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A model of mechanobiologic and metabolic influences on bone adaptation

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ABSTRACT—Bone adaptation, the process through which bone mass is modified in the body, plays a key role in the development of osteoporosis. Bone adaptation is known to be influenced by both mechanical and metabolic stimuli. Previous studies have concentrated on changes in bone adaptation caused by mechanical stimuli (mechanobiologic influences), yet current treatments for osteoporosis depend significantly on metabolic influences. We develop a theoretical model of bone adaptation that accounts for both mechanobiologic and metabolic influences. We demonstrate the utility of this model using a simulation of the cellular processes of bone adaptation on a representative volume of cancellous bone. Our long-term objective is the development of a more comprehensive computational model that will aid in the study of osteoporosis and other bone diseases.

Key words: *bone adaptation, computer modeling, mechanobiology, osteoporosis.*

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INTRODUCTION

Osteoporosis is a disease characterized by bone loss, decreased bone density, and an increased risk of fracture; it affects an estimated 25 million Americans and results in medical costs of nearly $14 billion per year (1). The cost of hip fractures alone is $9 billion per year (2). Although much is known about the causes of osteoporosis, much remains to be learned. It is clear that both genetic and epigenetic factors influence bone acquisition during childhood and adolescence. It is also clear that controllable epigenetic factors, such as nutrition, hormones, and mechanical stimuli (e.g., normal daily activity, exercise) play a particularly important role in bone development, maintenance, and loss throughout life. These controllable factors represent key targets of investigation in the search for more effective approaches to osteoporosis prevention and treatment.

Since the mid-1980s, much progress has been made in advancing our understanding of the role of mechanical stimuli in the development and adaptation of skeletal tissues. The mechanobiology of bone adaptation (the biological response to mechanics) has been a particularly fruitful area of investigation. Theoretical and computer models of bone remodeling have provided important new

insights on the role of mechanical stimuli in bone acquisition during childhood (3), bone loss from disuse (4), and adverse bone remodeling around total joint replacements (5–7).

Although it is clear that both metabolic and mechanobiological factors influence bone adaptation, most previous theoretical and computer models of bone remodeling have focused largely on mechanobiology and mechanical factors. It is also clear that current osteoporosis prevention and treatment protocols rely heavily on nutritional, hormonal, and pharmacological therapies that directly affect bone cell biology (8–10). Drugs in current use for the treatment of osteoporosis can target either the resorption or deposition phase of bone remodeling by modulating the actions of two primary types of bone cells, the osteoclasts and the osteoblasts. Osteoporosis drug treatment studies have shown promising results, but an optimal treatment or combination of treatments (drugs, hormones, and exercise) has not yet been identified. Thus there is a strong need for improved theoretical and computer models of bone adaptation that can account for the effects of biologic as well as mechanobiologic factors and do so in a way that is consistent with current knowledge of bone cell activity.

In this article we review a model of bone adaptation that was developed previously in our laboratory. We note the limitations of the model and discuss how the elaboration of it will allow us to describe more effectively the combination of mechanobiologic and metabolic influences. Computer simulations of bone cell activity during bone adaptation are presented and used to demonstrate how the cellular processes of bone adaptation can be modeled and how mechanobiologic and metabolic responses in bone could be introduced.

METHODS

Review of a Previous Bone Adaptation Model

The mechanobiologic model of bone adaptation developed by Carter et al. (11) and Beaupré et al. (12) is based on the concept that bone remodeling is an error-driven process in which the error signal is a function of the difference between the stimulus setpoint–referred to as the attractor state in Beaupré et al. (12)–and the applied daily stress stimulus caused by physical activity. The daily stress stimulus (ψ) was developed in order to quantify the mechanical stimulus in the bone by combining the influence of the number and magnitude of individual loading cycles over the course of a day (12–14). Mathematically it can be expressed as the summation of all loading activity in a day with the following equation:

$$\psi = \left(\sum_{day} n_i \sigma_i^m \right)^{1/m} \quad [1]$$

where each loading type, i, is applied with magnitude, ψ_i (the continuum level effective stress), for n_i, the number of loading cycles (15). The stress exponent, m, is a weighting factor for the relative influence of the magnitude of mechanical loading to that of the number of loading cycles. The daily stress stimulus (ψ) is therefore expressed in the units of stress per day (MPa/day).

An idealized representation of the relationship between the daily stress stimulus and the resulting mechanobiological rate of bone remodeling is shown in **Figure 1**. This figure expresses the observed trend: there is net resorption when the mechanical stimulus is low, net apposition when the mechanical stimulus is high, and very little net activity when the mechanical stimulus is near a physiologic level which we call the stress stimulus setpoint, ψ_s; hence, the mechanobiologic response drives the bone toward ψ_s. The development of this relationship and the idea of the stress stimulus setpoint is discussed in detail by Carter (16,17) and Frost (18).

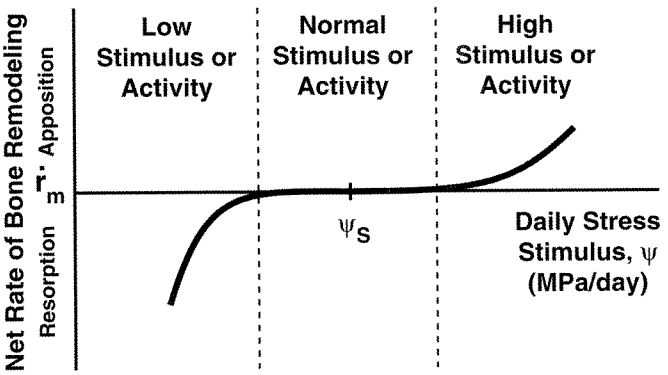

Figure 1.
Theoretical net rate of apposition/resorption as a function of mechanical loading. The net mechanobiologic rate of apposition/resorption ($\dot{r}_m$, mm/day) is related to the daily stress stimulus (ψ, MPa/day) in this idealized plot. When the daily stress stimulus is higher than the stress stimulus setpoint (ψ_S) there is net apposition, when the daily stress stimulus is less than the setpoint there is net resorption, and when the stress stimulus is near the setpoint there is little net resorption or apposition. Adapted from Carter (16).

A block diagram representation of the bone adaptation theory of Beaupré et al. (12) is shown in **Figure 2**. Two feedback loops are present in this diagram: an upper loop for biological influences and a lower loop for mechanobiological influences. In the lower loop, a load history results in the development of a daily stress stimulus. The daily stress stimulus (ψ) is compared to the stimulus setpoint (ψ_s) and the difference between the two generates a local mechanobiologic response. This causes a change in the local mechanobiologic bone apposition/resorption rate ($\dot{r}_m$). Bone apposition and resorption cause changes in the bone geometry and/or material properties. Those changes, in turn, result in modifications to the magnitude of the daily stress stimulus, completing the feedback loop. The diagram includes two mechanisms by which biologic factors may be influential. The first is the inclusion of the net biologic apposition/resorption rate ($\dot{r}_b$, right side of diagram). The other is presented in the upper loop of the diagram and illustrates how metabolic factors can change the mechanical setpoint thereby modulating the mechanobiologic response.

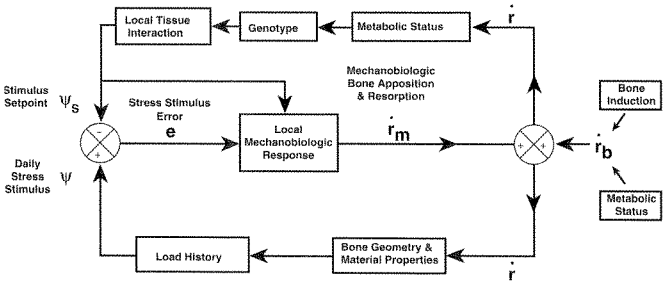

Figure 2.
Feedback diagram of bone remodeling. A daily stress stimulus (ψ) is compared to the setpoint (ψ_S) to generate a local mechanobiologic response. The mechanobiologic response generates a net mechanobiologic apposition or resorption rate ($\dot{r}_m$). The mechanobiologic apposition/resorption rate is combined with a net biologic apposition/resorption rate ($\dot{r}_b$) to form the total apposition/resorption rate ($\dot{r}$). In the lower loop the bone geometry and load history modify the daily stress stimulus (mechanobiologic response). In the upper loop metabolic factors modify the attractor stimulus. (Reprinted with permission of Cambridge University Press. Carter DR, Beaupré GS. Skeletal function and form. Cambridge University Press (19).

This model has been implemented in computer simulations using numerical values from experimental studies (4) and assuming that biologic factors remain constant so that only the mechanobiologic aspects of the model were subject to change (**Figure 2**, bottom). The finite element (FE) method was used to calculate stress distributions and remodeling was carried out for a number of simulated days. Starting from an initial state of uniform bone density, the remodeling simulation produced a distribution of bone density throughout the proximal femur (**Figure 3**) that compares favorably to radiological and histological observations. This FE model, generated by Beaupré et al. (4), demonstrates how a theoretical model of bone adaptation has been used to give insights into whole bone structure. Similar implementations have been used to predict bone adaptation around artificial implants as well as to improve the implant design process (6,7).

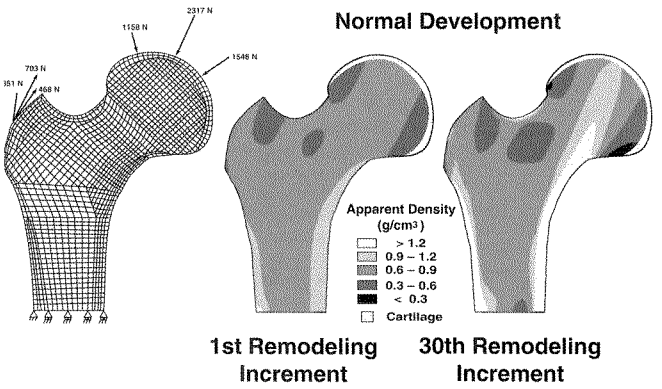

Figure 3.
Bone remodeling simulations using the FE method. An FE mesh represents the proximal femur (left). Initially the model is given a uniform apparent density. During the simulation, the apparent density changes with each remodeling time increment, eventually producing the normal adult density distribution shown on the right. For more details regarding the model, see Beaupré et al., from which this figure was adapted (4).

New Bone Adaptation Theory

Consideration of bone cell activity [it]*per se* was not necessary in the development by Beaupré et al. (12) since they modeled healthy adults and assumed that the biologic influences are constant. Furthermore, only net changes in bone were represented and the separate actions of osteoblasts and osteoclasts were not considered. To better represent cell activity, we propose a new representation of the feedback loop with an expanded description of the influence of biologic factors on osteoblasts and osteoclasts (**Figure 4**). The new feedback diagram includes a description of the mechanobiologic response conceptually identical to that presented by Beaupré and colleagues (**Figure 4**, lower loop). The primary advancement made

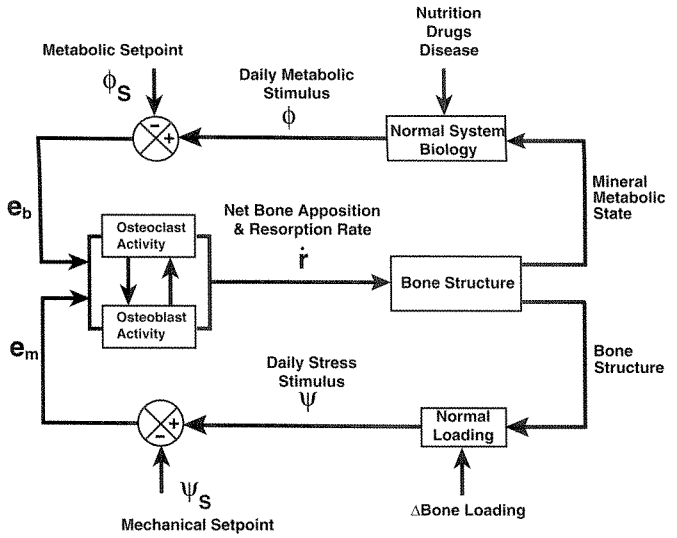

Figure 4.
Feedback diagram of bone remodeling with greater emphasis on the biologic influences. The lower loop represents the mechanobiologic response in bone due to differences between the daily stress stimulus (ψ) and the stress stimulus setpoint (ψ_S). The upper loop represents the biologic response due to differences between the daily metabolic stimulus (ϕ) and the metabolic setpoint (ϕ_S). Osteoclasts and osteoblasts carry out both responses. The stress stimulus setpoint and the metabolic setpoint may also be influenced by mechanical or biological stimuli.

in the new model is that the mechanobiologic response changes osteoclast and osteoblast activity rather than simply causing net apposition/resorption. This modification creates a more detailed description of adaptation and allows for interactions between the mechanobiologic and metabolic responses through their influences on osteoclasts and osteoblasts.

Bone adaptation to metabolic factors is described in the upper loop of the feedback diagram. Metabolic factors such as nutrition, drugs, and disease state affect the normal system biology and cause the generation of a daily metabolic stimulus. The daily metabolic stimulus is compared to the metabolic setpoint and the difference between the two results in changes in osteoclast and osteoblast activity. Changes in the bone structure result in modification of the bone's mineral metabolic state due to changes in local serum calcium concentrations. This modifies the system biology and completes the feedback loop. Both the metabolic and mechanobiologic setpoints (ϕ_S, ψ_S) can change in response to metabolic or mechanical factors in manners similar to that suggested by Beaupré et al. (**Figure 2**, upper loop). Implementation of this model would be similar to that of the Beaupré et al. model (4), but requires a number of modifications, including more detailed representations of bone tissue and the cellular activity underlying bone adaptation. Through implementation of this new feedback diagram, a predictive computational model could be derived to account for both the mechanobiologic and metabolic factors in bone adaptation.

A Cell-Based Bone Adaptation Model

When modeling the activity of cells within a volume of bone, a more specific description of the bone is needed than the apparent density measure used by Beaupré and colleagues. Bone tissue consists of three subvolumes: a mineralized volume, an osteoid volume, and a porous (marrow) volume (**Figure 5**). These measures can be generalized by expressing the subvolumes as volume fractions of the total volume (tissue volume). Bone adaptation processes act by converting one type of volume to another. For example, osteoclastic resorption is the conversion of mineralized volume into porous volume.

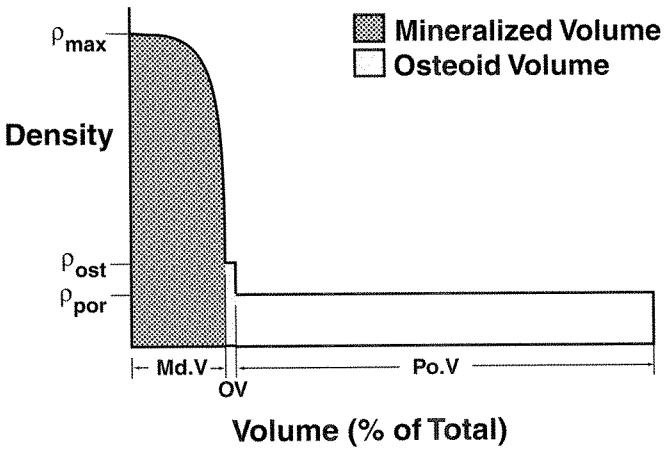

Figure 5.
Densities of the three constituent phases in a representative volume of bone. The plot divides an arbitrary bone volume into the mineralized volume (Md.V), the osteoid volume (OV), and the porous volume (Po.V). Any piece of bone can be represented by modifying the distribution of mineralized, osteoid, and porous volumes on the horizontal axis. The maximum density of mineralized volumes (ρ_{max}), density of osteoid (ρ_{ost}), and density of the marrow or porous volume (ρ_{por}) are represented.

Bone adaptation occurs on the trabecular surface in cancellous bone or on the walls of the Haversian canal in cortical bone. Adaptation is the result of the combined activity of a number of bone cells at a location in the bone

and is categorized as either remodeling or modeling (20,21). Remodeling involves the coupled activity of osteoclasts and osteoblasts. At a remodeling site, osteoclasts are first active, resorbing bone, followed by osteoblasts forming bone. Osteoclasts and osteoblasts that are active in concert make up a basic multicellular unit (BMU). As a whole, a BMU originates in the bone, progresses across the trabecular bone surface (or through the Haversian canal in cortical bone), and stops progressing at the end of its lifespan. Throughout its progression, a BMU is made up of a group of active osteoclasts followed by a group of active osteoblasts (**Figure 6**; 22). The process of bone modeling is different from remodeling in that it involves only the activity of osteoclasts or osteoblasts without any coupling between the two.

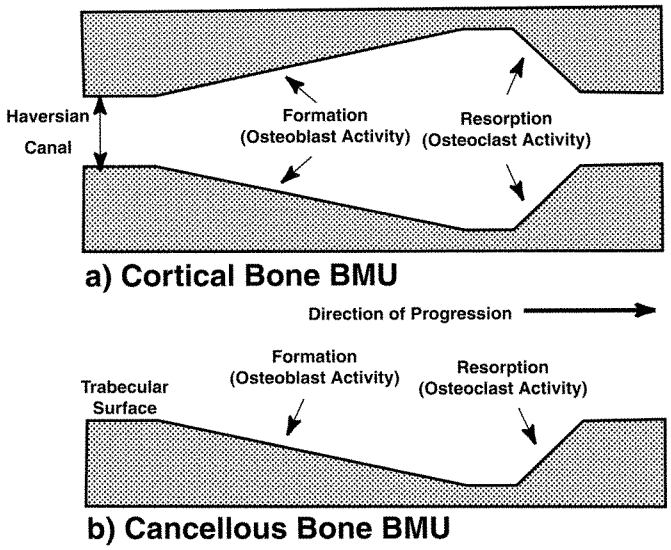

Figure 6.
The basic multicellular unit (BMU) in cortical and cancellous bone. BMUs progress across bone with osteoclastic resorption leading the way. Soon after resorption is complete at a given location, osteoblasts begin to deposit osteoid. In cortical bone, (a), remodeling takes place in Haversian canals; in cancellous bone, (b), remodeling takes place on the surfaces of the trabeculae.

Simulations of Bone Remodeling Activity

The bone adaptation theory and cell-based modeling approach are designed to describe both cancellous and cortical bone. An implementation of these ideas requires us to specify what type of bone will be modeled. In this section we develop a simulation of cancellous bone remodeling, for two reasons: bone remodeling (as opposed to bone modeling) is the primary cellular process in adult bone adaptation and is well described using BMUs; also, cancellous bone is the first to be affected by osteoporosis and the most sensitive to osteoporosis treatments.

We model a representative volume of cancellous bone using the bone volume fraction as the primary parameter. The model does not describe trabecular geometry or the distribution of BMUs. This model represents the center of the new feedback diagram (**Figure 4**), consisting of the osteoclast/osteoblast activity, the net bone apposition/resorption, and the resulting changes in bone structure (**Figure 7**). The section of the feedback diagram being implemented (**Figure 7**) does not include influences from mechanical or metabolic stimuli so that only changes in the number of BMUs and surface area avail-

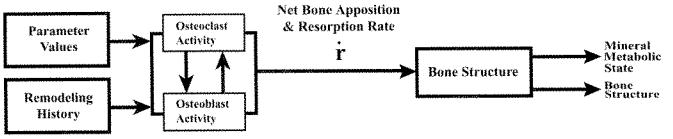

Figure 7.
Preliminary model implementation. The preliminary model is based on the center of the new feedback diagram (**Figure 4**). The input parameter values and the remodeling history dictate the osteoclast and osteoblast activity generating a net bone apposition/resorption, which modifies the bone structure. Modifications to the bone structure also result in changes to the local mineral metabolic state.

able for remodeling will affect the system. The exclusion of metabolic influences implies that the simulated bone is of a small enough size that hormonal, chemical, and vascular conditions can be considered uniform throughout the representative volume. The preliminary model is defined initially with parameter values taken from the literature. We chose five parameters to describe the progression and shape of the BMU, four to describe the bone resorption and formation carried out by a BMU, and one to represent the bone balance ratio (ratio of bone volume formed to that resorbed at a location on the bone surface). The parameter values and the remodeling history define the osteoclast and osteoblast activity at any time point. Cellular activity causes a net change in bone apposition/resorption rate, which modifies the bone structure and the mineral metabolic state. Any changes to the remodeling system (number of BMUs, surface area available for remodeling) are included in the remodeling history for use in succeeding time increments during a simulation. In this simplified model, the metabolic and

mechanobiologic stimuli are assumed to be constant so that the activity of the BMUs is the sole source of modifications in the bone volume fraction.

Each day that a BMU progresses, it starts remodeling a new volume of bone of a disklike shape (**Figure 8**). This shape is quantified using parameters describing the width of the BMU, the erosion depth to which the BMU resorbs, and the rate at which the BMU progresses across the cancellous bone surface. A BMU progresses across the surface of the bone for a number of days equal to its lifespan. The amount of new BMU activity in the bone is based on the birth rate, or origination frequency, of BMUs. The origination frequency is related to the width of the BMU, the lifespan of the BMU, the rate of progression of the BMU, and the histologically measured activation frequency, that is, the rate of appearance of remodeling activity on the bone surface (23). Using this relationship, the shape, origination, progression, and termination of BMUs are described with five independent parameters: the erosion depth, the width of the BMU, the lifespan of the BMU, the rate of BMU progression, and the histologically measured activation frequency.

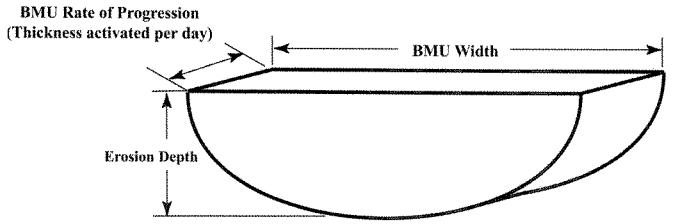

Figure 8.
Cross-section of a cancellous BMU. In cancellous bone, each day that a BMU progresses it activates a remodeling cycle in a small volume of mineralized bone. A newly activated volume is modeled using a semiellipsoidal cross section defined by the erosion depth and the width of the BMU. The thickness of a newly activated volume is expressed per day as a function of the BMU's rate of progression.

The processes of resorption and formation that take place during the progression of a BMU can be expressed in four distinct periods: the resorption period, reversal period, mineralization lag time, and formation period (defined in **Figure 9**). Each of these parameters can be determined from dynamic histology data. A final parameter, the bone balance ratio, allows for imbalances in the remodeling process. In this preliminary model we assume that any change in a BMU parameter is uniform throughout the representative volume being simulated.

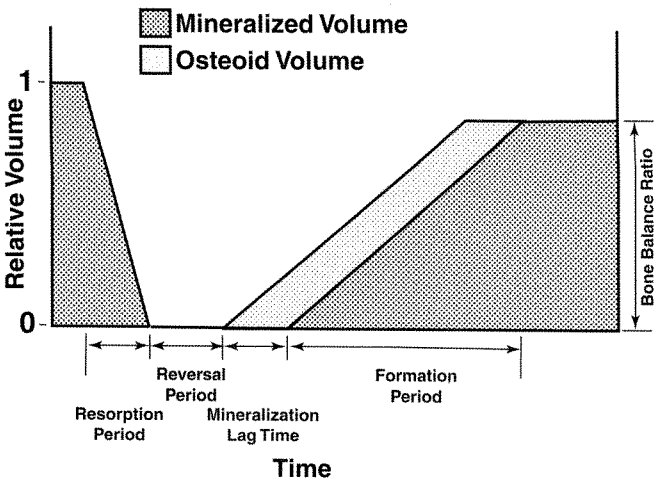

Figure 9.
Changes in the remodeling bone volume with time. During the resorption period, mineralized bone is converted into porous volume. During the reversal period, there is little change in the remodeling bone volume. During the mineralization lag time, osteoid is formed. Newly mineralized bone formation occurs during the formation period. The bone balance ratio relates the amount of bone volume formed to that resorbed at a given location.

Preliminary Implementation–Equilibrium

The cell-based model (**Figure 7**) is implemented with parameter values based on those found in histologic analyses (24) with a bone balance ratio set at 1 (the same amount of bone is formed as is resorbed with each cycle; see **Table 1**. The system is initiated without any osteoid or active BMUs. Using a time-dependent approach, new BMUs appear within the bone and the system is then allowed to reach an equilibrium where the number of BMUs and amount of osteoid is constant. This equilibrium state is necessary because the literature contains only a few estimates of the number of BMUs and amount of osteoid present in healthy cancellous bone (27).

Demonstration–Parameter Modification

Different aspects of bone remodeling are known to change during disease states. Starting with the equilibrium condition found in the preliminary implementation, it is possible to simulate changes in histologic parameters and study the effects of the parameters on the remodeling system. One or more parameters can be modified while the system is in the above equilibrium. The modification of the parameter causes changes in the bone volume fraction and the daily stress stimulus (even though any loading on the system is considered constant). Changes in the daily stress stimulus are expressed relative to the daily

Table 1.
Descriptive parameters of cancellous bone remodeling.

Parameter	Description	Value
Resorption Period	Time during which osteoclasts are active at location.	60 Days[a]
Reversal Period	Time between osteoclast and osteoblast activity.	57 Days[a]
Mineralization Lag Time	Time between osteoid formation and mineralization.	22 Days[a]
Formation Period	Time during which osteoid is mineralizing.	175 Days[a]
Bone Balance Ratio	Ratio of bone volume formed to that resorbed at each location.	$1mm^3/mm^3$[a]
BMU Width	Width of a BMU.	0.65mm[b]
Erosion Depth	Depth to which osteoclasts resorb into the bone surface.	0.05mm[a]
BMU Rate of Progression	Rate of BMU movement across the bone surface.	0.01mm/day[c]
BMU Lifespan	Amount of time that a BMU progresses.	100 Days[c]
Activation Frequency	Frequency of appearance of remodeling activity on the bone surface.	0.006/day[a]

Parameter=input parameter; Value=nominal values from literature; [a] value based on histologic data for healthy postmenopausal women (24); [b] value based on measurements by Kragstrup and Melsen (25); [c] value based on estimates by Parfitt (26).

stress stimulus at the equilibrium condition, which was assumed to be constant and equal to the stress stimulus setpoint (ψ_S).

RESULTS

From the nominal condition (without osteoid or BMUs), the system reaches the equilibrium state after roughly 500 simulated days (**Figure 10**). Because BMUs resorb bone before forming bone, there is a decrease in bone volume fraction as the system reaches equilibrium: this difference in volume is known as the remodeling space. The system's approach to equilibrium illustrates nonlinearities in the system stemming from interactions between the number of BMUs and the surface area available for remodeling.

Changes in the activation frequency or the bone balance ratio cause changes in the bone volume fraction in the model (**Figure 11**). An increase in the activation frequency causes an increase in BMU activity, an increase in bone turnover, and therefore an increase in the remodeling space (the volume that was recently resorbed and is in the process of reforming). The net result of an increase in activation frequency is a decrease in the bone volume

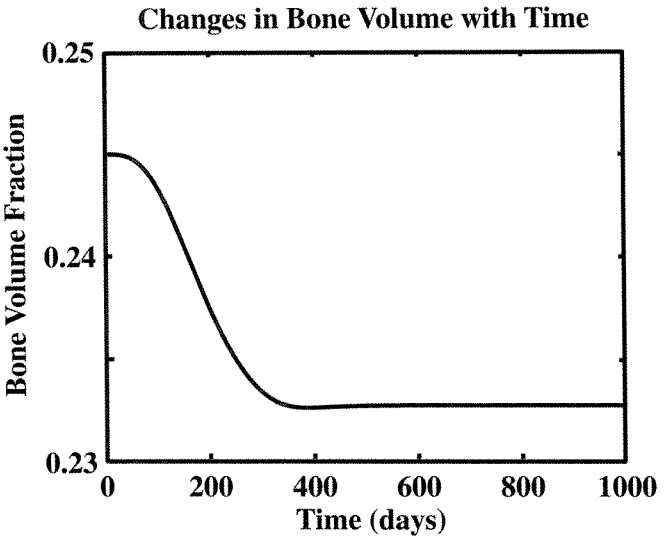

Figure 10.
Model advancement to an equilibrium state. At the start of the simulation (t=0 days), all parameters are at their nominal values with no osteoid or active BMUs present. As the simulation progresses, BMUs originate, causing resorption and a decrease in bone volume fraction. The rate of decrease is slowed as osteoblasts become active and an equilibrium state is reached (t=1,000 days). The equilibrium state is used as the starting point for future simulations.

fraction (**Figure 11**, left). When the bone balance ratio is increased, each remodeling cycle deposits more bone than is resorbed. This results in a steady rate of increase in the bone volume fraction (**Figure 11**, right). Among the parameters used in this model, the bone balance ratio is unique in that, when modified, it is the only parameter that results in steady rates of increase or decrease in bone volume fraction. All other parameters cause the formation of new equilibrium states.

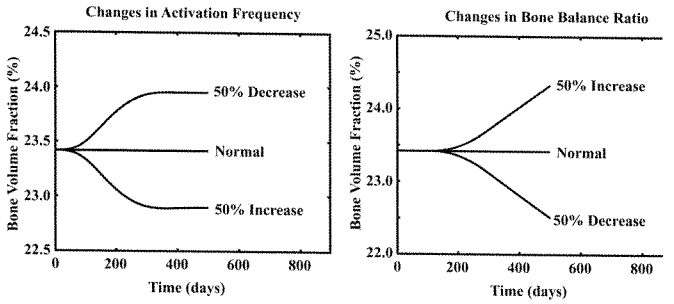

Figure 11.
Response of BMU model to changes in activation frequency and bone balance ratio. At the start of the simulation the system is in equilibrium. Left: A decrease in the activation frequency causes a decrease in the volume of bone undergoing remodeling, resulting in an increase in the bone volume fraction, consistent with clinical observations after estrogen treatment. Right: Changes in the bone balance ratio from the normal equilibrium lead to constant rates of increase or decrease in bone volume. Changes in the bone balance ratio do not result in a new equilibrium for this preliminary model.

The changes in bone volume fraction caused by changes in activation frequency or bone balance ratio result in modifications to the mechanical daily stress stimulus even when the mechanical loading history remains constant (**Figure 12**). An increase in the activation frequency results in an increase in the daily stress stimulus relative to the stress stimulus setpoint (**Figure 12**, left). Changes in the bone balance ratio result in steady increases or decreases in the daily stress stimulus (**Figure 12**, right).

DISCUSSION

The preliminary computational model presented here is intended to demonstrate the feasibility of using a cell-based description of bone adaptation. This model is preliminary because it does not yet include the BMU feedback response to mechanobiologic and metabolic influences (the upper and lower feedback loops in **Figure 4**). The mechanobiologic response is important because metabolic influences can result in changes in bone mass that in turn cause mechanobiologic responses. For example, an effect that modifies the bone balance ratio will result (after a period of time) in a significant change in the daily stress stimulus (**Figure 12**, right) even when mechanical loading remains constant. Because the mechanobiologic response is related to the difference between the daily stress stimulus and the stress stimulus setpoint, we would expect a change in the bone balance ratio to eventually result in a mechanobiologic response in the bone (28). Without inclusion of mechanobiologic responses, the model is only predictive when the daily stress stimulus remains near the stress stimulus setpoint, in which case the mechanobiologic response is expected to be small.

In its present form, this model could be used to simulate the changes in BMU activity caused by osteoporosis and drug treatments. For example, studies of women during the first few years after menopause have shown increased activation frequency and a decreased bone balance (24). The time course of bone loss in these women could be predicted using our model through direct modification of the parameter values (**Figure 7**). Bisphosphonates and other antiresorptive agents act primarily by reducing the activation frequency of BMUs and could therefore be simulated by changing a single parameter in the model (29–31). Because the metabolic feedback systems in the bone have not yet been developed in this model, these predictions would not account for any secondary changes caused by metabolic feedback (**Figure 4**, upper loop).

In a comprehensive implementation of our bone adaptation diagram (**Figure 4**), there would be a series of relationships between metabolic and mechanical stimuli and the rates of change in BMU parameters and metabolic and mechanical setpoints (ϕ_S, ψ_S) caused by those stimuli. These additions would connect the metabolic and mechanobiologic responses to changes in cellular activity, allowing incorporation of the metabolic and mechanobiologic feedback loops. A complete model would be able to simulate osteoporosis treatment with hormones, pharmaceutical agents, exercise, and combinations of the three over prolonged periods of time (decades). The cell-based model presented here could be used as a basis for FE simulations so that internal bone geometry would also be included. Such a model would be useful for identifying optimal treatment methodologies as well as changes in bone strength resulting from osteoporosis treatments.

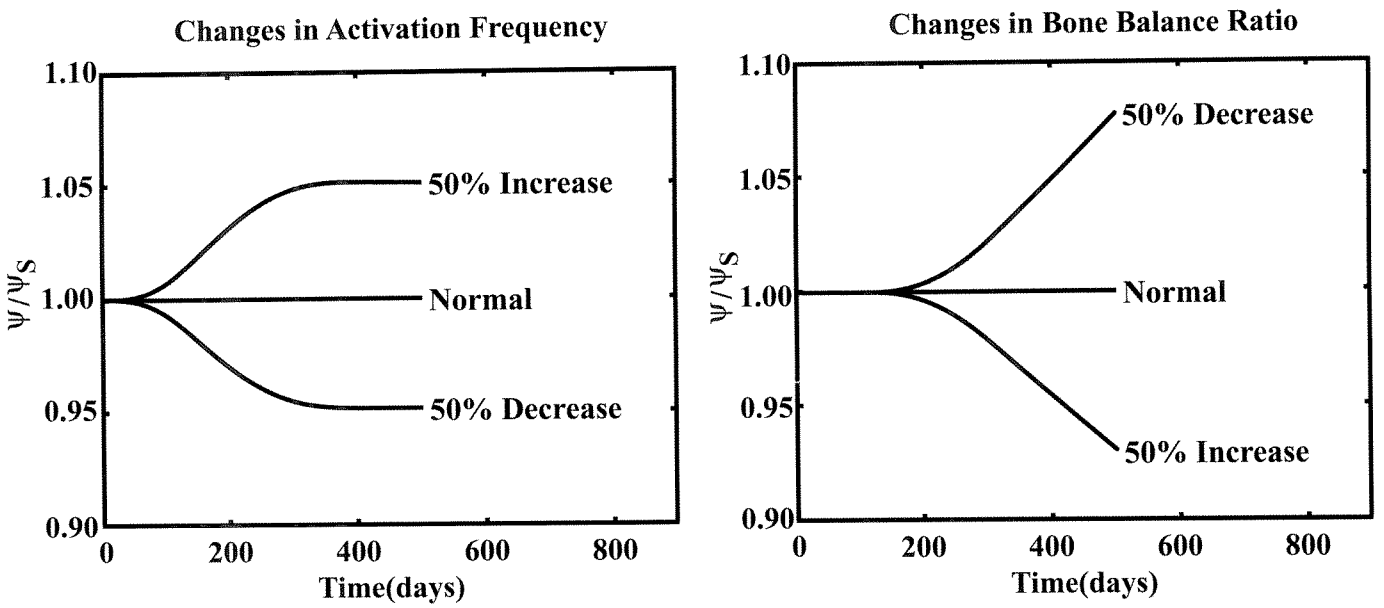

Figure 12.
Relative changes in the stress stimulus in response to changes in activation frequency and bone balance ratio. These plots show the changes in stress stimulus when mechanical loading remains constant but the bone volume fraction is modified due to remodeling (see **Figure 9**). At time=0, the system is at the equilibrium state and the stress stimulus (ψ) is assumed to be equal to the stress stimulus setpoint (ψ_S). Left: A decrease in the activation frequency causes a decrease in the stress stimulus due to an increase in the amount of bone present. The opposite is seen for an increase in the activation frequency. Right: Changes in the bone balance ratio from equilibrium show steady increases or decreases in stress stimulus.

CONCLUSION

In this study we have introduced a new theoretical framework for bone adaptation that can incorporate the effects of both metabolic and mechanobiologic factors. This new description is based at the level of the bone cell and builds on previous work from our laboratory that focused on the role of mechanical stimuli in bone adaptation at the tissue level. With the addition of biological and metabolic influences, it will be possible to simulate the effects of nutritional, hormonal, and pharmacological therapies in the treatment of osteoporosis. It will also be possible to study the interactions between metabolic factors and mechanical factors such as normal daily activities and exercise intervention, thereby identifying more optimal protocols for maintaining bone mass throughout life.

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