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Simulations of trabecular remodeling and fatigue: Is remodeling helpful or harmful?

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ABSTRACT

Microdamage-targeted resorption is paradoxal, because it entails the removal of bone from a region that was already overloaded. Under continued intense loading, resorption spaces could potentially cause more damage than they remove. To investigate this problem, we incorporated damage algorithms in a computer-simulation model for trabecular remodeling. We simulated damage accumulation and bone remodeling in a trabecular architecture, for two fatigue regimens, a 'moderate' regimen, and an 'intense' regimen with a higher number of loading cycles per day. Both simulations were also performed without bone remodeling to investigate if remodeling removed or exacerbated the damage. We found that remodeling tends to remove damage under the 'moderate' fatigue regimen, but it exacerbates damage under the 'intense' regimen. This harmful effect of remodeling may play a role in the development of stress fractures.

Introduction

Osteoclasts are believed to target both disused bone [1–3] and microdamaged bone [4–7] for resorption. Disuse-targeted resorption implies that osteoclasts are somehow informed about (the lack of) tissue strains. Osteocytes are believed to be their informants, as they are much better placed to assess bone strains [8,9] and show a metabolic response to strains [10,11]. This metabolic response involves signals that inhibit osteoclasts [12,13], so that loaded bone is preserved while disused bone can be resorbed. Microdamage-targeted resorption implies that osteoclasts are informed about the location of damage. Again, osteocytes are believed to be involved: several studies indicate that microdamage induces osteocyte apoptosis and that subsequent resorption coincides with these apoptotic regions [14,15].

A problematic aspect of microdamage-targeted resorption is that osteoclasts enter a bone region that just experienced intensive loading. Under continued loading, the resorption spaces could exacerbate the problem. Stress concentrations around the resorption spaces would lead to even more microdamage, inducing even more resorption, until fracture. This positive feedback between remodeling and damage accumulation was first observed by Martin [16], when he modeled the mathematical relationships between loading, damage, remodeling, porosity and elastic modulus. He found that too much loading caused the system to become unstable, with porosity and damage rapidly increasing. In a computer simulation of microdamage- and strain-induced bone remodeling on a trabecula, Mulvihill et al. [17] encountered similar runaway resorption: a resorption pit beyond a certain depth would cause perforation of the trabecula, not by a single fracture event, but by the continuous removal of microdamage forming underneath.

This phenomenon could play a role in the development of stress fractures [16,18]. Stress or fatigue fractures are common overuse injuries in army recruits [19] and athletes [20,21], but still poorly understood. Runaway resorption has been observed in histological studies on stress fractures: Johnson [22] described "explosive cavitation preceding a stress fracture", the appearance of remodeling cavities with resorption on all sides and no reversal to formation.

With these concepts in mind we want to investigate whether remodeling reduces or exacerbates damage accumulation in a trabecular architecture, under moderate and intense fatigue regimens. Microdamage-targeted resorption is incorporated in a model that we previously used to explain the development of trabeculae and osteons in relation to mechanical loading [23–25].

Methods: the model

The model used in this study is similar to the model used in an earlier study [25]. A bone structure is mapped onto a finite element mesh consisting of square elements of uniform size Δx [m]. We introduce, for each element, a relative bone density $m(\boldsymbol{x},t)$, where vector $\boldsymbol{x}$ [m] denotes element position and t [day] denotes time. The density $m(\boldsymbol{x},t)$ ranges from a minimal value m_{min} to 1. At m_{min} the element is considered to be a marrow element, above m_{min} it is considered to be a bone element. The time t is represented by increments Δt [day], during which the bone density of the elements

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can change. Hence, the $m(\boldsymbol{x},t)$-values of the elements constitute a changeable bone morphology. The $m(\boldsymbol{x},t)$-values also determine the stiffness of the elements, according to [26]:

$$E(\boldsymbol{x},t) = E_{\max}\cdot m(\boldsymbol{x},t)^3,$$

where $E_{\max}$ [Pa] is the Young's modulus for elements at maximal bone density. The structure is subjected to external loads. Load transfer through the structure is evaluated by finite element analysis (FEA). FEA is performed at the start of each increment to correct for the gradual morphological changes in the bone. (In the added damage model, FEA is performed more often, depending on damage growth.)

Osteocytes

Osteocytes, located within the bone tissue, are assumed to sense a mechanical stimulus R [$J\cdot m^{-3}\cdot s^{-1}$], a typical strain-energy-density (SED) rate [27,28]. Based on this sensation, the osteocytes emit a biochemical signal. This signal decreases exponentially in strength with increasing distance d [m] from the osteocyte. The exponential function represents the steady-state distribution of a signal molecule, where synthesis and decay are in balance [29]. Each element receives an accumulated signal S from nearby osteocytes, according to [27]:

$$S(\boldsymbol{x},t) = \sum_{i=1}^{n} R(\boldsymbol{x}_i,t)\cdot\mu\cdot e^{-d(\boldsymbol{x},\boldsymbol{x}_i)/D},$$

where μ [$J^{-1}\cdot m^3\cdot s$] is the osteocyte mechanosensitivity and D [m] is a diffusion-decay constant, $\boldsymbol{x}_i$ is the position of osteocyte i and n is the number of osteocytes within a distance d_{infl} [m] from $\boldsymbol{x}$, where d_{infl} is the truncation distance for the osteocyte signal.

Osteoclasts

When the osteocyte signal S is strong enough, it inhibits osteoclast attachment to the bone surface and their subsequent resorption activities. Osteoclasts are explicitly modeled, using a cell simulation method based on the cellular Potts model (CPM) [30,31]. This simulation method was extensively described in our previous paper [25]. What it amounts to is that an osteoclast adheres to bone surfaces where the osteocyte signal is weak and proceeds to resorb this bone. Two signal thresholds are used, S_0 and S_1. If the osteocyte signal is below S_0, osteoclast-bone adhesion is strong. Between S_0 and S_1 adhesion weakens and above S_1 there is no adhesion. The cell simulation method also ensures that osteoclast volume (the number of occupied elements) remains close to a target volume V_0. This volume is based on a typical osteoclast diameter of 50 μm [32]. New osteoclasts can originate, with origination probability P_{orig} [$m^{-1}\cdot d^{-1}$], on exposed (i.e., not covered by osteoclasts or -blasts) bone surfaces with weak osteocyte signals ($S<S_0$). Osteoclasts then resorb bone until strong osteocyte signals cause them to detach from the bone surface. They are removed if they remain detached for a period of more than T_d [d].

Osteoblasts

Osteoblasts are recruited to exposed bone surfaces where the osteocyte signal exceeds a threshold S_{obl} for a period T_r [d]. They then form bone according to:

$$\Delta m_{obl} = \tau\cdot(S(\boldsymbol{x},t) - S_{obl})\cdot\frac{\Delta t}{\Delta x},$$

where the change in $m(\boldsymbol{x},t)$ due to osteoblast activity is denoted with the index *obl*, and τ [$m\cdot day^{-1}$] determines the bone formation rate. The newly formed bone is assumed to have the same osteocyte density as pre-existing bone. It is covered with a layer of osteoblasts. Osteoclasts do not adhere to or originate on these surfaces.

If the signal falls below S_{obl} osteoblasts stop forming bone, but they remain on the bone surface as lining cells. If the signal decreases further below a threshold S_{lc}, lining cells retract exposing the bone surface to osteoclasts. This lining cell function was not present in our previous study [25]. There, osteoclasts could originate rather indiscriminately on all exposed bone surfaces where no osteoblasts were present ($S<S_{obl}$; $S_{obl} = 1.0\cdot10^6$), but their origination probability was quite low ($P_{orig} = 100\ m^{-1}\,d^{-1}$). Here less of the surface is exposed ($S<S_{lc}$; $S_{lc} = 0.5\cdot10^6$), but the osteoclast origination probability is higher ($P_{orig} = 1000\ m^{-1}\cdot d^{-1}$), to allow for a more focused response to areas of damage. All other parameter settings are as in [25].

Damage

The rules for damage accumulation in this study are similar to those used by McNamara and Prendergast [33], who in turn derived their damage rules from studies by Carter et al. [34]. We introduce, for each bone element, a relative damage $\omega(\boldsymbol{x},t)$ that ranges from 0 in undamaged bone to 1 in failed bone. Newly formed bone starts with zero damage. Damage then increases each increment according to:

$$\Delta\omega = \frac{d\omega}{dn}\frac{dn}{dt}\Delta t,$$

where dn/dt denotes the number of loading cycles per day, and $d\omega/dn$ the damage per cycle. We will treat dn/dt as an input parameter representing the intensity of exercise. The damage per cycle is calculated as:

$$\frac{d\omega}{dn} = C\,\sigma_1^q,$$

where $\sigma_1(\boldsymbol{x},t)$ is the maximum principal stress (amplitude) in the center of the element, and C and q are constants. For the derivation of this formula and parameters C and q, see Appendix A.

The damage has both biological and mechanical effects. We assume that osteocytes (if present in the element) die when the damage reaches a critical level ω_{crit}, which is set to 0.25. Osteocyte apoptosis has been observed in correlation with microdamage [14,15], possibly due to microcracks rupturing osteocyte cell processes

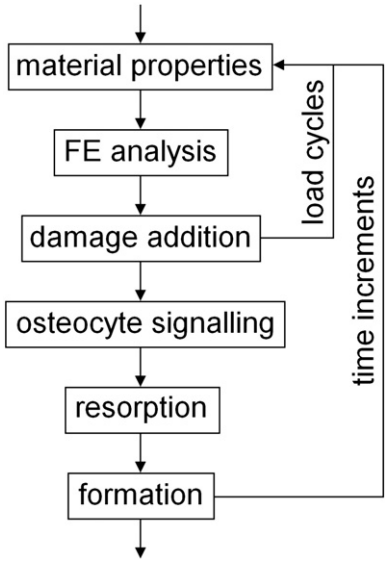

Fig. 1. Workflow scheme of the simulation.