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Coupling systems biology with multiscale mechanics, for computer simulations of bone remodeling ☆

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ABSTRACT

Bone remodeling is a process involving removal of mature bone tissue and subsequent formation of new bone tissue. This process is driven by complex actions of biological cells and biochemical factors, and it is sensitive to the loads applied onto the skeleton. Herein, we develop a mathematical framework describing this process at the (macroscopic) level of cortical bone, by combining, for the first time, bone cell population kinetics with multiscale bone mechanics. Key variables are concentrations of biological cells (osteoclasts, osteoblasts and their progenitors) and biochemical factors (RANK, RANKL, OPG, PTH, and TGF-β), as well as mechanical strains, both at the ("macroscopic") level of cortical bone and at the ("microscopic") level of the extravascular bone matrix. Multiscale bone mechanics delivers, as a function of the vascular porosity, the relation between the macroscopic strains resulting from the loads, and the microscopic strains, which are known to modulate, either directly, or via poromechanical couplings such as hydrostatic pressure or fluid flow, the expression or proliferation behavior of the biological cells residing in, or attached to the extravascular bone matrix. Hence, these microscopic strains enter the biochemical kinetics laws governing cell expression, proliferation, differentiation, and apoptosis. Without any additional phenomenologically motivated paradigm, this novel approach is able to explain the experimentally observed evolutions of bone mass in postmenopausal osteoporosis and under microgravity conditions: namely, a decrease of bone loss over time.

1. Introduction

Bone remodeling is a process involving removal of mature bone tissue and subsequent formation of new bone tissue. This process allows for removal of microcracks endangering the mechanical integrity of the system, as well as for provision of mineral homeostasis in the skeleton [1–4]. Bone remodeling is undertaken by teams of biological cells. Once activated, osteoclasts remove bone tissue, leaving a cavity, which is thereafter filled by another cell type, osteoblasts. More precisely, the latter lay down osteoid, a material mainly composed of type I collagen that becomes mineralized over time. The tuned cooperation of osteoclasts and osteoblasts often leaves spatial patterns in histological sections of cortical bone, called, after Frost [5], bone multicellular units (BMUs). The aforementioned tuning, however, is largely influenced by a third cell type, osteocytes [6–10], which originate from buried osteoblasts, and reside in lacunar pores inside the bone tissue. They maintain, via long cell processes, connections with the cells at the bone matrix surfaces, as well as with other osteocytes, thus making up a large network. Osteocytes respond to both biochemical factors (e.g. hormones and local cytokines) and mechanical stimuli (induced by deformation of the bone matrix), both of which are subsequently "translated" into biochemical signals regulating the behavior of cells within BMUs.

An imbalance between bone resorption and bone formation (triggered by perturbance of biochemical and/or mechanical regulation mechanisms) can lead to significant structural changes within bone and so (adversely) affect its load-carrying capacity. However, despite intensive research activity for decades, current understanding of BMU regulation and associated changes in mechanical properties of bone is still fragmented due to complex (feedback-type) interrelationships between bone cells and structural features of bone. Given this inseparable interplay, identifying mechanisms which coordinate the cell behaviour in BMUs and predicting changes in mechanical properties of bone requires a synergistic approach combining mathematical modeling and experimental testing [11,12].

Most of previous mathematical models have focused on describing the mechanical properties of bone using numerical approaches, such as the Finite Element method or molecular dynam-

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ics simulations [13–18]. As a computationally very efficient complement to these techniques, Hellmich and co-workers have proposed analytical and semi-analytical models for estimating bone stiffness, bone strength, and poroelastic properties of bone, based on the concept of multiscale continuum micromechanics [19–22]. These models take the hierarchical organization of bone into account, and are based on the volume fractions of the different bone constituents, their mechanical properties and their mechanical interactions.

In standard micromechanical applications, the constituent volume fractions are known as input values. However, during bone metabolism, the volume fractions change, and the question arises how to determine these changes. In order to answer this question, which is at the very focus of this paper, we note that the aforementioned volume fractions are either directly linked to chemical processes (such as biomineralization, when hydroxyapatite crystals precipitate inside a network of collagen molecules [23]) or to cellular activity (such as bone remodeling, when e.g. the volume fraction of bone tissue inside a piece of cortical bone changes); and that recently, the challenge of mathematically describing the biology and biochemistry of bone remodeling has been quite successfully met [24–26], in the framework of bone cell population models (BCPMs). Such models allow for estimation of temporal changes in bone cell numbers during bone remodeling, interpretable in terms of the corresponding evolution of the bone volume over time. While such BCPMs were previously used to give valuable information on the effects of bone disease and/or therapeutic treatment scenarios, one key novelty of the present paper is to use the output of BCPMs as input for bone micromechanics formulations.

However, also the (local) mechanical environment of osteocytes governs bone remodeling. Properties quantifying this mechanical environment can be derived from multiscale micromechanical models. This relates to the second key novelty of this paper, namely the extension of state-of-the-art BCPMs to micromechanically quantified strain stimuli.

With these conceptual novelties at hand, we address a fundamental question in bone biology:

Can bone remodeling, often associated to some "mechanostat-paradigm" with corresponding tuning parameters [27–29], be explained solely by combined effects of multiscale mechanics and bone cell population kinetics, which are exclusively based on physical properties such as chemical concentrations, volume fractions, geometrical shapes, and mechanical properties?

An attempt of a quite comprehensive answer to this question is made hereafter, within the following structure of the remaining paper: first, we introduce the mathematical systems biology of bone, starting from the work of Pivonka et al. [25,26], and extending it to mechanoregulatory feedback control (Section 2). Then, we introduce a continuum micromechanics representation adopted from Hellmich et al. [30], in order to scale elasticity and strains from the level of the extravascular bone matrix to that of cortical bone[1] and vice versa (Section 3). The micromechanics formulation is fed with composition quantities derived from the systems biology approach, which, in turn, is provided with mechanical stimuli gained from the micromechanics model. We then apply the coupled approach to biochemical and mechanical conditions typical for postmenopausal osteoporosis (Section 4) and microgravity exposure (Section 5), and discuss key sensitivity features (Section 6). After emphasizing the potentials and limitations of the presented approach (Section 7), we conclude the paper in (Section 8).

[1] In this paper, we restrict ourselves to cortical bone, due to its major importance in providing sufficient load-carrying capacity. However, extension of the coupled approach proposed here to trabecular bone is straightforward; it merely requires recalibration of underlying parameters.

2. Mathematical systems biology of bone

Adopting the choice made by Pivonka et al. [25,26], we explicitly consider the following types of bone cells (see Fig. 1): uncommitted osteoblast progenitors cells, also referred to as bone marrow stromal cells or mesenchymal stem cells (abbreviated to OB_u); osteoblast precursor cells, also referred to as preosteoblasts (OB_p); active osteoblasts (OB_a); osteoclast precursor cells, also referred to as preosteoclasts (OC_p); and active osteoclasts (OC_a). As an original contribution of the present work, we extend the approach of [25,26] to mechanoregulation. Hence, the following equations for the evolutions of the aforementioned bone cell populations (expressed in terms of molar concentrations C_i) contain not only biochemical, but also mechanobiological activator and repressor functions.

2.1. Evolution of osteoblasts

The evolution of the osteoblast precursor cells is quantified by the following kinetics law:

$$\frac{dC_{OB_p}}{dt} = \mathcal{D}_{OB_u} C_{OB_u} \pi^{TGF\text{-}\beta}_{act,OB_u} + \mathcal{P}_{OB_p} C_{OB_p} \Pi^{mech}_{act,OB_p} - \mathcal{D}_{OB_p} C_{OB_p} \pi^{TGF\text{-}\beta}_{rep,OB_p}. \quad (1)$$

In this mathematical formulation, we explicitly consider that the population of osteoblast precursor cells in a piece of cortical bone increases due to differentiation (with maximum differentiation rate $\mathcal{D}_{OB_u}$) of uncommitted osteoblast progenitor cells – this differentiation is promoted by transforming growth factor β, TGF-β [3,31], quantified by activator function $\pi^{TGF\text{-}\beta}_{act,OB_u}$, see Eq. (A.1) in Appendix A. Furthermore, the population of osteoblast precursor cells decreases due to differentiation (with maximum differentiation rate $\mathcal{D}_{OB_p}$) of osteoblast precursor cells into active osteoblasts – this differentiation is inhibited by TGF-β [3,31], as quantified by repressor function $\pi^{TGF\text{-}\beta}_{rep,OB_p}$, see Eq. (A.2) in Appendix A.

As a conceptual novelty, we introduced, in Eq. (1), an additional term, which is related to proliferation of osteoblast precursor cells (with maximum proliferation rate $\mathcal{P}_{OB_p}$), promoted by mechanical strains in the extravascular bone matrix, as quantified through the activator function Π^{mech}_{act,OB_p}. Current literature suggests at least two mechanisms by which osteoblast precursor cells may respond to mechanical stimuli: (i) directly via cell stretching due to matrix deformation and/or fluid flow [32,33], and (ii) indirectly via biochemical signals (such as sclerostin) derived from osteocytes [6,34–36]. Both of these mechanisms are thought to regulate preosteoblast proliferation. For the purpose of our study we do not further specify which of these mechanisms prevails, but employ a phenomenological activator function Π^{mech}_{act,OB_p} to regulate proliferation of preosteoblasts. As a straightforward scalar measure for the strains in the extravascular matrix, we choose the strain energy density (SED) in the extravascular bone matrix, Ψ_{bm} – this choice is inspired by classical contributions to the field of mechanobiology [37–39]. The SED Ψ_{bm} at the bone matrix level depends on the loading of the considered piece of cortical bone, as well as on this piece's microstructure and its vascular porosity – these relations can be quantified by means of the micromechanics representation given in Section 3. Also, we restrict ourselves to explicit consideration of strain amplitudes only, thereby taking a (constant) physiologically relevant frequency [6,40] as granted.

According to Eq. (1), the maximum proliferation rate $\mathcal{P}_{OB_p}$ is related to the maximum value of Π^{mech}_{act,OB_p}, $\max(\Pi^{mech}_{act,OB_p}) = 1$, and this maximum rate is attained upon sufficient mechanical activation of the osteoblasts. Low straining reduces the proliferation rate by some 25% to 50% according to the experiments of Jones et al. [41] and Kaspar et al. [42]; and this is considered by setting the minimum value of Π^{mech}_{act,OB_p}, related to a threshold SED $\check{\Psi}_{bm}$, only