Online Summer School on

„Multiscale Modeling and Bone Pathologies“

with a particular focus on the following topics:

(1) characterization of mechanical and fracture properties of bone; and

(2) realistic computational models and the influence of molecular and biophysical mechanisms on mechanical behavior in the case of osteoporosis, fracture, and healing

organized by the

Institute for Mechanics of Materials and Structures
TU Wien (Vienna University of Technology)

from May 23-24, 2022,

as part of the project

Increasing scientific, technological and innovation capacity of Serbia as a widening country in the domain of multiscale modeling and medical informatics in biomedical engineering (SGABU)

funded by the European Commission
in the framework of Horizon 2020

Meeting-Link: https://tuwien.zoom.us/j/99990916180?pwd=bkZoQkxqZmZTaUFKdEgreWlBdGl0QT09
Password: SGABU2022

May 23, 2022

9:55-10:00	**Welcome address - opening of summer school** Christian Hellmich & Stefan Scheiner / *TU Wien (Vienna University of Technology), Austria;* Nenad Filipovic / *University of Kragujevac, Serbia*
10:00-11:00	**Experimental bone fracture mechanics** Philipp J. Thurner / *TU Wien (Vienna University of Technology), Austria*
11:00-12:00	**Multiscale modeling of bone fracture and damage** Jean-Francois Ganghoffer / *University of Lorraine, Nancy, France*
12:00-13:00	**Lunch break**
13:00-13:30	**Variances and invariances in composition and microstructure across femoral tissues from different vertebrates** Luis Zelaya-Lainez / *TU Wien (Vienna University of Technology), Austria*
13:30-14:00	**Contiuum Micromechanics: From fundamentals to stiffness homogenization (and beyond)** Stefan Scheiner / *TU Wien (Vienna University of Technology), Austria*
14:00-15:00	**Multiscale characterization of mechanical properties of human cortical bone** Marie-Christine Ho Ba Tho / *University of Technology of Compiègne, France*
15:00-15:15	**Coffee break**
15:15-16:15	**Finite Element modeling of bone, bone fractures, soft tissue and skeletal muscle** Nenad Filipovic / *University of Kragujevac, Serbia*
16:15-16:20	**Closing of day 1** Stefan Scheiner / *TU Wien (Vienna University of Technology), Austria*

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May 24, 2022

9:55-10:00	**Opening of day 2** Stefan Scheiner / *TU Wien (Vienna University of Technology), Austria*
10:00-11:00	**Advances in mechanistic pharmacokinetic-pharmacodynamic modeling of postmenopausal osteoporosis treatments** Peter Pivonka / *Queensland University of Technology, Brisbane, Australia*
11:00-12:00	**Multiscale modeling of fracture healing** Hans van Oosterwyck / *KU Leuven, Belgium*
12:00-13:00	**Lunch break**
13:00-14:00	**Experimental investigation of implant-bone anchorage of pedicle screws** Werner Schmölz / *Medical University of Innsbruck, Austria*
14:00-15:00	**Mechanical stimuli potentially governing the mechanobiology of bone computed by means of micromechanics-based models** Stefan Scheiner / *TU Wien (Vienna University of Technology), Austria*
15:00-15:15	**Coffee break**
15:15-16:15	**Uncertainty quantification in multiscale modeling of bone elasticity** Vittorio Sansalone / *Université Paris-Est Créteil Val de Marne, France*
16:15-16:20	**Closing of summer school** Christian Hellmich & Stefan Scheiner / *TU Wien (Vienna University of Technology), Austria*

Meeting-Link: https://tuwien.zoom.us/j/99990916180?pwd=bkZoQkxqZmZTaUFKdEgreWlBdGl0QT09
Password: SGABU2022

EXPERIMENTAL BONE FRACTURE MECHANICS

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Abstract:

Bone fractures in humans, and, especially, fragility fractures in the elderly and the diseased are of high clinical interest. Currently, even modern diagnostic tools at hand to not outperform classical bone density measurements for predicting fragility fractures.

In the first part of this lecture, I will address this issue, give reasons why this happens and where the problems lie. This is a major motivation for bone research and in particular bone fracture mechanics.

In the second part of the lecture, I will address the factors influencing bone fracture. Here, three factors are identified and discussed in class:

- likelihood of an event leading to a fracture e.g., a fall (hip fracture) and load imposed during such an event (this is a case for movement biomechanics),
- the loads imposed and the geometry of the bone (organ) in question e.g., the femoral neck,
- the mechanical or material properties of the bone at the fracture location.

From these considerations the influence of geometry can be assessed through analytical and computations models. As an example, I will show an analytical study found in literature considering bone as a linear elastic and brittle material that allows variation of geometry, bone mass and in principle also material properties. This leads to the third part of the lecture, the investigation of the mechanical and material properties of bone and especially the fracture mechanics. In this part I will motivate fracture mechanics measurement, show some general insights into fracture mechanics of human bone, elucidate toughening mechanisms and where within the bone ultrastructure fractures initiate.

MULTISCALE MODELING OF BONE FRACTURE AND DAMAGE

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Abstract:

The yield and failure properties of trabecular bone are of key interest in understanding and predicting the fracture of bones and bone implant systems. The discrete homogenization technique is presently developed as a convenient micromechanical approach to construct the plastic yield surfaces of 2D and 3D bending-dominated periodic lattices of articulated beams considered as prototype topologies for cancellous bones. Thereby, the initial trabecular lattice is substituted by an effective Cauchy continuous medium at an intermediate scale, endowed with effective properties representative of an identified representative unit cell within the structure. The cell walls of the bone microstructure are modeled as Timoshenko thick beams taking into account stretching, transverse shearing, and bending deformations. In the case of plastic yielding, the cell struts of trabecular are assumed to behave in an elastic-perfectly plastic manner. The effective strength of trabecular bone is evaluated in the two situations of fully brittle (fracture with no tissue ductility) and fully ductile failure (yield with no tissue fracture) of the trabecular tissue.

A size-dependent non-classical plastic yield criterion is developed relying on the reduced Cosserat theory to capture the size-dependency of the trabecular bone structures. Size effects appear when the characteristic size of the bone sample is comparable to the bending length.

In the second part of the presentation, we propose a two-dimensional constitutive model for trabecular bone combining continuum damage with embedded strong discontinuity. The model is capable of describing the three failure phases of trabecular bone tissue which is considered herein as a quasi-brittle material with strains and rotations assumed to be small and without viscous, thermal or other non-mechanical effects. The performance, accuracy and applicability of the proposed model for trabecular bone fracture are evaluated and validated against experimental measurements. These comparisons include both global and local aspects through numerical simulations of three-point bending tests performed on ten single bovine trabeculae in the quasi-static regime.

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VARIANCES AND INVARIANCES IN COMPOSITION AND MICROSTRUCTURE ACROSS FEMORAL TISSUES FROM DIFFERENT VERTEBRATES

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Abstract:

There is a non-deniable macroscopic difference between organs of different species and osseous organs within the same individual [1,2]. In the case of the femoral bone, we can observe quite visible distinctions between vertebrates at the centimeter and meter scales. However, once we get deeper into the micro-scale, the extracellular space, which consists of hydroxyapatite crystals, collagen type I molecules, and water with non-collageneous organics [3,4], exhibits a "universal" pattern among different animals. This determination is based on investigating associated quantities within the extracellular bone matrix. The amounts as mentioned above were inspected in femoral shaft tissues from cow, horse, emu, frog, ostrich, pig, and rabbit through light microscopy and dehydration-demineralization tests; thereby revealing interesting invariances: The extracellular volume fractions of organic matter turn out to be similar across all tested non-amphibian tissues; as do the extracellular volume fractions of hydroxyapatite across all tested mammals [5]. Hence, the chemical composition of the femoral extracellular bone matrix is remarkably "invariant" across differently aged mammals. At the same time, the water content shows significant variations, as do the partitions of water between the different pore spaces. The latter exhibit strikingly varying morphologies as well. This finding adds to the ample "universal patterns" in the sense of evolutionary developmental biology [6], and it provides exciting design requirements for developing novel biomimetic tissue engineering solutions. Furthermore, considering the apparent mass densities from several mammalian and avian species, there emerges a unique bilinear relationship between mineral and organic matter [7].

References:

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CONTIUUM MICROMECHANICS: FROM FUNDAMENTALS TO STIFFNESS HOMOGENIZATION (AND BEYOND)

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Abstract:

Hierarchically organized materials are often, meahwile even standardly dealt with by means of so-called multiscale methods, implying that information on the various relevant observation scales are accounted for. One of these methods is referred to as continuum micromechanics, which turned out to be a reliable and accurate modeling concept for a range of different engineering materials, including bone tissue.

This presentation aims at explaining the fundamentals of continuum micromechanics, when focusing on its simplest form of application; i.e. on stiffness homogenization. In particular, the notion of a representative volume element [1] is introduced, and the boundary value problem leading to the well-known strain and stress averaging rules is reviewed [2]. Considering the studied material‘s microstructure in an approximative way, by means of materials phases, describing the constitutive behavior on the microscopic scale by means of Hooke‘s law, and accounting for the solution of the classical matrix-inclusion problem introduced by Eshelby [3] eventually allows for deriving a stiffness homogenization scheme [2].

Finally, application of the stiffness homogenization to bone tissue [4], as well as its extension to more intricate mechanical behavior, such as to strength [5] and to viscoelasticity [6] is briefly explained.

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MULTISCALE CHARACTERIZATION OF THE MECHANICAL PROPERTIES OF HUMAN CORTICAL BONE

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Abstract:

Mechanical properties of cortical human bone have been investigated for more than four decades. Numerous experimental investigations on bone characterization were performed; mechanical, vibrational, acoustical testing and morphological, physico-chemical investigations. Due to the techniques, different levels of investigation were performed and subsequently quantitative parameters are concerning different level of structure of bone (organ, tissue,...). According to our knowledge, few investigations were performed simultaneously on mechanical, morphological and physico-chemical properties of bone. The objectives of the present study were to investigate the

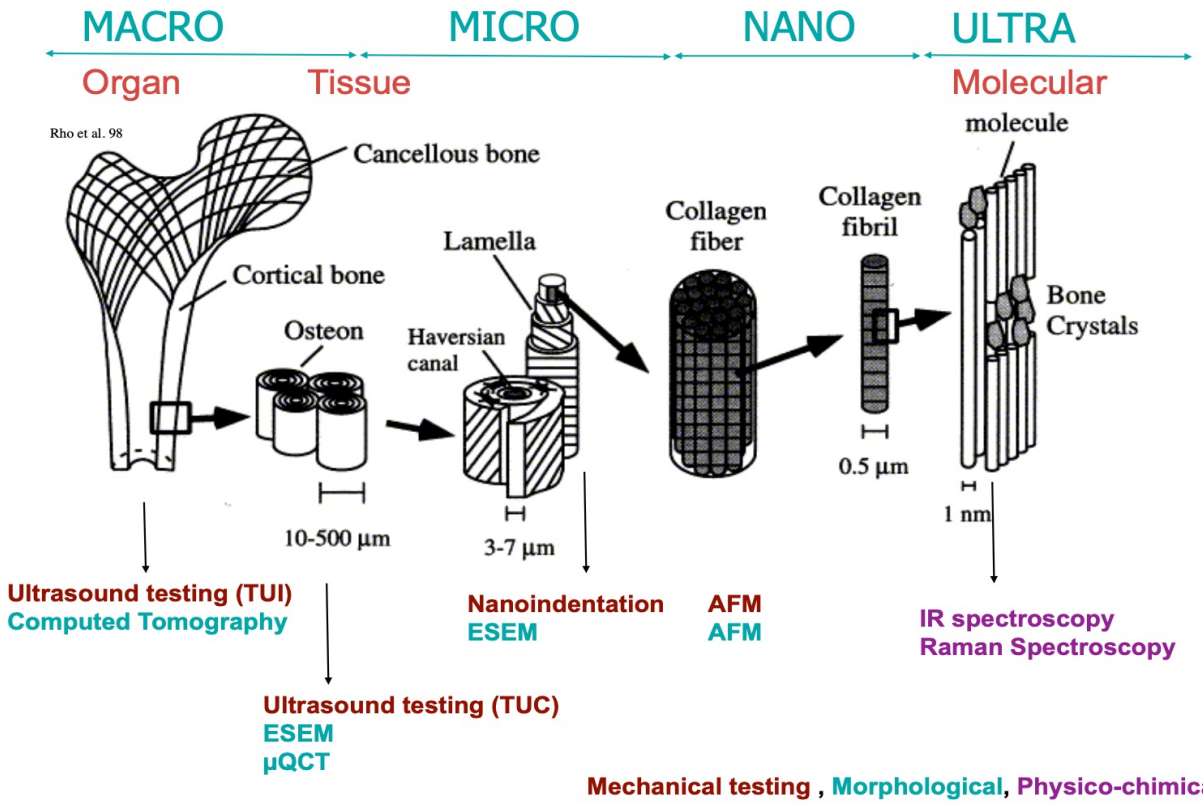

Figure 1: Identification of different techniques of measurements performed at different scales; Figure extracted from [2], modified.

influence of multiscale structural characteristics of the bone tissue on its mechanical behavior and to provide some estimations from micro-macro numerical modelling based on our experimental data.

These results will contribute to get a better understanding of the multiscale mechanical behavior of human cortical bone. In fact, the relationships between the mechanical behaviour of the bone at different scales will allow to get a better knowledge of the impact of the alterations of the mechanical properties from a scale to another scale. These results are of importance when dealing with numerical simulations to design, evaluate medical treatment (orthoses, implant devices, therapeutic medicine ...) for repairing or healing bone pathologies.

Different methods of measurements performed at different scales of the bone will be illustrated as shown in Figure 1. Examples of clinical, industrial applications will also be addressed.

References:

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FINITE ELEMENT MODELING OF BONE, BONE FRACTURES, SOFT TISSUE AND SKELETAL MUSCLE

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Abstract:

In this lecture, Finite Element (FE) modeling of bones, and bone fractures is presented firstly. The fundamentals of the structure and forms of bones are given. Then, the mechanical properties of bone tissue used in the FE models are described. Also, the general FE dynamics equations for bone analysis are given. Typical bone fractures are described next, including medical aspects and several practical solutions. The FE models and solutions are presented for: a) comminuted femur fracture, with fixation by the neutralization plate, and by the intramedullary nail; and b) hip fracture with internal fixation, using the solutions by parallel screws and by dynamic hip implant. The solutions for fracture fixation are compared with respect to the advantages in medical practice applications.

Then, the structure of biological soft tissue and basic experimental testing procedures for determining constitutive relations are presented. The most common expressions for the constitutive laws are given, including both tissue and surfactant which usually covers the tissue. The focus was on soft tissues of the planar (membrane) type which are met in hollow organs such as the lung parenchyma and pleura, stomach, mucous membranes, bladder, uterus, skin, eye, endocardium and pericardium. These tissues usually experience very large strains and stretches in the normal physiological conditions.

Finally fundamentals of skeletal muscle (further called muscle) mechanics and the numerical algorithms, based on the FE method, for the determination of the muscle response have been presented. Hill's three-component phenomenological model was used as a basis for analysis. In order to include muscle fatigue, an extension of Hill's model was introduced. Considering muscle as a bundle of sarcomeres of various physiological properties, modification of Hill's three-component model to take into account different fiber types has been presented. Two typical examples, a cylindrical muscle and a biceps muscle, are given as examples for which the corresponding software can be used to investigate muscle mechanical response for various geometrical and material parameters, as well as loading, activation, fatigue and relaxation conditions.

Each part of presentation has illustrative examples with finite element software PAK which has been developed at University of Kragujevac in Serbia many years.

References:

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ADVANCES IN MECHANISTIC PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF POSTMENOPAUSAL OSTEOPOROSIS TREATMENTS

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Abstract:

Osteoporosis (OP) is a chronic progressive bone disease which affects a large portion of the elderly population worldwide. OP is characterized by a slow reduction of bone matrix and changes in the bone matrix properties which ultimately leads to whole (organ) bone fractures [1].

Novel drug treatments are developed to more effectively reduce the risk of bone fractures. Assessing the effects of novel and existing treatments on OP is challenging due to the complexity of the bone remodeling process, its effects on the bone matrix and the different spatial and temporal scales involved. Identification and characterization of various bone biomarkers has significantly improved our understanding of OP pathophysiology. The bone matrix and its constituents are specific bone biomarkers measured at a particular bone site. On the other hand, biochemical ligands released during bone remodeling and measured in blood or urine are non-specific bone biomarkers. These biomarkers can be used to characterize the underlying bone mechanobiological system and drug treatment effects [1].

Recently, disease system analysis (DSA) has been proposed as a novel approach to quantitatively characterize drug effects on disease progression [1]. DSA integrates physiology, disease progression and drug treatment in a comprehensive mechanism-based modelling framework using a large amount of complementary biomarker data. In this summer school, I will present latest mechanistic pharmacokinetic-pharmacodynamic (PK/PD) models of osteoporosis treatment. Examples of currently used drug interventions including denosumab [2,3] romozosumab [4], and PTH [5] treatments will serve as discussion points on which mechanisms are essential for accurate bone remodeling simulations. Bone matrix mineralization turns out to be an essential model feature that is required to predict BV/TV changes for the case of anti-catabolic drug treatments of OP [3].

Acknowledgments: Dr. Pivonka acknowledges support from the Australian Research Council (IC190100020).

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MULTISCALE MODELING OF FRACTURE HEALING

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Abstract:

In my lecture I will present our previously published multiscale model of fracture healing and its application to the study of large, non-healing segmental bone defects. The model focuses on the importance of angiogenesis – the formation of new blood vessels from pre-existing ones – for bone regeneration, through its effect on oxygenation and the fact that oxygen affects cell survival, proliferation and differentiation and the secretion of vascular endothelial growth factor (VEGF). From a mathematical point of view, the model is composed of partial differential equations to capture the spatio-temporal dynamics of continuum variables that represent concentrations of cells, extracellular (soluble) signals and (insoluble) matrices. In addition, we made use of an agent-based representation of endothelial cells that can migrate based on local concentrations of VEGF and its effect on Notch signaling. The PDE and agent-based model are coupled, resulting in a hybrid, multiscale model.

I will illustrate the basic model ingredients, in particular the governing mechanisms and the way they are translated into equations. Furthermore, I will show how the model can help in understanding the etiology of large non-healing fractures as well as exploring treatment strategies.

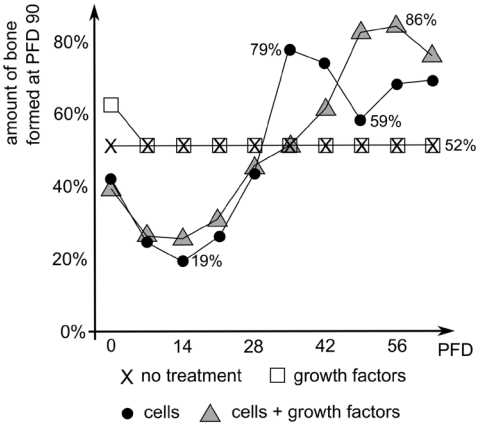

Figure 1: Predicted amount of bone formation at post fracture day (PFD) 90 in a large segmental bone defect as a function of the PFD at which the treatment was initiated. The treatment consists of a single injection of cells, growth factors or a combination thereof. Cellular injections before PFD 28 result in less bone than no treatment (taken from [1]).

References:

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EXPERIMENTAL INVESTIGATION OF IMPLANT-BONE ANCHORAGE OF PEDICLE SCREWS

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Abstract:

Introduction: For in vitro comparisons of various pedicle screw designs or augmentation techniques axial pullout tests are frequently used and published by some authors. Pullout tests are relatively easy and quick to perform. However, their clinical relevance is limited because in vivo investigations with instrumented implants pointed out that pedicle screws are mainly loaded in cranio-caudal direction with a superimposed bending moment and only with a very small component of axial pullout force. Therefore, a test setup applying an increasing cyclic load in cranio-caudal direction superimposed with a small bending moment was developed. In the course of several experiments the load protocol was refined to investigate pedicle screw anchorage with varying augmentation techniques and materials in vertebral bodies with reduced bone quality. The failure load magnitudes of the non-augmented and augmented pedicle screws were compared to in vivo measurements of an internal fixator instrumented with telemetric load sensors.

Material and methods: Several in vitro experiments to investigate pedicle screw loosening have been conducted. The design of all experiments was a left right pedicle screw comparison of different augmentation techniques and materials to improve screw anchorage. Overall a total of 128 pedicle screws implanted in 64 vertebral bodies were cyclically loaded until failure in a servohydraulic material testing machine. The vertebral body was fixed on an x-y bearing table to allow motion in one plane and the loading was applied with a lever arm of 15mm to the screw head and free rotation. The relative motion of the pedicle screw in the vertebral body was recorded with a motion analysis system attached to the screw head and the fixation of the vertebral body. In initial experiments the load was applied in force control with a continuously increasing load magnitude in compression. Further experiments were conducted in displacement controlled load application with stepwise increasing force limits in compression and a constant force limit in tension, which enabled a real time analysis of the force slope to detect the onset of pedicle screw loosening.

Results: In vertebral bodies pedicle screws implanted in a standard non augmented technique (n=51) showed a mean failure load around 230N with some screws implanted in vertebrae with reduced bone quality loosening already at 140N. Pedicle screws augmented with different techniques and cements (n=77) all reached a mean failure load above 400N in all techniques with some screws implanted in vertebrae with reduced bone quality becoming loose at 250N.

Discussion: For non-augmented screws the main failure mode was a cut out of the screw through the cranial endplate. Both, the force and displacement controlled load application showed comparable failure loads for augmented and non-augmented pedicle screws. However, in the force controlled loading the load application rate increased with increasing screw motion, while the displacement controlled load had a constant loading rate and allowed to evaluate the loosening mechanism due to loading in compression and tension. Comparing the failure loads with in vivio measurements with an internal fixator showed, that reported peak forces for everyday activities (200-250N) can be higher than the failure loads found for non-augmented screws, while with all augmentation techniques and materials the failure loads for pedicle screws was higher than reported loads during everyday activities.

COMPUTATION OF MECHANICAL STIMULI POTENTIALLY GOVERNING THE MECHANOBIOLOGY OF BONE BY MEANS OF MICROMECHANICS-BASED MODELS

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Abstract:

Bone is often referred to as „living material“, implying that it can adapt to its immediate environment (in terms of both its composition and even its shape). If the stimuli to which bone is exposed change, correspondingly modified activities of the cells residing inside bone are initiated, altogether inducing the aforementioned adaptations. Overall, this process is called bone (re-)modeling. The underlying signalling pathways are governed both biochemically and mechanically, rendering bone (re-)modeling a *mechanobiologically* regulated process. For example, it has been shown that the production of a specific ligand, called RANKL, decreases with increasing mechanical loading. Upon binding to the receptor RANK, RANKL is needed to maintain the differentiation of bone-resorbing osteoclasts [1]. Hence, reducing the mechanical loading leads to an increased resorption of bone tisse, and, in further consequence, to a higher bone porosity.

Mathematical models involving the activities of bone cells and the consequences thereof need to account for the mechanobiological regulation mechanisms, in order to yield results of satisfying accuracy. To that end, it is of particular interest which mechanical stimuli cells (or other biological factors involved in the process of bone (re-)modeling), which are located in the pore spaces distributed in bone across several orders of magnitude in length scale, actually sense, see Figure 1. In this context, several stimuli have been proposed over the past 90 years or so, including electromagentic fields, hydrostatic pressure, fluid flow-induced shear stresses, cell stretching, or damage [2]. All of these stimuli were shown to provoke cellular responses in vitro, hence they can be - in principle - considered as mechanobiologically effective. However, one may ask the crucial question as to which of the mentioned stimuli arrive, in response to physiologically relevant loading scenarios, at the sites of the relevant biological cells and factors in the bone pore spaces at sufficient magnitudes. Due to the small sizes of the involved pore spaces, it is virtually impossible to address this question experimentally. Continuum micromechanics-based multiscale models [3] provide a remedy to this predicament.

Continuum micromechanics provides strain and stress concentration relations, mathematically linking - via linear relations - macroscopic and the corresponding microscopic strains and stresses. This concept can be extended in order to also account for the presence of microscopic (and, consequently, also macroscopic) eigenstresses. Introducing the latter in terms of (hydrostatic) pressures which are exhibited by the fluid available in pore spaces (which, in turn, are represented as material phases), gives access to the concept of microporomechanics, which provides, in addition to stiffness homogenization, a mathematical framework for calculating the pressues occurring in the pore spaces of the studied material [4]. Utilizing some formal analogies [5] even allows for adapting the concept of stiffness homogenization to the homogenization of Darcy‘s law, giving eventually access to pore-scale fluid flow velocities, in response to macroscopically applied stress gradients.

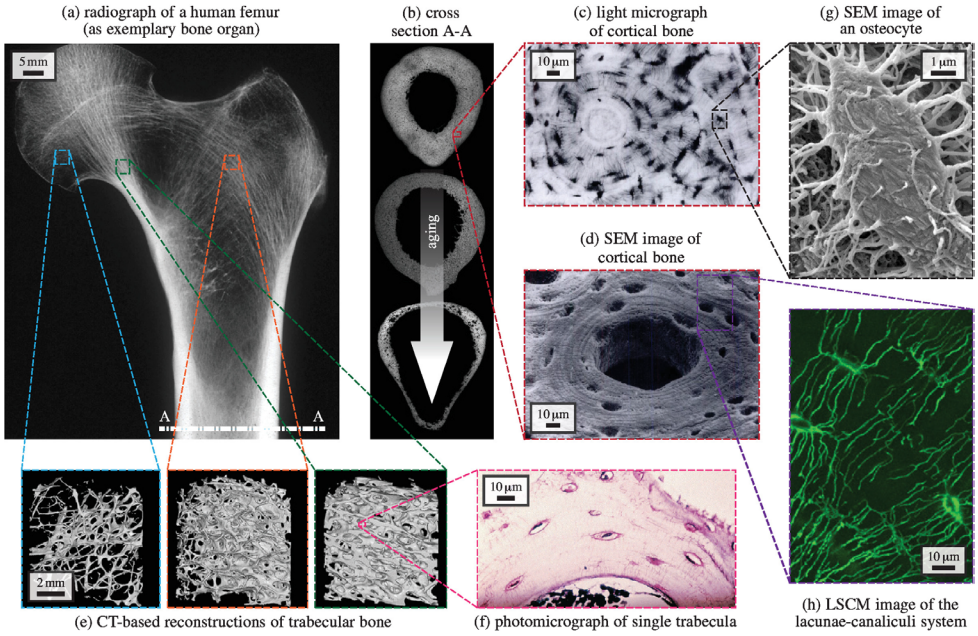

Figure 1: The bone remodeling-relevant part of the hierarchical organization of bone, comprising an exemplary human femur (a); cortical bone, showing vascular and lacunar pore spaces (b)-(d); trabecular bone, also showing vascular and lacunar pore spaces (e)-(f); osteocytes residing in the lacunar pores (g); and the lacunae-canaliculi network (h). This image has been reproduced from [7], where all image sources are listed.

The above-sketched theoretical concepts have been applied for estimating the microscopic strain energy density experienced by the extravascular bone matrix [6], the hydrostatic pressure to which the vascular and lacunar pores of bone are exposed [7], and the fluid flow velocities occurring in the vascular and canalicular pores of bone [8], in response to physiological macroscopic loading conditions. Briefly summarized, the mentioned studied have suggested that (1) the microscopic strain energy density is a reasonable approximation of the „true“ mechanical stimulus of bone (re-) modeling; that (2) the hydrostatic pressure is indeed a promising candidate as mechanobiologically relevant stimulus in bone; and that (3) the fluid flow-induced shear stresses are probably overrated in terms of their relevance in bone mechanobiology, especially for osteocytes. in conclusion, continuum micromechanics-inspired multiscale models have provided unprecedented insights as regards the mechanical stimuli relevant in bone mechanobiology. In the future, these findings could serve as valuable basis for more realistic models of bone (re-)modeling-related processes.

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UNCERTAINTY QUANTIFICATION IN MULTISCALE MODELING OF BONE ELASTICITY

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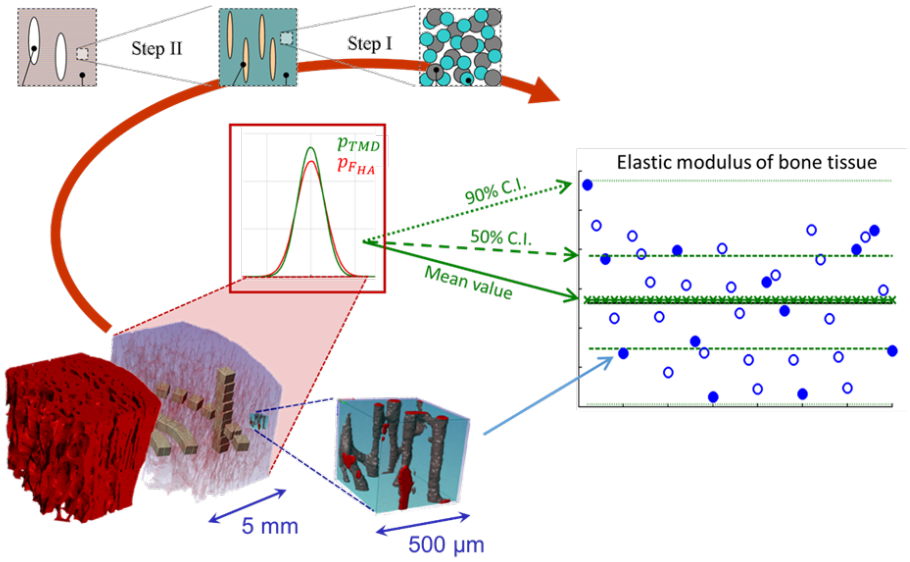
Abstract:

Accurate and reliable modeling of bone elasticity at the organ scale requires to take into account the specific microstructure of bone. High-resolution X-ray based methods, such as synchrotron radiation micro-computed tomography (SR-μCT), can provide accurate information on bone architecture and composition in vitro. Focusing on cortical bone, the most relevant microstructural information concerns the Haversian Porosity (HP) and the Tissue Mineral Density (TMD). This information can be used to set up detailed Finite Element (FE) or homogenization models of bone which allow studying the heterogeneous distribution of the elastic properties of bone tissue. Unfortunately, these approaches cannot be applied easily in vivo. Indeed, technical limitations of experimental devices prevent resolving details of bone microstructure accurately and may produce blurry, uncertain data. Since input data are uncertain, deterministic approaches are limited and new modeling paradigms are required.

Probabilistic approaches offer new and powerful opportunities to face these challenges. In this contribution, we will present an overview of the issues related to uncertainty in image-based modeling of bone elasticity and discuss the benefits and drawbacks of a new approach which may be used to tackle them in a multiscale setting [1-3]. In this scope, uncertain experimental data are modeled as random variables and the Maximum Entropy (MaxEnt) principle is used to build their probability laws. This approach is applied to a bone sample taken from the inferior femoral neck of



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an elderly patient by extending the deterministic homogenization model proposed in [4]. Results of the stochastic homogenization model are compared with those of detailed FE simulations in order to explore the capabilities of this new approach to describe the statistics (mean value, confidence intervals …) of the elastic coefficients of bone.

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