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The influence of bone surface availability in bone remodelling—A mathematical model including coupled geometrical and biomechanical regulations of bone cells

Peter Pivonka [a,*], Pascal R. Buenzli [a], Stefan Scheiner [a,b], Christian Hellmich [b], Colin R. Dunstan [c]

[a] Engineering Computational Biology Group, The University of Western Australia, Perth, WA 6009, Australia
[b] Institute for Mechanics of Materials and Structures, Vienna University of Technology, A-1040 Vienna, Austria
[c] Mechanical & Mechatronic Engineering, University of Sydney, Sydney, NSW 2006, Australia

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ABSTRACT

Bone is a biomaterial undergoing continuous renewal. The renewal process is known as bone remodelling and is operated by bone-resorbing cells (osteoclasts) and bone-forming cells (osteoblasts). An important function of bone remodelling is the repair of microcracks accumulating in the bone matrix due to mechanical loading. Cell–cell communication between cells of the osteoclastic lineage and cells of the osteoblastic lineage is thought to couple resorption and formation so as to preserve bone integrity and achieve homeostatic bone renewal. Both biochemical and biomechanical regulatory mechanisms have been identified in this coupling. Many bone pathologies are associated with an alteration of bone cell interactions and a consequent disruption of bone homeostasis. In osteoporosis, for example, this disruption leads to long-term bone loss and increased fragility, and can ultimately result in fractures.

Here we focus on an additional and poorly understood potential regulatory mechanism of bone cells, that involves the morphology of the microstructure of bone. Bone cells can only remove and replace bone at a bone surface. However, the microscopic availability of bone surface depends in turn on the ever-changing bone microstructure. The importance of this geometrical dependence is unknown and difficult to quantify experimentally. Therefore, we develop a sophisticated mathematical model of bone cell interactions that takes into account biochemical, biomechanical and geometrical regulations. We then investigate numerically the influence of bone surface availability in bone remodelling within a representative bone tissue sample. Biochemical regulations included in the model involve signalling molecules of the receptor–activator nuclear factor κB pathway (RANK–RANKL–OPG), macrophage colony-stimulating factor (MCSF), transforming growth factor β(TGFβ), and parathyroid hormone (PTH). For the biomechanical regulation of bone cells, a multiscale homogenisation scheme is used to determine the microscopic strains generated at the level of the extravascular matrix hosting the osteocytes by macroscopic loading. The interdependence between the bone cells' activity, which modifies the bone microstructure, and changes in the microscopic bone surface availability, which in turn influences bone cell development and activity, is implemented using a remarkable experimental relationship between bone specific surface and bone porosity. Our model suggests that geometrical regulation of the activation of new remodelling events could have a significant effect on bone porosity and bone stiffness in osteoporosis. On the other hand, geometrical regulation of late stages of osteoblast and osteoclast differentiation seems less significant. We conclude that the development of osteoporosis is probably accelerated by this geometrical regulation in cortical bone, but probably slowed down in trabecular bone.

1. Introduction

Bone is a biomaterial that has a variety of physiological functions. In addition to load bearing and support for locomotion, bone protects internal organs and participates in calcium and phosphorous homeostasis. From an engineering perspective the structural function of bone is most importantly characterised by its stiffness and strength. Daily activities (such as walking and running) subject bone to periodical loads which, over extended periods of time (weeks, months, and years), can lead to fatigue damage and the formation of microcracks. If these microcracks are not removed in due time, their conglomeration may result in a macroscopic structural failure, i.e., a fragility fracture. To prevent the occurrence of fragility fractures, nature has equipped bone tissues with a cellular mechanism of self-repair [1], referred to by biologists as 'bone remodelling'

* Corresponding author. Tel.: +61 8 6488 2708.
E-mail addresses: peter.pivonka@uwa.edu.au (P. Pivonka), pascal.buenzli@uwa.edu.au (P.R. Buenzli), stefan.scheiner@tuwien.ac.at (S. Scheiner), christian.hellmich@tuwien.ac.at (C. Hellmich), c.dunstan@usyd.edu.au (C.R. Dunstan).

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[2,3]. Bone remodelling is a coordinated process of bone resorption by cells called osteoclasts, and bone formation by cells called osteoblasts. Osteoclasts and osteoblasts usually operate together in self-contained groups processing the renewal of a localised portion of the bone tissue. These groups are called bone multicellular units (BMUs) and constitute a single 'remodelling event'. There are about 1.7×10^6 such BMUs in a normal adult skeleton [2–4]. Cell population and cell activity in a BMU are tightly controlled to establish local bone homeostasis (i.e., balanced bone resorption and bone formation). In bone pathologies, this cellular control is perturbed and homeostatic bone renewal is disrupted. In osteoporosis, bone is progressively lost, which results in reduced bone stiffness and strength.

Over the last decades, bone biologists have identified a large number of biochemical regulatory factors influencing bone remodelling. The formation of osteoclasts has been shown to rely crucially on macrophage colony-stimulating factor (MCSF) and on the receptor–activator nuclear factor κB (RANK) cell signalling pathway, which involves the receptor RANK, the ligand RANKL, and osteoprotegerin (OPG) [5,6]. RANKL activates the RANK receptor on precursor osteoclasts, which triggers their development and sustains their activity. The soluble molecule OPG is a decoy receptor of RANKL which can prevent RANKL from binding to RANK. Another important molecule mediating the communication between osteoblasts and osteoclasts is transforming growth factor β (TGFβ). TGFβ is stored in high concentrations in the bone matrix. It is released into the bone microenvironment, where it exerts its action on several bone cells, during bone matrix resorption by active osteoclasts [6]. The existence of a mechanical regulation of bone remodelling has long been suspected. It is now well established that mechanical feedback is a key regulatory mechanism to maintain bone mass [7–12]. The commonly accepted view is that osteocytes act as mechanosensors that transduce local mechanical signals into biochemical responses. These biochemical responses are thought to regulate the initiation of bone remodelling processes and to modulate the coupling between bone resorption and formation (see e.g. [1] and references cited therein).

The existence of biochemical and biomechanical regulations of bone cells is well-established and has been extensively studied. However, the notion that the morphology of the microstructure of bone may induce an additional regulation of bone cells of purely geometrical nature is not often mentioned in the recent literature. This may be due to the experimental difficulty of assessing the importance of a geometrical regulation. Biochemical and biomechanical regulations can experimentally be partially or fully repressed by selective gene knock-outs or monoclonal antibodies targeting key components in the bone cell signalling pathways. By contrast, one cannot simply "switch off" a geometrical regulation of bone remodelling when this self-repair process modifies the microstructure (and so the geometry) of the material.

Bone tissue is diverse and exhibits a broad variety of microstructures. However, two distinctive types of bone tissue are usually identified: cortical bone and trabecular bone [3] (see images in Fig. 1). Cortical bone has typical porosities of 0.05–0.15 while trabecular bone has typical porosities of 0.65–0.85 [2,3]. Mathematical models for the estimation of mechanical properties of bone tissue have shown that bone stiffness is predominantly determined by the porosity f_{vas},[1] the interaction of the different material phases

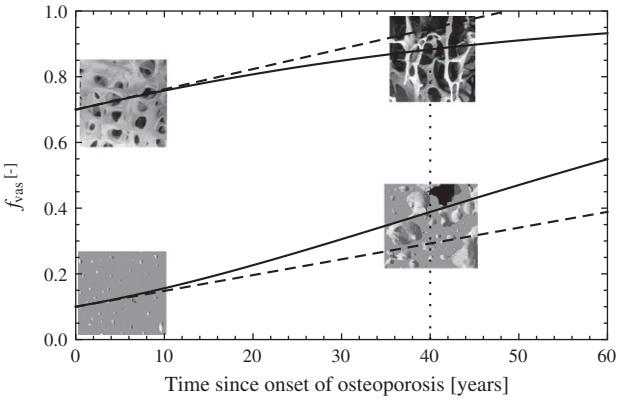

Fig. 1. Possible effect of geometrical feedback on the evolution of vascular porosity (f_{vas}) in osteoporosis, both in cortical bone (lower curves) and trabecular bone (upper curves) according to the computations of Martin [13]. Dashed curves show the linear increase in porosity that is obtained without geometrical feedback, while the solid curves incorporate geometrical regulation (a constant pathological skeletal imbalance of -2 μm/year is assumed). Images of typical bone microstructures for cortical bone (bottom, modified from Ref. [19]) and trabecular bone (top, modified from Ref. [20]) in normal subjects (left) and osteoporotic subjects (right) are also represented.

and pore shape, while other microstructural characteristics such as the exact pore distribution play a secondary role [14–16]. For biochemical processes, pore morphology can be expected to play a significant role. Indeed, pore morphology determines the so-called specific surface S_V (i.e., the amount of bone surface available in a representative volume element), which is an essential geometrical factor for the bone cells. Bone cells require a bone surface to fulfill their functions, whether to initiate a bone remodelling process or to operate resorption and formation. Osteoclasts require attachment to a particular area of the bone surface before resorbing. Osteoblasts are observed to only secrete osteoid (a collagen-rich substance which later mineralises and becomes new bone matrix) on existing bone surfaces. Finally, mechanical signals sensed by osteocytes embedded in the bone matrix are passed on to bone cells in the vascular cavity through the bone surface. Effects similar to chemical exchange reactions between pore walls and solutes in fluid-saturated porous materials can be expected to occur in this context.

The issue of quantifying the role of bone surface availability in bone remodelling was raised by bone biologists already some time ago [2,13,17]. In Ref. [13], Martin provides a first attempt to investigate theoretically the effect of a geometrical regulation of bone remodelling in osteoporosis (see Fig. 1). Osteoporosis is associated with increased porosity in both cortical and trabecular bone [18]. In Martin's own words: "*In [cortical] bone, increased porosity provides more surface area on which cells can work, thereby increasing the capacity for further porosity changes. In [trabecular] bone, increased porosity decreases the amount of surface available to the cells, thereby decreasing the capacity for further remodelling.*"

While the proposed mechanism of geometrical feedback on bone remodelling seems plausible, it is difficult to test its validity experimentally and to determine its importance quantitatively. Some researchers have employed the concept of geometrical feedback for simulations of bone remodelling [21]. However, to our knowledge, there is no systematic study in the literature of the effects of a possible geometrical regulation at several stages of the remodelling sequence. Also, the interplay between geometrical feedback and mechanical feedback in bone remodelling has not been investigated. A mechanical feedback has the potential to stabilise bone loss or gain [7,22] and may either compete with or enhance the effect of the geometrical feedback seen in Fig. 1, depending on the type of bone.

[1] The total porosity of bone is made of a vascular porosity, which contains marrow components, blood vessels, bone cells and their precursors, and the lacunae-canaliculi porosity, which contains osteocytes and their processes. The lacunae-canaliculi porosity is only a small fraction of the total porosity (see e.g. [13, Table 1]) and no remodelling occurs at these surfaces. Therefore, the lacunae-canaliculi porosity will not be considered in this work and we will refer to the vascular porosity simply as the bone porosity. Similarly, in the present context, we are not interested in the intercrystalline and intermolecular porosities, which we simply regard as part of the 'solid bone matrix'.