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A multiscale analytical approach for bone remodeling simulations: Linking scales from collagen to trabeculae

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ABSTRACT

Bone is a dynamic and hierarchical porous material whose spatial and temporal mechanical properties can vary considerably due to differences in its microstructure and due to remodeling. Hence, a multiscale analytical approach, which combines bone structural information at multiple scales to the remodeling cellular activities, could form an efficient, accurate and beneficial framework for the prognosis of changes in bone properties due to, e.g., bone diseases. In this study, an analytical formulation of bone remodeling integrated with multiscale micromechanical models is proposed to investigate the effects of structural changes at the nanometer level (collagen scale) on those at higher levels (tissue scale). Specific goals of this study are to derive a mechanical stimulus sensed by the osteocytes using a multiscale framework, to test the accuracy of the multiscale model for the prediction of bone density, and to demonstrate its multiscale capabilities by predicting changes in bone density due to changes occurring at the molecular level.

At each different level, the bone composition was modeled as a two-phase material which made it possible to: 1) find a closed-form solution for the energy-based mechanical stimulus sensed by the osteocytes and 2) describe the anisotropic elastic properties at higher levels as a function of the stiffness of the elementary components (collagen, hydroxyapatite and water) at lower levels. The accuracy of the proposed multiscale model of bone remodeling was tested first by comparing the analytical bone volume fraction predictions to those obtained from the corresponding μFE-based computational model. Differences between analytical and numerical predictions were less than 1% while the computational time was drastically reduced, namely by a factor of 1 million. In a further analysis, the effects of changes in collagen and hydroxyapatite volume fractions on the bone remodeling process were simulated, and it was found that such changes considerably affect the bone density at the millimeter scale. In fact, smaller tissue density induces remodeling activities leading to finally higher overall bone density. The multiscale analytical model proposed in this study potentially provides an accurate and efficient tool for simulating patient-specific bone remodeling, which might be of importance in particular for the hip and spine, where an accurate assessment of bone micro-architecture is not possible.

Introduction

Bone is a dynamic porous material which is continuously resorbed and subsequently formed in a process called bone remodeling influenced by both mechanical and biological factors [1–5]. Moreover, it is a hierarchical material whose architecture differs at each level of hierarchy and whose mechanical properties can vary considerably, even on the same specimen, due to bone heterogeneity [6–8]. The density of bone is modulated by two groups of cells: the osteoclasts which resorb bone and osteoblasts which deposit new bone [9]. The actions of these actor cells are thought to be mediated by osteocytes which are the most numerous cells in the bone. It has been hypothesized that the osteocytes can sense the local mechanical stimulus, in turn controlling the activity of osteoblasts and osteoclasts within a basic multicellular unit (BMU) [10–12].

Several mathematical models have been proposed in an attempt to elucidate the features of bone adaptation at the different scales, though at the organ, tissue and cell level, these models merely exist in isolation [13]. By integrating numerical equations into finite element models, it was shown that the load-driven bone remodeling algorithm based on mechanosensory theory can explain many features of bone adaptation at the tissue- and cell-level [14,15], e.g. the formation of load-adapted microstructures, as well as the loss of bone mass and microstructural integrity after disuse or increased osteoclast activity (associated with decreased estrogen levels). However, using such analyses for patient-

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specific predictions of bone remodeling is difficult because of the limited resolution of in-vivo imaging techniques and the huge computational cost involved for such detailed bone remodeling analyses.

A method to reduce the computational time in the abovementioned analyses and to deal with the fact that at most sites (e.g. hip and spine) no patient bone microarchitecture can be measured would be to implement the bone remodeling theory in a multi-scale framework that can translate structural changes at the cell-level to changes in bone density at the organ level. By using an analytical formulation of the bone remodeling equation integrated with multiscale micromechanical models, that use generalized structural models at each level of organization [16], such multi-step homogenization schemes can provide a very flexible framework to derive mechanical properties at any level. By integrating such models with bone remodeling equations, it will be possible to predict bone remodeling at these different levels in a very efficient manner.

The concept of integrating multi-scale modeling and bone remodeling has been introduced in earlier studies. Coelho et al. [17] presented a multiscale model for bone tissue adaptation that considered two levels, whole bone and trabecular architecture. The bone density distribution predictions were evaluated at the macroscale level, taking into account mechanical properties as well as surface density and permeability of the trabecular structure at the microscale level. Hambli et al. [18] developed a multiscale approach for bone remodeling simulation integrating finite element models at the macro level and 3D neural network computation techniques at the mesolevel. The authors did not, however, include in their bone remodeling formulation cellular activities and biological factors that affect bone apposition and resorption. In their investigation, Podshivalov et al. [19] presented a new 3D multiscale FE method based on domain-based multiresolution hierarchical geometric modeling and multiscale material properties of trabecular bone. The goal was to design a computational tool as infrastructure for computerized systems aiming at interactively analyzing bone structures. None of these models can explicitly account at the nanolevel for collagen and hydroxyapatite contributions on stiffness and volume fraction of the bone tissue at higher levels. Also, most of these studies rely on computational tools to solve equations at each included level, whereas a true multiscale approach would benefit from an analytical description that spans multiple levels.

Going in the direction to integrate bone structural information at different scales and the remodeling process, in recent works [20,21] we proposed an analytical model in which the bone remodeling process was studied on the basis of two connected scales, tissue and cell levels respectively, with the dependency on osteoblast and osteoclast activities in terms of bone apposition and resorption rates and on the estimation of strain energy density (SED), as mechanical stimulus. In that work, we were able to show that organ-level bone remodeling models that represented the bone microstructure by a simplified regular structure could predict bone density changes in good agreement with micro-structural models that represented the actual micro-architecture. However, the results were limited to two levels only and the remodeling signal was based on the average tissue-level SED, whereas for the bone remodeling more accurate SED values at the bone matrix surfaces are necessary.

In the present study we therefore extend this work by combining the earlier developed remodeling theory with a multi-scale framework that can account for (changes in) bone mechanical properties at all levels of bone structural organization (Fig. 1). Using this model it is possible to get more accurate estimates of the stresses that the osteocytes sense by using more elaborate models of the bone microstructure and bone tissue composition. In particular, specific goals of this study are: 1) to derive, as mechanical stimulus sensed by the osteocytes, the micromechanics-derived SED based on an Eshelby matrix-inclusion problem in order to accurately and efficiently predict the stress distributions in a representative volume element of trabecular bone; 2) to test the accuracy of the multiscale analytical model by comparing the bone volume fraction predictions to those obtained from the earlier computational models that represent the full bone microstructure; and 3) to demonstrate its multiscale capabilities by investigating in children bones the effects of age-dependent changes in collagen and hydroxyapatite content that are defined at the nanometer scale, on the bone volume fraction at the millimeter scale.

Methods

Analytical approach for bone remodeling simulations

In the bone remodeling theory adopted for this study, it is assumed that the osteocytes inside the bone tissue sense mechanical loading and transmit a signal to the osteoblasts on the bone matrix surface to form bone, while the osteoclasts are assumed to be attracted by effects of local micro-damage [22]. The formulation of this theory as implemented in a validated analytical model [21] is expressed in terms of net linear rate $dl_{BM}(x,t)/dt$ of bone apposition or resorption of bone matrix at a particular trabecular surface location x at time t determined by

$$\frac{dl_{BM}}{dt} = \frac{dl_{OBL}(x,t)}{dt} - \frac{dl_{OCL}(x,t)}{dt} \tag{1}$$

where $dl_{OBL}(x,t)/dt$ and $dl_{OCL}(x,t)/dt$ are the linear bone formation rate ($\mu m/day$) and linear bone resorption rate ($\mu m/day$), respectively.

Bone remodeling is assumed to occur on the internal surfaces of the bone matrix or on the walls of the voids and the rate of change of bone volume fraction is influenced by the amount of internal surface available for cellular activity as experimentally evidenced [9,10].

In the multiscale analytical framework proposed in this study, remodeling equations at the tissue level, that can account for bone tissue properties as determined by lower levels (cell and collagen levels) and that can represent the bone density evolution at higher levels (e.g. organ level), are developed (Fig. 1). As a starting point, we consider the analytical expression of the rate of change of bone volume fraction in the RVE of trabecular bone at the tissue level, when modulated by mechanobiological and geometric feedback as given in [23],

$$\frac{d(BV/TV)}{dt} = \left(\frac{dl_{OBL}(x,t)}{dt} - \frac{dl_{OCL}(x,t)}{dt}\right) \cdot \alpha \cdot BS/TV \tag{2}$$

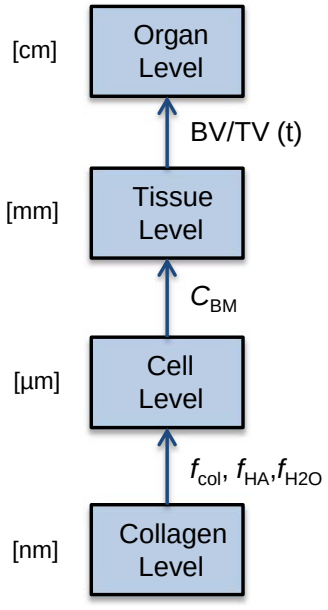

Fig. 1. Block-diagram of the proposed multiscale analytical model. Volume fraction of hydroxyapatite (f_{HA}), collagen (f_{col}) and water (f_{H2O}) at the nano scale affect the stiffness of the bone matrix (C_{BM}) at the micrometer scale, which in turn affect the strain energy density and bone volume fraction change over time (t) at the millimeter scale.