INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

Contents

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INSTITUTE FOR SURGICAL TECHNOLOGY AND BIOMECHANICS

EDITORIAL

We are pleased to present hereby the annual report 2015 of the Institute of Surgical Technology and Biomechanics (ISTB). Over the past years, the ISTB has grown into a highly interdisciplinary assembly of five complementary teams covering computational bioengineering, information processing in medical interventions, medical image analysis, musculoskeletal biomechanics and tissue/organ mechano-biology. The experimental projects of the institute are supported by a professional group in mechanical design and production.

The ISTB has gained a broad portfolio bridging the investigation of fundamental problems in tissue biology and mechanics to the translation of new technologies with numerous clinical units. This broad spectrum is motivated by the need to seed new ideas in the basic research addressing diseases of the musculoskeletal system and the expectation of our clinical partners to exploit current technologies to help resolve the complex problems they are facing daily.

At the same time the biomedical environment is facing an extraordinary challenge produced by the contrast of increasing availability of knowledge, technology and patient expectations with limited resources in medical personnel and time. This may be exemplified in one of our interdisciplinary focus areas. Biomedical images are continuously improving, can be calibrated, can be analyzed with powerful algorithms, can be registered intra-operatively and can be used as input for numerical simulations of organ function and optimization of the outcome of a given intervention. The association of personalized images with statistical information from anatomical databases offers fantastic opportunities for diagnosis, treatment and rehabilitation. Nevertheless, the outcome of this sometimes gigantic data flow must result in simple, cost-effective and evidence-based medical actions.

The ISTB continues to contribute very actively to the specialized Master Program in Biomedical Engineering (www.bme.unibe.ch) of the University of Bern offered in collaboration with the University of Applied Sciences of Bern. It is also involved in the Graduate School in Cellular and Biomedical Sciences (www.gcb.unibe.ch) where a specific commission could be established for the field of biomedical engineering. Together with the ARTORG Center (www.artorg.unibe.ch) the ISTB belongs to the Bern Bioengineering Network (www.bbme.ch) a large inter-institutional organization that brings together the competences of over 500 clinicians and researchers from the health disciplines in the Bern area.

In 2015 our group heads Guoyan Zheng (Information Processing in Medical Interventions) and Benjamin Gantenbein (Tissue and Organ Mechanobiology) were both appointed Associate Professor at the Medical Faculty. By this the University of Bern recognized their outstanding research, teaching and service over the past years.

As another highlight of 2015, we would like to mention our summer excursion on the river Aare executing real life fluid dynamics (see image below).

As a conclusion, we would like to take the opportunity to thank our collaborators for their hard work, our partners for their confidence, the faculty of medicine and the executive board of the university for their ongoing support in our changing environment. We wish an enjoyable reading of our 2015 activities.

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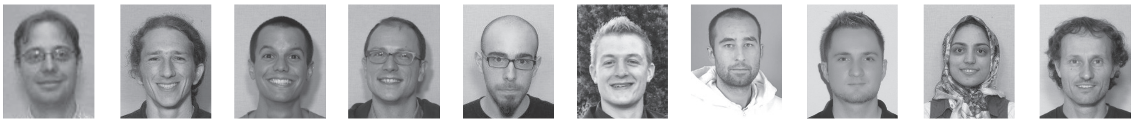

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Research Profiles

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 in to the evaluation of bone biomechanics.

The Human Anal Sphincter Complex

Fecal incontinence (FI) describes the involuntary loss of bowel content, which is responsible for stigmatization and social exclusion. It affects about 45% of retirement home residents and overall more than 12% of the adult population FI has considerable economic impact and severe consequences on the life quality of the affected persons. Severe fecal incontinence can be treated by the implantation of an artificial sphincter. Currently available implants, however, are not part of everyday surgery due to long-term re-operation

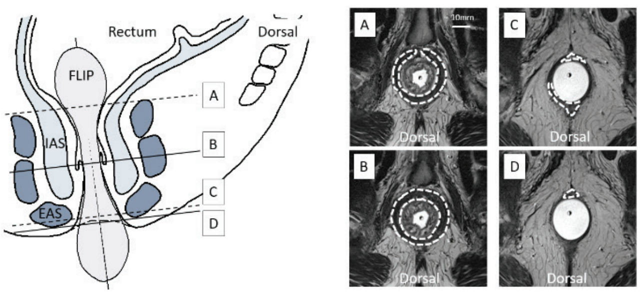

Figure 1: Sagittal sketch of the recto-anal region with catheter used to measure compliance in-vivo. MR-images were acquired during inflation of the balloon to measure inflation diameter and assign the mechanical compliance measurements with the underlying anatomical structures along the anal canal.

rates of 95 % and definitive explantation rates of 40%. These numbers suggest that the implants fail to reproduce the capabilities of the natural sphincter. The objective of this work is to better understand the mechanisms of continence and to quantify the biomechanical parameters required for the design of an artificial anal sphincter.

During the past year, a clinical study has been performed on healthy volunteers to quantify the active and passive properties of the tissues. The compliance was quantified in-vivo using a catheter gradually inflated inside the anal canal. Both pressure and diameter of the balloon were recorded during inflation.

The calculated compliance parameters showed an important inter-patient variability, even for healthy volunteers. Since measurements were performed within an MRI device, the biomechanical measurements can be associated to the underlying anatomy (Figure 1). Interestingly, MR observations showed that the external anal sphincter (EAS) muscle is not centered with respect to the position of smallest anal canal (AC) diameter, but is positioned more caudally. The position of the smallest opening of the AC corresponds approximately to the end of the EAS. An extension of this study on patients suffering from fecal incontinence is ongoing.

Macroscopic Brain Tumour Growth

Brain tumours represent a rare but serious medical condition, with glioblastoma multiforme (GBM) being the most frequent malignant histological type. These tumours are characterized by invasive

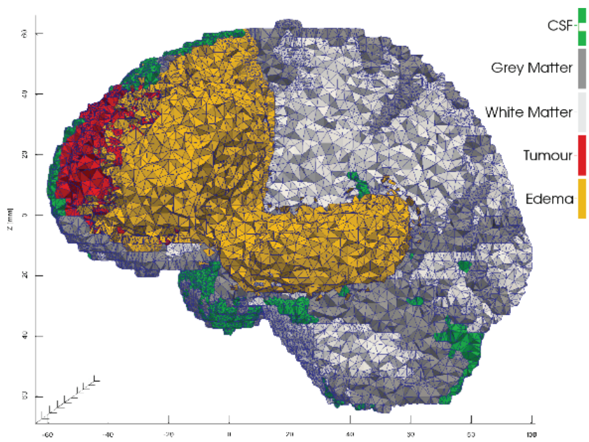

Figure 2: Tetrahedral mesh distinguishing several healthy-brain and tumour regions; generated from patient data using pre-processing pipeline.

growth, infiltrating surrounding healthy tissue, and poor long-term prognosis with 5-year survival rates below 3%. Growth and dynamics of brain tumours, and GBM in particular, have been studied extensively by means of different computational modelling approaches. Most macroscopic models of spatial tumour evolution within a patient-specific anatomy have been based either on reaction-diffusion models, accounting for the invasive growth of GBM, or on purely mechanical models, simulating the mass-effect caused by a growing solid tumour. Few models, consider both effects in a single 3D model in order to better understand disease progression and to support personalized treatments.

We use the finite element method (FE) for simulating the invasion of GBM into brain tissue and the mechanical interaction between tumour and healthy tissue components. The process of proliferation and invasion is modelled as a reaction-diffusion equation, while the simulation of the mechanic interaction relies on a linear-elastic material model. Both are coupled by relating local increase in tumour cell concentration to the generation of isotropic strain in the corresponding tissue volume element. In combination with image segmentation tools, the pre-processing pipeline permits rapid generation of patient-specific anatomical FE models for personalized simulations (Figure 2). Tumours have been seeded at different locations in FE models derived from publicly available human brain atlases. Their growth pattern has been studied in function of seed location. The model predicts non-isotropic growth patterns, similar to those observed in clinical cases. However, further attention needs to be directed to quantitative validation of model predictions, for example against longitudinal imaging data.

Trabecular Bone Structure

Patient-specific numerical models can be used to evaluate bone strength. The models are built from clinical CT scans, which allow assigning bone mechanical properties according to the spatial distribution of bone mineral density. However, it has been shown that bone density is not sufficient to accurately estimate bone strength and that adding information about the trabecular anisotropic material properties improves such calculations. One of the limitations of this approach is that high-resolution scans are required to obtain the bone anisotropy, which can only be used *in-vivo* for a few bones at the extremities. To improve the accuracy of strength calculations from finite element models, we proposed to rely on a statistical model of bone biomechanical properties (Figure 3) that can be adapted to each patient.

The statistical model of anisotropy indicates that almost all the information is contained in the average anisotropy. This result means that morphing the average bone anisotropy to the patient CT-scan is able to accurately predict the bone stiffness. This hypothesis was tested by comparing the bone stiffness calculated with FE simulations of the bone model derived from µCT with models solely relying on the average anisotropy calculated with our model. Results confirmed our hypothesis and no significant differences were found in the ultimate forces and displacements when the average anisotropy was used. On the other hand, using an isotropic material model produces significantly different results. Therefore, accurate patient-specific simulation could be achieved simply by projecting a map of the average bone architecture onto the patient clinical images. Additional investigations are required to confirm that the same results hold for other loading conditions, anatomical sites and pathologies.

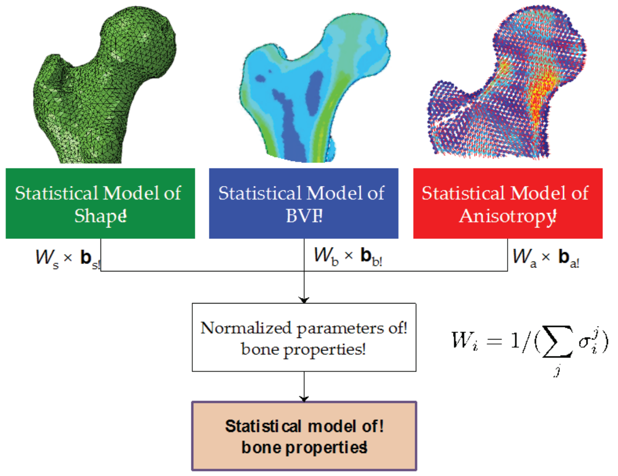

Figure 3: A statistical model of bone biomechanical properties was built from µCT scan datasets. The models of shape, BV/TV and anisotropy were built separately and combined after normalization.

Selected Publications

1. Elham Taghizadeh, Mauricio Reyes, Philippe Zysset, Adeliya Latypova, Alexandre Terrier, Philippe Büchler (2016) Biomechanical Role of Bone Anisotropy Estimated on Clinical CT Scans by Image Registration. Annals of biomedical engineering.
2. Can Gökgöl, Nicolas Diehm, Farhad Rikhtegar Nezami, Philippe Büchler (2015) Nitinol Stent Oversizing in Patients Undergoing Popliteal Artery Revascularization: A Finite Element Study. Annals of biomedical engineering 43: 12. 2868-2880.
3. Olivier Lieger, Benoit Schaller, Alexander Bürki, Philippe Büchler (2015) Biomechanical evaluation of different angle-stable locking plate systems for mandibular surgery. Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery 43: 8. 1589-1594.
4. Carol C Hasler, Daniel Studer, Philippe Büchler (2015) Metamorphosis of human lumbar vertebrae induced by VEPTR growth modulation and stress shielding. Journal of children's orthopaedics 9: 4. 287-293.

Information Processing in Medical Interventions

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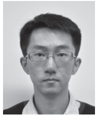
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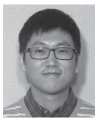
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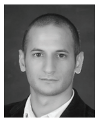
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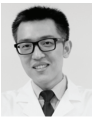
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Research Profile

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. We developed a unified, machine learning-based approach to address the challenging problems of localization and segmentation of intervertebral discs and vertebral bodies from 3D CT/MR images. Evaluated on open data sets, our method achieved better results than the state of the art methods.

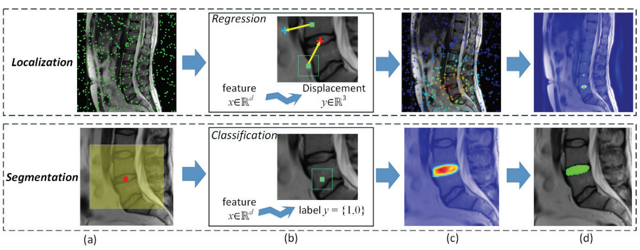

Figure 1. Overview of our method for IVD localization (top row) and segmentation (bottom row).

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.

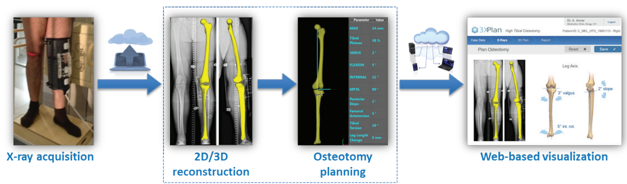

Figure 2. Overview of web-based planning and evaluation of orthopaedic interventions.

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.

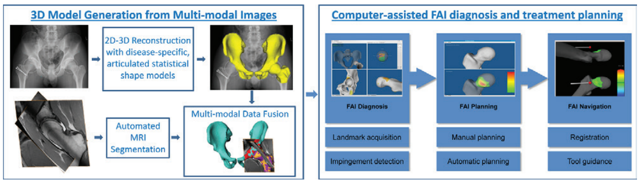

Figure 3. Multi-modal image computing for computer assisted interventions.

2.5D Quantification of femoral head coverage of patients with hip dysplasia (Sino-Swiss Science and Technology Cooperation)

Hip dysplasia is characterized by insufficient femoral head coverage (FHC). Quantification of FHC is of importance as the underlying goal of the surgery to treat hip dysplasia is to restore a normal acetabular morphology and thereby to improve FHC. Unlike a pure 2D X-ray radiography-based measurement method or a pure 3D CT-based measurement method, previously we presented a 2.5D method to quantify FHC from a single anteriorposterior (AP) pelvis radiograph. In a study, we quantified and compared 2.5D measurement with 3D measurement and proved that 2.5D measurement could be used as a surrogate for 3D CT-based measurement.

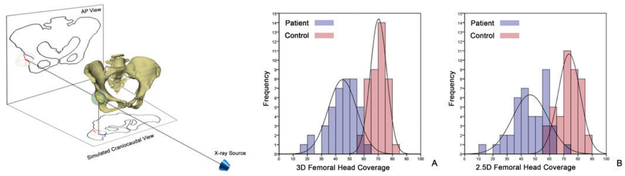

Figure 4. Quantification and comparison of 2.5D and 3D measurements of FHC.

Fully automatic segmentation and statistical shape modeling of musculoskeletal (MS) structures (Japanese-Swiss Science & Technology Cooperation)

Accurate segmentation of hip CT images is a pre-requisite step for many important applications such as computer assisted disease diagnosis, pre-operative planning, image-guided surgery, and post-operative treatment evaluation. We have developed a Multi-Atlas Segmentation Constrained Graph (MASCG) method which uses multi-atlas based mesh fusion results to initialize a bone sheetness based on multi-label graph cut for an accurate hip CT segmentation which has the inherent advantage of automatic separation of pelvic region from the bilateral proximal femur regions. We then introduced a graph cut constrained graph search algorithm to further improve the segmentation accuracy around the bilateral hip joint.

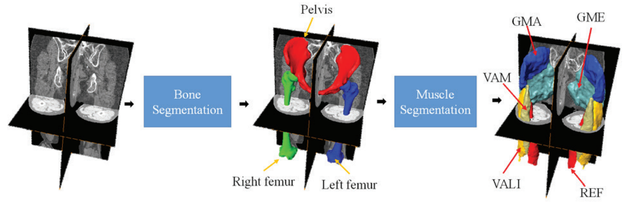

Figure 5. Fully automatic segmentation of MS structures of thigh region.

The segmented data can then be used to construct statistical shape models (SSMs) of compound MS structures. Together with Prof. Sato's group, we developed a hybrid registration scheme with an articulated SSM (aSSM) construction technique and applied it to construct an aSSM of compound MS structures around thigh region. The constructed aSSM has potential applications in model-based medical image computing tasks.

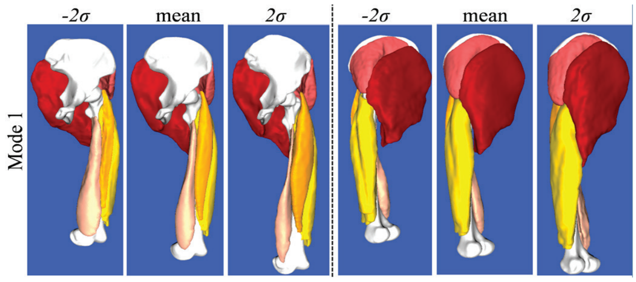

Figure 6. The variations of the first mode of the aSSM of the compound MS structures around thigh region.

Edited Book

1. G. Zheng and S. Li (eds): Computational Radiology for Orthopaedic Interventions. Springer 2015, ISBN 978-3-319-23482-3.

Selected Publications

1. G. Zheng and L.P. Nolte (2015). Computer-assisted orthopaedic surgery: current state and future perspective. Frontiers in Surgery, 2015; 2:66. doi: 10.3389/fsurg.2015.00066.
2. H. Cheng, L. Liu, W. Yu, H. Zhang, D. Luo and G. Zheng (2015). Comparison of 2.5D and 3D quantification of femoral head coverage in normal control subjects and patients with hip dysplasia. PLOS ONE, 2015;10(11):e0143498.
3. C. Chu, D.L. Belavy, G. Armbrecht, M. Bansmann, D. Felsenberg and G. Zheng (2015). Fully automatic localization and segmentation of 3D vertebral bodies from CT/MR images via a learning-based method. PLOS ONE, 2015;10(11):e0143327.
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5. S. Schumann, Y. Sato, Y. Nakanishi, F. Yokota, M. Takao, N. Sugano and G. Zheng (2015). Cup implant planning based on 2-D/3-D radiographic pelvis reconstruction - first clinical results. IEEE Trans Biomed Engineering, 62(11):2665-73, 2015.
6. C. Chu, J. Bai, X. Wu and G. Zheng (2015). MASCG: Multi-Atlas Segmentation Constrained Graph Method for Accurate Segmentation of Hip CT Images. Medical Image Analysis, 26:173-184, 2015.
7. G. Zheng and S. Li (2015). Medical image computing in diagnosis and interventions of spinal diseases. Computerized Medical Imaging and Graphics, 45:99-101, 2015.
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11. S. Berger, O. Marcello, S. Schumann, J. Schneider, D. Studer, C. Hasler, G. Zheng, P. Büchler (2015). Patient-specific spinal stiffness in AIS: a preoperative and noninvasive method. European Spine Journal,.24(2):249 – 255, 2015
12. C. Chu, C. Chen, L. Liu, and G. Zheng (2015). FACTS: Fully Automatic CT Segmentation of A Hip Joint. Annals of Biomedical Engineering., 43(5):1247-1259, 2015.
13. M. Tannast, M.S. Hanke, G. Zheng, S.D. Steppacher, and K.A. Siebenrock (2015). What Are the Radiographic Reference Values for Acetabular Under- and Overcoverage? Clinical Orthopaedics and Related Research, 473:1234-1246, 2015.
14. M Tannast, S Fritsch, G Zheng, KA Siebenrock, SD Steppacher (2015). Which Radiographic Hip Parameters Do Not Have to Be Corrected for Pelvic Rotation and Tilt? Clinical Orthopaedics and Related Research, 473:1255-1266, 2015.
15. W Xie, J. Franke, C Chen, PA Grützner, S Schumann, LP Nolte,G Zheng (2015). A complete-pelvis segmentation framework for image-free total hip arthroplasty (THA): methodology and clinical study. International journal of medical robotics and computer assisted surgery, 11:166-180, 2015.

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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, which aims on the one hand to understand the natural anatomical and physiological variability encountered in a population and, on the other hand, to use this understanding to overcome imaging limitations hindering patient treatment.
During the last years our group has focused on three major questions that align with the paradigm of evidence-based modeling and personalized-medicine:

- *How to effectively combine Magnetic Resonance Imaging information for a comprehensive spatial and temporal characterization of brain lesions?*
- *How to design planning and post-operative simulation algorithms and systems to assist cranio-maxillofacial and oral surgeons?*
- *How to effectively encompass anatomical and physiological variability for the understanding of musculo-skeletal diseases, the design of orthopaedic devices, and less-invasive, yet more effective orthopaedic surgical approaches?*

Computational Anatomy

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 2015 we used these techniques to evaluate the performance of cochlear electrodes, used to reestablish 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 prediction engines able to estimate, directly from the clinical images, mechanical and bone structural information in a fast and accurate way. During 2015 we developed 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), which also received an award at the IMIC workshop, Miccai 2015. Similarly, we developed segmentation and quantification algorithms for high-resolution micro-CT kidney scans employed for the design of modern image-based stereology techniques.

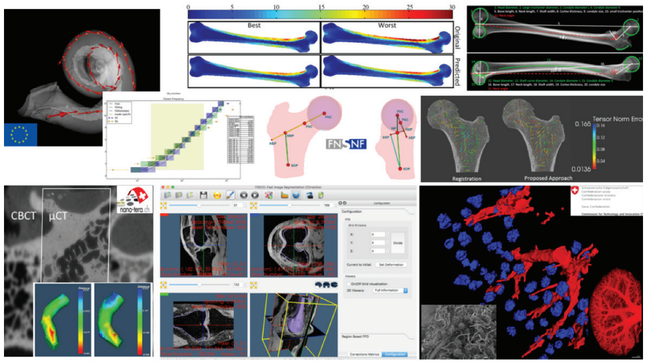

Fig.1 Modeling anatomical variability and its application to applications such as cochlear surgery, bone fracture prediction, Sarcopenia and characterization of organ complexity.

Oral and Cranio-Maxillofacial Surgery

Our group develops algorithms and systems to perform prediction of soft-tissue deformations after cranio-maxillofacial surgery. The algorithms have been developed with a strong emphasis on its clinical usability (i.e. compliance to imaging protocol, computation speed and usability). The simulation framework features high accuracy by incorporating non-homogeneous and anisotropic tissue properties as well as sliding contact considerations. During 2015 we focused on developing a dedicated software for soft tissue simulation in CMF interventions, termed Sotirios MxFx (Soft Tissue Reconstruction for Intra-Operative Simulation - Maxillofacial). Through a multicenter study, the software is currently being evaluated.

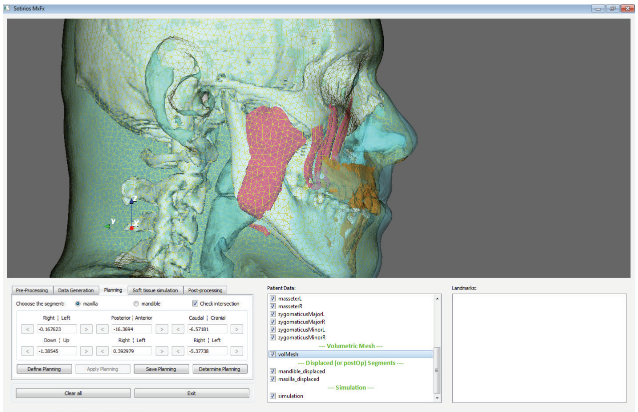

Fig.2 Sotirios MxFx Software: "Soft Tissue Reconstruction for IntraOperative Simulation - Maxilofacial". Sotirios enables a fast and accurate simulation of postoperative skin deformation for CMF surgery.

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 sequences, 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 2015 we performed clinical evaluations of our software BraTumIA (Brain Tumor Image Analysis), and tested it on longitudinal set-ups and for neurosurgical procedures. We developed algorithms to deal as well with low-grade gliomas and multiple sclerosis. In collaboration with our partners at the Institute of Diagnostic and Interventional Neuroradiology, we further extended initial developments started in 2014 for the segmentation of acute ischemic stroke lesions, which led to a first prize at the ISLES segmentation challenge, Miccai 2015.

In collaboration with the Dana Farber Cancer Institute in Boston, we compared the association of tumor sub-compartment volumes generated by BraTumIA with volumes generated by manual segmentations. We found automatically generated volumes are equally prognostic as manual ones, suggesting their use as a prognostic biomarker. The findings from this work support the use of automated tools, needed to overcome the heavy load of manual tumor volumetry, and to effectively leverage the understanding of glioblastomas, and design new prognostic biomarkers in high-throughput data analyses.

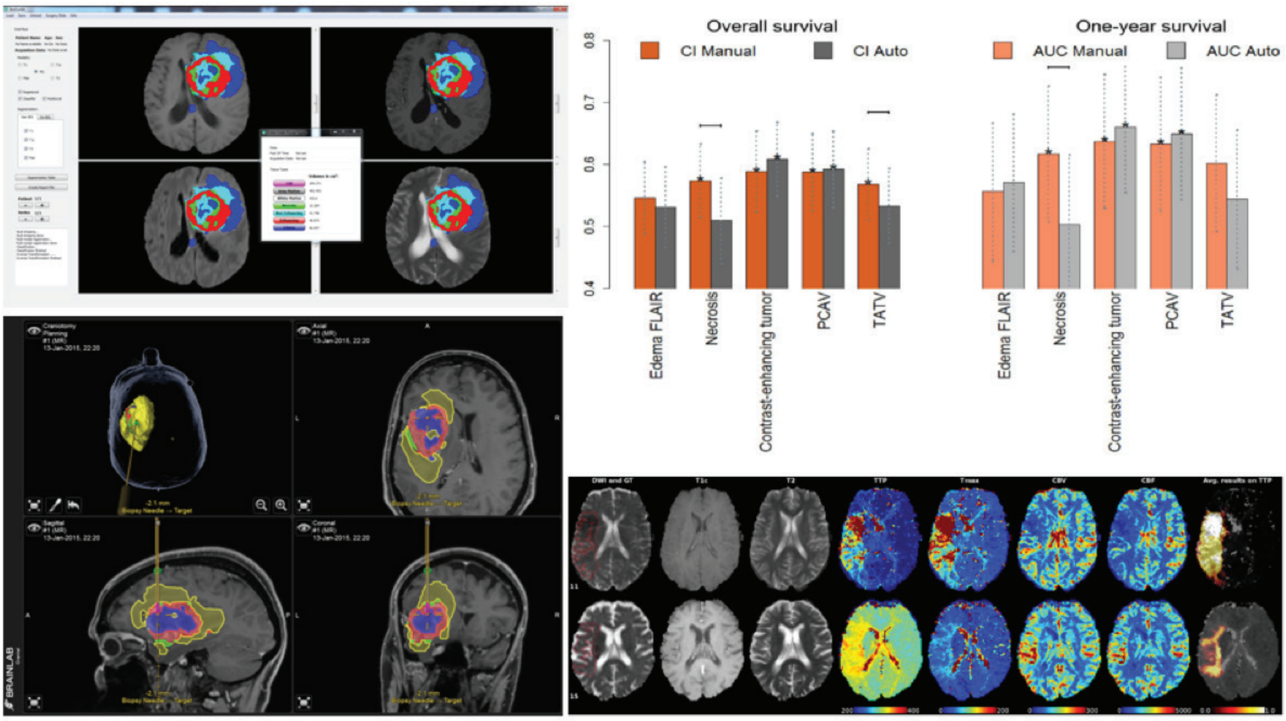

Figure 3. Brain image lesion analysis. Top row: Main interface of the BraTumIA software (left) for multimodal automatic image segmentation of high-grade gliomas. Towards automated tumor volumetry biomarkers for patient survival (right). Bottom row: Integrating BraTumIA segmentation results for neurosurgical procedures (left). Automated ischemic stroke lesion segmentation: functional and structural imaging for segmentation of penumbra and infarct core.

Selected Publications

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2. Cerrolaza J.J., Reyes M., Summers R.M., González-Ballester M.A., and Linguraru M.G. Automatic multi-resolution shape modeling of multi-organ structures. Medical Image Analysis, 25(1):11–21, April 2015.
3. Chappuis V., Engel O., Shahim K., Reyes M., Katsaros C., and Buser D. Soft tissue alterations in esthetic post-extraction sites: A 3-dimensional analysis. Journal of Dental Research, 94(9 suppl):187S–193S, 2015.
4. Rios-Velazquez E., Meier R., Dunn W., Alexander B., Wiest R., Bauer S., Gutmann D., Reyes M., and Aerts H. Fully automatic GBM segmentation in the TCGA-GBM dataset: Prognosis and correlation with vasari features. Nature Scientific Reports, 5:16822, 2015.
5. Chandran V., Zysset P., and Reyes M. Prediction of trabecular bone anisotropy from quantitative computed tomography using supervised learning and a novel morphometric feature descriptor. In Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015, Lecture Notes in Computer Science, pp 621-628, October 2015.

Musculoskeletal Biomechanics

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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.

Multi-scale bone mechanics

Extensive mechanical testing of human compact bone samples is performed in compression, tension and torsion with an emphasis on the coupling of damage between the various overloading modes. The overall morphology of such samples is investigated with microCT and 2D histomorphometry with a special attention to the cement lines. At a lower scale, micro- and nanoindentation provides the elastic and some dissipative properties of the bone extracellular matrix. Finally, composition of bone is quantified with Raman spectroscopy. The obtained data allow to explore the relationships between composition, microscopic properties and the macroscopic properties relevant for patients as a function of age. The use of nanoCT allows extension of the above paradigm to the morphology of microcracks produced in various loading modes.

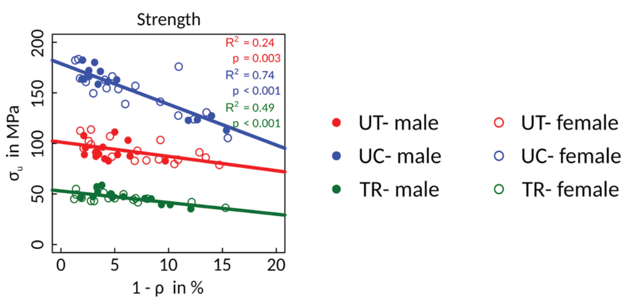

Figure 1. The most important determinant of compact bone strength in uniaxial tension (UT), compression (UC) and torsion (TR) is porosity and the relationships are similar for females and males.

Computational bone modeling

A nonlocal constitutive model of bone, reducing the sensitivity of our FE analyses to mesh size, is continuously developed. The model's ability to identify regions of bone damage was tested against experimental stepwise loading data of human trabecular bone biopsies and vertebral sections. It was then applied to simulate the fracture patterns of two spine segments loaded via intervertebral disks up to large compression. The predicted fracture patterns matched the experimental ones fairly well. An improved FE methodology was further validated against experimental compression tests of twenty-four human most distal radius sections with unprecedented accuracy. The validated methodology is being implemented into commercial software to help assess the strength of the distal radius within a few minutes and with higher accuracy compared to the current densitometric standards. This represents a further step towards in silico diagnosis of osteoporosis.

Bone drilling (NanoTera, HearRestore)

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). This was confirmed in an in vivo sheep study in which the dependence of bone density on the temperature elevation of the drilling process was investigated. A temperature prediction model was developed to assess the risk of a minimally invasive robotic cochlear surgery. The latest research focuses on optimizing the process parameters (feed movement and irrigation) and improving the drill bit design. A comparison of a standard and a newly designed drill bit revealed a significantly decreased risk of tissue damage due to the optimized geometry. Further research includes the investigation of the thermal conductivity of cortical and cancellous bone samples using

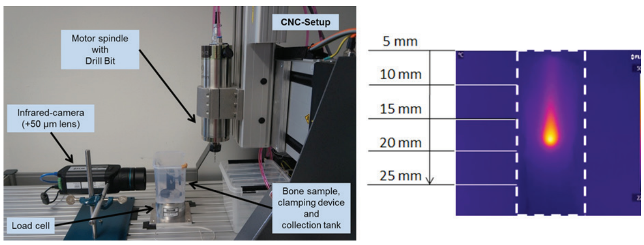

Figure 2. Left: Experimental setup to measure the force, torque and temperature elevation of the drilling process in bone; Right: The high resolution thermal camera enables the investigation of process parameters and drill bit design on tissue damage.

a custom steady state experimental setup and corresponding finite element models.

Finite element analysis of the human intervertebral disc (SNF grant 147153)

Focus of this research area is to provide a functional diagnostic tool for early assessment of degenerative intervertebral disc disease. Similar to previously developed CT-based Finite Element Method (FEM) models of bone, MRI-based FEM models of soft tissues, specifically the intervertebral disc, are developed. Animal discs are scanned in a clinical MR scanner, the image data is segmented, converted into FEM models and analyzed using appropriate constitutive laws. The same discs are measured on a custom-designed spine testing system. Five loading cases (flexion, extension, lateral bending, axial rotation and compression) are applied in the experimental as well as in the numerical environment. The experimental data is used to calibrate and validate the numerical model. Our current aim is to improve the disc model by including a more realistic collagen fiber distribution.

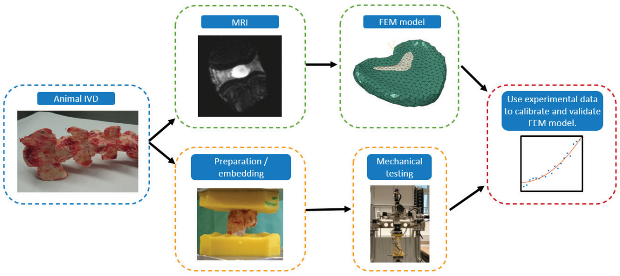

Figure 3. Framework for a MRI-based FEM model of an intervertebral disc.

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

Apparent multiaxial yield properties of trabecular bone represent an important input for homogenized nonlinear finite element (FE) analysis of the proximal femur. These properties can be assessed in silico by using microFE analysis on cubical trabecular volume elements. Nevertheless, the influence of the boundary conditions (BCs) on the obtained yield properties remains unknown. Our work compares the homogenized yield properties of human femoral trabecular bone obtained by applying classical kinematic uniform BCs

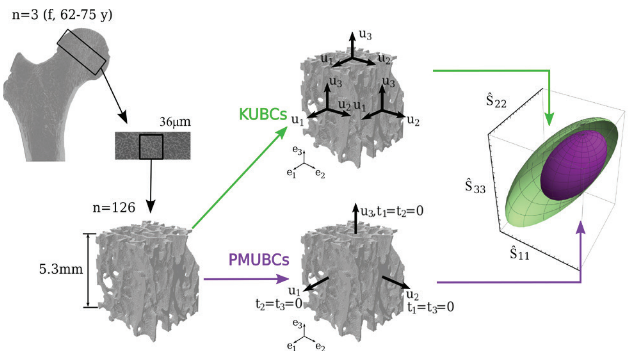

Figure 4. Nonlinear FE analysis of cubic femoral trabecular bone specimens. Comparison of the obtained yield surfaces for KUBCs and PMUBCs in stress space.

(KUBCs) and periodicity-compatible mixed uniform BCs (PMUBCs). Seventeen loading cases were applied on 126 biopsies to obtain yield stresses in all directions of the 6D stress space. PMUBCs lead to remarkably lower yield stresses compared to KUBCs. These two BCs will be compared with in situ BCs and their impact on homogenized FE will be evaluated at the whole bone level.

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 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. The project is supported by the Gebert Rüf foundation and is in early stages. However, 28 cadavers have already been scanned with soft and hard tissue protocols to evaluate the robustness of our simulations. Meanwhile, research has been conducted to determine which parameters are most relevant for modelling the elastic and yield behaviors of bone and worth accounting for in our simulations.

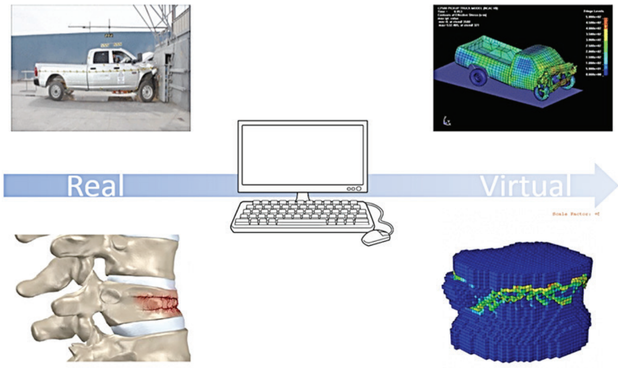

Figure 5. CT Recycling: a virtual crash test of a patient’s bone.

Biomechanical testing

Biomechanical experiments were performed for industrial contract research, clinical projects and internal research. For instance, immediate loading of dental implants after surgery is a growing trend because of the decreased costs and burden for the patient. In order to decide on immediate loading, primary stability of the implant should be assessed. In a project with a dental implant manufacturer, primary stability at the trabecular bone-implant compound was investigated with cyclic tests in compression according to novel biomechanical testing standards. In collaboration with the Department of Reconstructive Dentistry & Gerodontology, School of Dental Medicine, University of Bern, the influence of the zirconia and titanium abutment on the stiffness, strength and failure modes of monolithic crowns was assessed.

Selected Publications

1. Maquer Ghislain, Khadri Sarah, Wandel Jasmin, Gross Thomas and Zysset Philippe, “Bone volume fraction and fabric anisotropy are better determinants of trabecular bone stiffness than other morphological variables”, J Bone Miner Res 30(6):1000-1008, 2015.
2. Mirzaali Mohammad, Schwiedrzik Jakob, Bürki Alexander, Zysset Philippe and Wolfram Uwe “Continuum damage interactions between tension, compression, and shear in osteonal bone”, J Mech Behav Biomed Mater, 49:355-369, 2015.
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4. Schwiedrzik Jakob and Zysset Philippe, “Quantitative analysis of imprint shape and its relation to mechanical properties measured by microindentation in bone”, J Biomech 48:210-216, 2015.
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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 delayed or the non-healing of ACL following injury (or rupture). The common focus of the TOM group is to advance *in vitro* organ culture models, which mimics as closely as possible the human situation and where regenerative therapeutic strategies, such as novel biomaterials and cells, can be tested in a most authentic *in vitro* set-up.

Intervertebral Disc Degeneration, Regeneration and Low Back Pain

The TOM group conducted research in the field of IVD research in the area of regeneration but also in the area of non-successful spinal fusion to understand the development of pseudo-arthrosis.

The group presented new research in two main directions (i.e. improve fusion or rescue/improve the disc cell phenotype) using *ex vivo* bioreactor research at the Biospine 5 Meeting, which took place in Berlin in April 2015. The main research foci of the group are understanding the balance between BMP agony and antagony and how IVD can be regenerated using BMP signaling. For this we use a combination of 3D tissue/organ culture approaches.

Furthermore, the TOM group received the best poster award at the International Society of the Study of the Lumbar Spine (ISSLS) meeting in San Francisco (8-12 June) on BMP signaling and possible involvement of BMP antagonists in the secretome of IVD cells. Current research is ongoing to identify the main proteins involved in the secretome and in this important signaling pathway.

In a Gebert Rüf financed project, a novel type of silk material is currently being investigated for IVD repair (Figures 1 and 2).

Here, the TOM group started to investigate into new growth-factor-enriched silk, which is produced from genetically transducted silk worms (*Bombyx mori*), which covalently link 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 (Figure 3 is NPPC). Here, D. Frauchiger won the best poster award at the annual meeting of the Swiss Society for Biomaterials and Regenerative Medicine in Lausanne. The TOM group advanced further into the understanding of complex forces such as compression and torsion onto IVD cells in situ in organ culture. In a Swiss National Science Foundation project, we investigated towards the understanding of duration of mechanical loading for IVD cells. We investigated the effect of compressive loading (8h per day) on the IVD cells apoptosis. The group developed a strong *ex vivo* model using bovine IVD organ culture. This model has been used to explore fast and reliable models for disc degeneration using non-clinical relevant enzymes such as papain.

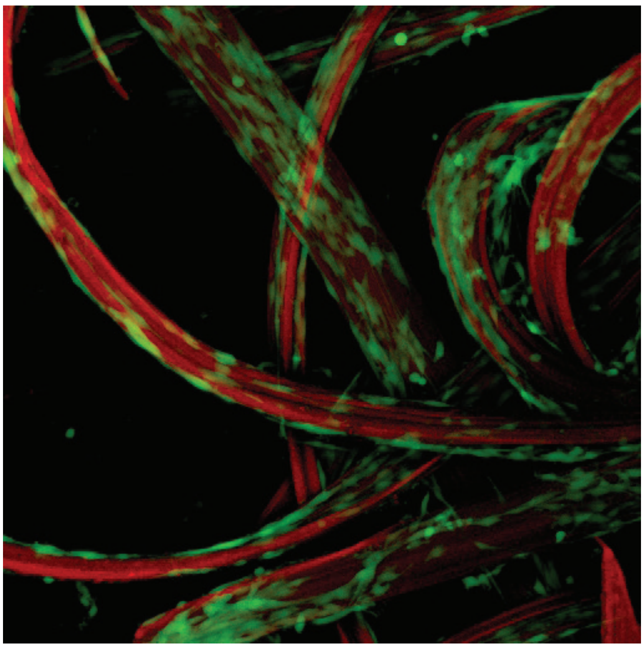

Figure 1. Z-projections of ~500 µm thick confocal laser scanning microscopy scans into GMP-compliant silk fleece with bovine intervertebral cells (annulus fibrosus cells). Cells were seeded onto 5x5mm^2 scaffold area and kept in culture for 4 days. Annulus fibrosus cells were stained with calcein-AM (green) and silk auto-fluorescences in the red wavelength range.

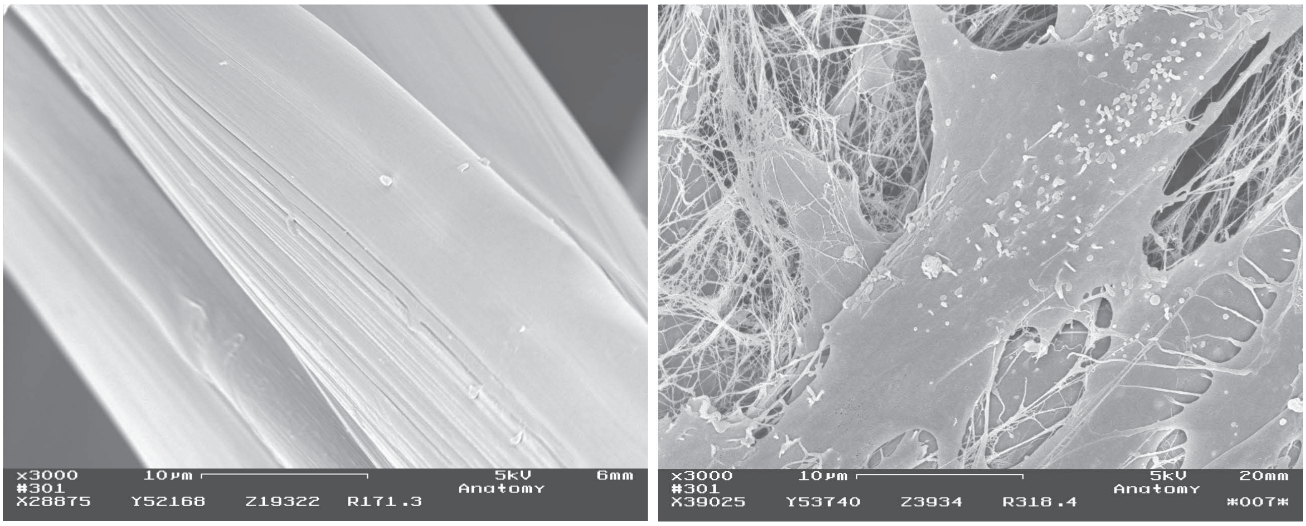

Figure 2. Scanning electron microscopy images of genetically engineered silk fibers (left) and seeded with human mesenchymal stem cells (hMSC) for 7 days (right) at 3000x magnification. The silk is obtained from *Bombyx mori* and is designed such that a growth factor known to drive hMSC towards a disc like phenotype is incorporated into the silk. Currently the silk is tested in our lab in cell culture and on bovine IVDs in organ culture to assess its suitability for disc regeneration and repair.

Finally, our group investigated in the nature of nucleus pulpous progenitor cells (NPPC). We concentrated on the presence of NPPC in bovine tail disc, their differential capacity (Figure 3) and their application potential for IVD regeneration..

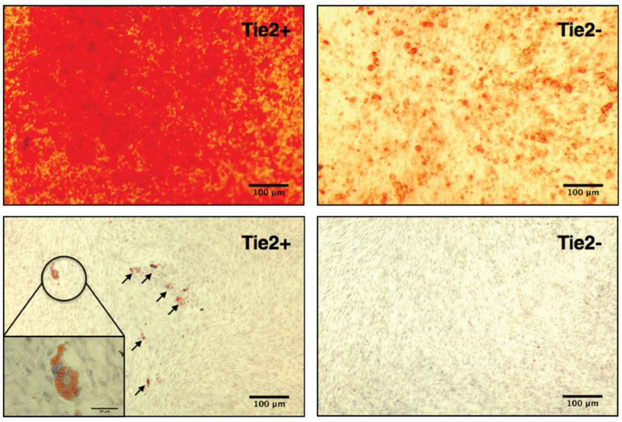

Figure 3. Bovine coccygeal-derived nucleus pulposus cells were isolated and sorted for the angiopoietin-1 receptor (Tie2). The obtained Tie2- and Tie2+ subpopulation of cells were subjected to differentiation assays *in vitro* to address their multipotency potential. After 3 weeks of culture, Tie2+ cells deposited an extensive mineralized matrix suggesting their osteogenesis, in contrast to Tie2- cells (top row). Similarly, only Tie2+ were able to differentiate into adipocytes and form lipid droplets as highlighted by arrows (bottom row).

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 this study 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.

Selected Publications

1. Chan SC, Tekari A, Benneker LM, Heini PF, Gantenbein B (2015) Osteogenic differentiation of bone marrow stromal cells is hindered by the presence of intervertebral disc cells. Arthritis Res Ther 18(1):29. doi: 10.1186/s13075-015-0900-2
2. Chan SC, Walser J, Ferguson SJ, Gantenbein B (2015) Duration-dependent influence of dynamic torsion on the intervertebral disc: an intact disc organ culture study. Eur Spine J : doi: 10.1007/s00586-015-4140-6
3. Gantenbein B, Gadhari N, Chan SCW, Kohl S, Ahmad S (2015) Mesenchymal stem cells and collagen patches for anterior cruciate ligament repair. World J Stem Cells 7(2):537-550 doi: 10.4252/wjsc.v7.i2.537
4. Gantenbein B, Illien-Jünger S, Chan SC, Walser J, Haglund L, Ferguson SJ, Iatridis JC, Grad S (2015) Organ Culture Bioreactors - Platforms to Study Human Intervertebral Disc Degeneration and Regenerative Therapy. Curr Stem Cell Res Ther 10(4):339-352
5. Frauchiger DA, Chan SCW, Benneker LM, Gantenbein B (2015) Repair of annulus fibrosus with genipin enhanced fibrin hydrogel and silk membrane fleece. European Spine Journal 24(3):624-660 doi: 10.1007/s00586-015-3794-4
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7. May R, Frauchiger DA, Gazdhar A, Geiser T, Benneker LM, Gantenbein B (2015) Non-Viral Gene Delivery of Growth and Differentiation Factor 6 (GDF6) to whole bovine Intervertebral Disc. European Spine Journal 24(3):624-660 doi: 10.1007/s00586-015-3794-4
8. Tekari A, Chan SCW, Wuertz K, Saikai D, Benneker LM, Grad S, Gantenbein B (2015) Tie2+ cells of the bovine Nucleus Pulposus are Progenitor Cells capable of differentiating into Osteocytes and Adipocytes. Global Spine J 05(A127): doi: 10.1055/s-0035-1554231
9. Evangelopoulos DS, Kohl S, Schwienbacher S, Gantenbein B, Exadaktylos A, Ahmad SS (2015) Collagen application reduces complication rates of mid-substance ACL tears treated with dynamic intraligamentary stabilization. Knee Surg Sports Traumatol Arthrosc doi: 10.1007/s00167-015-3838-7

Mechanical Design and Production

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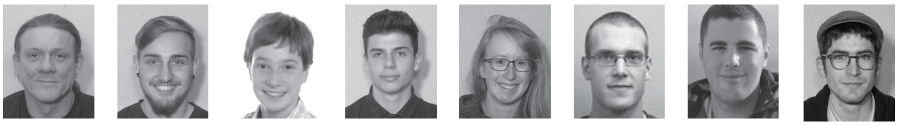


Urs Rohrer · Lukas Rufener · Julien Meister · Fabio Spena · Meret Ruch · Ronald Ramseier · Danaël Gasser · Christoph Flühmann

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.
Julien Meister was employed as a polytechnician's apprentice until the end of January, 2015. Unfortunately, he decided to give up his apprenticeship, as he couldn't find enough satisfaction working as a polytechnician. This gave him the chance to reorientate himself and he finally got an apprenticeship as an automation engineer in the industry. For the vacant position we employed Fabio Spena as a new apprentice. In August 2015 he officially started his polytechnician's apprenticeship.
To further strengthen our team we employed Meret Ruch in part-time as a polytechnician. But since she changed her career plans, she is now working again in full-time in the industry since March 2015.
Because of the increased workload, we further searched for additional staff. Thus, Christoph Flühmann joined out team in August 2015. But due to professional reasons he decided to leave our team by the end of 2015. During his employment, he was mainly responsible to introduce the CAD-CAM technology to Lukas. We would like to take the opportunity to thank him for his commitment.
We wish all the best for the future to our three former co-workers.

Research Equipment Design & Manufacturing ISTB

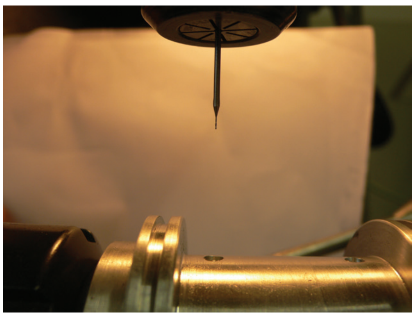
As expected, the requirements of a machine shop supporting research in the biomedical engineering field are as diverse as the research field itself. The variety of subjects researched in the ISTB yield a number of diverse design and production requests from prototype clinical and surgical tooling to 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.

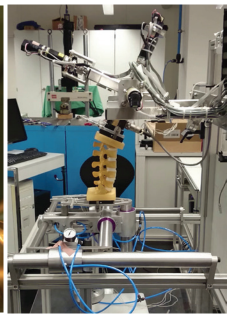
Project: Dental implant testing

Within this project we have compared different embedding materials for testing dental implants. In order to apply load to the implants at different angles, Benjamin Voumard has constructed a special appliance. For the generation of the different specimen, a custom-made casting device was manufactured. This device comprises two components, controlling the orientation of the specimen and the position of the dental implants.

Project: Conversion of the Spine-testing-machine

The spine-testing machine was originally designed by Philippe Gédet and manufactured by the MPD in 2006. Its primary functionality was based on a linear guidance system comprising linear ball bearing. But due to its inherent friction, smallest forces and motions could not be reproduced. Therefore, Alexander Bürki constructed a friction-free air suspension of all three axes. The construction of the bearing parts was a very demanding task. Thereby, the drilling of holes with a diameter of 0.2 mm has been the greatest challenge.





Project: Medium Bad

In close cooperation with one of our research partners we have produced 9 new fluid baths. Our major task was the optimization of the various parts in terms of shape and dimension. Especially the application of a different, more highly alloyed steel grade posed a special challenge to us. The previously produced fluid baths had been made out of lower alloyed steel. However, the lower alloyed steel started to oxidize, when being exposed to the saline solution. The oxidation resulted in an increased contamination of the testing facility, which consequently had to be cleaned more often. Besides the change of steel grade, a special surface treatment finally solved this problem.

Research Equipment Design & Manufacturing ARTORG

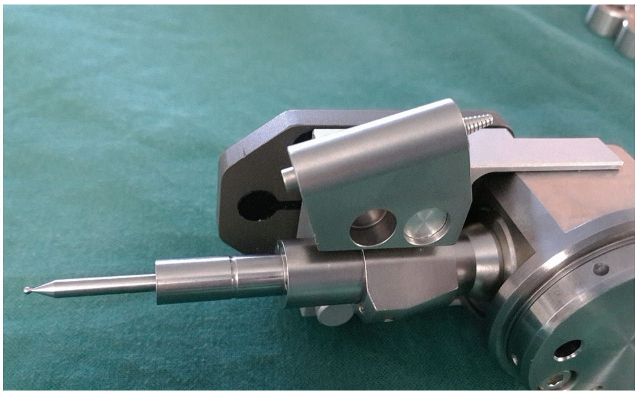
The workshop at the ARTORG Center was managed part time by Ronald Ramseier, and this year the machine shop at the ARTORG Center manufactured some different project-parts, for the IGT, Cardiovascular Engineering- and Computational Bioengineering Group.

To support the Cardiovascular Engineering Group Danaël Gasser was integrated into the group as a Polymechaniker until end of June 2015. His function was it to design parts of devices himself and to manufacture these parts afterwards in the machine shop. He will be employed full time as a Polymechanic from January 2016 on.

The ARTORG workshop pursues many of the same aims as the MDP group at the ISTB. The partnership between the two groups is growing and will be strengthened in the coming years. Some highlights of this year projects is shown in the following illustrations.

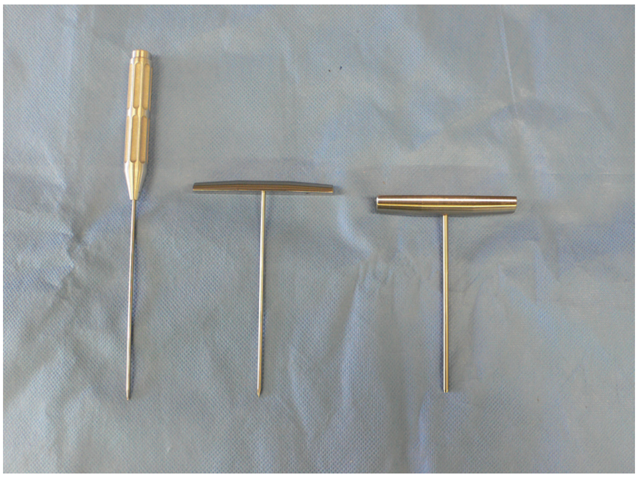
Project: Cochlea Robot

Within the scope of this project different modifications and improvements were done. For instance, the milling head has been equipped with a water irrigation system. The arrangement ensures a cooling of the milling head and an unrestricted flow of the chips. Moreover, we have further revised the camera mounting and manufactured a new patient marker frame out of titan to minimize X-ray artefacts.



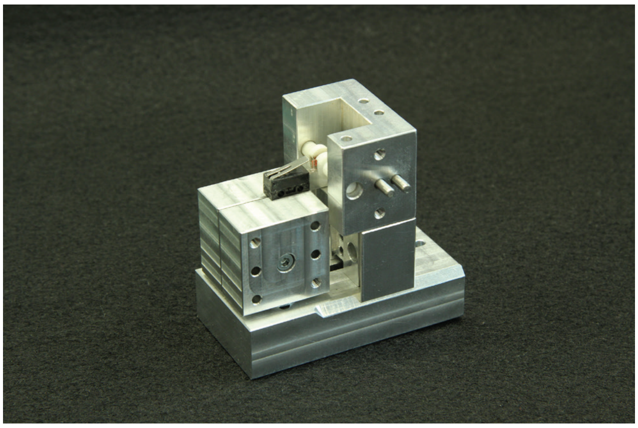
Project: neurosurgery toolset

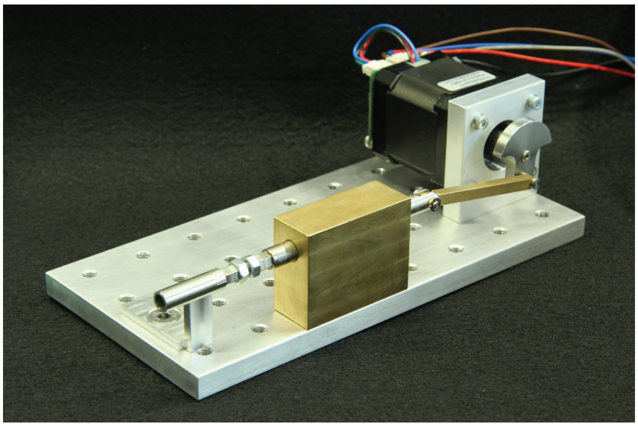
In order to screw in fiducial screws into the bone under sterile conditions, the MDP had previously developed (in 2012), in collaboration with the department for neurosurgery at the Inselspital, a special toolset. Since then, additional applications have been identified. Thus, we have further improved the tools and adapted them to the particular area of application.



Project: Cardio

This project deals with various concepts of energy generation for tight spaces. Two prototype systems have been designed and manufactured. Even though these prototypes are composed of rather simple parts, the requirements in terms of precision and minimum tolerances are extremely high.





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COMPLETED DISSERTATIONS

Benjamin Schweizer

“Advanced Intracranial Electrode Localization using Multimodal CT and MR Imaging”. June 2015.

AWARDS & PRIZES

Award Nomination “Young Scientist Publication Impact Award” Medical Image Computing and Computer Assisted Interventions.
Awardee: **Stefan Bauer.**

Award at Interactive Medical Image Computing Workshop, Miccai 2015.
Awardee: **Waldo Valenzuela.**

First prize ISLES (Ischemic Stroke Lesion Segmentation) Challenge, Miccai 2015.
Awardee: **Richard McKinley.**

Best Poster Award: "Nucleus pulposus Cells inhibit Osteogenesis of Mesenchymal Stem Cells." Proceedings of the 42nd Congress of the International Society of the Study of the Lumbar spine (ISSLS), 8-12 June, 2015, Special emphasis poster. San Francisco, CA.
Awardees: **Chan SCW, Tekari A, Benneker LM, Heini P, Gantenbein B.**

Best Poster Award: "Annulus Fibrosus Repair with the help of a novel Silk membrane-fleece and Genipin-enhanced Fibrin Hydrogel". 21st Swiss Conference on Biomaterials and Regenerative Medicine (SSBRM). June, 2015, Lausanne, CH.
Awardees: **Frauchiger DA, Chan SC, Benneker LM, Gantenbein B.**

Travel Award: "Nucleus pulposus contain progenitor-like cells able to differentiate into osteogenic and adipogenic lineages *in vitro*". 21st Swiss Conference on Biomaterials and Regenerative Medicine (SSBRM). 2015, Lausanne, CH.
Awardee: **Adel Tekari.**