Formulation of a Mathematical Model for Mechanical Bone Remodeling Process*

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This paper is concerned with the formulation of a mathematical model to describe mechanical bone remodeling process. Firstly, mechanical stimulus is defined as a function of the rate-of-deformation power per unit mass. Physiological signal transmission processes of remodeling from the mechanical stimulus to change of bone density are described by $n+1$ sequential evolution equations with $n+1$ macroscopic internal state variables. The evolution equations are established on the basis of the experimental results in a literature. The value of the internal variable in the last step specifies the balance level of bone density, which is the target of the current bone density. The comparison of the predicted results with the corresponding experimental ones shows that this model can quantitatively describe a time-dependent process of bone remodeling.

***Key Words*:** Biomechanics, Mathematical Model, Bone, Remodeling

1. Introduction

Mass density, structure and morphology of bone adapt themselves to mechanical circumstances. These phenomena have been known as mechanical remodeling, but its physiological mechanisms have not been clarified yet.

A mathematical model to describe such mechanical remodeling is indispensable to perform numerical simulation for clinical problems related with bone reconstruction and/or bone resorption. The model is also necessary to understand the optimal structure of organisms. These problems are some of the most important subjects in the field of biomechanical engineering.

Several mathematical models have been proposed so far to describe the remodeling phenomena. But most of them are formulated on the basis of the idea that strain or mass density, for example, approaches its optimal value[(1)-(9)], because the major purposes of those models are to represent the optimal morphology of bone or trabecular structure. Thus it is difficult to describe the time-dependent characteristics of bone remodeling, namely the actual history of bone remodeling behavior. Therefore there are some limitations to apply those models to simulations for training or rehabilitation in which the actual history is important.

The purpose of this study is to formulate a mathematical model that can describe actual time-dependent process of bone remodeling. For this purpose, some internal state variables are introduced to represent the physiological process of bone remodeling, and the evolution equations of those variables are established referring to literatures on macroscopic experiments of bone remodeling. The validity and the

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Table 1 Effects of mechanical factors on bone response

Factor	Response of Bone
Effects of No Load	· Bone Resorption[10][11][12]
Effects of Static Load	· No bone mass change after growth period[13]
	· Bone remodeling[14]
Difference between Dynamic and Static Load	· Bone resorption under static load, bone formation under dynamic load[15]
	· Dynamic load is more effective than static load[16]
Effects of Cycles and Frequency	· Maintained under a few cycles / day, saturated under the loading more than certain number of cycles[10]
	· Change in frequency of bending affects bone formation[17]
Effects of Overload	· Bone resorption around micro crack[18]

characteristics of the proposed model are examined by comparing simulation results with the experimental results in the literature[10].

2. Formulation of Mechanical Bone Remodeling

2.1 Characteristic features of bone remodeling phenomena and basic assumptions

Characteristic features of bone remodeling obtained from the literatures on experimental studies are summarized in Table 1. In the table, inconsistent results are included, and there is no definite opinion on the dependence of the type and the magnitude of load on the amount of remodeling.

In this study we consider the bone remodeling has the following characteristic features:

(1) Under no load condition, bone resorption occurs.

(2) Variable load is more effective for bone formation than static load.

(3) There is a saturated value for the amount of bone remodeling.

In addition to these, we also adopted the following features observed in many experimental results:

(4) Time delay exists between the start of mechanical stimuli and the beginning of remodeling.

In order to formulate a mathematical model we further introduce the following hypotheses:

(a) The bone is approximated by a hypothetical macroscopic uniform continuum with no vacancy, and the change of apparent density of the continuum is considered. In other words, only the macroscopic internal bone remodeling is formulated, and the change in bone shape, namely the macroscopic surface bone remodeling is not taken into account.

(b) The mechanical properties of the continuum mentioned above are represented by a linear elastic material.

(c) The consideration is restricted to uniaxial cases. And the effect of tension load on the remodeling is equal to that of compression load.

Finally, in order to establish the framework of the remodeling model, we considered the bone remodeling is the following process: firstly a given mechanical stimulus is recognized by some sensing functions. Then the stimulus is transmitted to osteoclasts and osteoblasts by several steps of a physiological transmission function, and these bone cells are activated. These cells, osteoclasts and osteoblasts, cause antagonistic phenomena, namely bone resorption and formation, respectively. But those functions are controlled to keep an equilibrium suitable for the current internal state. The change of the equilibrium is observed as bone remodeling phenomenon.

On the basis of the above consideration, we further assume the following:

(d) The mechanical stimulus can be defined by a function of mechanical variables.

(e) The physiological transmission processes of mechanical stimulus can be represented by macroscopic internal state variables and their evolution equations.

(f) We do not formulate the individual activities of osteoclast and osteoblast. In other word, the result of the balance of bone resorption and bone formation is formulated, and can be described by internal state variables and their evolution equations. In the following, we call these internal variables the bone remodeling stimulus transmission variables.

2.2 Formulation of a mathematical model

Firstly, based on the model by Fyhrie et al.[5], a mechanical stimulus S for bone remodeling is defined by an absolute value of power per unit apparent mass

$$S=|\sigma\cdot\dot{\varepsilon}/\rho| \qquad (1)$$

where σ and $\dot{\varepsilon}$ are a uniaxial stress and strain rate, and ρ is an apparent mass density. By this equation we can represent that an input power for lower density bone is recognized as the stronger stimulus than the same input power for higher density one. Furthermore by using the absolute value we represent that loading and unloading have the same effect on remodeling.

Though the mechanisms of transmission processes of a mechanical stimulus are not clarified yet, we can imagine that those processes include several steps such as electrical and biochemical reactions, production of cytokines and activation of bone cells. Rubin et al. showed the existence of time delay between the start of mechanical stimuli and the beginning of remodeling[10]. This may be probably due to the delay properties of transmission processes of the stimulus.

Therefore we assume that the transmission processes are approximated by $n+1$ bone remodeling stimulus transmission variables $R_i(i=0, \cdots, n)$ and that their evolution equations can be represented by

$$\dot{R}_0=S-r_0R_0{}^l \quad (2)$$

$$\dot{R}_i=r_i\{R_{i-1}-R_i\} \quad (i=1, \cdots, n) \quad (3)$$

where l and $r_i(i=0, \cdots, n)$ are constants. We emphasize that the individual evolution equation in Eqs. (2) and (3) dose not describe a particular physiological elementary process in the actual bone remodeling, but that it is a part of a mathematical model to represent the phenomenological bone remodeling.

In Eq. (2), the rate of the variable R_0 is increased with the mechanical stimulus S, and under continuation of the stimulation in a certain period, R_0 is increased by the integration effect of S. Thus the variable R_0 represents the accumulation of the mechanical stimulus S. Due to the existence of the second term, however, the value of R_0 always has the tendency to reduce to zero. Thus this term prevents the value of R_0 from an increasing to infinity. Moreover the variable R_0 varies smoothly in comparison with the stimulus S, because the variable R_0 is obtained from the integration of Eq. (2) that is the relation between the mechanical stimulus S and the rate of the variable R_0.

Similarly, we can interpret the role of Eq. (3) as a stimulus transmission process from the variable R_{i-1} to R_i. For example, when the stimulus S is applied continually, the value of R_0 increases. Then the difference between R_0 and R_1 is induced, and increases the rate $\dot{R}_1$. This process continues until the difference becomes zero. Therefore the variable R_1 follows the variable R_0 with the period of delay by integration, and simultaneously the variation of R_1 is smoothened in comparison with that of R_0. Through each integral process of $i=1, \cdots, n$, the variation of R_0 is transmitted to R_n.

Next we formulate the evolution equation of apparent bone density ρ based on the following consideration. Firstly we hypothesize that an ideal equilibrium value of apparent bone density ρ_t can be specified by the variable R_n. For the relation between ρ_t and R_n, we used

$$\rho_t=\rho_{\min}+(\rho_{\max}-\rho_{\min})[1-\exp\{-(hR_n)^2\}] \quad (4)$$

where $\rho_{\max}$ and $\rho_{\min}$ are the maximum and minimum values of bone density, respectively, and h is a constant. This function has the properties that ρ_t approaches $\rho_{\max}$ gradually when R_n tends to infinity, and that ρ_t approaches $\rho_{\min}$ when R_n tends to zero.

The evolution equation of the apparent bone density ρ is established so that the current bone density ρ approaches the equilibrium ρ_t as the results of the bone resorption by osteoclasts and the bone formation by osteoblasts,

$$\dot{\rho}=\alpha(\rho)\{a_f\langle\rho_t-\rho\rangle-a_r\langle\rho-\rho_t\rangle\} \quad (5)$$

where a_f and a_r are constants that represent the rate of bone formation and resorption, respectively. The symbol $\langle\ \rangle$ denotes the Macauley bracket defined as $\langle x\rangle=xU[x]$, where $U[x]$ is the unit step function. Thus this equation can represent the difference between the rates of bone formation and resorption. The function $\alpha(\rho)$ is introduced to macroscopically take account of the fact that the bone remodeling is produced on the free surface of the trabecular bone and that the rate of bone remodeling significantly depends on the area of the surface[19]. With referring to Martin[19] and van Rietbergen et al.[8], we normalized the relation between the free surface of trabeculae and apparent bone density per unit volume by the maxima, and approximated it by a polynomial of degree three. The relation $\alpha(\rho)$ is shown in Eq. (12) in the following in a non-dimensional form.

Finally, in the present study, we approximate the bone by a linear elastic material. The Young's modulus E is given by

$$E=g\rho^k \quad (6)$$

where g is a constant, and the exponent k is a parameter to express the structural characteristics of a lattice. This equation is derived by noting that the structure of cancellous bone is similar to a form structure, and that the elastic modulus of the form is represented by a power function of the apparent bone density[20]. The k takes the value 1, 2 or 3 depending on the type of cancellous bone structure. It is noted that the dependence of the elastic modulus of bone on the strain rate is neglected in this study.

3. Examination of Mathematical Model of Bone Remodeling

3.1 Accuracy of the model

To examine the validity of the proposed model we simulated the experimental results by Rubin et al.[10] They applied repeated loads of the waveform shown in Fig. 1 to roosters' ulnae for 0, 4, 36, 360 or 1 800 cycles in a day, and kept them unloaded state in the remaining part in the day. They continued the experiments for 6 weeks, and examined the changes

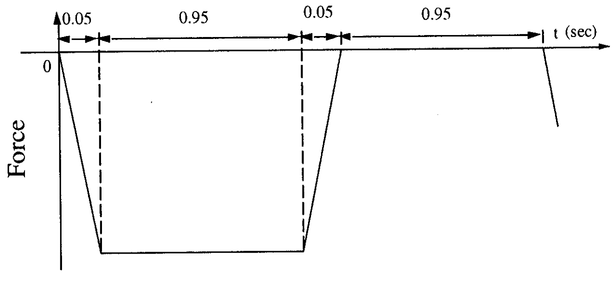

Fig. 1 Wave form of applied load[10]

Table 2 Material constants and initial values of variables

$r_0^* = 4.5\times10^{-12}$,	$r_i^* = 0.4 \quad (i=1,\cdots,8)$,	$l = 8.0$
$\rho_{min}^* = 0.0$,	$\rho_{max}^* = 3.9$,	$h^* = 1.77\times10^{-2}$
$\alpha_f^* = 0.234$,	$\alpha_r^* = 0.018$	
$R_i^*(0) = 30.67 \quad (i=0,\cdots,8)$		
$\rho^*(0) = 1.0$		

of the apparent bone density.

Before performing the simulation, we rewrote the model in a non-dimensional form to reduce the time of identification of material constants, to stabilize the calculation, and to make the evaluations of the results easier. We used strain $\bar{\varepsilon}$, bone density $\bar{\rho}$, time $\bar{t}$, stress $\bar{\sigma}(\equiv g\bar{\rho}^k\bar{\varepsilon})$, and stimulus $\bar{S}(\equiv\bar{\sigma}\bar{\varepsilon}/\bar{\rho}\bar{t})$ as the standard values to derive the non-dimensional equations. In the following, to denote the non-dimensional variables we asterisk the corresponding original variables. Then, Eqs.(1) through (6) and the function $a(\rho)$ are rewritten in the form

$$S^* = |\sigma^*\cdot\dot{\varepsilon}^*/\rho^*| \tag{7}$$

$$\mathring{R}_0^* = S^* - r_0^* R_0^{*l} \tag{8}$$

$$\mathring{R}_i^* = r_i^*\{R_{i-1}^* - R_i^*\} \tag{9}$$

$$\rho_t^* = \rho_{min}^* + (\rho_{max}^* - \rho_{min}^*)[1-\exp\{-(h^* R_n^*)^2\}] \tag{10}$$

$$\mathring{\rho}^* = a^*(\rho^*)\{\alpha_f^*\langle\rho_t^* - \rho^*\rangle - \alpha_r^*\langle\rho^* - \rho_t^*\rangle\} \tag{11}$$

$$a^*(\rho^*) = 0.04653\rho^{*3} - 0.5934\rho^{*2} + 1.455\rho^* \tag{12}$$

$$E^* = \rho^{*k}, \tag{13}$$

where the non-dimensional material constants and operators are defined as

$$r_0^* \equiv r_0\bar{t}^l\bar{S}^{l-1},\ r_i^* \equiv r_i\bar{t},\ a^*(\rho^*) \equiv a(\rho)$$

$$\alpha_f^* \equiv \alpha_f\bar{t},\ \alpha_r^* \equiv \alpha_r\bar{t}$$

$$\rho_{max}^* \equiv \rho_{max}/\bar{\rho},\ \rho_{min}^* \equiv \rho_{min}/\bar{\rho},\ h^* \equiv h\bar{t}\bar{S}$$

$$(\dot{\ }) \equiv \frac{d}{dt}(\ ) = \frac{1}{\bar{t}}\frac{d}{dt^*}(\ ) \equiv \frac{1}{\bar{t}}(\mathring{\ })$$

In this study, values of 0.2%, 0.45 g/cm^3 and one day are chosen for $\bar{\varepsilon}$, $\bar{\rho}$ and $\bar{t}$, respectively. Table 2 shows the set of material constants and the initial values of stimulus transmission variables R_0^* and R_i^* in the case of $n=8$ and $k=2$, where the $k=2$ corresponds to the case of isotropic form structure as will be mentioned later. For the initial values of R_0^* and R_i^*, on the other hand, we gave the saturated values in the case of 4 cycles in a day, where the bone density does not change from the initial value. In other words, we assume that the physiological state of bone before loading is equal to the state obtained by the loading of 4 cycles in a day.

Figure 2 shows the comparison of the simulation results with the corresponding experimental ones. The ordinate denotes the relative bone density ρ^*, where the initial value is unity, and the abscissa is the period of stimulation. It is found that the simulation results can reproduce the characteristic features of the experimental results, namely the time delay of about 10 days between the start of mechanical stimulation and the beginning of remodeling, the bone resorption under no load condition, the constant bone density in the case of 4 cycles in a day and the saturation of bone density with the time or with the number of cycles.

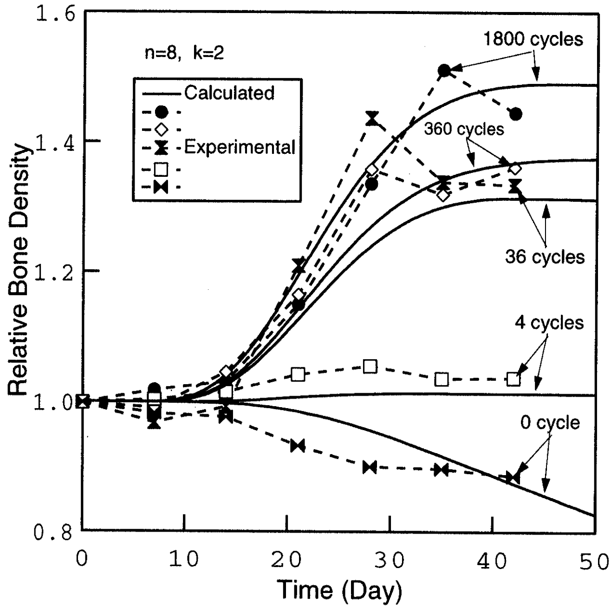

Fig. 2 Comparison of simulation results with experimental results[10] ($n=8$, $k=2$)

3.2 Effect of the step number n of transmission processes on the remodeling behavior

In Section 3.1 we chose $n=8$ as the number of steps of the transmission processes. When applying the proposed model to finite element analyses, it is preferable to use smaller number of n for the reduction of CPU time. Thus the effect of n on the accuracy of simulations is examined by comparing the simulation results for the cases of $n=2$, 4, 6, 8 and 10. The 1 800 cycles in a day are chosen for these simulations.

The material constants listed in Table 2 except $r_i^*(i=1,\cdots,n)$ were used for the simulations, and the initial values of the stimulus transmission variables $R_9^*(0)$ and $R_{10}^*(0)$ were set at the same value 30.67 as $R_i^*(0)(i=1,\cdots,8)$. The material constants r_i^* influence the length of time delay as well as the rate of convergence; larger r_i^* gives shorter time delay and shorter convergence time. Larger value of n, on the other hand, gives longer time delay. Thus the constants r_i^* and n correlate each other. When we adopt larger value of n, we should generally increase the value of r_i^* in each step in order to keep the length of the time delay of the whole system in the same level. The purpose of this study is to describe the behavior

Table 3 Material constants of r_i^*

$r_1^* = r_2^* = 0.1$	$(n=2)$
$r_1^* = r_2^* = r_3^* = r_4^* = 0.2$	$(n=4)$
$r_1^* = r_2^* = r_3^* = r_4^* = r_5^* = r_6^* = 0.3$	$(n=6)$
$r_1^* = r_2^* = r_3^* = r_4^* = r_5^* = r_6^* = r_7^* = r_8^* = 0.4$	$(n=8)$
$r_1^* = r_2^* = r_3^* = r_4^* = r_5^* = r_6^* = r_7^* = r_8^* = r_9^* = r_{10}^* = 0.5$	$(n=10)$

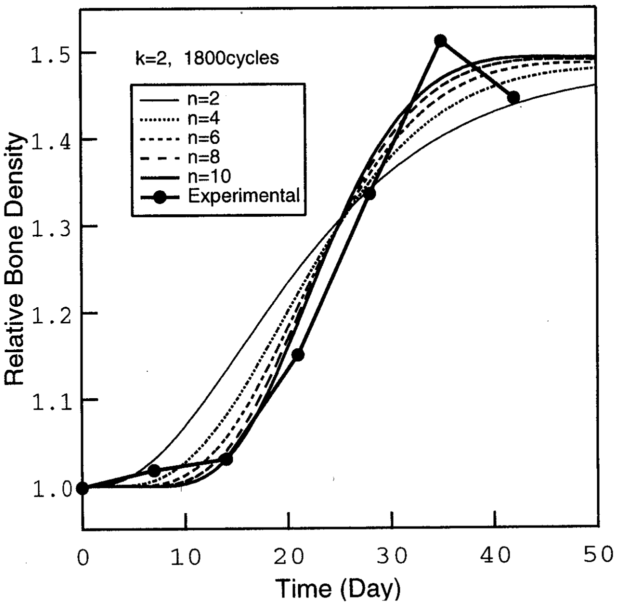

Fig. 3 Effects of the value n on remodeling process (k=2, 1 800 cycles)

of the whole system phenomenologically, and is not to describe the phenomenon of the stimulus transmission process in each step that is not clarified yet from physiological point of view. For this reason, we used the same value for every material constant r_i^* for each n. Based on the above discussion, we identified the sets of material constants that could reproduce the time variation of apparent bone density observed in the experiments[10], which are listed in Table 3.

Figure 3 shows the simulation results. We observe the tendency that the model of a larger n gives more accurate predictions for the experimental results. But the accuracy predicted by any model is not so bad.

3.3 Effect of the exponent *k* on the remodeling behavior

As described above, an elastic modulus of a form structure is proportional to a power function of the apparent bone density, and the exponent k of the power function depends on the structure and the orientation of the form. For a form with an isotropic structure, the value of k is equal to two. For a form having oriented structure, the value of k depends on the direction; it is unity to the strongest direction to support loads mainly, and three for the directions perpendicular to the former[20]. Then we performed the simulations for k=1, 2 and 3 by using the model of n=8. Figure 4 shows the results. Except the case of no load condition, the saturation value depends on the k, and the larger k gives the larger saturation value. The difference is a little remarked in the case of 36 cycles in a day. It is noted, however, that such significant difference in material properties induces little difference in the behavior of bone density change. This suggests that we have the possibility to apply the proposed model to various trabecular structures.

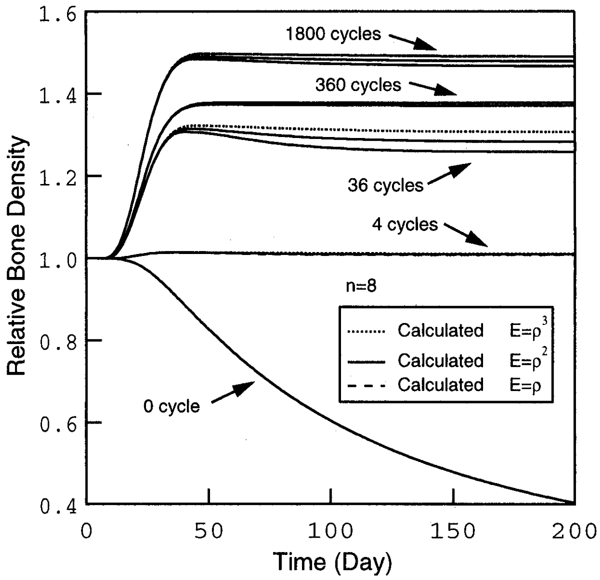

Fig. 4 Effects of the value k on remodeling process (n=8)

3.4 Effect of the loading history on the remodeling behavior

The relation between history of stimulation and bone density is examined in order to clarify the characteristic features of the proposed model. Figure 5 shows the simulation results of the model of n=8 and k=2 for 7 types of loading history (A) through (G). The histories (A), (B) and (C) give 1 800, 36 or 0 cycles in a day for 600 days, respectively. In the history (D) or (E) the number of cycles in a day is increased or decreased step by step such as 0-36-1800 or 1800-36-0 in every 200 days. The history (F) or (G) is the stimulation to give 36 cycles in a day in the last 200 days such as the history 0-1800-36 or 1800-0-36, respectively. As found from Fig. 5, the stabilized value of bone density in each step of every history tends to coincide with the one in which the same number of cycles in a day is applied from the beginning. In other words, the bone density predicted by this model is independent of history of stimulation.

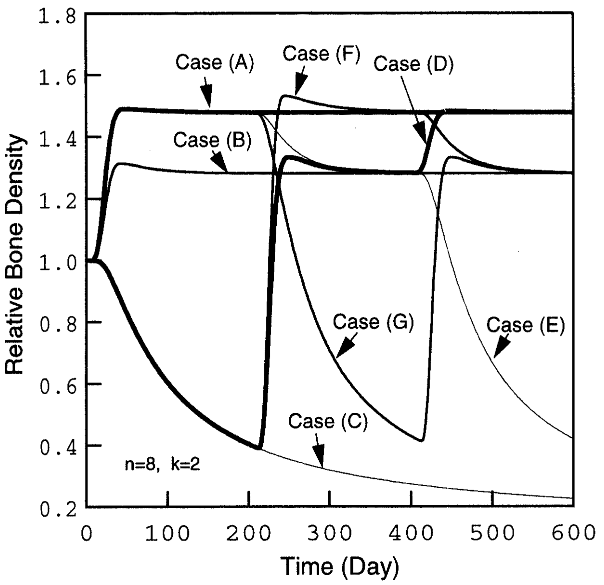

Fig. 5 Evaluation of history effects of stimuli ($n=8$, $k=2$)

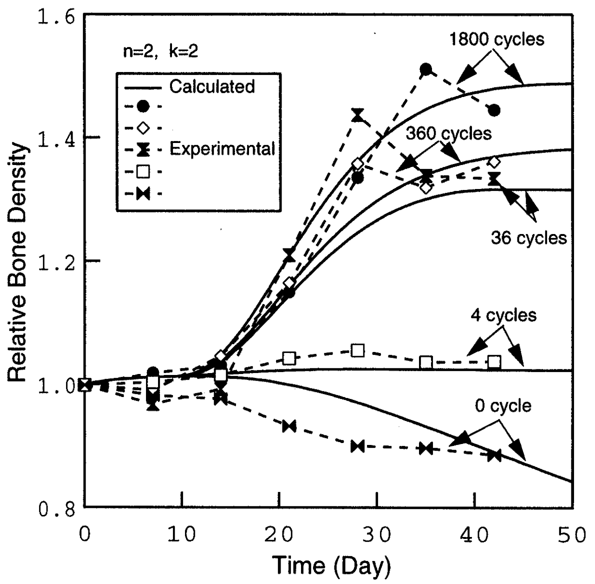

Fig. 6 Evaluation of Eq. (13) ($n=2$, $k=2$)

But the history dependence can be expected in the cases in which bone is damaged by mechanical loading or bone resorption occurs by overload as shown by Howshaw[18]. Those cases will be discussed in the future study.

4. Examination of the Model Including Explicit Time Delay Parameters

In Chapters 2 and 3 we represented the time delay of bone remodeling by the evolution equations of stimulus transmission variables, namely Eq. (3) or (9). By the above discussion it is clarified that the number of steps n of the stimulus transmission processes should be larger to reproduce the time delay accurately. In this chapter we examine another expression introducing a delay time explicitly, for example,

$$\dot{R}_i^* = r_i^*\{R_{i-1}^*(t^*-t_i^*)-R_i^*\} \quad (i=1, \cdots, n). \quad (14)$$

where t_i^* is a delay time in each step.

Figure 6 shows the results of simulations using Eq. (14) with $n=2$. The material constants for $n=2$ in the previous model is used except r_i^*. For the constants r_i^* and t_i^*, we used $r_1^*=0.15$, $r_2^*=0.2$, $t_1^*=0$ and $t_2^*=9$. It is found from Fig. 6 that by the introduction of the delay times sufficiently good accuracy is obtained even for small n. However, in order to use this model, we must evaluate the variables in the past by t_i^*, namely $R_{i-1}^*(t^*-t_i^*)$ in Eq. (14), and it may be not necessarily convenient for the incorporation into finite element analyses.

5. Conclusions

In this study we proposed a mathematical model that represents an actual time process of phenomenological bone remodeling behavior by introducing internal state variables, which we called bone remodeling stimulus transmission variables, and by formulating their evolution equations based on the experimental results in the literature[10]. The results obtained from this study is summarized as follows:

(1) The framework that correlates bone remodeling stimulus transmission variables, bone density, elastic modulus was proposed, and their evolution equations were formulated.

(2) The proposed model was applied to the experimental results by Rubin et al.[10], and was ascertained to represent the characteristic features of bone remodeling, such as time delay between the start of stimulation and the beginning of remodeling, the saturation of bone density with the time or with the number of cycles.

(3) The effect of the exponent k in the elastic modulus versus bone density relation on the remodeling process was examined. It is found that the saturation value depends on the k, but the difference is not so significant. From this result, it is suggested that the model may be applied to the simulations for various trabecular structures.

(4) This model has the properties independent of stimulation history. To take account of the bone resorption caused by overload, we need to modify this feature of the model.

(5) The second model to introduce the explicit delay times into the evolution equations of stimulus transmission variables was proposed to describe the time delay between the start of stimulation and the beginning of remodeling. The simulation results by the second model were compared with that by the first

model. The comparison showed that the second model predicted the bone remodeling behavior with a sufficient accuracy even if the number of internal state variables was less. But it was pointed out that the model had the demerit that the history of the stimulus transmission variables must be memorized.

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