Computer Simulation of a Bone Remodeling Model Including Cellular Accommodation Effect

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Abstract  
A regulatory mechanism for mechanical adaptation of trabecular bone proposed by Huiskes and colleagues [1] is implemented and studied in a MATLAB code. In addition to simulating the Osteocyte mechanosensory role and separation of Osteoclast and Osteoblast activity as proposed in [1], we improved this theory by including effect of Turner’s cellular accommodation [2]. We obtained trabecular-like structures for different loading conditions. The model was able to predict stress shielding and also showed qualities of global mechanical optimality.  

Keywords: Mechanical adaptation of bone, Trabecular bone, Finite element method, Bone remodeling

Introduction  
Bone cells come into existence with the genetic blueprint for skeleton and sculpt it during growth until the skeletal design meets the loading demands. This process, termed bone adaptation (including modeling and remodeling), requires bone cells to detect mechanical signals and integrate these signals into proper changes in the bone architecture. Specialized cells, osteoclasts and osteoblasts, respectively are in charge of bone resorption and formation. Although mechanisms involved in the regulation of these ‘actor’ cells are still vague, it is evident that mechanical feedback must be involved ([3]; [4]).  
By closely following the latest developments in bone physiology, many researchers have tried to develop mathematical models for the bone adaptation process. In 1976, Cowin and Hegedus [5] developed a sophisticated continuum, thermo-mechanical theory so-called adaptive elasticity theory. In this model, bone is defined as a porous medium with two phases: an elastic structure and an extracellular fluid. According to this model, adaptation is controlled by strain. Following adaptive elasticity theory, many other theories have been developed by others. For example, Rouhi et al. [6] replaced volume fraction by free surface density in the constitutive equations; Also Rouhi et al. [7] added a microcrack factor in the remodeling equations; Huiskes et al. [8] suggested that instead of strain, strain energy density (SED) can be used as a suitable mechanical stimulus for remodeling. In the beginning of the 21st century, Huiskes and co-workers [1] developed a more refined semi-mechanistic theory.

The new theory was based on the regulation scheme depicted in Figure 1. The purpose of this research is to simulate and improve their theory by developing a computer code using finite element method, as well as incorporating cellular accommodation effect. In addition, effects of the initial configuration, the external load and loading direction on the predicted morphology will be studied. Also two other simulation series including stress shielding simulation and a comparison with a topology optimization code will be performed.

Figure 1. The regulatory process proposed by Huiskes et al [1]. Both enhanced external load intensity (amplitude and frequency) and resorption cavities provoke bone formation.

Methods  
In the computational model presented and simulated by Huiskes et al. [1] bone tissue is assumed to contain n osteocytes per cubic millimeters located in the mineralized matrix with a total of N in the domain considered. Each osteocyte i measures a mechanical signal \( R(t_i) \) (in \( \text{Jm}^{-3}\text{s}^{-1} \)), the strain energy density (SED) rate in its location. In turn the osteocyte recruits osteoblasts to form new bone depending on the difference between the measured signal and a reference signal, \( k \). The influence of an osteocyte on its environment is assumed to decrease exponentially with increasing distance from the osteoblasts. The influence of osteocytes i on the osteoblast at location x is described by the spatial influence function (Figure 2) [9]

\[
f_i(x) = \exp(-d_i(x)/D),
\]

Where \( d_i(x) \) is the distance between osteocyte i and location x. the parameter D represents the distance.
The osteoblast recruitment stimulus is given by the stimulus value \( P(x,t) \) to which all osteocytes contribute relative to their distance from \( x \), hence \([1]\)
\[
P(x,t) = \sum_{i=0}^{N} \frac{f_i(x)\mu_i R_i(t)}{f_i(x)} = \mu_i = \text{mechanosensitivity of osteocyte } i.
\]

The regulation of the relative density \( m \) in location \( x \) is governed by \([10]\)
\[
\frac{dm}{dt} = \tau \left\{ P(x,t) - k_0 \right\} - r_{oc} \quad \text{for} \quad P(x,t) > k_0
\]
\[
\frac{dm}{dt} = -r_{oc} \quad \text{for} \quad P(x,t) \leq k_0
\]
where \( \tau \) is a constant regulating the rate of the process, \( k_0 \) is the threshold level for bone formation and \( r_{oc} \) is the relative amount of mineral resorbed by osteoclasts per day \([1]\).

This model includes a probability \( p \) of osteoclast activation per surface site at any time. This probability is assumed to be regulated either by the presence of microcracks or by disuse. The probability of resorption by microcracks was considered spatially random and was expressed as \([1]\)
\[
p(x,t) = \text{constant}, \quad \text{if} \quad P < a
\]
\[
p(x,t) = 0 \quad \text{if} \quad P \geq a
\]
where \( a=12.5 \) and \( \alpha=1.6 \).

In the above mentioned model a constant threshold stimulus is assumed. On the other hand numerous cellular biochemical responses to mechanical loading are transient, indicating a cell’s ability to adapt its behavior to a habitual mechanical environment \([11];[12];[13]\).

Turner \([2]\) introduced the principle of cellular accommodation based on an ever changing threshold stimulus; He hypothesized that the transient nature of many cellular biochemical responses to mechanical loading is a result of adaptation in cellular mechanical behavior, whereby the cell becomes mechanically tuned to its mechanical environment \([14]\).

Principal of cellular accommodation was based on experimental results suggesting that when a strain threshold is surpassed the sensor cells will gradually accommodate to the new state for example by cytoskeletal reorganization. It is interesting to know that latest experimental findings also support Turner’s hypothesis. For example Saez et al. \([15]\) showed that an epithelial cell can adapt its stiffness to maintain a specific range of habitual cellular deformations \([15]\). Also latest findings of Jaasma et al. \([16]\) support the hypothesis that osteoblast cells become mechanically adapted to their surrounding environment via cytoskeletal modifications and, accordingly, regulate the magnitudes of mechanical stimuli that initiate mechanotransduction signaling.

On the basis of Turner’s cellular accommodation theory \([2]\), which says that bone cells react strongly to transients in their environment, but eventually “accommodate” to steady state signals, we replaced \( k_0 \) with the following function\([2]\):
\[
F(k,t) = k_0 + (k - k_0) (1 - e^{-\frac{t}{\tau}})
\]
where \( \tau \) reflects the time needed for the cells to accommodate and \( k \) equals \( P(x,t) \).

In response to a change in environment, the bone cells accommodate by changing their set point, \( k_\phi \) as described by the relaxation function \( F(k,t) \); under steady state conditions (i.e. when \( t \to \infty \)) \( F(k,t) = k = k_\phi \), thus
\[
\frac{dm}{dt} = 0.
\]

The elastic modulus \( E(x,t) \) at each location is calculated from density according to \([17]\)
\[
E(x,t) = b \times m(x,t)\gamma
\]
where \( b \) and \( \gamma \) are constants.

Earlier computational models of bone adaptation used static loads to measure the mechanical signals. It is, however, known that bone only responds to dynamic loads. In the new theory the stimulus sensed by osteocytes is assumed to be a ‘typical’ strain energy density rate in a recent loading history. Cyclic loading conditions, characterized by frequency and magnitude, were imposed and it was assumed that osteocytes respond to the maximum SED-rate during the loading cycle. It was shown that the maximal SED-rate is related to the SED value for a substitute static load and that it could be evaluated by static finite element analysis \([11];[10]\).

The simulations were performed on a \( 2 \times 2 \text{ mm}^2 \), two dimensional bone FEA model (Figure 3). The structure was loaded by distributed stresses of \( 2 \text{ MPa} \) at the edges, which is a value in a naturalistic range for human trabecular bone the frequency of the load was sinusoidal at \( 1\text{Hz} \).[1]

We created the two-dimensional model by implementing the above mathematical expressions in a MATLAB code. Harmonic loads were imposed that were compressive in vertical and tensile in horizontal directions with a combination of shear loads. Osteocytes were assumed sensitive to the maximal SED-rate during one loading cycle.

![Figure 2. The spatial influence of sensor i, expressed as \( f_i(x) \) as shown in the graph](image)
In the FE model used, the stress components $\sigma_i$ and the strain components $\varepsilon_i$ are determined at the integration points of each element, and interpolated per element to give their values in the sensor points. The strain energy density is calculated from the tensor product:

$$U_i = \frac{1}{2} \varepsilon_i \sigma_i$$

(8)

where $i$ refers to the sensor number. The signal per sensor point $R_i(t)$ is then determined. The stimulus $P(x,t)$ is evaluated using equation (2) and a new density value $m_j$ is calculated in element $j$, in accordance with equation (3), from

$$m_j(x,t+\Delta t) = m_j(x,t) + \Delta t \times \frac{dm_j(x,t)}{dt}$$

(9)

where $\Delta t$ is the time step in the iteration process. The iteration is continued until no more significant changes in the density distribution occur.

The bone tissue is assumed to be isotropic. The maximal density is $\rho = 1$, minimal density $\rho = 0.01$, $b = 5$ GPa and $\gamma = 3$ [1].

**Results**

Seven different simulations were performed. The first and second ones tested whether the theory produces trabecular-like 2D configurations from conceptual initial architectures, representing bone in the post-mineralized fetal stage and from a uniform density (Figure 3). Simulations were prolonged until no more gross architectural changes occurred, representing the homeostatic mature stage.

In these two simulations the structures remodeled toward similar homeostatic configurations, in which trabecular-like structures were created and trabeculae were aligned to the loading direction (Figure 3). Increasing the number of elements produced the same results.

In the third simulation when the external load applied to the homeostatic architecture was rotated by $25^\circ$, the orientation of the trabeculae gradually reoriented as well, to align again with the external load (Figure 4).

In the forth simulation the regulatory mechanism was able to adapt the structure to alternative loading conditions. A $25\%$ increase in loads produced increased trabecular thickness and gain of bone mass (Figure 5). The effect of overloading and unloading on trabecular adaptation was investigated in the fifth simulation where we artificially disconnected two trabeculae while the same externally applied load was maintained. The disconnected and therefore unloaded trabeculae disappeared, while the neighboring overloaded trabeculae thickened (Figure 6).

In the sixth simulation by increasing Young’s modulus for the upper side of square plate a simple model of stress-shielding of bone around prosthesis was simulated. Bone resorption happened close to the implant surface and this continued until a new homeostasis was obtained (Figure 7).

In the seventh simulation the question was how will this remodeling theory compare to a topology optimization model? We obtained very similar final configurations (Figure 8) by using our code (bone adaptation theory prediction) and the topology optimization code by ole Sigmund [18].

Although this simulation was performed for a simple loading condition (compressive ramp load) but the similarity between the two final configurations is interesting.
Biochemical processes to take place [1]. Simulation of stress-shielding was another capability of the theory. A major problem threatening the long-term integrity of total hip replacement is the loss of proximal bone often found around non-cemented stems in the long term [20]. It is generally accepted that ‘stress shielding’ is the cause for this problem: after implantation of the prosthesis the surrounding bone is partially ‘shielded’ from load carrying and starts to resorb. In our sixth simulation, this phenomenon can be observed and further investigation of it will be possible by changing various parameters in the model.

Another interesting result was that when the global optimization procedure was applied to structures similar to those we used in this research, they produced results that are analogous. The implication is that the trabecular architecture predicted by this bone adaptation model has qualities of global mechanical optimality.

Even though, this research showed that including effect of cellular accommodation would not change the final morphology when time constant (τ) is large enough; but, it must be considered in the simulations, because it shows how long a load will be effective in the remodeling process. Furthermore, this research showed that instead of constant loads, variable loads similar to those in a real bone must be applied to FE model if the accurate prediction of final morphology is desired.

Understanding and modeling bone remodeling processes need knowledge from different disciplines; it is an excellent example of a multidisciplinary problem in biomechanics. It is hoped that more realistic theories will appear as our knowledge of mechanotransduction of bone cells, continuum mechanics, mixture theory and many other related fields increases.

References


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