CONTENTS

1 BACKGROUND AND PERSPECTIVES

Background

The Maurice E. Müller Institute for Biomechanics (MIB) was established as a joint venture between the Maurice E. Müller Foundation and the Medical Faculty of the University of Bern when Prof. M.E. Müller retired (in 1981) as Chairman of the Department of Orthopaedic Surgery at the Inselspital. The MIB attained legal status as a full University Institute on 1. January 1995, this decision having been reached by the Bernese Government in May 1994 and endorsed by the Canton the following month. The objectives of the MIB are to conduct basic and applied biomechanical research of the locomotor system at the physiological, tissue, cellular and molecular levels. The Institute is supported by a basic operation grant from the Maurice E. Müller Foundation, by funds from the University of Bern, by a grant from the AO/ASIF Foundation and by project grants from the Swiss National Science Foundation and various other foundations and industrial sources. The MIB is currently under the Directorship of Prof. Ernst B. Hunziker, who was elected to this position by the Bernese Government in the autumn of 1989.

Objectives

The MIB is committed to understanding the structure and function of the musculoskeletal system at the physiological, tissue, cellular and molecular levels, and to developing and optimizing information, materials and techniques for the clinical detection and treatment of musculoskeletal diseases. It is thus conceived as a link between academic research, surgical practice and industrial development. Active collaborations with several other research institutes at Bern and other universities, with the Department for Orthopaedic Surgery at the Inselspital, with the AO/ASIF Foundation's Research Institute in Davos and with industrial partners, play an important part in building up the larger and more objective picture of the musculoskeletal system as a whole.

Previous and Current General Research Program

From the time of its foundation in 1981 until 1988, the MIB was directed by Prof. Stephan S. Perren. Its goals during this period were to study the normal and disturbed loading patterns of the locomotor apparatus, to advance our understanding of this system and to profit therefrom by improving the principles, techniques, instrumentation and implants applied in orthopaedic surgery. When Prof. Ernst B. Hunziker took over the Directorship in 1989, he broadened the MIB’s scope of research activities to include basic and applied aspects of skeletal tissue biology, from the physiological down to the molecular level. These activities include: improving the microstructure of preserved tissue, applying morphometric methods in the histological analysis of tissue, testing the evaluating interfacial (adhesion) biology and assessing the micromechanical properties of skeletal tissues, as well as their responses to mechanical stimuli at the tissue, cell and molecular levels. Research activities in the field of classical biomechanics are under the supervision of Prof. Lutz-P. Nolte, who has extended the MIB's research activities in this area to include computerassisted surgery. In 1993, Dr. Nolte was appointed Head of the MIB's Division of Orthopaedic Biomechanics. In addition to being its Director, Prof. Hunziker is also Head of the MIB's Division of Biology, Prof Dr. Beat Trueb being its Associate Head.

With these new dimensions, the MIB is now in a better position to tackle questions raised in connection with the biomechanics of the musculoskeletal system, with prostheses, with endoprostheses, with fracture treatment and with novel biologically-based treatment strategies.

Organization

The Institute is comprised of a staff of about 70 people, including graduate students, medical scientists, biologists, engineers, computer specialists, technicians and research fellows. It consists of two divisions, with a central unit for administration and maintenance. The research activities of one division relate to orthopaedic biomechanics and surgical techniques, whilst those of the other pertain to basic and applied biological aspects of the musculoskeletal apparatus. The two divisions collaborate with one another and are supported by a basic technical staff furnishing histological, computer, mechanical and electronic services. Further information relating to the MIB is available on the Internet at http://www.iti.unibe.ch.

Significance of Research Program

Research activities conducted at the MIB are contributing to our basic understanding of the structure and function of the musculoskeletal system and of the mechanisms underlying its control at the physiological, tissue, cellular and molecular levels. Knowledge thus gained will facilitate the development and optimization of materials for clinical application, the conception of novel, biologically based treatment strategies and the following of a more rational, scientific approach to the treatment of musculoskeletal diseases.

Future

By mutual agreement, the M.E. Müller Foundation and the University of Bern have decided to end prematurely the contract between these two bodies at the end of the current year. The M.E. Müller Institute of Biomechanics will thus no longer exist after 31. December 2002. The Division of Biology of the MIB will form the core of a new ITI Research Institute for Dental and Skeletal Biology at the University of Bern. The Division of Orthopaedic Biomechanics will form the basis of a new Institute for Surgical Technology and Biomechanics within the new M.E. Müller Research Center for Orthopaedic Surgery at the University of Bern (http://www.memcenter.unibe.ch).

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2 RESEARCH ACTIVITIES

2.1. <u>Division of Biology</u>

2.1.1 Molecular Biomechanics

Activities in this research area are directed towards elucidating the composition and functional properties of skeletal tissue elements at the molecular level. Experimental methodology involves principally in-vitro systems - cartilage and skeletal connective tissues being the main tissues investigated. Current topics dealt with include an analysis of the structural and functional properties of components contained within adult human articular cartilage, foetal cartilages and connective tissues. Newly-identified constituents of the extracellular matrix are being cloned, sequenced and analyzed from a functional viewpoint.

The Lipoma Preferred Partner LPP Interacts with α-Actinin
Li B., Zhuang L., Reinhard R. and Trueb B.

Zyxin is the prototype of a small family of proteins (zyxin, LPP, Trip6) that are found at focal adhesion sites where they might be involved in the transduction of mechanical stress from the extracellular matrix to the cytoskeleton. Similar to zyxin, LPP contains a proline-rich N-terminus and three C-terminal LIM domains. We have found that the structural similarities observed between zyxin and LPP also extend to their interaction capabilities. Similar to zyxin, LPP binds to α-actinin in vitro. This interaction was confirmed in yeast and mammalian cells. Studies utilizing the three-hybrid system further indicated that zyxin and LPP compete for the same binding site in α-actinin. This site was mapped to the central rod of α-actinin containing spectrin-like repeats 2 and 3. In the case of LPP, a conserved motif present at the amino terminus was shown to be responsible for the interaction. Constructs lacking this motif did not bind to α-actinin in the yeast two-hybrid system and were not able to recruit α-actinin to an ectopic site in mammalian cells. Quantitative data obtained with the two-hybrid and the three-hybrid system suggest that LPP has a lower affinity for α-actinin than zyxin. It is likely that this difference leads to slightly different roles played by LPP and zyxin during the assembly and disassembly of focal adhesions.

An FGF Receptor-like Protein of Vertebrates
Trueb B. and Wiedemann M.

We have recently identified a novel transmembrane protein (FGFRL1) that is closely related to the family of the fibroblast growth factor receptors. This protein is composed of three extracellular Ig-like domains and of a histidine-rich intracellular domain. It is expressed in all cartilaginous tissues and appears to be involved in the formation of the skeleton. By molecular cloning, we have found homologous proteins in man, mouse and chicken. We therefore investigated whether other species might also possess a gene similar to FGFRL1. The sequences of the genomes from several organisms have recently been elucidated and stored in public databanks. These sequences were compared to the sequence of human FGFRL1 by a computer algorithm. Neither Drosophila melanogaster nor Caenorhabditis elegans were found to possess any gene that would give rise to a transmembrane protein with three similar Ig domains. A highly related sequence, however, was identified in the genome of the pufferfish Fugu rubripes. Obviously, this organism contains a gene with six exons, which can be transcribed and translated into a protein of 500 residues. The putative fish protein shares 68% sequence identity with the FGFRL1 protein from man and this similarity increases to 75% if conservative amino acid replacements are included. There is evidence that Fugu rubripes harbors even a second related gene, which has not yet been fully sequenced. Thus, vertebrates from fish to man possess a novel, homologous protein that belongs to the FGFR family. Lower animals including insects and nematodes do not appear to contain any related protein.

Molecular Cloning of a Dentin-specific Gene

Trueb J., Täschler S. and Trueb B.

The bulk of our teeth is formed by dentin, a mineralized tissue resembling bone. Dentin is synthesized by a single cell type, the odontoblasts. As found with all extracellular matrices, the proteins of dentin belong to the families of the collagens, the proteoglycans and the glycoproteins. Type I collagen is the predominant collagen of the tooth, making up 70-90% of the organic material. Versican, decorin and biglycan are proteoglycans found in dentin. Finally, the extracellular matrix of dentin contains several glycoproteins, including osteonectin, osteopontin, osteocalcin, matrix Gla protein, bone sialoprotein and dentin matrix protein. Thus far there are only two proteins that are specifically found in dentin, namely dentin phosphoprotein (DPP) and dentin sialoprotein (DSP). Interestingly, DPP and DSP are derived from a single gene that is transcribed and translated into a large precursor of nearly 1000 amino acid residues. DSP is derived from the amino-terminal portion of this precursor, whereas DPP is derived from the C-terminal portion. To learn more about these fascinating proteins, we cloned a probe for human DSP. Genomic DNA was isolated from human brain and used as a template for genomic PCR. Synthetic primers were selected that allowed the amplification of a 600 bp fragment from the fourth exon of the DSP gene. The DNA sequence of this fragment corresponded to the published mRNA sequence. On Northern blots, the fragment hybridized to a mRNA of 5 kb that was specifically expressed in the pulpa of human teeth, but not in the skin or the muscle. This probe will be useful as a marker to study growth and development of our teeth.

2.1.2 Cellular Biomechanics

This research area concerns the mechanism by which fibroblasts in tissues exposed to large tensile stress, i.e. in skin, ligaments, tendons and muscle, remodel their extracellular matrix in response to variable forces. The goal is to understand how these cells sense the mechanical signals and transform them into a specific biosynthetic response. Several matrix proteins have recently been identified, whose rates of synthesis correlate with the degree of tensile stress to which the cells are exposed in vivo. In vitro, fibroblasts are cultured on elastic substrates and subjected to controlled strain, in order to determine the effects on gene transcription of these proteins. Such knowledge should help to devise means of manipulating not only the quantity but also the composition (and hence the mechanical properties) of repair tissue formed in response to injury.

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Identification of Nuclear Proteins binding to Mechano-Responive Elements in Collagen XII and Tenascin-C Gene Promoters
Huber F. and Chiquet M.

Mechanical forces are important in tissue homeostasis. An essential part in transducing these forces between tissues and from cell to cell is played by extracellular matrix (ECM) proteins. We showed recently that the expression levels of some ECM proteins like collagen XII and tenascin-C are regulated by mechanical stress. While it is not known in detail how the mechanical stress is transformed into signals that regulate the expression of ECM proteins, recent studies have found consensus sequences in promoters of genes that are regulated by shear stress in endothelial cells. This shear stress responsive element (SSRE) consists of a six base pair GAGACC sequence, which was reported to bind the nuclear factor κB (NFκB). The same consensus sequence can be found in the promoters of the collagen XII and the tenascin-C gene, where it also influences expression levels under mechanical load. Using electrophoretic mobility shift (EMS) assays we try to show whether NFκB or other nuclear factors are involved in the mechanical control of the collagen XII and tenascin-C genes. We used nuclear extracts from chicken embryo fibroblasts to bind to a 23 base pair sequence containing the GAGACC from the collagen XII and tenascin-C gene promoters. We were able to identify several band shifts, the major of which could not be competed with a general NFκB consensus sequence indicating that there are other factors binding to the collagen XII and tenascin-C GAGACC sequences. We are now in the process of identifying the different factors using magnetic beads coupled with double strand oligonucleotides containing a GAGACC sequence to capture and extract the factors. We were able to detect specifically bound proteins on a PAGE, which however showed a molecular weight different from NFκB.

Extracellular Mechanical Stimuli and Cytoskeletal Prestress in Fibroblasts

Sarasa Renedo A., Tunç-Civelek V. and Chiquet M.

Using a device specially designed to apply tensional, equi-biaxial strain to chick embryo fibroblasts plated on a silicone membrane, we could observe a tension-mediated up-regulation of tenascin-C mRNA levels and protein secretion. Tenascin-C is an extracellular matrix (ECM) protein known for its anti-adhesive properties. We believe that tenascin- C might play an important role in the adaptation of cells to external forces, preventing them from overstretching. In vivo, tenascin-C is normally expressed in tissues bearing high tensile stress, such as myotendinous junctions.

We are interested in the mechanisms involved in the mechanotransduction events that lead to the up-regulation of the tenascin-C mRNA and protein levels. In order to find out which pathways might be involved, we performed a series of experiments with different inhibitors. We observed that the Rho-dependent internal prestress of the cell, and therefore its cytoskeletal organization, were crucial for the transduction of mechanical signals from the surface to the cell nucleus. Induction of tenascin-C mRNA by tensile stress was suppressed by the ROCK inhibitor Y-27632, and enhanced by thrombin. With immunocytochemistry techniques we could also describe the changes in focal contacts and in the actin cytoskeleton that the cells suffered with the mechanical stress.

We are currently developing further experiments in this direction, to determine a more precise role of the cellular architecture and internal prestress in the cell's response to external mechanical strain, and in how this response, via the secretion of different ECM components, may modify the mechanical properties of the matrix making it more resistant to tensile stress.

2.1.3 Tissue Biomechanics

Research in this area is directed towards understanding the structural-functional relationships pertaining in skeletal connective tissues, i.e., in cartilage, bone, ligaments and tendons. Emphasis is being placed on the role not only of physiological, but also of non-physiological, mechanical loading during musculoskeletal development, remodelling, disease and injury. Methodologies employed include the stereological and histological characterization of tissue microstructure, molecular and biochemical assaying of connective tissue metabolism, and the measurement of tissue biophysical properties. These projects are being undertaken with a view to improving our understanding of the aetiology of diseases such as osteoarthritis and to developing new therapeutic strategies for their treatment.

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The Mechanosensitivity of Cartilage Oligomeric Matrix Protein (COMP)
Giannoni P., Siegrist M., Hunziker E.B. and Wong M.

Physical forces are known to influence the synthesis, assembly and degradation of the cartilage extracellular matrix. The expression of cartilage oligomeric matrix protein (COMP) was found to be sensitive to long term cyclic compression. Explants of calf articular cartilage as well as cylindrical alginate/chondrocytes constructs were subjected to uniaxial unconfined dynamic compression for 18 hours after which total mRNA was extracted from samples. COMP expression was assessed by means of semi-quantitative RT-PCR and Northern blot techniques. The COMP transcript was found to be significantly enriched upon compression in both experimental systems. Incubation with anti-β 1 integrin blocking antibodies abolished the mechanosensitivity of COMP expression. In addition, the presence of a fully developed pericellular matrix was shown to be a prerequisite for enhanced COMP expression with cyclic loading. Cell/matrix interactions are therefore one of the key events in mechanotransduction in chondrocytes.

The Expression of Angiogenic Factors is Differentially Regulated By Tension and Hydrostatic Pressure
Wong M., Siegrist M. and Goodwin K.

Cartilage is generally considered an avascular tissue which synthesizes high levels of anti-angiogenic factors. During several physiologic and disease states, there is a shift in the balance of angiogenic stimulating and inhibitory factors so that cartilage does become vascularized. During endochondral bone formation, for example, the hypertrophic chondrocytes synthesize angiogenic factors including vascular endothelial growth factor (VEGF) and connective tissue growth factor (CTGF) which induce the local degradation of the calcified cartilage matrix and invasion of endothelial cells. In avascular parts of cartilage, inhibitory factors like chondromodulin-1 dominate. In this study, the expression of angiogenic factors by articular chondrocytes was investigated under 3 types of *in vitro* mechanical stimulation. Loading has a significant effect on gene expression of CTGF ($p<0.001$), TIMP-1 ($p=0.001$), TIMP-2 ($p=.002$) and chondromodulin-1 ($p<0.001$). Tensile loading upregulated the expression of CTGF, a potent stimulator of angiogenesis with high expression levels in hypertrophic chondrocytes. The increased expression of MMP13 by tensile loading ($p<0.07$) and the concurrent inhibition of TIMP-1 expression, also suggests that tensile loads have a pro-angiogenic effect on chondrocytes.

2.1.4 Microbiomechanics and Structural Biology

The main activities in this research area are directed towards elucidating the structural characteristics of skeletal tissues, particularly of cartilage and bone, and their functional correlates, using both *in vitro* and *in vivo* systems. Current topics include analysis of the mechanical properties and structural composition/organisation of growth- and articular cartilages and tendons, as well as investigations relating to the basic physiological mechanisms underlying the differentiation and activity regulation in these tissues.

With respect to bone tissue, studies pertain to mechanisms of osseoinduction and tissue integration processes (particularly as regards to implant materials). These projects are being undertaken with a view to developing new strategies for the treatment of traumatized or diseased cartilage and bone tissue.

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Chondromodulin I is Dispensable during Enchondral Ossification and Eye Development.

Brandau O., Aszodi A., Hunziker E.B., Neame P.J, Vestweber D. and Fässler R.

Chondromodulin I (chm-I), a type II transmembrane protein, is highly expressed in the avascular zones of cartilage but is downregulated in the hypertrophic region, which is invaded by blood vessels during enchondral ossification. In vitro and in vivo assays with the purified protein have shown chondrocyte-modulating and angiogenesis-inhibiting functions. To investigate chm-I function in vivo, we generated transgenic mice lacking chm-I mRNA and protein. Null mice are viable and fertile and show no morphological changes. No abnor-malities in vascular invasion and cartilage development were detectable. No evidence was found for a com-pensating function of tendin, a recently published homologue highly expressed in tendons and also, at low levels, in cartilage. Furthermore, no differences in the expression of other angiogenic or antiangiogenic factors such as transforming growth factor β1 (TGF-β1), TGF-β2, TGF-β3, fibroblast growth factor 2, and vascular endothelial growth factor were found. The surprising lack of phenotype in the chm-I-deficient mice suggests either a different function for chm-I in vivo than has been proposed or compensatory changes in uninvestigated angiogenic or angiogenesis-inhibiting factors. Further analysis using double-knockout technology will be necessary to analyze the function of chm-I in the complex process of enchondral ossification.

GDF-5 Deficiency in Mice Delays Achilles Tendon Healing

Chhabra A., Tsou D., Clark R.T., Gaschen V., Hunziker E.B. and Mikic B.

Clinically, growth factors such as the growth/differentiation factors (GDFs) represent a unique class of molecules that may have the potential to augment the repair of tendon and ligament. To administer these agents effectively in a clinical setting, a complete understanding of their mechanisms of action is required. Mice deficient in these growth factors provide a unique opportunity to examine the effects of the GDFs in vertebrates. The aim of this study was to examine the role of one of these molecules, GDF-5, in more detail. Specifically, we tested the hypothesis that GDF-5 deficiency in mice would result in delayed Achilles tendon repair. Using histologic, biochemical, and ultrastructural analyses, we demonstrate that Achilles tendons from 8-week-old male GDF-5 -/- mice exhibit a short term delay of 1-2 weeks in the healing process compared to phenotypically normal control littermates. Mutant animals took longer to achieve peak cell density, glycosaminoglycan content, and collagen content in the repair tissue, and the time course of changes in collagen fibril size was also delayed. Revascularization was delayed in the mutant mice by one week. GDF-5 deficient Achilles tendons also contained significantly more fat within the repair tissue at all time points examined, and was significantly weaker than control tissue at 5 weeks after surgery, but strength differences were no longer detectable by 12-weeks. Together, these data support the hypothesis that GDF-5 may play an important role in modulating tendon repair, and are consistent with previously posited roles for GDF-5 in cell recruitment, migration/adhesion, differentiation, proliferation, and angiogenesis.

Mechanical Anisotropy of the Human Knee Articular Cartilage in Compression

Jurvelin J.S., Buschmann M.D. and Hunziker E.B.

Articular cartilage exhibits anisotropic mechanical properties when subjected to tension. However, mechanical anisotropy of mature cartilage in compression is poorly known. In this study, both confined and unconfined compression tests of cylindrical cartilage disks, taken from the adult human patellofemoral groove and cut either perpendicular (normal disk) or parallel (tangential disk) to the articular surface, were utilized to determine possible anisotropy in Young´s modulus (E), aggregate modulus (Ha), Poisson´s ratio (n) and hydraulic permeability (k) of articular cartilage. Our results indicated that Ha was significantly higher in the direction parallel to the articular surface as compared to the direction perpendicular to the surface (Ha=1.237+0.486 MPa vs. Ha=0.845+0.383 MPa, p=0.017, n=10). The values of Poisson´s ratio were similar, 0.158+0.148 for normal disks compared to 0.180+0.046 for tangential disks. Analysis using the linear biphasic model revealed that the decrease of permeability during the offset compression of 0-20% was higher (p=0.015, n=10) in normal (form 25.5 to 1.8 (x10-15 m4/Ns)) than in tangential (from 12.3 to 1.3 (x10-15 m4/Ns)) disks. Based on the results, we conclude that the mechanical characteristics of adult femoral groove articular cartilage are anisotropic also during compression. Anisotropy during compression may be essential for the normal cartilage function. This property has to be considered when developing advanced theoretical models for cartilage biomechanics.

Determination of the Interstitial Deformation Profile of Articular Cartilage in Unconfined Compression

Jurvelin J.S., Kolmonen P., Hunziker E.B. and Buschmann M.D.

Cartilage deformation, induced by joint loading and motion, may act as an important mechanism by which the mechanical signals are transmitted to dynamic alterations in chondrocyte metabolism. In this study, we investigated axial strain profile of unconfined, full thickness bovine articular cartilage samples under variable (0%, 15% and 30%) axial compression, with a special emphasis on how the subchondral bone affects the deformation characteristics. Using microscopic tissue sections the number of hexaammine trichloride (RHT) - induced grains, previously shown to be linearly proportional to local glycosaminoglycan (GAG) content, was mapped in 10 compartments from the articular surface to the subchondral bone. The relative change of the spatial grain density, i.e. local GAG concentration, indicated a depth-dependent axial strain under unconfined compression. The highest axial strains in the superficial tissue of compressed samples nearly doubled the mean axial strain of the sample.Axial strain decreased in the deeper regions with the lowest strains,15-50% of the mean axial strain, systematically found in all groups at the depth of 80-90% from the cartilage surface. In the deep tissue close to cartilage/bone interface high axial strain was recorded under both 15% and 30% unconfined compression, more so if the cartilage layer was removed from the subchondral bone. We conclude that the RHT-chemography technique provides a quantitative technique for the analysis of intrinsic deformation of articular cartilage and makes possible characterization of the spatial inhomogeneity of cartilage stiffness. The RHT-technique shows an advantage over some previous methods by enabling analysis of intrinsic equilibrium strain patterns in arbitrary loading geometries.

Proteins Incorporated into Biomimetically-Prepared Calcium Phosphate Coatings Modulate their Mechanical Strength and Dissolution Rate
Liu Y., Hunziker E.B., Randall N.X., de Groot K. and Layrolle P.

In a previous investigation, we demonstrated that when bovine serum albumin (BSA) is biomimetically co-precipitated with Ca2+ and PO43- ions upon titanium alloy implants, it becomes incorporated into the crystal lattice and is not merely deposited on its surface. Moreover, the coating elicited a change in crystal structure from an octacalcium phosphate type to a carbonated apatite one, which bears a closer resemblance to natural bone mineral. In the present study, we investigated the dissolution rate and mechanical strength of such BSA-containing coatings as a function of protein concentration within the bathing medium (10 ng/ml to 1.0 mg/ml). BSA-containing coatings released Ca2+ ions more slowly (5 ppm/minute) than did non- BSA-containing ones (10 ppm/minute), but this rate did not change as a function of protein concentration within the bathing medium. In contrast, the strength of coatings increased almost linearly as a function of protein concentration within the bathing medium, indicating that BSA incorporated into the crystal lattice enhances its mechanical strength in a concentration – dependent manner.

In Vitro and in Vivo Induction of Mineralization by a Non-Collagenous Protein Matrix

Liu Y., Layrolle P., Hunziker E.B., Calvert P.D. and van Blitterswijk C.A.

Calcium phosphate and bovine serum albumin were co-precipitated (under physiological conditions of temperature and pH) upon the surfaces of titanium-alloy samples, which thereby became coated with a dense, proteinaceous mineral layer 30-50µm in thickness. Dissolution of the inorganic phase by treatment with acidic saline yielded a self-supporting protein scaffold, 7-10µm in thickness. Energy-dispersive X-ray analysis and Fourier-transform infrared spectroscopy confirmed the absence of inorganic components from the demineralized albumin scaffolds. When titanium-alloy samples bearing these demineralized protein scaffolds were immersed in a supersaturated solution of calcium phosphate (again at physiological temperature and pH), they remineralized. These redux albumin-calcium phosphate layers corresponded in thickness to those of the original coatings. Titanium-alloy discs either lacking or bearing the demineralized protein scaffolds had become impregnated with calcium phosphate crystals. No uniform mineral layer was deposited upon the surfaces of naked titanium-alloy implants. To the best of our knowledge, this is the first demonstration of remineralization within the interstices of a non-collagenous protein scaffold, either *in vitro* or *in vivo*.

BMP-2 Incorporated into Biomimetic Coatings Retains its Biological Activity

Liu Y., Hunziker E.B., de Groot K., Layrolle P. and de Bruijn J.D.

We have recently shown that proteins can be incorporated into the latticework of calcium phosphate layers when biomimetically co-precipitated with the inorganic component upon the surfaces of titanium alloy implants. In the present study, we wished to ascertain whether recombinant human bone morphogenetic protein 2 (rhBMP-2) thus incorporated retained its bioactivity as an osteoinductive agent. Titanium alloy implants were coated biomimetically with a layer of calcium phosphate in the presence of different concentrations of rhBMP-2 (0.1-10µg/ml). RhBMP-2 was successfully incorporated into the crystal latticework, as revealed by protein blot staining. RhBMP-2 was taken up by the calcium phosphate coatings in a dose-dependent manner, as determined by ELISA. Rat bone-marrow stromal cells were grown directly upon these coatings for 8 days. Their osteogenicity was then assessed quantitatively by monitoring alkaline phosphatase activity. This parameter increased as a function of rhBMP-2 concentration within the coating medium. RhBMP-2 incorporated into calcium phosphate coatings was more potent in stimulating the alkaline phosphatase activity of the adhering cell layer than was the freely-suspended drug in stimulating that of cell layers grown on a plastic substratum. This system may be of osteoinductive value in orthopaedic and dental implant surgery.

2.2 Divison of Orthopaedic Biomechanics

The activities of this Division are directed towards two major areas of research: basic and clinical orthopaedic biomechanics (BCB) and computer assisted surgery (CAS).

In basic and clinical biomechanics, the major areas of research are state-of-the-art implant evaluations, muskuloskeletal injury mechanisms and appropriate treatment strategies. Research methodologies involve primarily *in vitro* and *ex vivo* experiments, as well as mathematical (finite element) models. The focus of the work is the biomechanics of the normal and pathologic human spine. Other anatomic areas of interest are the hip and shoulder.

Research in the area of computer assisted surgery covers orthopaedic-, ENT-, maxillo-facial-, and dental surgical procedures. Proposed and established CAS-systems allow advanced image data acquisition and processing, pre-operative surgical planning and simulation, and intra-operative real-time control and visualization of surgical tools.

The Orthopaedic Biomechanics Division can be reached through the World Wide Web at http://cranium.unibe.ch.

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2.2.1 Computer Assisted Surgery (CAS)

Hybrid CT-free ACL Navigation Module
Ebert B., Kunz M. and Nolte L.-P.

Recent studies have shown that the use of intra-operative images combined with computer assistance can significantly reduce graft placement variability in anterior cruciate ligament (ACL) reconstruction surgery. The purpose of our research is to develop a surgery module that will utilize a combination of radiographic images and computer assistance to construct a surgical plan which identifies ACL graft insertion points, allows analysis of the graft location in the virtual world, and finally provides assistance in the execution of the surgical plan.
An opto-electronic space digitizer is placed in the operating theater, and dynamic reference bases (DRB's) are attached to the femur, tibia and several instruments. This setup enables us to track the relative position of the objects in the room.
A tracked C-arm is used to capture registered images of the knee in both the sagittal and coronal planes. With the use of a back-projection algorithm, 3D landmarks are reconstructed using the 2D C-arm images. These reconstructed

landmarks will be used as the basis of an algorithm that will determine the most suitable graft insertion points on both the femoral and tibial sides. As there is currently no consensus on the ideal ACL graft insertion point, we are considering several published techniques to identify these target insertion points.
Once the insertion points have been identified, the surgeon will have the opportunity to make any fine adjustments that he/she feels are necessary to achieve a successful reconstruction.
When the surgeon is satisfied with the surgical plan, the system will provide assistance with the execution of the plan.

Octree Registration Techniques for Computer Assisted Orthopaedic Surgery

Ioppolo J., Nolte L.-P., Wood D., Styner M. and Price R.

Introduction: The development of advanced registration strategies requires the formulation of hierachical distance map representations. Such techniques allow the possibility to perform coarse-to-fine rigid registration approaches that result in more computationally efficient matching procedures.
Materials and methods: A modified version of the octree distance map (ODM) representation according to Lavallee *et al* [32] was implemented. To perform a baseline assessment of its performance a retrospective evaluation of the Restricted Surface Matching (RSM) procedure [4] used with the SurgiGATE (Medivision, Oberdorf, Switzerland) computer-assisted surgical system was performed for one test subject. To augment the intraoperative bone surface points collected with a pointer-probe, segmented bone contour points were obtained from a series of US images that were acquired during the surgical procedure. The heuristical RSM algorithm was re-executed using these data and compared to results of the Iterative Closest Point (ICP) when using a closest point distance map (CPDM) and ODM as input to the algorithm. To assess the validity of each retrospective registration, results were compared with the mean registration error (MRE) and the component-wise, absolute rotational and translational deviations from the "gold-standard" surface matching.
Results: The gold-standard registration featured a mean registration error of 1.53 mm.Retrospective RSM results consisted of an absolute translational deviation DT= (2.25± 0.87) mm and an absolute rotational deviation DR = (2.05 ± 0.38) with an MRE= (0.98 ±0.11) mm, closest point ICP results consisted of DT = 2.44 mm and DR= 2.42 ± with an MRE = 0.88 mm and ICP-ODM results consisted of DR = 2.66 mmand DR = 2.05 with MRE = 1.07 mm.
Conclusions: ICP registration using ODM generated results similar to those obtained with ICP using CPDM. Both methods produced results in the range of RSM.

Ultrasound Based Registration for Minimally Invasive Spinal Surgery

Kowal J., Styner M. and Nolte L.-P.

Introduction: CT based surgical navigation has been successfully introduced for open dorsal spinal stabilization nearly ten years ago. Since then significant effort has been invested into supporting associated minimally invasive approaches by means of computer assistance, which require accurate and reliable percutaneous registration. Mechanical registration devices and CT/Fluoroscopy matching techniques have been suggested with limited clinical success. Recently a few groups have reported promising results on the application of minimally invasive brightness-mode (B-mode) ultrasound registration for pelvic and long bone surgery. However, to gain broad clinical acceptance associated systems should preferably work fully automatic in order to minimize user interactions and in particular to avoid manual intraoperative segmentation. Based on our prior research in this field, the goal of this paper was to develop and clinically evaluate an automatic B-mode minimally invasive registration technique for dorsal spinal surgery.

Materials and methods: A commercial surgical navigation system (SurgiGATE, Medivision, Oberdorf, CH) was modified by integrating an off-the-shelf B-mode ultrasound device (SONOLINE Sienna, Siemens Medical Systems, Erlangen, D). The used 7.5MHz linear array-probe was integrated into the tracking concept by attaching light emitting diodes to it. The device was calibrated in a water bath prior to the surgical intervention. During surgery a reference base was first attached minimally invasively to the spinous process. B-Mode images showing the transverse processes and the lamina were interactively acquired. The orientation of the images was computed in real-time from the marker positions relative to the surgical reference base. Data was stored on the computer for postoperative analysis. Conventional open computer assisted surgery was then performed using our well-established surface matching technique. Data was recorded to provide a reference for registration to validate the ultrasound-based approach. The prototype setup has been used so far during seven surgeries. Most of the interventions were stabilisation surgeries in the area of the lumbar spine.

Results: The applied automatic image segmentation approach delivered reliable segmentation results. The registrations obtained in our in vivo experiments indicate concordance between the ultrasound based registration and the reference registration. The average voxel displacement in a defined volume of interest after applying the ultrasound-based registration in comparison to the pointer based registration was below 2.5mm in each direction. Due to inter-vertebral motions, the image acquisition, which is restricted to the tracked vertebra only, was challenging for the surgeon.

Conclusions: The results of our initial clinical trials are promising, in particular the registration accuracy achieved. Considering the rather steep learning curve for the intraoprative image acquisition procedure we expect an increase of the registration accuracy in future investigations. Additionally next generation ultrasound technology may open the door for minimally and non-invasive spinal surgery.

A Computer Guidance System for Preoperative Planning and Intraoperative Placement of the Femoral Component During Total Hip Replacement Surgery

Kubiak-Langer M., Langlotz F., Bächler R., Richolt J., Nolte L.-P. and Kerschbaumer F.

Objectives: To extend the SurgiGATE-Prosthetics system (Medivision, Oberdorf, Switzerland) for planning and placing of the acetabular components to a complete total hip replacement (THR) system.

Background/Introduction: The most common reason for possible complications after THR is improper positioning of the implant components within the bone during operation. Systems for planning and navigation during THR have been developed [DiGioia1998, Langlotz1999]. However, these established modules focus on the acetabular implant component only, disrespecting the fact that proper implant functioning relies upon correct placement of both components relative to each other. Therefore, we developed an extension to the existing SurgiGATE-Prosthetics system that guides in the positioning of the stem prosthesis during preoperative planning and assists to prepare a cavity in the femur that the shaft implant can fit precisely according to that plan.

Design/Methods: The well-known SurgiGATE-Prosthetics system facilitates planning and navigated placement of the cup prosthesis into the acetabulum during THR surgery. We extended this system to provide the surgeon with the possibility to plan and implant also the femoral component. Preoperatively, the appropriate size and position of both components is planned within a CT scan. Achieving a perfect plan is facilitated by the real-time calculation of femoral antetorsion, varus/valgus rotation, change in leg length, and lateralization of the hip joint. During the operation, after resection of the femoral head, the placement of the acetabular implant is navigated. Within the stem part of the application, to register the patient's anatomy with its preoperative planning data a dynamic reference base is fixed to the thighbone. On the accessible proximal femur and percutaneously near the knee joint preoperatively defined landmarks and at least 12 surface points are digitized. To shape and hollow out the femur special rasps with play-free connections to an LED holder were developed. The surgical action during preparation of the cavity is navigated, and the shape of the femoral instrument within the patient's CT image is displayed on the computer screen. In addition the surgeon is provided with online information about the depth of tool insertion, antetorsion angle, and the postoperative change in leg length and lateralization, which helps achieving more reliable and accurate positioning of the components with respect to the preoperative plan and the anatomy of the individual patient. Currently, the PPF (Biomet-Merck, Darmstadt, Germany) endoprosthesis is supported.

Results: After extensive validation and accuracy analysis performed on plastic models the presented system has successfully been used during one operation. An extended clinical study is currently being started.

Conclusions: The modified SurgiGATE-Prosthetics system, which consists of the cup and the stem module, will help to plan the appropriate size and position of the THR prosthesis and will supply in real-time the feedback of the position of the surgical instruments relatively to the patient's anatomy and to the preoperatively planed data, which can lead to safer and more accurate placement of the implant's components during free-hand hip replacement surgery.

Intraoperative Feedback of Patello-Femoral Joint Alignment during Total Knee Arthroplasty

Kunz M., Marx A., Bernsmann K., Liang J. and Nolte L.-P.

Objectives: To develop and experimentally test an advanced computer aided system for intraoperative feedback of the patello-femoral joint alignment during total knee arthroplasty.

Background: Total knee arthroplasty (TKA) is a standard procedure in orthopaedic surgery. Postoperative complications related to the extensor mechanism are a common reason for revision surgery in aseptic knees. Alignment between patella and the femoral groove can clinically only be assumed during passive flexion-extension movements of the knee. By the extension of existing computer navigation technology the registration of bone contacts during the entire range of motion may become available, and its visualization may help to prevent malfunctioning of the patello-femoral joint after TKA.

Design/Methods: The current work is based on a modified Surgi*GATE*® Module KneeTKA (Medivision, Oberdorf, Switzerland) originally developed at our institute. The posterior-stabilized knee prosthesis CKS (Biomet, Warsaw, IN, USA) was implanted in three Thiel-fixated right cadaver knees. Dynamic reference bases (DRB) were tightly attached to femur and tibia. In addition, a custom lightweight DRB was fixed to the patella. The surface of the patella backside and the femoral component groove were digitized. Further, the center of the patella surface and four prominent border points were captured. For each cadaveric knee the tibial component was implanted with computer guidance in three different positions: 10° internal rotation, straight, and 10° external rotation. Relative motions between all anatomies were stored through full range of motion after implantation of the knee prostheses. Custom software was used to compute the number of contact areas, their centers, magnitudes, and spatial locations (in terms of three translations and three rotations) at incremental flexion steps of 5°. The influence of the tibial rotation on the glide slope of the patella could be visualized.

Results: The proposed technique allowed for efficient monitoring of the effect of prosthesis placement on the extensor mechanism of the lower limb. The patella gliding slope and the axial patella motion on the femoral implant component was accurately computed and graphically presented to the surgeon. Dominating contact areas were found in all specimens with a magnitude of up to 331mm^2. Patella rotations, as described in the literature, could be detected and visualized. The limited cohort size did not allow for detailed statistical analysis of the resulting data, particularly regarding the various influences of tibial component rotation.

Conclusions: This is first study on the use of advanced surgical navigation to provide intraoperative feedback of the patello-femoral joint alignment during TKA, which may become a key feature in future TKA navigation systems.

Is CT-Based Navigation Suitable for Total Elbow Arthroplasty?
Langlotz F., Herren D., Simmen B. and Baumgartner W.

Objectives: To evaluate the potential of CT-based planning and navigation for the accurate placement of the humeral component of an elbow endoprosthesis using an existing CAS system for spinal surgery.
Background: It has been proven that the correct placement of the total elbow endoprosthesis is one of the most critical factors for the long-term success of an artificial joint. The correct restoration of the center of rotation is critical for the clinical and functional outcome. In order to evaluate whether surgical navigation has the potential to improve surgical accuracy during Total Elbow Arthroplasty (TEA), an existing CAS system was applied within a pilot study on one plastic model and three patients.
Design/Methods: For the pilot study, SurgiGATE™-Spine (Medivision, Oberdorf, Switzerland) was used. In order to apply this system during TEA, a standard 3.5-mm drill guide was instrumented with infrared LEDs and calibrated. A special dynamic reference base (DRB) was developed. The base of this device consisted of an X-shaped, scissors-like construct with locking screw that could be rigidly clamped onto the distal humerus after conventional exposure. In a first trial on a plastic model, the DRB design was evaluated, and three landmarks potentially suitable for paired-points matching were identified: The medial and lateral epicondyles as well as the deepest point in the fossa olecrani. Subsequently, the modified Spine system was applied during three TEA surgeries. In the first surgery, the design of the DRB, its intraoperative visibility by the tracking camera, and the accessibility of the planned landmarks were verified. No preoperative CT scan was acquired for this patient. For the two other cases, CT scans of the elbows were made preoperatively. Planning consisted of 3-D segmentation as well as the definition of landmarks and of one trajectory representing the position of a Steinmann pin, with which four degrees of freedom of the humeral implant position are defined. Intraoperatively, after conventional exposure the DRB was fixated, and data for paired-points and surface matching was acquired. Using the Guidance mode of SurgiGATE™-Spine, the instrumented drill guide could then be aligned according to the planned trajectory.
Results: The newly developed instruments proved to be suitable for intraoperative usage. For the second patient (the first one with CT scan), a sufficiently accurate matching could not be achieved. This surgery was completed conventionally. The last patient could be registered precisely, and the Steinmann pin was placed as planned.
Conclusions/Future Work: Our preliminary results show that CT-based navigation can be applied during TEA. A testing series involving a larger cohort of patients is under way to assess the clinical benefit that can be gained by a CAS

approach during this type of intervention. Given a positive output of this study, the development of a special TEA navigation system is planned.

Image Guided Therapy in ORL, Maxillo-Facial, Reconstructive and Dental Surgery

Pappas I. P., Olsen B., Liu J., Sigrist C., Chapuis J., Malik P. and Caversaccio M.

New registration procedures: In order to allow easy, non-invasive registration of the patient's head anatomy with the preoperative CT image, two concepts for acquiring intraoperative point data were developed and tested. These are based on A- and B-mode ultrasound probes, which were integrated with the SurgiGATE system for ORL. The accuracy of the A-mode based digitizing device derived from in-vitro experiments was found to be 1.0 - 1.4 mm. The advantage is that capturing of the surface point data is significantly simplified, and this registration becomes less time-consuming.

Image-guided surgical microscope: Current CAS navigated microscopes are used for complex surgery on the lateral and anterior skull base. As the first step, the Leica M500 surgical microscope was integrated into the existing ORL system. This allows the microscope to be used as a simple pointing device. In addition, it is possible to display views of the 3D preoperative data perpendicular and parallel to the optical axis of the microscope, thus enabling the simultaneous display of corresponding pre- and intra-operative views of the anatomy.

Dental and maxillo-facial planner and navigator: The exact positioning of dental implants has a high impact on the stability of the implants and functionality. A basic planning module allowing the positioning of multiple implants was developed. In addition to an arbitrary placement of the implants, several constraints can be imposed, e.g., positioning of the implant with respect to the arch of the jaw bone, or forcing multiple implants to be aligned along one axis. Several ergonomic aspects of the first planner implementation have been improved. Furthermore, to enable the study of stress distributions on the implants during the planning phase, a fast finite element solver library for real-time simulation has been implemented. In addition, a basic navigation module has also been implemented, which allows intra-operative patient to CT registration, visualization of planned implant positions and navigation of surgical tools. In particular, a 3D graphic alignment tool has been added to allow a more intuitive alignment of the drill with the implant axis.

In parallel, the requirements for a maxillo-facial planning and navigation module were compiled from interviews with different experienced surgeons. Distance and angle measurement modules as well as a highlighting and mirroring module were developed based on the requirements, as these were found to be the basic planning aids. To allow the comparison of postoperative outcome with the preoperative state, a versatile image registration and fusion module was developed that allows visualizing differences between two 3-D image data sets or to combine them into a new fused view. Additionally, we developed an automatic assessment algorithm for the quality of a CT-MR registration/fusion

Funded within NCCR CO-ME (http://www.co-me.ch/)

Use of Agent Based Technology in the Computer Assisted Surgery (CAS) Domain: Presentation of a Concrete Implementation and its Applicability to Dependable Medical Robotics.

de Siebenthal J. and Langlotz F.

Introduction: Agent technology is gaining increasing interest not only from the scientific community, but also from the manufacturers. This technology is used in several areas: image processing, expert systems, robotic for some of the most well known areas of application. Anywhere we want to give intelligence, more specifically autonomy of decision to a computer system, the agent concept is in focus.

Motivation: Currently, few systems use an approach based on agent, even fewer are used in a medical context. Our work is motivated by the European project VOEU that is aiming to produce new training tools for orthopedic surgery.

Formulation: The problem we aim to solve is to provide an autonomous system for supporting the surgeon in learning and even in performing real CAS procedures. Till now, mostly none of the CAS systems provide the user with augmented monitoring and supervising capabilities.

Discussion: The solution proposed is based on the concept of a Virtual Supervisor. The corresponding implementation, ViSu, is following an agent design and is able to intercept and understand user's interactions. The CAS module used currently with ViSu is the SurgiGATE CT based system for Total Hip Replacement (THR). This application is composed of two modules, the first one allows the surgeon to plan position of the cup implant, the second one let the surgeon navigate CAS tools used for placing intra-operatively the cup implant. Currently, ViSu is setup for these two modules in order to provide supervising support to let the user learn the CAS system. This feature can be extended or simply adapted to other systems where augmented monitoring is useful: we develop a general design for dependable robotic in the CAS domain. Several test were done to evaluate ViSu efficiency and reliability.

Conclusion: A system, ViSu, for supporting the user in doing CAS procedures is developed. This system was specifically designed to be adapted to several kinds of CAS modules including dependable medical robotic solutions.

Use of a New Tracking System Based on ArToolkit for a Surgical Simulator: Accuracy Test and Overall Evaluation

De Siebenthal J., Langlotz F.

Introduction: Nowadays, Computer Assisted Surgery (CAS) uses expensive optoelectronic tracking systems, as the Polaris (Northern Digital, Canada). These

cameras use IR detection and give sub-millimeter accuracy for tracking surgical tools in a real surgical context. In simulation, such accuracy is not mandatory. ArToolkit can track the same tools as the ones used in CAS.
Motivation: Medical simulators are quite seldom and expensive. To replace the standard tracking systems used in CAS simulation, we promote the use of video tracking systems, easy to setup and less expensive. Our work was motivated by the 5th European Framework project VOEU that is aiming to produce new training tools for orthopedic surgery.
Formulation: A simulator for CAS procedures was implemented using a video tracking system based on ArToolkit. This system aims to demonstrate the feasibility of a simulator by implementing each step of a real CAS procedure.
Discussion: There is an increasing demand for new training components in the surgical domain. Such training technologies can be used during surgical lessons given to medical students, or delivered to surgeons for preparing CAS procedures. With the outcome of new computer technologies based on PC, surgical simulators can be built supporting video tracking for low cost. Tracking is a key-part of a simulator in the CAS domain, since surgical tools are used and need to be located in space. ArToolkit gives a strong starting point for building a simulator. Several test series have been carried out according to confidence values given by ArToolkit to evaluate its accuracy in varying different parameters (size and number of markers, light condition, background, volume of interest). Moreover, the tracking is used only to provide position of a surgical tool displayed as a 3D OpenInventor model. By this way, the simulator's implementation proposes a new interface to ArToolkit displaying indeed a 3D scene without showing the image sequence captured by the video camera. Our 3D module is entirely based on an OpenInventor (SGI, USA) engine and can be easily included as a subcomponent of a complex User Interface. One to several tools can be displayed in real-time allowing the completion of a CAS procedure.
Conclusion: A simulator for supporting the surgeon in CAS procedures was developed. Preliminary evaluation based on the beta version of the simulator is promising. Accuracy test series were performed and demonstrate that video based tracking can provide a millimeter precision for a surgical simulator.

Virtual Reduction of Pelvic and Acetabular Fractures

Tarte S., Langlotz F., Hüfner T. and Nolte L.-P.

Objectives: Provide a user-friendly planning software enabling to virtually reduce pelvic and acetabular fractures by means of mouse-guided motion of the fragments models resulting from the segmentation of the preoperative CTs.
Background: Surgeries like pelvic fracture fixations are surgeries requiring a lot of precision during their accomplishment. For this reason, the planning of such a surgery is a prevailing step, which substantially conditions the success of the intervention. While planning the fixation of a pelvic fracture, the most important task is to define accurately the fracture lines and surfaces. Combined with the precision of the surgical act, this accuracy is a basic condition for a good reconstruction and a prerequisite for realistic simulation in a computer assisted

system. Our computer assisted surgery system enables to display the concomitant movements of several bone fragments. More than providing 3D information, it is aimed to provide also user-friendly active planning as well as a visual feedback of fragments movements.

Design/Methods: A CT-based software has been written. Its development focused on two main achievements: accuracy and ease of use. To fulfill the accuracy and efficiency requirements on the fragments motion and image rendering, it was decided to deal with both volumetric and surface models. The surface models are used for the manipulation of the fragments during the virtual reduction of the fracture. They are extrapolated from the volumetric models given by the segmentation. Thus, our pelvic fracture planner involves three main easy-to-follow steps. The first one is segmentation, which enables editing actions on the CT thresholded slices, and therefore precise generation of volumetric models of the bone fragments. The second one is a volume to surface converter, which takes as input the volumetric models produced by the segmentation and outputs the same fragments as surface models. Those models are then injected in the third part of the software, the actual fracture reduction simulation. This part enables the surgeon to define the fracture surfaces, to move the fragments so to make those fracture surfaces appropriately coincide -simulating this way the reduction- and to control visually the accuracy of his reduction.

Conclusions/Future work: Planning is an essential step for pelvic or acetabular fracture reduction for its quality induces the fixation's outcome. Two main goals were headed to: usability and precision; usability through the effort made on the interface and the sequence of the tasks to perform, precision in the use of both volume and surface 3D models. To add to the precision, a study is been lead to evaluate if the reduction's quality can be quantified. A quantification method of the virtual reduction's quality would then add a numerical feedback to the visual one already provided, which in turns could also later be used in a pelvic and acetabular fracture fixation intraoperative navigation module.

Endoscope Based Navigation

Wang H., Liang J., Kunz M., Kowal J. and Nolte L.-P.

After its introduction in the late seventies, endoscopy has set revolutionary landmarks in the field of orthopedic surgery. The most prominent are in joint arthroscopy, where it has replaced a wide variety of open surgical procedures. Additionally, novel areas such as minimally invasive spinal interventions and trauma reconstruction have also been tackled successfully using this technology.

So far, surgical endoscopes have only been used to provide visual feedback of areas that are not directly visible by surgeon.

We are developing an endoscope based orthopedic navigation system to help surgeons achieve greater accuracy when performing minimally invasive surgery. Due to characteristics of the lenses, endoscopic images contain significant

distortion. In order to use these images for navigation, a camera calibration routine has been developed. During this routine a set of correction parameters, namely distortion center and expansion coefficients are determined. These are used to compensate for the optical distortion. Additionally a back projection algorithm was implemented to reconstruct 3D landmarks from multiple 2D images. Finally an easy to use graphical user interface was developed to allow the user to pick landmarks from 2D images.
We are obtaining the first clinical results from an in-vitro study. This clinical study will focus on the spine area and will verify the accuracy and feasibility of using endoscopic images in minimally invasive registration.
Funded within NCCR CO-ME (http://www.co-me.ch/)

Computer Aided Less Invasive Stabilization for metaphyseal Femoral and Tibial fractures
Zheng G., Grützner, P.-A. and Nolte L.-P.

Introduction: Several studies have shown a direct relationship between complications of fracture treatment and invasive operative techniques, which may damage the blood supply to the bone, delay fracture healing, and increase the risk of infections. In recent years, a new type of bridging osteosynthesis has evolved using a so-called Less Invasive Stabilization System (LISS, Stratec Medical, Oberdorf, CH), which is inserted between the muscles and the periosteum. However, the success of such a surgical approach is strongly technique dependent.
Methods: Fractured bone fragments, all surgical instruments and the LISS osteosynthesis plates are equipped with light emitting diodes. Based on calibration procedures recently introduced by our group for fluoroscopic navigation a three-dimensional (3D) virtual reality is established. CAD models of the LISS plates and fixation screws are registered to the associated real world implant components using modified paired-points matching algorithms. These calibrated surgical devices are tracked by an optoelectronic camera during their actions on the bony anatomies and can be visualized interactively in the said virtual world. In addition, a virtual 3D model is reconstructed for each principal bone fragment. This done by identifying their contours on two or more registered fluoroscopic images, and its projection is used to define an image area for the associated bone fragment. Back projection and warping algorithms allow radiation free image updates in situ, and thus interactive visual control of the closed fracture reduction. The plate is positioned and fixed by means of less invasive techniques through the virtual reality guidance of the navigation system. The set-up was initially tested on plastic bones, which were covered by foam material to simulate the percutaneous approach. In an initial clinical trial the system was used on four patients.
Results: In all laboratory tests, a complete X-ray free long bone fracture reduction and plate stabilization was possible after taking a few single fluoroscopic images. Excellent correlation between the virtual updates of fluoroscopic images and live fluoroscopy during navigation was observed.

During our preliminary clinical trials, all cases were successfully supported by the system. No intraoperative and postoperative complications related to the use of the system occurred. All patients healed uneventfully. The additional need of OR time was found to be about 15 minutes (range from 10 to 20).
Discussion: A novel image guided surgery system has been developed, which can provide a realistic intraoperative visual feedback of fracture reduction, implant positioning and fixation. Compared to the conventional approach, there are several advantages as observed during the laboratory testing and the preliminary clinical trial. First, based on four pre-acquired fluoroscopic images, fracture reduction could be achieved and monitored for the whole surgical procedure without acquisition of image updates. Besides significantly reducing the radiation exposure this would have been equivalent to the use of four C-arms operating in constant mode placed from different viewing angles, an unrealistic clinical scenario. Next, the visualization of fracture reduction and the implant placement could be achieved simultaneously. Third, all implants could be optimally placed in the first try due to the direct visual feedback provided by the reality augmented virtual system. No intraoperative correction was necessary.

A Hybrid CT-free Approach for Total Hip Replacement

Zheng G., Langlotz U., Widmer K.-H., Grützner P.A. and Nolte L.P.

Introduction: Recently there is a trend towards minimally invasive approach for total hip replacement (THR). The associated smaller incision requires intraoperative feedbacks to the surgeon during instrument manipulation and prostheses placement, which could be provided using image-based navigation technology. CT-based approach was recently introduced [DiGioia, 2002] despite the high X-ray exposure resulting from the required CT scan and the difficulty and challenge of the associated intraopeative matching procedure. In this investigation, based on our previous work on CT-free cup navigation system [Langlotz, 2001], a hybrid CT-free approach was developed for THR which including image-based navigation for preparation and implementation of both cup and stem placement.

Material/Methods: A hybrid concept was developed for the landmark acquisition, which involves percutaneous point-based digitization and non-invasive bi-planar landmark reconstruction using multiple registered fluoroscopy images. Two patient specific reference coordinate systems are computed based on the acquired landmarks: (a) for the pelvis, based on the well-known anterior pelvic plane (APP) concept and (b) for the femur, using the center of the femoral head, the posterior condylar tangential line, and the medullary canal axis of the proximal femur. An optoelectronic camera (Optotrak 3020, Northern Digital Inc., Waterloo, Ontario, Canada) mounted on a movable stand was used to track the position of optical targets equipped with infrared light emitting diodes (LEDs). These targets are attached to the surgical objects, all surgical tools, and the image intensifier of a C-arm. The following clinical parameters are computed in real time: cup inclination and anteversion, antetorsion and varus/valgus of the stem, overall changes in leg length and lateralization for a complete THR. In addition, instrument actions such as reaming, impaction, and rasping are visualized to the surgeon by superimposing virtual instrument representations onto the fluoroscopic images.

CT-based approach was used to verify the system accuracy using a plastic femur (SAWBONES EUROPE AB Krossverksgatan 3, SE-216 16 Malmoe, SWEDEN) in a laboratory study, which involves four surgeons: two experienced hip surgeons and two junior orthopaedic surgeons. An on-going clinical study, which so far involves 18 patients, is designed to evaluate the applicability and the clinical benefit of the proposed approach.

Results: The laboratory study on computer-assisted measurement of antetorsion and varus/valgus of the stem, lateralization and limb leg length change demonstrated the high precision of the proposed approach. Compared with CT-based measurement, mean deviation of 1.0°, 0.6°, 0.7 mm, and 1.7 mm was found for antetorsion, varus/valugs, change in leg length, and lateralization with a standard deviations (SD) of 0.5°, 0.5°, 0.6 mm, and 0.7 mm, respectively. The on-going clinical evaluation showed that this novel system could be used as a valid instrument for the surgeon to achieve less invasive hip surgery through precise calculation of all functional parameters and realistic visual feedback of all surgical actions.

Discussions: Minimally invasive surgery intends to disrupt less of the soft tissue that surrounds the joint. However, it is also a technically demanding procedure, especially in anatomically complex situation e.g. hip surgery. Its success depends on the surgeon's experience as well as the development of specialized techniques and instruments due to restricted vision and mobility, difficult hand-eye coordination, and difficult handling of the instruments. The accurate computing of functional parameters, the realistic visualization of all surgical actions, and the further superimposing the visualization results onto several intraoperatively acquired fluoroscopic images make it possible for the surgeon to develop less invasive surgical techniques for THA, when using the proposed novel navigation system.

2.2.2 Basic and Clinical Biomechanics (BCB)

Motion patterns and facet joint geometry of the canine caudal lumbar spine – a combined kinematic and computer tomography study
Benninger M., Seiler G., Robinson L., Ferguson S.J., Busato A. and Lang J.

Lumbosacral angle, alignment and range of motion have been analyzed as possible causes of degenerative lumbosacral stenosis (DLSS) in the dog. However, many questions with regard to the biomechanics of the lumbosacral junction and the etiology of DLSS remain open. Previously, differences in shape and angle direction of the articular facets have been associated with high (95%)

prevalence in degeneration of the lumbosacral disc. The purpose of this study was to evaluate three-dimensional motion patterns including main and coupled movements of the caudal lumbar spine in relationship with the geometry of the facet joints. Lumbar spines (L4-S1) of dogs between 1 and 8 years of age were used. The specimens were tested in a specially designed apparatus, which allows application of known pure moments to the spine. Four different loads (0.75, 1.5, 2.25 and 3.0 Nm) were applied and motion of the specimen was measured using an optoelectronic camera system. The specimens were then scanned in a multi-slice CT scanner and geometry of the facet joint was measured using a method previously described. All specimens showed similar motion patterns. During flexion/extension motion increased from 5-10° at the L4-5 level to 40° in the L7-S1 intervertebral space. The highest amount of lateral bending was present in the L4/L5 segment, although the difference between the levels was small. Very little axial rotation was observed in all segments. Besides the main motions, a substantial amount of coupled motions was present. During flexion/extension the coupled motions increased from cranial to caudal, the main component being axial rotation. Facet joint angles were relatively uniform in the segments between L4 and L7. In comparison with the cranial segments, the lumbosacral facet joint angle was much wider in the transverse plane and smaller in the dorsal plane. The motion of the canine caudal lumbar spine follows a complex pattern consisting of main and a large amount of coupled motions. The lumbosacral motion segment shows a different motion pattern and facet joint geometry compared with the more cranial segments, which could result in an increased mechanical demand on the lumbosacral intervertebral disc.

The influence of vertebral endplate porosity on the compressive creep behaviour of intervertebral discs

Beutler T., Ito K. and Ferguson S.J.

The intervertebral disc is the largest avascular structure in the body. It has been often suggested that fluid flow into and out of the disc, via the porous vertebral endplate, may enhance the transport of larger molecules. Calcification and occlusion of pores in the endplate may alter endplate permeability and limit the magnitude of fluid exchange. The goal of the study was to determine the correlation between endplate porosity and endplate permeability. The compressive creep behaviour of bovine lumbar intervertebral discs was measured. The creep data were fit to a three-parameter fluid-transport model to determine endplate permeability (k), strain dependence due to swelling pressure (D) and time dependence due to annular creep (G). Following testing, all soft tissue were digested and osseous endplate specimens were prepared for light microscopy. Backlit digital microscope images were processed to determine the following morphological parameters: size distribution of endplate holes (diameter and area), endplate porosity (flow area / mm^2) and hole density (number / mm^2). For the skeletally mature specimens, there was a weak positive correlation between endplate porosity and endplate permeability ($r^2 = 0.30$, $p = 0.34$) and a stronger positive correlation between hole density and endplate permeability ($r^2 = 0.90$, $p = 0.014$). Therefore, it was not the size of flow channel which was important, but rather the total number of flow channels available. Occlusion of individual endplate pores by endplate calcification may result in a disturbed exchange of fluid to and from the disc, and therefore a reduction in the nutritional supply and the removal of metabolic waste products

A new prosthetic design for proximal humeral fractures: reconstructing the glenohumeral unit

DeWilde L.F., Berghs B.M., Beutler T., Ferguson S.J. and Verdonk R.C.

The strength of the tuberosity fixation to a new trauma shoulder prosthesis was investigated in a cadaveric study. Artificial four-part fractures were created in 18 human, fresh frozen, paired shoulder joints, with intact rotator cuffs. Two methods of tuberosity fixation were used in a matched-pair fashion. In group I the tuberosities were sutured to the rim of the prosthetic head, and in group II the tuberosities were circumferentially tension band wired. Strength testing was performed on a material testing machine and tuberosity displacement was recorded with an opto-electronic device. Both fixation methods proved to be equally reliable in the force range of activities of daily living without significant displacement of the fracture fragments.

Primary stability of a robot-implanted anatomical stem versus manual Implantation

Nogler M., Polikeit A., Wimmer C., Brückner A., Ferguson S.J. and Krismer M.

The high costs of surgical robots and the increased perioperative efforts can only be justified if measurable benefits for patients can be achieved. Increased initial stability of the stem as an early indicator for better bone ingrowth would be such a benefit. The objective of this study was to compare the primary stability of anatomical stems implanted in manually broached femoral cavities versus cavities milled with a robotic system. The bone – prosthesis interface motion was measured in pairs of cadaveric femora comparing manual and robot – assisted implantation. In seven pairs of fresh frozen human cadaveric femora anatomical stems were implanted either manually or robot – assisted. Initial micromotions were measured during simulated gait cycles with loads up to 1500 N and both groups were compared pair wise. Relatively high motion of the prostheses and no statistical differences between robot - supported and implantation by an experienced surgeon were found.
We concluded that the robotic system did not enhance the primary stability of the tested anatomical prosthesis compared to manual implantation.

Fully automatic pre-operative assessment of dental implant stability via finite element analysis
Olsen S., Ferguson S.J., Nolte L.-P. and Caversaccio M.

In complex dental replacement surgery several titanium implants are used along with a superstructure and attached crowns to restore normal function and appearance of missing teeth. Any mechanical forces (e.g. chewing) will be transmitted through implant structure and into the bone. Failure at the implant-bone interface is frequently caused by mechanical overloading resulting in fracture of the implant itself or gradual bony degeneration with concomitant loosening. Controlling the magnitude of loading of dental implants by design is desirable since structural bonding of an implant to bone is in part regulated by mechanical factors. We have developed a novel methodology and computer program to perform fully automatic, real-time patient-specific finite element analysis. Special emphasis has been placed on facilitating accurate analysis and intuitive output of the implant-bone interface performance. By determining the manner in which the applied forces are processed by the implant-bone interface, areas of abnormal mechanical distribution can be identified. This analysis system has been integrated with a surgical planning software for dental implantology where virtual implants are planned in the CT stack. We present preliminary analysis results of various configurations for a dental reconstruction which illustrates our new method.

The effect of cement augmentation on the load transfer in an osteoporotic functional spinal unit, finite element analysis
Polikeit A., Nolte L.-P. and Ferguson S.J.

Osteoporosis is the most frequent skeletal disease of the elderly, leading to weakness of the bony structures. Cement injection into vertebral bodies has been used to treat osteoporotic compression fractures of the spine. The clinical results were encouraging. Experimental biomechanical studies showed significant increases in stiffness and strength of treated bodies. However, little is known about the consequences for the adjacent, non-treated levels. Therefore, the effect of cement augmentation on an osteoporotic lumbar functional spinal unit was investigated using finite element analysis. 3D finite element models of L2-L3 were developed and the material properties adapted to simulate osteoporosis. The influence of augmentation level, uni- and bipedicular filling with polymethyl-methacrylate were investigated. Compression, flexion and lateral bending were simulated. Augmentation increased the pressure in the nucleus pulposus and the deflection of the adjacent endplate. The stresses and strains in the vertebrae next to an augmentation were increased and their distribution changed. Larger areas were subjected to higher stresses and strains. The treatment clearly altered the load transfer. Changes to the overall stress and strain distribution were less pronounced for unipedicular augmentation. Cement augmentation restores the strength of treated vertebrae, but leads to increased endplate bulge and an altered load transfer in adjacent vertebrae. This supports the hypothesis that rigid cement augmentation may facilitate the subsequent collapse of adjacent vertebrae. Further study is required to determine the optimal reinforcement material and filling volume to minimise this effect.

3 PUBLICATIONS

3.1 Division of Biology

Original Articles

Brandau O., Aszodi A., Hunziker E.B., Neame P.J., Vestweber D., Fässler R.: Chondromodulin I is dispensable during enchondral ossification and eye development, Mol. Cell. Biol. 22(18):6627-6635, 2002

Datta A., Huber F. and Boettiger D.: Phosphorylation of beta3 integrin controls ligand binding strength. J Biol. Chem. 277: 3943-3949, 2002.

Giannoni P., Siegrist M., Hunziker E.B. and Wong M.: The Mechanosensitivity of Cartilage Oligomeric Matrix Protein (COMP), Biorheology, 40:101-109, 2002

Hunziker E.B.: Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects, Osteoarthritis Cartilage. 10(6):432-463, 2002

Hunziker E.B., Quinn T.M. and Häuselmann H.J.: Quantitative structural organization of normal adult human articular cartilage, Osteoarthritis Cartilage. 10(7): 564-572, 2002

Korhonen R.K., Wong M., Arokoski J., Lindgren R., Helminen H.J., Hunziker E.B. and Jurvelin J.S.: Importance of the superficial tissue layer for the indentation stiffness of articular cartilage, Med. Eng. Phys. 24: 99-108, 2002

Moser M., Bosserhoff A.K., Hunziker E.B., Sandell L., Fässler R. and Buettner R.: Ultrastructural cartilage abnormalities in MIA/CD-RAP-deficient mice, Mol. Cell. Biol. 22(5): 1438-1445, 2002

Quinn T.M. and Hunziker E.B.: Controlled enzymatic matrix degradation for integrative cartilage repair: effects on viable cell density and proteoglycan deposition, Tissue Eng. 8(5):799-806, 2002

Quinn T.M., Schmid P., Hunziker E.B. and Grodzinsky A.J.: Proteoglycan deposition around chondrocytes in agarose culture: Construction of a physical and biological interface for mechanotransduction in cartilage, Biorheology. 39(1,2):27-37, 2002

Schild C. and Trueb B.: Mechanical stress is required for high-level expression of connective tissue growth factor. Exp. Cell Res. 274, 83-91, 2002

Zapf J., Gosteli-Peter M., Weckbecker G., Hunziker E.B. and Reinecke M.: The somatostatin analog octreotide inhibits GH-stimulated, but not IGF-I-stimulated, bone growth in hypophysectomized rats, Endocrinology. 143(8):2944-2952, 2002

Book Articles

Jin M., Grodzinsky A.J., Wuerz T.H., Emkey G.R., Wong M. and Hunziker E.B.: Influence of tissue shear deformation on chondrocyte biosynthesis and matrix electromechanics. In: Kuettner KE, Hascall VC, eds. The Many Faces of Osteoarthritis, Basel: Birkhauser Verlag AG, 2002: 397-408.

3.2 <u>Division of Orthopaedic Biomechanics</u>

Original Articles

Bächler, R.; Nolte, L.-P.: Prinzipien der computerassistierten Chirurgie. OP-Journal, 1, 4-6, 2002

Berlemann U., Ferguson S.J., Nolte L.-P. and Heini P.F.: Adjacent vertebral failure following vertebroplasty: a biomechanical evaluation. Journal of Bone and Joint Surgery, 84:748-52, 2002

Caversaccio, M.; Nolte, L.-P.; Häusler, R.: Present state and future perspective of computer aided surgery in thCe field of ENT and skull base, Acta Otorhinolaryngol Belg, 56(1), 51-59, 2002

Ferguson S.J., Winkler F. and Nolte, L.-P., Anterior fixation in the osteoporotic spine: cut-out and pull-out characteristics of implants. European Spine Journal, 11:527-34, 2002

Frei H., Oxland T.R. and Nolte L.-P.: Thoracolumbar spine mechanics contrasted under compression and shear loading, Journal of Orthopaedic Research, 20:1333-8, 2002

Grützner, P.A.; Rose, E.; Vock, B.; Holz, F.; Nolte, L.-P.; Wentzensen, A.: Computer-assistierte perkutane Verschraubung des hinteren Beckenrings – Erste Erfahrungen mit einem Bildwandler basierten optoelektronischen Navigationssystem, Unfallchirurg, 105, 254-260, 2002.

Hüfner, T.; Pohlemann, T.; Tarte, S.; Gänsslen, A.; Geerling, J.; Bazak, N.; Rosenthal, H.; Nolte, L.-P., Krettek, C.: Computer assisted fracture reduction of pelvic ring fractures – An in vitro study, Clin Orthop, Jun, 399, 231-239, 2002

Langlotz F.: State-of-the-Art in Orthopaedic Surgical Navigation with a Focus on Medical Image Modalities. Journal of Visualization and Computer Animation 13:77-83, 2002

Li D., Ferguson S.J., Beutler T., Cochran D.L., Sittig C., Hirt H.P., Buser D.: Biomechanical comparison of the sandblasted and acid-etched and the machined and acid-etched titanium surface for dental implants", Journal of Biomedical Materials Research, 60:325-32, 2002

Peters P., Langlotz F., Nolte L.-P. and Siebel T.: Computer Assisted Screw Insertion into Real 3-D Rapid-Prototyping Pelvis Models. Clinical Biomechanics 17(5):376-382, 2002

Van Hellemondt G., de Kleuver M., Kerckhaert A., Anderson P., Langlotz F., Nolte L.-P. and Pavlov P.W.: Computer Assisted Pelvic Surgery: An In Vitro Study Of Two Registration Protocols. Clinical Orthopaedics and Related Research 405:287-293, 2002

Zheng G., Marx A., Langlotz U., Widmer K. H., Buttaro M., Nolte L. P.
A Hybrid CT-free Navigation System for Total Hip Arthroplasty
Computer Aided Surgery, 7(3):129-145, 2002

Book Articles

Bächler R., Nolte L.P., Prinzipien der computer-assistierten Chirurgie, OP-Journal, Thieme-Verlag, 1(18):4-7, 2002

LanglotzF., Marx A., Kubiak-Langer M., Zheng G. and Langlotz U.: Prothesenschaftnavigation mit dem SurgiGATE System. In: Navigation und Roboter in der Gelenk- und Wirbelsäulenchirurgie. Konermann W., Haaker R., eds., Heidelberg: Springer, 118-125, 2002

Langlotz F.: Visionen der Navigation. In: Navigation und Roboter in der Gelenk- und Wirbelsäulenchirurgie. Konermann W., Haaker R., eds., Heidelberg: Springer, 429-434, 2002

Kunz, M.; Langlotz, F.; Nolte, L.-P.: Computer assisted surgery – Principles and perspectives (in German), in: Neues in der Knieendoprothetik, S. Fuchs, C. O. Tibesku (eds), Steinkopff, Darmstadt, 104-108, 2002.

Nolte L.-P. and Langlotz F.: Grundlagen der Computerassistierten Chirurgie (CAOS). In: Navigation und Roboter in der Gelenk- und Wirbelsäulenchirurgie. Konermann W., Haaker R., eds. Heidelberg: Springer, 3-10, 2002

4 RESEARCH PROJECT GRANTS

The M.E. Müller Institute for Biomechanics is indebted to the M.E. Müller- and AO-/ASIF-Foundations for their generous annual contributions to its budget.

The support of a large number of specific research projects by various foundations and firms, in particular the Swiss National Science Foundation, is gratefully acknowledged.

* * *

Alonso J., Gebhard F., Grützner P.A., Hüfner T., Krettek C., Langlotz F., Messmer P., Nolte L.-P., Schmucki D, Stöckle U.: CARIM – Computer Assisted Reduction and Imaging, AO/ASIF Foundation, 1.12.2002-30.11.2003

Berlemann U. and Ferguson S.J.: Changes to the local and global biomechanical response of the spine following cement augmentation in osteoporotic vertebrae, AO Research Foundation, Switzerland. 1.3.2001-28.2.2002

Chiquet M.: Regulation of extracellular matrix protein expression by mechanical stress. Swiss National Science Foundation, Bern. 1.4.1999-31.3.2002

Chiquet, M.; Regulation and functional adaptation of extracellular matrix in response to mechanical stress. Swiss National Science Foundation, Bern. 1.4.2002-31.3.2005

Chiquet M.; The role of tenascin-C in the adaptation of fibroblasts to tensile stress. Novartis Foundation for Biomedical Research. 1.10.2002-31.3.2003

Ferguson S.J.: Marrow Contact channel occlusion and disc degeneration, Natural Sciences and Engineering Research Council, Canada. 1.5.2000-30.4.2002

Ferguson S.J. and Beutler T.E.: Tuberosity fixation in hemiarthroplasty of the proximal humerus in traumatic cases, DePuy, France. 1.9.2001-31.1.2002

Ferguson S.J. and Cripton, P.A.: Development and validation of a three-dimensional finite element model of a human cervical spine segment, AO Research Foundation (Switzerland), 1.5.2002 – 30.4.2003

Ferguson S.J. and Auer, J.: BoneWelding, Bundesamt für Berufsbildung und Technologie, Kommission für Technologie und Innovation KTI, 1.9.2002 – 31.8.2003

Grodzinsky A. and Hunziker E.B.: Mechanisms of chondrocyte response to mechanical stimuli, NIH, Bethesda, MD, USA. 1.10.1998-30.09.2003

Hunziker E.B.: Osteoarthritic disease modification by intra-articular injection of bone-marrow-derived mesenchymal stem cells. Osiris Therapeutics, Baltimore, MD, USA. 1.10.2000-30.6.2002

Hunziker E.B.: Osteoarthritis prevention and chondroprotection, Synovart, Toronto, Canada. 1.1.2001-30.6.2002

Hunziker E.B., Park Y.D. and Sugimoto M.: Synovial-derived chondrogenic precursor cells for articular cartilage repair, Swiss National Science Foundation, Bern. 1.10.2001-30.9.2004

Langlotz F.: A Versatile Preoperative Planner for Orthopaedic Surgery (project within the National Center for Competence in Research "CO-ME – Computer Aided and Image Guided Medical Interventions"), Swiss National Science Foundation. 1.7.2001-30.6.2005

Langlotz F. and Siebenrock K.: Interactive Software for 2D and 3D standardization of Pelvic Radiographs and CT-Scans for Accurate Evaluation of Hip Joint Morphology. NCCR CO-ME, 1.12.2002-30.6.2003

Langlotz F., Huefner T.: CT Based Reduction, AO Development Institute, 1.12.2002 – 1.6.2004

Nolte L.-P. and Langlotz F.: VŒU - A virtual orthopaedic European University, 5th Research Framework Program of the European Union. 1.5.2000-30.04.2003

Nolte L.-P.: Minimally Invasive Approaches to Orthopaedics (project within the National Center for Competence in Research "CO-ME"), Swiss National Science Foundation. 1.7.2001 – 30.6.2005

Nolte L.-P.: A novel approach for the percutaneous location of bone structure by ultrasound; towards new minimally invasive computer assisted surgery, Swiss National Science Foundation, Switzerland. 1.10.1999-1.10.2002

Nolte L.-P.: Dental navigation, Institut Straumann, Waldenburg, Switzerland. 1.1.2000-31.3.2002

Nolte L.-P. and Langlotz F.: VŒU - A virtual orthopaedic European University, 5th Research Framework Program of the European Union, 1.5.2000-30.04.2003

Shintani N.: Grant from Protein Research Laboratories, Mitsubishi Pharma Corporation. 1.11.2002 – 31.10.2004

Studer D.: Vitrifying, cutting, observing – the dream method for electron microscopy. Swiss National Science Foundation, Bern. 1.10.2000-30.9.2003

Trueb B.: Structure and function of novel cartilage proteins. Swiss National Science Foundation, Bern. 1.10.2000-30.9.2003

Trueb B.: Applications of the FGFRL1 gene and of the protein encoded thereby. Osiris Therapeutics, Baltimore MD, USA. 1.10.2001-30.9.2002

Unser U. and Thévenaz Ph.: Fluoroscopy-based 3D/2D registration for minimally-invasive approaches in trauma and spine surgery, AO Research Commission, Switzerland. 1.10.2000-30.9.2002

Wong M., Hunziker E.B. and Hubbell J.A.: Regulation of matrix synthesis in tissue-engineered constructs for cartilage repair, Swiss National Science Foundation. 1.4.2000-31.3.2003

Wong M.: The Role of Mechanical Stimuli in the Differentiation of Adult Mesenchymal Stem Cells: Applications for Skeletal Tissue Engineering. Olga Mayenfisch Foundation. 1.10.2002- 31.09.2003

Zheng G., Gruetzner F.: Virtual Implants, AO Development Institute, Davos. 1.12.2002 – 1.12.2004

Zheng G., Gruetzner F.: Fluoroscopy Based Reduction, AO Development Institute, Davos. 1.12.2002 – 1.3.2004

5 TEACHING ACTIVITIES

University of Basel:

- 4562 and 6673: New literature in extracellular matrix biology
- 8552: Cell adhesion in development and disease

University of Bern:

- Cytologisch-Histologisches Praktikum für Medizin- und Tierarzt-Studenten im 1. Jahr
- W4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Tutorial
- S4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Tutorial
- S4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Concept Lecture KV 26-1; Introductory Lecture EV 28-3
- S7313: Applied Molecular Biology, interfakultäre Vorlesung für Vorgerückte an der Universität Bern
- W7322: Connective Tissue Research, Kolloquium für Studierende an der Universität Bern
- W7240.0: Zellbiologie II, Vorlesung für Studierende der Biologie und Biochemie an der Universität Bern
- W7311.1: Praktikum zu Immunologie II, für Studierende der Zellbiologie, Mikrobiologie und Immunologie
- S7239.1 Praktikum zu Mikrobiologie II, für Studierende der Zellbiologie und Biochemie an der Universität Bern

Inselspital Bern:

- Biomechanics for Physiotherapists

6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

6.1 Dissertations Completed

Kowal, J.: B-Mode Ultrasound Based Registration for Computer Assisted Orthopaedic Surgery, Ph.D., University of Bern, CH, 2002

Langlotz, U.: Computer assisted reconstruction and replacement of the human hip joint, Ph.D., University of Bern, CH., 2002

Li B.: Interaction of Zyxin with Focal Adhesion Proteins, Dr. phil. II, University of Bern, CH, 2002

Polikeit, A: Finite element analysis of the lumbar spine: Clinical application., Ph.D., University of Bern, CH, 2002

Zheng, G.: Advancements of Fluoroscopy-based Navigation for Less invasive Orthopaedic Interventions, Ph.D., University of Bern, CH, 2002

7 HONORS AND AWARDS

03.2000 to date Hunziker E.B.: Member of the Special Review Panel of the German Ministry of Education and Science for Tissue Engineering Projects, Germany

03.2000 to date Hunziker E.B.: Member of the National Institutes of Health-review panel for tissue engineering and related bioengineering research partnership grant applications (NIH, Bethesda) USA

07.2001 to date Nolte L.-P.: Co-director of the Swiss National Center for Competence in Research "Computer Aided and Image Guided Medical Interventions" (http://co-me.ch/)

03.2002 to date Trueb B.: President of the Swiss Society for Biochemistry

06.2002 to date Hunziker E.B.: Associate Editor of Osteoarthritis and Cartilage

15.-18.06.2002 Hunziker E.B.: Co-Organizer of the 4th ICRS Symposium, Toronto, Canada

28.07.-2.08.2002 Hunziker E.B.: Chairman of the Gordon Research Conference of Musculoskeletal Biology and Bioengineering, Andover, NH, USA

08.2002 Chiquet M.: Visiting Professor pro tempore (The Cleveland Clinic Educational Foundation, Dept. Biomed. Engineering, Cleveland, Ohio)

11.2002 Chiquet M.: Nomination for Examiner at preclinical exams (Bundesamt für Gesundheit, Bern)

2003 Hunziker E.B.: Co-founder and vice-chair of the Gordon Research Conference for Cartilage Biology and Pathology, Ventura, CA, USA

8 GUEST PRESENTATIONS

15.1.2002 – Dr. Wolfgang Birkfellner: Stereoscopic Augmented Reality Visualization in a Head-Mounted Operating Binocular. University Hospital Basel, Switzerland

23.1.2002 – Dr. med. dent. G. Gehl: Aesthetic Design in Facial and Somato Restauration. University Hospital Zürich, Switzerland

25.1.2002 – Deborah Baker: Liver Repair using an Argon Beam Coagulator with Albumin. Oregon Graduate Institute of Science and Technology, USA

1.2.2002 – Shannon Vittur: The Effect of an In Vitro Mechanical Environment on the Proliferation and Phenotype of Bladder Smooth Muscle Cells. Georgia Institute of Technology, Atlanta, USA

4.2.2002 – Prof. Michael Liebschner: Tissue Engineering meets CAS – The Future of Spinal Surgery. Department of Bioengineering, Rice University, Houston, Texas, USA

7.3.2002 – Dr. Martin Styner: Morphometry in Medical Imaging. Duke Image Analysis Lab, Dunham, USA

26.3.2002 – Dr. Bernhard Wehrle-Haller: Walk like an Egyptian; analysing melanocyte migration in two and three dimensions. Department of Pathology, University of Geneva, Geneva, Switzerland

25.4.2002 – Riccardo Lattanzi: The Hip-OP Surgical System: A CT-based Software to plan Total Hip Replacement Surgery. Laboratorio Di Technologia Medica, Istituti Orthopedici Rizzoli, Bologna, Italy

21.5.2002 – Prof. Dr. Gabor Székely: Medical Imaging and Image Processing. An Overview. ETH Zürich, Institut für Kommunikationstechnik, Zürich, Switzerland

5.7.2002 – Prof. Zhuang Tian-Ge: Single Rotation Volume Computed Tomography. University of Shanghai, Department of Biomedical Engineering, Shanghai, China

9.7.2002 – Christoph Zolliker: Computer Assisted Paleoanthropology and Virtual Surgery: From Fossils to Patients and Vice Versa. University of Zürich, Multimedia Laboratory and Anthropological Institute, Zürich, Switzerland

16.8.2002 – Daniel Herren: Concepts and Results for the Arthroplastic Elbow Replacement. Schulthess Clinic, Zürich, Switzerland

9.9.2002 – Dr. Robert Gassner: Effects of mechanical strain on osteoblast like periodontal ligament cells. University of Pittsburgh Medical Center, USA

18.9.2002 – Herbert Bühler: E-Learning: How does it work and what is it good for. MindSpring GmbH, Switzerland

16.10.2002 – Prof. Dr. Erich Schneider: Mechanics of Implant Fixation in Osteoporosis: The LISS. AO Research Institute, Davos, Switzerland

9 PERSONNEL

9.1 Faculty

Hunziker Ernst B., M.D., Prof.	Director	11.89 –

* * *

Nolte Lutz-Peter, Ph.D., Prof.	Division Head	05.93 –
Trueb Beat, Ph.D., Prof.	Deputy Division Head	04.95 –
Chiquet Matthias, Ph.D., Prof.	Research Group Head (80%)	05.95 –
Bächler Richard, Ph.D.	Research Group Head	06.96 – 12.02
Ferguson Stephen, Ph.D.	Research Group Head	02.00 –
Langlotz Frank, Ph.D.	Research Group Head	05.93 –
Pappas Ion, Ph.D.	Research Group Head	06.02 –
Studer Daniel, Ph.D.	Research Group Head (20%)	03.92 –
Styner Martin, Ph.D.	Research Group Head	07.02 –
Wong Marcy, Ph.D. PD	Research Group Head (80%)	02.92 –

9.2 <u>Research Associates</u>

Astephen Janie	Ph.D.-Student	10.02 –
Bärtschi Stefan, cand. Phil. Nat.	Diploma-Student	11.01 –
Beutler Thomas, dipl. Ing. HTL	Assistant	05.99 –
Chapuis Jonas	Ph.D.-Student	
Crottet Denis, dipl. Ing./Phys.	Ph.D.-Student	05.01 –
de Siebenthal Julien, dipl. Phys.	Ph.D.-Student	07.00 –
Doll Sara	Exchange Student	06.02 – 12.02
Douta Gisèle, dipl. Inf.	Ph.D.-Student	12.01 –
Driesang Iris, Dr. med. vet.	Assistant	06.96 –
Ebert Brenton	Ph.D.-Student	07.02 –
Gédet Philippe	Assistant	06.02 –
Griessen Roland, dipl. Ing. HTL	Assistant	11.96 –
Goodwin Kelly, M.S.	Assistant	06.00 – 03.02
Hamdan Rida	Ph.D.-Student	11.02 –
Huber François, Dr. Phil. Nat.	Postdoc	08.01 –
Ioppolo James, dip. Ing.	Ph.D.-Student	08.01 – 10.02
Jurgen Stina, dipl. Ing.	Ph.D.-Student	05.01 – 06.02
Kowal Jens, dipl. Ing.	Ph.D.-Student	10.97 –
Kubiak Monika, dipl. Inf.	Ph.D.-Student	11.99 –
Kübele Petra, dipl. Phil. nat.	Assistant	11.01 –
Kurkijärvi Jatta Elina, Student	Practicant	06.02 – 12.02
Künzi Manuel, dipl. Ing.	Assistant	12.01 –
Kunz Manuela, dipl. Inf.	Ph.D.-Student	06.98 –
Li Bo, dipl. Phil. II	Ph.D.-Student	06.99 –
Liang Jane, Mech. Ing.	Ph.D.-Student	08.01 –
Liu Jubei, Dr. Ing.	Postdoc	11.01 –
Malik Puja	Exchange Student	09.02 –
Marx Axel, M.D.	Exchange Student	04.01 – 03.02
Montanari Javier H., Biom. Ing	Ph.D.-Student	10.00 – 04.02
Nolte Michael, Biomed. Ing.	Exchange Student	08.01 – 01.02
Olsen Bjorn	Postdoc	01.02 –
Park Yong Doo, Ph.D.	Postdoc	01.01 – 08.02
Paulonis Jason	Exchange Student	10.02 –
Polikeit Anne, dipl. Ing.	Ph.D. Student	03.98 –
Rajamani Kumar	Ph.D.-Student	09.02 –
Robinson Leanne, Mech. Ing.	Exchange Student	06.01 – 05.02
Rodriquez Paloma, Mech. Ing.	Exchange Student	07.01 – 05.02
Sagbo Serge	Ph.D.-Student	09.02 –
Sarasa Renedo Ana, lic. Biol.	Ph.D.-Student	09.01 –

Schild Christof. dipl. Phil. II	Ph.D.-Student	06.99 –
Schulze Ina, Biomed. Ing.	Exchange Student	08.01 – 01.02
Shintani Nahoko, Ph.D.	Postdoc	11.02 –
Siegrist Mark, dipl. Phil. Nat.	Assistant	07.97 –
Sigrist Christian	Ph.D.-Student	06.02 –
Sing Digvijay	Student	08.02 –
Sinnoqrot Hayel, B.Sc.Inf.	Exchange Student	08.01 –
Sun Jiuai, Dr. Ing.	Postdoc	03.00 – 11.02
Sugimoto Masayuki, M.D.	Postdoc	03.00 – 02.02
Talib Haydar	Student	09.02 –
Tarte Ségolène, dipl. Ing.	Ph.D.-Student	09.99 –
Wang Gongli, dipl. Ing.	Ph.D.-Student	04.00 –
Wälti Heinz, dipl. Inf.	Assistant	12.96 –
Watrin-Pinzano Astrid, Ph.D.	Postdoc	01.02 – 12.02
Wong Ka Ho Stanley, El. Ing.	Exchange Student	07.01 – 06.02
Wyser Urban, Mech. Ing.	Ph.D.-Student	08.01 –
Xue Jinghao, El. Ing.	Postdoc	11.01 –
Zheng Guoyan, Dr. Ing.	Postdoc	03.99 –
Zhuang Lei, dipl. Phil. II	Ph.D.-Student	04.02 –

9.3 Technical and Administrative Staff

Berger Elke	Res. Technologist (50%)	01.90 – 07.02
Fahnemann-Nolte Karin	Secretary (60%)	03.96 –
Fiechter Esther	Secretary (90%)	07.95 –
Gaschen Véronique	Res. Technologist (50%)	09.95 –
Gerber Thomas	Apprentice in Fine Mechanics	08.01 –
Gnahoré Esther	Secretary (70%)	12.90 –
Haarmann Urs	System Manager	10.02 –
Haller Manuela	Secretary (50%)	11.00 – 03.02
Hutzli Walter	Aid Lab. Technician	11.89 –
Kapfinger Eva	Res. Technologist (75%)	11.89 –
Mühlheim Erland	Mechanicien (60%)	01.92 –
Neuenschwander Annelies	Secretary (35%)	04.95 –
Nüssli Simon	Res. Technologist	12.00 –
Reist David	Res. Technologist	06.97 – 10.02
Rohrer Urs	Head Mech. Workshop	07.91 –
Seifriz-Bieri Franziska	Res. Technologist (50%)	08.02 –
Stalder Verena	Secretary (40%)	07.02 –
Täschler Sara	Res. Technologist	08.00 –
Trueb Judith	Res. Technologist	03.01 –
Tunc-Civelek Vildan	Res. Technologist (80%)	09.99 –

9.4 Scientific Consultant

Prof. Dr. Robert K. Schenk, Clinic for Oral Surgery, University of Bern, Switzerland

9.5 Guest Scientists

Dr. Thomas M. Quinn, Biomedical Engineering Laboratory, Department of Applied Physics, Swiss Federal Institute of Technology, Lausanne, Switzerland

Dr. Pierre Mainil-Varlet, Institute of Pathology, University of Bern, Bern, Switzerland

10 MISCELLANEOUS

10.1 Conferences Organized

4th International Meeting of the ICRS, International Cartilage Repair Society, Toronto, Canada, June 15-18, 2002 (Hunziker E.B. Co-Organizer)

Gordon Research Conference of Musculoskeletal Biology and Bioengineering, Andover, NH, USA, July 28 – August 7, 2002 (Hunziker E.B. Chairman)

12th Swiss Cytomeet, Bern, October 30, 2002 (Chiquet M. Co-Organizer)

11 MEMBERS OF THE SCIENTIFIC ADVISORY BOARD (KURATORIUM)