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A mathematical multiscale model of bone remodeling, accounting for pore space-specific mechanosensation

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ABSTRACT

While bone tissue is a hierarchically organized material, mathematical formulations of bone remodeling are often defined on the level of a millimeter-sized representative volume element (RVE), "smeared" over all types of bone microstructures seen at lower observation scales. Thus, there is no explicit consideration of the fact that the biological cells and biochemical factors driving bone remodeling are actually located in differently sized pore spaces: active osteoblasts and osteoclasts can be found in the vascular pores, whereas the lacunar pores host osteocytes – bone cells originating from former osteoblasts which were then "buried" in newly deposited extracellular bone matrix. We here propose a mathematical description which considers size and shape of the pore spaces where the biological and biochemical events take place. In particular, a previously published systems biology formulation, accounting for biochemical regulatory mechanisms such as the RANK-RANKL-OPG pathway, is cast into a multiscale framework coupled to a poromicromechanical model. The latter gives access to the vascular and lacunar pore pressures arising from macroscopic loading. Extensive experimental data on the biological consequences of this loading strongly suggest that the aforementioned pore pressures, together with the loading frequency, are essential drivers of bone remodeling. The novel approach presented here allows for satisfactory simulation of the evolution of bone tissue under various loading conditions, and for different species; including scenarios such as mechanical dis- and overuse of murine and human bone, or in osteocyte-free bone.

1. Introduction

It is well known that bone takes on a number of vital roles, including provision of the vertebrate skeleton's load-carrying capacity. For that purpose, it is essential that the microstructural integrity of the bone tissue is continuously maintained. The mechanism concerned with this important task is bone remodeling, involving numerous biochemically and mechanically stimulated processes, in concert leading to removal of bone tissue by cells called osteoclasts, and to concurrent addition of bone tissue by cells called osteoblasts, while a third cell type, osteocytes, has been identified as bone remodeling "conductor" [1–6]. Under normal physiological conditions, the activities of osteoclasts and osteoblasts are finely tuned, and the volumes of removed and added bone tissue are the same. However, disturbance of this balance (caused, e.g., by bone disorders or a changed mechanical loading regime) can lead to changes in the bone composition [7–9]; in the worst case, the load-carrying capacity becomes significantly impaired [10–12].

The focus of this paper is the presentation of a mathematical model that is able to quantify (in predictive fashion) the effects of changes in the mechanical loading environment on the bone composition. A key novelty of this paper is that it takes into account the different characteristic lengths at which mechanical forces are transduced and the occurrence of cells and biochemical factors are quantified. In particular, the proposed modeling concept involves consideration of the exact spaces *within* a representative volume element (RVE) where bone remodeling takes place. Both bone-forming and -resorbing cells at various differentiation stages are located in the *vascular pores*, where they are activated or inhibited by biochemical factors to initiate the remodeling process; at this stage of cell maturation, they are attached to the pore walls and work in basic multicellular units (BMUs), resorbing old and forming new bone [13,14]. Moreover, osteocytes reside in the *lacunar pores* and release biochemical factors such as sclerostin (SCLR); the

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latter is transported to the vascular pore space, where it upregulates osteoblast precursor proliferation via WNT [15,16]. As concerns the mechanical stimuli of cell activities, it is well known that oscillating hydrostatic pressure in the order of tens of kPa activates a variety of different biological cells, including bone cells [17–33]. Scheiner et al. [34] have recently shown that pressures of this order of magnitude may indeed occur in the lacunar and vascular pore spaces of bone under physiologically relevant loading conditions. The main aim of the research presented in this paper was to integrate these different aspects into a comprehensive mathematical multiscale model of bone remodeling, considering concentrations of bone cells and biochemical factors at the respective pore fluid scales, accounting for changes in concentration due to pore volume changes, as well as incorporating mechanical stimuli at the relevant length scales, in order to reasonably provide mechanobiological feedback for bone remodeling.

2. Methods

2.1. Model representation of bone tissue

As basis for developing a suitable model representation of bone tissue, we first discuss the pore spaces found in bone tissue which are most relevant for the bone remodeling process:

- The largest pore space in bone is formed by the blood vessel-hosting vascular pores, with characteristic diameters of approximately 50 to 80 $\times 10^{-6}$ m [35–38]. In cortical bone, the vascular pores occur in form of a branching structure [36], with the main branches (often referred to as Haversian canals) running longitudinally through the bone cortex, see Fig. 1(b), and the smaller, less frequently occurring branches (often referred to as Volkmann canals) connecting the Haversian canals. The vascular porosity in cortical bone typically ranges, depending on the bone type and on the anatomical location, from 3 % under normal physiological conditions to 35 % in the cases of disease or drug treatment [39–41]. In trabecular bone, the vascular pores occur in interpenetrating fashion between the struts or plates called trabeculae, see Fig. 1(d), at porosities of 50 to 90 % of the total bone volume [42]. The vascular pores contain the majority of cells (such as osteoblastic and osteoclastic cells, both ranging from the stem cell to mature stages [43–45]), as well as a large variety of biochemical factors [1,3,46,47], out of which we deem the transforming growth factor β (TGF β), the receptor activator of nuclear factor κB and its ligand (RANK and RANKL), osteoprotegerin (OPG), the parathyroid hormone (PTH), as well as the WNT proteins, as the most important ones [15,16,48-50].
- The extravascular bone matrix hosts another class of pore space, namely the lacunar pores, see Figs. 1(c), (e), and (f). Each lacunar pore contains one osteocyte, which is considered to be the major mechanosensory cell of bone [6].

Applied macroscopically (e.g. via physical exercise or simply the dead weight), the mechanical loading is somehow transferred to the different pore spaces where bone cells sense and transduce the mechanical signals. In this context, two mechanisms associated with mechanosensing appear to be particularly important: (i) increased mechanical loading leads to a decrease of the RANKL/OPG ratio [55,56] (via nitric oxide as intermediate agent [57,58]), which eventually causes downregulation of the osteoclast precursor differentiation; and (ii) increased mechanical loading also induces reduced sclerostin (SCLR) levels [4,59], leading to removal of the WNT β-catenin inhibition and to upregulation of the proliferation of osteoblast precursors [60,61].

The subsequently presented model representation of bone tissue, spanning several orders of magnitude in length scale, rests upon defining so-called representative volume elements (or, in short, RVEs). Importantly, such RVEs must meet the requirement of scale separation: the characteristic length of an RVE, ℓ_{RVE}, must be considerably larger than the characteristic lengths of inhomogeneities within the RVE, d, but considerably smaller than the characteristic length of the geometry of a structure built up by the material defined on the RVE, $\mathscr{L}$, as well as than the characteristic length of the

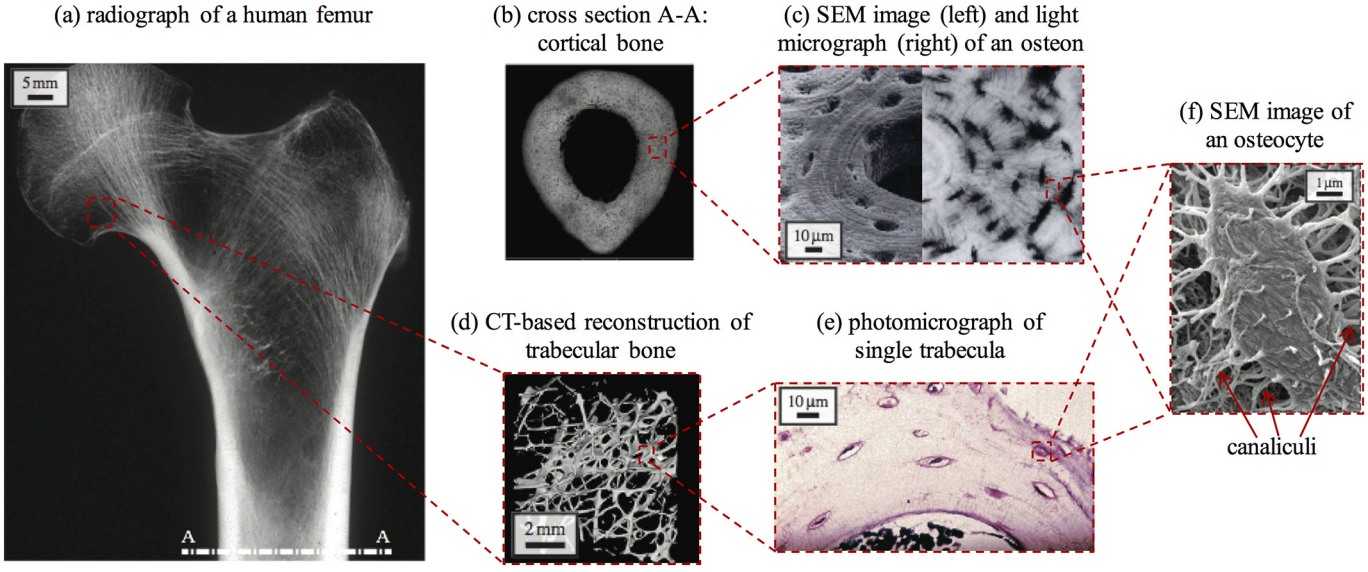

Fig. 1. Hierarchical organization of bone showing the various pore spaces discernible at different observation scales: (a) X-ray image of the proximal part of a human femur, reproduced from [51], with permission from Elsevier B.V.; (b) midshaft cross section A-A, showing the cortical shell, by courtesy of John G. Clement and David Thomas (taken from the Melbourne Femur Collection); (c) cortical bone microstructure, revealing an osteon with vascular and lacunar pores, shown by means of (left) scanning electron microscopy (SEM), reprinted from [52], with permission from the American Academy of Orthopaedic Surgeons (AAOS), and (right) light microscopy, reprinted from [53], by courtesy of Randy H. Kardon; (d) computed tomography (CT) image of trabecular bone; (e) photomicrograph of a single trabecula showing the composition of trabecular bone with vascular and lacunar pores, reproduced from [54], with permission from Elsevier B.V.; and (f) SEM image of an osteocyte and canaliculi, reprinted from [157], with permission from Macmillan Publishers Ltd. on behalf of Cancer Research UK: IBMS BoneKey, 2009.