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A Generalized Procedure for Predicting Bone Mass Regulation by Mechanical Strain

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Summary. Understanding of the mechanisms that control the modifications of the bone weight-bearing attitude in response to external load conditions attracted considerable attention from researchers in the biological, medical, and radiological fields. This study presents a general approach for predicting the reaction of the bone tissue to cyclic loads with different intensity and temporal distribution. Empirical relationships are generated that incorporate the wealth of published experimental data, obtained from *in vivo, ex vivo,* and *in vitro* studies, into an integrated analysis. The developed procedure was guided by and is in close agreement with the published experimental data. The approach provides a general framework for predicting the effect of mechanical strain deviation from the physiological strain environment only, without consideration of the influence of any other changes in the biochemical, physiological, or psychological mechanisms controlling bone growth and damage. Further clinical investigations with controlled exercise and systematic bone scanning are necessary to check the applicability of the coefficients generated in the proposed method for general use on human subjects.

Key words: Bone modeling — Mechanical strain — Resorption — Fatigue damage.

Although numerous careful studies were undertaken since J. Wolff published his law in 1884, bone behavior under stress is still far from being fully understood. Under the normal daily activity or physiological load history (PLH), the bone is subjected to a continued turnover within the extracellular matrix in order to maintain blood calcium levels and skeletal integrity [1]. When a load-bearing bone is exposed to a strain level different from PLH, it reacts with alterations of its shape and mineralization. Usually, increased functional loading is associated with increased bone mass and decreased functional loading with bone loss [1–6].

It has been observed that decreased or null loads can induce reduction of the cross-sectional area (CSA) or bone mineral content (BMC); in other words, reduction of the load-bearing aptitude [7–15].

During bedrest experiments, the bones which in normal physiological conditions are more loaded, react to the new environment with a more pronounced mineral loss than those less loaded [12, 15, 16]. This supports the hypothesis that the bone behavior is related to the deviation of the functional strain environment from the normal physiological strain environment [17, 18]. We will define the strain ratio as the ratio between the strain levels that occur during bedrest, exercise, or overload, and the physiological strain levels imposed on the bone in normal daily activity.

The long-term resorption-induced experiments (bedrest, immobilization, real or simulated weightlessness) indicate a progressive reduction of resorption rate, which becomes zero after a reduction of the CSA of approximately 50% [14, 15]. It is not clear if this stabilization occurs because of a physiological resorption limit or because any reduction in CSA automatically causes a proportionate increase in the strain ratio and consequently increases deposition.

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Some experiments, which were conducted to understand the relation between strain history and osteogenetic response, show that only time-variable strain histories have osteogenetic effect [19]. In general, the experimental observations show correlation between osteogenesis and the intensity, rate (cycles per day), and duration (number of days) of the strain history [18].

During *in vitro* experiments, bone shows a fatigue behavior similar to porous composite materials. Some fatigue tests indicate that the strain induced during the usual daily activity can be high enough to generate fatigue micro-damage in relatively few cycles. Under this assumption, the fatigue damage could be a physiological rather than pathological condition [4, 20]. As the bone does not fail under normal load conditions, a continuous deposition of new material has to repair the damage, preventing its accumulation and propagation [4, 21].

In experiments on young adults who are unaccustomed to physical activity, Margulies and coworkers [22, 23] found that about 40% of the trainers did not complete their training course mainly because of stress fractures. The bone mass in those subjects also increased significantly, though less than in those who completed their training. Chamay and Tschantz [24] gave results showing that stress fracture can often occur with bone hypertrophy.

Most of these studies attempt to explain specific observations of bone growth or damage and do not provide a generalized unified theory for predicting reaction of the bone to a particular strain history. This study is therefore undertaken to investigate the feasibility of developing a unified approach to integrate the different experimental findings that are available in the literature into a procedure that can be used to predict growth and failure of bone under a given cyclic load history.

Method

Our analysis is based on the fundamental assumption that bone at each moment of its life is subjected to three distinct processes: osteoclastic resorption, fatigue microdamage of the inorganic matrix, and osteoblastic deposition of new bone. The method of analysis assumes that the final result is generated by the superposition of the three effects. Although the system is not linear with complexd interactions, this assumption is necessary to make a predictive model tractable.

Although these assumptions provided a good vehicle for correlating the published *in vivo* animal data, further studies will be needed to check the accuracy of the assumption and to modify the coefficients used in the proposed analysis, if necessary, for human use.

We will define the sum of the destructive actions (resorption and fatigue) as damage and the osteoblastic activity as deposition. The equilibrium between these two gives the final adaptive resultant variation of BMC and/or CSA. We will use the change in CSA (as most of the experimental data are reported in this form) as an equivalent measure for quantifying any increase or reduction of the load-bearing attitude.

The basic step in the proposed procedure is to develop equations for quantifying the damage and deposition effects. The equations can then be used in a systematic procedure to generate appropriate coefficients for predicting the daily change in the load-bearing attitude that is consistent with the published *in vivo* animal data.

The Resorption Law

The resorption law is based on published data related to bedrest, weightlessness, and immobilization [7–15]. The long-term data from [14] shows a progressive reduction of the resorption rate after about 15 weeks. We can assume that this is caused by the increase of the effective strain due to the reduction of the CSA, with a corresponding increase of the deposition as a partial compensation mechanism. For this reason we have used the initial rate at the early stages of immobilization to represent the resorption effect. This is found from all the data to be equal to 0.35% of the CSA/day. Under an absolute absence of deposition, this model would predict 100% damage of the bone after 286 days. Accordingly, the resorption law without deposition can, therefore, be stated as:

$$\text{resorption percent} = 0.35\ (\text{number of days}) \quad (1)$$

The Fatigue Failure Law

On the basis of the Carter studies [2, 20, 27–29], we adopted the following relation between peak strain and number of cycles to failure:

$$N_f = \text{number of days} \cdot (\text{CPD}) \quad (2)$$

$$\log_{10}(\epsilon_f) = 4.4 - [(0.19)\log_{10}(N_f)] \quad (3)$$

where ϵ_f is the peak strain expressed in microstrain which generates *in vitro* failure in N_f cycles. This relationship is used to represent the inorganic response of the bone as the tools and protocols of the experimental work are similar to those used in the engineering characterization of materials.

The Damage Law

Equation 1 gives the resorption rate which represents organic damage of bone at bedrest without any load strain. In addition to this loss, any cyclic microstrain is also expected to cause an inorganic damage, similar to what occurs in engineering ma-

terials, which accumulates with repeated strain cycles. The relationship between damage and strain is assumed to be similar to that suggested by Corten and Dolan [25], and corrected in consideration of the resorptive mechanism.

The Corten-Dolan damage criterion, which is illustrated in Seireg [26] shows that each strain cycle causes some infinitesimal damage depending on the strain magnitude. The damage grows exponentially with the accumulated number of cycles. The 100% damage characterizes the appearance of a detectable crack.

A generalized damage criterion is therefore developed to evaluate the total damage due to resorption and cyclic strain. It is expressed as:

$$\text{total damage (percent)} = \frac{.35\ (\text{number of days})}{\left(1 - \left(\frac{\epsilon_d}{\epsilon_f}\right)^2\right)^{1/2}} \quad (4)$$

where ϵ_d is the microstrain at any particular day as modified to account for the change in the CSA during the previous days, and ϵ_f is calculated from equation 3 to represent the microstrain that causes fatigue fracture with the total number of cycles N_f accumulated up to that day [N_f = (CPD)(N_d)].

The Deposition Law

If we assume that the percent change in CSA that is reported in the experimental data is the difference between deposition and damage, we can therefore generate deposition data. The deposition law was therefore derived to give the best fit with the long-term experimental data of Woo et al. [30] and Lanyon et al. [32] by daily accounts of the damage and growth (as explained later) and found to take the following form:

$$\text{deposition} = K\ N_d\ \epsilon_d \quad (5)$$

where K is an empirical function of the number of days N_d, and ϵ_d is the strain after N_d days.

For $N_d < 17$

$$K = (0.47)\ 10^{-3}\ \frac{N_d}{17} - (0.05)\ 10^{-3} \sin\left(\frac{N_d}{17}\right) 360°$$

For $N_d > 17$

$$K = (0.47)\ 10^{-3} \quad (6)$$

A graphical representation of the function K is given in Figure 1.

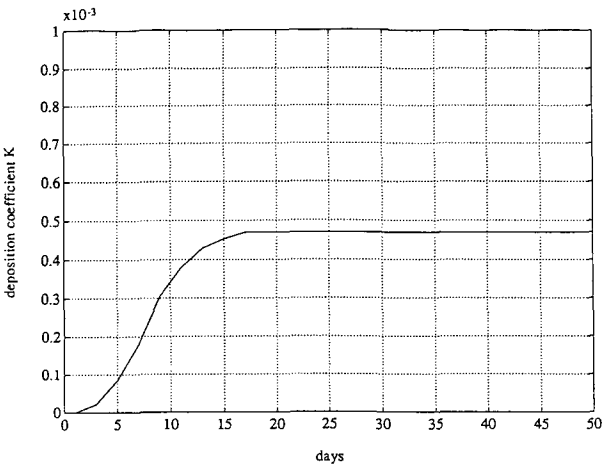

Fig. 1. Deposition coefficient K.

Computational Procedure

The computational procedure is therefore carried out as follows to simulate the daily change in the bone load bearing aptitude. Given the initial load strain ϵ_1 as the number of load cycles per day (CPD), the bone condition at the end of the first day can then be calculated as:

1. From equation 5 the deposition (percent) = K ϵ_1, where K is calculated from equation (6) for $N_d = 1$
2. From equation 3 the microstrain ϵ_f which generates *in vitro* failure after N_f = CPD (1) is calculated (for example, if N_f = 100 cycles ϵ_f = 10,000).
3. Equation 4 is then used to calculate the cumulative damage after the first day as:

$$\text{percent damage} = \frac{.35\ (1)}{\left[1 - \left(\frac{\epsilon_1}{\epsilon_f}\right)^2\right]^{1/2}}$$

4. The percent change in bone strength (load bearing) aptitude after the first day is evaluated as:

$$\Delta_1 = K\ \epsilon_1 - \frac{.35\ (1)}{\left[1 - \left(\frac{\epsilon_1}{\epsilon_f}\right)^2\right]^{1/2}}$$

5. The load microstrain for the following day ϵ_2 is then modified to reflect the strengthening (positive Δ_1) or weakening (negative Δ_1) according to the following equation:

$$\epsilon_2 = \epsilon_1 \left(\frac{100}{100 + \Delta_1} \right)$$

6. Steps 1–5 are then repeated for each day until the test period is completed or failure occurs.
7. Bone failure is characterized by either of the following conditions: bone fracture occurs on the day where ϵ_d is greater than or equal to ϵ_f; detectable cracks occur on the day where Δ_d is greater than or equal to 100.
8. If the load microstrain is given as a ratio of the normal physiological strain (which is approximately equal to 1,000), then the value of the microstrain is determined by multiplying the ratio by 1,000.

Correlation Between the Proposed Approach and Published Data

The accuracy of the derived relationships is illustrated by applying the computational procedure to the conditions used in several of the published animal experiments and comparing the predictions with the reported results.

Figure 2 shows a comparison with the experiment on beagle dogs [14]. Long-term immobilization of the right forelimb showed gradual bone loss reaching approximately 50% in the 3rd metacarpal after 40 weeks. The predicted results are based on the assumption that the bone is subjected to a typical daily number of cycles (10,000 CPD) but with 15% of the normal physiological strain (taken to be equal to 1,000).

This method was also applied to predict the daily change in bone cross-sectional area reported by Woo et al. [30] on 5 young swines subjected to 12 months of exercise training. The predicted curve in Figure 3 shows almost identical value to the average 23% increase in area reported at the end of the test period. This is to be expected as this result was used in evaluating the coefficients of the K function in the deposition law. The number of cycles per day considered in the computation is also 10,000 CPD. The strain ratio used in this case is 1.31 which represents a 31% increase over the physiological level as suggested by Lowin et al. [31] for this type of exercise.

The experiments by Lanyon et al. [32] show an average increase of approximately 22% of the CSA of the radius 1 year after performing an ulnar osteotomy on sheep. The experimental conditions reported by the authors (5000 CPD and 1.2 strain ratio) were used in the prediction. As would be expected, the final result shown in Figure 4 is in excellent agreement with the computed curve for the entire test period as it was also used in evaluating the coefficients of the K function.

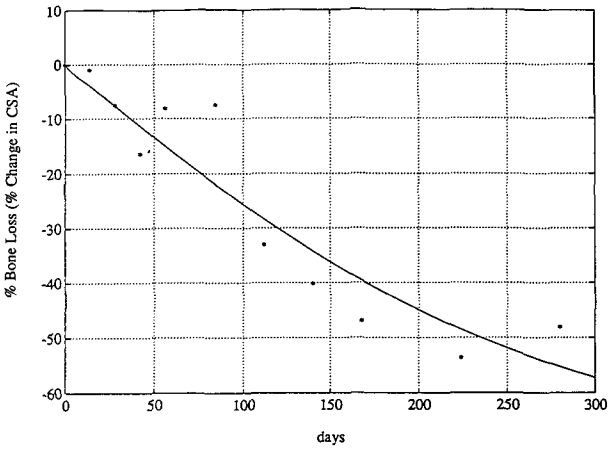

Fig. 2. Comparison between predicted bone loss (——) and results from long-term immobilization experiments (*) [14].

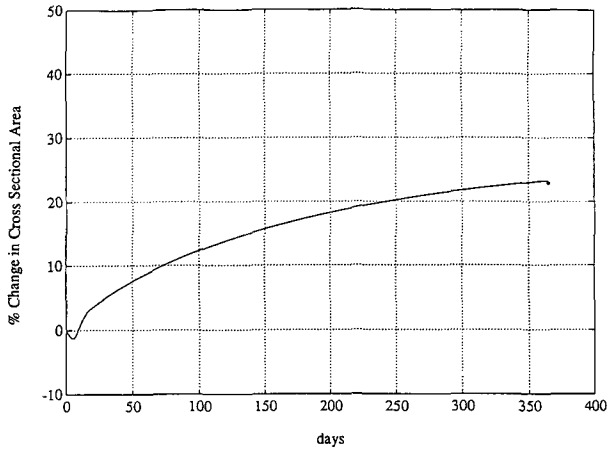

Fig. 3. Comparison between predicted change in CSA (——) and experimental finding (*) after 1 year of physical training [30].

O'Connor et al. [33] conducted tests on the radius and ulna of sheep using intermittent loads applied by surgically implanted devices. Their results are plotted in Figure 5 and show the same trend as the predicted results using the developed model where fracture occurred after an initial increase in the CSA. Similar experiments are reported by Churches et al. [34, 35] and show an increase of up to approximately 8% in the CSA. It is interesting to note from the reported data of the last three tests that the proposed method may provide an explanation why three seemingly similar experiments gave different results. The O'Connor et al. experiments, which were conducted at a rate of 7,000 CPD, are near to a critical condition where fracture can occur. The tests reported by Churches et al. [34, 35]

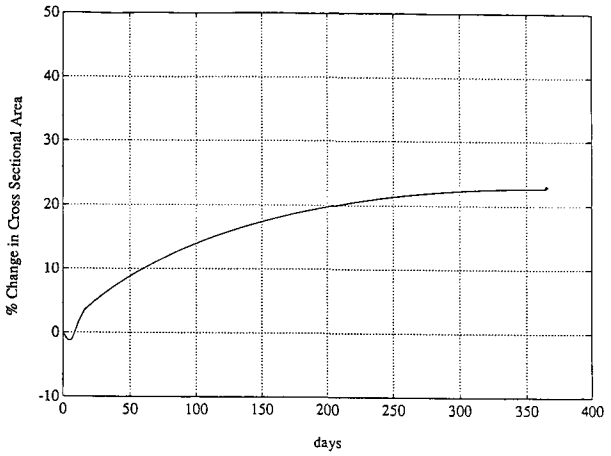

Fig. 4. Comparison between predicted change in CSA (———) and experimental results (*) from ulnar osteotomy on sheep [32].

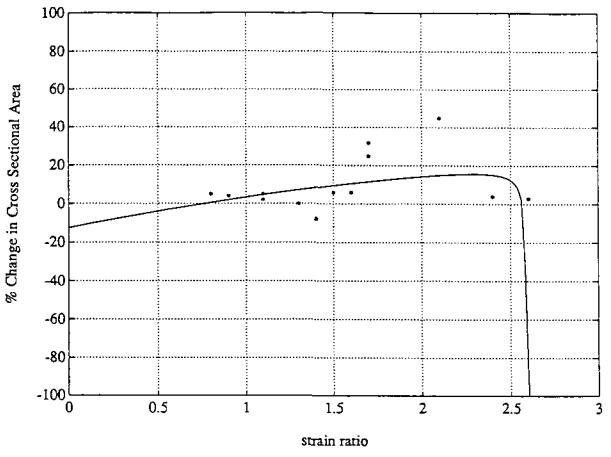

Fig. 5. Comparison between predicted change in CSA (———) and results (*) from bending and compressive load on the radius of sheep ulna applied intermittently by a surgically implanted device [33].

were conducted at 2,280 CPD where the proposed approach would predict a net increase of the CSA.

Another set of experiments were undertaken by Rubin and Lanyon [36] who fixed the load rate at 100 CPD and varied the peak strain magnitude. After 8 weeks of daily application, the turkeys were suppressed and the change in the cross-sectional areas of the trained ulna were evaluated. A sample of the result is re-plotted in Figure 6 together with the computed predictions for the same test conditions. Good agreement can be seen in the figure between the test data and the computed results by the proposed method.

Conclusions

The approach presented in this paper appears to

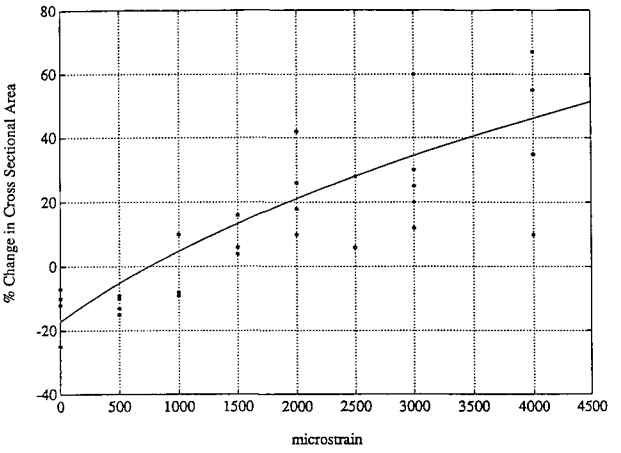

Fig. 6. Comparison between predicted change in CSA (———) and results from experiments (*) on mature adult turkeys [36].

give a reasonable estimation of the strengthening and weakening of bone due to different intensity of cyclic strains applied at different cycles per day. The correlation with the experimental data given in Figures 2 through 6 is excellent especially when taking into consideration the lack of compensation for biological variations and differences between experimental subjects, techniques, and test conditions. It should be noted that the data in Figures 5 and 6 were not used in developing the model coefficients.

The proposed approach is intended to provide a systematic procedure for evaluation of the effect of exercise on bone. More accurate coefficients may be expected after controlled experiments are conducted to verify or modify the quantitative information (i.e., the constants in the different equations) to give the best correlation with the experimental data.

An interesting observation from the results, as shown in Figure 5, is the ability to predict fatigue failure after initial osteogenetic strengthening, for high strain conditions applied at large number of cycles per day.

Although the model coefficients were developed based on the experimental data of Carter et al. [20, 27–29], Woo et al. [30], and Lanyon et al. [1, 18, 19, 32], the model also gave good correlation with the test results reported by O'Connor et al. [33], Churches et al. [34, 35], and Rubin and Lanyon [36]. The reliability of the developed coefficients for clinical use in humans can only be insured after conducting controlled experiments. Such experiments should combine systematic monitoring of the bone CSA and mineral content with computation of the strain ratios in controlled exercise. The latter can be readily evaluated based on the analysis of the forces in the musculoskeletal system as described by Seireg and Arvikar [37].

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