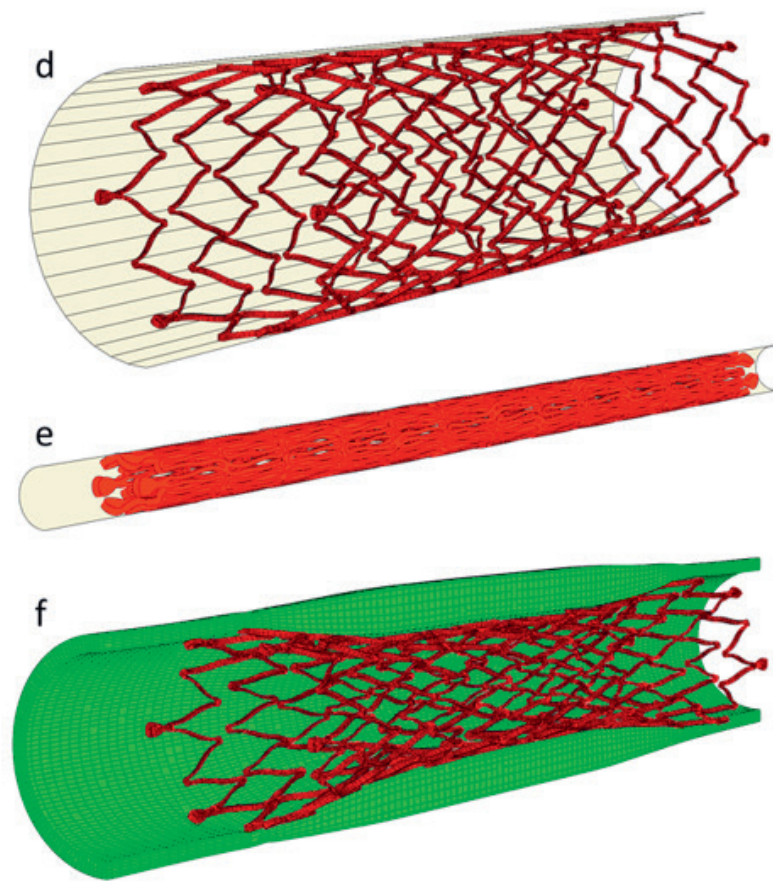
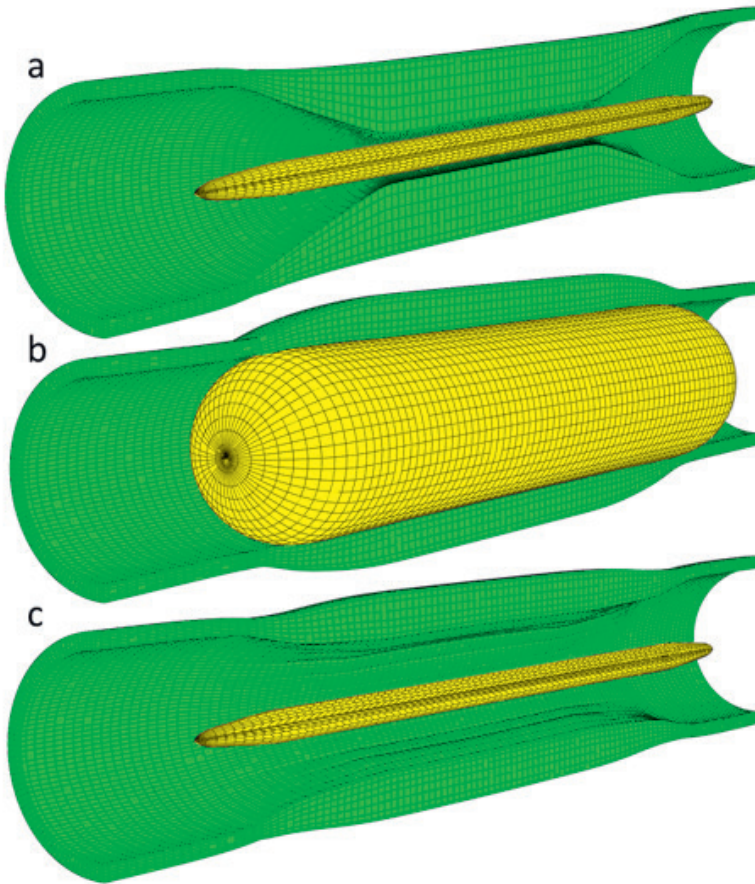


# Annual Report 2017





# INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

## Contents

|                                                       |    |
|-------------------------------------------------------|----|
| Editorial .....                                       | 2  |
| Organization .....                                    | 3  |
| Computational Bioengineering.....                     | 4  |
| Information Processing in Medical Interventions ..... | 6  |
| Medical Image Analysis.....                           | 8  |
| Musculoskeletal Biomechanics.....                     | 10 |
| Tissue and Organ Mechanobiology .....                 | 12 |
| Mechanical Design and Production.....                 | 14 |
| Acknowledgments .....                                 | 16 |
| Dissertations .....                                   | 16 |
| Awards & Prizes .....                                 | 17 |
| Impressions .....                                     | 18 |



University of Bern  
Institute for Surgical Technology and Biomechanics  
Stauffacherstrasse 78  
3014 Bern, Switzerland  
Phone +41 31 631 59 59  
Email [backoffice@istb.unibe.ch](mailto:backoffice@istb.unibe.ch)  
[www.istb.unibe.ch](http://www.istb.unibe.ch)

## EDITORIAL

We are very proud to present the annual report 2017 of the Institute of Surgical Technology and Biomechanics! The ISTB comprises a multidisciplinary team of about 50 co-workers from more than 10 countries. It is further closely integrated into the Bern Bioengineering Network ([www.bbn.ch](http://www.bbn.ch)), which is an inter-faculty and inter-institutional collaborative research network from the university hospital, Inselspital Bern, institutes of the University of Bern, the Bern University of Applied Sciences and various external partners.

In 2017, 9 students earned their PhD degrees in Biomedical Engineering in the frame of the Graduate School for Cellular and Biomedical Sciences ([www.gcb.unibe.ch](http://www.gcb.unibe.ch)) with an excellent research output and well-attended presentations. The ISTB contributed again substantially to the Master's Program in Biomedical Engineering ([www.bme.master.unibe.ch](http://www.bme.master.unibe.ch)) with hundreds of teaching hours and 35 master theses.

On the research side, our publication record reached 31 peer-reviewed journal and conference publications. In addition, members of the ISTB team have edited 2 books throughout the past year. Our IPMI group head, Dr. Guoyan Zheng, was elected as a member of the board of directors of the Medical Image Computing and Computer Assisted Intervention (MICCAI) Society, recognizing his high-level contributions to the field and his continuous services to the organization. Congratulations for this remarkable accomplishment. Several awards and prizes were also obtained, among others, the Best Paper Award on Machine Learning in Medical Imaging at MICCAI and the Ypsomed Innovation Award (2nd).

External funding was maintained at a high level. Our five research groups continued to be successful in convincing national and international funding agencies, NGOs, and the Medtech industry to support our research and development activities with appropriate funds. In particular three new projects were granted by the Swiss National Science Foundation and two from the Federal Innovation Promotion Agency CTI. Our teams have been successfully involved in organizing and co-organizing national and international workshops and conferences striving themes such as bone biomechanics, spinal interventions, repair

and regeneration of interconnecting soft tissue and medical image computing. On a local level, a joint initiative of the ISTB, the Departments of Orthopaedics and Rheumatology and the Bone Biology Group of the DBMR - the "Bone Bar" - became one of the highlights of the university's "Night of Research".

On the facilities and laboratory equipment side, a compact laser extensometer could be installed on our servo-hydraulic testing system that allows for contact free and high precision measurement as well as control of displacements with a resolution of 0.04 microns. This extensometer represents an indispensable addition to a state of the art biomechanical testing environment. In 2017, the ISTB's summer excursion, masterly organized by Julia Spyra on a beautiful day, took us to the Rigi on the North-South transit route of Europe where merchants were transferring their goods over lakes and land through the "Hohle Gasse". A superb view and a hearty barbecue with healthy salads rewarded the participants at Ruodisegg. All volunteers of the ISTB could finally test their crossbow shooting skills on apple targets under the benevolent supervision of the Swiss legend Wilhelm Tell.

We would like to welcome our new coworkers who initiated their PhD thesis, postdoc and administrative, technical or scientific jobs in the course of the year. Despite the ongoing challenges in biomedical engineering, we hope they will enjoy the friendly and international atmosphere of our research organization and wish them an excellent start.

Our special thanks go not only to the funding agencies for their ongoing support, but especially to our research partners for their faith in our competences and their efforts towards our common goals. Finally, we would like to acknowledge our group heads and their teams for their unyielding strive in teaching, research and translational medicine. We wish you a captivating report.



Lutz-P. Nolte  
Director ISTB

Philippe Zysset  
Co-director ISTB

# INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

## ORGANIZATION

### Management



L. P. Nolte  
Director



Ph. Zysset  
Co-Director

### Administration



A. Zürn



E. Gnähöré

### Scientific Groups



P. Büchler  
Computational Bioengineering



G. Zheng  
Information Processing in Medical Interventions



M. Reyes  
Medical Image Analysis



Ph. Zysset  
Musculoskeletal Biomechanics



B. Gantenbein  
Tissue and Organ Mechanobiology

### IT-Support



D. Damopoulos

### Master of Science in Biomedical Engineering



Ph. Zysset  
Program Director



U. Jakob-Burger  
Study Coordinator



A. Neuenschwander Salazar  
Study Coordinator



J. Spyra  
Study Coordinator

### Mechanical Design and Production



U. Rohrer  
Head



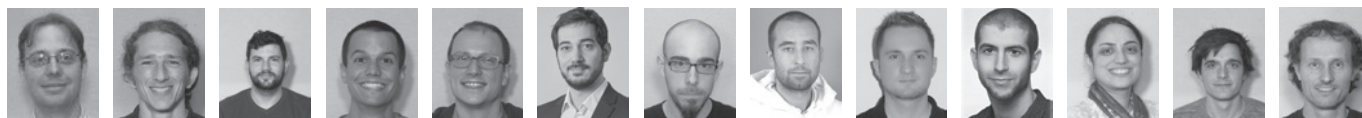
M. Reyes  
Master Thesis Coordinator

# COMPUTATIONAL BIOENGINEERING

Philippe Büchler, Head of Research Group

Email: philippe.buechler@istb.unibe.ch

Phone: +41 31 631 59 47



**Philippe  
Büchler**

Daniel  
Abler

Miguel Ángel  
Ariza Gracia

Steve  
Berger

Tobia  
Brusa

Stefan  
Funari

Can  
Gökgöl

Michael  
Kistler

Roman  
Niklaus

Nino  
Sutter

Elham  
Taghizadeh

Oskar  
Truffer

Thomas  
Wyss

## Clinical Research Partners

Prof. Dr. Carol Hasler, Orthopedic Dept., University Children's Hospital Basel

Prof. Dr. Nicolas Diehm, Vascular Institute Central Switzerland

PD Dr. Lukas Brügger, Dept. of Visceral surgery, Inselspital, Bern University Hospital

Prof. Dr. Bojan Pajic, Swiss Eye Research Foundation

PD. Dr. Olivier Lieger, Dept. of Cranio-Maxillofacial Surgery, Inselspital, Bern University Hospital

Prof. Dr. Alain Farron, Service of Orthopedics and Traumatology, Lausanne University Hospital

Dr. Fabio Becce, Department of Diagnostic and Interventional Radiology, Lausanne University Hospital

Prof. Dr. Radu Tutuian, University Clinic of Visceral Surgery and Medicine, Inselspital, Bern University Hospital

Dr. Christian Gingert, Dept. of Visceral and Thoracic Surgery, Hospital of Winterthur

PD. Dr. Lorenz Räber, Department of Cardiology, Inselspital, Bern University Hospital

## Research Profiles

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. Another important research focus of the group is the development of numerical models of soft tissues such as cornea or peripheral arteries.

## Mathematical Modeling of the Biomechanical Forces Causing Brain Tumor Mass-Effect

Gliomas are the most frequent malignant primary brain tumors in adults. Their most frequent and malignant subtype, Glioblastoma multiforme (GBM), present with a range of growth phenotypes; from predominantly invasive tumors without notable "mass-effect" to strongly displacing lesions that induce high mechanical stresses resulting in healthy-tissue deformation, midline shift or herniation. Biomechanical forces shape the tumor micro-environment by compression of blood and lymphatic vessels, thus reducing blood perfusion and generating hypoxia. Therefore, we expect these forces to be important for tumor evolution, for the formation of distinct growth phenotypes and tumor shape.

With the aim to quantitatively characterize different growth phenotypes, to better understand the role of mechanical forces in their formation and to study possible implications for treatment, we started developing a framework for brain tumor growth simulation. The underlying mathematical model captures the invasive growth characteristics of GBM and the biomechanical stresses caused by tumor growth. As structural anisotropy is known to affect the preferred directionality of tumor cell migration and the mechanical

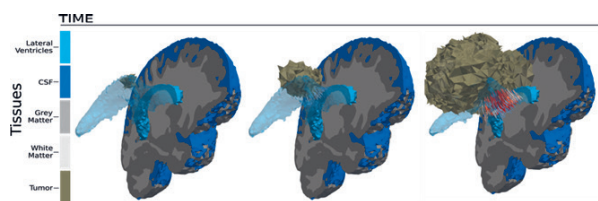


Figure 1. Simulated temporal evolution of brain tumor.

behavior of brain tissue, we extended a previous version of the framework to account for the orientation of axons in white matter using information from Diffusion-Tensor-Imaging (Fig. 1). Future research aims at model validation and development towards enabling patient-specific characterization of distinct "invasive" and "displacive" growth phenotypes.

## Planning of Refractive Interventions

Over the past decade, laser surgery became a widespread technique for vision correction such as myopia or astigmatism. The cornea of the patient is reshaped by laser ablation of stromal tissue. The amount of tissue to remove is traditionally estimated based on experimental nomograms or geometrical approaches. Unfortunately, the refractive correction is frequently over- or under-estimated.

We proposed an opto-mechanical simulation framework to quantify the optical outcome induced by alternation of the corneal biomechanics. The framework has been used to simulate the effect of laser ablation of stromal tissue. The optimal ablation profile was defined based on the wavefront calculated using the patient's corneal topography. The post-surgical visual acuity can be simulated and it can be shown that the clinical outcomes depend on the mechanical deformation of the tissue induced by the ablation profile (Fig. 2). While small variations of the mechanical parameters of the tissue or of the intra-ocular pressure only have small effects on the optical outcome, mechanical deformation plays a major role in the final visual acuity. Therefore, a simulation approach that accounts for the mechanical deformation of the cornea, could be used to determine patient-specific ablation profile.

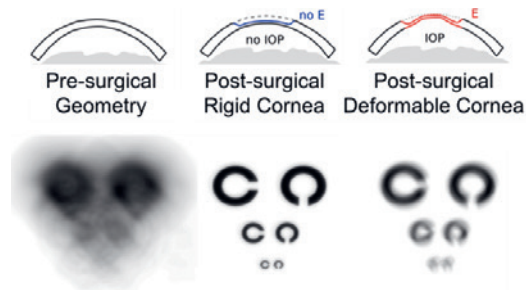


Figure 2. Simulated Landolt C vision test before (left) and after wavefront guided PRK surgery (center and right). The mechanical deformation affects the visual outcome (right) compared to the situation assuming a rigid cornea without mechanical deformation (center). This example shows that the mechanical deformation of the tissue must be accounted for to ensure optimal visual acuity.

### Finite Element Analysis of Peripheral Arterial Disease

The femoro-popliteal (FP) segment is the most commonly diseased artery of the peripheral circulation. Obstructions of these peripheral arteries are frequent and even with the new generation of drug-eluting Nitinol stents, the rate of restenosis in FP arteries is much higher than coronary arteries following endovascular revascularization. These high failure rates have been mainly linked to the presence and severity of the mechanical deformations of the FP artery during leg flexion. However, certain clinical practices, which are subjective with respect to the performing clinicians' expertise, have also been hypothesized to contribute to the poor outcomes observed after treatment. Chief among them is Nitinol stent oversizing, which is commonly performed in peripheral arteries to ensure strong wall apposition and increased luminal gain immediately after treatment. However, the effects of oversizing on the mechanical behaviour of diseased peripheral arteries remain unclear.

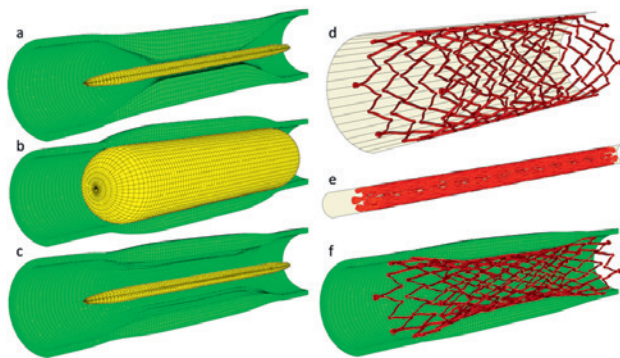


Figure 3. Simulation of the complete procedure of an endovascular therapy in an artery. Positioning of the angioplasty balloon (a), expansion of the balloon and plaque failure (b), folding of the angioplasty balloon and evaluation of the expanded lumen diameter (c), representation of the Nitinol stent and the crimp tool in their unconstrained diameters prior to crimping of the stent (d), crimping of the Nitinol stent to insertion diameter (e), and the deployment of the stent into the artery (f).

Therefore, we developed finite element analyses of the endovascular therapy of pathologic arteries to examine the influence of Nitinol stent oversizing on the arterial stresses and acute lumen gain. Additionally, different plaque types have been implemented to comment on relationship between the severity of the

calcification and the treatment outcomes. The analyses included the simulation of balloon angioplasty (a step that has been largely ignored in previous studies), followed by Nitinol stent implantation. Results showed that balloon angioplasty was crucial in determining the stress levels of the artery prior to stent implantation and heavily affected the outcome of endovascular therapy. For all plaque types, Nitinol stent oversizing was found to produce a marginal lumen gain in contrast to a significant increase in arterial stresses. For the arteries with lightly and moderately calcified plaques, oversizing was found to be non-critical; whereas for the arteries with heavily calcified plaques, the procedure should be avoided due to a risk of tissue failure.

### Quantitative Analysis of Rotator Cuff Muscles in 2D CT Images

Knowing the condition and functioning of rotator cuff (RC) muscles is desirable and important in various shoulder disorders, such as gleno-humeral osteoarthritis. MRI is the imaging examination of reference to accurately assess RC muscles due to its high soft tissue contrast capabilities. However, MRI is limited for analyzing cortical bone and it does not offer 3D volume-rendered reconstructions. In contrast, CT is the preferred imaging method for cortical bone and is routinely performed in the preoperative planning of shoulder arthroplasty to acquire information on glenoid version, scapula-humeral subluxation, glenoid bone quality.

We proposed a method to automatically quantify the atrophy of the muscle in patients as well as the level of fatty infiltration, degeneration and osteochondroma. The approach is based on machine learning techniques to determine, in the CT image of the pathological shoulder, the size and position of the muscles before pathological degeneration (Fig. 4). With this method, we were able to accurately reproduce the muscle delineation of expert radiologists. In addition, this approach precisely quantified the fatty infiltration and muscle degeneration. Due to its automatic nature, this approach is more reproducible than the techniques used clinically, which are semi-quantitative and therefore more subjective.

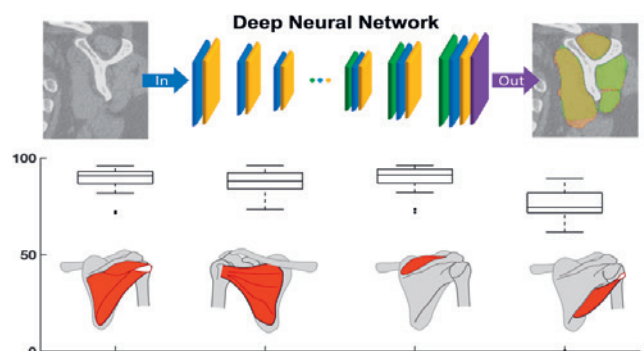


Figure 4. Automatic segmentation of rotator-cuff muscles, using deep neural networks. The neural network was trained based on manual annotations by an expert on 2D CT scans of osteoarthritic patients. The method was able to reproduce the manual segmentations by the expert (high values of dice coefficients).

### Selected Publications

1. Taghizadeh E, Chandran V, Reyes M, Zysset P, Büchler P. Statistical Analysis of the Inter-Individual Variations of the Bone Shape, Volume Fraction and Fabric and Their Correlations in the Proximal Femur. *Journal of Bone* 103. 252-261 Oct. 2017.
2. Schumann S, Gökgöl C, Diehm N, Büchler P, Zheng G. Effect of Stent Implantation on the Deformations of the Superficial Femoral Artery and Popliteal Artery: In Vivo Three-Dimensional Deformational Analysis from Two-Dimensional Radiographs. *Journal of vascular and interventional radiology : JVIR* 28: 1. 142-146 Jan. 2017.
3. Berger S, Hasler CC, Grant CA, Zheng G, Schumann S, Büchler P. A software program to measure the three-dimensional length of the spine from radiographic images: Validation and reliability assessment for adolescent idiopathic scoliosis. *Computer methods and programs in biomedicine* 138: 57-64 Jan. 2017.
4. Gökgöl C, Diehm N, Büchler P. Numerical Modeling of Nitinol Stent Oversizing in Arteries with Clinically Relevant Levels of Peripheral Arterial Disease: The Influence of Plaque Type on the Outcomes of Endovascular Therapy Accepted for publication in *Annals of Biomedical Engineering*. 2017.
5. Brusa T, Abler D, Tutuiian R, Studer P, Fattorini E, Gingert C, Heverhagen JT, Brügger LE, Büchler P. MR-FLIP: a new method that combines a functional lumen imaging probe with anatomical information for spatial compliance assessment of the anal sphincter muscles. *Colorectal disease* 19: 8. 764-771 Aug. 2017.

# INFORMATION PROCESSING IN MEDICAL INTERVENTIONS

Guoyan Zheng, Head of Research Group

Email: guoyan.zheng@istb.unibe.ch

Phone: +41 31 631 59 56



**Guoyan Zheng**



Naoki Kamiya



Wenyong Liu



Yuanhao Gong



Silvio Pflugi



Weimin Yu



Alper Akcoltekin



Benedikt Thelen



Dimitris Damopoulos



Guodong Zeng



Zenglin Shi



Jing Li

## Research Partners

Prof. Dr. med. Klaus Siebenrock, Inselspital, University of Bern, Switzerland

Prof. Dr. med. Moritz Tannast, Inselspital, University of Bern, Switzerland

Prof. Dr. Hiroshi Fujita, Dept. EE & Computer Engineering, Gifu University, Japan

Prof. Dr. Yoshinobu Sato, Nara Institute of Science and Technology, Nara, Japan

Prof. Dr. Kensaku Mori, Graduate School of Information Science, Nagoya University, Japan

Prof. Dr. Shuo Li, The University of Western Ontario, Canada

Prof. Dr. Daniel Belavy, Deakin University, Australia

Prof. Dr. Rolf Krause, Center for Computational Medicine in Cardiology, University of Lugano, Switzerland

Prof. Jerome Schmid, Haute école de santé Geneva, Switzerland

Prof. Dr. Bill Taylor, Institute for Biomechanics, ETH Zurich, Switzerland

Dr. med. Philipp Fürnstahl, Balgrist Clinics, Zurich, Switzerland

Dr. Daniel Haschtmann, Schulthess Clinics, Zurich, Switzerland



Rens Janssens



Kenan Niu

## 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.

## Fully Automatic Segmentation of 3D MR/CT Spinal Images (SNSF Grant 157207)

In clinical routine, lower back pain (LBP) caused by spinal disorders is reported as a common reason for clinical visits. Both CT and MR imaging technologies are used in computer assisted spinal diagnosis and therapy support systems. In this project, we are aiming to develop unified, machine learning-based approaches to address the challenging problems of localization and segmentation of intervertebral discs and vertebral bodies from 3D CT/MR images of patients with spinal diseases. In year 2017, we developed a cascaded 3D fully convolutional networks (FCN)-based method consisting of a localization FCN and a segmentation FCN for fully automatic segmentation of lumbar vertebrae from clinical CT images and

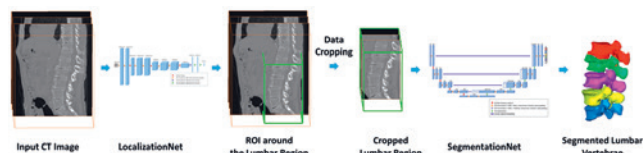


Figure 1. A Schematic view of the cascaded FCN-based approach

achieved a mean segmentation error of  $0.37 \pm 0.06$  mm.

## Web-based Planning and Evaluation of Orthopedic Interventions (KTI 18193.1 PFLS-LS)

Standard orthopedic interventions are commonly planned based on one planar X-ray. For many procedures, a true 3D planning would be important, but a CT scan is not adequate due to costs and radiation exposure. In this project, together with Medivation AG, we would like to bring a unique 2D-3D technology into the market, which enables full 3D planning and evaluation with only two X-rays. This technology is highly automated and provided as a web-based medical product to the orthopedic community. In year 2017, we validated our technology on data acquired from 43 patients when used for pre-operative knee prosthesis planning and post-operative treatment evaluation. The results demonstrated the efficacy of our



Figure 2. An example of using our 2D-3D reconstruction technology for post-operative treatment evaluation in total knee arthroplasty (TKA).

novel technology.

## Multi-modal Image Computing for Computer Assisted Interventions (SNF Grant 163224)

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 2017, we developed a deep learning-based, focused semantic segmentation method for fully automatic segmentation of hip joint from MR images, winning the best paper award in 2017 MICCAI Workshop on Machine Learning in Medical Imaging. A mean segmentation error of 0.22 mm was achieved.

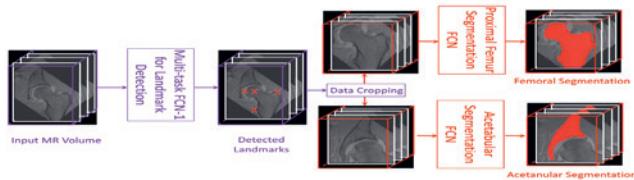


Figure 3. A schematic view of deep learning-based, focused semantic segmentation of hip joint from MR images.

### Video-Fluoroscopy-Based Tracking of In-Vivo Knee Kinematics (KTI 17078.1 PFLS-LS)

This project aims to provide scientific evidence for the improved medial stability of the GMK sphere knee prosthesis of Medacta SA. The overall goal is achieved through the advancement of the ETH-Zürich automated video-fluoroscope (led by Prof. Bill Taylor, Institute for Biomechanics, ETH Zürich) coupled with the development of software (developed by IPMI Group) to analyse the 3D motion of the knee during unrestricted daily activities in subjects with and without total knee replacements.

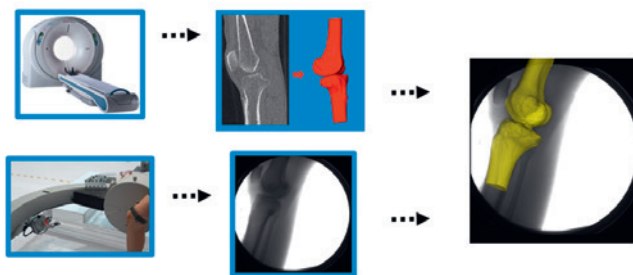


Figure 4. A schematic view of video-fluoroscopy-based tracking of in-vivo knee kinematics

### HEARTFUSION: Imaging-Driven Patient-Specific Cardiac Simulation (SNSF Grant 169239)

Cardiac disease remain as one of the most significant health problems. In 2011, in the USA alone, 813'000 deaths resulted from cardiovascular disease. Clearly, the understanding, diagnosis, and treatment of heart failure are of major importance for our society and has a strong impact on economics and social life. Together with Prof. R Krause, Center for Computational Medicine in Cardiology, University of Lugano, Switzerland, we are aiming to develop an automated approach for personalized simulation in cardiology, integrating numerical simulation and medical image computing as tightly as possible. In year 2017, we developed deep learning-based fully automatic whole heart segmentation algorithms from MR images and achieved the best performance in the MICCAI 2017 Multi-modality whole heart segmentation challenge (MM-WHS 2017) dataset.

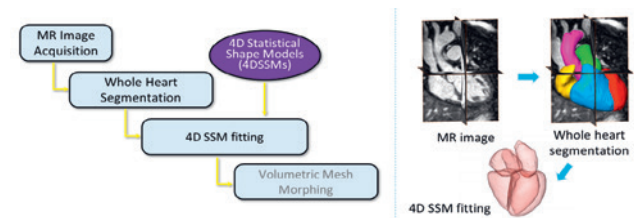


Figure 5. A schematic view of the cardiac image analysis pipeline that we developed (left) and an example of whole heart segmentation and 4D SSM fitting (right)

### Edited Book

1. Zheng G, Li S and Székely G (eds.): Statistical shape and deformation analysis: methods, implementation and applications. Elsevier, 2017. ISBN: 978-0-12-810493-4
2. Yao J, Vrtovc T, Zheng G, Frangi A, Glocker B (eds.): Computational Methods and Clinical Applications for Spine Imaging – The 4th International Workshop and Challenge, CSI2016, Held in Conjunction with MICCAI 2016, Athens, Greece, October 17, 2016, Springer 2016, ISBN: 978-3-319-55049-7.

### Book Chapters

1. Zheng G and Yu W. Statistical shape and deformation models based 2D-3D reconstruction. In: G Zheng, S Li and G Székely (eds.), Statistical shape and deformation analysis: methods, implementation and applications (pp 329 – 349), Elsevier, 2017.

### Patent

1. Zheng G, Dong X and Nolte L-P (2017), Method and devices for patient-specific acetabular component alignment in total hip arthroplasty. Patent No. EP2442757, Date of Patent: 02. Feb., 2017.

### Selected Publications

1. Pflugi S, Vasireddy R, Lerch T, Ecker TM, Tannast M, Boemke N, Siebenrock K, and Zheng G. Augmented marker tracking for peri-acetabular osteotomy surgery. International Journal of Computer Assisted Radiology and Surgery, in press, 2017.
2. Simson KJ, Miller CT, Ford J, Hahne A, Main L, Rantalainen T, Teo WP, Teychenne M, Connell D, Trudel G, Zheng G, Thickbroom G, Belavy DL. Optimising conservative management of chronic low back pain: study protocol for a randomised controlled trial. Trials, 18:184, 2017.
3. Karasawa K, Oda M, Kitasaka T, Misawa K, Fujiwara M, Chu C, Zheng G, Rueckert D, Mori K. Multi-atlas pancreas segmentation: Atlas selection based on vessel structure. Medical Image Analysis, 39:18-28, 2017.
4. Gökgöl C, Schumann S, Diehm N, Zheng G and Büchler P. In-vivo quantification of femoro-popliteal artery deformations: percutaneous transluminal angioplasty vs. nitinol stent placement. Journal of Endovascular Therapy, 24(1):27-34, 2017.
5. Schumann S, Gökgöl C, Diehm N, Büchler P, Zheng G. The effect of stent implantation on the deformations of the SFA and the popliteal artery: In-vivo 3D deformational analysis from 2D radiographs. Journal of Vascular and Interventional Radiology, 28:142-146, 2017.
6. Yu W, Tannast M, and Zheng G. Non-rigid free-form 2D-3D registration using a B-spline-based statistical deformation model. Pattern Recognition, 63:689 – 699, 2017.
7. Zheng G, Chu C, Belavy DL, et al. Evaluation and comparison of 3D intervertebral disc localization and segmentation methods for 3D T2 MR data: a grand challenge. Medical Image Analysis, 35:327-344, 2017.
8. Berger S, Hasler C, Grant O C A, Zheng G, Schumann S, Büchler P. A software program to measure the three-dimensional length of the spine from radiographic images: validation and reliability assessment for adolescent idiopathic scoliosis. Computer Methods and Programs in Biomedicine, 138:57-64, 2017.
9. Zeng G, Yang X, Li J, Yu L, Heng P-A and Zheng G. 3D U-net with multi-level deep supervision: fully automatic segmentation of proximal femur in 3D images. MLMI@MICCAI 2017:274-282, 2017.
10. Yu W and Zheng G. Atlas-Based 3D Intensity Volume Reconstruction of Musculoskeletal Structures in the Lower Extremity from 2D Calibrated X-Ray Images. BIVPCS/POCUS@ MICCAI 2017: 35-43, 2017.

# MEDICAL IMAGE ANALYSIS

Mauricio Reyes, Head of Research Group

Email: mauricio.reyes@istb.unibe.ch

Phone: +41 31 631 59 50



Mauricio Reyes



Waldo Valenzuela



Raphael Meier



Simon Habegger



Alain Jungo



Yannick Suter



Fabian Balsiger



Tobias Rothen



Urspeter Knecht

## Clinical Research Partners

Prof. Dr. med. Roland Wiest, Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern Univ. Hospital

Prof. Dr. med. Andreas Raabe, University Clinic for Neurosurgery, Inselspital, Bern Univ. Hospital

Prof. Dr. med. Daniel Aebbersold, University Clinic for Radiation Oncology, Inselspital, Bern Univ. Hospital

## Research Profile

The Medical Image Analysis group conducts theoretical and applied research in image processing, computer vision, and artificial intelligence for the analysis of medical image datasets. The focus of our research relies on the paradigm of evidence-based image modeling and personalized medicine, aiming at effectively using medical image information, and image computing technologies, to leverage the understanding of diseases and medical conditions of the central nervous system, and to support and improve the healthcare system relying on the analysis of medical image information.

## 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

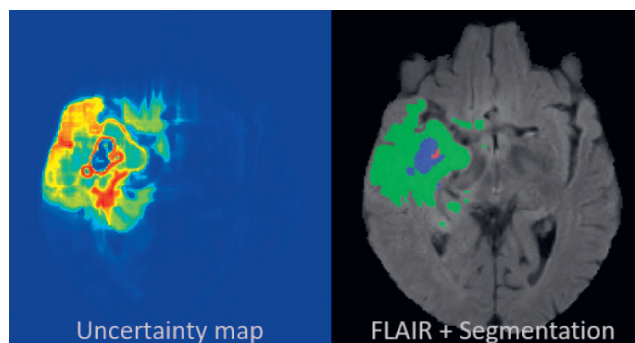
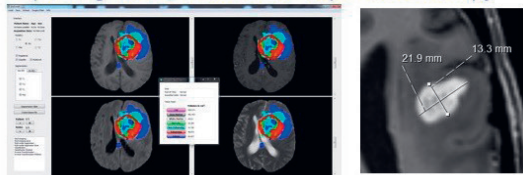


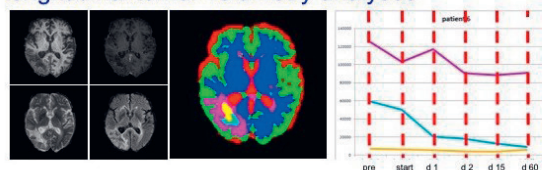
Figure 2. The MANAGE project aims at developing radiomics technologies and non-invasive biomarkers capable of better characterizing disease progression and patient response to therapy through longitudinal multisequence MRI information, and machine learning technologies. Advanced brain tumor quantification for neurosurgery and radiotherapy. Robust and clinically-validated longitudinal brain tumor quantification.

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.

### Improving the assessment of response to therapy



### Leveraging therapy assessment through large-scale longitudinal tumor volumetry analyses



### Radiomics: Advanced imaging biomarkers

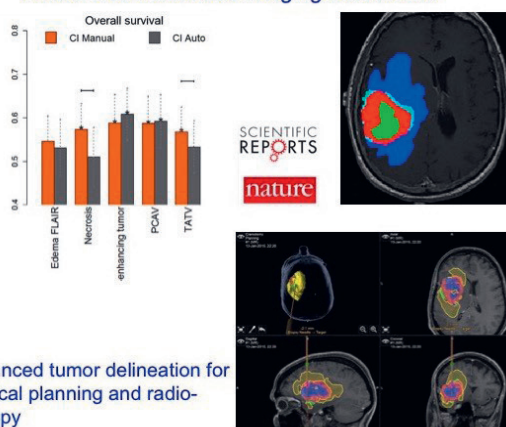


Figure 1. Brain image lesion analysis (In clockwise order): Improving the assessment of response to therapy through automated brain tumor quantification. Radiomics, and the role of tumor volumetry for patient survival analysis. Advanced brain tumor quantification for neurosurgery and radiotherapy. Robust and clinically-validated longitudinal brain tumor quantification.

## 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 within the MANAGE project, for Multidimensional Response Assessment in Glioma Patients, which is an interdisciplinary effort aiming at developing longitudinal radiomics technologies and non-invasive biomarkers providing a better assessment of disease progression and patient response to therapy.

## 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. During 2017, 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 at creating 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

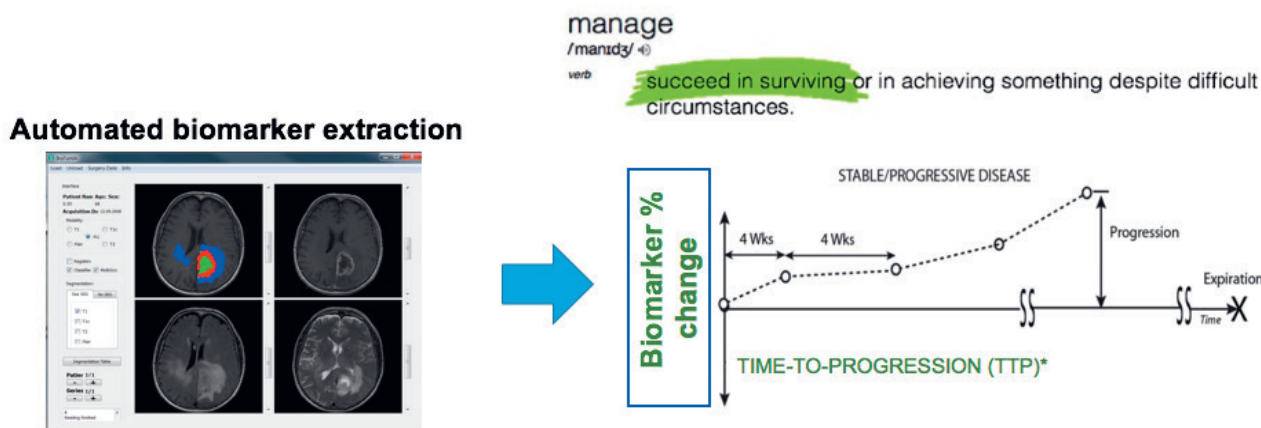


Figure 3. The MANAGE project aims at developing radiomics technologies and non-invasive biomarkers capable of better characterizing disease progression and patient response to therapy through longitudinal multisequence MRI information, and machine learning technologies.

## Selected Publications

- Meier R, Porz N, Knecht U, Loosli T, Schuch P, Beck J, Slotboom J, Wiest R, and Reyes M. Automatic estimation of extent of resection and residual tumor volume of patients with glioblastoma. *Journal of Neurosurgery*, pages 1-9, 2017.
- Gerber N, Reyes M, Barazzetti L, Kjer H, Vera S, Stauber M, Mistrik P, Ceresa M, Mangado N, Wimmer W, Stark T, Paulsen R, Weber S, Caversaccio M, and Ballester-Gonzalez M A multiscale imaging and modelling dataset of the human inner ear. *Nature Scientific Data*, 4:170132 EP - 09 2017.
- Chandran V, Reyes M, Zysset P. A Novel Registration-based Methodology for Prediction of Trabecular Bone Fabric from Clinical QCT: A Comprehensive Analysis. *PLOS ONE*, in Press, 2017.
- Lu P, Barazzetti L, Chandran V, Gavaghan K, Weber S, Gerber N, and Reyes M. Highly accurate facial nerve segmentation refinement from CBCT/CT imaging using a super resolution classification approach. *IEEE Transactions on Biomedical Engineering*, PPs(99):1-1, 2017.
- McKinley R, Haeni L, Gralla J, El-Koussy M, Bauer S, Arnold M, Fischer U, Jung S, Mattmann K, Reyes M, and Wiest R. Fully automated stroke tissue estimation using random forest classifiers (FASTER). *Journal of Cerebral Blood Flow and Metabolism*, 37(8):2728-2741, August 2017.
- Kellner-Weldon F, Stippich C, Wiest R, Lehmann V, Meier R, Beck J, Schuch P, Raabe A, Reyes M, and Bink A. Comparison of perioperative automated versus manual two-dimensional tumor analysis in glioblastoma patients. *European Journal of Radiology*, 95:75-81, Oct 2017.

# MUSCULOSKELETAL BIOMECHANICS

Philippe Zysset, Head of Research Group

Email: philippe.zysset@istb.unibe.ch

Phone: +41 31 631 59 25



Philippe Zysset



Alberto Cerutti



Lorenz Hufeld



Michael Indermaur



Christopher Lenherr



Ghislain Maquer



Remo Odoni



Marzieh Ovesy



Jarunan Panyasantisuk Schenk



Denis



Georg Siroky



Marc Stadelmann



Roland Stocker



Benjamin Voumard



Charlotte Voutat



Benjamin Werner



Patrik Wili

## Research Partners

Dr. André Butscher, Robert Mathys Foundation (RMS), Bettlach

Dr. Ainara Irastorza Landa, Nobel Biocare (NB), Kloten

Prof. Dr. med. Kurt Lippuner, Polyclinic of Osteoporosis (PO), Inselspital, Bern

Dr. Jiri Nohava, Anton Paar Tritec SA (APT), Kloten

Prof. Dr. Dieter Pahr, Vienna University of Technology (VUT), Vienna

Prof. Dr. Françoise Peyrin, European Synchrotron Radiation Facility (ESRF), Grenoble

Dr. Jakob Schwiedrzik and Dr. Johann Michler, Swiss Federal Laboratories for Materials Science and Technology (EMPA), Thun

Dr. Peter Varga, AO Research Institute, Davos

Prof. Dr. Peter Vermaaten, Department of Diagnostic, Interventional, and Pediatric Radiology (DDIPR), Inselspital, Bern

Prof. Dr. Jasmin Wandel, Bernese University of Applied Sciences (BFH), Burgdorf

Prof. Dr. Uwe Wolfram, Heriot-Watt University (HWU), Edinburgh

## 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 and intervertebral disc tissue 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 these tissues 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, bone-implant interface failure and intervertebral disc degeneration.

## Micro-meso Scale Transition of Bone Strength (SNF Grant 165510 with EMPA and ESRF)

Recent micropillar and mesoscopic compression experiments demonstrated an important micro-meso scale effect in the compressive yield and failure properties of bone. The aim of this project is to assess the scale effect in tensile yield and failure properties of bone using microscopic and mesoscopic tensile experiments and to integrate the obtained results in a unified theory describing the mechanical consequences of growing compressive and tensile crack families. Investigation of imaging and staining protocols for visualization of these cracks was initiated. A focused ion beam (FIB) milling protocol was developed to manufacture dumbbell shape micro-samples from ovine osteonal bone that can be gripped and tested in tension using a nano-actuator located within a scanning electron microscope (SEM). features of bone tissue damage and delivers an excellent agreement with the experiments.

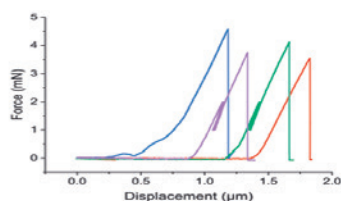
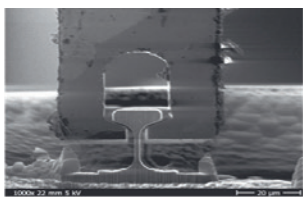


Figure 1. Micro-tensile test of ovine compact bone (Courtesy of Daniele Casari, EMPA).

## Bone Damage (with HWU)

Bone is a quasi-brittle hierarchical composite that exhibits damage with distinct crack morphologies in compression and tension. A recent mechanistic model could reproduce the complex damage response of

bovine compact bone under four different cyclic overloading experiments combining compression and tension. The aim of the present work was to develop a more efficient continuum model by which bone yielding accumulates residual strain and reduces elastic modulus in distinct compressive and tensile overloading modes. The obtained model reproduces the key features of bone tissue damage and delivers an excellent agreement with the experiments.

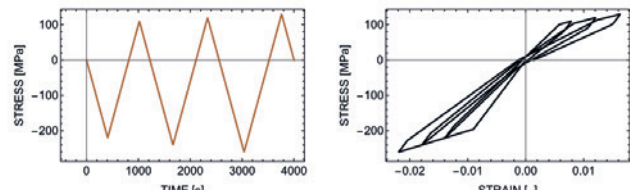


Figure 2. Cyclic overloading of bone under load control and the resulting damage in compression and tension.

## Effective Properties of Trabecular Bone (SNF Grant 143769 with VUT)

Homogenization of trabecular bone is required for QCT-based finite element analysis, but depends heavily on the size of the considered volume element and the applied boundary conditions (BCs). In this work, a new set of “embedded” BCs were explored to quantify both the multi-axial elastic and yield properties of human trabecular bone. A direct comparison was then made with mixed uniform (PMU) and kinematic uniform (KU) BCs. The mechanical properties obtained with embedded BCs were bound between PMUBCs and KUBCs, but were closer to the PMUBCs. These results

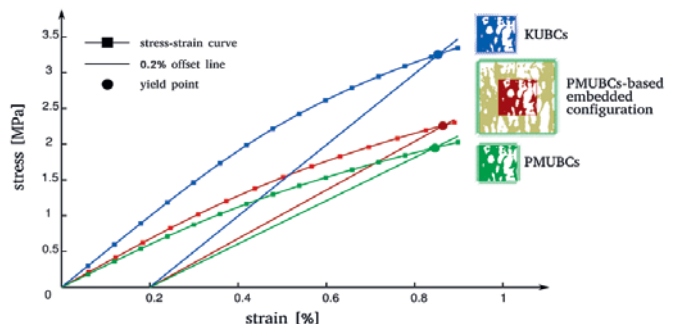


Figure 3. Mechanical behavior of a volume element of trabecular bone using kinematic uniform (KU), embedded and periodic-mixed (PM) boundary conditions.

properties to finite element analysis of bone and bone-implant systems.

### HR-pQCT-Based Homogenized Finite Element Model of the Distal Radius (with PO)

Osteoporosis is a major burden on both ageing individuals and health care systems. Its most severe consequences are fractures, including at the radius. Bone strength, a critical determinant of osteoporotic fractures, depends primarily on bone density and 3D architecture. These morphological variables are captured *in vivo* by HR-pQCT (60.7 $\mu$ m). A two-phase segmentation enables to account for distinct mechanical properties of cortical and trabecular bone and provides the necessary information for homogenized finite element (hFE) based prediction of bone strength. However, the reproducible and longitudinal assessment of wrist strength in a clinical environment requires a reduced evaluation time and a simplification of the computational model.

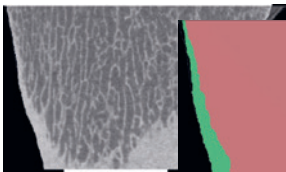


Figure 4. Grey-scale HR-pQCT image (left); cortical and trabecular mask (middle); two-phase segmentation (right).

### FEA of the Human Intervertebral Disc (SNF Grant 147153 with DDIPR)

Intervertebral disc (IVD) degeneration causes alterations in the disc's shape, composition and in its mechanical behavior, which can lead to chronic back pain. Accordingly, the aim of this project is to provide a patient-specific functional diagnostic tool for early assessment of degenerative IVD disease using finite element simulations. A human IVD was measured in a high field MR scanner (Bruker, 9.4T) using proton density (PD) weighted and diffusion tensor weighted (DTI) sequences.

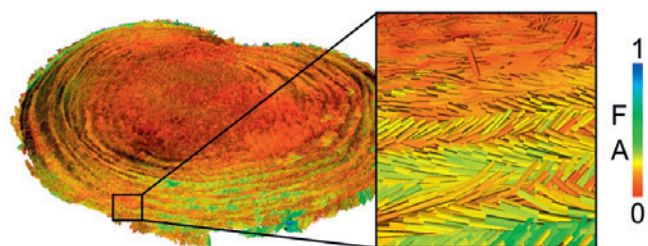


Figure 5. The rods show the direction of highest diffusion as measured by DTI and their color codes for fractional anisotropy (FA). The criss-cross organization of the annulus compares favorably with the collagen fiber orientations known from histology.

### Selected Publications

- Schwiedrzik J, Taylor AA, Wolfram U, Zysset PK and Michler J. Nanoscale deformation mechanisms and yield properties of hydrated bone extracellular matrix. *Acta Biomaterialia* 60:302-314, 2017.
- Zysset P and Wolfram U. A 1D rate-independent continuum model for bone tissue with interaction of compressive and tensile microdamage. *J Mech Behav Biomed Mater* 74:448-462, 2017.
- Wili P, Maquer G, Panysantisuk J and Zysset P. Estimation of the effective yield properties of human trabecular bone using nonlinear micro finite element analyses. *Biomech Model Mechanobiol* 16:1925-1936, 2017.
- Feldmann A, Ganser P, Klocke F, Nolte LP and Zysset P. Orthogonal cutting of cortical bone: Temperature elevation and fracture toughness. *Int Mach Tools Manuf*, 118-119:1-11, 2017.
- Varga P, Inzana J, Schwiedrzik J, Zysset PK, Gueorguiev B, Blauth M, Windolf M. New approaches for prophylactic augmentation based on bone remodeling simulations provide improved strengthening of the osteoporotic proximal femur as predicted by non-linear finite element simulations. *Clin Biomech*, 44:7-13, 2017.
- Hosseini H, Dünki A, Fabech J, Stauber M, Vilayphiou N, Pretterklieber M, Pahr D, Van Rietbergen B and Zysset P. Fast estimation of Colle's fracture load of the distal radius by non-linear finite element analysis based on high resolution peripheral computed tomography. *Bone* 97:65-75, 2017.
- Daszkiewicz K, Maquer G and Zysset P. In Situ Elastic Properties of Human Trabecular Bone Computed by Micro Finite Element Analysis. *Biomech Model Mechanobiol* 16:731-742, 2017.
- Musy S, Maquer G, Panasyantisuk J, Wandel J and Zysset P. Not only stiffness, but also yield strength of the trabecular structure determined by non-linear  $\mu$ FE is best predicted by bone volume fraction and fabric tensor. *J Mech Behav of Biomed Mater* 65:808-813, 2017.

The PD images were used to map the disc's heterogeneity to the model. The DTI images were processed to yield two principal fiber directions for each of the finite elements. *In vitro* biomechanical testing was performed on the IVD sample to calibrate the material parameters and validate the model.

### Homogenized Finite Element Model of the Bone-Implant Interface (with RMS)

Primary mechanical stability of the bone-implant interface is an essential condition for osseointegration in the implant surface and prediction of implant failure. It is related to the peripheral bone volume fraction, the orientation of the trabeculae and the contact between implant and the bone. The use of large strain hFE models with prediction of progressive damage accumulation and densification of the bone may help in prediction of the bone-implant interface behavior. The global aim of this project is to develop a homogenized FE methodology to better predict the macroscopic mechanical behavior of the bone-implant system observed experimentally in both loading and unloading modes.

### Biomechanical Testing (with APT, BFH & NB)

A large number of biomechanical experiments were performed in the laboratory for industrial contract research, clinical project and internal needs. Five MSc students were introduced to the laboratory work and conducted various tests. One master thesis focused on staining of trabecular bone damage induced by overloading.

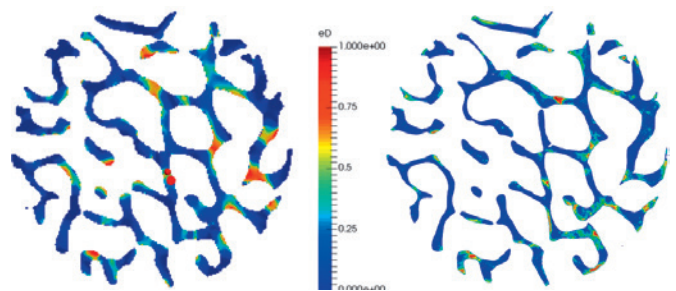


Figure 6. Left: damage calculated by microFE analysis. Right: staining of damage with BaSO4 in  $\mu$ CT.

Another thesis quantified the frictional properties of the bone-implant interface. A further thesis examined the indentation properties of metastatic vertebral bone. In an industrial project, trabecular bone compaction around a dental implant during implantation and cyclic loading was visualized using  $\mu$ CT. In conclusion of the NanoTera project HearRestore, thermal conductivity of trabecular bone was assessed as a function of volume fraction and fabric with a combined experimental and finite element (FE) methodology. In the frame of a clinical project, the stability of anterior cruciate ligament adjustable loops was evaluated using cyclic tests.

# TISSUE AND ORGAN MECHANOBIOLOGY

Benjamin Gantenbein, Head of Research Group

Email: benjamin.gantenbein@istb.unibe.ch

Phone: +41 31 631 59 51



**Benjamin Gantenbein**

**Ezgi Bakirci**

**Samanta Chan**

**Martina Calìo**

**Emina Džafo**

**Daniela Frauchiger**

**Marie Larraillet**

**Rahel May**

**Eva Roth**

**Selina Steiner**

**Karin Tschan**

**Simon Wüest**

## Clinical Partners

Dr. med. Christoph Albers, Department of Orthopaedics, Spine Unit, Insel Hospital, University of Bern

Dr. med. Sufian Ahmad, Department of Orthopaedics, Knee Team, Insel Hospital, University of Bern

Prof. Dr. med. Lorin Benneker, Department of Orthopaedics, Head of Spine Unit, Insel Hospital, University of Bern

PD. Dr. med. Frank Klenke, Department of Orthopaedics, Knee Team, Insel Hospital, University of Bern

Dr. med. Sven Hoppe, Department of Orthopaedics, Spine Unit, Insel Hospital, University of Bern

Dr. med. Sandro Kohl, Department of Orthopaedics, Knee Team, Insel Hospital, University of Bern

Prof. Dr. Klaus Siebenrock, Department of Orthopaedics, Insel Hospital, University of Bern

Prof. Dr. med Moritz Tannast, Department of Orthopaedics, Hip Surgery, Insel Hospital, University of Bern

Prof. Dr. Paul Heini, Spine Surgeon, Orthopaedics, Sonnenhof Clinic

## 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. Their 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-arthrose. 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 antagonism. Besides the investigation of the exogenous stimulation of BMP antagonists on mesenchymal stem cells and osteoblast, the main focus is on the observation of the interaction between IVD cells and osteoblast, by performing co-cultures.

In a Gebert RUF financed project a novel type of silk material has been successfully investigated for IVD repair. Here, the TOM group conducted research into new growth-factor-enriched silk, which has been produced from genetically transduced silk worms (*Bombyx mori*), which embed the growth factor of interest directly into the silk (Figure 2). The new "advanced" biomaterial has been tested *in vitro* on disc cells and mesenchymal stem cells but also in our 3D bovine organ culture model and the complex loading bio-reactor together with a FDA-approved fibrin hydrogel. Therefore,

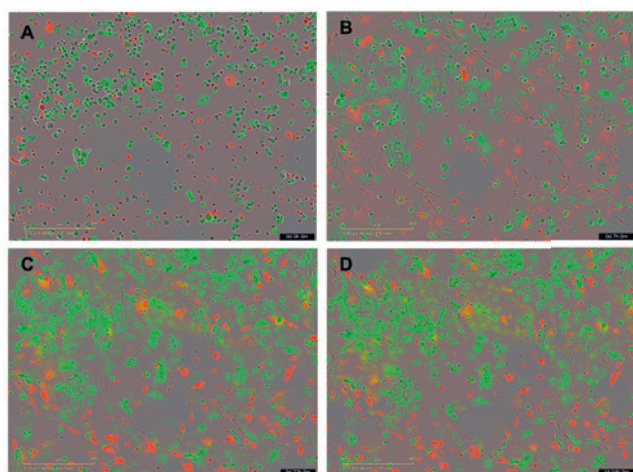


Figure 1. Time-lapse microscopy of co-cultured populations of donor-matched human primary mesenchymal stromal cells (green cytoplasmic dye) and cartilaginous end-plate cells (red membrane dye). **A)** Plating of cells (baseline) **B)** after 7h **C)** and after 22h and **D)** after 1d and 14 min of cultivation. Picture acquired with Incucyte S3 Microscope (Essen Bioscience, inc.).

## Genetic engineering of silk worm larvae for intervertebral disc repair

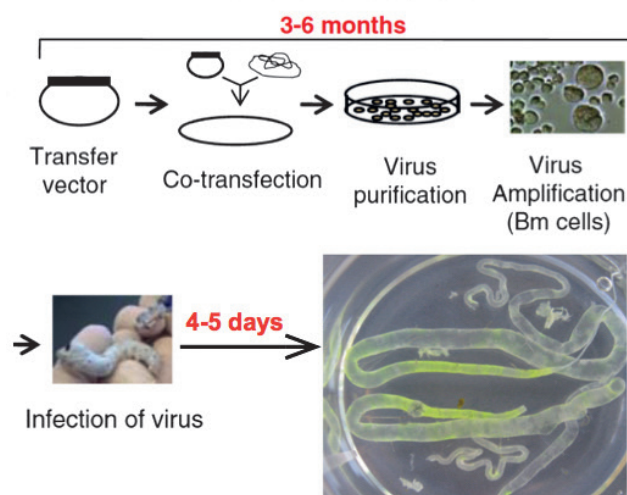


Figure 2. Genetically enriched silk fleece scaffolds were produced by transduction of *Bombyx mori* larvae with a baculovirus construct containing GDF6 or TGFβ3. Silk fleeces were produced under GMP-compliant conditions for the purpose of intervertebral disc repair.

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 Orthopaedic Research.

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 pulposus 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 (Figure 3). 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.

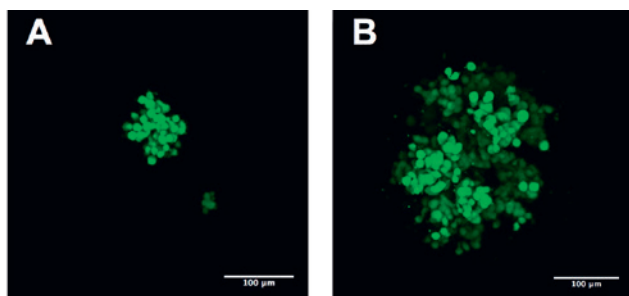


Figure 3. Confocal Laser Scanning Microscopy of **A)** nucleus pulposus progenitor cells (NPPC) and **B)** nucleus pulposus cells (NPC) after seven days of colony unit forming assay in a viscous medium. NPPC do result in more dense and spherical colonies whereas NPC form more loose and wider spread colonies. Cells were stained with a live dye in green. Scale bar = 100 µm.

The most recent branch of research in the TOM group is the investigation into non-viral gene transfer to regenerate the IVD. Here, first results were achieved to identify efficient parameters to electroporate human and bovine IVD cells and to transfer plasmid DNA to manipulate transiently the expression profile.

## Biological Repair of the Ruptured Anterior Cruciate Ligament

Anterior Cruciate Ligament (ACL) injuries are very common. In Switzerland, the incidence of ruptures is estimated at 32 per 100,000 in the general population and in the sports community

this rate more than doubles. Current gold standard for ACL repair is reconstruction using an autograft. However, this approach has shown some limitations. A new method has been heralded by the Knee Team at the Bern University Hospital (Insel Hospital) and the Sonnenhof clinic called Dynamic Intraligamentary Stabilization (DIS), which keeps the ACL in place in order to promote biological healing and makes use of a dynamic screw system. Here, cell-based approaches using collagen patches or application of platelet-rich plasma (PRP) are of interest. The aim of our research was to investigate the use of collagen patches, the application of PRP and platelet-rich fibrin (PRF) in combination with DIS to support regeneration of the ACL and to quantify the biological response. In a scientific excellence project (Turkey-Switzerland) 3D printed scaffolds for miniaturised ACL are currently being investigated (Figure 4). Furthermore, molecular investigations in combination with live cell imaging are ongoing to find evidence for the reduced wound healing potential of the ACL (Figure 5).

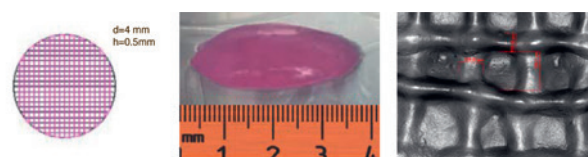


Figure 4. The computer-aided design (CAD) model that was chosen for 3D bioprinting of a gelatine and fibrin hydrogel for ACL engineering. The construct was then further characterized by the fibre and pore size under the light microscope.

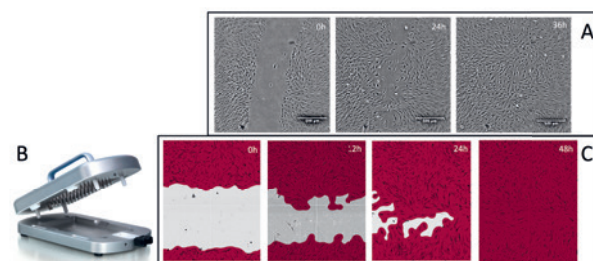


Figure 5. Wound scratch assays (WSA) using live cell imaging systems of primary ligamentocytes isolated from human anterior cruciate ligament (ACL). **A)** WSA with Nikon Biostation CT (Nikon) **B)** Woundscratcher tool™ by Essen Bioscience and **C)** WSA using Incucyte S3 Microscope (Essen Bioscience, inc.).

## Publications

1. Tekari A, May RD, Frauchiger DA, Chan SCW, Benneker LM, Gantenbein B (2017) The BMP2 variant L51P restores the osteogenic differentiation of human mesenchymal stromal cells in the presence of intervertebral disc cells. *Eur Cell Mater* 33: 197-210 doi: 10.22203/eCM.v033a15
2. Frauchiger DA, Tekari A, Wöltje M, Fortunato G, Benneker LM, Gantenbein B (2017) A review of the application of reinforced hydrogels and silk as biomaterials for intervertebral disc repair. *Eur Cell Mater* 34: 271-290 doi: 10.22203/eCM.v034a17
3. Frauchiger DA, Heeb SR, May RD, Wöltje M, Benneker LM, Gantenbein B (2017) Differentiation of MSC and annulus fibrosus cells on genetically-engineered silk fleece-membrane-composites enriched for GDF-6 or TGF-β3. *J Orthop Res* [epub ahead of print] doi: 10.1002/jor.23778
4. Krismer AM, Cabra RS, May RD, Frauchiger DA, Kohl S, Ahmad SS, Gantenbein B (2017) The biologic response of human anterior cruciate ligamentocytes on collagen-patches to platelet-rich plasma formulations with and without leucocytes. *J Orthop Res* [epub ahead of print] doi: 10.1002/jor.23599
5. May RD, Tekari A, Frauchiger DA, Krismer A, Benneker LM, Gantenbein B (2017) Efficient non-viral transfection of primary intervertebral disc cells by electroporation for tissue engineering application. *Tissue Eng Part C Methods* 23(1):30-37 doi: 10.1089/ten.TEC.2016.0355

## Selected Conference Contributions

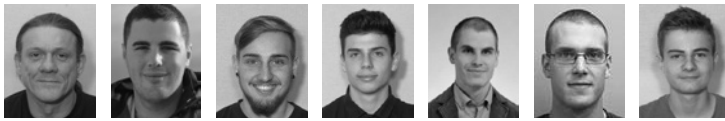
1. Frauchiger DA, Heeb S, Wöltje M, Benneker LM, Gantenbein B. Proliferation and differentiation on engineered silk scaffolds: From MSC towards NP-like cells. AOSpine Masters Symposium-Novels and Emerging Medicine. Bern. 2017.
2. May RD, Frauchiger DA, Benneker LM, Gantenbein B. Comparison of gene expression of discs from Diffuse Idiopathic Skeletal Hyperostosis (DISH) and healthy (trauma) patient. AOSpine Masters Symposium-Novels and Emerging technologies in Translational Medicine. Bern. 2017.
3. Bakirci E, Guenat O, Hugli A, Ahmad SS, Kohl S, Gantenbein B. Optimization of 3D printed hydrogels with primary cells for tissue engineering. AOSpine Masters Symposium-Novels and Emerging Technologies in Translational Medicine. Bern. 2017.
4. Frauchiger DA, May RD, Koch AK, Benneker LM, Gantenbein B. SPECIAL EMPHASIS POSTER: Real-time monitoring of glucose consumption of intervertebral disc cells in 3D culture. Proceedings of ISSLS Meeting. Athens, Greece, 28 May - 2 June. 2017.
5. Krismer A, Geissberger C, Bakirci E, Cabra R, Kohl S, Gantenbein B. (2017) Strain-controlled organ culture of bone-ligament-bone human-derived anterior cruciate ligaments - an ex-vivo model to investigate degenerative and regenerative therapy. Proceedings of TERMIS-EU Chapter Meeting. Davos. 2017.
6. Frauchiger DA, Tekari A, Benneker LM, Sakai D, Gantenbein B. The Fate of Allogeneic Injected Angiopoietin-1 Receptor Tie2+ Cells in Intervertebral Disc Organ Culture. Proceedings of the ORS. San Diego, USA. 2017.
7. May RD, Tekari A, Chan SCW, Frauchiger DA, Benneker LM, Gantenbein B. The Natural Expression of BMP Antagonists in Intervertebral Disc Cells. Proceedings of the ORS. San Diego, USA. 2017.

# MECHANICAL DESIGN AND PRODUCTION

Urs Rohrer, Head of Mechanical Design and Production

Email: urs.rohrer@istb.unibe.ch

Phone: +41 31 631 59 35



**Urs  
Rohrer**

**Danaël  
Gasser**

**Lukas  
Rufener**

**Fabio  
Spena**

**Jan  
Prortrai**

**Ronald  
Ramseier**

**Simon  
Lüthi**

## 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 & 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 2016 we have selected Simon Lüthi as our new apprentice and he began his training this year on 1st of August as a Polymechanic apprentice.

We employed also our former apprentice Lukas Rufener until end of March 2017 part-time as a polytechnician. For the work he performed we are very grateful and wish him all the best in his future. Our apprentice Fabio Spena completed his basic training exam at the end of the second year with good results and we congratulate him. In the coming two years his training will focus more on CAD-CAM technologies and manufacturing more ambitious parts.

Due to a high demand of workload, we recruited two polytechnicians, Ronald Ramseier and Jan Riedo 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.

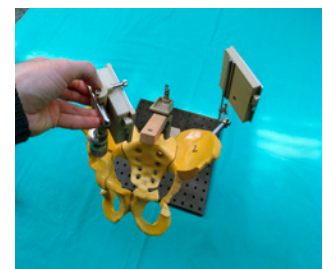
## Research Equipment Design & Manufacturing ISTB

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: A Local Navigation System for the Bernese Periacetabular Osteotomy (PAO)

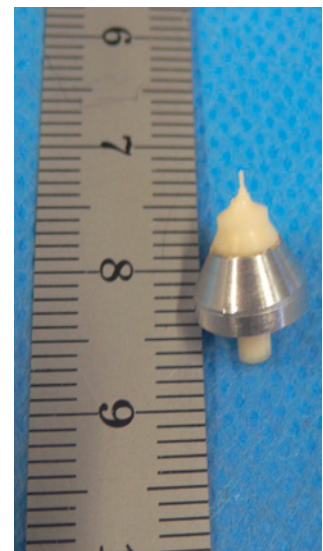
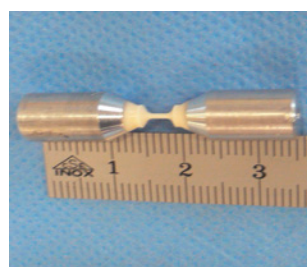
A camera with a casing for a tracking systems was developed in strong collaboration with Silvio Pflugi and the Orthopaedic

Department at Bern General Hospital (INSEL). The casing design allows one to seal non-sterile electronic components in a sterile casing and therefore make them usable in the operation room. To obtain optimal wireless connection, sterilisable polymers were used. Furthermore, to achieve sufficient cooling for the camera system, aluminum was chosen for the camera case cover plate. The two components (tracking and camera system) allow the surgeon to locally track fragments during a periacetabular osteotomy.



### Project: Micro Meso

The MicroMeso-Project aims to better understand crack formation and crack morphology in human cortical bone. Synchrotron Radiation based computed tomography was used to visualize these cracks. Our target was to produce cylindrical and rectangular cortical bone samples in large quantities. The biggest challenge was to accurately produce samples with diameters varying from 1.0mm down to few micrometers without inducing additional damage. Furthermore, process parameters had to be determined that allowed precise production of more than 100 samples.oblique viewing.



### Project: Cylinder Holder Fixture

In strong collaboration with our scientific partners, we manufactured a total of six implant-fixations. The aim was to demonstrate optimal shape and weight of the system using two prototypes. High strength stainless steel allowed not only to meet the requirements with respect to mass, but also optimal corrosion resistance since the fixations are used in highly corrosive media. Therefore we had to execute an electro-polishing surface treatment and finally a high gloss polishing by hand.



### Research Equipment Design & Manufacturing ARTORG

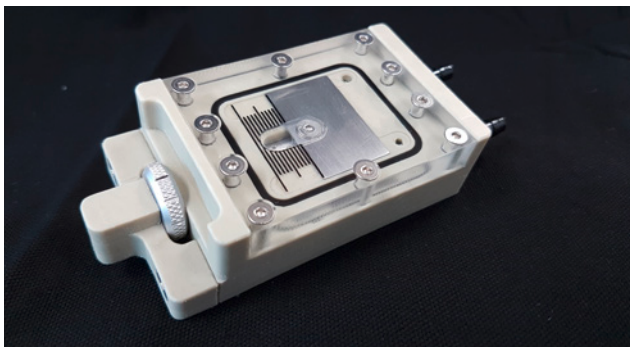
The workshop at the ARTORG Center was managed by Danaël Gasser as a full time polytechnician. He manufactured some different project-parts, mainly for the CVE (Cardiovascular Engineering) and IGT (Image Guided Therapy) groups.

His function was it 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 was growing and strengthened as a “core facility” sharing work and knowledge.

Some highlights of this year projects are shown in the following illustrations.

### Project: Resistor Units

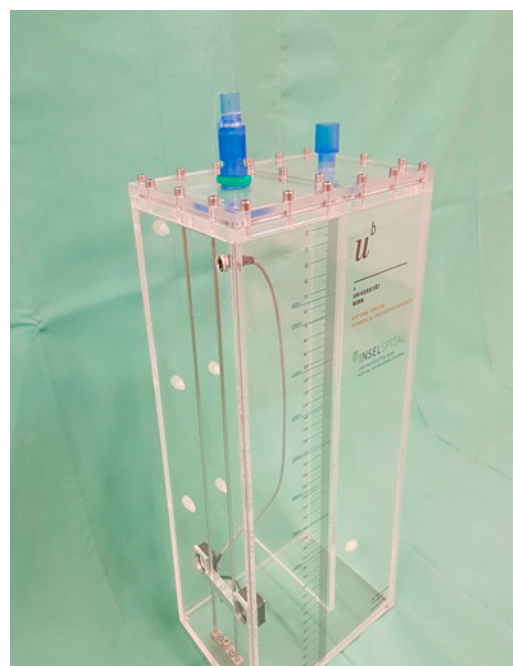
Flow resistors with linear behaviour are usually made from porous material. As this filters small particles out of the fluids, porous material can't be used for particle tracking velocimetry (PIV). In the present project, two flow resistors were developed, which do not filter these small particles and allow a linear adaption of the flow resistance. The higher resistor is used to mimic the resistance of human tissue in an aortic valve model with flow rates of 5l/min, whereas the smaller one is used in an in-vitro coronary network with flow rates of 50ml/min. The design of these flow resistors was a special challenge. The different parts all needed to fit perfectly together for the assembly to be impermeable. As an example, one of the pistons was 0.4mm in diameter.



### Project: Miss-Plexi

Miss-Plexi is a box made from acrylic glass. It supports the calibration of pulmonary function testing systems. Two different sizes, one for adult lungs and the other for children lungs, are currently in use at the Inselspital in Bern. The box can be filled with different gases. A piston engine simulates respiration activity and pushes the gas through the pulmonary function testing system, where it is analysed. A scale on the exterior helps to compare data.

The design must meet special requirements: perfect visibility through the box, installation of fans, electronic modules in physically closed space and complete sealing. Due to the large dimensions of the box, assembling their parts was a challenge for us.



## ACKNOWLEDGMENTS

- The ISTB depends significantly on financial support from public funding agencies including governmental and non-governmental institutions, the Swiss and international medical technology industry, as well as from private sponsors.
- We are indebted to the University of Bern, the Inselspital Bern and other collaborating partners for their generous contributions towards base funding and infrastructural support of all listed groups.
- We graciously and specifically would like to thank the Swiss National Science Foundation (SNSF) for their support and Innosuisse (formerly known as the federal KTI/CTI Innovation Promotion Agency) for providing R & D matching funds.
- We would also like to thank all of our research partners for their collaboration and cooperation, most notably, the Swiss Institutes of Technology in Zurich and Lausanne, the Swiss Federal Laboratories for Materials Science and Technology (EMPA), the European Synchrotron Radiation Facility (ESRF), the Università della Svizzera Italiana (USI), the Haute Ecole de Santé of Geneva (heds), the Universitäts-Kinderspital beider Basel (UKBB), the Centre Hospitalier Universitaire Vaudois (CHUV), the Schulthess Klinik, the Universitätsklinik Balgrist and the Kantonsspital Winterthur.
- In addition, support in the form of equipment, donations, or finances provided by various foundations and companies for a large number of specific research projects is gratefully acknowledged. We would like to thank the AO Spine, the Swiss Institute for Computer Assisted Surgery (SICAS), the Gebert-Rüf Foundation, the Lindenhof Group, the Seventh Framework Program funded by the European Commission, the State Secretariat for Education, Research and Innovation (SERI), the Metis Fondazione Sergio Mantegazza, the Center for Applied Biotechnology and Molecular Medicine (CABMM), the Swiss Heart Foundation, the Swiss Eye Research Foundation and the Swiss Cancer League. We are thankful for the generous funding from Hansjörg Wyss and the Wyss Medical Foundation, US.
- Finally, we would like to thank all the members who dedicated their time and talent to the ISTB in 2017.

## COMPLETED DISSERTATIONS

**Chandran Vimal**, "*Comprehensive and Effective Machine Learning based Computational Modelling of the Human Proximal Femur*". February 2017.

**Berger Steve**, "*Patient-specific quantification of spinal flexibility in AIS patient: methods for pre- and intra-operative assessment*". March 2017.

**Feldmann Arne**, "*Thermal and Drilling Properties of Bone*". March 2017.

**Meier Raphael**, "*Towards Automatic Segmentation of Longitudinal Brain Tumor Imaging Data*". April 2017.

**Lu Ping**, "*Advanced Medical Image Analysis of the Human Facial Nerve based on Machine Learning Technologies*". May 2017.

**Yu Weimin**, "*Hardware accelerated, non-rigid intensity-based 2D-3D registration for orthopaedic applications*". June 2017.

**Brusa Tobia**, "*The In Vivo Biomechanics of the Human Anal Continence Organ*". July 2017.

**Wyss Balmer Thomas**, "*Electrical Bone Properties to enable Modelling of Functional Guidance Using Neuro - Monitoring*". July 2017.

**Ariza Gracia Miguel Ángel**, "*Methods for Characterising Patient-Specific Corneal Biomechanics*". September 2017.

**Pflugi Silvio**, "*Development and validation of cost-effective navigation technology for peri-acetabular osteotomy surgery*". October 2017.

## AWARDS & PRIZES

"3D U-net with Multi-level Deep Supervision: Fully Automatic Segmentation of Proximal Femur in 3D MR Images". Best Paper Award at 2017 MICCAI Workshop on Machine Learning in Medical Imaging (MLMI@MICCAI), Quebec City, Canada, 2017.

**Awardees: Zeng G, Yang X, Li J, Yu L, Heng P-A and Zheng G.**

"Real-time monitoring of glucose consumption of intervertebral disc cells in 3D culture". Special Emphasis Poster at ISSLS. Proceedings of ISSLS Meeting. Athens, Greece, 2017.

**Awardees: Frauchiger DA, May RD, Koch AK, Benneker LM, Gantenbein B.**

"Nucleus pulposus progenitor cells – isolation and injection into degenerative disc". Best poster Award. AOSpine Masters Symposium— Novel and Emerging Technologies in Translational Medicine, 2017.

**Awardees: Frauchiger DA, Tekari A, Benneker LM, Sakai D, Grad S, Stoyanov J, Bertolo A, Gantenbein B**

Award "Best Poster Presentation", EFORT 2017.

**Awardee: Taghizadeh Elham**

Award "Best Presentation at Spanish Chapter ESB 2017", Sevilla, Spain, 2017.

**Awardee: Ariza Gracia Miguel Ángel**

Award "The Best One-Page Master Thesis Summary at the 9th Biomedical Engineering day", Bern, Switzerland, April 2017

**Awardee: Indermaur Michael**

"Brain Tumor Segmentation Challenge", Survival Prediction, 2nd prize. BRATS 2017.

**Awardee: Jungo Alain**

"Automated Brain Lesion Analysis using Human-Machine Intelligence", Ypsomed Innovation Award, 2017.

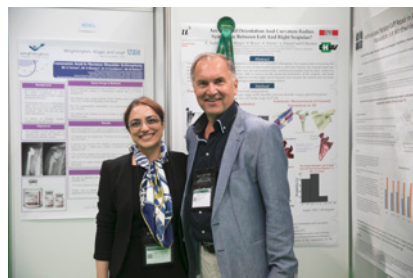
**Awardee: Reyes Mauricio**



Alain Jungo being awarded at BRATS 2017



Gudong Zeng being awarded at MICCAI 2017



Elham Taghizadeh being awarded at the EFORT 2017



Mauricio Reyes winning the Ypsomed Innovation Award



Michael Indermaur at 9th Biomedical Engineering Day



Daniela Frauchiger being awarded at AOSpine 2017

# IMPRESSIONS

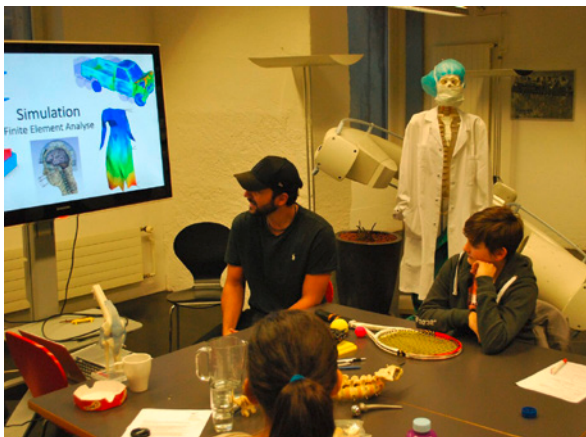
## Summer Trip to Rigi Region



## Christmas Party at Heitere Fahne



## Zukunftstag at ISTB



## Bone Bar at Nacht der Forschung



## FUNDING AGENCIES



FONDS NATIONAL SUISSE  
SCHWEIZERISCHER NATIONALFONDS  
FONDO NAZIONALE SVIZZERO  
SWISS NATIONAL SCIENCE FOUNDATION



Schweizerische Eidgenossenschaft  
Confédération suisse  
Confederazione Svizzera  
Confederaziun svizra

Swiss Confederation

Commission for Technology and Innovation CTI



STIFTUNG LINDENHOF  
Partnerin Schweizerisches Rotes Kreuz



Swiss Eye Research Foundation



Schweizerische  
Herzstiftung



krebsliga schweiz  
ligue suisse contre le cancer  
lega svizzera contro il cancro



## PARTNERS



UNIVERSITÄTSSPITAL BERN  
HOPITAL UNIVERSITAIRE DE BERNE  
BERN UNIVERSITY HOSPITAL



Universitäts-Kinderspital  
beider Basel



KANTONSSPITAL WINTERTHUR



SCHULTHESS CLINIC  
Musculoskeletal Centre



Bern University  
of Applied Sciences



Eidgenössische Technische Hochschule Zürich  
Swiss Federal Institute of Technology Zurich



Swiss Institute for  
Computer Assisted Surgery



ÉCOLE POLYTECHNIQUE  
FÉDÉRALE DE LAUSANNE



Materials Science & Technology



Università  
della  
Svizzera  
italiana



The European Synchrotron



TECHNISCHE  
UNIVERSITÄT  
WIEN  
Vienna University of Technology



DEAKIN  
UNIVERSITY AUSTRALIA



FRIEDRICH-ALEXANDER  
UNIVERSITÄT  
ERLANGEN-NÜRNBERG



Western  
UNIVERSITY - CANADA



名古屋大学  
NAGOYA UNIVERSITY



## Imprint

Institute for Surgical Technology and Biomechanics Annual Report 2017  
Editor: University of Bern, Institute for Surgical Technology and Biomechanics  
Layout: Marzieh Ovesy, ISTB, University of Bern  
Print: Länggass Druck AG Bern, Länggassstrasse 65, CH-3000 Bern 9  
Cover: Computational Bioengineering Group, ISTB

University of Bern  
Institute for Surgical Technology and Biomechanics  
Stauffacherstrasse 78  
3014 Bern, Switzerland

Phone +41 31 631 59 59  
Email [backoffice@istb.unibe.ch](mailto:backoffice@istb.unibe.ch)

[www.istb.unibe.ch](http://www.istb.unibe.ch)