15th. Annual (International) Conference on Mechanical Engineering-ISME2007
May 15-17, 2007, Amirkabir University of Technology, Tehran, Iran
ISME2007-1751

Computer Simulation of a Bone Remodeling Model Including Cellular Accommodation Effect

A. Vahdati
MSc student, Sahand University of Technology ,Tabriz, Iran
a_vahdati@sut.ac.ir

G. Rouhi
Assistant professor, University of Ottawa, Canada
grouhi@uottawa.ca

F. Ghalichi
Assistant professor, Sahand University of Technology, Tabriz, Iran
fghalichi@sut.ac.ir

M. Tahani
Assistant professor ,Ferdowsi University Mashad, Iran
mtahani@um.ac.ir

Abstract
A regulatory mechanism for mechanical adaptation of trabecular bone proposed by Huiskes and collegues [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.

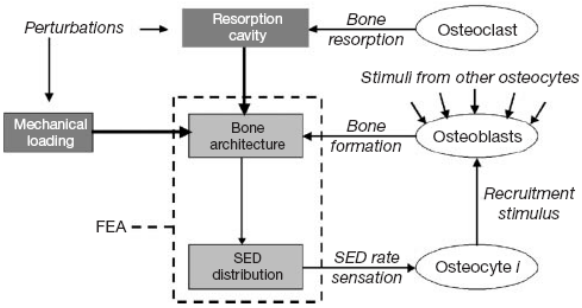

Figure 1. The regulatory process proposed by Huiskes et al [1]. Both enhanced external load intensity (amplitude and frequency) and resorption cavities provoke bone formation.

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)* (in $\mathrm{J\,m^{-3}s^{-1}}$), 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]

$$f_i(x) = \exp(-d_i(x)/D), \qquad (1)$$

Where $d_i(x)$ is the distance between osteocyte *i* and location x, the parameter *D* represents the distance

from an osteocyte at which location its effect has reduced to e^{-1}; i.e. 36.8%.

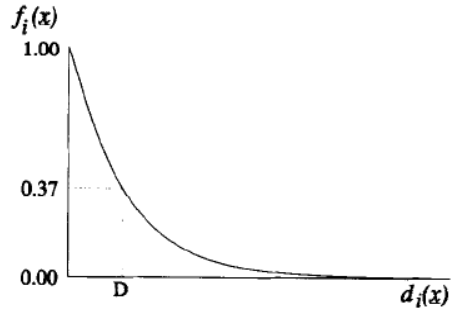

Figure 2. The spatial influence of sensor *i*, expressed as $f_i(x)$

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]

$$P(x,t) = \sum_{1}^{N} f_i(x)\mu_i R_i(t) \qquad (2)$$

where μ_i is mechanosensitivity of osteocyte i.

The regulation of the relative density m in location x is governed by [10]

$$\frac{dm}{dt} = \tau\left\{P(x,t) - k_0\right\} - r_{oc} \quad \text{for } P(x,t) > k_0$$

$$\frac{dm}{dt} = -r_{oc} \quad \text{for } P(x,t) \le k_0 \qquad (3)$$

where τ 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]

$$p(x,t) = \text{constant}, \qquad (4)$$

where this constant was selected to be 10%. When assuming osteoclastic activation by disuse, the probability of resorption is higher in areas of lower strain. This strain dependent probability was formulated as [1]

$$p(x,t) = c\left[a - P(x,t)\right] \quad \text{if } P < a$$

$$p(x,t) = 0 \quad \text{if } P \ge a \qquad (5)$$

where *c*=12.5 and *a*=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]:

$$F(k,t) = k_0 + (k - k_0)(1 - e^{\frac{-t}{\tau}}) \qquad (6)$$

where τ 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_0 as described by the relaxation function $\mathbf{F(k,t)}$; under steady state conditions (i.e. when $t \to \infty$ `) $\mathbf{F(k,t) = k = k_0}$, thus $\frac{dm}{dt} = 0$.

The elastic modulus *E*(*x,t*) at each location is calculated from density according to ([17])

$$E(x,t) = b \times m(x,t)^{\gamma} \qquad (7)$$

where *b* and γ 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 ([1];[10])

The simulations were performed on a $2 \times 2 \quad mm^2$, two dimensional bone FEA model (Figure 3). The structure was loaded by distributed stresses of 2 *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*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.

In the FE model used, the stress components σ_i and the strain components ε_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:

$$U_i = \frac{1}{2}\varepsilon_i \sigma_i \qquad (8)$$

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

$$m_j(x,t+\Delta t) = m_j(x,t) + \Delta t \times \frac{dm_j(x,t)}{dt} \qquad (9)$$

where Δt 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°, the orientation of the trabeculae gradually reorientated 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 tarbeculae 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.

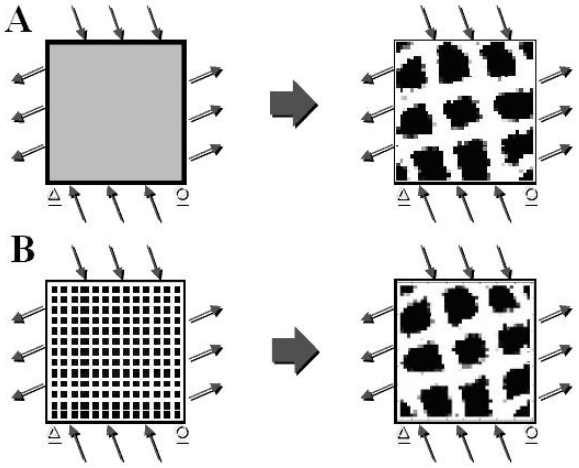

Figure 3. Transformation of morphology for (A) uniform density (B) post-mineralized fetal stage initial configurations.

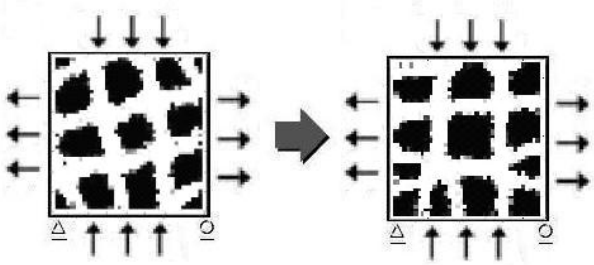

Figure 4. Orientation of the applied stresses was changed from 15° to 0° and the architecture adapted to align with the new stress orientation.

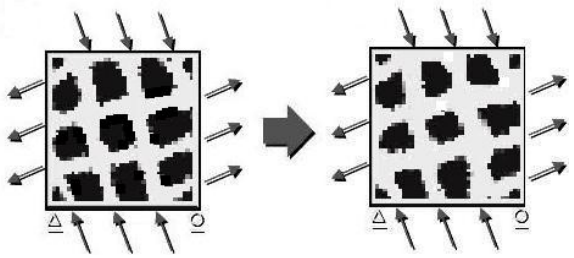

Figure 5. Effect of increasing loading magnitude by 25%. All trabeculae thicken.

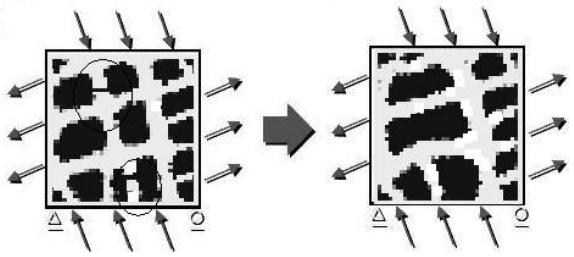

Figure 6. Two struts are artificially disconnected, while the external stress is maintained. After adaptation, the existing architecture is again adapted to the applied stresses by removal of the unloaded trabeculae and thickening of the overloaded trabeculae.

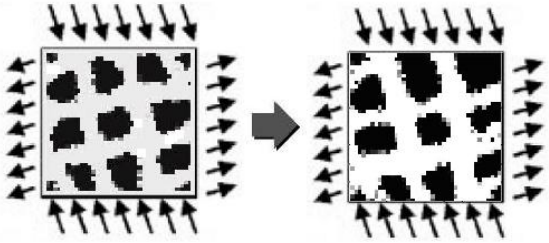

Figure 7. Stress shielding is simulated by increasing the young modulus of upper side of the square.

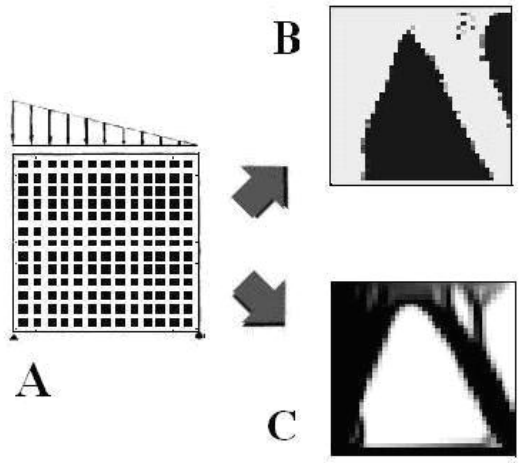

Figure 8. (A) Two-dimensional plate model of bone tissue subjected to a compressive load as indicated (B) Architecture after applying the bone adaptation theory (C) Architecture after applying the topology optimization code.

Discussion and Conclusion

From first five simulations it was concluded that the theory was able to explain both modeling as well as remodeling of trabecular-like architectures as governed by external forces. Although we implemented the mathematical model in a computer code from scratch, we obtained final configurations very similar to the ones obtained by Huiskes et al. The differences between the figures shown here and the figures from Huiskes et al. [1] are due to a difference in the time increments and time constant used in the formulation. Osteoblasts and osteoclasts were often assumed to work together in bone. In a recent paper Pogoda et al. [19] discuss that bone resorption is independent of bone formation. Studying transgenic mice, they induced a near-complete and reversible osteoblast ablation. In these animals, osteoblast ablation led to a complete arrest of bone formation accompanied by bone loss, thus illustrating that, in mice, the bone resorption function is independent of bone formation [19]. They also provide clinical evidence that the sympathetic regulation of bone does exist in humans and plays a clinically important role in diseases.

A merit of this theory is that it is not in contrast with these latest findings in bone physiology because in this theory there is still a place for biochemical factors and central control of bone remodeling. This model does not imply that biochemical pathways or central control are irrelevant, but it does show that mechanical feedback can be a potent coupling factor for the relevant 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

[1] Huiskes R., Ruimerman R., Van Lenthe G.H., Janssen J.D., 2000. Effects of mechanical forces on maintenance and adaptation of form in trabecular bone. *Nature* 405, 704–706.

[2] Turner CH, 1999. Toward a mathematical description of bone biology: the principle of cellular accommodation. *Calcif Tissue Int* 65:466–471.

[3] Lanyon, L.E., 1992. Control of bone architecture by functional load bearing. *Journal of Bone and Mineral Research* 7, S369–S375.

[4] Van Langendonck, L., Lefevre, J., Claessens, A.L., Thomis, M., Philippaerts, R., Delvaux, K., Lysens, R., Renson, R., Vanreusel, B., Vanden Eynde, B., Dequeker, J., Beunen, G., 2003. Influence of participation in high-impact sports during adolescence and adulthood on bone mineral density in middle-aged men: a 27-year follow-up study. *American Journal of Epidemiology* 158, 525–533.

[5] Cowin, C. S. & D. H. Hegedus. 1976. Bone remodeling I: A theory of adaptive elasticity. *J. Elasticity* 6, 313–326.

[6] Rouhi G, Herzog W, Sudak L, Firoozbakhsh K, Epstein M, 2004. Free surface density instead

of volume fraction in the bone remodeling equation: theoretical considerations, *FORMA* 19 (3) 165–182.

[7] Rouhi G, Epstein M., Herzog W, Sudak, L., 2006. Free Surface Density & Microdamage in the Bone Remodeling Equation: Theoretical Considerations, *Int. J. of Eng. Sci.*,Vol. 44, Issue 7, pp. 456-469.

[8] Huiskes R., Weinans H, Grootenboer J, Dalstra M, Fudala M & Slooff T.J. 1987. Adaptive bone remodeling theory applied to prosthetic-design analysis. *J. Biomech.* 20, 1135–1150.

[9] Mullender, M.G., Huiskes, R., Weinans, H., 1994. A physiological approach to the simulation of bone remodeling as a selforganizational control process. *J. Biomech.* 27, 1389–1394.

[10] Ruimerman R., Huiskes R., van Lenthe G.H. & Janssen J.D., 2001. A Computer-simulation Model Relating Bone-cell Metabolism to Mechanical Adaptation of Trabecular Bone. *Comp Meth in BioMech & BioMed Eng*, Vol 4, pp 433-448.

[11] Chen, N.X., Ryder, K.D., Pavalko, F.M., Turner, C.H., Burr, D.B., Qiu, J., Duncan, R.L., 2000. Ca (2+) regulates fluid shear-induced cytoskeletal reorganization and gene expression in osteoblasts. *American Journal of Physiology and Cell Physiology* 278, C989–C997.

[12] Kreke, M.R., Huckle, W.R., Goldstein, A.S., 2005. Fluid flow stimulates expression of osteopontin and bone sialoprotein by bone marrow stromal cells in a temporally dependent manner. *Bone* 36, 1047–1055.

[13] Nauman, E.A., Satcher, R.L., Keaveny, T.M., Halloran, B.P., Bikle, D.D., 2001. Osteoblasts respond to pulsatile fluid flow with short-term increases in PGE (2) but no change in mineralization. *Journal of Applied Physiology* 90, 1849–1854.

[14] Turner, C.H., 1998. Three rules for bone adaptation to mechanical stimuli. *Bone* 23, 399–407.

[15] Saez, A., Buguin, A., Silberzan, P., Ladoux, B., 2005. Is the mechanical activity of epithelial cells controlled by deformations or forces? *Biophysical Journal* 89, L52–L54.

[16] Jaasma, M.J., Jackson, W.M., Tang, R.Y., Keaveny, T.M., 2006. Adaptation of cellular mechanical behavior to mechanical loading for osteoblastic cells. *J. Biomech,* doi:10.1016/j.jbiomech.2006.09.010

[17] Currey, J.D., 1988. The effect of porosity and mineral content on the young's modulus of elasticity of compact bone. *J. Biomech*. 21, 131–139.

[18] Sigmund, O. 2001. A 99 line topology optimization code written in matlab. *Struct. Multidisc.Optim.* 21, 120–127.

[19] Pogoda, p., Priemel, M., Rueger, J.M., Amling, M., 2005. Bone remodeling: new aspects of a key process that controls skeletal maintenance and repair, *Osteoporos Int* 16: S18–S24.

[20] B. Petera, N. Ramanirakaa, L.R. Rakotomanana, P.Y. Zambelli and D.P. Pioletti, 2004. Peri-implant Bone Remodeling after Total Hip Replacement Combined with Systemic Alendronate Treatment: A Finite Element Analysis. *Computer Methods in Biomechanics and Biomedical Engineering* Vol. 7, No. 2, pp. 73–78.