Multiscale modelling and nonlinear finite element analysis as clinical tools for the assessment of fracture risk

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The risk of osteoporotic fractures is currently estimated based on an assessment of bone mass as measured by dual-energy X-ray absorptiometry. However, patient-specific finite element (FE) simulations that include information from multiple scales have the potential to allow more accurate prognosis. In the past, FE models of bone were limited either in resolution or to the linearization of the mechanical behaviour. Now, nonlinear, high-resolution simulations including the bone microstructure have been made possible by recent advances in simulation methods, computer infrastructure and imaging, allowing the implementation of multiscale modelling schemes. For example, the mechanical loads generated in the musculoskeletal system define the boundary conditions for organ-level, continuum-based FE models, whose nonlinear material properties are derived from microstructural information. Similarly microstructure models include tissue-level information such as the dynamic behaviour of collagen by modifying the model’s constitutive law. This multiscale approach to modelling the mechanics of bone allows a more accurate characterization of bone fracture behaviour. Furthermore, such models could also include the effects of ageing, osteoporosis and drug treatment. Here we present the current state of the art for multiscale modelling and assess its potential to better predict an individual’s risk of fracture in a clinical setting.

Keywords: bone strength; multiscale modelling; nonlinear; finite element

1. Introduction

Osteoporosis is a disease characterized by a reduction of mineralized bone and an altered bone microstructure leading to an increased risk of fracture. It is a large and growing concern for public health, as one in three women and one in five men over the age of 50 years are predicted to suffer a fracture in their
remaining lifetime (US Department of Health and Human Services 2004; Bouxsein 2008). Owing to the increasing elderly population, the incidence in osteoporotic fractures is expected to rise dramatically over the next decades. Fractures in elderly patients can be fatal. The risk of mortality is 3–4 times higher among hip fracture patients during the first three months after the fracture, when compared with the risk among individuals of similar age who have not previously suffered a fracture. As of today, several drug therapies are able to reduce the number of fractures; however, they are not able to eliminate osteoporotic fracture completely (Black et al. 1996).

For a better understanding of the underlying structural and systemic changes caused by osteoporosis as well as its pharmacological treatment and how they relate to bone strength, there is a need for simulations to assess the mechanical properties and failure mechanisms of bone. This can be achieved using the finite element (FE) method. Moreover, FE simulations would allow clinicians to directly predict bone strength, estimate the risk of fracture and implement relevant preventative measures in individual patients. Simulations of bone’s mechanical properties could also be used for evaluating the effectiveness of pharmacological interventions preventing bone loss (Keaveny et al. 2007).

In clinical practice the functional competence of bone is currently assessed by quantifying the amount of mineralized tissue using dual-energy X-ray absorptiometry (DXA). However, skeletal stability is determined not only by the mineralization of the bone, but also by the cortical and trabecular microarchitecture (Ulrich et al. 1999), which cannot be assessed using DXA measurements. In addition to bone mineralization and microstructure, a multitude of factors have been identified that determine the bone’s ability to withstand fractures. Individual variations of the bone geometry can strongly influence the distribution of load throughout the bone. Simulations considering patient-specific bone geometry have been shown to predict local strains and failure in the proximal femur more accurately (Schileo et al. 2007). Loading through muscles and possible loading scenarios such as falls can dramatically alter how bones are loaded and thus also determine the likelihood of fractures. Variations in external loading conditions are demonstrated by studies that acquire measurements from instrumented implants (Bergmann et al. 2004). At much lower scales, the intrinsic material properties of bone, i.e. the heterogeneous distribution of organic and inorganic constituents, determine the strength of bone (Rho et al. 1998; Tai et al. 2007). Additionally, most of the above factors are influenced by bone remodelling, which in turn is determined by an individual’s level of activity (Cummings et al. 1995), their age, disease state and treatments, if any (Riggs et al. 1998). Predicting bone strength is therefore a problem spanning both time and multiple scales, from the tissue level to organ level up to the body level (figure 1; Cristofolini et al. 2008; Viceconti et al. 2008).

Assessing the mechanical properties of human bones and thus predicting their failure is a problem that can be suitably addressed using the FE method. Here, we review the current linear and nonlinear FE models and how they incorporate information from multiple scales to optimize the prediction of bone strength. We then address the issues associated with the implementation of this multiscale approach to better predict a patient’s individual risk of fracture in a clinical setting.
Figure 1. Schematic of a multiscale modelling approach, containing (from the left) a body-level model, an organ-level model of the femur, a micro-CT image of a cylindrical specimen extracted from the femoral head with a histological image from the diaphysis, and images of the osteonal structures in the cortex. Copyright of the Living Human Digital Library Consortium (LHDL, www.livinghuman.org); reproduced with permission.

2. Organ-level FE models

Organ-scale FE models do not resolve the bone’s microstructure (figure 2) but describe the complete geometry of the bone organ in question. To compensate for the lack of structural detail, this approach enhances the accuracy of the prediction by using apparent, nonlinear material properties (Keyak 2001; Schileo et al. 2008) and elastic moduli computed from local bone mineral density values (Dalstra et al. 1995; Keyak et al. 1998; Kopperdahl & Keaveny 1998; Kopperdahl et al. 2002; Taddei et al. 2004). Typically, these models attempt to map local values of Young’s moduli according to the local value of bone mineral density. However, the nature of this mapping has been quite controversial and a consensus has not yet been reached (Helgason et al. 2008). Furthermore, yield and failure criteria are ill defined. Recently, a yield criterion for trabecular bone depending on site and structural parameters has been proposed based on nonlinear FE models at the microstructure level for the femoral neck (Bayraktar et al. 2004a). To successfully determine the failure criterion for individuals, a systematic investigation of several sites of interest would be needed for different populations in order to create an atlas, providing a yield criterion, which could then be mapped to a specific patient depending on preliminary measurements. The specific yield criterion could then be included in the material description for a nonlinear FE model of the whole organ to increase the predictive power.
Figure 2. A typical mesh for a FE simulation of the proximal femur generated from a CT image contains a few thousand elements. Reprinted from Keyak et al. (1998), with permission from Elsevier.

Varga et al. (2009) presented and validated an organ-scale FE model for the human radius based on homogenized mechanical properties of the trabecular bone microstructure as determined from high-resolution computed tomography (CT) measurements. Bone mineral density and the anisotropy of the microarchitecture were quantified at evenly spaced grid points and were used to derive the local nonlinear, anisotropic material properties (Zysset & Curnier 1995; Garcia et al. 2009). While the reported accuracy cannot be directly compared with similar studies using linear and nonlinear FE at the microstructure level, the strength prediction appears to be improved by considering the specific microstructure of the samples in addition to geometry and mineralization (Pistoia et al. 2002; MacNeil & Boyd 2008).

In contrast to the trabecular bone, cortical bone’s anisotropic tissue properties and the orientation of canal networks are often neglected (Thurner et al. 2006). Especially at sites where large forces must be supported by the cortex, i.e. in the proximal femur, cortical thinning and increased porosity of the cortex can have a significant influence on the risk of fracture (Mayhew et al. 2005; Ural 2009).

3. Loading conditions

Fracture prediction must account for the forces imposed by impact and the reaction of connecting muscles during falls or other potential loading scenarios (Speirs et al. 2007). The importance of this is highlighted when considering
Figure 3. Micro-finite element (μFE) analyses were created from a subsection of distal radii based on HR-pQCT images with a resolution of 90 μm. (a) Strain energy density as calculated by μFE. Part of the bone was removed to show the trabecular core. Image courtesy of G. Harry van Lenthe, ETH Zurich. (b) Bone strength as determined from μFE correlated well to bone volume for 34 distal radii (17 cases and 17 controls) from an elderly, female population (78.4 ± 7.9 years). Nevertheless, the region outlined in the vertically oriented box demonstrates that substantial strength variation occurs for individuals with identical bone volume. It is notable that the two subjects with the stronger bones belong to the non-fracture group, whereas the two subjects in the lower-strength region have actually fractured their bones. Controls (blue squares), $y = 1.20x + 140.22$, $R^2 = 0.79$. Fracture cases (red diamonds), $y = 1.15x + 77.28$, $R^2 = 0.83$. 

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that a simple stumble can magnify the contact forces in the hip by a factor of 8 (Bergmann et al. 1993). To accurately define boundary conditions there are well-established approaches on how to estimate fall loads in many of the sites susceptible to osteoporotic fractures, such as the distal radius, proximal femur and spine (Robinovitch et al. 1991; Hayes et al. 1993; Myers & Wilson 1997). Up to now, the validation studies looking at the accuracy of bone strength assessed by FE simulations have used a varying level of detail and accuracy in defining the boundary conditions of the volume of interest. At the distal radius, MacNeil & Boyd (2008) defined FE models to simulate compression of a subsection of the distal radius between two endplates, thereby neglecting the load pathways via the metacarpal bones. To balance a relevant application of the load and the ability to reliably replicate it in the simulation, Varga et al. (2009) compared results from a direct loading of excised radii to the FE simulations. Pistoia et al. (2002) attempted to introduce a greater level of detail by modelling the cartilage of the metacarpal bones and applying a distributed force over its surface. However, whether or not these boundary conditions accurately replicate typical fracture-inducing scenarios remains to be established. At the proximal femur, relevant failure modes used to predict fractures are still under dispute. It is not clear whether the failure loads occur while standing or as a result of falling sideways. These are considerations that affect the probability of a fracture occurring and have to be addressed in simulations of femoral neck fractures (Lotz et al. 1995; Keyak et al. 1998). Estimating physiological loads in the spine is more difficult (Myers & Wilson 1997), as a vast number of muscles and ligaments are interacting in order to provide stability, and there is currently no method available for the non-invasive quantification of muscle forces in vivo. Most often a simplified compression of an individual vertebra is simulated. As an alternative, functional spinal units composed of two or three adjacent vertebrae, the vertebral disc(s) and adjoining ligaments can be simulated, leading to a more accurate replication of the physiological loading conditions (Yoganandan et al. 1996). However, the intervertebral disc is difficult to model, as the assumed material properties strongly influence the transfer of load to the vertebrae (Polikeit et al. 2004). Furthermore, these FE models tend to become very large and a possible instability of the individual bodies has to be prevented by constraining each of them to a point in space or to an adjacent body without altering the load transfer.

4. Linear and nonlinear micro-finite element models

There is increasing evidence that strength predictions using continuum-level models are limited in their ability to predict failure, owing to the inter-patient variability of microstructure (Kleerekoper et al. 1985; Boutroy et al. 2008). Thus, unless a person’s microarchitecture is included in the model, it is difficult to accurately estimate failure loads (figure 3). Bone microstructure assessment was traditionally based on histology (Carbonare et al. 2005), a method that is limited by its two-dimensional and destructive nature. To overcome these limitations, micro-computed tomography (μCT) has been proposed as an alternative technique (Feldkamp et al. 1989). This method allows bone microstructure to be visualized in three dimensions at a resolution of a few tens of micrometres while preserving the integrity of the sample. With the
development of desktop μCT systems (Ruegsegger et al. 1996) and their commercial distribution, this technology has become readily available and widely used. Based on three-dimensional microstructural imaging, micro-FE (μFE) simulations have become feasible using direct conversion of image voxels to either hexahedral or tetrahedral FEs (Hollister & Riemer 1993; Muller & Ruegsegger 1995; van Rietbergen et al. 1995). By resolving the bone microstructure, the complex anisotropic behaviour of trabecular bone (Keaveny et al. 2001) could be accurately modelled using an isotropic material model, which was also validated by comparing the computational results to biomechanical tests on bone biopsies (Ladd et al. 1998; Kabel et al. 1999; Niebur et al. 2000; Homminga et al. 2003; Bayraktar et al. 2004b). A clear advantage of μFE is the ability to rerun simulations using different types of loading and boundary conditions. Furthermore, stresses and strains can be analysed locally for individual structures. However, such simulations, although straightforward, are computationally expensive as they typically contain millions to hundreds of millions of elements. Various methods have been developed to improve computational efficiency. The element-by-element (EBE) method (van Rietbergen et al. 1995) saves memory by using uniformly shaped elements, allowing large models to be computed on commonly available computer hardware. More recently, more effective preconditioners optimized for massively parallel computer architectures (Adams et al. 2003; Arbenz et al. 2008) have reduced the execution times of simulations with around a billion unknowns from weeks to hours (Bekas et al. 2008).

Furthermore, linear FE has been shown to adequately predict the failure of bone. Pistoia et al. (2002) performed uniaxial mechanical tests on human cadaver forearms and created linear FE models from high-resolution peripheral quantitative computed tomography (HR-pQCT) measurements. By assuming that bone failure would initiate as soon as a significant part of the bone tissue was strained beyond a critical limit, they demonstrated that failure as predicted by linear FE correlated well with failure as observed experimentally ($R^2 = 0.75$). Nevertheless, this study also concluded that prediction could be further improved, and obtained more directly by describing bone’s post-yield, nonlinear behaviour. When analysing the nonlinear properties of bone tissue experimentally, results from four-point bending tests indicate ductile failure modes (Nalla et al. 2003) involving microcrack damage combined with a plasticity component originating from the collagen fibres (Fratzl et al. 2004; Thurner et al. 2006). Data from such experiments have been incorporated into a model’s constitutive law (Kosmopoulos et al. 2008) and have been used to define a failure criterion, resulting in nonlinear μFE models (Bayraktar et al. 2004a; MacNeil & Boyd 2008). The most frequently used nonlinear material model is a bilinear elastic–plastic model with different Young’s moduli for tension and compression, combined with a reduction of the elastic modulus if strains exceed a previously defined yield strain. MacNeil & Boyd (2008) showed that structural failure of human radii as predicted by nonlinear FE models correlated extremely well with in vitro mechanical tests ($R^2 = 0.95$). However, this approach differed from the previously described study (Pistoia et al. 2002) in that only a slab of the distal radius was imaged, simulated and subjected to mechanical testing. The computation time of the nonlinear models was a major concern and limited the size of the analysed region, as they took about 10 times longer (about 24 h

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per sample) than the linear simulations (about 2.5 h per sample) on roughly comparable computing clusters. In addition to the bilinear elastic–plastic model, there are more complex nonlinear models, assuming finite-plasticity, strain-rate-dependent elastic–plastic behaviour or a perfect damage model (Papadopoulos & Lu 2001; Kosmopoulos et al. 2008; Natali et al. 2008). While they are typically very versatile and closely match the findings from mechanical tests of the bone ultrastructure, they are often computationally even more expensive. Furthermore, some models have not been yet validated and the determination of required parameters needs further investigation.

While current nonlinear models are able to describe ductile, plastic material behaviours, some experimental observations at micro- and nanoscales are yet to be included. Toughening effects due to ligament bridging of microcracks and the role of heterogeneity at the nanoscale are more difficult to model in a constitutive law, as they are intrinsically stochastic and little is understood about their effects (Nalla et al. 2005; Tai et al. 2007). Simulating the dynamic behaviour of bone at the ultrastructural level is even more challenging, as the growth rates of microcracks have to be assessed and translated into viscous properties. Furthermore, there is an indication that failure can only be predicted when nonlinear geometric behaviour due to large displacements such as buckling and bending of trabeculae is considered (figure 4; MacNeil & Boyd 2008; Verhulp et al. 2008). Up until recently it was not possible to incorporate such geometric nonlinear effects into FE simulations of cancellous bone of sufficient and relevant size. Recently, a specialized FE solver has been presented that is capable of simulating geometric non-linearities in extremely large models using finite deformations (Adams et al. 2003). This will allow better insight into the structural mechanisms past the onset of yielding and occurrence of failure, as well as a better localization of where failure will initiate.

5. Bone remodelling

In addition to the accurate definition of external loading conditions, the incorporation of microstructure and the description of nonlinear changes in material properties, if future models are to be able to accurately predict fracture risk they must also account for age, disease and treatment. Ageing, osteoporosis and pharmacological interventions affect both bone density and its microarchitecture (Majumdar et al. 1997; Khosla et al. 2006; van Lenthe & Müller 2006). For example, in osteopenic patients, these changes include a decrease in trabecular number, a decrease in trabecular thickness and an increase in trabecular spacing. The consequence is a structure more prone to buckling (Snyder et al. 1993), further necessitating the use of nonlinear FE simulations. Drugs preventing bone loss not only affect formation and resorption rates, but also its tissue properties and the quality of the microarchitecture. Bisphosphonates have been shown to produce thicker, but possibly more brittle, structures due to a prolonged secondary mineralization phase and the suppressed resorption of bone (Boivin et al. 2000; Borah et al. 2006). Daily injections of parathyroid hormone have been shown to stimulate the formation of new bone via an anabolic effect on osteoblasts while the bone remodelling process remains intact (Dempster et al. 2001; Jiang et al. 2003). In contrast, by

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reducing the bone turnover, antiresorptive drugs are assumed to lead to an accumulation of microdamage as the ageing of the bone tissue is decreasing its toughness (Mashiba et al. 2001). In combination, these effects decrease the ability of the bone to absorb energy before it fractures, while making the tissue appear stronger if only linear-elastic behaviour is assumed (Wang et al. 1998). The temporal changes in bone microarchitecture and material properties attributed to age, disease and treatment have not yet been incorporated into FE simulations. However, several computational approaches exist that attempt to simulate these catabolic and anabolic changes in bone as reviewed elsewhere (Gerhard et al. 2009). While these models are not yet fully validated, they could be integrated into a multiscale approach aimed at monitoring the long-term fracture risk of patients.
6. The multiscale approach

To summarize, current FE models that focus on the material properties of bone and its architecture often oversimplify relevant boundary conditions (Stolken & Kinney 2003; Bayraktar et al. 2004a; MacNeil & Boyd 2008). Conversely, most simulations using complex boundary conditions strongly simplify material properties (Pistoia et al. 2002; Speirs et al. 2007), either by employing a continuum-based approach or by assuming a linear homogeneous microstructure. To improve the accuracy of predictions, these models must come together in a multiscale fashion such that all of the discussed complexities are incorporated into a single model. Perhaps the most precise multiscale approach to predict fracture risk is to combine accurate loading definitions with organ-level, nonlinear FE models that resolve bone microstructure. Furthermore, both microstructure and material properties would be expressed as a function of time to incorporate the effects of age, disease and treatment.

7. Clinical outlook

It could be argued that estimating the strength of bone (in a clinical setting) will be a challenge that will increasingly concern information technology rather than classical mechanics. More specifically, clinics will need at their disposal high-resolution image acquisition systems capable of resolving bone microstructure in acceptable amounts of time and computer infrastructures that can not only readily reconstruct the image data but also run large prognostic simulations. To achieve the necessary high-resolution images, clinically applicable imaging techniques need to be further developed to achieve higher resolutions. Currently, HR-pQCT is only suitable for peripheral sites such as the distal radius and tibia. For more central applications, fluoroscopy-based cone-beam computed tomography with a flat-panel imager (Jaffray et al. 2002) appears promising. With very short acquisition time it is possible to achieve a resolution in the sub-millimetre range. Therefore, this technology would be suitable for imaging bone microstructure in the spine and the hip in vivo. However, the exact resolution and reproducibility with respect to bone histomorphometry still need to be investigated. A more established technology is multi-slice helical CT with multiple-row detector arrays for the concurrent acquisition of several slices (Hu 1999; McCollough & Zink 1999). Depending on the scanning requirements, it can be used to significantly reduce acquisition time, causing fewer motion artefacts, or to decrease the slice thickness to isotropic resolutions of about 1 mm. Much progress has been made in the field of magnetic resonance imaging (MRI) (Wehrli 2007; Majumdar 2008), a technique that is not only non-invasive but also non-ionizing. However, the long acquisition times required for bone microstructural imaging and the challenging segmentation of hard and soft tissue currently prevent its use for large-scale clinical studies.

Increased image resolution allows FE models to contain more but smaller elements, leading to more accurate simulations. However, this will pose higher demands on FE solvers and computational facilities. The capabilities of high-performance computing are still increasing at a tremendous rate (see www.top500.org). At present, progress in the speed of individual processors

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is slowing down and deviating from Moore’s law, however. This limitation is compensated by the increased parallelization of calculations via multiple processing cores integrated onto a single chip. Because of this parallelism, a further increase in computational performance can only be exploited if the software is specifically optimized for parallel architectures. While this is relatively simple for small degrees of parallelism, modern supercomputers can have several hundred thousand computing nodes and hierarchical architectures so that developing applications benefiting from increased parallelism becomes very challenging. Existing simulation methods profit differently from this increase in absolute performance, depending on how well the underlying algorithms scale with the number of computing nodes used. In general, FE simulations are able to scale remarkably well when specialized algorithms are being used (Adams et al. 2003; Arbenz et al. 2008). In the near future, this might allow for the processing of FE models large enough to span whole bones while at the same time resolving the microstructure (Verhulp et al. 2008a). Alternatively, radically different simulation methods for kinetic problems are becoming increasingly popular, such as particle or meshless methods, which were originally developed for the simulation of astrophysical problems and later extended to simulate the mechanics of solid materials (Lucy 1977; Libersky et al. 1993). While applications in bone are still rare, they are expected to become more common, as the method is very well suited for parallelization and the precision is comparable to conventional FE analysis (Taddei et al. 2008).

8. Conclusion

Assessing a patient’s risk of bone fracture is a multiscale problem. Information from several different scales needs to be considered. At the body scale, musculoskeletal forces acting on the bones during typical fracture-inducing scenarios need to be characterized. At the organ level, the geometry of the bone must be accurately described, while at the micro- and nanoscales, alterations of the mechanical tissue properties and bone microarchitecture due to exceeding mechanical forces should be quantified. Finally, the effects of ageing, disease and drug therapy on bone need to be considered. Limited by computational power and complexity, current FE models incorporate information from some of the afore-mentioned scales. Nonlinear μFE models capture a section of the organ and apply simplified boundary conditions while being able to describe the nonlinear mechanical behaviour of bone subject to overloading. Whole-organ FE models assign nonlinear material properties to a continuum model of the bone and apply more realistic loading conditions. Computational approaches also exist that simulate the changes of bone microarchitecture and material properties in response to ageing, disease and treatment. The knowledge therefore exists to accurately determine the strength of bone. However, the challenge is to combine all of this knowledge into a single model. In terms of accuracy, the optimal solution would be to create an FE model that includes information from all scales, i.e. a nonlinear organ-level model, which accurately defines loading conditions and which resolves the microstructure. However, this comes at a massive computational cost, not only to run the simulations but also to reconstruct very large high-resolution image datasets. Furthermore, in vivo imaging technologies
are currently limited in resolution. Developments in computational methodologies and infrastructures as well as imaging technologies are therefore key to the successful implementation of such a multiscale approach in a clinical setting. Nevertheless the recent progress made in these areas is encouraging. In vivo imaging techniques capable of resolving the bone microstructure are becoming available, e.g. fluoroscopy-based cone-beam computed tomography. More complex simulation models are also becoming possible by the increasing capabilities of modern supercomputing facilities. Finally, novel simulation methods optimized for the increasingly parallel computer architectures are being developed, enabling an optimal use of the clustered computer systems.

In conclusion, the current state of technology suggests that the realization of patient-specific FE models to predict fracture risks is not far away. Thus it is foreseeable that multiscale, nonlinear FE models will replace current clinical practices for predicting fracture risk.

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