Bone Distribution simulation during damage-repair bone remodeling in human proximal femur

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Abstract. A new damage-adaptive bone remodeling model, in which an algorithm incorporating both strain and damage stimuli, is developed in this paper. Typically, a human proximal femur model is established to predict the bone mass distribution during bone remodeling process. And human physiology damage-repair cycle is considered in the model. The governing equations of the mathematical model, digesting the predecessors’ ideas, are numerically solved and implemented into ANSYS software via the user interface of finite element algorithm. With the aid of this novel model, the whole healing behavior of human proximal femur is elucidated properly.

Introduction

Fatigue and fracture may form and grow in a bone as a result of daily loading activities. On the other hand, as a living tissue bone can sense the damage area and repair itself within a certain damage level. During its entire lifetime, bone is able to adapt its internal microstructure and, subsequently, mechanical properties to the varying mechanical and physiological environments in a process which is commonly known as bone remodeling [1]. Numerous algorithms and biomechanical theories have been proposed to predict such remodeling process. However, to the authors’ knowledge, there is no report from the literature on numerical simulation and theoretical investigation which can rationalize the damage-repair evolution law during the repairing process of a cortical bone. It should be noted that bones stand repeated loadings on mixed mode (shear, tensile and compression) in daily activities. When experiencing cycle-loading, bone, as a structure of human body, gradually turn into fatigue and fragile like common engineering materials. In the past decades, the crucial to conduct the research on bone damage caused by bone fractures and related diseases are widely recognized, especially those for the soldiers and athletes. According to the research in modern biology, fatigue and fracture form and grow in the bone the accumulation of the bone damage is superior to the ability of bone repairing. As a result, the study on the bone fatigue and damage became an important branch in biomechanics and clinical medicine. Taylor et al. [2] performed an experiment to test the fatigue life of human tibia and the result showed the fatigue life expectancy under the condition of continuous loading lasts was only 3 years. In clinical medicine circle, it is generally agreed that the actions of osteoclasts and osteoblasts are coupled during bone remodeling[3-4].These cells combine to form a basic multicellular unit (BMU)—a cavity, about 200 µm in diameter, which moves along the length of the bone at a speed of about 40 µm per day(Fig. 1).

Figure 1 Bone’s repair mechanism. A BMU in which osteoclasts and osteoblasts work in sequence to absorb dead bone and generate new bone. [2]
As mentioned above, bone tissue is able to adapt its internal microstructure and mechanical properties to the external (mechanical and electrical environments [5-7], electromagnetic field [8,9], etc) and internal factor (microdamage [10]). In order to describe and predict the adaption process as well as bone damage-repair mechanism, researchers have proposed numerous theories based on biological experiments. Nowadays, there are two popular bone remodeling models based on phenomenological approach and mechanical approach respectively. The phenomenological model [11] is dependent on BMU damage and porosity change. On the other hand, the mechanical model has the same basis that the apparent density is designed as a direct response to a certain mechanical stimulus [12-14], where mathematical formulas is established to quantitatively describe bone remodeling process. And numerical computational techniques are employed to predict the formation and the absorption of bone. With the advance in bone damage repair mechanism understanding, more and more researchers start to use this method on the clinical attempt [15-17].

Quite a few researchers [18-19] consider the crack damage and the fatigue as the inducer of bone remodeling. Taylor et al. [1] proposed that bone tissue is a continuous system incorporating the growing and repairing of microcrack. Great attention was paid to the relationship of damage evolution and behavior of the osteocyte. Corollary [20] held the view that microdamage was able to outgoing a series of biological signals to activate the local remodeling process. This opinion, which carried great weight from the researchers, considers microscopic fluid potential and osteocyte bone tube damage being bound up with the microdamage. McNamara et al. [21] proposed a mechano-regulatory system incorporating both strain and microdamage stimuli to simulate the formation and healing of the damage in a trabecula bone model. In his model, the grow/repair process of microdamage in trabecula bone under mechanical loading was simulated. The stimuli that activated the bone remodeling were not only the stress and strain, but also the local damage rate which was defined using Miner’s rule [22]. Wang et al. [23] developed the remodeling algorithms used in the dental implants model. Below a critical damage threshold, strain-adaptive remodeling was deemed to be dominant in the remodeling process. After exceeding a critical value, damage-induced remodeling would prevail, which involves a biological process in grow/repair of microdamage assuming a stochastic manner of BMU activities.

These works, in spite of lacking of enough experiential evidences, could explain the bone remodeling mechanism very well. However, a macroscopic bone remodeling model with clinic reference significance is desired to be set up to complement the numerical simulation work. The object of this study is then to make the evolution and approximate location of the damage in bone visible and close to the reality. To this end, a new damage-adaptive remodeling model is proposed, which incorporates both strain and damage stimuli. As an example, a human proximal femur algorithm is derived from the proposed model to predict the bone mass distribution during bone remodeling process.

Methods and Model

2.1 Methods

To evaluate the distribution of apparent density in human femur, the Stanford model [12,24] is employed to characterize the bone state. This model uses apparent density in a single scalar. It assumes that the remodeling activity is related to a homeostatic condition:

\[
\dot{\rho} = krS, \dot{\rho}
\]

where the added or removed bone is assumed to be completely mineralized, that is, the bone with maximum density \( \dot{\rho} \), \( S \), is the specific surface (internal surface per unit volume) that depends on the apparent density, and \( k \) is the ratio of the available surface for remodeling and the total internal surface. It can be approximated by a fifth order polynomial of the apparent density.
Our damage model of bone remodeling is described as follows. At first, damage accumulation ($\omega$) is defined to assess the state of damage. Miner’s rule is employed to define the damage rate $\dot{\omega} = \frac{1}{N_f}$[21], where $N_f$ is the number of cycles needed for the material to reach failure for a given stress level.

The empirical equation of Carter et al.[25] is used to calculate $N_f$:

$$\log N_f = H \log \sigma' + JT + K \rho' + M,$$

where $\sigma'$, $T$, and $\rho'$ are stress (MPa), temperature (°C) and density of the material ($g cm^{-3}$), respectively, and $H = -7.789$, $J = -0.0206$, $K = 2.364$ and $M = 15.47$ are all empirical constants. Then, the damage accumulates is calculated by

$$\omega = \int_0^t \dot{\omega} dt, \omega \leq 0.98$$

(2)

where $\omega$ represents the state of local damaged bone tissue and $t$ the duration of calculation.

A damage threshold $\omega_{\text{crit}} = 2.6 \times 10^0$ is determined assuming that critical damage corresponds to the damage occurring during one cycle at $3500 \mu e$.

If damage accumulation $\omega$ is below the damage threshold $\omega_{\text{crit}}$, adaptive remodeling program is employed. Strain energy density at location $i$ is given by $U^i = \frac{\epsilon^i E^i}{2 \rho^i}$, where $\epsilon^i$ is the strain and the unit of $U^i$ is $MPa (g cm^{-3})^{-1}$. At a given location $i$, the stimulus for the element is $S^i$, defined as $S^i = U^i - U_{\text{ref}}$

The density change rate is expressed as:

$$\frac{d \rho(x^i, t)}{dt} = C_i S_{\text{strain}}^i$$

(3)

In order to establish the ‘dead zone’ of remodeling equilibrium strains whereby bone mass reduces below $1000 \mu e$ and increases above $2000 \mu e$, $\epsilon_{\text{ref}}$ is dependent on the strain of the element $j$, $\epsilon^j$ is determined based on the following criteria: If the strain of the element $\epsilon \leq 1000 \mu e$, $\epsilon_{\text{ref}} = 1000 \mu e$ and $C_i = 3.87$; If the strain $1000 \mu e < \epsilon \leq 2000 \mu e$, $\epsilon_{\text{ref}} = 1000 \mu e$ and $C_i = 0$; If the strain $2000 \mu e < \epsilon \leq 3500 \mu e$, $\epsilon_{\text{ref}} = 1000 \mu e$ and $C_i = 198$

If damage accumulation $\omega$ is above the critical value $\omega_{\text{crit}}$, the damage algorithm is activated. Thus

$$\frac{d \rho_a(x^i, t)}{dt} = B \sum_{j=1}^{N} f^j(a, x^j) S^j(x) \quad 0 < \rho_a < \rho_{\text{max}}$$

(4)

where $\rho_a$ is the bone density mediated by adaptive remodeling, parameter $B$ and $\rho_{\text{max}}$ are the proportion coefficient and the maximal bone density, respectively $B = 0.05 (g cm^{-3})^2/MPa^{-1} \text{day}^{-1}$ and $\rho_{\text{max}} = 1.80 g cm^{-3}$. $f^j(x, x^j)$ is spatial influence function, describing the decay in signal intensity relative to distance $d(x, x^j)$ and decay parameter $D$. according to

$$f^j(a, x^j) = e^{-d(a, x^j)/D} \quad (5)$$
With the distance $d(a,x)$ is the distance between the actor cell $a$ and the sensor cell $x$, where the parameter $D$ denoting the distance from an actor cell at which location its effect has reduced to $e^{-1}$, which is assumed to be 0.05 mm. $N$ denotes the number of sensor cells contributing to the total stimuli. The elastic modulus and the Poisson ratio are calculated by

$$
E = \begin{cases} 
1007 \times \rho^2, & \text{if } 0.01 \text{g/cm}^3 \leq \rho < 0.25 \text{g/cm}^3 \\
255 \times \rho, & \text{if } 0.25 \text{g/cm}^3 \leq \rho < 0.40 \text{g/cm}^3 \\
2972 \times \rho^2 - 933 \times \rho, & \text{if } 0.40 \text{g/cm}^3 \leq \rho < 1.20 \text{g/cm}^3 \\
1763 \times \rho^{3.25}, & \text{if } 1.20 \text{g/cm}^3 \leq \rho \leq 1.80 \text{g/cm}^3 
\end{cases}
$$

(6)

$$
\nu = \begin{cases} 
0.2, & \text{if } 0.01 \text{g/cm}^3 \leq \rho < 1.20 \text{g/cm}^3 \\
0.32, & \text{if } 1.20 \text{g/cm}^3 \leq \rho < 1.80 \text{g/cm}^3 
\end{cases}
$$

(7)

2.2 Numerical assessment

2.2.1 Finite element analysis

In order to illustrate the application of the microdamage-based mechanisms in numerical computation, the proximal femur bone remodeling model was predicted using finite element method (Fig. 2).

![2-D mesh of the proximal extremity of the femur](image)

Figure 2 2-D mesh of the proximal extremity of the femur

As shown in Figure 2, the number of elements and nodes used for modeling the systems was 925 and 1925, respectively. A mesh is generated using four-node quadrilateral plane strain elements. We assume the bone tissue as compressible isotropic material. Thus the Young’s modulus, the permeability, the Poisson’s ratio and the density were defined initially and may change with time, these parameters are all defined by the mineral density in the algorithm.

The bone tissue subjects to dynamic loading in our daily activities, however, the peak of the dynamic loading dominate in the whole remodeling process [26]. Thus we take a steady force and fixed constrain as the boundary condition of this model.

2.2.2 A human proximal femur model

A human proximal femur model is built based on the mechano regulation, considering the stain energy and stress of each element affected by the daily stimulus. The remodeling was considered for initial model with a uniform density distribution of $1.80 \text{g/cm}^3$. The biomechanical stimulus was, as a
rule, calculated for each element and bone density was also renewed each element. After 1000 iteration steps, it is clear the formation of the two higher density external cortical layers along the model, a zone of low density corresponding to the medullar channel and the complex distribution of densities of the femoral head including two higher density regions in the femoral neck and head surrounded by two lower density zones. Then we introduce the damage mechanism into the algorithm, with initial damage area defined in [Fig.3], and continued simulating by controlling the boundary condition. The initial damage is neither a loss of elastic modulus nor a captivity planted in the finite element model. Instead, it is a constant \(3.0 \times 10^{10}\) that above a damage threshold \(2.6 \times 10^{10}\) here to activate the damage repairing mechanism.

Additionally, to enhance understanding the human physiology damage-repair cycle, we divide the whole remodeling process into 3 periods: Absorption period (20 days), Reversion period (10 days) and Formation period (90 days) [27]. The finite element method was used during every cycle to analyze the stress and strain field inside the femur model. Thus we can see what kind of remodeling process is to be taken in the next iteration step for each element.

![Figure 3 The proximal femur model with initial damage in the cortical bone area.](image-url)
The bone remodeling algorithm was implemented into the FE software ANSYS12.0 (Analysis System Inc., USA), where each element was considered as an individual model. The bone remodeling algorithm [Fig.4] can be summarized as follows. Firstly, the initial material properties are assumed and boundary condition loading is applied. The stress and strain fields are calculated based on Eqs. (1) (2) and the mechanical signal is calculated at each sensor location in the tissue. When a mechanical stimulus is detected according to the above criteria a signal is emitted to initiate remodeling according to mechanism above. Based on the magnitudes of these signals, the change in density of the element is calculated and a new density is predicted. The new elastic modulus is determined for elements whose density has already changed.

Results

Figure 5(a) shows the changes of the elastic modulus in the proximal femur during the repairing bone remodeling process. Piecewise linear function is used to illustrate the relationship between the apparent density and elastic modulus, which is more suitable for the proximal femur with abundant cancellous bone and trabecular architecture. As is shown in Figure 5, the phenomenon can be explained as follows. the damage area can be detected by the sensor cell and corresponding stimulus signal is sent out during the absorption period from day 1 to day 20. After exceeding a critical value, damage remodeling would prevail. In addition, the absorption phenomenon occurs and subsequently, tends to diffuse in the adjacent area. The bone mass could reduce to the minimum (72.5%) in the model, see Figure 5(b). Although the physiological mechanism is unknown, the reversion period from day 20 to day 30 is a dynamic equilibrium process, so we can assume that the absorption and formation rate in the model is identical. Finally, the bone remodeling enters the formation period from day 30 to day 110, in which the mechanical properties and microstructure gradually restore to the initial situation with the new bone deposit. However, the formation rate is much less than the absorption rate in the first period, about 1:4.
Figure 5 (a) Time-dependent evolution of elastic modulus during 110 days repairing remodeling.

Figure 5(b) Change of the bone mass in the damage region.

Figure 6 shows the evolution of the damage in the proximal femur model. As similar as the changes of the elastic modulus, the damage signal is spreading to the adjacent area with the iterative step. We can draw a conclusion that not only the damage area but the whole model perform a series of repairing activities. The interrelationships between different sensor cells depend on the quantity of the spatial influence function. For the osteocyte mechano-sensors it was assumed that the osteocytes could signal strongly (i.e. >36.8%) to any surface elements perpendicular to them. Damage, as shown by the reduction of stiffness, was estimated using the expression [28,29].

\[ D_{f,i} = \left( \frac{E_0^i - E_i^i}{E_i^i} \right) \]

\[(8)\]

Figure 6 Change of the bone damage in the model.
Discussion and Conclusion

In this paper, we established a human proximal femur algorithm, which was planted an initial damage area in a certain level, to illustrate the whole bone repairing process. With a set of mechanical stimulus and human physiology damage-repair cycle considered in the bone remodeling algorithm, the numerical result obtained in the simulation are very similar to reality in the case of an intact femur. The use of FE method was able to simulate the microstructure and damage evolution of each individual BMU and, subsequently, the whole model during bone remodeling process. Therefore, the FE simulation allows us to perform a cheap and extensive qualitative comparison between them, becoming a very important guidance in clinical treatment [30]. With the aid of this algorithm, the whole healing behavior of human proximal femur was elucidated properly.

In conclusion, finite element simulations were implemented to predict the evolution of bone damage healing remodeling process by using a model that combines both strain-adaptive and damage-adaptive mechanism. In this paper the advantage of bone remodeling simulations to predict the healing behavior in the proximal femur has been shown. However, it is necessary to remark again that several important simplifications have been performed in this model. For instance, we consider the bone as an elastic isotropic material simulated in a continuum 2D model, which can be better implemented in a 3D model of an actual femur. And damage level must exceed some critical value before a repair process is triggered. We didn’t consider in the repairing processes like biological and metabolic effects, alterations of the interface conditions. And the resorption and formation rates in the algorithm should be experimentally measured. In the earlier future, it will be necessary to improve these models including some of these effects.

A human proximal femur algorithm was developed and relatively accurate results were achieved after 1000 iteration steps in the Stanford model[12,13]. Also, two different regulatory mechanisms are chosen, in which strain energy density and damage level were selected as the mechanical stimulus respectively. Human physiology damage-repair cycle and damage factor [28] is considered in the algorithm too. Consequently, the mathematical equations used to describe the bone remodeling process are provided with more biological significance.

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