal strength in M-scans. In this project we investigated in OCT-controlled SRT in ex-vivo porcine test series and built the base for an upcoming human in vivo study.

For the experiments, the Spectralis Centaurus system was built, adapted, and tested for controlled treatment of excised porcine eyes. This device provides OCT in parallel to SRT and uses a dedicated laser manufactured for this project according to parameters that are mostly chosen in recent SRT studies.




(A) HuCE-optoLab Spectralis Centaurus system. (B) artificial eye used for porcine RPE explant measurements. (C) presents a M-scan with two so-called signal washouts showing a change of OCT signal strength (i,ii). (D) RPE sample evaluated under a fluorescence microscope with typical SRT (iii) and LPC marker lesion (iv).

To verify the laser's capability for SRT, experiments with different laser pulse durations in the microsecond range were carried out. Therefore, entire porcine eyes or porcine RPE explants were treated. Evaluation of the samples took place by using a live/dead staining kit (EthD-1, Calcein AM) and visualization by a fluorescence microscope and histological sections with hematoxylin and eosin (H&E) staining. Furthermore, the clinical potential of the system's OCT M-scans dosimetry was evaluated at the Medical Laser Center Lübeck.

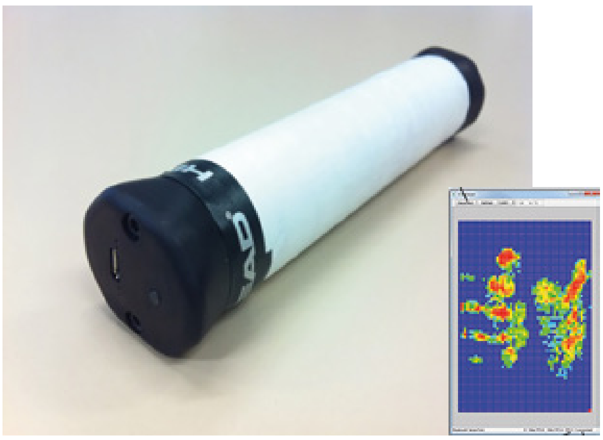



(A) histological sections with H&E stain of porcine retina at a LPC marker lesion (i). (B) RPE sample with rectangular SRT lesion (ii) evaluated under a fluorescence microscope.

Results: Histological sections with H&E stain showed LPC marker lesions but SRT lesions were not found. For the applied treatment parameters, changes of OCT signal strength in M-scans were observed when the Spectralis Centaurus system and the laser were able to create SRT lesions in porcine RPE. The novel Spectralis Centaurus system and the laser fulfill the requirements for OCT-controlled SRT. However, the sensitivity of the signal washout detection in OCT M-scans has to be improved. Regarding the experiments with different laser pulse durations, the results obtained correspond to the findings of similar studies. In general, OCT as real-time dosimetry has the potential to establish SRT as standard therapy for RPE-related retinal pathologies. A patient study at the University Hospital Bern (Augenklinik, Inselspital) is planned for 2019.

**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 about the biomechanical activity and of the hand and all fingers as the actual devices on the market. A high-resolution tactile sensor and a dedicated readout electronic has been developed allowing

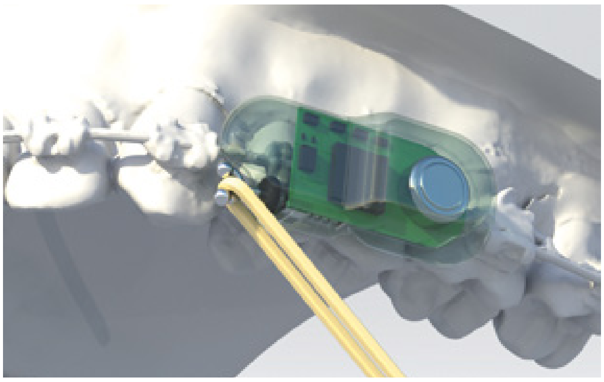


3000 pixels representing a hand imprint to be delivered in real time. This wireless device transmits data to a smartphone or another smart device for direct analysis. It can also be shared or stored. Data analysis algorithms have also been developed to facilitate the diagnosis. This project has been performed with EoSwiss Ldt. in Geneva. A patent application on this device has been submitted, and a clinical study is ongoing.

### Research Area: Medical Monitoring

**Monitoring system for the wearing time of orthodontic elastics**

Fixed multi-bracket appliances are used to correct tooth and jaw misalignments. In most cases, intermaxillary elastics are worn between the upper and lower jaw to adjust the position of the jaws in relation to each other. The wearing time of these intermaxillary elastics determines the duration of treatment and the quality of the treatment results. Clinical studies have shown that patient compliance is improved by monitoring the wearing time. While micro-sensors are increasingly being used for removable appliances to monitor patient compliance, there is still no such possibility worldwide for fixed appliances. The project goal (Innosuisse/CTI with partner Universitäres Zentrum für Zahnmedizin Basel and Otmar Kronenberg AG) is to develop a miniaturized low-power monitoring system for measuring patient cooperation with fixed braces by measuring the wearing time of the intermaxillary elastics in a multi-bracket therapy. The orthodontist can visualize the wearing time of the elastics at the patients visits and thus gains better control over the cooperation of patients.



Design study to investigate patient comfort for direct measuring the presence of elastics and wear-out conditions as opposed to measurements via secondary parameters.

**Hospital 4.0: Self-coordinating and distributed sensor network for patient monitoring in a hospital setting**

Compliant Concept AG produces an under-the-mattress pressure sensor enabling pressure ulcer risk prevention and fall prevention for hospitalized patients. Nevertheless, configuration of alarms and measurement setup, tailored to the specific patient case, is a cumbersome task severely reducing the usability of the sensor. Our approach is to interface the sensor with a mobile monitoring device integrated into a sensor network framework enabling:

- Monitor and bed positioning;
- Patient recognition;
- Connection to the hospital's patient database for an auto-configuration of alarms and measurement setup;
- Nurse presence detection

Such an integrated monitoring setup enables an optimized smart care process and it makes it possible to extend the current sensor use to optimization of sleep patterns / medication, assessment, automated risk profile evaluation, and automated care process statistic reports. This project is financed by Innosuisse and conducted with the industrial partner Compliant Concept AG and the Inselspital in Bern.

Mobile Monitor and Pressure Sensor.

### Selected Publications


Reto Andreas Wildhaber, Dominik Bruegger, Nour Salami, Hampus Malmberg, Josef Goette, Marcel Jacomet, Hildegard Tanner, Andreas Haeberlin, Hans-Andrea Loeliger, "Estimation of the Cardiac Field in the Esophagus Using a Multipolar Esophageal Catheter," IEEE Transaction on Biomedical Circuits and Systems, Aug. 4th, 2018

Reto A. Wildhaber, Nour Zalmai, Marcel Jacomet and Hans-Andrea Loeliger, "Windowed State-Space Filters for Signal Detection and Separation," IEEE Transactions on Signal Processing, July 15, 2018

Huaiqi Huang, Claudio Bruschini, Christian Antfolk, Christian Enz, Tao Li, Jörn Justiz, Volker M. Koch, "Automatic hand phantom map generation and detection using decomposition support vector machines," BioMedical Engineering OnLine, BioMed Eng OnLine, June 13, 2018

Thomas Niederhauser, Elena S. Hafner, Tarcisi Cantieni, Michelle Grämiger, Andreas Häberli, Dominik Obrist, Fiona Burkhard, Francesco Clavica, "Detection and qualification of overactive bladder activity in patients: Can we make it better and automatic?" Neurology and Urodynamics. 2018;37:823-831, February 2018

Rakesh Vasireddy, Corinne Roth, Johannes Mathis, Josef Goette, Marcel Jacomet, Andreas Vogt, "K-band Doppler radar for contact-less overnight sleep marker assessment: a pilot validation study," Journal of Clinical Monitoring and Computing, Springer, 11.09.2017

Ronchetti, T., Maloca, P., Jud, C., Meier, C., Orgül, S., Scholl, Jud,C., Hasler,P., Považay, B., Cattin, P. C., "Detecting early choroidal changes using piecewise rigid image registration and eye-shape adherent regularization," International Workshop Ophthalmic Medical Image Analysis (MICCAI OMIA), Springer, Lecture Notes in Computer Science book series (LNCS), 9. Sept. 2017

Huaiqi Huang, Tao Li, Claudio Bruschini, Christian Enz, Jörn Justiz, Christian Antfolk, Volker M. Koch, “Multi-modal Sensory Feedback System for Upper Limb Amputees,” presented at 2017 New Generation of CAS (NGCAS), IEEE, September 6, 2017

Huaiqi Huang, Tao Li, Claudio Bruschini, Christian Enz, Jörn Justiz, Christian Antfolk, Volker M. Koch, “Multi-modality sensory feedback system for upper limb amputees,” presented at the SSBE Annual Meeting in Winterthur, August 30, 2017

Daniel Kaufmann, Christian Burri, Patrik Arnold, Volker M. Koch, Christoph Meier, Boris Považay, Joern Justiz, “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, August 1, 2017

Kaufmann, D., Burri, C., Arnold, P., Koch, V. M., Meier, C., Považay, B., & Justiz, J. , “Dosimetry control and monitoring of selective retina therapy using optical coherence tomography,” European Conference on Biomedial Optics, 24. June 2017

Mooser, M., Burri, C., Stoller, M., Luggen, D., Peyer, M., Arnold, P., Meier, C., Považay, B, “Quantitative , Simultaneous %26 Collinear Eye-Tracked , High Dynamic Range Optical Coherence Tomography at 850 and 1060 nm,” 24. June 2017

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T. Marisa, T. Niederhauser, A. Haeberlin, R. A. Wildhaber, R. Vogel, J. Goette, and M. Jacomet, “Pseudo Asynchronous Level Crossing ADC for ECG Signal Acquisition,” IEEE Transaction on Biomedical Circuits and Systems, IEEE, 01.04.2017

Reto A. Wildhaber, Nour Zalmai, Marcel Jacomet and Hans-Andrea Loeliger, “Signal Detection and Discrimination for Medical Devices using Windowed State Space Filters,”IASTED International Conference, Biomedical Engineering, 21.02.2017

# BFH Centre for Technologies in Sports and Medicine

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## Members

The BFH Centre for Technologies in Sports and Medicine has established a partnership among four members: the Institute for Human Centred Engineering HuCE, the Institute for Rehabilitation and Performance Technology IRPT, the Health Division of Bern University of Applied Sciences, and the Swiss Federal Institute of Sport Magglingen SFISM. In this way, complementary key technologies can be optimally linked, efficiently developed, and effectively transferred to other areas (list of board members only see photos above).


Member research groups at the BFH Centre for Technologies in Sports and Medicine.

## Application-oriented Profile

In application-oriented research and development, the interdisciplinary collaboration of a wide range of specialists from science and engineering is crucial for developing high-quality and user-friendly solutions for practical use. Technologies and procedures are researched with a view to implementing innovative and marketable products for SMEs, medical practices, hospitals, and sports associations. The research areas of the four member institutions form the basis for the interdisciplinary-oriented approaches. These technologies and procedures are developed further by specialists from science and engineering in close collaboration with the direct end-users in competitive sports and in medicine. The aim is both to enhance the performance of top-class athletes with the aid of monitoring technologies and to provide doctors with new diagnostic technologies and rehabilitation devices. The BFH Centre for Technologies in Sports and Medicine is located in Switzerland Innovation Park Biel/Bienne SIPBB.

## Medical Devices – Qualified Management System ISO 13485:2016

Requirements for medical devices are strictly regulated by the European Union to ensure efficacy and safety of the patient. Class II and III medical devices, in particular, require a quality-management system so that the complete life cycle of a product can be controlled. However, consistently increasing requirements for market access (CE-registration) and surveillance guided by the new medical device regulation (MDR) raise the burden likewise for suppliers, manufacturers, and distributors of any kind of medical devices. Start-ups and SMEs are specifically challenged to provide adequate resources for this regulatory framework. The specific research sub-unit at HuCE has been certified for its quality-management system according to the international standard ISO-13485 for design, development, and production of as well as the software-life-cycle for medical devices. A cleanroom according to level ISO class 7 for the manufacturing of medical devices requiring a controlled environment has been set up and validated. In combination with the applied research capabilities, the BFH Centre for Technologies in Sports and Medicine consequently offers a complete package to start-ups and SMEs in the field of medical technology, from research ideas to medical-compliant product development and manufacturing. We offer consistent processes guaranteeing compliance with international regulations and accepted standards. We also provide the facilities needed for production of device prototypes during the feasibility phase up to small series intended for the design verification / validation phase.

HuCE at the BFH Centre for Technologies in Sports and Medicine has setup and runs a certified clean room qualified as ISO class 7, used for medical device manufacturing at Switzerland Innovation Park, Biel/Bienne.

### Special Equipment

The research and development at the associated institutes of the BFH center is typically application oriented. Our state-of-the-art equipment in various areas is thus an important aspect to support the application-oriented approach. In the following, some special machine equipment is listed from one of the member institutes. Similar equipment for the corresponding specialization fields can be found in the other member institutes. Research labs, start-ups, and SME project partners can easily have direct access to the equipment.

### 3D Scanner and Rapid Prototyping Printers for Biomaterials

Advanced software and devices for rapid mechanical prototyping such as 3D printers as well as a 3D scanner allow us to quickly design and produce innovative prototype products including biocompatible objects. This allows for a more rapid development and testing of innovative designs.

3D Scanner for rapid prototyping.

### Low-Volume SMD/BGA Production Line

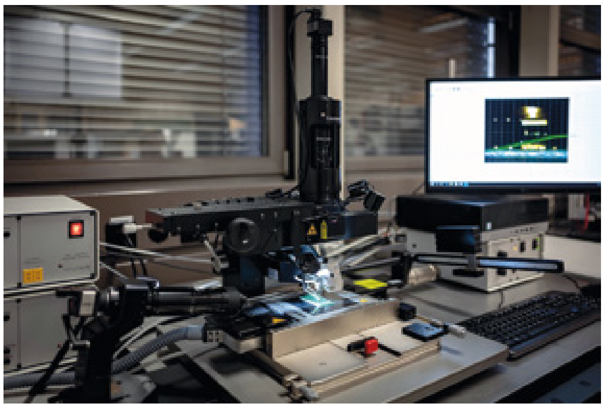
We have a complete SMD/BGA production line for fast electronic prototyping for R&D and NPI (new product introduction). We have machines for stencil printing, pick and place in a component range from 01005 to 50mm x 50mm, and a reflow oven with a vapor phase soldering system. Moreover, we have a selective soldering machine for SMD/THT combination. Quality control is achieved with a quality inspection system.

### Wire Bonder for ASICs

We can achieve a very high miniaturization by directly bonding our non-packaged ASICs (bare silicon dies) onto various substrates, including rigid or flex PCBs. We carry out classic wire bonding with a wire bonder from F&S BONDTEC, either wedge/wedge bonds or ball/wedge bonds with aluminum or gold bonding wires. The machine also has the capability to perform pull and shear tests of individual bonds or of the entire die.

### Die Bonder

Our newest investment is a multi-purpose die bonder from Finetech. This versatile platform is used in a wide range of micro assembly applications, such as flip-chip bonding, flex-on-flex connection, chip-on-flex, chip-on-board, and likewise. The chips may be attached by thermocompression, thermosonic bonding, or conductive adhesive films such as ACF (anisotropic conductive film). We use this die bonder for die attaching, standard reflow soldering, and components requiring a novel bonding approach when small dimensions are required. Novel medical catheters including microelectronics circuits or active transducers will be possible to be fabricated with the die bonder.



**Laser Welding Machine**

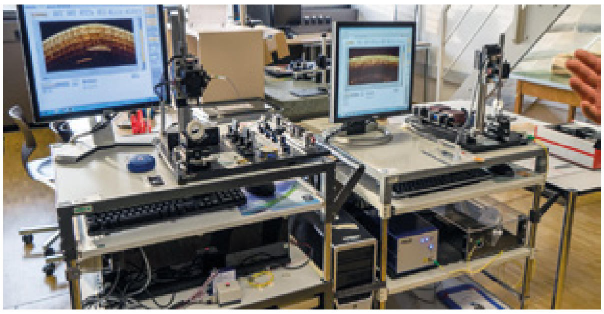
Laser welding machine used to connect fine thermoplastic tubes. The machine is ideal for welding of various types of medical diagnostic and therapeutic catheters. The technology allows short, soft, and flexible welding-connections. The results are precisely and highly reproducible. All movement axes are very accurate, and the machine is optimized for quick and easy maintenance.

**Collaborative Robot Platform**

For research in smart workspaces, we use various platforms that allow the intuitive control of collaborative robots in medical applications. The following collaborative robots are available for R&D: one Kuka LBR iiwa, two Universal Robots UR3, one Franka-Emika Panda, one Fanuc CR-7iA.

**OCT System Platform**

For research we have a comprehensive OCT-System infrastructure, containing Spectrometer-based and Swept-Source based Fourier-domain OCT Systems. In particular, OCT-Systems at wavelengths ranging from 800nm -1500nm are ready to use to inspect the tomographic scattering properties of arbitrary samples. Depending on the application, the scanning speed is a crucial parameter. Therefore, fast spectrometer cameras up to 250KHz and Swept-Source laser systems up to 200kHz are available. Moreover, polarization-sensitive measurements can be performed. As a speciality, we have a high-power super-continuum fiber laser covering the super broad wavelength range from 400nm-2400nm and to this end, reaching an axial resolution as small as 1.2um in the current setup. In addition to the versatile hardware equipment, OCT data processing implementations are available in Matlab, LabView, C++ and CUDA (GPU) to analyze the acquired data in more detail and speed.



**Laser Doppler Interferometer**

With a high-end PSV-500 Scanning Vibrometer non-contact vibration mapping and analysis of vibrating structures can be analyzed. This laser Doppler vibrometer allows determination of a vibrating velocity or displacement over area ranging from $mm^2$ to $m^2$. It finds applications in acoustics, structural dynamics, and ultrasound measurement, for example.

# Institute for Rehabilitation and Performance Technology IRPT

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**Kenneth Hunt** | Farouk Chrif | Juan Fang | Jan Riedo | Corina Schuster-Amft

## Clinical Partners

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Dr Angela Frotzler, Swiss Paraplegic Centre (SPZ), Nottwil

### 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 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 and master 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 in Burgdorf (Canton of Bern) on the campus of the Department of Engineering and Information Technology of Bern University of Applied Sciences.

### 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 causes. 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.

IRPT rehabilitation robotics lab.

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 impairments, based upon dynamic leg-press technology (collaboration with Dynamic Devices AG).

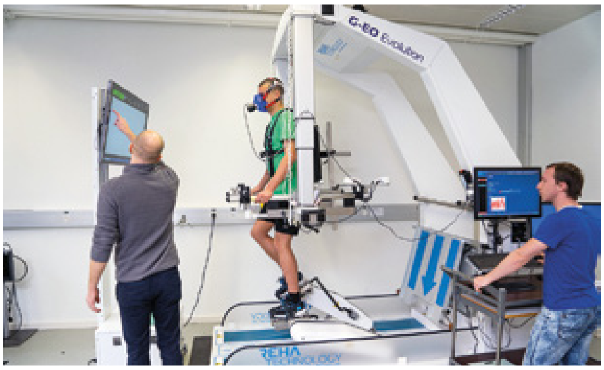
The group also develops recumbent cycling systems for people with complete lower-limb paralysis. These systems use functional electrical stimulation (FES) of the paralysed muscle groups. The IRPT teamed with the Swiss Paraplegic Centre (Nottwil) to participate in the FES Bike Race at Cybathlon 2016. Team IRPT/SPZ won the bronze medal at this event.


Team IRPT/SPZ at the FES Bike Race, Cybathlon 2016.

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.

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

- Cardiopulmonary rehabilitation of stroke patients using robotics-assisted treadmill exercise (RATE)
- Active control and neurological stimulation of the ankle joint during RATE
- Cardiopulmonary rehabilitation of patients with incomplete spinal cord injury or stroke using a robotics-assisted tilt table
- Rehabilitation tricycle incorporating FES




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

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.

IRPT sports engineering lab

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
- 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
- Automatic control of position and physiological variables while cycling on a treadmill

The IRPT labs in Burgdorf are equipped with high-performance treadmill (Venus, 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 through a computer. The institute also has modern cardio-respiratory monitoring systems for on-line breath-by-breath monitoring, ECG recording, and HRV analysis.

**Selected Publications**

K. J. Hunt and J. Saengsuwan, "Changes in heart rate variability with respect to exercise intensity and time during treadmill running," BioMedical Engineering OnLine, vol. 17:128, 2018
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M. Laubacher, E. A. Aksöz, R. Riener, S. Binder-Macleod, and K. J. Hunt, "Power output and fatigue properties using spatially distributed sequential stimulation in a dynamic knee- extension task," Eur. J. Appl. Physiol., vol. 117, no. 9, pp. 1787–1798, 2017
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K. J. Hunt, S. E. Fankhauser, and J. Saengsuwan, "Identification of heart rate dynamics during moderate-to-vigorous treadmill exercise," BioMedical Engineering OnLine, vol. 14:117, 2015.
https://doi.org/10.1186/s12938-015-0112-7

O. Stoller, E. D. de Bruin, M. Schindelholz, C. Schuster-Amft, R. A. de Bie, and K. J. Hunt, "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, 2015
https://doi.org/10.1097/NPT.0000000000000095

# Applied Research and Development Physiotherapy

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Meier, Michael L.; Integrative Spinal Research Group, Balgrist University Hospital, Zürich
Reinhard, Andreas; Ortho-Team AG Bern
Verra, Martin; Department of Physiotherapy, University Hospital Bern

### Research Profile

The Applied Research and Development Physiotherapy Unit of the Department of Health Professions at the Bern University of Applied Sciences focusses on the analyses of functional human movements in relevant daily life activities and situations. The movement laboratory is equipped with essential kinematic, kinetic, and neuromuscular analysis methods to provide an excellent environment for movement science research. In addition to general facilities necessary for teaching physiotherapy bachelor, master, or doctoral students, the profile of the lab has several foci that include pelvic floor muscle activity and displacement, neuromuscular control of the spine and the lower extremity, and specific fields of application such as training in elderly cohorts.

### Pelvic Floor Muscle Contraction Characteristics and Mechanism of Continence

Group Head: Prof. Dr. Lorenz Radlinger
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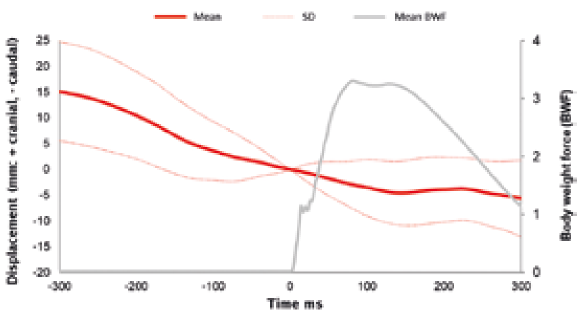
To maintain continence, the involuntary reflex contraction behavior of the pelvic floor muscles (PFM) plays an important role: It is hypothesized that during impact activities like jumping, the intra-abdominal pressure is transmitted to the urethra through the laterally subvesicular attachment to the arcus tendineus fascia pelvis and the PFM. This fibromuscular structure is stiffened during the contraction of PFM, thus forming a supportive layer onto which the urethra is compressed and closed. With regards to diagnostics, for measurement of PFM displacement - as a surrogate of this continence mechanism - ultrasound and magnetic resonance imaging are applicable to measure PFM displacement during voluntary contractions and reflexive PFM tasks such as coughing in supine position, but not during whole-body movements like jumps. Additionally, devices' sampling rate is too low to adequately represent PFM displacement during short impacts. However, enhanced comprehension of PFM displacement and its contraction characteristics (isometric, concentric, eccentric, eccentric-concentric) could be clinically relevant for the development of specific approaches in rehabilitation. Therefore, the behaviour of PFM displacement in continent women during drop jumps was investigated by means of electromagnetic tracking.

Theoretically, a commonly called eccentric-concentric «stretch-shortening cycle» would be expected to occur, i.e., the neuromuscular system's anticipation of the impending impact in the pre-activation phase and the according activation of the PFM, resulting in concentric PFM contraction and cranial displacement. Immediately after the impact, an eccentric (caudal) and subsequent concentric (cranial) displacement would have been expected due to the high and fast force impact.




Pelvic floor displacement (mean: bold red line, standard deviation: dotted red line) and body weight force (BWF, mean: bold grey line) from 300 ms before to 300 ms after impact of drop jump landings of continent women. Although the force impulse starts at the time T0 (= 0 ms) and rises above three times the body weight force within less than 100 ms, the displacement of the pelvic floor already shows in the phase of the pre-activation (300-0 ms) and in the phase of the reflex activation (0-300 ms) a systematic and continuous eccentric caudal movement of PFM of about 20 mm. The impact at T0 does not result in an immediate and strong reaction of the PFM displacement as would be expected.

**Lower Extremity Neuromuscular Control**

Group Head: Heiner Baur (Ph.D.)
heiner.baur@bfh.ch

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, orthotic devices, or pathology 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. Injury to the ACL and especially rupture of the ACL occurs during physical activity and leads to severe impairment of knee function. The treatment can be either surgical reconstruction or non-surgical training therapy. Long-term clinical outcome is comparable irrespective of therapy. Eventually all patients experience a high risk for the development of knee osteoarthritis. Adequate rehabilitation strategies and especially preventive measures are therefore crucial. Beside mechanical stability, adequate neuromuscular control secures necessary joint stability and protection. Muscle pre-activation before and reflex activity just shortly after potentially harmful perturbations of knee stability are of upmost importance to achieve sound knee. The evaluation of sensorimotor control in functionally relevant situations may therefore serve as a key element in functional diagnostics.


Left: Walking downstairs; Right: (1) electromagnet, (2) falling barbell weight, (3) stopper, (4) wire rope, (5) force transducer, (6) brace, (7) monitor for feedback, (8) headphones and attenuator, (9) force platform.

The approach is to evaluate persons with acute ACL injury in daily life activities (e.g. level walking, walking upstairs, walking downstairs). Moreover, neuromuscular control is evaluated during artificially induced tibia perturbation (Picture). The analysis of neuromuscular control has the goal of extracting potentially differing neuromuscular characteristics that differentiate healthy cohorts and patients. Gender specificity must be considered since mechanical differences (e.g. landing strategies) and differences in neuromuscular activation between genders are reported. Eventually, this leads to a diagnostic tool with validated outcomes, which can be used for further research questions. Objective parameters 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. Furthermore, preventive measures may be developed on a more evidence-based level.

**Spinal Movement Biomechanics**

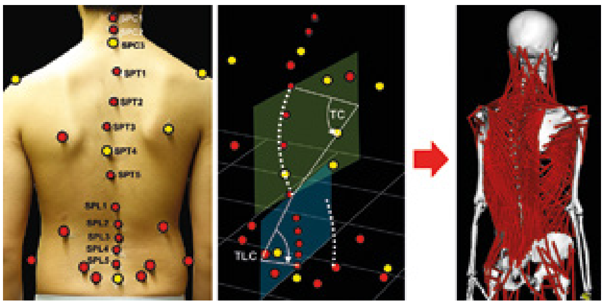
Group Head: Stefan Schmid (PT, Ph.D.)
stefan.schmid@bfh.ch.

The Spinal Movement Biomechanics Group focuses on the identification of biomechanical parameters that help clinicians to better understand musculoskeletal spine disorders and to develop new or more effective prevention and treatment strategies. Using optical motion-capturing and 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. In addition, we are evaluating portable and cost-effective commercially available measurement systems to conduct prospective trials on the identification of predictive factors for spinal pathologies. Our particular interest lies on structural deformities of the spine, non-specific chronic low back pain (CLBP), as well as secondary spinal deviations that occur as a consequence of altered limb function.

Past projects include investigations on spinal gait kinematics in children and adolescents with idiopathic scoliosis, hemiplegic cerebral palsy, and structural leg length discrepancy as well as on the effects of sling-based infant carrying and high-heeled walking in young adults. In addition, we established a normative dataset for spinal gait kinematics in healthy adolescent, adult, and elderly populations.

Currently, we are working on the definition of appropriate objective functional parameters that can be used as outcome parameters in future clinical studies seeking the improvement of non-specific CLBP treatment methods. Non-specific CLBP is defined as back pain without a known underlying condition and accounts for about 90% of all low back pain cases. Given the weak effects of available treatment methods, a deeper insight into the underlying mechanisms of non-specific CLBP appears to be of high importance. Our approach is to collect detailed spinal motion data of individuals with and without CLBP while performing daily living activities (i.e. walking, running, standing up from a chair, lifting an object, etc.) and to use these data to drive OpenSim-based multibody thoracolumbar musculoskeletal spine models.

Furthermore, we are collaborating on a study of the Balgrist University Hospital aiming at the identification of differences in the cortical sensory representation of the back along the thoraco-lumbar axis between healthy controls and non-specific CLBP patients and its potential link to spinal movement patterns.




Analysis of spinal biomechanics.

**Foot Function Assessment**

Group Head: Patric Eichelberger (Ph.D., M.Sc. Biomed Engineering), patric.eichelberger @bfh.ch.

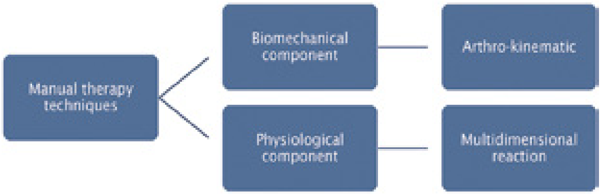
Consisting of 28 bones and 33 joints that are actuated by 21 muscles, the foot represents a complex biomechanical subsystem of the human body. From a mechanical point of view, the foot must on one hand be compliant for shock absorption and on the other hand, stiff for power generation. This broad range of functionality depending on the proper interplay of many biological structures, under the circumstance that the foot is subjected to high repetitive loading, makes it prone to injury and dysfunction. As it is the end-effector of the closed lower extremity kinematic during stance, it also affects more proximal joint like the knee and hip. Hence, it is important to assess and understand foot function in lower extremity therapy schemes. While clinical assessment often relies on static structural criteria, researchers can use multi-segment foot models driven by three-dimensional (3D) motion capture data to get insight into foot biomechanics. Although representing the sophisticated gold standard, the latter approach is not suitable for clinical practice due to reasons like infrastructure, time-consumption, and complexity. However, dynamic analysis is needed since static parameters are weak predictors of dynamic foot function. Therefore, a recent project developed a straightforward and clinically more feasible approach for foot function assessment by 3D foot kinematics. It was previously shown that assessment of foot kinematics can not only model the subtalar joint as a mitered hinge, and therefore shifting the focus from rearfoot to midfoot seems to be necessary. The clinical concepts of navicular drop and drift were therefore adapted to dynamic situations. A set of four landmarks on the foot allows for measurement of midfoot kinematics by vertical and mediolateral translation at the navicular bone. A first study guaranteed the accuracy of the movement laboratory setup to capture small intrinsic foot motions simultaneously to standard lower extremity gait protocols. The reliability of the method was subsequently quantified and the sensitivity could be demonstrated in terms of effects of walking versus running and increased walking and running speeds. A validation study confirmed the appropriateness of the translations at the navicular bone as surrogates of forefoot-hindfoot angles. The minimal markerset allows the expansion of standard gait protocols by assessment of intrinsic foot kinematics with less effort than with common multi-segment foot models and hence, lessens the gap between clinical and research practice in foot function assessment.

Foot loading response (left) and Foot Toe-Off (right).

**Manual Mobilization Techniques**

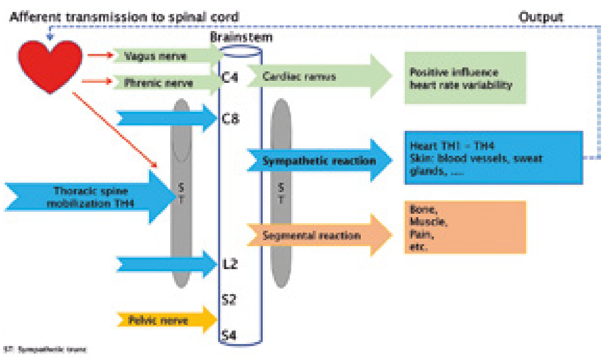
Group Head: Slavko Rogan (Ph.D., P.T.)
slavko.rogan@bfh.ch

Manual therapy techniques (MT) are commonly utilized to treat limited joint mobility (joint restrictions). This treatment approach is based on a biomechanical explanatory model. However, new neurophysiological evidence shows that a holistic approach is more feasible. The biomechanical approach is shifted to a more multidimensional approach. MT on the spine may activate different reflex pathways via sympathetic nervous systems (SNS), parasympathetic nervous systems (PSNS), and peripheral nervous systems pathways (PNS). The literature describes that manual manipulation techniques may increase output of the SNS. There is a lack of mode of action how manual mobilization acts on the autonomic nervous systems (ANS). Our research line investigated the impact of thoracic spine mobilization on the ANS. The outcome parameters were heart rate variability (HRV), heart rate (HR), blood pressure (BP), erythema (ET), and skin perfusion (SP).




Holistically approach of manual therapy techniques (own compilation).

The research line is structured as followed: 1) Systematic review is ongoing and registered (PROSPERO 2017: CRD42017062560). 2) Single case study: thoracic mobilization in anterior thrust and posterior thrust (published). 3) Feasibility study: short-term effects (published): thoracic (T6 and T4) mobilization in anterior thrust and posterior thrust. 4) Feasibility study: long-term effects: thoracic (T4) rotatory mobilization, three times/week over two weeks (all together six treatments); thoracic spine mobilization with rotatory thrust (ongoing; preliminarily results were presented at the SAMM congress 2018 in Interlaken, Switzerland)




Neurophysiological explanatory model of thoracic mobilization (own compilation).

Our results indicate that T6 mobilization in posterior thrust and T4 mobilization in anterior thrust may change HRV activity, HR activity, erythema, and skin perfusion. It is preliminarily suggested that rotatory mobilization increased PSNS responses. Thoracic spine mobilization could therefore possibly trigger reaction of the SNS and PSNS.

### Selected Publications


Blasimann A, Eichelberger P, Lutz N, Radlinger L, Baur H (2018): Intra- and interday reliability of the dynamic navicular rise, a new measure for dynamic foot function: A descriptive, cross-sectional laboratory study. Foot (Edinb), 37:48-53

Eichelberger P, Blasimann A, Lutz N, Krause F, Baur H (2018): A minimal markerset for three-dimensional foot function assessment: measuring navicular drop and drift under dynamic conditions. J Foot Ankle Res, Apr 18;11:15

Jaspers T, Taeymans J, Hirschmüller A, Baur H, Hilfiker R, Rogan S (2018): Continuous passive motion does improve range of motion, pain and swelling after ACL reconstruction: a systematic review and meta-analysis. Z Orthop Unfall, Oct 15. [Epub ahead of print]

Leitner M, Moser H, Eichelberger P, Kuhn A, Baeyens J-P, Radlinger L (2018). Evaluation of pelvic floor kinematics in continent and incontinent women during running: An exploratory study. Neurourology and Urodynamics, 37(2);609-618

Moser H, Leitner M, Baeyens J-P, Radlinger L (2018). Pelvic floor muscle activity during impact loads in continent and incontinent women: a systematic review. Int Urogynecol J, 29(2):179-196

Moser H, Leitner M, Eichelberger P, Kuhn A, Baeyens JP, Radlinger L (2018): Pelvic floor muscle activity during jumps in continent and incontinent women: An exploratory study. Arch Gynecol Obstet, 297(6):1455-1463

Pohl J, Jaspers T, Ferraro M, Krause F, Baur H, Eichelberger P (2018): The influence of gait and speed on the dynamic navicular drop -- A cross sectional study on healthy subjects. Foot (Edinb), 36:67-73

Rogan S, Haehni M, Luijckx E, Dealer J, Reuteler S, Taeymans J (2018): Effects of Hip Abductor Muscles Exercises on Pain and Function in Patients With Patellofemoral Pain: A Systematic Review and Meta-Analysis. J Strength Cond Res, Aug 2 [Epub ahead of print]

Rogan S, Radlinger L, Baur H, Schmidtbleicher D, de Bie RA, de Bruin ED (2016): Sensory-motor training targeting motor dysfunction and muscle weakness in long-term care elderly combined with motivational strategies: a single blind randomized controlled study. Eur Rev Aging Phys Act, May 28;13:4

Schmid S, Stauffer M, Jäger J, List R, Lorenzetti S (2018): Sling-based infant carrying affects lumbar and thoracic spine neuromechanics during standing and walking. Gait Posture, 67:172-180

Sotelo M, Eichelberger P, Furrer M, Baur H, Schmid S (2018): Walking with an induced unilateral knee extension restriction affects lower but not upper body biomechanics in healthy adults. Gait Posture, 65:182-189

# Continuing Education in Digital Health, Medical Informatics and Medical Technology

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**Daniel Zahnd**

**Brand New Program MAS Digital Health**
In 2018, we relaunched our continuing education program in medical informatics and medical technology. The new program leads to a degree of a Master of Advanced Studies (MAS) in Digital Health. We enable the graduates to master the growing challenges in connection with digitization in the health sector, including digitization in patient care, hospital, medical technology, biotechnology, and pharmaceutical technology.

The part-time postgraduate courses include topics such as the introduction of the electronic patient dossier, the advent of artificial intelligence in diagnostics, personalized medicine in the pharmaceutical industry, or new production frameworks in medical technology. Furthermore, it includes knowledge and skills to deal with efficient development, design, and regulatory approval of products and processes in healthcare, medical technology, or the biotech industry.

In the healthcare sector, there are fundamental changes that are essentially induced by two drivers: new legal requirements and advancing digitization in the field of medicine, technology, and society (digital transformation). We also see big innovations in health tech, pharma, and patient processes leading to an increasing dilution between the traditional specialities of medical informatics, medical technology, and life science.

The keywords are biological systems, bioinformatics, network theory in clinical practice, and the topic of digital and mobile health. It is all about personalized, stratified, or even "precision" medicine, which means the data-based interaction of prevention, diagnosis, and treatment based on individual patient characteristics. The methods of information technology are subsequently an essential element of these new promising developments. Common to them is the application of medical informatics and information technology for improving the treatment of patients. It all goes towards using innovative and flawless technical solutions.

Our DAS, MAS, and EMBA programs for practitioners and innovators in the department for continuing education offer a modular, part-time university degree, which is unique in Switzerland. The curriculum is part of the Continuing Education in the Department of Engineering and Information Technology, where complementary courses in management, innovation, business creation, and information technology can be completed.

The courses are primarily geared towards engineers, technical professionals, and natural scientists. Students are prepared to carry out demanding projects in the domain of development, procurement, marketing, and maintenance of medical technology products, and for assuming managerial responsibilities in the field of digital health and in research and development of medical devices and products. In our regulatory affairs courses, we teach students to be fully aware of and to comply with the growing demands of the governmental authorities.
See www.ti.bfh.ch/mas-dh.

### Selected Recent Master's Theses

Hiller, Ch. (2018) New System – Lower Incidence of Liver Injury. Development and validation of a new cell-based system to screen compounds inducing cholestasis

Schöpfer, S. (2018) Das EPD kommt – wie weit sind die Anbieter von Primärsystemen?

Marty, D. (2018) Entwicklung eines Clinical Decision Support Systems für Sepsispatienten in einem klinischen Informationssystem

Triep, K. (2018) The Robson Classification for Caesarean Section – Routinely Collected Health Data at a Swiss Tertiary Care Center from 2014–2017

Vaccaro, A. (2018) Temperaturentwicklung bei schablonengeführter Implantatbett- Präparation

Schweizer, M.P. & Demostene, D. (2017) Umsetzung Risikomanagement nach SN EN 80001-1 an der Insel Gruppe AG in Bern

Janser C. Reichlin H, Ritter A (2017) Einführung eHealth – eine Guideline für Spitäler und Heime

Mühlemann D, Isler A (2015) Unser Spital - Bauen mit Zukunft. Handbuch für interdisziplinäre Umsetzung

Parkel T (2015) IMU based Gonyometry Monitoring on Patients. quo vadis?

Fuhrer, M. (2015) In-vitro Untersuchung der mechanischen Eigenschaften von Primärkonstruktionen aus Hochleistungspolymer


EXIT

# ACADEMIC EDUCATION AND TEACHING

Academic education is a cornerstone of the Bern Biomedical Engineering Network. At Master's level, a joint program in Biomedical Engineering (BME) was established by the Medical Faculty of the University of Bern and the Department of Engineering and Information Technology of the University of Applied Sciences of Bern with the aim of training multidisciplinary engineers capable of developing scientifically founded and cost-effective solutions for biomedical problems in research and industry.

For graduates of the MSc in Biomedical Engineering and other candidates from related areas who are interested in an in-depth training in experimental and computational research and/or who aim for an academic career, a corresponding doctoral degree (PhD in Biomedical Engineering) can be earned at the inter-faculty Graduate School for Cellular and Biomedical Sciences (GCB) of the University of Bern. The GCB is jointly administered by the Faculties of Medicine, Science, and Vetsuisse, and offers tailored, structured training programs at international level.

The recently established sitem-insel School aims to promote researchers and train executives in the fields of translational medicine and biomedical entrepreneurship. Lecturers and supervisors of the school are representatives from research and development-oriented private companies, scientists from universities, clinicians, collaborators from regulatory agencies, and financial experts.

Philippe Zysset
Program Director Master of Biomedical Engineering
University of Bern

Marlene Wolf
Coordinator Graduate School for Cellular and Biomedical Sciences
University of Bern

Lukas Rohr
Head of Department
Bern University of Applied Sciences
Engineering and Information Technology

Jürgen Burger
Director
sitem-insel School

# Master of Science in Biomedical Engineering

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 over the years. The first curriculum consisted of a number of individual courses that were either mandatory or elective, but their coherence with regards to contents 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 the complexity of the curricular structure. The main idea was to guide 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. In addition, 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 are now offering 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. In 2018, the basic module "Biomedical Engineering" was re-structured and augmented by new courses in "Medical Informatics" and "Introduction to Biomechanics".

## The Curriculum

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

The full-time study program takes four semesters, which corresponds to 120 ECTS points, 1 ECTS point 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) 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, biology or related fields, do not fulfill all prerequisites for the courses of the master's program. Therefore, introductory courses in MATLAB, C++ programming, Electrical Engineering and Engineering Mechanics, as well as the tutorial-based course "Selected Chapters in Mathematics" were introduced and allow for a tailor-made curriculum for these students. Students with a background in engineering, on the other hand, have the possibility to select these courses freely if they feel the need to refresh some of the knowledge provided.

### Basic Modules

The basic modules provide the students with the necessary background to be able to fully understand the highly complex subject matter in the specialized courses. All students with an engineering background (for other students, individual study plans are set up which may contain certain variations) 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 and third semester, the courses from the basic modules make up for approximately 30 percent.

### Major Modules

The choice of one of three major modules Biomechanical Systems, 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.

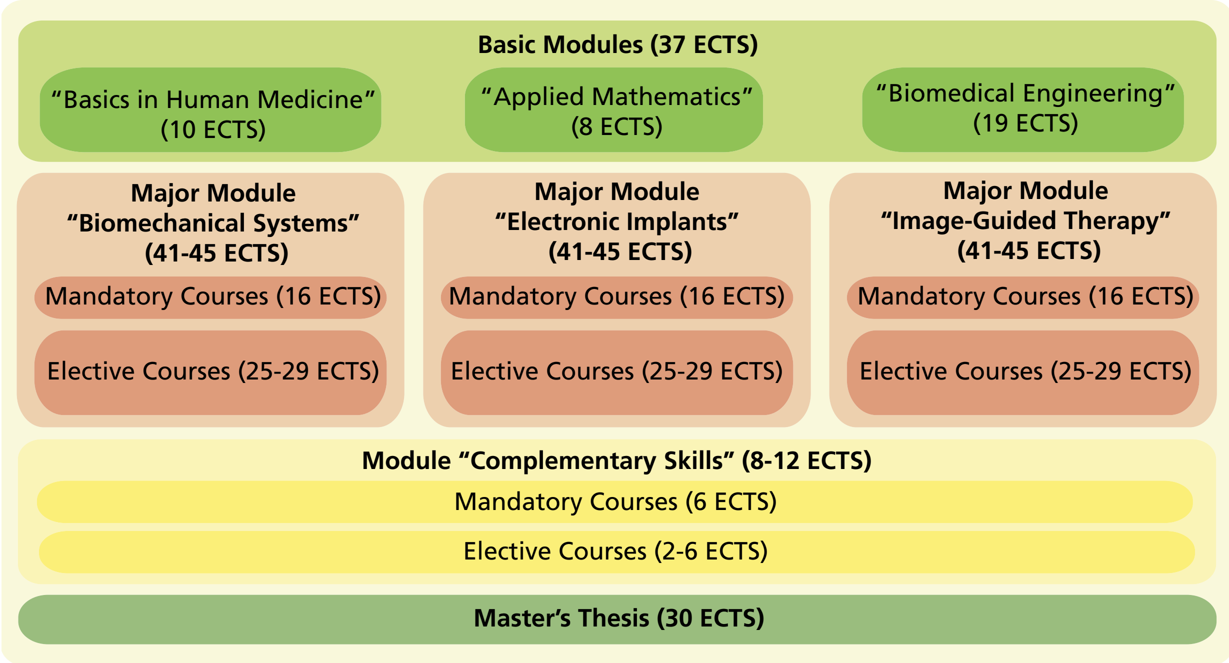
This is why the responsible lecturers developed a recommended study plan to guide the students through the course selection process and to avoid organizational problems such as overlapping courses. If a student follows the recommended path, he or she can be sure to establish a sound professional profile.

### 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 introduction of a new module called "Complementary Skills" where students are required to complete two mandatory courses (Innovation Management; Regulatory Affairs and Patents) as well as two ECTS from the electives courses (Ethics in Biomedical Engineering; Scientific Writing in Biomedical Engineering; Introduction to Epidemiology; and Health Technology Assessment). If a student selects more than two ECTS from the elective part, the additional points can be credited in the student's major module.

### 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 points 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
Biomechanics Labs
Biomedical Acoustics
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
Cutting Edge Microscopy
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
Image-Guided Therapy Lab
Innovation Management
Intelligent Implants and Surgical Instruments
Introduction to Biomechanics
Introduction to Digital Logic
Introduction to Electrical Engineering
Introduction to Engineering Mechanics
Introduction to Medical Statistics
Introduction to Programming
Introduction to Signal and Image Processing
Introductory Anatomy and Histology for Biomedical Engineers
Low Power Microelectronics
Machine Learning
Medical Image Analysis
Medical Image Analysis Lab
Medical Informatics
Medical Robotics
Microsystems Engineering
Molecular and Cellular Biology Practical
Numerical Methods
Ophthalmic Technologies
Orthopaedic Surgery – Practical Course
Osteology
Principles of Medical Imaging
Programming of Microcontrollers
Regenerative Dentistry for Biomedical Engineering
Regulatory Affairs and Patents
Rehabilitation Technology
Scientific Writing in Biomedical Engineering
Selected Chapters in Mathematics
Short Introduction to MATLAB
Technology and Diabetes Management
Tissue Biomechanics
Tissue Biomechanics Lab
Tissue Engineering
Tissue Engineering - Practical Course
Wireless Communication for Medical Devices

## Major Module: Biomechanical Systems

Philippe Zysset

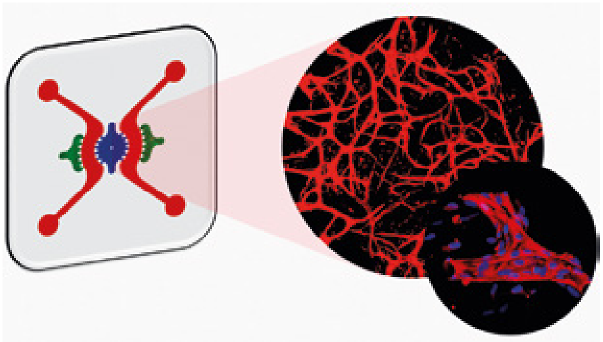
The respiratory, cardiovascular, and musculoskeletal systems are the transport and structural bases for our physical activities, and their health have a profound influence on our quality of life. Lung diseases, cardiovascular diseases, musculoskeletal injuries, and pathologies are costly ailments facing our health care 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, vessel 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 bench top 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 evaluation of the frictional behaviour of biomaterials on articular cartilage, development of a new breathable lung alveoli on a chip, characterization of an ultrasonic microscalpel, and finite element analysis of human bones, diastolic blood flow, or tissue-mimicking biomaterials.

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 engineering, orthopaedics, dentistry, rehabilitation engineering, and pharmaceuticals are strongly represented within the Swiss Medical Technology industry and, despite the strong Swiss franc, 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 health care domain.



Microfluidic chip of in vitro perfusable microvasculature network. Microvasculature network immuno-stained for endothelial cell marker PECAM-1.

## Major Module: Electronic Implants

Volker M. Koch

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 already provide more than 320’000 people worldwide with 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 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, and microsystems engineering, including MEMS technology. Application-oriented elective courses are also taught, e.g., cardiovascular technology, biomedical sensors, 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 are 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 e.g., to measure forces in knee implants.

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

Cochlear implant surgery requires drilling near the facial nerve. The goal of the DrillMon project is to develop, optimize and characterize a system that combines a surgical drilling device with an electrical nerve stimulation probe. This allows surgeons to continuously monitor nerves while drilling with up to 80’000 rpm.

## Major Module: Image-guided Therapy

Stefan Weber

Image-Guided Therapy 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 foundation for successful careers both in the industrial and academic sector.

Mandatory courses of this module are concerned with the fundamentals of Signal and Image Processing and Medical Image Analysis. 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.

Robotic Cochlear implantation, Inselspital Bern (© ARTORG Center, 2017)

## Faculty

### University of Bern

Christiane Albrecht, Prof. Dr.
Juan Ansó, Dr.
Philippe Büchler, Prof. Dr.
Julia Bohlius, PD Dr.
David Bommes, Prof. Dr.
Jürgen Burger, Prof. Dr.
Roch-Philippe Charles, Dr.
Marcel Egger, Prof. Dr.
Paolo Favaro, Prof. Dr.
Christian Fernandez Palomo, Dr.
Martin Frenz, Prof. Dr.
Benjamin Gantenbein, Prof. Dr.
Amiq Gazdhar, Dr.
Kate Gerber, Dr.
Olivier Guenat, Prof. Dr.
Wilhelm Hofstetter, Prof. Dr.
Doris Kopp
Jan Kucera, Prof. Dr.
Ruth Lyck, PD Dr.
Ange Maguy, Dr.
Laura Marchal Crespo, Prof. Dr.
Ines Marques, Dr.
Beatrice Minder
Stavroula Mougiakakou, Prof. Dr.
Tobias Nef, Prof. Dr.
Dominik Obrist, Prof. Dr.
Mauricio Reyes, Prof. Dr.
Anne Rutjes, Dr.
Shankar Sachidhanandam, Dr.
Walter Martin Senn, Prof. Dr.
Adrian Spörri, Dr.
Nicole Steck, Dr.
Jürg Streit, Prof. Dr.
Raphael Sznitman, Prof. Dr.
Prabitha Urwyler, Dr.
Stefan Weber, Prof. Dr.
Wilhelm Wimmer, Dr.
Guoyan Zheng, Prof. Dr.
Adrian Zurbuchen, Dr.
Marcel Zwahlen, Prof. Dr.
Philippe Zysset, Prof. Dr.

### Bern University Hospital (Inselspital) and School of Dental Medicine

Daniel Aeberli, PD Dr.
Tommy Baumann, Dr.
Dieter Bosshardt, Prof. Dr.
Marco-Domenico Caversaccio, Prof. Dr.
Vivianne Chappuis, PD Dr.
Timo Ecker, PD Dr.
Rainer Egli, Dr.
Sigrun Eick, Prof. Dr.
Jens Fichtner, Dr.
Michael Fix, Prof. Dr.
Andreas Häberlin, Dr.
Tim Joda, Prof. Dr.
Joannis Katsoulis, Prof. Dr.
Martin Kompis, Prof. Dr.
Kurt Laederach, Prof. Dr.
Kurt Lippuner, Prof. Dr.
Martin Maurer, Prof. Dr.
Thomas Pilgrim, Prof. Dr.
Lorenz Räber, Prof. Dr.
Christoph Andreas Ramseier, PD Dr.
Thiago Saads Carvalho, PD Dr.
Waldo Valenzuela, Dr.
Christophe Von Garnier, Prof. Dr.

### Bern University of Applied Sciences

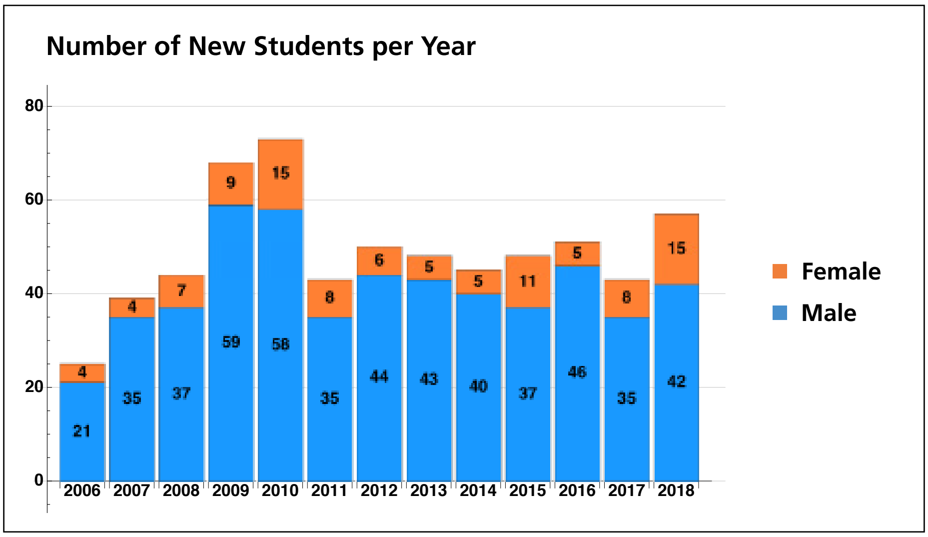
Patrik Arnold, Prof. Dr.
Norman Urs Baier, Prof. Dr.
Heiner Baur, Prof. Dr.
Daniel Debrunner, Prof.
Bertrand Dutoit, Prof. Dr.
Juan Fang, Dr.
Laëtitia Galea, Dr.
Josef Götte, Prof. Dr.
Andreas Habegger, Prof.
Kenneth James Hunt, Prof. Dr.
Marcel Jacomet, Prof. Dr.
Jörn Justiz, Prof. Dr.
Theo Kluter, Prof. Dr.
Volker M. Koch, Prof. Dr.
Martin Kucera, Prof.
Alexander Mack, Dr.
Christoph Meier, Prof.
Thomas Niederhauser, Prof. Dr.
Heinrich Schwarzenbach, Prof.
Andreas Stahel, Prof. Dr.
Jasmin Wandel, Prof. Dr.

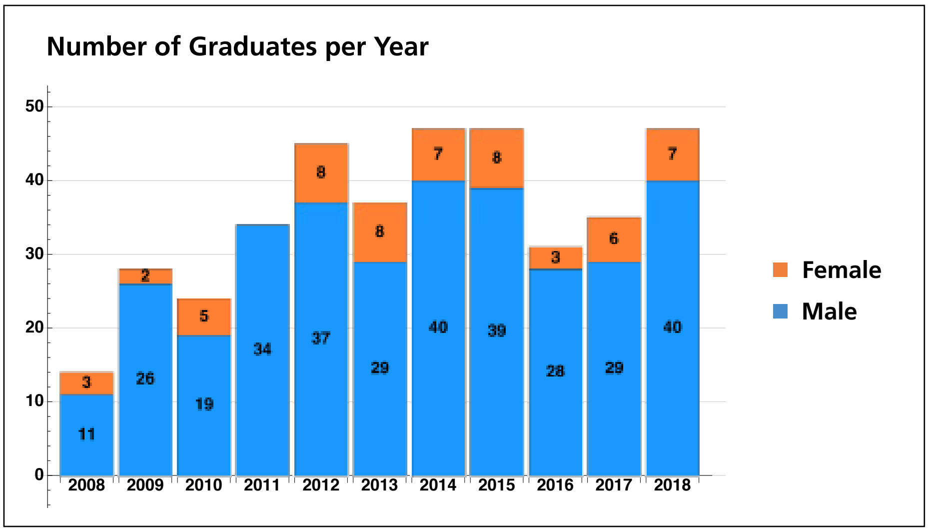
### Partner Institutions and Industry

Daniel Baumgartner, Prof. Dr.
Alessandro Bertolo, Dr.
Marc Bohner, Prof. Dr.
Alessandro Cianfoni, PD Dr.
Emmanuel de Haller, Dr.
Nicolas Alexander Diehm, Prof. Dr.
Nicola Döbelin, Dr.
Alex Dommann, Prof. Dr.
Stefan Eggli, Prof. Dr.
David Eglin, Dr.
Lukas Eschbach, Dr.
Gerhard Flückiger, Dr.
Marie-Noëlle Giraud, PD Dr.
Reinhard Gruber, Prof. Dr.
Janosch Häberli, Dr.
Daniel Haschtmann, PD Dr.
Bernd Heinlein, Prof. Dr.
Philipp Henle, Dr.
Roman Heuberger, Dr.
Ulrich Hofer, Dr.
Thomas Imwinkelried, Dr.
Björn Jensen, Dr.
Herbert Keppner, Prof. Dr.
Marc Kleinschmidt, Dr.
Jens Kowal, PD Dr.
Beat Lechmann
Reto Lerf, Dr.
Reto Luginbühl, Dr.
Katharina Maniura, Dr.
Simon Milligan, Dr.
Walter Moser, Dr.
Richard Nyffeler, PD Dr.
Jean Pascal Pfister, Prof. Dr.
Benjamin Pippenger, Dr.
Felix Reinert, Dr.
Barbara Rothen-Rutishauser, Prof. Dr.
Jorge Sague, Dr.
Birgit Schäfer, PD Dr.
Matthias Schwenkglenks, Prof. Dr.
Jivko Stoyanov, PD Dr.
Peter Varga, Dr.
Jürgen Vogt, Dr.
Bruno Wägli
André Weber, Dr.
Tobias Wyss, Dr.
Andreas Zumbühl, Prof. Dr.

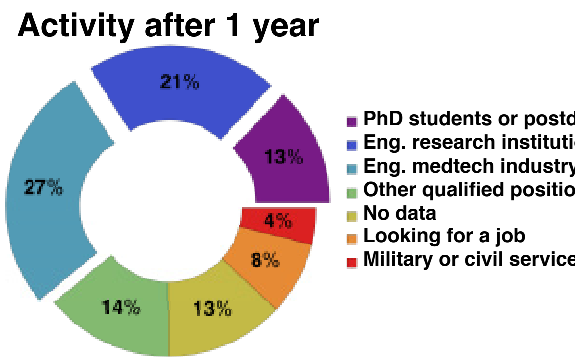
## Statistics

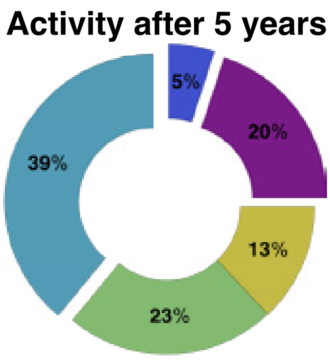
### Number of New Students and Graduates per Year




### BME Alumni: Career Directions



## Completed Master Theses in 2018

**Hector Alvarez**
*Signal Processing on 2- and 3 Dimensional EECG Data Sets From Clinical Trial*
Supervisors: Dr. med. Reto Wildhaber, Dr. med. Romy Sweda
Institutions: Bern University of Applied Sciences, Institute für Human Centered Engineering, University of Bern, University Hospital (Inselspital)
Examiners: Prof. Dr. Marcel Jacomet, Prof Dr. Josef Goette

**Bruno Bahnmüller**
*Design of an Electrospray Device for Targeted Drug and Gene Delivery*
Supervisors: Dr. med. Amiq Gazdhar, Prof. Dr. David Hradetzky
Institutions: University Hospital Bern (Inselspital), Department of Pulmonary medicine, University of Applied Sciences and Arts Northwestern Switzerland, Institute for Medical Engineering and Medical Informatics
Examiners: Prof. Dr. Dominik Obrist, Dr. med. Amiq Gazdhar

**Christian Burri**
*Optical Coherence Tomography Controlled Selective Retina Therapy for In-vivo Treatment*
Supervisors: Prof. Christoph Meier, MSc Daniel Kaufmann
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering
Examiners: Prof. Christoph Meier, Dr. Boris Považay

**Alberto Cerutti**
*Definition of Personalized Load Cases for the Human Distal Radius*
Supervisors: Prof. Dr. Philippe Zysset, MSc Denis Schenk, Dr. Patrik Christen
Institutions: University of Bern, Institute for Surgical Technology and Biomechanics Institut für Biomechanik, Eidgenössische Technische Hochschule, Zurich
Examiners: Prof. Dr. Philippe Zysset, Dr. Patrik Christen

**Lea Tiziana Dal Fabbro**
*Frictional Behaviour of Polycarbonate-Urethane to Cartilage – an Experimental Study*
Supervisor: Prof. Dr. Daniel Baumgartner
Institution: Zurich University of Applied Sciences, Institute of Mechanical Systems (IMES)
Examiners: Prof. Dr. Daniel Baumgartner, Prof. Dr. Stephen Ferguson

**Marco Dubach**
*Detection and Removal of Pacing Artifacts in Multi-Channel Esophageal ECG Signals*
Supervisors: Dr. med. Reto Wildhaber, Prof. Dr. Josef Goette
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering, University Hospital Bern (Inselspital), Department of Cardiology
Examiners: Prof. Dr. Josef Goette, Dr. med. Reto Wildhaber

**Dario Ferrari**
*Mimicking and Investigation of the In-Vivo Stiffness of the Lung Alveolar Milieu*
Supervisors: Prof. Dr. Olivier Guenat, Dr. Janick Stucki
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier Guenat, Dr. Janick Stucki

**Marta Ferrer i Subirana**
*Predicting Glaucoma Progression via Long Short-Term Memory Networks*
Supervisors: Serife Seda Kucur, Prof. Dr. Raphael Sznitman
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Dr. Carlos Ciller

**Luca Ferriroli**
*Tricking the Human Brain: Does Human Visual Self-Perception Bias Motor Planning?*
Supervisors: Prof. Dr. Laura Marchal-Crespo, MSc Joaquín Á. Peñalver-Andrés
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Laura Marchal-Crespo, MSc Joaquín Á. Peñalver-Andrés

## Completed Master Theses in 2018

**Nicolas R. Franzina**
*A Novel Lead- and Batteryless Pacemaker driven by an Endocardial Mass-Imbalance Oscillation Generator*
Supervisors: Dr. med. et phil. Andreas Häberlin, Dr. Thomas Niederhauser
Institutions: University of Bern, ARTORG Center for Biomedical Engineering Research, Bern University of Applied Sciences Engineering and Information Technology
Examiners: Dr. med. et phil. Andreas Häberlin, Dr. Adrian Zurbuchen

**Philipp Gerber**
*Visual Surveying for Automated Needle Injection System*
Supervisors: Prof. Dr. Raphael Sznitman
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, MSc Lino Schüpbach

**Martin Hofmann**
*Ultrasonic Microscalpel for High-Precision Surgery*
Supervisor: Prof. Dr. Jürgen Burger
Institution: University of Bern, Faculty of Medicine Swiss Institute for Translational and Entrepreneurial Medicine sitem-insel
Examiners: Prof. Dr. Jürgen Burger, Prof. Dr. Andreas Stahel

**Joël Illi**
*Experimental Modelling of Calcified Native Aortic Valves in a Transcatheter Aortic Valve Intervention*
Supervisor: MSc Silje Ekroll Jahren
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiner: Prof. Dr. Dominik Obrist, MSc Silje Ekroll Jahren

**Mathieu Jaquet**
*Low Cost Robotic Prosthesis for Children and Adolescents*
Supervisors: Prof. Dr. Gabriel Gruener, Dr. med. Martin Berli
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering, Universitätsklinik Balgrist
Examiners: Prof. Dr. Volker M. Koch, Prof. Dr. Gabriel Guener

**Yves Jegge**
*Impedance Spectroscopy to Assess Facial Nerve Proximity during Robotic Drilling in the Mastoid*
Supervisors: Dr. Juan Ansó, Dr. med. A. Sauter
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr.-Ing. Stefan Weber, Dr. Juan Ansó

**Dominique André Karlen**
*Development of a Reproducible 3D In Vitro Microvasculature Architecture*
Supervisors: Prof. Dr. Olivier Guenat, Soheila Zeinali
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier Guenat, Soheila Zeinali

**Samuel E. J. Knobel**
*Head-Mounted Display VR-Training for Hemi-Spatial Neglect Patients: A Usability and Acceptance Study*
Supervisors: Prof. Dr. Tobias Nef, MSc Stephan Gerber
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Tobias Nef, MSc Stephan Gerber

**Samuel Kreuzer**
*Design and Development of a Miniaturized ECG Front-End for Dry Electrodes*
Supervisors: Dr. Thomas Niederhauser, Prof. Dr. Josef Götte
Institution: University of Applied Sciences, Institute for Human Centered Engineering
Examiners: Dr. Thomas Niederhauser, Prof. Dr. Marcel Jacomet

**Gerhard Kuert**
*Next Generation of Cardiovascular Catheters based on Flex-Print Technology*
Supervisors: Dr. Thomas Niederhauser, Prof. Dr. Marcel Jacomet
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering
Examiners: Dr. Thomas Niederhauser, Prof. Dr. Josef Götte

**Paul Kulyk**
*Fully Automatic Planning of Total Shoulder Arthroplasty without Segmentation: A Deep Learning Based Approach*
Supervisors: Prof. Dr. Guoyan Zheng, PD Dr. Matthias Zumstein
Institutions: University of Bern, Institute for Surgical Technology and Biomechanics, University Hospital Bern (Inselspital), Department of Orthopedic Surgery and Traumatology
Examiners: Prof. Dr. Guoyan Zheng, Guodong Zeng

**Vikas Mathew**
*Erythrocyte-Based Nanotechnology for Personalized Drug Delivery Systems*
Supervisor: PD Dr. Jivko Stoyanov
Institution: Swiss Paraplegic Research, Nottwil
Examiners: Prof. Dr. Benjamin Gantenbein, PD Dr. Jivko Stoyanov

**Jonas Maturo**
*Innovative Multilayer Deposition for Biomedical Devices*
Supervisors: Prof. Dr. Juergen Burger, Dr. Jérôme Steinhauser
Institutions: University of Bern, Coat-X SA (La Chaux-de-Fonds)
Examiners: Prof. Dr. Juergen Burger, Dr. Jérôme Steinhauser

**Marcel Meier**
*Diabetic Retinopathy Classification from Fundus Photography*
Supervisor: Prof. Dr. Raphael Sznitman
Institutions: University of Bern, ARTORG Center of Biomedical Engineering Research, University Hospital Bern (Inselspital), Department of Ophthalmology
Examiners: Prof. Dr. Raphael Sznitman, Dr. Pablo Marquez Neila

**Camilo Mendez Schneider**
*Patient-to-image Registration for Lateral Skull Base Surgery Utilizing the Patient Tracker Attachment: Concept, Design and Evaluation*
Supervisors: Dr. Kate Gerber, Daniel Schneider
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Stefan Weber, Dr. Kate Gerber

**Slaviša Obradović**
*Smartphone Based Cataract Screening*
Supervisors: Prof. Dr. Raphael Sznitman
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Dr. Sandro De Zanet

**Saskia Perret-Gentil**
*Effects of Low Oxygen Pressure on Iron Metabolism in Osteoclasts*
Supervisor: Prof. Dr. Willy Hofstetter
Institution: University of Bern, Department for BioMedical Research
Examiners: Prof. Dr. Willy Hofstetter, PD Dr. Benjamin Gantenbein

**Jacob Rasmussen**
*Feasibility of large scale Machine Learning based Ballistocardiography*
Supervisors: MSc Narayan Schütz, MSc Angela Botros
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Tobias Nef, MSc Narayan Schütz

**Michael Rebsamen**
*Fast and Accurate Human Brain Morphometry Estimation with Deep Learning*
Supervisors: MSc Yannick Suter, Dr. rer. nat. Christian Rummel
Institutions: University of Bern, Institute for Surgical Technology and Biomechanics, University Hospital Bern (Inselspital), Support Center for Advanced Neuroimaging (SCAN), University Institute for Diagnostic and Interventional Neuroradiology
Examiners: Prof. Dr. Mauricio Reyes, Dr. rer. nat. Christian Rummel

**Joy Roth**
*Development of an In Vitro Platform for Investigating Biofilm Formation and Testing Novel Devices in the Lower Urinary Tract*
Supervisors: Dr. Francesco Clavica, Dr. Marc Schneider
Institutions: University of Bern, ARTORG Center for Biomedical Engineering Research, University Hospital Bern (Inselspital), Department of Urology
Examiners: Prof. Dominik Obrist, Prof. Fiona Burkhard

## Completed Master Theses in 2018

**Tobias Rothen**
*Modality Crawler: Using Deep Learning for Automated Brain MRI Sequence Classification*
Supervisors: Dr. Raphael Meier
Institution: University of Bern, Institute for Surgical Technology and Biomechanics
Examiners: Prof. Dr. Mauricio Reyes, Dr. med. Urspeter Knecht

**Simon Sänger**
*Development of a 3D Virtual Urban Environment to Stimulate Critically Ill Patients*
Supervisors: Prof. Dr. sc. Tobias Nef, Stephan Gerber
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. sc. Tobias Nef, Stephan Gerber

**Luca Sahli**
*Intraoperative 3D Ultrasound-Based Planning for Surgical Resection of Liver Tumors*
Supervisors: MSc Iwan Paolucci, Prof. Dr.-Ing. Stefan Weber
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr.-Ing. Stefan Weber, MSc Iwan Paolucci

**Yann Schaeffer**
*Finite-Element Simulation and Characterization on Tissue-Mimicking Gelatin Phantom of Focused Ultrasound Stimulation*
Supervisors: Prof. Dr. Andreas Stahel, Loïc Sottas
Institution: BFH TI, Creaholic SA, Biel
Examiners: Dr. Prof. Andreas Stahel, Prof. Dr. Philippe Büchler

**Simon Patrick Scheurer**
*Optimization and Validation of a Fall Detection System through Trial*
Supervisors: Prof. Martin Kucera, Dr. Prabitha Urwyler
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering, University of Bern, ARTORG Center for Biomedical Engineering Reasearch
Examiners: Prof. Martin Kucera, Dr. Prabitha Urwyler

**Patrice Seifriz**
*Computational Assessment of Blood Trauma due to Diastolic Flow through the Leaflet Clearance in the Lapeyre-Triflo Valve*
Supervisor: MSc Hadi Zolfaghari
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Dominik Obrist, MSc Hadi Zolfaghari

**Yannick Soom**
*Segmentation of Peripheral Nerves in Thigh Magnetic Resonance Neurography Using Deep Learning*
Supervisors: MSc Fabian Balsiger, MSc Alain Jungo
Institutions: University of Bern, Institute for Surgical Technology and Biomechanics, University Hospital Bern (Inselspital), Institute of Diagnostic and Interventional Neuroradiology
Examiners: Prof. Dr. Mauricio Reyes, Dr. Olivier Scheidegger

**Jan Stapelfeldt**
*Smartphone-based Perimetry for Fast and Low-cost Visual Field Acquisition*
Supervisor: Prof. Dr. Raphael Sznitman
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Serife S. Kucur

**Dorian Thomet**
*Sensor-Connected Glove for Hand Mobility Improvement*
Supervisors: Prof. Dr. Jörn Justiz, Anke Bossen
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering, Kinntek Sàrl
Examiners: Prof. Dr. Jörn Justiz, Anke Bossen

**Emily Thompson**
*Development of an in silico and in vitro Dynamic Lung Microvasculature Model*
Supervisors: Prof. Dr. Olivier Guenat, Soheila Zeinali
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier Guenat, Soheila Zeinali

**Phuong-Anh Tran**
*Signal Fusion for the Determination of Higher Neurological Functions in Preterm Infants*
Supervisors: Dr. phil. Thomas Niederhauser, Dr. med. Reto Wildhaber
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering
Examiners: Dr. phil. Thomas Niederhauser, Prof. Dr. Marcel Jacomet

**Flavio Traversa**
*Motor Learning Studies with Novel Error Modulating Strategies*
Supervisors: Prof. Dr. Laura Marchal-Crespo, MSc Özhan Özen
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Laura Marchal-Crespo, MSc Özhan Özen

**Marcel Vogt**
*In Vitro Investigation of Mechanical and Bioprosthetic Aortic Valve Leaflet Kinematics with Dual-Camera Stereo Photogrammetry*
Supervisor: MSc Leonardo Pietrasanta
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Dominik Obrist, MSc Leonardo Pietrasanta

**Stephan Weilenmann**
*Mutual Validation of a 3D Bone Damage Label with MicroFE Analysis*
Supervisors: Prof. Dr. Philippe Zysset, Benjamin Voumard
Institution: University of Bern, Institute for Surgical Technology and Biomechanics
Examiners: Prof. Dr. Philippe Zysset, Benjamin Voumard

**Raphaël Wenger**
*Inkjet 3D Printing of Polycaprolactone for Tissue Engineered Vascular Grafts*
Supervisors: PD Dr. Marie-Noelle Giraud, Prof. Fritz Bircher
Institutions: University of Fribourg, Faculty of Sciences and Medicine – Cardiology, School of Engineering and Architecture of Fribourg, iPrint Insitute
Examiners: PD Dr. Marie-Noelle Giraud, Prof. Dr. Olivier Guenat

**Martin Wigger**
*Optimized Path Planning to enable Robotic Surgical Milling Operations*
Supervisors: MSc Jan Hermann, Dr. med. Markus Huth
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Stefan Weber, MSc Jan Hermann

**Simon Wüthrich**
*Development of a New Breathable Lung Alveoli on a Chip Based on a Biological Membrane*
Supervisors: Prof. Dr. Olivier Guenat, Pauline Zamprogno
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier Guenat, Pauline Zamprogno

**Christian Wüthrich**
*In Vitro Diagnostic / Interventional Method for Assessing and Quantifying the Effects of No-Reflow Phenomenon in Coronary Models*
Supervisors: Dr. Sabrina Frey, Dr. Francesco Clavica
Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Dominik Obrist, Dr. Sabrina Frey

# Graduate School for Cellular and Biomedical Sciences

**Organization**

The Graduate School for Cellular and Biomedical Sciences (GCB) of the University of Bern is headed by the Ph.D. Committee (executive committee), which is composed of members from the Faculty of Medicine, the Faculty of Science, the Vetsuisse Faculty Bern, and the Program Coordinator. Taking turns, each faculty member acts as president.

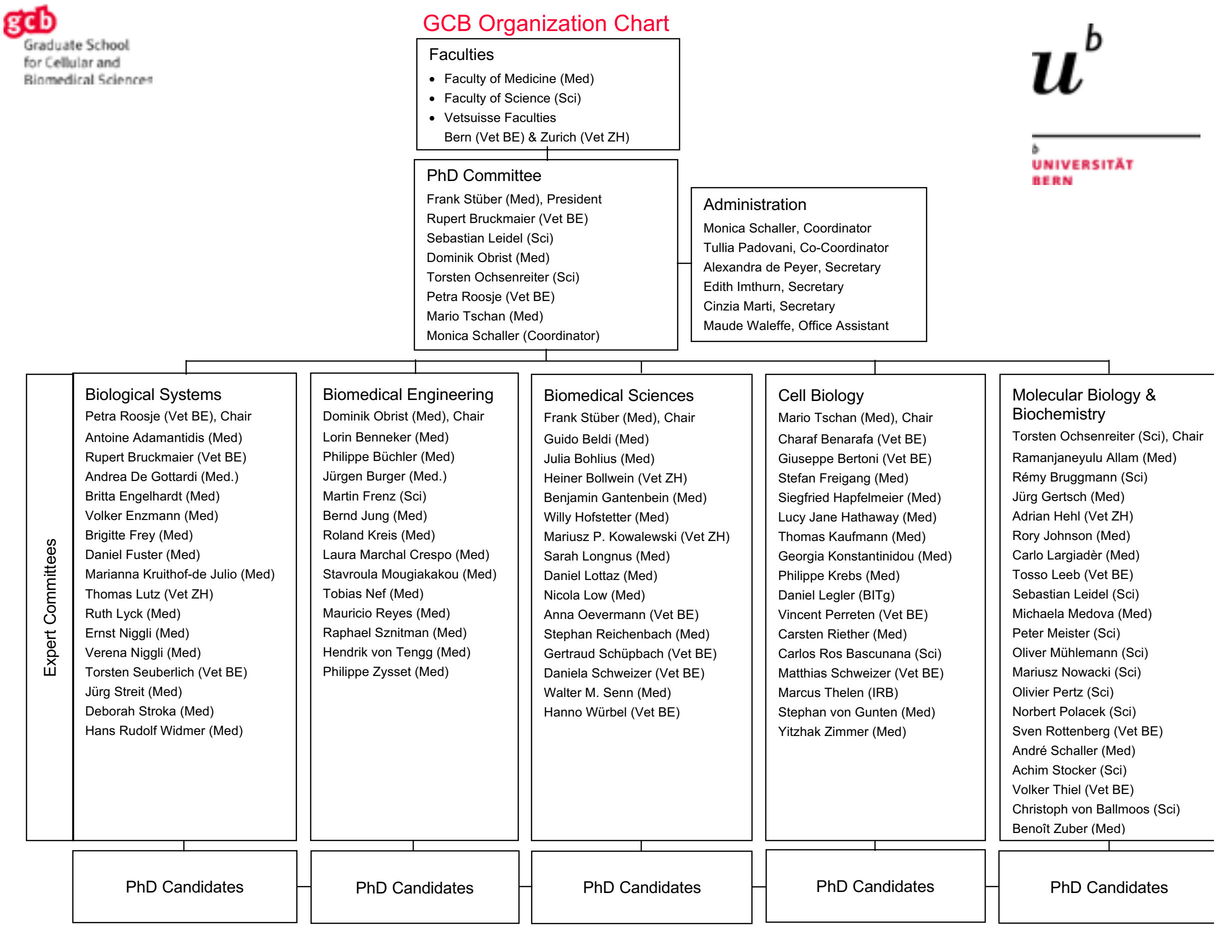
Currently, Prof. Dr. Frank Stüber (Faculty of Medicine) acts as president of the GCB and since January 2019, PD Dr. Monica Schaller is the coordinator.

Five Expert Committees with competences in

- Biological Systems
- Biomedical Engineering
- Biomedical Sciences
- Cell Biology
- Molecular Biology and Biochemistry

are responsible for the admittance, guidance, and evaluation of the Ph.D. candidates. Each research project is assigned to one of the GCB Expert Committees, one of its members acting as mentor to the Ph.D. candidate; together with the supervisor, they decide upon the individual training program of the Ph.D. candidate.

For details on the organization of the GCB and the GCB Committees' membership in 2018, see the GCB Organization Chart below.




GCB Organization Chart.

**PhD Program**
The GCB offers structured training in experimental research in the fields of biochemistry, cell and molecular biology, immunology, biomedical sciences, epidemiology, neuroscience, and biomedical engineering, leading to a Ph.D., M.D.,Ph.D, or DVM.,Ph.D. degree.

The thesis projects are carried out at laboratories of the three participating faculties or at affiliated institutions, which include, among others, the Institute of Virology and Immunology (IVI) in Mittelhäusern (now as part of the Vetsuisse Faculty Bern), the Institute for Research in Biomedicine (IRB) in Bellinzona, the EMPA, and the Swiss Paraplegic Research in Nottwil.

A thesis committee consisting of the supervisor, a co-advisor, and a member of the appropriate GCB Expert Committee (mentor) supervises each Ph.D. candidate.

The supervisor is responsible for the research project, adequate supervision, the laboratory infrastructure, and the salary of the candidate.

The co-advisor must not be affiliated with the same institute as the supervisor but should be an expert in the research area of the thesis project. He meets with the candidate at least twice a year to discuss and assess progress of the thesis work, as well as advising and supporting him/her.

The mentor decides, together with the candidate and the supervisor on the individual training program, taking into account the candidate's previous education.

Moreover, in order to promote independent evaluation, an external co-referee assesses the Ph.D. thesis of the candidate at the end of the study course.

The training program requires at least 6.0 ECTS of learning credits, which can be obtained by participating in approved, project-related and interdisciplinary courses, workshops, seminars, and lectures. In the course of the second year, candidates present their work in a scientific seminar in the presence of the thesis committee, to document in-depth knowledge of the research field («Mid-term Evaluation»).

By granting a financial contribution, the GCB actively supports the participation of candidates in national and international conferences and in special training courses offered by recognized institutions in Switzerland and abroad.

A further aim of the structured doctoral program of the GCB lies in the promotion of a lively scientific exchange between Ph.D. candidates and senior scientists, and the stimulation of networking activities such as regular discussions with the thesis committee and exchange among peers during the annual GCB Symposium. Moreover, Ph.D. candidates have the opportunity to invite internationally renowned scientists for a seminar or to organize a small workshop or meeting on a specific topic.

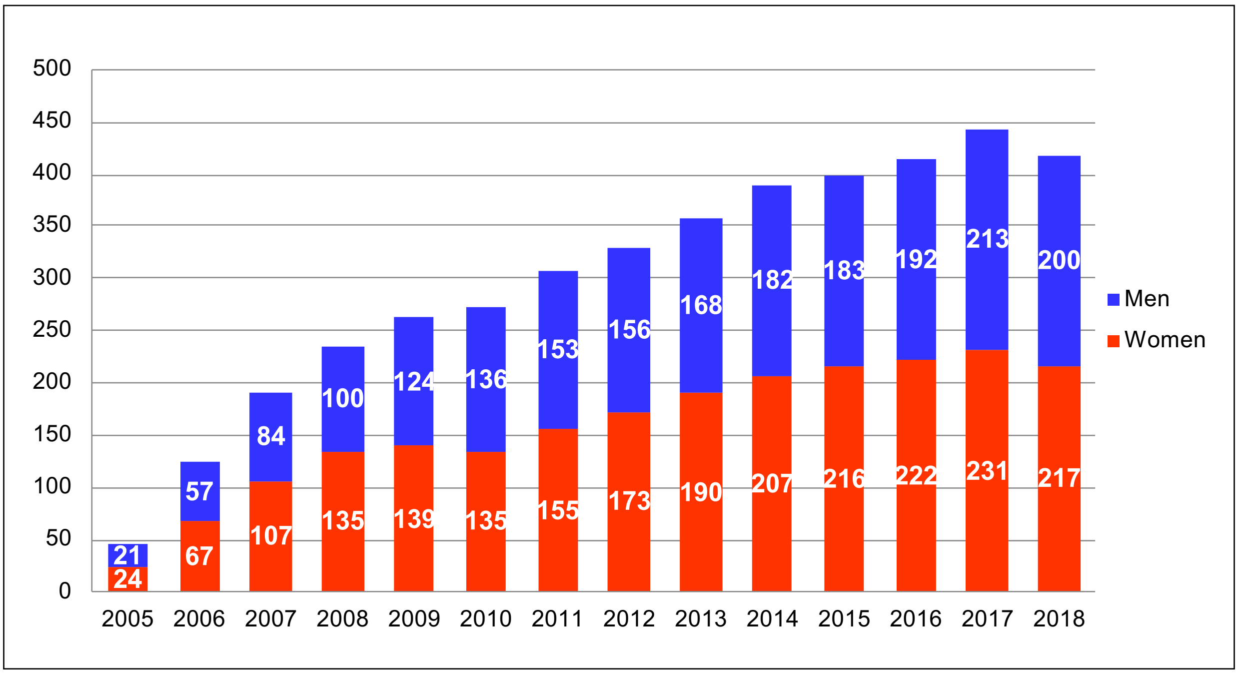
**M.D.-Ph.D. Program and M.D.-Ph.D. Fellowships**
The M.D.-Ph.D. program is intended for medical graduates interested in experimental research and aiming at an academic career. A structured training program within the framework of the GCB enables them to acquire a high standard of knowledge in natural sciences and physiology. The National M.D.-Ph.D. Program, which is supported by the Swiss National Science Foundation (SNSF), the Swiss Academy of Medical Sciences (SAMW), and several other foundations, awards nine to 13 fellowships every year to outstanding candidates studying at Swiss Universities. For more information, see http://www.samw.ch/en/Funding/MD-PhD-Programme.html.

**Doctoral Candidates**

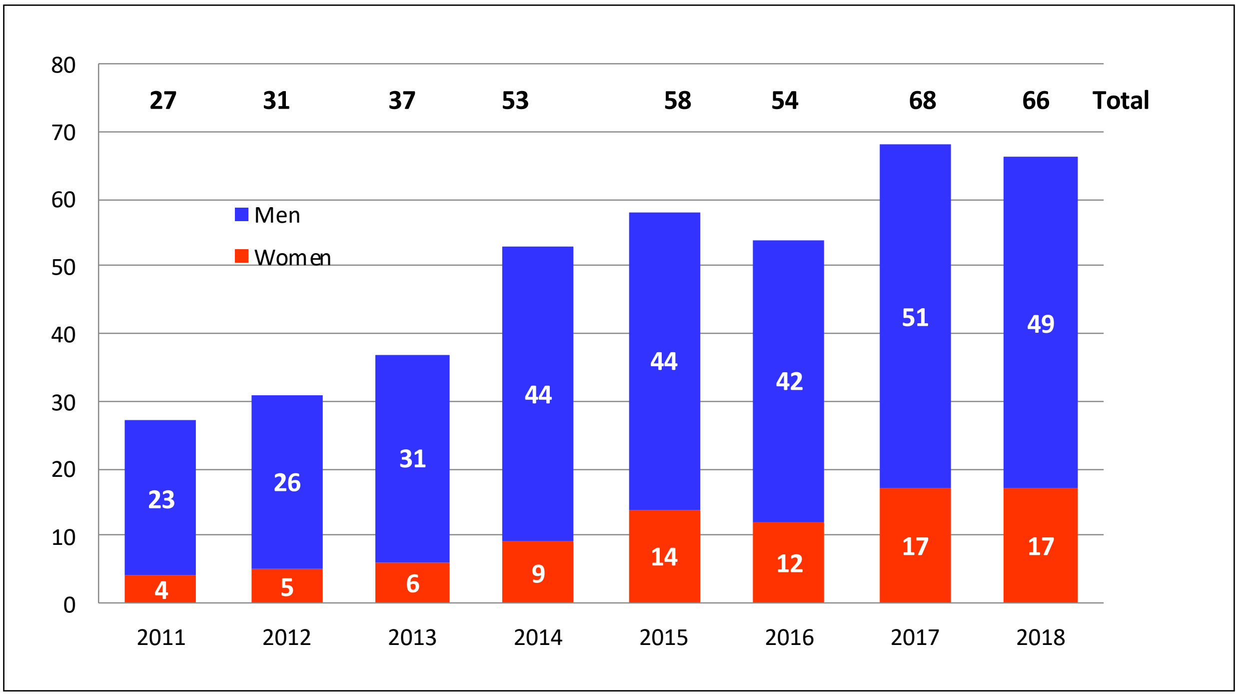
Candidates can apply three times per year for admission to the GCB: on 15 April, 15 August, and 15 December. In the course of 2018, 127 Ph.D. candidates were newly admitted.

The GCB is currently represented by doctoral candidates with degrees from 43 different countries. At the end of 2018, 417 candidates were enrolled in the GCB. 226 candidates (54.2%) held a degree from a foreign university, and 52.0% of the doctoral candidates were women (Ph.D. Candidates 2005-2018).

The number of candidates aiming for a Ph.D. in Biomedical Engineering in 2018 was 66, 17 of them are women and 49 men (Ph.D. Candidates aiming for a Ph.D. in Biomedical Engineering 2011-2018).




Number of GCB Ph.D. Candidates in the Years 2005-2018.




Number of Ph.D. Candidates Aiming for a Ph.D. in Biomedical Engineering 2011-2018.

**Courses and Seminars**

The curriculum comprises courses organized and supported by the GCB, courses scheduled by the teaching units of the faculties, as well as courses offered by other Swiss Universities, in particular by the ETHZ or the EPFL for the field of Biomedical Engineering. In addition, inter-university programs like the NCCRs «TransCure» and «RNA and Disease», the Doctoral Program in Biology and StarOmics (both CUSO), the Doctoral Program in Population Genomics (Universities of Basel, Bern, Fribourg & Lausanne), the Forum for Genetic Research (sc | nat, Swiss Academy of Sciences), the BENEFRI Neuroscience Program (Universities of Bern, Neuchâtel & Fribourg), the Swiss Institute of Bioinformatics (SIB), or the Swiss School of Public Health Ph.D. program (SSPH+) offer courses that are taken by GCB students. Some candidates also take part in internationally organized Summer Schools, which provide high-quality training in specific fields.

**GCB Seminars**

GCB Seminars give Ph.D. candidates the opportunity to invite internationally renowned specialists from their field of research for an interactive teaching lecture and a research seminar intended for a broad audience.

**GCB Symposium**

Since 2007, the GCB has organized an annual symposium for all Ph.D. candidates and their thesis committees, as part of the doctoral training. From the second year onwards, doctoral candidates are called to present their research projects in the form of posters or short talks, and since 2016, initiated in context with the 10th anniversary program, also in the form of a science slam («GCB Slam»). The presentations illustrate the wide range of topics covered by the GCB and demonstrate the candidates' high level of competence in the fields of cellular and biomedical sciences, epidemiology. and biomedical engineering. The GCB Symposia offer an excellent opportunity for both GCB candidates and their supervisors and mentors to engage in reciprocally rewarding and highly stimulating discussions on the research work going on at the GCB, and for active networking among peers. As a regular highlight, an invited keynote speaker delivers a lecture on a broad topic covering the wide interests of the GCB's young researchers.

In 2018, the distinguished keynote speaker was Prof. Dr. Martin E. Schwab from the Brain Research Institute of the University of Zürich and the Department of Health Sciences and Technology of ETH Zürich. The topic of his lecture was «Neurobiological mechanisms of functional recovery after spinal cord injury or stroke; the long way from the lab bench to the clinic with a neurite growth enhancing therapy».

**GCB Award for Best PhD Thesis**

At the start of each year, the Ph.D. Committee selects one of the most promising graduates of the past year for the «GCB Award for Best Ph.D. Thesis».

On 31 January 2019, at the GCB Symposium 2019, the «GCB Award for Best Ph.D. Thesis 2018» was awarded to Anina Bauer, Ph.D. in Biomedical Sciences, for her work entitled «Genetic analysis of genodermatoses». Anina performed her research work under the supervision of Prof. Dr. Tosso Leeb at the Institute of Genetics of the Vetsuisse Faculty, University of Bern, and defended her Ph.D. thesis successfully on 12 December 2018.

**Graduations**

In the course of 2018, 94 candidates successfully completed the Ph.D. program of the GCB and obtained their doctoral degree, jointly issued by the Faculty of Medicine, the Faculty of Science, and the Vetsuisse Faculty. Out of these, 12 Ph.D. theses focus on a biomedical engineering topic.

## Completed Ph.D. Theses in 2018, Focussing on a Biomedical Engineering Topic

**Lukas David Bereuter, Ph.D. in Biomedical Engineering**
*Leadless Cardiac Multisite Pacing*
Supervisors: Andreas Häberlin & Hildegard Tanner

**Nuno Miguel Da Silva Mendes Pedrosa de Barros, Ph.D. in Biomedical Engineering**
*Improving the Clinical Use of Magnetic Resonance Spectroscopy for the Analysis of Brain Tumours using Machine Learning and Novel Post-Processing Methods*
Supervisor: Johannes Slotboom

**Patric Eichelberger, Ph.D. in Biomedical Engineering**
*Foot function assessment by three-dimensional foot kinematics – A straightforward and clinically more feasible approach*
Supervisor: Fabian Krause

**Daniela Angelika Frauchiger, Ph.D. in Biomedical Sciences**
*Engineered Silk, Reinforced Hydrogel and Progenitor Cell Therapy for Intervertebral Disc Repair*
Supervisor: Benjamin Gantenbein

**Sabrina Elena Frey, Ph.D. in Biomedical Engineering**
*Hemodynamics in peripheral arterio-venous malformation*
Supervisor: Dominik Obrist

**Echrak Hichri, Ph.D. in Biomedical Engineering**
*Ephaptic coupling in the heart: a myth or a practical reality?*
Supervisor: Jan Kucera

**Silje Ekroll Jahren, Ph.D. in Biomedical Engineering**
*Impact of aortic root asymmetry and compliance upon performance of aortic valve bioprosthesis*
Supervisor: Dominik Obrist

**Christoph Martin Rathgeb, Ph.D. in Biomedical Engineering**
*Computer-Assisted Personalized Cochlear Implantation*
Supervisor: Wilhelm Wimmer

**Lars Marius Schwalbe, Ph.D. in Biomedical Sciences**
*Vascular Image Guidance to Aid Endovascular Treatments*
Supervisor: Stefan Weber

**Marc Stadelmann, Ph.D. in Biomedical Engineering**
*Finite element modeling of the human spine: Applications on metastatic vertebral bodies and intervertebral discs*
Supervisor: Philippe Zysset

**Ioannis Vogiatzis Oikonomidis, Ph.D. in Biomedical Engineering**
*Synchrotron X-ray tomographic microscopy and analysis of the rat pulmonary acinus at the micrometer scale - A close look deep into the acinar dynamics and development*
Supervisor: Joannes Schittny

**Simon Wüest, Ph.D. in Biomedical Engineering**
*Cartilage Tissue Engineering and Electrophysiological Recordings on Microgravity Platforms*
Supervisor: Benjamin Gantenbein


DePuy Synthes

# NETWORKING

Networking activities are at the heart of delivering successful projects by the BBN. The Biomedical Engineering Day (BME Day) is a great example of facilitating interaction and exchange in the three main areas the BBN has set-out to support:

- Encouragement of present and potential BME students to further their careers through the alumni Biomedical Engineering Club
- Potential partnering and commercial networking of medtech and life science companies at the BME Day
- Exploration of academic – commercial projects to benefit industry-driven project proposals through the skills and knowledge of the research community and industry partners

This year's BME Day celebrated the 10th anniversary of the BME Alumni Club and many graduates from previous years attended the event. It also was the largest industry partner exhibition at a BME Day, with a significant number of live job openings and related recruitment activities. Plans for the next BME Day and other dedicated networking activities for engagement with policy makers and funders at cantonal, national and international level are underway. And the BBN hopes to see many readers of this report there in the future.

# Biomedical Engineering Day

**The industry, medical doctors, and engineers meet for the Biomedical Engineering Day at the Inselspital in Bern with great success.**

On May 4, 2018, the Biomedical Engineering Day took place in the auditorium Ettore Rossi at the Inselspital in Bern. The Master in Biomedical Engineering program of the University of Bern organized this event for the tenth time.

The event is an efficient platform in Switzerland for networking of master and PhD graduates and Swiss and international medical technology companies. This year's companies introduced themselves through oral presentations and gave insight into their commercial activities and their company philosophies as well as showed their demands on junior employees. Students thus had the opportunity to get to know potential future employers and contact them directly. This was made possible between the sessions in personal conversations and at the exhibitors' booths.

The BME Day offered great opportunities for the Bernese biomedical researchers, too. The ARTORG Center for Biomedical Engineering Research and the Institute for Surgical Technologies and Biomechanics as well as the Bern University of Applied Sciences, a partner within the master's program, used the possibility of presenting current research projects to more than 250 participants. Interestingly, master and PhD students play an important role in many of these projects. Thereby, this event was a demonstration of scientific achievements, too.

Besides company representatives, scientists, researchers, and young academics, medical doctors participated in this year's event as they had the chance for intensive communication with the biomedical engineers.

One highlight of the day was the successful live surgery by Marco Caversaccio, Department of ENT, Head & Neck Surgery, University Hospital Bern (Inselspital). Illustrative explanations in the auditorium were given by Georgios Mantokoudis, from the same department.

The talk by Berhard Pulver, President of the Bernese government at the time, "Importance of the medical sector for the development of the canton of Bern" was another highlight of the event.

Bernhard Pulver, Regierungspräsident, Kanton Bern.
Photo: Adrian Moser

Participants in the auditorium.
Photo: Adrian Moser


Participants testing the 3D technology used in the OR.
Photo: Gianni Pauciello

Students check out a new software.
Photo: Adrian Moser

Research exhibition.
Photo: Adrian Moser

**Awards**
At the end of the day, six 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):
**Samuel Stucky**
*Building online mosaics for low-cost intra-ocular imaging*

Swiss Engineering Award for the best master's thesis (innovation):
**Gerhard Kuert**
*Next generation of cardiovascular catheters based on flex-print technology*

Swiss Engineering Award for the best master's thesis (basic science):
**Emily Thompson**
*Development of an in silico and in vitro dynamic lung microvasculature model*

SICAS Award for the best PhD thesis:
**Arne Feldmann**
*Thermal and drilling properties of bone*

BME Club Award for the best poster:
**Can Gökgöl**
*The effects of nitinol stent oversizing in patients undergoing femoropopliteal artery revascularization: a finite element study*

BME Club Award for the best master's thesis abstract:
**Christopher Lenherr**
*Indentation properties of metastatic vertebral bone*

BME Club travel grant:
**Stephan Gerber**
*Virtual reality for activities of daily living training in neurorehabilitation: a usability and feasibility study in healthy participants (ECMB 2019, Hawaii)*

Emily Thompson, Arne Feldmann, Samuel Stucky and Gerhard Kuert (Photo: Adrian Moser)

Can Cökgöl and Stephan Gerber (Photo: Adrian Moser)

**We thank our sponsors and exhibitors**

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# The Biomedical Engineering Club

**The BME Club and Its Mission**

The BME Club is an alumni club whose mission is to provide and promote networking among its interdisciplinary members. We are a constantly growing group of biomedical engineers, scientists, past and present students, and medical technology corporates; eager to bring together the principles of engineering, biology, and clinical medi- cine. The club accomplishes these goals by hosting events such as information sessions on the latest cutting-edge research in different fields of biomedical engineering, attendance at international conferences, and organizing visits of various industrial plants and laboratories. The BME Club is recognized as an official alumni association of the University of Bern under the umbrella organization
– Alumni UniBE. A dedicated executive committee follows the principles of our constitution.

We are an enthusiastic and versatile group with diverse activities:

- bi-monthly “Stammtisch” in a local restaurant as an amiable platform to exchange, discuss, brainstorm, or simply chat
- visits to Swiss medical and engineering companies
- organization of the annual MEDICA trip
- information on career opportunities (incl. job offers)
- organization of the annual welcome event for new students of the BME Master program
- organization of an annual alumni gathering
- sponsorship of the poster and abstract awards at the annual BME day
- sponsorship of conference travel grants
- provide access to the Medical Cluster events
- automatic joint membership with Alumni UniBE
- offer joint membership with SSBE (Swiss Society for Biomedical Engineering)

In short, the BME club represents a unique platform for professional, lifelong communication, and networking. For further details, visit our website at http://www.bmeclub.ch.

**How to Join**

Becoming a member is easy! Simply sign up at any BME Club event or visit us at http://www.bmeclub.ch.
We look forward to seeing you!

**The BME Club Board in 2018**

Prabitha Urwyler
President & PR

Andrea Nienhaus
Secretary & Treasurer

Tobias Imfeld
Webmaster

Fatih Toy
Alumni

Stephan Gerber
PhD Students

Tamara Melle
Master Students

A spontaneous student stammtisch in Biel, April 2018

Welcome day for the new students ends in the old city of Bern. Thanks to our dynamic student representative Tamara Melle!

The GP Bern as usual motivates more members year by year. The runners from May 2018 pose on a gloomy day.


The sudden downpour towards the end of the GP Bern didn’t dampen our spirits.

Seniors and juniors exchange experiences at the alumni BBQ, August 2018.

# ACKNOWLEDGMENTS


The BBN becomes better with each supporter that joins the wide variety of visionary partners, stakeholders, and funders. Every year the network has been fortunate to have more endorsements and this year the spin-outs of the ARTORG Center Alvelolix AG, RetinAI AG and CAScination AG have joined the roster and contributed on many levels. Infrastructure resources and core funding from the University of Bern and the Bern University of Applied Sciences continues to provide baseline backing for existing collaborations and new projects. Project funding like the BRIDGE Program, a joint Swiss National Science Foundation and Innossuisse - Swiss Innovation Agency funding tool for translational and matched R&D funding has been instrumental in moving a number of projects towards the clinic. Our academic and clinical partners at the Swiss Institutes of Technology in Zurich and Lausanne, the Basel University Hospital and a number of other clinical centers of excellence in Europe deserve a special mention. Because of their collaboration, the BBN is able to transition ideas and innovations to a national and international level. The number, variety, and generosity of our sponsors and commercial collaborators from private, Swiss, and International medical technology industries is still a great source of gratitude for us and we look forward to more and closer work together. Open and collaborative teams that develop solutions to meet needs in the clinical and humanitarian arenas should be the measure of success for the BBN. Our outlook for the BBN is optimistic and the "graduation" of BBN technologies into routine clinical care is testament to the success of our collaboration model.

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