Summer-Workshop
Mechanics in Biology

JULIUS WOLFF INSTITUT

Berlin, September 16th to 17th 2013

About the Workshop

In a two-day workshop, we will address the aspects of mechanical properties of cells and tissues as well as the impact of mechanical signals on cellular processes from nano to macro scale. Focus will be given to aspects of biological tissue mechanics, tissue adaptation to loading, the role of mechanics in the organization of cells and extracellular matrix, as well as pathologic changes.

Guest Speakers

Georg Duda (Julius Wolff Institute)

Peter Fratzl (Max-Planck Institute of Colloids and Interface)

Patric Garcia (Universitätsklinikum Münster)

Robert Harten (DePuy Synthes)

Kay Raum (Julius Wolff Institute)

Robert L. Sah (University of California)

Ulrich Schwarz (Ruprecht-Karls-Universität Heidelberg)

Joachim P. Spatz (Max Planck Institute for Intelligent Systems)

Bert van Rietbergen (Eindhoven University of Technology)

Viola Vogel (ETH Zürich)

Hands on Session

BOSE Corporation

JPK Instruments AG

Julius Wolff Institute

Venue

Charité – Campus Virchow-Klinikum
Julius Wolff Institute
Institutsgebäude Süd
Föhrer Straße 15 in 13353 Berlin

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Time schedule

Monday, 16th September 2013

08:30 am	**Georg Duda** Julius Wolff Institute, Germany	Welcome
08:35 am	**Bert van Rietbergen** Eindhoven University of Technology, The Netherlands	Biomechanics and mechanical signals on the tissue level (I)
09:15 am	**Joachim P. Spatz** Max Planck Institute for Intelligent Systems, Germany	Structural and mechanical characterization of cells and cell-ECM interactions
09:55 am	**Patric Garcia** Universitätsklinikum Münster, Germany	Biological and technical materials and their functional limitations from a clinical perspective
10:35 am	*Coffee break*	
10:50 am	**Georg Duda** Julius Wolff Institute, Germany	Tissue formation and adaptation during bone healing – the influence of mechanics and biologics
11:30 am	**Viola Vogel** ETH Zürich, Switzerland	How the extracellular mechanical microenvironment impacts the cellular response and cell fate decisions
12:10 pm	*Lunch break*	
01:30 pm	**Poster Session**	
02:30 pm to 05:30 pm	**Hands on session I** Introduction into measurement and stimulation techniques	02:30 pm **BOSE Corporation** Multi-axial loading and characterization of biological tissue and tissue engineered constructs 04:00 pm **JPK Instruments AG** Atomic Force Microscopy, measurement of cellular properties and interactions
07:00 pm onwards	**Social gathering**	Ampelmann Restaurant Stadtbahnbogen 159 in 10178 Berlin

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Time schedule

Tuesday, 17th September 2013

08:30 am	**Robert L. Sah** University of California, USA	Mechanical blueprints for functional tissue engineering
09:10 am	**Ulrich Schwarz** Ruprecht-Karls-Universität Heidelberg, Germany	Physical principles of cell mechanics and cellular forces
09:50 am	**Kay Raum** Julius Wolff Institute, Germany	Tissue structure and elastic properties – from the nansoscale to the macroscale
10:30 am	*Coffee break*	
10:50 am	**Robert Harten** DePuy Synthes	Biomechanics and mechanical signals on the tissue level (II)
11:30 am	**Peter Fratzl** Max Planck Institute of Colloids and Interfaces, Germany	Hierarchical organization of bone – the link between cell-, ECM-, and tissue mechanics
12:10 pm	*Lunch break*	
01:30 pm	**Poster Session**	
02:30 pm to 05:30 pm	**Hands on sessions II** Application of measurement and stimulation techniques (parallel sessions)	The role of mechanics in tissue organogenesis, -adaptation and -regeneration. Mechanical characterization of soft and mineralized biological material, mechanical loading of tissue and tissue-engineered constructs.

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Hands on sessions

BOSE Corporation	• Introduction of basic mechanical principles • Categorization of materials (poro-/visco-/elastic) • Introduction of the technical equipment • Hands on measurements for material characterization of biological material • Discussion of testing results	BOSE Electroforce 3200 Series
JPK Instruments AG	• Cell and ECM mechanical properties - the basis for tissue functionality • Material characterization on the nano- and microscale. • Introduction into the AFM technique • Hands on measurements for characterization of cell and tissue properties • Discussion of results	CellHesion® 200 NanoWizard® 3 Atomic Force Microscope
Julius Wolff Institute + Laboratoire d'Imagerie Paramétrique , Université Paris 6	• Imaging of soft and mineralized tissue organization and mechanical characterization via ultrasound • Mechanical stimulation of cells in vitro (ultrasound and bioreactors) • Introduction into setups and devices • Hands on experiments and discussion of data evaluation	Scanning Acoustic Microscopy Ultrasound Palpation Resonant Ultrasound Spectroscopy Bioreactors

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Abstracts of lectures

Biomechanics and mechanical signals on the tissue level (I)
Bert van Rietbergen (Eindhoven University of Technology)

It is well know that bone can adapt its density and its microstructure to changes in external mechanical loading, a phenomenon generally referred to as Wolff's law. According to this law, bone would be added to high loaded locations and removed at low loaded locations. It is still not well understood though, how bone can achieve this task, nor is it known to what extent bones are actually optimized for this load carrying task.

Over the last decades, computational models have been developed that can represent the actual bone microarchitecture in detail. Such models have provided new insights in the mechanical signals at the bone tissue level and the 'optimality' of the bone structure. Also during the last decades, hypothetical bone remodelling models based on Wolff's law have been developed that can simulate the process of bone remodelling at the level of the tissue. Such models have provided new insight in the formation and adaptation of trabecular architectures and the role of bone cells therein, and made it possible to predict microstructural changes due to changes in loading or cell activity.

In this presentation, an overview of the state-of-the-art insights in the role of mechanical signals in the formation and adaptation of bone is given. It will be shown that local loading conditions can explain the seemingly optimized organization of bone tissue, in agreement with Wolff's law. It will also be shown that this form-function relationship can be used in an inverse way: to calculate the external loading history a bone was subjected to from its microstructure. Finally, it will be shown that, by combining such techniques with clinical images of bone structure measured in-vivo, it is possible to identify to what extent the bone microstructure is actually optimized for mechanical loading, and to what extent the adaptation of bone microstructure may be predictable.

Structural and mechanical characterization of cells and cell-ECM interactions
Joachim P. Spatz (Max Planck Institute for Intelligent Systems)

No abstract available

Biological and technical materials and their functional limitations from a clinical perspective
Patric Garcia (Universitätsklinikum Münster)

No abstract available

Tissue formation and adaptation during bone healing – the influence of mechanics and biologics
Georg Duda (Julius Wolff Institute)

Bone is a unique and highly regenerative tissue in vertebrates. Unlike to most injuries that lead to fibrotic scar formation and incomplete restoration of the tissue structure and function, bone healing restores pre-fracture properties under optimal conditions. Thus, a scarless repair of structures such as after fracture is possible leading the path to unravel mechanism of true regeneration. Consequently, the investigation of bone regeneration has significant impact on our understanding of how such processes of regeneration are driven and how it is affected by risk factors such as aging. An understanding of the underlying mechanisms and processes might serve as blue-print to other organ systems where regeneration appears even more challenging.

The formation of callus tissue - as intermediate material to reconstitute the body's own structure and function - proved to be mechano-responsive in both, the type and the amount of tissue formed. Demanding mechanical conditions such as in instable fracture fixations lead to a delay of bone bridging, a prolonged cartilaginous phase of endochondral ossification, a reduced and delayed angiogenesis and a prolonged inflammatory phase. All of the relevant cascades of bone healing and formation are directly influenced by mechanical means.

Abstracts of lectures

The way tissues are formed, the way they mature and aspects of their re-organization are directly influenced by mechanical constrains. Even though the general nature of mechano-sensitivity are widely known, details of their interplay and specially how the mechano-sensitivity at the various length scales from macroscopic mechanics to sub-cellular signaling are yet not fully understood.

Further, the process of bone healing seems to recapitulate aspects of the embryonic skeletal tissue formation and development. It is yet unclear if the processes of formation and repair are indeed similar. To what degree the key-regulator, the mechano-sensitivity, remains constant with time and across processes such as development, maintenance and regeneration is also relatively unknown. Using mesenchymal stromal (or stem) cells (MSCs) as a key element of regenerative capacity, studies from our and other groups in humans and animals have demonstrated an age dependent regeneration potential that seems to decline with increasing age. The reduced mechano-sensitivity of one of the key-elements of regeneration – mesenchymal stroma cells - combined with a shift in material characteristics and change in tissue straining in aged species compared to their younger counterparts illustrates the importance to characterize mechano-senstivity of biological systems not as static and somehow stable systems but as adaptive systems with changing capacities in all stages of aging.

Mechano-biology seems to be apparently a central aspect of the phases of bone healing and regeneration; it plays a key role in maintenance and seems to be also important in early developmental phases. A further understanding of the underlying mechanism of the link between biology and mechanics and their direct interactions at the various lengths scales and across aging seems to be essential to understand healing cascades, their interaction and limitations in healing in clinically demanding situations. This understanding is mandatory to allow effective stimulation of regenerative cascades even under compromised healing conditions.

How the extracellular mechanical microenvironment impacts the cellular response and cell fate decisions
Viola Vogel (ETH Zürich)

Investigations of the mechanisms how the extracellular microenvironment directs cell fate and tissue repair has gained major momentum only very recently. While it is well recognized that fibrosis is the most typical tissue response of the body to biomedical implants, little is known how to effectively prevent it. We will discuss new insights into the mechanisms how cells recognize implant surfaces and how this directs their ability to assemble and remodel extracellular matrix. Since rigidity and topography sensing is crucial for tissue formation and homeostasis, we will further discuss some fundamental processes that cells exploit to sense the physical properties of their environments. Insights how environmental factors direct cell fate are urgently needed to advance (stem) cell-based regenerative therapies

Mechanical blueprints for functional tissue engineering
Robert L. Sah (University of California)

No abstract available

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Abstracts of lectures

Physical principles of cell mechanics and cellular forces
Ulrich Schwarz (Ruprecht-Karls-Universität Heidelberg)

During the last decade, it has become increasingly clear that the response of tissue cells to the physical and biochemical properties of their environment is strongly linked to their ability to generate and sense forces at cell-matrix adhesion sites. Because the systems of interest are very complex, mathematical models can help to identify essential processes and to provide deeper insight. First we will discuss experimental techniques to measure cellular forces. In particular, we will discuss traction force microscopy on soft elastic substrates, which can be used to dissect the force generating processes inside cells. We then will discuss the relation between cellular forces and cell shape, which leads to deeper insight into the specific material properties of cells. In particular, we will introduce the notion of actively contracting cable networks as a powerful modelling framework to understand the mechanics, forces and shape of cells. Finally we will contrast the mechanical properties and traction patterns of single cells to the ones of cell monolayers, which show surprising similarities, but also some marked differences. We conclude that momentum conservation and the specific properties of force generation by actomyosin contraction are the two most important physical processes for the mechanobiology of animal tissue cells, both on the cell and on the tissue level.

Tissue structure and elastic properties – from the nansoscale to the macroscale
Kay Raum (Julius Wolff Institute)

Several ultrasound techniques have been developed during the last decade with the intention to assess elastic properties of soft and hard biological tissues and cells. The basic measurement principles can be divided into bulk and guided wave transmission, focused sound reflection and backscatter measurements and resonance spectroscopy. This lecture will be divided into three sections: The first part covers the physical principles, technological developments to potentials and limitations of these principles. The second part will focus on quantitative multi-scale imaging elastic properties of hard tissues and their applications in bone research (e.g. elastic phenotyping, fracture repair, and numerical modeling). In the last part, several technologies for soft tissue and cell characterization and acoustic live cell imaging will be demonstrated.

Biomechanics and mechanical signals on the tissue level (II)
Robert Harten (DePuy Synthes)

No abstract available

Hierarchical organization of bone – the link between cell-, ECM-, and tissue mechanics
Peter Fratzl (Max Planck Institute of Colloids and Interfaces)

Bone is a hierarchically structured dynamic tissue, continuously undergoing processes of remodeling, during which the local characteristics of organic tissue and mineral particles are changing. During the growth of new tissue, bone forming osteoblasts get embedded in the bone matrix becoming osteocytes, which are the most frequent cell type in mammalian bone. The situation is even more complex during bone healing where callus tissue is laid down, matures and eventually gets resorbed or remodeled into bone. The mechanical answer to loading depends on bone structure at all levels of hierarchy. As a consequence of this complexity, the relation between bone composition/structure and fracture incidence is poorly understood. To help answering such questions in relation to bone development, osteoporosis as well as bone regeneration, it is important study structure and composition of bone tissue at all scales, in relation to cell activity and mechanical behavior of the same tissue. The presentation will review recent advances in our understanding of bone tissues based on multi-modal imaging techniques combined with mechanical testing.

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Curricula vitae of lecturers

Georg Duda

Prof. Dr. Georg Duda, born in 1966 in Berlin, received a degree in Precision Engineering and Biomedical Engineering from the Technical University in Berlin. After working as a Special Project Associate in the Biomechanics Lab at the Mayo Clinic (USA) in 1991 and 1992, he became a Ph.D. student in the Biomechanics Department of the Technical University in Hamburg-Harburg where he received his Doctorate in 1996. He was also engaged as a Post Doc in the Section Trauma Research and Biomechanics at the University Ulm. In 1997 he became Head of the research department at the Center for Musculoskeletal Surgery (CMSC) at the Charité. In 2001 he habilitated and accepted a call to a Professorship in „Biomechanics and biology of bone healing". Prof. Duda is vice-director of the Berlin-Brandenburg Center for Regenerative Therapies and vice-chairman of the Center for Sports Science and Sports Medicine Berlin (CSSB) since 2006. He is also the speaker of the DFG-Graduate School GSC 203 Berlin-Brandenburg School for Regenerative Therapies and since 2008 director of the Julius Wolff Institute.

Contact: Charité – Universitätsmedizin Berlin, Julius Wolff Institute, Augustenburger Platz 1, Institutsgebäude Süd, 13353 Berlin, Germany

Peter Fratzl

Peter Fratzl is director at the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany, and honorary professor at Humboldt University Berlin and Potsdam University. He holds an engineering degree from Ecole Polytechnique in Paris, France, and a doctorate in Physics from the University of Vienna, Austria. His scientific interests include the relation between structure and mechanical behaviour of biological and bio-inspired composite materials, including biomaterials systems for mechanosensing and actuation. He also conducts research on osteoporosis and bone regeneration and has published more than 400 research papers. Peter Fratzl is Fellow of the Austrian Academy of Sciences and of the Materials Research Society. He holds an honorary doctorate of University Montpellier and is recipient of the Leibniz Prize from the German Science Foundation.

Contact: Max-Planck Institute of Colloids and Interfaces, Department of Biomaterials, 14424 Potsdam, Germany

Patric Garcia

PD Dr. Patric Garcia was born in 1977 in Zweibrücken, Germany. He studied medicine at the University of Saarland and graduated in 2005. He completed his clinical education for orthopaedic and trauma Surgery at the Department for Trauma, Hand and Reconstructive Surgery at the University of Saarland, Germany (Director: Prof. Dr. T. Pohlemann). At the Institute for Experimental Surgery, University of Saarland, Germany (Director: Prof. Dr. M. Menger) he developed several experimental models to study fracture healing in mice. In 2012, he presented his habilitation treatise with the title: „Fracture healing and non-union formation in mice: model development, pathophysiology and novel treatment strategies". Since July 2012, he is working as a consultant at the Department for Trauma, Hand and Reconstructive Surgery at the University Hospital Muenster, Germany. His clinical interests are the treatment of critical fractures and non-unions with a special focus on bone substitutes and biomaterials.

Contact: Universitätsklinikum Münster, Klinik für Unfall-, Hand- und Wiederherstellungschirurgie, Waldeyerstraße 1, 48149 Münster, Germany

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Curricula vitae of lecturers

Kay Raum

Kay Raum graduated from Martin-Luther-University of Halle-Wittenberg with the diploma and Ph.D. degrees in physics in 1997 and 2002, respectively. From 1995 to 1996 he was with the Bioacoustics Research Laboratory at the University of Illinois at Urbana-Champaign as a Visiting Scholar. From 1997 until 2003 he was a research assistant at the Medical Faculty of the Martin Luther University. In 2004 he received a post-doctoral fellowship from the French National Center of Scientific Research (CNRS) and joined the Laboratoire d'Imagerie Paramétrique at University Pierre et Marie Curie, Paris VI, France. In 2006 he became the Research Head of the Interdisciplinary Center for Musculoskeletal Diseases and in 2008 he received his Habilitation in "Experimental Orthopedics" at the Medical Faculty of the Martin Luther University. In 2008 he received his Habilitation in "Experimental Orthopedics" at the same faculty. Since 2008 he is a Professor of Engineering, Berlin-Brandenburg School for Regenerative Therapies (DFG GSC 203), and Head of the Ultrasound Biomicroscopy group of the Julius Wolff Institute at Charité - Universitätsmedizin Berlin. He is the German coordinator of the European Associated Laboratory "Ultrasound Based Assessment of Bone" and a member of the IEEE, the IEEE Ultrasonics Society, and the VDE. He has been working with high frequency ultrasound for more than 15 years, and he has contributed specifically to the establishment and validation of quantitative acoustic microscopy in bone research. His current research is focused on the development of innovative parametric imaging techniques and their application in musculoskeletal research.

Contact: Charité – Universitätsmedizin Berlin, Berlin-Brandenburg School for Regenerative Therapies, Augustenburger Platz 1, Institutsgebäude Süd, 13353 Berlin, Germany

Ulrich Schwarz

Prof. Dr. Ulrich Schwarz studied physics at Freiburg, Baltimore and Munich. After a PhD on modelling the phase behaviour of water-lipid mixtures at the Max Planck Institute of Colloids and Interfaces at Potsdam, in 1998 he moved to the Weizmann Institute in Israel to work as a Minerva postdoctoral fellow with Prof. Samuel Safran at the Department for Materials and Interfaces. He quickly became interested in the central role that the physical properties of soft matter material play for the functioning of biological systems. In particular, he started to work on modelling the role of elasticity for cell adhesion, in close collaboration with different experimental groups. From 2000-2007 he headed an Emmy Noether junior research group, first at the Max Planck Institute of Colloids and Interfaces at Potsdam and then at the Center for Modelling and Simulation (BIOMS) at Heidelberg. In 2008, he was appointed professor for theoretical biophysics at the Karlsruhe Institute of Technology (KIT). In 2009, he became the chair for the physics of complex systems at the Institute for Theoretical Physics (ITP) at Heidelberg University. At Heidelberg, he is also member of the Faculty for Life Sciences, of the cluster of excellence CellNetworks, and of the Interdisciplinary Center for Scientific Computing (IWR). From 2011-2013 he was speaker of the division for Biological Physics (BP) of the German Physical Society (DPG). He also serves as editor for BMC Biophysics and New Journal of Physics.

Contact: Ruprecht-Karls-Universität Heidelberg, Institute for Theoretical Physics, Philosophenweg 19, 69120 Heidelberg, Germany

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Curricula vitae of lecturers

Bert van Rietbergen

Dr. Bert van Rietbergen is an associate professor in the Faculty of Biomedical Engineering of the Eindhoven University of Technology. He received his M.S. in mechanical engineering from the same university in 1988. After graduation, he was appointed at the Orthopaedic Research Lab of the University of Nijmegen, The Netherlands, where he received his PhD (cum laude) in 1996. In 1997 he was appointed as a post-doc researcher at the Institute of Biomedical Engineering of the ETH in Zürich. In 1999 he moved back to the Eindhoven University of Technology to be appointed at the newly formed department of Biomedical Engineering. His research is aimed at the evaluation of bone structural and mechanical properties for the study of bone strength, in particular in order to improve the diagnosis of osteoporosis. During his Ph.D period he has developed a new computational approach for mechanical analysis of bone structures from high-resolution images. This approach, called the micro- finite element approach, has become a well-accepted tool for the evaluation of bone mechanical properties, also in clinical studies. Apart from the diagnosis, he is also interested in developing methods for the prognosis of bone strength. For this he is developing bone remodelling simulation models that can predict changes in bone architecture as a result of changes in cell activity and physical activity. Bert van Rietbergen also acts as a consultant for Scanco Medical AG and occasionally for pharmaceutical and other industries.

Contact: Eindhoven University of Technology, Mechanical Engineering Materials Technology, PO Box 513, GEM-Z 4.118, 5600 MB Eindhoven, The Netherlands

Viola Vogel

Viola Vogel is a Professor in the Department Health Sciences and Technology (D-HEST), heading the Laboratory of Applied Mechanobiology at the ETH Zurich. After completing her graduate research at the Max-Planck Institute for Biophysical Chemistry, she received her PhD in Physics at the Johann-Wolfgang Goethe University in Frankfurt/Main, followed by two years as a postdoctoral fellow at the University of California Berkeley, Department of Physics where she applied nonlinear optical techniques to analyze fluid interfaces. She became an Assistant Professor in Bioengineering at the University of Washington/ Seattle in 1991, with an Adjunct appointment in Physics. She launched a new program in Molecular Bioengineering, and was later promoted to Associate (1997) and Full Professor (2002). She was the Founding Director of the Center for Nanotechnology at the University of Washington (1997-2003), and moved to the ETH in 2004.

Her work has been internationally recognized by multiple awards (including Otto-Hahn Medal; NIH FIRST Award; Philip Morris Foundation Research Award; Julius Springer Prize 2006 for Applied Physics; ERC Advanced Grant (2008), major lectureships (including the Lacey Lectureship at CalTech (2007), the Timoshenko Lectures at Stanford University (2011), the International Solvay Chair in Chemistry Brussels (2012), an Honorary Doctorate from the University of Tampere Finland (2012), and services for International Organizations (US Representative on the Council of Scientists of the Human Frontier Science Program), as well as jury duties for the European Research Council, the British Marshall Fund, the Humboldt Foundation, the National Research Council (USA); NASA, NIH, NSF, DOE and the German Government (BMBF). She was also a member of the Gordon Research Conferences Selection and Scheduling Committee and of the PCAST subpanel that finalized the National Nanotech Initiative (White House). She currently serves on several scientific advisory boards, including the Wyss Institute at Harvard, the Max-Planck Institute for Colloids and Interfaces (Golm), the Institute of Bioengineering and Nanotechnology (Biopolis Singapore), the Nano-Initiative-Munich (DFG Excellence Cluster), CeNIDE Duisburg-Essen, and is a Member of the Hochschulrat (Board of Regents) at Ludwig-Maximilians-Universität München.

Contact: ETH Zürich, Laboratory of Applied Mechanobiology, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland

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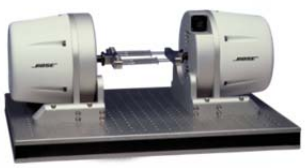

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About JPK Instruments AG

JPK Instruments AG is a world leading manufacturer of nanoanalytic instruments that enable unparalleled access at the nanotechnology level. The product portfolio is based around atomic force microscopes and optical tweezers for a wide range of applications, from soft matter physics to nano-optics, from surface chemistry to cellular and molecular biology. Leading-edge instruments from JPK are used by the most renowned research institutes across the world. Headquartered in Berlin and with operations in Dresden, Cambridge (UK), Singapore, Tokyo (Japan) and Paris (France), JPK maintains a global network of distributors and support centers and provides on the spot applications and service support to an ever-growing community of researchers.

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Contact

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Julius Wolff Institute

About the institute

The Julius Wolff Institute is a research institute of the Charité – Universitätsmedizin Berlin and integral part of the CharitéCenter 09 for Traumatology and Reconstructive Surgery. Its main research field is the regeneration and biomechanics of the musculoskeletal system as well as the improvement of joint replacement. Various scientific methods and laboratories, amongst others imaging methods, biomechanical testing, electronic instrumentation of implants, motion analysis, histology, immuncytology, molecular biology and a cell biology are available.

The Julius Wolff Institute which is named after Julius Wolff (1836 - 1902), the so called father of orthopaedics, brings together national and international scientists from different areas of musculoskeletal research, i.a. medicine, biology, chemistry, physics and engineering sciences. Through various scientific and personal links to international research institutions, the institute enables a regular exchange of information and experiences with scientists worldwide.

Scanning Acoustic Microscopy - SAM

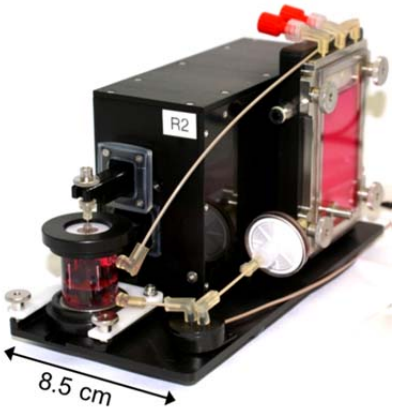
This technology measures the linear elastic response of soft and hard tissues and cells non-invasively and contact-free by scanning a highly focused acoustic beam over the sample. The interaction volume is scalable from the centimeter to the microcometer range by adjusting the acoustic excitation frequency. SAM provides large scale elastic images with micrometer resolution.

Ultrasound Palpation – USPalp

The Ultrasound Palpation device measures articular cartilage thickness and stiffness is situ by handheld palpation of the cartilage layer and real time recording of applied stress and strain. The software controls strain rate, contact and compliance during the measurement. Furthermore, it allows an easy adaptation of the measurement range to other soft tissue samples by changing the probe tip.

Bioreactor for mechanical stimulation and analysis

A bioreactor system for monoaxial stimulation and mechanical characterization of cell-loaded constructs is available in the Julius Wolff Institute for research purposes.



The design of the in-house developed bioreactor was motivated by the idea to mimic the situation during bone healing in an established sheep osteotomy model by an in vitro system. The system allows the application of various compression and load patterns to 3D constructs mimicking the fracture hematoma or soft callus. This happens in a closed environment under dynamic cultivation (medium circulation) and control of cell culture parameters like oxygen and pH. As a special feature, the mechanical properties of cell seeded constructs can be measured in situ and monitored online over the time of cultivation. This allows analyzing the impact of cellular behavior and newly formed extracellular matrix on the macroscopic mechanical properties of the “microtissue” or investigating the synergistic influence of mechanical and biochemical signals on cell function. By implementing the gas exchange into the medium reservoir and by utilizing gas mixing devices, specific environments (e.g. hypoxia) can be realized. Additionally the individual bioreactors units can be run in any temperature controlled environment and outside of CO2 incubators.

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Laboratoire d'Imagerie Paramétrique

About the lab

The "Laboratoire d'Imagerie Paramétrique" (LIP UMR 7623) is located at the "Centre de Recherches Biomédicales des Cordeliers (UPMC Paris)". Its research activity is focused on biomedical applications of ultrasound with an emphasis on: methods to characterize bones, high-frequencies ultrasound imaging (small animals), functionalized imaging, and the characterization of biological and biomimetic nanosize systems.

Resonant Ultrasound Spectroscopy – RUS

Resonant ultrasound spectroscopy is an accurate and efficient method to characterize the viscoelastic properties of isotropic or anisotropic solid materials. The full stiffness tensor is assessed from the resonant frequencies of a freely vibrating small sample (a few millimeters), while viscoelastic damping is inferred from the resonance peaks width. The method is available for low damping materials (crystals or metals) and high damping materials (bone, tooth, rocks, ...).

Effects of cyclic tensile strain on mRNA levels of extracellular matrix proteins in chondrocytes

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Introduction: Mechanical loading is a key factor for proper assembly and maintenance of the cartilage extracellular matrix (ECM). The ECM proteins COMP (cartilage oligomeric matrix protein), matrilin-3 and collagen IX provide matrix stability by binding to collagen II and to each other [1; 2]. It is not completely understood if and how their expression levels are affected by mechanical loading. In an in vitro experiment with primary murine chondrocytes we tested the hypothesis if moderate mechanical loading alters the mRNA levels of COMP, matrilin-3, collagen IX, and collagen II.

Methods: Murine chondrocytes were cultivated on collagen I coated culture plates with deformable membranes. Cells were exposed to 6 % cyclic tensile strain at 0.5 Hz for 30 min on 3 consecutive days (Flexcell Tension Plus; Flexcell Corp. Mc Keespot, USA). Control cells were cultivated identically but did not undergo mechanical loading. mRNA was isolated at 7 time points (0, 0.5, 1, 2, 4, 8, 24 hours) after the last loading session. Expression levels of COMP, matrilin-3, collagen IX, and collagen II mRNA were determined by semi-quantitative reverse transcriptase polymerase chain reaction. GAPDH served as control gene. In addition, 24 after loading cell layers were analyzed using immunofluorescence staining.

Results: Increased COMP mRNA levels were detected already after 0.5 hours and 2 hours in loaded cells. However, 8 hours after loading the levels decreased even below these of unloaded cells. Interestingly, no changes were detected in the mRNA expression levels of collagen IX, matrilin-3 or collagen II at any time point. Immunofluorescence staining demonstrated an increased diameter of COMP positive fibrils 24 hours after loading.

Conclusion: We show that COMP is a mechanosensitive gene and that its expression is regulated by cyclic tensile strain. This suggests that COMP plays a role in providing mechanical stability of the cartilage matrix. This function is not shared by other ECM proteins as their expression remained unaffected even though it cannot be excluded that other loading protocols would induce changes.

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Size-Dependent Mechanical Properties of Single Polyurethane Nanofibres

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Electrospinning is a versatile technique for processing polymers in solution into dense, non-woven fibrous networks comprising random or aligned fibres. These micro-porous structures are promising candidates for use in tissue engineering applications where there is a desire to emulate the fibrous nature of the extracellular matrix. While the bulk and surface properties of the scaffold may be optimized for a particular application, the relationship between the mechanical properties of individual fibres from which these porous scaffolds are made and the bulk properties of the structure as a whole, is poorly understood. The aim of this study was to investigate the elastic properties of individual fibres at magnitudes of strain comparable to those exerted by mammalian cells. Two medical-grade balloon catheter materials (b9 'A' series thermoplastic polyetherurethanes, Biomer Technology, Runcorn, UK) were either cast directly into glass Petri dishes or electrospun from solution (13.1 and 14.7 % w/w, respectively, in N, N dimethyl acetamide) onto the surface of polycarbonate filters having pores 5 µm in diameter. Suspended fibres were located and the modulus of elasticity determined by applying forces in the range of 3nN - 5nN to isolated fibres in three-point bending using an atomic force microscope (Asylum Research MFP-3D, Bicester, UK). The bulk properties of cast films were significantly different in terms of elastic modulus. While this observation was borne out for the measurements made on isolated fibres made from each polymer, the difference became more marked with decrease in fibre diameter: the modulus of elasticity increased exponentially, from 20 MPa for Z1A1 fibres greater than 450nm, to more than 100 MPa for those less than 300 nm in diameter.

We conclude that small changes in fibre diameter may have disproportionate impact on cell-material interactions within fibrous scaffolds. Variation in the elastic modulus of fibres with different diameters, as shown in this research, highlights the need for close monitoring of fibre diameters when fabricating artificial scaffolds for use in Tissue Engineering and Regenerative Medicine. In applications where scaffolds of varying stiffness are to be constructed from the same or differing material, this phenomenon may be exploited by tailoring the fibre dimensions to illicit the desired cellular responses in order to satisfy the functional requirements of the engineered tissue.

Ultrasound-based thickness measurement during a fully-automated stress-relaxation test on cartilage-bone constructs

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Introduction: Non-destructive, ultrasound-based thickness measurement of cartilage-bone constructs has been described in the literature for several years [1,2,3]. For articular cartilage two basic measurement methods exist that differ in using a sensor that is in contact with the target or not.

Material and Methods: In this study an ultrasonic sensor with contact to the surface of the specimen was used (ovine osteochondral cylinders, n=5, Ø=10 mm from the medial femur condyle). The device was integrated into a universal testing system that carried out a stress-relaxation experiment on two compression levels. As soon as the equilibrium level in the force channel has been reached, an ultrasonic speed of sound measurement was arranged by using a 15 MHz sensor. With the equations published by Suh et al. (2001) [4], the cartilage thickness was determined.

Results: The augmentation of the mechanical test by ultrasound-based thickness measurement has been realized successfully. For each specimen an individual sound velocity at around 1600 m/s (2.70% accuracy) and cartilage thickness between 1.05 and 2.32 mm was determined (4.16% accuracy) using compression rates of 5 and 10%.

Discussion: With the integration of the non-invasive cartilage thickness measurement into a fully-automated test procedure more loading protocols can be studied. The determination of individual sound velocities also opens the field for measurements on arthritic cartilage, to gain more information about osteoarthritis.

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Mechanical properties of collagen-I scaffolds investigated by AFM measurements

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Interactions between cells and substrates in the extracellular matrix (ECM) play an important role for the physiological cell behavior, e.g. adhesion, morphology and cell differentiation. Tissue engineering scaffolds may be used as a model system of the ECMs in nearly all tissues and organs. The interplay between cells and the ECM are investigated with this model system accordingly. Mechanical properties of macroporous collagen-I scaffolds were investigated at the nanoscale by atomic force microscopy (AFM) nanoindentation measurements. Cryocuts of collagen-I scaffolds placed on a glass wafer were measured at different temperatures with AFM scanning and forcemapping methods (Figure 1). These nanoscale mechanical properties were directly compared with the macroscopic properties measured by mechanical compression of the whole scaffold, which are already published in [1].

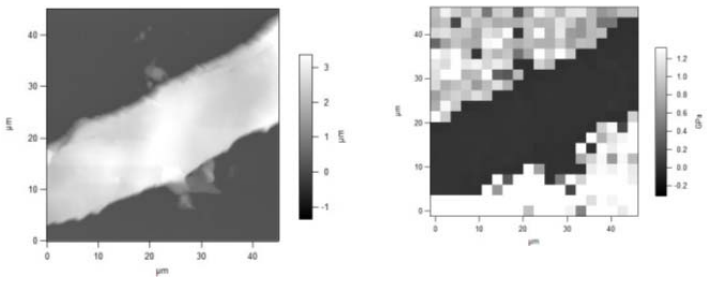

Figure 1:
a) Height profile and
b) elasticity profile of a collagen-I scaffold cryocut measured by 30 °C in a PBS buffer solution.

References:
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Assessing bone quality during fracture healing in the ovariectomized (OVX) rat model of osteoporosis

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Introduction: Osteoporosis predisposes individuals to be more susceptible to fractures and contributes to delayed or impaired bone healing [1]. In such instances of fracture non-unions, the healing process could be augmented by the addition of potent anabolic agents, such as bone grafts or growth factors, and anti-catabolic agents such as bisphosphonates [2-3]. In this study, our aim is to characterize the quality of bone formed during fracture healing in ovariectomized rats when subjected to specific treatments.

Methods: Five treatments were considered: i. Saline, ii. Autograft, iii. the growth factor BMP-7, iv. Autograft + the bisphosphonate Zoledronate (ZO) and v. BMP-7 + ZO. From a pool of 94 female Sprague-Dawley rats, 48 rats underwent ovariectomy at 12 weeks of age, while the remaining 46 rats acted as healthy controls. The rats were randomly allocated to one of the five treatment groups. Mid-diaphyseal fractures were introduced at 24 weeks of age in the right femur and fixed with an intramedullary wire [2-3]. Treatments were administered based on the group to which each rat was assigned. At 6 weeks post-op, the rats were sacrificed and the fractured femurs were harvested. Bone quality has so far been assessed by: i. X-rays, ii. microCT, iii. 3-point bending mechanical tests.

Results:

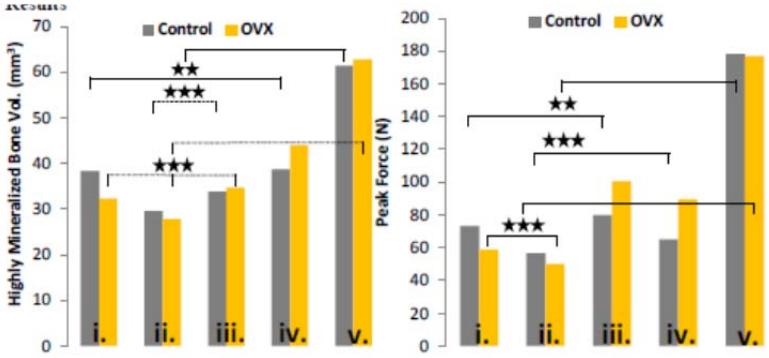

Figure 1. Left: Mineralized bone volume determined by microCT. Right: Peak force determined by mechanical 3-pt-bending. The treatment groups are: i. Saline, ii. Autograft, iii. BMP-7 iv. Autograft + ZO, v. BMP-7 + ZO. Statistical significance based on Mann-Whitney U test. ** p<0.01, *** p<0.001.

Significance: Preliminary results demonstrate that fracture repair in osteoporotic bone can he enhanced through the synergistic efficacy of the anabolic agent BMP-7 in conjunction with the anti-catabolic agent ZO (i.e. Group v.). Additional analysis is pending.

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Co-Culture Spheroids as at tool for angiogenic research

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Introduction: Rapid vascularization of tissue engineered grafts is still an enormous challenge. The 3D culture of relevant cell types reflects the *in vivo* situation better than 2D cell culture due to more intensive cell contacts. Spheroids as 3D cell constructs have been used in tumor research since decades and also increasingly in angiogenesis research during the last years.

We evaluated the performance of three techniques to generate co-culture spheroids consisting of human osteoblasts (HO), fibroblasts (HF) and endothelial cells (HEC) in terms of reproducibility and rate of yield. The size of the spheroids was determined *in vitro* and a method was established to evaluate the cellular arrangement within the spheroid. Spheroids were implanted in mice in order to analyze neovascularization and inosculation with the host's vasculature.

Materials & Methods: Three techniques (hanging drop (HDT), carboxy methyl cellulose (CCT), liquid overlay (LOT)) were used to generate 3D mono and co-culture spheroids (n= 6-10). Different cellular compositions were chosen over a wide range of cell numbers (500-100,000). The size of the spheroids was measured on day 1, 3 and 6 and the results were tested in terms of significance. The cellular distribution was observed on cryosections of spheroids generated with cells stained with living fluorescence dyes. Spheroids (50,000 cells) were implanted into the dorsal skinfold chamber of CD1 nu/nu mice. Inosculation of newly formed capillaries was checked by means of intravital fluorescence microscopy (IVM) after injection of 5% fluorescein isothiocyanate (FITC)-labeled dextran (150 kDa). After 2 weeks, the spheroids were explanted and paraffin sections were stained.

Results: The LOT was suitable to generate spheroids reproducibly with a high rate of yield. All seeded cells were organized in one spheroid with a very low standard deviation in size. The size of the spheroids, which decreased over time due to organizational processes, can easily be adjusted by varying the number of seeded cells. Staining of different cell types with living fluorescence dyes prior to the formation of the spheroids is a useful tool to study the cellular arrangement within the construct.

Conclusions: HO/HEC as well as HO/HEC/HF co-culture spheroids showed signs of neovascularization *in vivo*. Perfusion was detected by means of IVM on day 14 in 8 out of 66 spheroids. HE-stained sections of the explanted spheroids showed the presence of erythrocytes (HEC 8 out of 15, HO/HEC 16 out of 21, HO/HEC/HF 12 out of 24) localized in capillaries formed by human HEC as could be shown by means of immunohistochemical staining for the co-culture spheroids (4 out of 4).

The 3D co-culture of different cell types is a powerful tool to study angiogenic phenomena. Neovascularization is enhanced by co-cultivation of relevant cell types. Other cell types related to angiogenesis like pericytes, smooth muscle cells or stem cells will be included in this model.

The use of adipose derived stem/stromal cells and biocompatible matrices in regenerative medicine and tissue engineering

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Background: Adipose derived stem/stromal (ASCs) have a high regenerative potential. The combination of ASCs and biomaterials, such as collagen elastin matrices, is a promising approach in regenerative medicine and tissue engineering of soft tissue. However, the clinical and intra-operative feasibility of using biomaterials for ASC transplantation must be tested in advance.. The time span in which isolated ASCs adhere on scaffolds as well as ASCs isolation procedures and seeding conditions may affect clinical outcome significantly. Furthermore, for tissue engineering, isolation and culture conditions as well as the used biomaterials affect the character of the resulted tissue. Thus, in this study we used *in vitro* methods for testing ASCs adherence behaviour on biomaterials, demonstrating the practicability of an intraoperative cell transplantation using biomaterials as carrier.

Methods: After abdominal liposuction procedures (10 patients) using conventional Coleman cannula (3 mm, blunt tip). ASCs were isolated directly and transplanted onto collagen elastin matrices (Matriderm) without further culturing and passaging processes. The viability and adherence rate were tested after different incubation periods (1, 3 and 24 h) by alamarBlueTM assay. Furthermore, ASC adherence on the Matriderm matrices was visualized by two photon microscopy.

Results: The relative number of adhered ASCs on collagen elastin matrices was almost two-fold higher after 3 h incubation than after 1 h. A 24 h incubation period could increase the number of adhered cells 3-4 fold. An attachment of transplanted ASCs to the Matriderm matrix could be already demonstated after 1 hour of incubation by live cell two photon imaging.

Conclusion: Freshly isolated ASCs after liposuction procedure can be transplanted safely onto Matriderm matrices in short time without time demanding cell culture steps. Thus, this study suggests that in the time interval of a surgical procedure, e.g. treatment of burn patients, dermal substitutes such as Matriderm can be enriched successfully with potentially regenerative ASCs.

Nevertheless, it is necessary to optimize this approach for a clinical use. In particular, the type of ASC that adhere predominately to the matrix and the regenerative potential of an ASC-enriched matrix,and therefore the benefit for the patients have to be cleared in further studies. In addition, this approach may be useful for *in vitro* engineering of soft, bone, and other types of tissues.

An electro-mechanical bioreactor providing physiological cardiac stimuli

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In cardiac tissue engineering it has been widely demonstrated the fundamental role of physical stimuli in improving structural and functional properties of the engineered cardiac constructs [1,2]. An electro-mechanical bioreactor has been designed and developed to provide physiological uniaxial stretching and electrical stimuli for inducing functional differentiation and promoting morphological and structural maturation of cultured cardiac constructs obtained from stem cell-seeded scaffolds. The bioreactor (Fig. 1) is composed of: a transparent and sterilizable culture chamber for housing four cell-seeded scaffolds and the culture medium (working volume = 70 ml); a mechanical stimulation system, with a dedicated grasping system, to provide cyclic stretching (strain up to 20%, cycling frequency up to 2 Hz); an electrical stimulation system to provide electrical monophasic square pulses (1-6 V/cm, 0.25-10 ms, 1-5 Hz); a recirculation system for the automated medium change; a control system for data acquisition and mechanical stimulation.

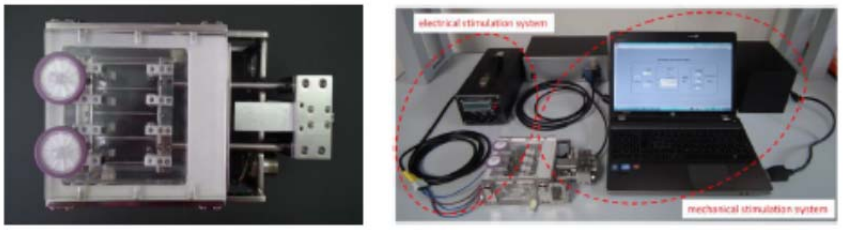

Figure 1. Top view of the bioreactor (left) and set-up of physical stimulation systems (right).

Preliminary in-house tests confirmed the suitability and the performances of the bioreactor as regards fittingness of chamber isolation, grasping system, and physical stimulation systems. Cell culture tests are in progress for investigating the influence of stretching and electrical stimuli on development of engineered cardiac constructs. Due to its high versatility, this bioreactor is a multipurpose adaptable system for dynamic culture of cell-seeded scaffolds for tissue engineering research and applications.

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Model-based Traction Force Microscopy as Novel Tool to Estimate the Intracellular Distribution of Tension

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Animal tissue cells use self-generated mechanical forces to probe the mechanical properties of the extracellular environment and to adapt to it. Therefore cells build up tension within the cytoskeleton and transmit resulting forces via adhesions to the substrate or to neighboring cells. A technique called *traction force microscopy* (TFM) has been implemented to successfully reconstruct traction patterns of single cells or monolayers of cells on planar soft elastic substrates [1, 2]. However, mathematical reconstruction of traction fields is an ill-posed problem, which makes correlations with the intracellular distribution of tension difficult. To achieve this aim, we developed a TFM approach that utilizes theoretical cell modeling to provide crucial missing information. In practice we estimate the distribution of intracellular tension from elastic substrate data by minimizing the difference to predictions of a detailed theoretical model based on active cable networks. Previously this type of model was successfully used to predict cell shapes on micropatterned substrates [3, 4]. In our study, we consider not only active network contraction, but also contributions of various types of contractile bundles modeled as contractile one-dimensional line element [5]. Subsequent computer simulations of network contraction and parameter optimization allows us to estimate the most likely distribution of tension over various contractile structures and focal adhesions. The simulations lead to comparable results as from studies with force sensitive fluorescent probes [6].

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Dermis mechanical behaviour: influence of cell removal treatment

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In the field of reconstructive plastic surgery, engineered skin substitutes can bring significant medical benefit, in particular to patients with extensive burn wounds, even if current skin substitutes do not restore normal skin anatomy and its natural mechanical properties. This work concerns the mechanical characterization of a particular layer of skin: dermis. Decellularized dermis can be used as a filling material and as support in different areas of reconstructive plastic surgery such as post mastectomy reconstructive surgery and abdominal surgery. The aim of the study was to investigate the influence of NaOH decellularization treatment duration on mechanical properties of human dermis collected from cadavers. The specimens were subjected to uniaxial static tests performed with Bose Electroforce® 3200 and experimental data were represented with engineering [1] and real time stress-strain curves [2]. Descriptive parameters were identified for stress vs. strain curves, such as ultimate tensile strength (UTS) and maximum Young's modulus (E), and subsequently they were compared through multivariate analysis of variance to determine the influence of specimen cut orientation and decellularization treatment duration. Dermis subjected to 5 or 6 weeks of decellularization treatment exhibited mechanical properties comparable with natural ones and ultimate tensile strength and maximum Young's modulus were shown to be considerably higher in real time curves than in engineering ones (Table 1).

Weeks		Untreated	T5	T6		Untreated	T5	T6
Engineering	UTS (MPa)	7,01 ±1,00	5,92 ±0,35	5,85 ±0,44	E (MPa)	12,31 ±1,27	15,07 ±0,69	9,44 ±0,85
Real time		24,11 ±3,24	21,17 ±2,24	21,62 ±0,74		75,41 ±2,74	77,19 ±9,99	62,29 ±9,02

Table 1: UTS and E values obtained for engineering and real time curves in function of the period of treatment for specimens cut along mediolateral direction.

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Correcting drift-impaired image alignment in combined atomic force and confocal microscopy

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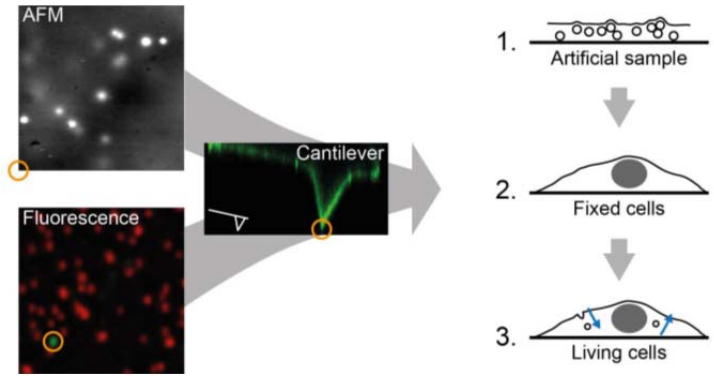
Combining the biological specificity of fluorescence microscopy with topographical features revealed by atomic force microscopy (AFM) provides new insights into cell biology. However, the lack of systematic alignment capabilities especially in scanning tip AFM has limited the application of combined fluorescence microscopy and AFM. Despite precise alignment procedures at experimental startup, drift leads to an increasing image mismatch over time. We present an alignment correction method using the cantilever tip as reference landmark. As the exact tip position is known in both, the fluorescence and AFM image, exact re-alignment becomes possible. We demonstrate the validity of the method in a complex, artificial sample using beads. Next, we expanded this method to biological samples depicting membrane structures in fixed as well as in living primary human fibroblasts. We were able to map nanoscale membrane structures such as clathrin-coated pits to the respective fluorescent spots. Reliable alignment between fluorescence signals and topographic structures opens possibilities to assess key biological processes at the cell surface such as endo- and exocytosis.



Light-triggered ionic crosslinking using caged Ca2+: alginates with photomodulated mechanical properties

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Biomaterials able to re-engineer the cellular microenvironment using cell-compatible and remotely actuated light sources promise great potential for dynamic guiding cell function during application. Here we present a strategy to photomodulate the mechanical properties of alginate hydrogels by incorporating a photosensitive Ca2+ cage (nitr-T) in the alginate formulation. Ca2+ cages are water-soluble chelators that bind Ca2+ with high affinity (*Kd* of several to hundreds nM). Upon light exposure, Ca2+ cages undergo an irreversible molecular change that significantly lowers their affinity for Ca2+ to the mM range. As a consequence, free Ca2+ is released to the medium. When incorporated in alginates, Ca2+ cages can mediate light-triggered ionic crosslinking. The crosslinking degree and derived mechanical properties of the hydrogel can be modulated by the exposure dose within physiological relevant ranges (1-100kPa). Our results open a way to generate responsive ionically crosslinked alginates with interesting properties for drug delivery and tissue engineering, as they allow active tuning of the swelling and mechanical properties of the scaffold during application and, therefore, active control over drug release or cell behaviour and tissue formation.

Numerical simulation of the strain environment of osteocytes

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Osteocytes (OCs), the most abundant bone cells are situated in the lacunarcanalicular network (LCN) and are believed to regulate bone remodeling guided by both biological and mechanical stimuli [1]. The in situ strain environment of OCs is to date not known and cannot be assessed experimentally. Numerical simulation has a great potential to provide insight into these details, but requires accurate input. Synchrotron X-ray phase nano-tomography (SR-PNT) [2] provides unprecedented geometrical details of the LCN. The aim of this study was to investigate the local deformation of OCs using finite element models incorporating the case specific, SRPNT-based LCN geometry. Each model included a single OC lacuna and the surrounding extracellular matrix. Geometries of the cell and the peri-cellular soft tissue were approximated based the LCN shape. Simplified material properties were used and the models were subjected to uniaxial compressive loading of 1‰ deformation, corresponding to the physiological *in vivo* mesoscopic bone matrix strain [3]. High strain concentrations of 3-4% were observed at the cell body–dendrite junctions, which suggest that the mesoscopic strain can be amplified by a factor up to 30-40 while reaching the cell. In a 2 µm vicinity of the lacuna, a substantial portion (30-60%) of the OC dendrite volume was deformed ten times more compared to the strain applied externally. Further strain concentrations of similar magnitude occurred along the dendrites. These strain magnitudes are in the order of what has been reported to induce cell activity *in vitro* [4]. These results contribute to the understanding of the strain magnification effect required to bridge the one order of magnitude gap between the strain magnitudes available in bones on the mesoscale in physiological activities and the ones required to stimulate OCs.

Cartilage mechanics on the nanoscale

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The joints in our body are highly effective and adapt very quickly to changes in load and moving direction. These features come from the very unique properties of articular cartilage. It is an impact damping, load-bearing and wear resistant material. It provides a smooth sliding with low friction at speeds from slow walking till fast running.

By now the mechanics on the nano- and microscale of this biologic tissue are not fully understood. To tackle this problem an atomic force microscope (AFM) is used to characterize the mechanical properties of cartilage by surface imaging and friction force microscopy (FFM). For FFM, a cantilever with a colloid instead of a sharp tip is used. To acquire absolute forces the cantilever is directly calibrated with a magnetic spring. The setup also allows the control of environmental conditions such as the surrounding fluid and temperature.

We investigate the effects of different lubricants on the frictional properties of lamb cartilage. We also compare the surface topography of hydrated, dehydrated and rehydrated samples. In addition we will determine the critical components of cartilage by digesting selected cartilage components and checking their influence on the mechanics.

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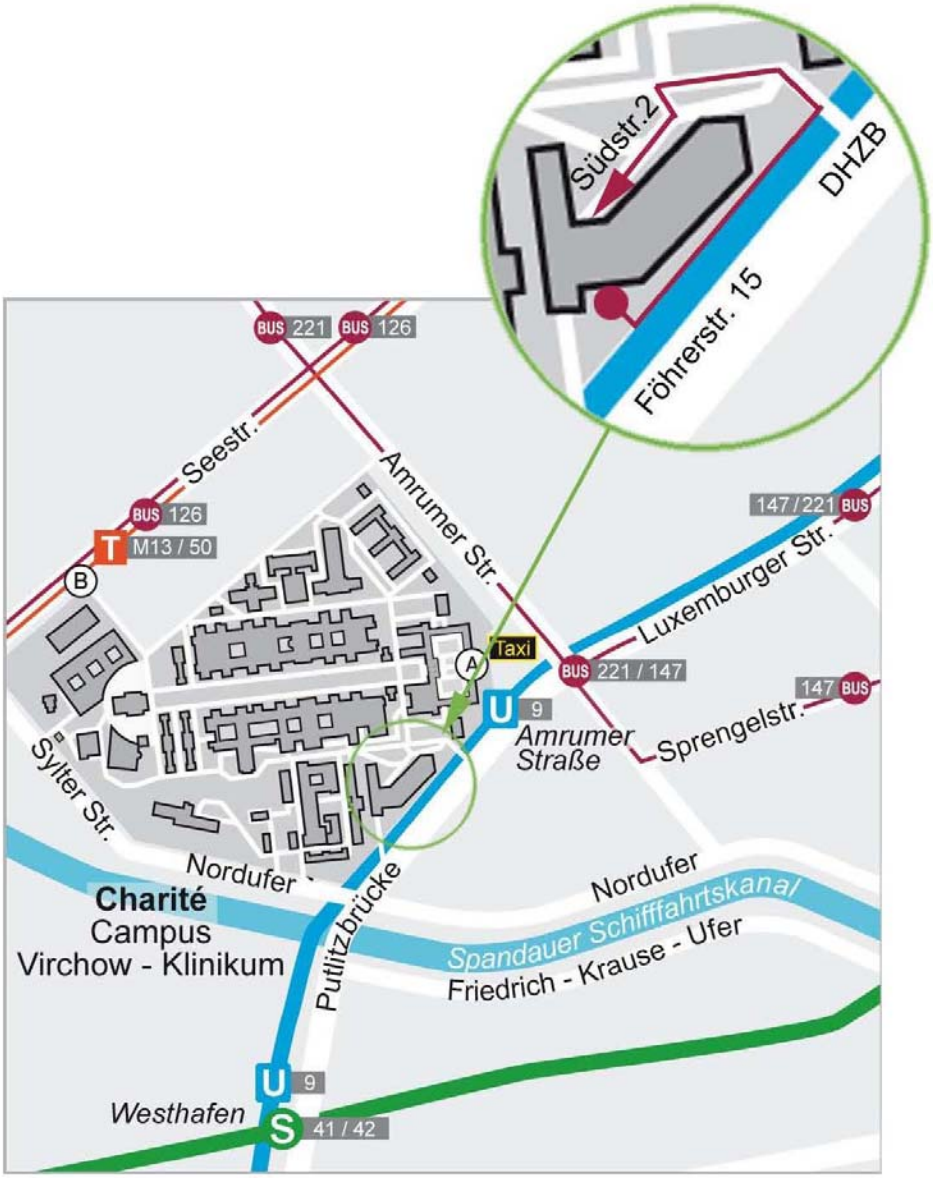

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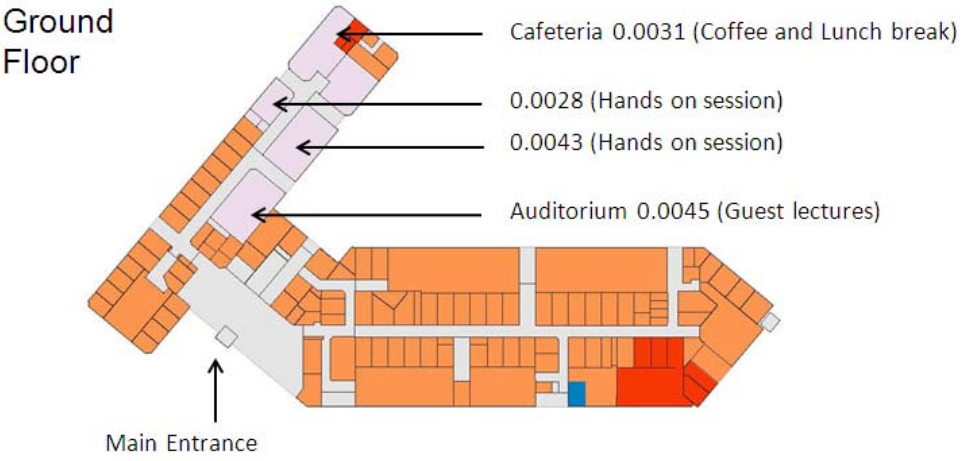

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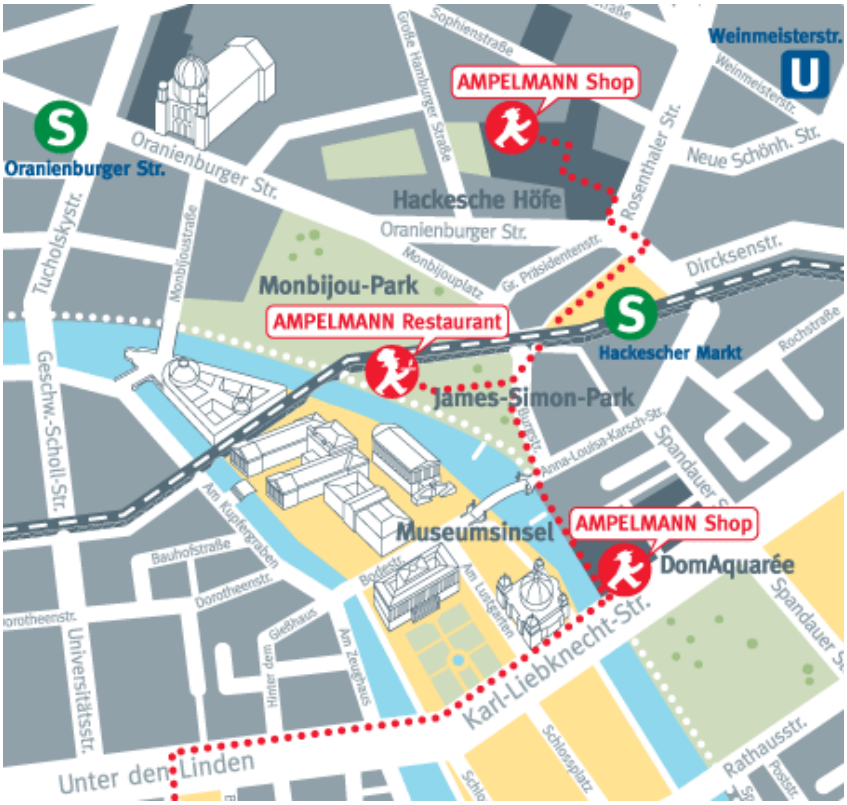

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