WORKSHOP 2

Personalized Fracture Risk Assessment and Treatment in Osteoporosis: From Population-Based to Patient-Specific Medicine

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A personalized, integrative approach towards the estimation of bone fracture risk

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In spite of the considerable work done in the area of fracture risk estimation, our ability to predict which patients are at greater risk of experiencing a low-energy bone fracture in the coming few years is still not satisfactory.

Attention so far has been focused on fragility of the skeleton, induced by physiological age-related osteopenia, or by pathological osteoporosis. While it is already possible to generate physics-based organ models from medical imaging data that are capable of predicting the biomechanical strength of a patient’s bones with great accuracy, this is clearly not sufficient for daily clinical diagnosis. To accurately predict the risk of bone fracture we need also to account for the risk of falling and overloading during the daily life of the patient.

Even assuming we can accurately predict the strength of the patient’s skeleton, as well as the loading spectrum that the skeleton will be exposed to during the patient’s daily life, the risk of fracture can at best be predicted for the patient in the current condition. However, any useful risk indicator must provide a probability of fracture risk over a significant period of time, that, in this context, is usually assumed to be between five and ten years. To account for the progression of the disease over time, we need to predict how the cellular activity will change over time, how such activity will transform the bone tissue, and how the strength of the bone will be affected by such changes.

To summarize: in order to accurately predict the risk of low-energy bone fracture over ten years for each patient we should account for the spectrum of loads applied to the skeleton (which can be defined at the body scale); the strength of the bones (which can be defined at organ scale); the effect of changes to the bone tissue morphology on its strength (which can be defined at the tissue scale); and how alterations in the metabolism of bone cells modifies over time the tissue morphology (which can be defined at the cell scale).

It is possible to use gait analysis, electromyography, whole body imaging, and wearable sensors to quantify the physical activity at the body level [1]; in cadaver bones, it is possible to measure their strength in relation to the bone properties [2]; we can measure the bone tissue morphology and its biomechanical properties in relation to given pathologies [3, 4]; and animal models can be used to create controlled experiments on how the metabolic and biomechanical modulation of cellular activity modifies the tissue morphology [5]. The same animal model can be used to investigate the effect of pharmacological treatment, while cadaveric models can provide information on the effect of interventional treatment [6]. But how can we put everything together? How can we account for the interactions and interdependences that all these processes have, especially considering they are defined at radically different scales?

In this workshop we shall propose a strategy where computer models that capture the current knowledge of each process described are composed into a hypermodel, a multiscale and probabilistic computational framework, so as to account for all processes simultaneously and in an integrative fashion. In addition, we shall briefly explain how these models can be informed with a combination of patient-specific and population-specific data, so as to obtain highly personalized predictions of the risk of fracture.
Bibliography


Internal forces of many multiples of body weight are known to act within the musculoskeletal structures of the human body during normal functional activities of daily living. Access to these forces is critical for allowing subject-specific prediction of fracture risk, but is also required before an in-depth understanding of mechano-sensitive adaptation processes can be gained. Implants capable of measuring the in vivo forces have only been implanted in a few individuals, however, and these offer an assessment of the loading conditions only at very specific regions. Validated musculoskeletal models that consider subject-specific anatomy, kinematics, and kinetics are able to provide the loading conditions in individuals throughout the body, but can also utilize computational power to provide access to the conditions in larger populations. A comprehensive understanding of an individual’s spectrum of loading, however, cannot be achieved by considering the subject-specific loading conditions during typical activities alone. One key aspect for determining a more complete picture of the musculoskeletal load spectrum in an individual requires additional access to the frequency of occurrence of different activities. Here, novel technologies allow access to the frequency of normal activities of daily living and expand the understanding gained from well-controlled experiments in the laboratory to conditions experienced in a subject’s native environment.

This workshop presentation focuses primarily on approaches that provide access to the spectrum of subject-specific internal loading conditions that occur in the proximal femur and thoracolumbar spine, but will also examine methods that allow rapid access to the range of conditions to be found within target populations.

Methodological accuracy and validation of musculoskeletal modelling approaches is known to be critical for accessing subject-specific conditions. Here, we will demonstrate approaches for examining the accuracy of loading predictions in the thoracolumbar spine as well as proximal femur, but also introduce methods on how these techniques can be utilized to identify factors that critically influence the internal loading conditions in an individual but also across populations.
With advances in patient-specific simulations of bone competence, we have arrived at the point where a reliable and precise prediction of the risk of fracture can be made. Combining data on bone density, musculoskeletal loading, organ-scale geometry and tissue-scale morphology for the prediction of fracture risk, we propose that each individual patient should be assigned to a preferential treatment path, reflecting the urgency of their prognosis. This assignment represents an important decision, with profound consequences for the clinical outcome. Options include continued observation, pharmacological treatment or direct intervention to mechanically reinforce weakened bone e.g. with a biomaterial. Our goal is to provide the clinician with software tools to facilitate this decision.

In this workshop we cover the current state-of-the-art in predictive algorithms for exploring and quantifying the probable outcomes of both pharmacological treatment and bone augmentation procedures.

On the cellular level, osteoporosis originates from an imbalance of osteoblastic and osteoclastic activity, resulting in changes to the bone microstructure. Since the time scale of the remodelling process is on the order of months or years, computational modelling offers a unique approach to study long-term processes. A microstructural model that calculates the respective strain energy density rate and uses this as indicator for the amount of bone formation directly from cellular activity has been introduced and validated against in vivo data from a mouse model. This model reflects bone alterations in response to estrogen depletion by ovariectomy (OVX) and/or treatment with parathyroid hormone (PTH) and bisphosphonates (BIS) as well as cyclic mechanical loading (Figure 1). Errors for bone volume density in all studies ranged from 0.1-2.4%. Trabecular number was also accurately simulated with errors of less than 5% and errors in trabecular spacing ranging from 0.7-8.7%. This microstructural prediction model opens the door to patient-specific simulation of microstructural changes over time with respect to aging, disease and treatment.

In the event that the remodelling simulations predict an unsatisfactory response to e.g. pharmacological treatment, the option remains to directly intervene and mechanically reinforce the bone with an injected biomaterial. This treatment option has found rapid acceptance for the stabilization of vertebral compression fractures (“vertebroplasty”), however the effectiveness remains controversial and the prophylactic application a potentially promising but unproven option. In the workshop, we outline the development and application of multi-scale, multi-physics simulations for interventional treatment planning, covering the prediction of biomaterial flow characteristics through porous bone and the mechanical reinforcement achieved in the mixture of bone and biomaterial, again in a patient-specific fashion. Starting with a clinician’s proposed treatment approach – location and volume of delivered biomaterial – multi-phase flow simulations are used to determine biomaterial filling patterns in trabecular bone, and to predict any potential complications related to leakage (Figure 2). The mechanical performance of the bone / biomaterial composite has been re-examined at the microstructural level, employing microCT-based simulation models to explore the biomaterial-specific outcome of augmentation, considering also subtle interactions at the bone / biomaterial interface related to adhesion that are not captured in a conventional rule-of-mixtures approach. Currently, error levels of < 10% and < 15 % have been shown for the biomaterial flow and mechanical models, respectively. Simulations of the organ-scale bone augmentation can be thus carried out in an iterative fashion until an optimal treatment effect can be achieved (Figure 3).

Closing the circle to the remodelling simulations, the influence of a biomaterial augmentation on the post-treatment adaptation of bone around the reinforced region can then be carried out. Here we demonstrate simulations based on microstructural models of whole vertebrae, which have proven the feasibility of predicting bone remodelling on the trabecular scale for the whole bone and have highlighted the variation in bone adaptation provoked by the presence of an augmenting biomaterial (Figure 4). With the further improvement of such simulation models, the clinician faced with an at-risk patient will be able to plan a pharmacological and/or interventional treatment and explore predictions.
of both the short- and long-term clinical outcome, with the ultimate goal to optimize the benefit for each individual patient.

Figure 1: Correspondence between simulated and experimentally measured bone adaptation to PTH and BIS therapy

Figure 2: Fluid streamlines for micro-scale simulation of biomaterial flow through bone

Figure 3: Normalized bone failure prediction, post-augmentation

Figure 4: Bone remodelling simulation reflecting micro-architectural changes in a full vertebra model