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A model for the change of cancellous bone volume and structure over time

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ABSTRACT

A model is presented for characterizing the process by which cancellous bone changes in volume and structure over time. The model comprises simulations of local changes resulting from individual remodelling events, known as bone multicellular units (BMU), and an ordinary differential equation for connecting the number of remodelling events to real time. The model is validated on micro-CT scans of tibiae of normal rats, estrogen deprived rats and estrogen deprived rats treated with bisphosphonates. The model explains the asymptotic trends seen in changes of bone volume over time resulting from estrogen deprivation as well as trends seen subsequent to treatment. The model demonstrates that both bone volume and structure changes can be explained in terms of resetting remodelling parameters. The model also shows that either current understanding of the effects of bisphosphonates is not correct or that the simplest description of remodelling does not suffice to explain both the change in bone volume and structure of rats treated with bisphosphonates.

1. Introduction

Bone is a dynamic tissue that changes over time both in terms of volume and structure through a process called remodelling. In humans, the entire skeletal system turns over in five to ten years. The process is local in that overall changes result from the accumulation of large numbers of individual remodelling events, known as bone multicellular units (BMU) in bone literature. At the most simplistic level, a single remodelling event comprises a resorption phase during which cells called osteoclasts remove a quantity of bone and a formation phase during which cells called osteoblasts deposit new bone material. Net gain or loss of bone volume depends on the balance between resorption and formation volumes. The average difference between the formation volume and resorption volume over many remodelling events determines whether bone volume increases, decreases or remains steady over time. The rate of bone volume increase or decrease over time depends both on the average gain or loss per remodelling event and on number of remodelling events completed per unit time.

Bone volume normally decreases with age after reaching a peak value in young adults. Bone volume may also decrease as a consequence of disease such as osteoporosis. In cancellous bone, decreases in bone volume are inevitably associated with changes in trabecular structure. Treatment with bisphosphonates is thought to arrest the effects of osteoporosis and perhaps restore bone volume and structure to some degree. Whether these changes are brought about primarily through changes in resorption volume or formation volume is not clear nor is the role of the number of remodelling events per unit time. In addition, other mechanisms may play a significant role in how the bone volume and structure change over time. A review of biological aspects and clinical consequences of bone remodelling can be found in [1] and the references therein.

In this paper, a model is developed for the effect of remodelling process on the local structure of cancellous bone. The model comprises simulations of the effects on structure of many BMU coupled with a differential equation that tracks the change in bone volume over time and so provides a time reference for determining the number of remodelling events per unit time. The model elucidates how the balance of the remodelling parameters differ in disease, treatment and normal states. In addition, the model demonstrates that, in the case of treatment with bisphosphonates, mechanisms beyond the simple remodelling process described above are needed to explain the observed changes in bone volume and structure.

The potential benefit and also the pitfalls of mathematical models for remodelling have long been recognized [2] and reiterated in context of more recent developments [3]. Models overlap in terms of their scope and scale of application, but may be classified roughly as focussing on either biochemical and cellular aspects, mechanical and tissue aspects or larger scale biomechanical aspects.

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At the biochemical and cellular level, Komarova et al. have developed systems of ordinary differential equations (ODE) to model the autocrine and paragrine regulation in osteoclasts and osteoblasts [4] and used similar models to understand the role of Parathyroid Hormone (PTH) in stimulating osteclasts [5]. Later, a system of integro-differential equations was used to describe the movement and action of osteoclast, and subsequently of osteoblasts, based on models of spatio-temporal distributions of the proresorptive cytokine RANKL and its inhibitor osteoprogerin (OPG) [6,7]. The models developed by Komarova et al., were also extended by Moroz and Wimpenny to include allosteric regulation [8]. Lemaire et al. [9] modelled the chemical binding of PTH with its receptors as ordinary differential equations. Pivonka et al. [10] built on this model and included ideas from enzyme kinetics. The resulting model forms the basis of an application to modelling the interaction of multiple myeloma cells and bone in a later paper by the same group [11]. A further step was taken by including the spatial distributions of osteoclasts and osteoblasts within a single bone multicellular unit (BMU) leading again to a system of partial differential equations [12].

At the small scale mechanical and tissue level, models have been developed to understand the mechanisms that target bone remodelling to sites of microdamage and that guide remodelling so that trabecular structure adapts to changes in loading [13,14]. These models do not include biochemical or cellular aspects but focus on porous structure of bone and the implications on fluid shear stresses, cellular communication and hence on remodelling. A completely different approach is taken in [15]. Here the effect of remodelling is viewed as that of maximizing the structural stiffness while minimizing the metabolic cost leading to a two scale optimization problem – one scale for the full bone structure and shape and the other scale for local trabecular structure.

The ramifications of remodelling to large scale properties of bone have been studied by Huiskes et al. in a sequence of papers making use of finite element models for large and small scale structure of bone. In [16] trabecular (and cortical) bone was viewed as an unknown continuous function of density constrained by response to external load. The relationship between trabecular structure and loading was studied in [17] and was extended to determine that bone surface interactions do not suffice to regulate adaptation of bone to load [18]. Further papers have explored the theoretical basis for the interaction of mechanical loading and adaptation in trabecular bone [19–21].

The model presented in this paper fits between the scales of the work reviewed above. The aggregate effect of many BMU on the local structure of trabecular bone is investigated. In doing so, models for the consequences of the action of BMU are implemented but models for the biological and mechanical signalling controlling individual BMU are not considered.

2. Scope of the model and data

The basic biological processes that underly remodelling are thought to be largely conserved across many species. Inevitably, though, there is some variation between different animals and according to circumstance. The modelling choices made in this study are aimed at describing changes in cancellous bone volume and structure in young female rats in three states: normal, estrogen deprived and estrogen deprived treated with bisphosphonates.

More specifically, thirty Sprague–Dawley rats, aged eight weeks, were randomly assigned to three experimental groups of ten rats each. Sham ovariectomies were performed on rats in the first group (Sham group) and true ovariectomies were performed on rats in the second group (OVX group). Ovariectomies were also performed on rats in the third group, but these rats were treated with bisphosphonate Zoledronic acid (1.6μg/kg s.c.) two weeks later (OVX + Zol group). Bisphosphonate treatment of rats in the OVX + Zol group continued weekly until week 11. Sham and OVX rats received equivalent saline injections at times of bisphosphonate treatment of OVX + Zol rats. Throughout, time will be measured in days with respect to the event of ovariectomy or sham ovariectomy. Thus ovariectomies were performed at $t = 0$ and OVX + Zol rats started treatment with bisphosphonate at $t = 14$. Micro-CT scans of the right tibiae of all rats were obtained using a Skyscan 1076 X-ray μCT system at $t = 0, 14, 28, 56, 84$ (weeks 0, 2, 4, 8 and 12). The raw scan data was reconstructed using standard software Nrecon (Skyscan, Belgium). The reconstructed arrays were binarized using a global threshold to arrive at 3-dimensional representations of the bone structure at resolution $8.702 \times 8.702 \times 8.702$ μm per voxel. From each array, a section of $82 \times 82 \times 80$ voxels (0.7135 mm $\times$ 0.7135 mm $\times$ 0.6961 mm), comprising cancellous bone was selected manually. These $82 \times 82 \times 80$ voxel arrays will be referred to as *measured bone cubes*. Care was taken to extract the measured bone cube from the same location at each time point by counting the number of μCT slices (134) below the growth plate. While this protocol sufficed to identify the same general location within the tibia, voxel by voxel alignment could not be reproduced. Between day 56 and day 84, two rats from the OVX group died as the result of an adverse reaction to anaesthetic and one rat from the OVX + Zol group died from necrotised toes in the right foot. Hence a total of 147 measured bone cubes were available for analysis.

For each measured bone cube, 15 attributes related to bone structure were computed: bone volume fraction (B), (Fig. 1), total bone surface area, (S), specific bone surface area (BS/BV), trabecular bone pattern factor (TBPF) structure model index (SMI) Euler–Poincaré characteristic (EUL), connectivity density (CONND) and eight thickness measures, $T_n,\ n = 1, 2, \ldots, 8$. Standard methods were used to compute these attributes [22–24] except the thickness measures. The thickness measures were obtained by estimating the number of voxels representing locations of bone of thickness in the range $[2n, 2n + 1]$ via the formula

$$V(n) = |(E^{(n-1)}X - DE^nX)|,$$

where X is the original 3D binary array, E is the erosion operator with the unit ball as structure element, D is the dilation operator with the same structure element and $|\cdot|$ denotes the number of voxels. The thickness measure T_n is the normalized version given by $T_n = V(n)/\sum_k(V(k))$. This measure of thickness is a variation of granulometry [25].

Attributes were rejected if they correlated highly with other attributes or if values measured at $t = 84$ did not significantly vary between the three experimental groups of rats. The final set of structure attributes was BS, BS/BV, SMI, EUL and T_1.

3. The remodelling model

The model for a single remodelling event includes three parameters: resorption volume, formation volume, and a parameter that determines the depth of the resorption cavity. These parameters are described in detail below (Section 3.3). To model changes of bone over time requires knowledge of the number of remodelling events per unit time. This parameter is not well known and likely to vary according diseases state. Accordingly, a separate model was developed to link absolute time to change in bone volume. This part of the model will be described first.

3.1. Model for change in bone volume

Let $B(t)$ denote the amount of bone per unit volume at time t (technically, B is bone volume fraction (Section 3.2)). The base model is