INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

Contents

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INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

EDITORIAL

Welcome to the annual report 2016 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), 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 2016, eight students earned their PhD degrees in Biomedical Engineering in the frame of the Graduate School for Cellular and Biomedical Sciences (www.gcb.unibe.ch) with an outstanding research output and careful presentations. The ISTB contributed again substantially to the Master's Program in Biomedical Engineering with hundreds of teaching hours and several master theses.

On the research side, our publication record reached 50 peer-reviewed journal and conference publications. The ISTB participants to the NanoTera "HearRestore" project headed by Prof. Stefan Weber could celebrate together with ARTORG and the ENT team of Prof. Marco Caversaccio, the worldwide first successful robotic cochlear implantation surgery. Congratulations for this remarkable accomplishment.

Several awards and prizes were also obtained - at the Swiss Society of Bone and Mineral (SSBM), the German Society for Computer and Robotic Assisted Surgery (CURAC), the international conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), and most notably the prestigious Stefan M. Perren Research Award of the European Society of Biomechanics (ESB) given to our Co-director.

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. Our teams have been successfully involved in organizing conferences such as MIAR 2016 in Bern as well as workshops and challenges, e.g., at ECTS 2016 and MICCAI 2016.

On the facilities and equipment side, with the support of our medical faculty, a micro-computed tomography system could be installed in the laboratory that allows the scanning of samples up to 10cm in size with a resolution down to a few microns. An automated sample holder will enhance the throughput for the morphological investigations of hard tissues.

In 2016, the ISTB's summer excursion, carefully organized by Julia Spyra, took us to Meiringen on the tracks of Sir Arthur Conan Doyle and his character Sherlock Holmes. We discovered the tiny but surprising Sherlock Holmes museum, savored lunch on a wonderful terrace and enjoyed a spectacular view of the Reichenbach falls where Holmes fought Professor Moriarty in The Final Problem.

We would like to welcome Anke Zürn and Esther Gnahoré who took over the secretary's office and the related administrative tasks in the course of the year. Despite the ongoing challenges in personnel and financial management, 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 pleasant reading.

Lutz-P. Nolte
Director ISTB

Philippe Zysset
Co-director ISTB

INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

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Information Processing in Medical Interventions

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Information Processing in Medical Interventions

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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 novel statistical finite element methods for the incorporation of uncertainty in bone shape and mechanical properties into the evaluation of bone biomechanics.

Evaluation of Macroscopic Brain Tumor Growth

Brain tumors represent a rare but serious medical condition. With an incidence of six cases per 100000, gliomas are the most frequent primary brain tumors in adults, accounting for 70% of cases. Gliomas are classified into four grades by increasing aggressiveness, based on their microscopic structure and cellular activity. Glioblastoma multiforme is the most frequent and most malignant sub-type of glioma. Despite the recognized importance of the biomechanical environment for tumor evolution, the mass-effect caused by the growing tumor received less attention from the modeling community.

We conducted a comparative study that evaluates the ability of a simple computational model of mechanically-coupled diffusive tumor growth to reproduce characteristics of pathologies found in patients. Glioblastoma multiforme invasion into brain tissue and the mechanical interaction between tumor and healthy tissue components were simulated using the finite element method (Figure 1). We showed qualitative agreement of resulting tumor invasiveness with simulation parameters and found tumor-induced pressures of realistic magnitude. Comparison to real tumor shapes confirmed previous observation from a pure reaction-diffusion model that tumor shape depends on seed position and that asymmetric shapes cannot be reproduced by isotropic growth assumptions.

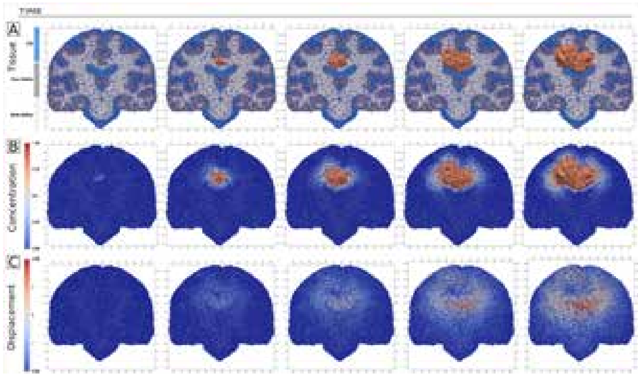

Figure 1. Temporal evolution of the brain tumor (Glioblastoma multiforme) simulated using mechanically-coupled reaction-diffusion model.

Stiffness of Spinal Motion Segments

Back pain and degenerative spine problems are the main cause for inability to work, premature pension and by far the most frequent reason for back surgery with accordingly high economic and social impacts. The demographic development will aggravate this situation. Operative treatment most commonly includes bony fusion of the spine, even for young individuals with scoliosis. New strategies, such as artificial discs, interspinous process spacers, posterior transpedicular dynamic stabilization and target-oriented conservative approaches aim at preserving spine function. However, little is known about the complex functional behavior and the force-motion relation of the normal and degenerated spinal segment under in-vivo conditions. The purpose of this study is to develop a robotic system to accurately measure the three-dimensional segmental stiffness of patient's spine in-vivo.

A parallel kinematic robot – the SpineBot – with six degrees of freedom was developed for the intra-operative stiffness measurements (Figure 2). The SpineBot will be used prior to surgery and transmits loads to adjacent vertebrae using the pedicle screws implanted as part of the regular surgical procedure. The segmental flexibility is quantified using pure moments applied along the main anatomical axes. A force/torque load cell is mounted in the SpineBot to accurately measure the force applied by the device on the motion segments. Safety mechanisms such as a quick release mechanism and safety-enabling switch were designed to ensure the security of patients. Since the spinal shape and mechanical properties showed important variation across patients, the quantitative information provided by the SpineBot is critical for the development of planning solutions that consider patient-specific biomechanics. Furthermore, it allows measurement in all anatomical axes with high repeatability. Such tools will become increasingly important in the future due to the ever-increasing complexity of surgical instrumentation and procedures and to provide a better understanding of the complex biomechanical properties of the spine.

Figure 2. A robotic system has been developed to quantify spinal biomechanics intra-operatively.

In-vivo Quantification of Electrical Bone Properties

Nerve monitoring is a safety mechanism to detect the proximity between surgical instruments and important nerves during surgical bone preparation. In temporal bone, this technique is highly specific and sensitive at distances below 0.1 mm, but remains unreliable for distances above this threshold. A deeper understanding of the patient-specific bone electric properties is required to improve this range of detection. A sheep animal model has been used to characterize bone properties in-vivo. Impedance measurements have been performed at low frequencies (<1 kHz) between two electrodes placed inside holes drilled into the sheep mastoid bone. An electric circuit composed of a resistor and a Fricke constant phase element was able to accurately describe the experimental measurements. Bone resistivity was shown to be linearly dependent on the inter-electrode distance and the local bone density (figure 3). Based on this model, the amount of bone material between the electrodes could be predicted with an error of 0.7 mm. Our results indicate that bone could be described as an ideal resistor while the electrochemical processes at the electrode-tissue interface are characterized by a constant phase element. These results should help increasing the safety of surgical drilling procedures by better predicting the distance to critical nerve structures.

Continence of the Anal Sphincter Complex

Continence results from a complex interplay between anal canal (AC) muscles and sensory-motor feedback mechanisms. The AC's passive ability to withstand opening pressure – its compliance – has recently been shown to correlate with continence. Functional lumen imaging probe (FLIP) is used to assess AC compliance, although it provides no anatomical information. Therefore,

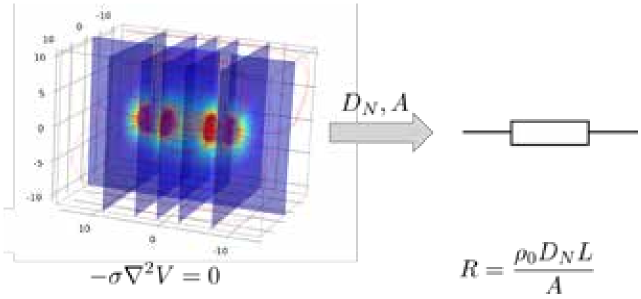

Figure 3. Finite element simulations were used to determine the electric properties of the tissue based on the distribution of the local bone density and electrode position derived from imaging data.

compliance assessment of specific anatomical structures has not been possible, and the anatomical position of critical functional zones remains unknown. To address this shortcoming, we implemented a new research method (MR-FLIP) that combines FLIP with MR-imaging. The method has been assessed on twenty healthy volunteers who underwent MR-FLIP and conventional FLIP assessment. MR-FLIP was validated by comparison with FLIP results. Anatomical markers were identified, and the cross-sectional shape of the orifice was investigated. MR-FLIP provides compliance measurements identical to those obtained by conventional FLIP. Anatomical analysis revealed that the least compliant AC zone was located at the proximal end of the external anal sphincter. The AC cross-sectional shape was found to deviate only slightly from circularity in healthy volunteers.

The proposed method proved to be equivalent to classical FLIP. It establishes for the first time a direct mapping between local tissue compliance and anatomical structure, which is key for gaining novel insights into (in)continence. In addition, MR-FLIP provides a tool for better understanding conventional FLIP measurements in the AC by quantifying its limitations and assumptions. Current investigations aim at providing a nomogram of the normal anatomy as well as passive and active properties of the sphincter muscles (figure 4).

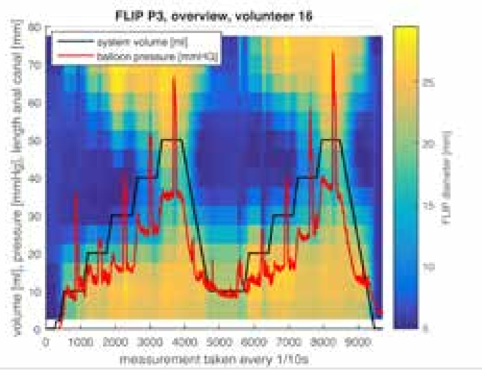

Figure 4. An inflatable cylindrical balloon (FLIP) is placed in the anal canal (AC). The balloon is inflated up to a volume of 50ml (black line) while pressure (red line) and diameter (color plot) were recorded. Higher balloon volume decrease the length of the closed AC segment (color plot, blue-green regions). The local compliance is quantified by the ratio of diameter and pressure.

Selected Publications

1. Wyss Balmer, T., J. Ansó, E. Muntane, K. Gavaghan, S. Weber, A. Stahel, and P. Büchler. In-Vivo Electrical Impedance Measurement in Mastoid Bone. Ann. Biomed. Eng. 34:2013, 2016.
2. Schumann, S., C. Gökgöl, N. Diehm, P. Büchler, and G. Zheng. The Effects of Stent Implantation on the Deformations of the SFA and the Popliteal Artery: In-Vivo 3D Deformational Analysis from 2D Radiographs. J. Vasc. Interv. Radiol. , 2016.
3. Gökgöl, C., S. Schumann, N. Diehm, G. Zheng, and P. Büchler. In Vivo Quantification of the Deformations of the Femoropopliteal Segment: Percutaneous Transluminal Angioplasty vs Nitinol Stent Placement. J. Endovasc. Ther. , 2016.
4. Fattorini, E., T. Brusa, C. Gingert, S. E. Hieber, V. Leung, B. Osmani, M. D. Dominietto, P. Büchler, F. Hetzer, and B. Müller. Artificial Muscle Devices: Innovations and Prospects for Fecal Incontinence Treatment. Ann. Biomed. Eng. 44:1355–69, 2016.
5. Businaro, E., H. Studer, B. Pajic, and P. Büchler. Gaussian process prediction of the stress-free configuration of pre-deformed soft tissues: Application to the human cornea. Med. Eng. Phys. 0:1-7, 2016.
6. Abler, D., P. Büchler, and G. S. Stamatakos. CHIC – A Multi-scale Modelling Platform for in-silico Oncology. Radiother. Oncol. 118:S1, 2016.
7. Taghizadeh, E., M. Reyes, P. Zysset, A. Latypova, A. Terrier, and P. Büchler. Biomechanical Role of Bone Anisotropy Estimated on Clinical CT Scans by Image Registration. Ann. Biomed. Eng. , 2016.

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 during past twenty years. 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. Most importantly, the combination of these models with multimodal images, sensor data from spatial tracking or force sensors, visual displays, or other feedback systems in a computer assisted intervention will facilitate personalized therapy. In collaboration with national and international experts from both industry and academia, the group has focused strongly on translational research in different stages of medical interventions, 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. MR imaging becomes the preferred modality for diagnosing various spinal disorders such as spondylolisthesis and spinal stenosis. At the same time, CT images are required in specific applications such as measuring bone mineral density of vertebral bodies for diagnosing osteoporosis. In this project, we are aiming to develop unified, machine learning-based

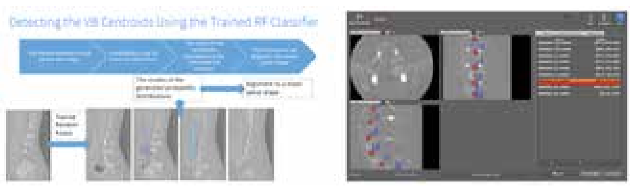

Figure 1. Left: an overview of the pipeline for the detection of VB centroids in CT scans; Right: the vertebral centroid detection software.

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 2016, we developed an integrated software based on random forest classification framework for computational spine imaging.

Web-based Planning and Evaluation of Orthopaedic 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 2016, we finished a clinical study involving 24 patients, taking pre-operative CT scans as the ground truth. A mean surface distance of about 1.1 mm was found.

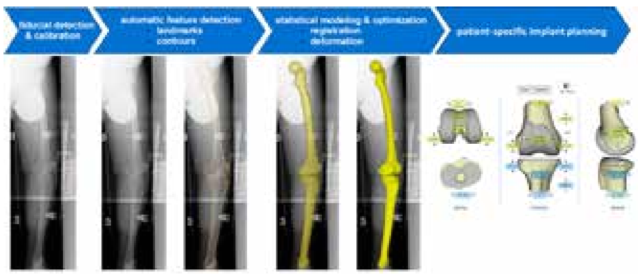

Figure 2. Overview of 2D-3D reconstruction-based implant planning for total knee arthroplasty.

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. It is expected that the proposed CT-free 3D anatomical model generation approach will facilitate a future wide-spread access of computational simulation and virtual surgical planning techniques for patients with FAI. In year 2016, a semi-automatic 3D MR image segmentation system was developed. The system can segment a 3D hip joint MR image in about 10 minutes while a slice by slice manual segmentation will take as long as 3 to 4 hours.

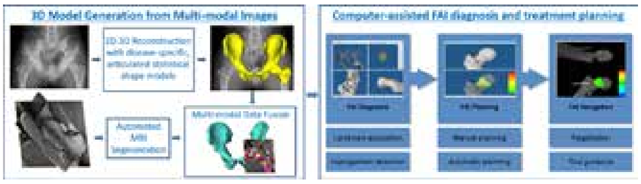

Figure 3. Multi-modal image computing for computer assisted interventions.

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.

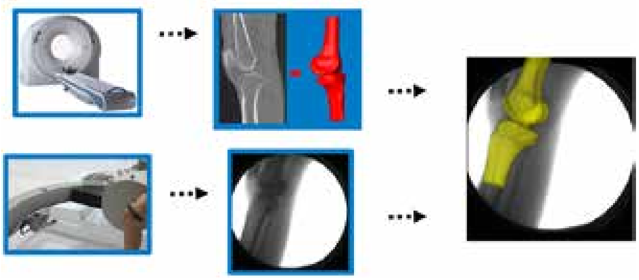

Figure 4. A schematic view of video-fluoroscopy-based tracking of in-vivo knee kinematics.

Hybrid Tracking for Peri-acetabular Osteotomy Surgery (Insel-Ortho-IPMI Cooperation)

Surgical navigation is mainly based on optical tracking which has an inherent disadvantage that the tracking cameras need to maintain a line-of-sight to the patient and the instruments. This inconvenience and the relative high costs are two reasons why modern computer assisted surgery (CAS) systems are not yet widely used. The aim of this project is to develop and evaluate a cost-effective, smart marker-based hybrid navigation system for PAO surgery. Our system consists of a tracking unit which is directly placed on the patient's pelvis and a smart marker which consists of a planar Aruco marker with an integrated Inertial Measurement Unit (IMU). The tracking unit tracks the planar marker whereas the IMU directly sends orientation data to a host computer. The IMU is calibrated with respect to the Aruco marker. A host computer visualizes the reorientation process on an external monitor. Taking the measurements from an optical tracking system as the ground truth, our system achieved a mean absolute difference of less than 2 degrees for both anteversion and inclination.

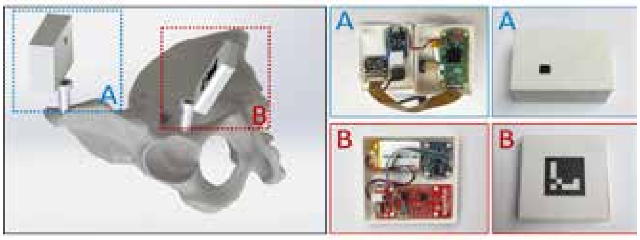

Figure 5. Left: a schematic view of the hybrid tracking for PAO surgery; right: internal and external views of tracking camera (A) and smart marker (B).

Edited Book

1. G Zheng, H Liao, P Jannin, P Cattin and S-L Lee (eds.): Medical Imaging and Augmented Reality – The 7th International Conference, MIAR 2016, Bern, Switzerland, August 24-26, 2016. Springer 2016, ISBN 978-3-319-43774-3.
2. T Vrtovec, J Yao, B Glocker, T Klinder, A Frangi, G Zheng and S Li (eds.): Computational Methods and Clinical Applications for Spine Imaging – The 3rd International Workshop and Challenge, CSI2015, Held in Conjunction with MICCAI 2015, Munich, Germany, October 5, 2015, Springer 2016, ISBN 978-3-319-41826-1.

Selected Publications

1. C Gökgöl, S Schumann, N Diehm, G Zheng and P Büchler. In-vivo quantification of femoro-popliteal artery deformations: percutaneous transluminal angioplasty vs. nitinol stent placement. Journal of Endovascular Therapy, in press, 2016.
2. S. Schumann, C. Gökgöl, N. Diehm, P. Büchler, G. Zheng. 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.
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5. S. Berger, C. Hasler,O. C.A. Grant, G. Zheng, S. Schumann, P. Büchler. 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.
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8. M. Valenti, G. Ferrigno, D. Martina, W. Yu, G. Zheng, M.A. Shandiz, C. Anglin and E. De Momi. Gaussian Mixture Models based 2D-3D registration of bone shapes for orthopaedic surgery planning. Journal of Medical & Biological Engineering & Computing, 54:1727-1740, 2016.
9. J. M. Jennings, T.R. Randell, C. L. Green, G. Zheng and S.S. Wellman. Independent evaluation of a mechanical hip socket navigation system in total hip arthroplasty. Journal of Arthroplasty, 31:658-661, 2016.
10. M. Valenti, E. De Momi, W. Yu, G. Ferrigno, M.A. Shandiz, C. Anglin and G. Zheng. Fluoroscopy-based tracking of femoral kinematics with statistical shape models. Int J Comput Assist Radiol Surg., 11:757-765, 2016.
11. L. Liu, G. Zheng, JD Bastian, MJ Keel, LP Nolte, KA Siebenrock, TM Ecker. Periacetabular osteotomy through the pararectus approach: technical feasibility and control of fragment mobility by a validated surgical navigation system in a cadaver environment. Int. Orthop, 40:1389-1396, 2016.
12. S. Pflugi, L. Liu, T. M. Ecker, S. Schumann, J. Cullmann-Bastian, K. Siebenrock and G. Zheng. A cost-effective surgical navigation solution for periacetabular osteotomy (PAO) surgery. Int J Comput Assist Radiol Surg., 11:271-280, 2016.
13. L. Liu, TM Ecker, S Schumann, KA Siebenrock, G. Zheng. Evaluation of Constant Thickness Cartilage Models vs. Patient Specific Cartilage Models for an Optimized Computer-Assisted Planning of Periacetabular Osteotomy. PLOS ONE, 2016;11(1):e0146452, 2017.

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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, with main applications to machine learning based analysis of brain lesions from multi-sequence MRI, multi-resolution computational anatomy from CT imaging, and advanced techniques for clinically-relevant human-machine interfacing.

Brain Lesion Image Analysis

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.

During 2016 we performed clinical evaluations of our software BraTumIA (Brain Tumor Image Analysis), and tested it on longitudinal set-ups, for neurosurgical procedures, and compared against other FDA-approved tools for neurosurgical planning. During 2016 we also started a CE marking process and licensing of this technology to a leader in the medical imaging field. In addition, our group was awarded Young Scientist Publication Impact Award 2016 for our seminal 2011 Miccai work. In collaboration with our partners at the Institute of Diagnostic and Interventional Neuroradiology, we further extended initial developments for the prediction of lesion outcome in ischemic stroke patients, leading to a second place in the ISLES2016 segmentation challenge. Similarly, the seminal work on multiple sclerosis allowed us to obtain the first prize in the multiple sclerosis segmentation challenge at Miccai 2016.

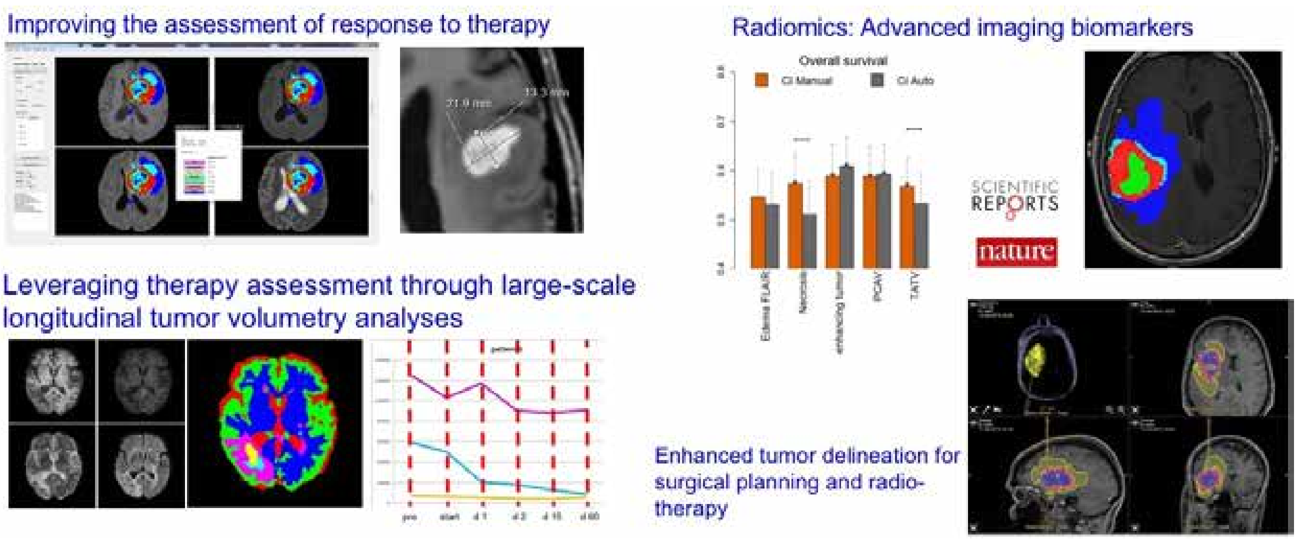

Figure 1. Brain image lesion analysis (In clockwise order): Improving the assessment of response to therapy through automated brain tumor quantification. Radiomics, and the role of tumor volumetry for patient survival analysis. Advanced brain tumor quantification for neurosurgery and radiotherapy. Robust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

Computational Anatomy

Computational anatomy enables analysis of biological variabil-
Computational anatomy enables analysis of biological variability throughout a population. Using statistical mathematical techniques, models can be built to represent the typical shape of an anatomical structure and its predominant patterns of variability across a given population. During 2016 we used these techniques to evaluate the performance of cochlear electrodes, used to re-establish hearing on patient suffering from moderate to severe hearing loss, as well as super-resolution techniques able to enhance the quality and the accuracy of segmentations of the facial nerve, needed for cochlear implantation planning procedures. In combination with Machine Learning techniques, we have developed modeling engines able to yield, directly from the clinical images, patient-specific models compliant with FE analysis. During 2016 we continued the development of algorithms and tools to perform fast corrections of segmentations. The results of this research were released to the community in the form of a software tool, FISICO (Fast Image Segmentation Correction). Similarly, we developed fast and accurate segmentation and quantification algorithms for high-resolution micro-CT kidney scans employed for the design of modern image-based stereology techniques.

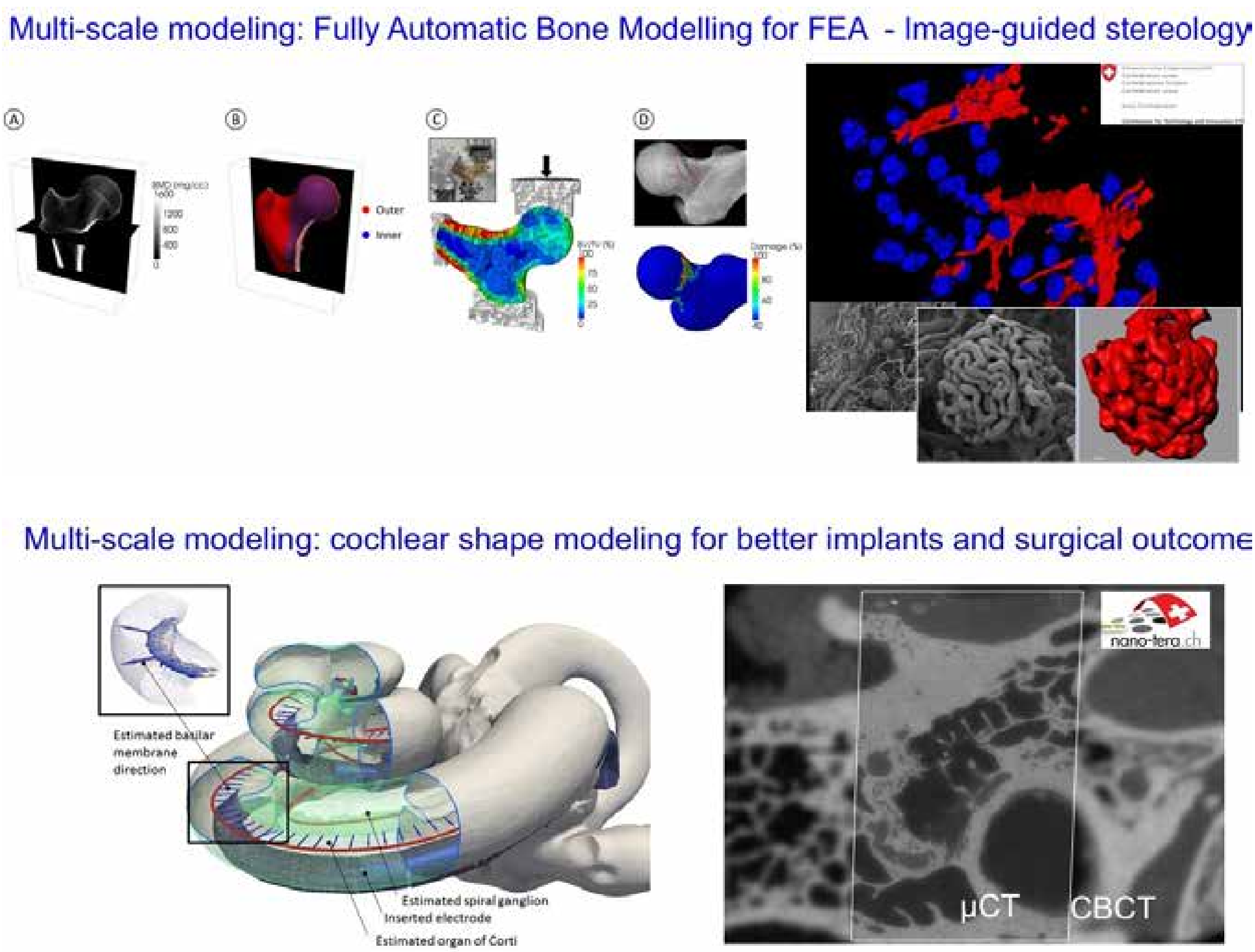

Figure 2. Modeling anatomical variability and its application to applications such as cochlear electrode assessment, sub-voxel facial nerve segmentation, direct bone modeling for FE analysis, and modern image-based stereology.

Selected Publications

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9. Reyes M., Shahim K., and Jürgens. Computational Image-Guided Technologies in Cranio-Maxillofacial Soft Tissue Planning and Simulation. In Computer-Assisted Musculoskeletal Surgery, pp. 43-56. Springer International Publishing, 2016.

Musculoskeletal Biomechanics

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Prof. Uwe Wolfram, Heriot-Watt University, Edinburgh
Prof. Ron Alkalay, Harvard Medical School, Boston
Prof. Jasmin Wandel, Bern University of Applied Sciences, Burgdorf

Research Profile

Motivated by prevention, diagnosis, treatment and follow-up 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 musculoskeletal tissues in the course of growth, aging, disease and treatment. The group provides also specialized biomechanical testing services and cooperates with local, national as well as international partners from academia, hospitals and industry to help reduce the burden of osteoporosis and other degenerative diseases.

Bone Damage

Bone is a quasi-brittle hierarchical composite that exhibits damage with distinct crack morphologies in compression and tension. A recent study reported 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 mechanistic model by which cracking bone accumulates residual strain and reduces elastic modulus in distinct compressive and tensile overloading modes. A statistic of simple rheological units was assembled in parallel to compute the response of a macroscopic bone sample in which compressive and tensile cracks are opened, closed or propagated towards failure. The obtained model reproduces the key features of bone tissue damage and delivers an excellent agreement with the experiments.

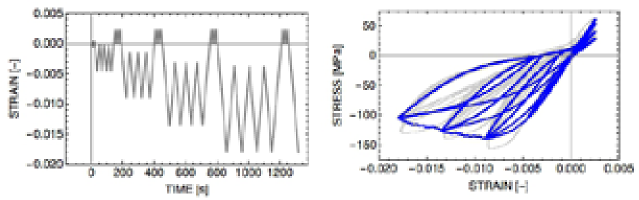

Figure 1. Cyclic overloading of bone in compression showing the impact on the elastic modulus in tension: experiment versus model.

Finite element analysis of the human proximal femur (SNF grant 143769)

QCT-based FE models are employed to calculate femoral strength. Due to the low resolution, trabecular fabric anisotropy cannot be derived from QCT images accurately and material properties of FE models are assumed isotropic. However, fabric anisotropy is a major determinant of bone material properties. Alternatively, fabric anisotropy can be taken from a high resolution CT template image of the cadaveric proximal femur. The aim of this project was to establish a new standard for QCT-based FE analysis of the proximal femur by including trabecular orientation to the local vBMD field.

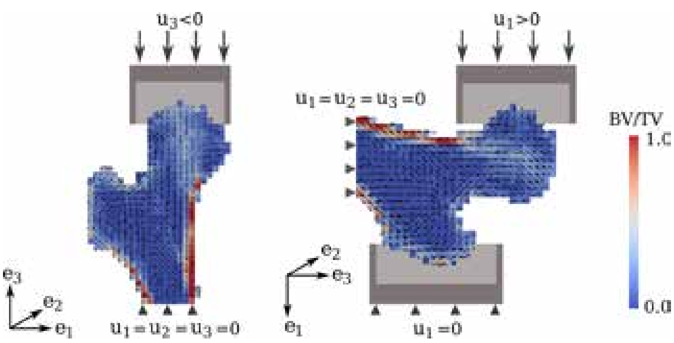

Figure 2. Homogenized voxel FE models in stance and side-fall configurations. Fabric anisotropy (small black lines) was mapped from HR-pQCT cadaveric proximal femora.

Computational Bone Modeling

Finite element models of bone and bone-implant systems rely on appropriate material laws for simulating the mechanical behavior of bone tissue. To ascertain their reliability, those models are validated against in vitro biomechanical tests. Yet, material parameters are often tuned to a specific test performed on a given bone. Such practice

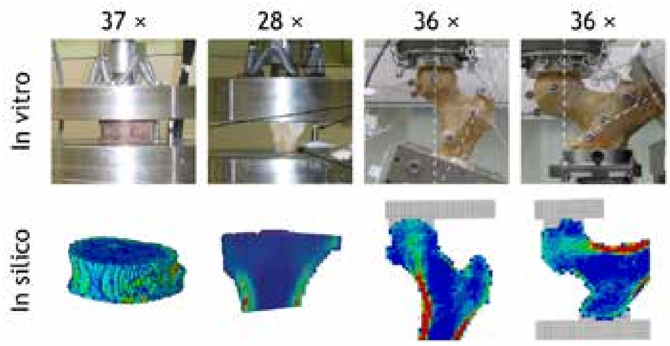

Figure 3. A single material law was used in finite element models (in silico) to replicate 137 biomechanical tests (in vitro) conducted on vertebral bodies, distal radii and femurs.

should not be necessary if the material law properly replicates bone mechanics. To prove this assumption, we replicated four in vitro tests performed on three distinct anatomical locations via finite element models based on a single modelling scheme.

Bone drilling (Nano-Tera, Hear Restore)

Many surgical interventions require the use of cutting tools and drill bits. These tools generate heat which can lead to an irreversible damage to bone or surrounding soft tissue (e.g. nerves). Therefore, we aim at understanding and improving the cutting process parameters and cutting tool geometry. The latest research includes an investigation of the basic principles of the cutting process. Therefore, a so called "orthogonal cutting experiment" was performed at the Fraunhofer Institute for Production Technology at the RWTH Aachen (see Figure 4). This experiment allows high-speed measurements of the temperature elevation, chip formation and cutting forces. The results enable the improvement of surgical tools like drill bits to reduce the thermal risk of procedures close to vulnerable structures.

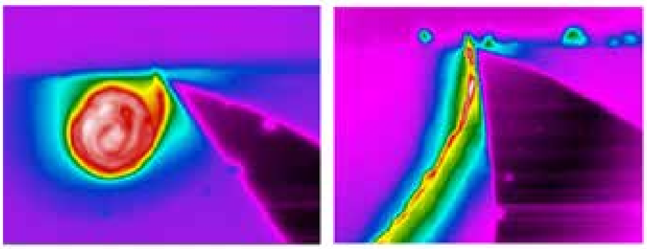

Figure 4. High speed optical and thermal videos of orthogonal cutting experiments. Different cutting tool geometries and cutting depths were investigated.

FEA of the human intervertebral disc (SNF grant 147153)

The aim of this project is to provide a functional diagnostic tool for early assessment of degenerative intervertebral disc (IVD) disease. IVD degeneration can cause alterations in its mechanical behavior. Previous studies proposed to capture those changes using MRI-based

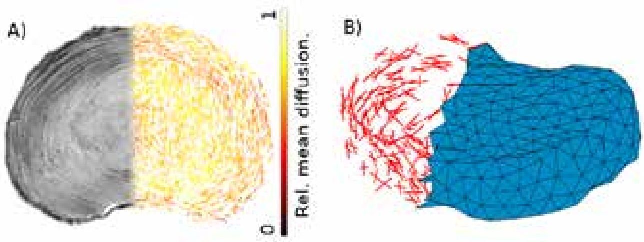

Figure 5. A) T1-weighted image of a human IVD and its principal diffusion direction. The color represents a normalized local mean diffusion. B) Corresponding mesh and computed fiber orientations.

finite element analysis (FEA). However, two main contributors to the IVDs mechanical behavior, the collagen fiber density and its orientation distribution were not accounted for. We propose to capture the fibrous structure of the IVD using diffusion MRI. Therefore, we measured human, bovine and porcine IVDs in a high filed MR scanner (Bruker, 9.4T) using a diffusion weighted echo planar imaging sequence. From these data we could estimate a local fiber density and two principal fiber directions and assign these to each finite element. The IVDs used for the MRI are now in preparation for in vitro biomechanical testing to calibrate and validate our FE models.

CT Recycling (Gebert Rüf Foundation)

Having back pain? You might suffer from osteoporosis ("porous bones") just as half of the population over 50. As mass screening is not an option for the authorities, we proposed to recycle Computed Tomography (CT) scans. Though not intended for bone densitometry, they can be reused to build accurate computer (finite elements) models. The patient's bone is then virtually crushed to evaluate its resistance before fracture occurs. To some extent, such analysis resembles a virtual crash test. The benefits for the clinics? Two diagnoses for the radiation dose and cost of one. A software pipeline has already been developed and is currently being validated on in vitro datasets. The next step is its application to clinical data.

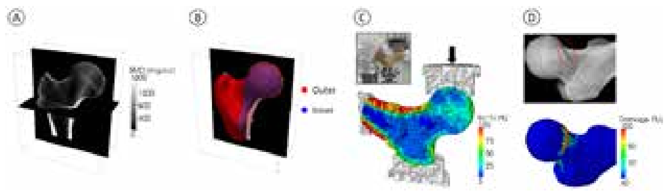

Figure 6. A femur is scanned (A) and a mesh is generated (B). The finite element model is oriented, embedded and loaded as in the experiment (C). The simulated damage matches the in vitro failure (D).

Biomechanical Testing

Biomechanical experiments were performed for industrial contract research, clinical projects and internal research.

Biomechanical experiments were performed for industrial contract research, clinical projects and internal research. For instance, a study measured the passive knee motion on cadavers for an intact, transected and implanted anterior cruciate ligaments (ACL). The benefit of the implant such as the range of motion and its loading during flexion was evaluated. Implantation site errors were simulated in order to assess the impact on the range of motion of the knee and the implant effectiveness. Another project in collaboration with the Dental School evaluated the mechanical properties of ceramic dental implants according to industrial testing standards.

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4. Schwiedrzik Jakob, Gross Thomas, Bina Markus, Pretterklieber Michael, Zysset Philippe and Pahr Dieter, "Experimental validation of a nonlinear µFE model based on cohesive-frictional plasticity for trabecular bone", Int J Num Meth Biomed Eng, e02739, DOI: 10.1002/cnm, 2016.
5. Maquer Ghislain, Dall'Ara Enrico, Chevalier Yan, Lu Yongtao, Krause Matthias, Yang Lang, Eastell Richard, Lippuner Kurt and Zysset Philippe, "The initial slope of the variogram, foundation of the trabecular bone score, does not predict vertebral strength in three distinct biomechanical tests", J Bone Miner Res 31(2):341-346, 2016.
6. Feldmann Arne, Anso Juan, Bell Brett, Williamson Tom, Gavaghan Kate, Gerber Nicolas, Rohrbach Helene, Weber, Stefan and Zysset Philippe, "Temperature prediction model for bone drilling based on density distribution and in vivo experiments for minimally invasive robotic cochlear implantation" Annals of Biomedical Engineering, 44(5):1576-1586, 2016.
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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. 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 antagony. 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 Rüf financed project a novel type of silk material is currently being investigated for IVD repair. Here, the TOM group investigated into new growth-factor-enriched silk, which is produced from genetically transduced silk worms (*Bombyx mori*), which embed the growth factor of interest directly into the silk. The new 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 bioreactor together with a fibrin hydrogel. 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 (Figure 1). These results were recently reported in the November issue of the "Orthopädische Nachrichten" in a special issue on low back pain. Daniela Frauchiger presented her data at the Annual Meeting of the German Spine Society in Hannover.

Figure 1. Histology of bovine IVDs after 14 days of *ex vivo* culture; top: Hematoxylin/Eosin, bottom: Safranin-O/Fast Green. **(A)** healthy control disc **(B)** injured IVD using a 2mm biopsy punch **(C)** IVD repaired with genipin-enhanced fibrin hydrogel and silk fleece-membrane composite. (Scale bar 100µm)

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. In organ culture experiments, we labelled isolated NPPC and injected them back into an artificially degenerated bovine IVD to study their behaviour in the native IVD environment (Figure 2). Future research is to understand how these cells can be isolated best and whether these cells can be maintained *in vitro* to regenerate the IVD.

Figure 2. **(A)** nucleus pulposus progenitor cells (NPPC = Tie2+ cells) and Tie2- cells were isolated from bovine NP tissue and labelled with Vybrant™ DIL dye and seeded in fibrin hydrogel or phosphate buffered saline (PBS. Cells were then injected into a previously degenerated IVD cavity using papain. IVDs were then cultured for 7 days and stained with calcein AM and DAPI (live/dead assay). **(B)** Faith of injected NPPC and Tie2- cells was assessed using 3D stacks of confocal microscopy. NPPC injected with PBS (top row) and with fibrin hydrogel (bottom row). Live injected: yellow; dead injected: red ; live native: green; dead native: blue, (scale bar 100 µm).

Here, a selection of biomaterials and 3D cell culture systems might help to find suitable culture conditions to expand these cells.
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 electroporize human and bovine IVD cells and to transfer plasmid DNA to manipulate transiently the expression profile (Figure 3).

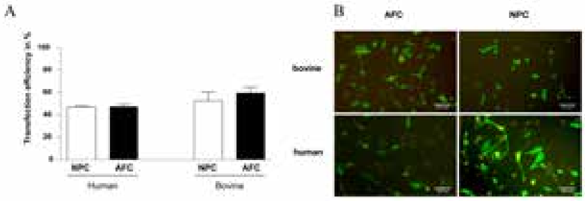

Figure 3. **(A)** Percentage of transfection efficiency of human (N = 4) and bovine (N =5) NPC and AFC as quantified by flow cytometry. The percentages of transfection efficiencies are (mean ± SEM): hNPC 46.7 ± 1.4 %, hAFC 47.1 ± 2.4 %, bNPC 52.44 ± 7.9 %, bAFC 59.6 ± 5.0 %. **(B)** Green fluorescent protein (GFP)-positive human and bovine annulus fibrosus (h- and bAFC) and nucleus pulposus cells (h- and bNPC) after 48 hours of transfection with pCMV6-AC-GFP were detected under a light microscope.

Biological Repair of the ruptured 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 (Inselspital) and the Sonnenhof clinic called Dynamic Intraligamentary Stabilization (DIS) which keeps ACL remnants 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-derived plasma (PRP) are of interest. The aim of our research was to investigate the use of collagen patches, the application of platelet rich plasma (PRP) and platelet rich fibrin (PRF) in combination with DIS to support regeneration of the ACL and to quantify the biological response. Furthermore, a novel bioreactor has been designed and realized to culture full human ACL (Figure 4). Here, first results were reported by mechanical stimulation of live ACLs for seven days.

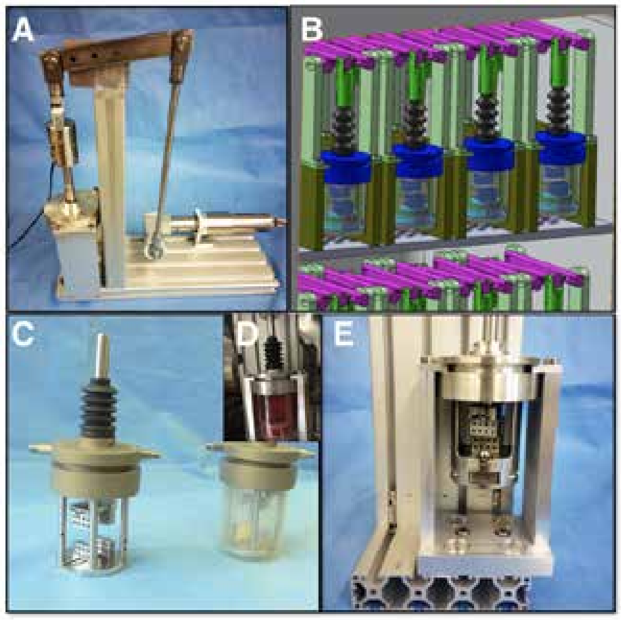

Figure 4. Strain-controlled bioreactor to culture human full ACL. **(A)** Side-view of ACL Bioreactor **(B)** CAD view of planned 4-stations bioreactor inside CO2-controlled incubator **(C)** Side-view of new culture chamber design **(D)** ACL in culture with culture medium **(E)** Close-up view of bioreactor set-up.

Original Peer-reviewed Journal Articles

1. Chooi WH, Chan SC, Gantenbein B, Chan BP (2016) Loading-Induced Heat-Shock Response in Bovine Intervertebral Disc Organ Culture. PLoS ONE 11(8):e0161615. doi: 10.1371/journal.pone.0161615.
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3. Schmocker AM, Khoushabi A, Frauchiger DA, Gantenbein B, Schizas C, Moser C, Bourban P-E, Pioletti D (2016) A photopolymerized poly-ethlyene-glycol composite hydrogel and surgical implanting tool for a nucleus pulposus replacement. Biomaterials 88: 110-119 doi: 10.1016/j.biomaterials.2016.02.015.
4. Tekari A, Chan SC, Sakai D, Grad S, Gantenbein B (2016) Angiopoietin-1 receptor Tie2 distinguishes multipotent differentiation capability in bovine coccygeal nucleus pulposus cells. Stem Cell Res Ther 7(1):75. doi: 10.1186/s13287-016-0337-9.

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Mechanical Design and Production

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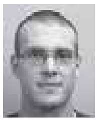


Ronald Ramseier

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. Trial apprenticeships are used as a means to evaluate candidates for a full apprenticeship in the MDP group. This year we performed three courses and at we selected Simon Lüthi as our next apprentice. He will begin his training in August of 2017 as a polymechanic EFZ apprentice.

From April to August, Andreas Beck reinforced our team by working part-time as design engineer. He worked mainly on a forearm-rotating device. Since September, he works in industry. We are very grateful for the work he perfomed.

Due to a high demand, we recruited our former polymechanic apprentice Ronald Ramseier as cilvil-service employee. He performed administrative tasks and increased the productivity of our team from mid-August to October. We thank him also for the work he performed in our workshop.

This year we could welcome for the first time a student from ETH for a construction internship. David Flückiger spent five weeks in our workshop and worked actively on the construction of mechanical pieces. During this short period, he performed practical work with machines.

In June Lukas Rufener completed his apprenticeship with a very good result and we congratulate him. He will be employed until end of February 2017 part-time as a polytechnician.

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: Prosup Arm Bed Twist Device

This device was developed and produced in collaboration with Dr. Philipp Fürnstahl from Balgrist University Hospital. The radiolucent pieces were made of acrylic glass or by 3D-printing. With this device, the medical doctors are able to analyse the motion of the forearm. The device is either powered directly by muscle force or additional motors can guide the motion.

Project: Endoscope Calibration

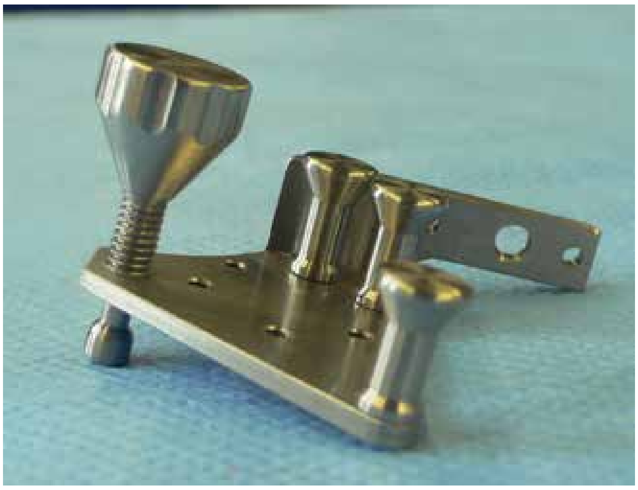
We built a device that allows the calibration of endoscopes with oblique viewing. The challenge of the project was to define the angles of the plates and its assembly. With this calibration system, the endoscopes can now be calibrated for angles from 30° to 70°.

Project: Ligastretch Extension

In this project, an existing system for testing crucial ligaments was improved. Compared to the previous version, this new system allows the testing of longer specimens. Additionally, the cell nutrition medium can now be replaced without moving the rest of the setup. The construction of two such devices was realized by Lukas as a part of the final exam of his apprenticeship.

Project: Instrument Adapter

Three prototypes of this device were built for an external research partner. The first two were simple to produce, however the third version required 3D-freefrom surfaces with an inner radius of 0.5 mm. This small radius required a special milling tool as an elaborate programing of the drilling stage.



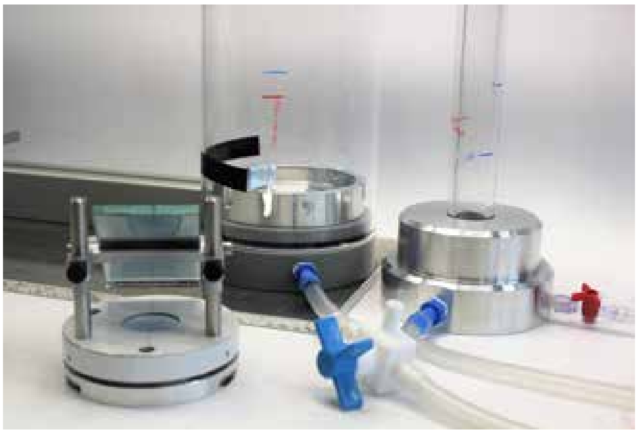
Research Equipment Design & Manufacturing ARTORG

The workshop at the ARTORG Center was managed since 1st of January 2016 by Danaël Gasser as a full time polytechnician. He manufactured some different project-parts, mainly for the CVE and IGT 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 grew and strengthened. Since the workshop of the ARTORG is not equipped with a CNC milling-system, Daniel followed an appropriate training for CNC programing and production at our workshop.

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

Project: C-Patch Testing Setup

A cellulose membrane is stretched to failure using a static pressure from a water column. With a camera and pressure sensors, the strain and the pressure can be measured. The challenge of this project was to keep the system leak-free. In addition, the membrane had to be visible from every side. A bayonet-closure allows the user a fast replacement of the cellulose membranes.



Project: Beam Tip

The Beam-tip is a part of an energy harvesting system that gathers energy from the blood flow. The challenge of this project was the very small mass of the system. The relatively thin wall diameter of 0.5mm requires a high precision. The device had to be assembled using magnification glasses.

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- Finally, we would like to thank all the members who dedicated their time and talent in 2016 to ISTB.

COMPLETED DISSERTATIONS

Michael Kistler. "*A database framework to incorporate statistical variability in biomechanical simulations*". January 2016

Li Liu. "*Development and validation of computer assisted diagnosis, planning and navigation systems for periacetabular osteotomy*". March 2016.

Elham Taghizadeh. "*Statistical Shape Model of the Leg to Improve the Treatment of Patella Pathology in Total Knee Arthroplasty*". May 2016.

Waldo Valenzuela. "*Effective Human Machine Interfaces for Medical Image Analysis*". August 2016.

Jarunan Panysantisuk. "*Inclusion of Fabric in QCT-based Patient-specic Finite Element Analysis of the Proximal Femur*". September 2016.

Can Gökgöl. "*Characterization of the Deformation Behavior and Mechanical Response of the Femoro-popliteal Arterial Tract after Stent Placement*". October 2015

Chengwen Chu. "*Musculoskeletal image analysis: detection, segmentation and modelling*". November 2016.

Carlos Correa Schokiche. "*MicroCT based kidney morphometry: A machine learning approach*". December 2016.

AWARDS & PRIZES

"A statistical damage model for bone tissue based on distinct compressive and tensile cracks", Stefan M. Perren Research Award of the European Society of Biomechanics, Lyon, 2016.
Awardees: Philippe Zysset, Jakob Schwiedrzik and Uwe Wolfram.

"Bone volume fraction and fabric anisotropy are better determinants of trabecular bone stiffness than other morphological variables". SBMS President Award, Bern, 2016.
Awardees: Ghislain Maquer, Sarah Musy, Jasmin Wandel, Thomas Gross, Philippe Zysset.

The 2016 Award for the Best PhD Thesis at the 8th Biomedical Engineering Day, Bern, Switzerland
Awardee: Li Liu.

Award "Young Scientist Publication Impact Award", MICCAI 2016.
Awardee: Stefan Bauer.

Second prize BRATS, Longitudinal Brain Tumor Segmentation Challenge, MICCAI 2016.
Awardee: Raphael Meier.

First prize MSSEG (Multiple Sclerosis Segmentation Challenge), MICCAI 2016.
Awardee: Richard McKinley.

Second prize ISLES (Ischemic Stroke Lesion Segmentation), MICCAI 2016.
Awardee: Richard McKinley.