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Numerical Modeling of Long Bone Adaptation due to Mechanical Loading: Correlation with Experiments

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Abstract

The process of external bone adaptation in cortical bone is modeled mathematically using finite element (FE) stress analysis coupled with an evolution model, in which adaptation response is triggered by mechanical stimulus represented by strain energy density. The model is applied to experiments in which a rat ulna is subjected to cyclic loading, and the results demonstrate the ability of the model to predict the bone adaptation response. The FE mesh is generated from micro-computed tomography (μ CT) images of the rat ulna, and the stress analysis is carried out using boundary and loading conditions on the rat ulna obtained from the experiments [Robling, A. G., F. M. Hinant, D. B. Burr, and C. H. Turner. *J. Bone Miner. Res.* 17:1545–1554, 2002]. The external adaptation process is implemented in the model by moving the surface nodes of the FE mesh based on an evolution law characterized by two parameters: one that captures the rate of the adaptation process (referred to as gain); and the other characterizing the threshold value of the mechanical stimulus required for adaptation (referred to as threshold-sensitivity). A parametric study is carried out to evaluate the effect of these two parameters on the adaptation response. We show, following comparison of results from the simulations to the experimental observations of Robling *et al.* (*J. Bone Miner. Res.* 17:1545–1554, 2002), that splitting the loading cycles into different number of bouts affects the threshold-sensitivity but not the rate of adaptation. We also show that the threshold-sensitivity parameter can quantify the mechanosensitivity of the osteocytes.

Keywords

Cortical bone adaptation; Rat ulna; Loading bouts; Finite element modeling; Evolution law

INTRODUCTION

Bone is a living tissue that adapts its shape, size, density, and internal structure depending on its mechanical environment.¹⁰ Bone adaptation is often separated into two types: (a) external (surface) bone adaptation, involving changes in size and shape of bone,¹⁶ and (b) internal bone adaptation, which results in changes in local density (material properties) of

bone and changes in architecture of the trabecular bone structure.¹⁷ Numerous experimental investigations on cortical bone have shown that the application of cyclic loads produces a growth response in cortical bone.³⁹ This growth response has been shown to depend on a number of parameters such as magnitude and bouts of applied load,^{7,25,36} number of loading cycles,^{35,40} rest periods,^{32–34,37} and loading frequency.^{7,20,25,26,42} These various experimental parameters need to be interpreted in terms of local mechanical fields such as stress, strain, strain energy, strain rate, or other measures for the purpose of mathematical modeling.

Most of the existing mathematical models that have been used to describe bone adaptation employ an evolution equation of the form^{9,11,12,15,21,22,31,41}

$$\frac{db}{dt} = A(S - S_{\text{ref}}), \quad (1)$$

where b is a material characteristic (density, mass, topology, or shape), A is a proportionality constant that measures the rate of the adaptation response, S is the mechanical stimulus, S_{ref} is a reference mechanical stimulus, and t is time of growth. Various mechanical stimuli have been proposed as triggers for bone adaptation, including strain,¹² strain energy density,^{21,22,43} tissue damage,^{27,29,31} daily stress stimulus,^{8,9,41} and different forms of effective stress.¹⁴

Our focus in this work is on the modeling of external cortical bone adaptation in long bones induced by mechanical stimulation. The literature contains many experimental studies of external bone adaptation.^{7,20,25,26,33–35} There are also numerous published computational models that attempt to predict internal adaptation response.^{8,14,21,22} However, there are relatively few models in the literature that concentrate on modeling of cortical bone adaptation.^{5,9,11,15,28,29,31,41} These works use either simplified geometric models of bone or account for the complexity of the bone shape using either the finite element method (FEM), in which the entire volume is meshed and analyzed, or the boundary element method (BEM), in which a surface mesh is used and volumetric information is computed via spatial kernels. Further details on these methods can be found, for example, in Zienkiewicz and Taylor⁴⁵ for the FEM and in Brebbia and Dominguez⁶ for the BEM. Cowin and Firoozbakhsh¹¹ modeled external adaptation analytically using a circular cylindrical model, assuming isotropic elastic material properties, and strain as the stimulus in the remodeling law. Carter and coworkers developed a daily stress stimulus, based on the number of load cycles, and the applied stress, to devise a general theoretical framework for bone modeling simulations.^{5,9} Van der Muelen *et al.* used the daily stress stimulus and modeled the adaptation process on long bones of circular cross-section.⁴¹ Fridez *et al.*¹⁵ examined bone adaptation in a FE model, using simple geometries and complex mechanical stimuli based on a plasticity criterion. Prendergast and co-workers^{29,31} simulated the ulnar osteotomy experiment of Lanyon *et al.*²⁵ on sheep forearms, using a simplified three-dimensional FE model of the radius and ulna, and a damage parameter as the stimulus. Recently, Garcia-Aznar and co-workers modeled the adaptation of cortical bone using the BEM on simple geometries, such as a rectangular beam and a uniform cylindrical model of a sheep radius.²⁸ They used a stimulus based on the strain and damage in the remodeling law. The results of their remodeling algorithm were compared qualitatively with the experiments of Lanyon *et al.*²⁵ by comparing the final shape of the computed and experimentally measured cross sections of the adapted cortical bone. While all these models address the subject of external adaptation effectively, some drawbacks of these models are:

- a. External adaptation was limited to simple geometrical models

- b. Only qualitative comparisons were made between the results from the simulations and existing experimental results

Our objective in this study is to extend these previous studies to develop a numerical framework that is capable of predicting external adaptation response on actual cortical bone geometries, using FE analysis coupled with a growth law. We demonstrate that a two parameter growth law (similar to Eq. 1) can predict realistic structural changes in cortical bone subjected to mechanical loading. We are particularly interested in modeling the outcomes of the experiments, performed by Robling *et al.*,³⁴ which focus on the effect of bouts of loading on the adaptation response in the rat ulna. In those experiments rats were subjected to cyclic compressive loading of 17 N at 2 Hz on their forearms, using two different loading regimens: one bout of 360 load cycles (360×1) or four bouts of 90 load cycles (90×4). More bone growth was observed in the 90×4 loading regimen than when the loading was completed in a single bout. Robling *et al.* hypothesized that when the external loading was applied in a single bout, the osteocytes become de-sensitized to the load, resulting in a lower adaptation response. On the other hand, when the loading cycles are divided into multiple bouts with rest periods between them, the osteocytes have an opportunity to regain their mechanosensitivity, giving rise to an improved adaptation response for the same magnitude of load. This observation relates the effect of a loading parameter (multiple bouts) to the mechanosensitivity of the osteocyte. We first validate the results from our model by comparing them with the experimental observations, and we then use this model to identify and understand the biological significance of the two parameters used in the growth law. We note that this experimental study did not consider the effects of frequency and number of load cycles on adaptation, and we, therefore, leave these phenomena to future work.

In order to ensure a more accurate geometric representation of the cortical bone, we used a realistic bone geometry extracted from micro-computed tomography (μ CT) images of a rat ulna to build a finite element model. We then modeled bone adaptation in the ulna through evolution of its shape using a growth law similar to Eq. (1). We tested two hypotheses: (1) that the model could accurately predict the structural change along the entire ulna in response to mechanical loading; and (2) that the effect of multiple bouts of loading on the growth response could be predicted quantitatively in the model by varying only the reference mechanical stimulus term in the evolution equation.

METHODS

Finite Element Model of the Bone

A series of micro-computed tomography (μ CT) images was obtained from the ulna of an adult female Sprague–Dawley rat. The ulna was mounted in the scanning plane of a SkyScan 1172 benchtop μ CT machine (SkyScan, Aartselaar, Belgium) while bathed in 70% ethanol. The entire bone was scanned every 0.3° using a 60 kV source with a 0.5 mm Al filter at $10 \mu\text{m}$ resolution. An average of four frames per field was used to generate the projections. The projections were reconstructed into 3170 transverse slices using the SkyScan software, with an isotropic voxel size ($10 \mu\text{m}$). The images were imported into Amira,⁴ where a three-dimensional surface model of the rat ulna was constructed. The surface model was then exported to Hypermesh,³ where we generated a FE mesh consisting of 37,949 parabolic tetrahedral elements and 62,782 nodes.

Portions of the rat ulna, near both the proximal and distal ends, were extremely porous due to the presence of trabecular bone. In these highly porous regions, Amira was unable to produce a contiguous surface mesh, resulting in bad quality tetrahedral elements. To circumvent this problem, these regions were filled in with tetrahedral elements, as though

the regions were solid, to obtain an analyzable FE mesh. We expected this approach to the trabecular bone region to have very little effect on the adaptation behavior in the diaphyseal cortical bone, because the trabecular bone is confined to small regions near the ends, and the loading is primarily an axial force. We will show later, by varying the modulus in the trabecular region, that this approach is valid. Thus, we modeled the rat ulna as a homogeneous material in this study.

The experiments of Robling *et al.*³⁴ were simulated via elastic stress analysis performed using the commercial FE code ABAQUS.¹ In the experiment, a compressive load of 17 N was applied to the rat forearm. This load was borne by both the radius and ulna, and we estimate that the ulna is subjected to an effective load of 9 N, based on strain gage data that were measured for the whole forearm and the extracted ulna. We describe these measurements briefly, as follows. Single element strain gages (EA-06-015DJ-120; Vishay Micro-Measurements, Raleigh, North Carolina) were bonded onto both the medial and lateral surfaces of the ulna at distances of 15.85, 11.14, and 6.20 mm from the distal end, using M-Bond 200 adhesive (Vishay Micro-Measurements). Once the gages were attached, the ulna was subjected to cyclic axial compression by an electromagnetic actuator with feedback control (Bose Enduratec 3200, Eden Prairie, Minnesota). Five trials were run per gage location. The average measured strains (in μ strain) on the medial surface were -3710, -3552, and -3064, and on the lateral surface were 3141, 3123, and 2817 at the various gage locations. These strains were used to establish the elastic modulus of the bone material and the end loads applied to the FE model. Because the ulna is curved, the compressive load results in bending along the length of the bone.

Figure 1 shows the FE mesh and boundary conditions. To simulate the loading conditions in the FE model, a compressive load of 9 N was applied on one node on the proximal side along the z-axis (while the displacements in the other two directions at that node were restrained), and one node was constrained in all three directions on the distal end. The constrained nodes were selected such that they were in a straight line so that the compressive loading by itself did not induce a moment on the bone.

We modeled the cortical bone of the ulna as a linear elastic, homogeneous, isotropic material with an elastic modulus of 17 GPa and Poisson's ratio of 0.3. The modulus was obtained by comparing the strains computed in the FE model to those measured by the strain gages described above. For an elastic modulus of 17 GPa and Poisson's ratio of 0.3, the strains from the FE simulation at the same locations as the strain gages were: -3715, -3491, -3046 on the medial surface and 2777, 3112, and 2751 on the lateral surface. The strains in the FE simulations at five of the six locations thus match the experimentally measured average strains within less than 2% of the measured strain. The sixth gage, where the measured and computed strains differ by 13%, is at a section of the bone where the strain varies rapidly. Thus the larger discrepancy can be attributed to a small error in exactly locating the sixth strain gage and the fact that the strain gage itself, which is of 5 mm $\times$ 3 mm, averages the strains over the area. Based on these results, we used the stated constant values for the elastic modulus and Poisson's ratio in the simulations presented in this paper. It is well known that cortical bone is an anisotropic, nonlinear, hierarchical elastic material. Mechanical properties of cortical bone were reported to be transversely isotropic by number of authors in the literature, with longitudinal modulus of around 17–20 GPa, transverse modulus of 8.5–10 GPa and Poisson's ratio of 0.3.^{2,10} In order to investigate the possible effect of transverse anisotropy on the adaptation response, we considered a case where the transverse modulus was set to 9.5 GPa, while maintaining the axial modulus of 17 GPa. We found that this variation in transverse isotropy resulted in only a 2% change in the adaptation behavior compared to the isotropic case. The details of this simulation are given in the Discussion section.

Surface Evolution

External adaptation was implemented in this work by displacing the surface nodes of the FE model in the normal direction using an adaptation law similar to Eq. (1). Strain energy density was used as the mechanical stimulus that triggers bone adaptation since it is a scalar quantity that includes stress and strain, and has been used by researchers previously.^{21,22,27} No resorption was observed in the experiments of Robling *et al.*, so we modified Eq. (1) to preclude resorption by restricting the growth to be non-negative:

$$\frac{db_i}{dt} = \begin{cases} A(\varphi_i - \varphi_{\text{ref}}), & \varphi_i \geq \varphi_{\text{ref}} \\ 0, & \varphi_i < \varphi_{\text{ref}} \end{cases}, \quad (2)$$

where b_i is the normal displacement of surface node i , A is a proportionality constant, φ_i is the local strain energy density (interpolated to node i within each element containing that node, then averaged), and φ_{ref} is the reference strain energy density. The proportionality constant A ($\text{m}^3/\text{N}/\text{timestep}$) plays the role of a “gain” in the adaptation process, whereas the sensitivity of the osteocytes to the mechanical stimulation is represented by the reference strain energy density φ_{ref} . Hereafter, we use the terms “gain” and “threshold-sensitivity,” respectively to refer to A and φ_{ref} . It is important to understand that there are three different time scales in the experiments: (a) the time scale for the loading cycles, on the order of seconds; (b) the time scale for the bouts over which the load is administered, varying from minutes to hours; and (c) the time scale for growth and adaptation, which was 16 weeks in the experiments of Robling *et al.*³⁴ In this work, the time t in Eq. (2) refers to the latter growth/adaptation time scale. There were no measurements of the temporal evolution of adaptation in the experiments of Robling *et al.*,³⁴ so the growth-timestep t should be viewed as a pseudo-timestep. We chose timesteps such that the total adaptation occurred over 20 growth timesteps. Scaling Eq. (2) in terms of a different pseudo-time variable $\tau = ct$, where c is a constant, and applying the chain rule for differentiation, the adaptation law becomes:

$$\frac{db_i}{d\tau} = \begin{cases} \frac{A}{c}(\varphi - \varphi_{\text{ref}}), & \varphi \geq \varphi_{\text{ref}} \\ 0, & \text{otherwise} \end{cases}, \quad (3)$$

Thus, we see that A and t are convolved, and choosing the time step size such that the growth occurs over 20 time steps ensures that the results are independent of the scaling. It should be noted that the form of the growth law in Eq. (2) admits the possibility that given sufficient time to adapt, the bone will eventually grow enough that $\varphi < \varphi_{\text{ref}}$ everywhere, i.e., a steady-state or saturation is achieved. None of the simulations reported in the next sections reached steady-state.

The procedure for simulation of bone adaptation begins with an elastic stress analysis. Since the frequency and total number of load cycles were the same in all of the experiments of Robling *et al.*,³⁴ we performed a quasi-static elastic stress analysis using the prescribed magnitude of loading. The strain energy density at each surface node was then computed, and Eq. (2) was then integrated forward for a fixed amount of growth-time Δt . After computing db_i/dt from Eq. (2), a putative displacement at each surface node i can be computed using a simple forward time-stepping scheme,

$$b_i^{t+\Delta t} = b_i^t + \frac{db_i}{dt} \Delta t. \quad (4)$$

We found that using the displacements given by Eq. (4) directly to update the mesh resulted in a jagged surface. We therefore defined a distance-weighted average displacement $\widehat{b}_i^{t+\Delta t}$ given by

$$\widehat{b}_i^{t+\Delta t} = w b_i^{t+\Delta t} + (1 - w) \left(\frac{\sum_{n=1}^{N_{\text{neigh}}} \frac{b_n^{t+\Delta t}}{|x_i - x_n|}}{\sum_{n=1}^{N_{\text{neigh}}} \frac{1}{|x_i - x_n|}} \right) \quad (5)$$

where N_{neigh} is total number of nearest-neighbors for node i , $|x_i - x_n|$ is the distance between the nodes i and n , and w is a weighting function between 0 and 1. Numerical experiments varying the weighting function w , illustrated in Fig. 2, showed that $w = 0.5$ gave a good balance between obtaining a smooth surface and retaining local information, and this value is used in all of the simulations in this paper. The position $\mathbf{X}_i$ of each surface node i is then updated using the computed displacement as

$$\mathbf{X}_{i,j}^{t+\Delta t} = \mathbf{X}_{i,j}^t + (\widehat{\mathbf{n}} \cdot \mathbf{e}^{(j)}) \widehat{b}_i^{t+\Delta t} \quad (6)$$

where the subscript j denotes the component of the position vector $\mathbf{X}_i$ and $\mathbf{e}^{(j)}$ is the unit vector along the coordinate axis j .

This process of analysis and updating the FE model depending on the current local mechanical stimuli was carried out for a fixed number of growth-timesteps. The complete algorithm for the bone adaptation simulations is summarized schematically in the flowchart shown in Fig. 3. The adaptation simulations were carried out to a maximum of 20 timesteps. In order to quantify the adaptation behavior, we computed the maximum and minimum principal moments of inertia (I_{max} and I_{min} , respectively), similar to the approach of Robling *et al.*,³⁴ using the μCT sections along the length of the ulna.

We computed the cross-sectional areas and the maximum and minimum principal moments of inertia for the original and grown bone from the adaptation simulations. We carried out a series of growth simulations using different values of the growth parameters (A and ϕ_{ref}) to accomplish the following: (a) to compare the change in the geometric properties (I_{max} and I_{min}) between the simulations and the experiments of Robling *et al.*,³⁴ and (b) to investigate the effect of variations in A , ϕ_{ref} , and timesteps on the adaptation behavior.

RESULTS

We present the results of growth simulations for a set of baseline parameter values and investigate the effect of a systemic variation of the parameters on the simulation results. The baseline value of ϕ_{ref} was determined using the data of Hsieh and Turner,²⁰ who reported a deformation of 1820 μstrain for a rat ulna loaded with 9 N at 1 Hz. The approximate strain energy density corresponding to this strain value was found to be $2.7 \times 10^4 \text{ J/m}^3$, using a 1-D approximation. Based on this calculation, we simulated adaptation for $\phi_{\text{ref}} = 1 \times 10^4, 2 \times 10^4, 3 \times 10^4$, and $5 \times 10^4 \text{ J/m}^3$, taking the value of 3×10^4 as the baseline. The baseline value of $A = 1 \times 10^{-10} \text{ m}^3/\text{N/timestep}$ was determined by numerical experimentation to find a value that gave significant growth in 20 timesteps. As noted earlier, time should be regarded as a pseudo-time in this analysis.

The distribution of strain energy density in the adapted bone at the end of 20 growth timesteps of adaptation using the baseline parameter set is shown in Fig. 4b. The regions shown in grey correspond to elements whose strain energy exceeds $1.1 \times 10^5 \text{ J/m}^3$. One can

clearly see that the strain energy density is reduced in the adapted bone, due to the added bone. This indicates that the adaptation enables the bone to resist the applied bending load. Figure 5a shows an overlay of the computed cross sections of the original and adapted bone at the ulna midshaft, and Fig. 5b shows a similar overlay at the ulna midshaft obtained in the experiments of Robling *et al.*³⁴ This result shows that the simulation captures the adaptation observed in the experiments qualitatively. We now examine more quantitative comparisons of the experimental and computational results.

Three measures of the geometric properties of the bone are distributions of the cross-sectional area, $I_{\min}$ and $I_{\max}$ along the length of the bone. Robling *et al.*³⁴ observed that all three of these measures increased due to adaptation, with $I_{\min}$ showing the greatest variation. Figure 6 shows the distribution of computed changes in these geometric properties, expressed as a percentage difference between the original and adapted ulna after 20 growth timesteps. We can see that the change in $I_{\min}$ is much more significant than the change in $I_{\max}$ and area, consistent with these experimental observations. We can understand this behavior by noting that the stress due to unsymmetrical bending is given by

$$\sigma_{zz} = \frac{-M_{x'} y'}{I_{x'}} - \frac{-M_{y'} x'}{I_{y'}} = \frac{-M_{x'} y'}{I_{\min}} - \frac{-M_{y'} x'}{I_{\max}}, \quad (7)$$

where x' and y' are the principal axes, and $M_{x'}$ and $M_{y'}$ are the components of the applied moment vector about the principal axes, considering x' as the principal axis corresponding to $I_{\min}$ and y' as the principal axis corresponding to $I_{\max}$. $1/I_{\min}$ is of a higher magnitude than $1/I_{\max}$ and thus changes in $I_{\min}$ influence the stress and strain energy density stimulus more substantially than changes in $I_{\max}$. For this reason, we present only the changes in $I_{\min}$ in the results that follow.

Figure 7 shows (as filled symbols) the computed distribution of $I_{\min}$ after 20 growth-timesteps using $A = 1 \times 10^{-10} \text{ m}^3/\text{N/timestep}$ and two values of ϕ_{ref} . Figure 7 also includes measured distributions of $I_{\min}$ from the experiments of Robling *et al.* corresponding to two different loading regimens: 360 cycles administered in one bout per day (360×1); and 360 cycles administered in four separate bouts of 90 cycles each separated by 3 h (90×4) per day for 16 weeks. These results demonstrate that using the baseline value of A and $\phi_{\text{ref}} = 3 \times 10^4 \text{ J/m}^3$ (estimated from strain gage data) does indeed match well to the experimental results, corresponding to the loading of 360 cycles in one bout. From this comparison, we also can deduce a physical context for the growth-timestep (which is a pseudo-time). The results from simulation after 20 timesteps were compared with those from the experiments after 16 weeks. So on an average, each growthtimestep in the model is equivalent to 0.8 weeks or about 6 days. Further, the effect of separation of loading into bouts can be incorporated in the model as a reduction in ϕ_{ref} , by comparing the results from the simulation corresponding to $\phi_{\text{ref}} = 1.0 \times 10^4 \text{ J/m}^3$ to the experimental results, corresponding to the loading of 360 cycles in four bouts. The next sections examine the effect of variation in each of the parameters on the adaptation response.

Effect of Timesteps

Figure 8a shows the variation of the adaptation response of the ulna at several growth-timesteps in the adaptation simulation. One can see that as the number of timesteps increases, the percentage change in $I_{\min}$ tends to saturate. This can be seen more readily in Fig. 8b, which shows the evolution of the peak height. The saturation in the response occurs because as the bone grows, the strain energy density decreases, leading to a slower growth rate.

Effect of Variation in Gain

Figure 9a shows that increasing the gain A increases the rate of the adaptation response. The results are shown as the percent increase of $I_{\min}$ for the adapted bone after 20 timesteps for various values of A and a fixed value of $\phi_{\text{ref}} = 3.0 \times 10^4 \text{ J/m}^3$. Figure 9b shows the variation of the maximum percent increase in $I_{\min}$ with respect to the gain parameter A . The saturation in the adaptation response with A occurs for the same reason as for the timesteps: As A increases, the bone grows faster, thus reducing the strain energy density stimulus.

Notice that increasing A increases the rate of bone formation in the adaptation region, but that there is virtually no change in the regions near the proximal end (between 8 and 11 mm) and the distal end (29–32 mm), where the percent increase of $I_{\min}$ is close to zero. The width of the adaptation region at half the peak value of the ordinate, referred to as w_{half} , width at half-peak hereafter, is independent of the value of A .

Effect of Variation in Threshold-Sensitivity

Figure 10a shows the effect of changing the threshold-sensitivity ϕ_{ref} on the bone adaptation response after 20 growth-timesteps with a fixed value of $A = 1.0 \times 10^{-10} \text{ m}^3/\text{N/timestep}$. Decreasing the value of the reference strain energy (ϕ_{ref}) produces a greater increase in the percent change in $I_{\min}$ in the diaphyseal region. Unlike the gain A , with decreasing values of ϕ_{ref} , the curves widen approximately linearly. This can be seen even more clearly in Fig. 10b, which shows the value of w_{half} for each curve in Fig. 10a. The increase in width at half-peak clearly indicates that the region of adaptation extends toward both ends for decreasing values of threshold-sensitivity. Since the experimental results of Robling *et al.*³⁴ show a similar trend of expanding region of adaptation, we can infer that the parameter ϕ_{ref} can capture the effect of multiple bouts of loading on the adaptation response in the model.

DISCUSSION

In this study, we developed a numerical framework to simulate the cortical bone adaptation, using a simple phenomenological growth law. We validated the results of the simulation by comparing them with experimental results from Robling *et al.*³⁴ Figure 7 demonstrates that the model predicts the cortical bone growth that is quantitatively consistent with experimental observations over the whole length of the bone. This is one of the first studies to demonstrate such consistent quantitative predictions. We made several simplifying assumptions in performing the analyses, which bear further examination. In particular, we consider the significance of filling-in the trabecular regions with solid elements, and the assumption of isotropy in the modulus.

To examine the effect of filling in the trabecular region with solid elements, we performed two simulations where the value of Young's moduli in these regions was reduced to 5 and 10 GPa, respectively, while maintaining the baseline value of 17 GPa in the central cortical bone. In both of these simulations, the adaptation was exactly the same as the adaptation computed using a Young's modulus of 17 GPa everywhere. This result is not too surprising for several reasons: (a) the load was applied as an axial force, which implies that the bending stresses in the diaphysis region were unaffected by the reduction in modulus; (b) the trabecular region is small and confined to the ends of the bone so that there is little effect on the stress and strain energy density solution in the diaphyseal region; and (c) although the strain energy density in the trabecular region did increase slightly, it never reached the threshold-sensitivity, whereas the strain energy density in the diaphyseal region remained unaffected.

In order to assess the possible effect of transverse isotropy on the adaptation response, we performed a simulation using 17 GPa as the longitudinal modulus and 9.5 GPa as the

transverse modulus. We observed a difference in adaptation of about 2% between the distribution of percent change in $I_{\min}$ for the cases of isotropic and transversely isotropic properties. This result is also not surprising because the bending stress is the major contributor to the strain energy density stimulus, and the magnitude of bending stress is governed mainly by the value of the longitudinal stiffness.

There are two parameters in the model: the gain A and threshold-sensitivity ϕ_{ref} . We now discuss the role that each parameter plays in the adaptation response, with the goal of relating the model parameters to biological phenomena. We found that increasing the gain A increases the rate of adaptation (db/dt) at any given location of the bone, as long as the mechanical stimulus there exceeds the threshold-sensitivity ϕ_{ref} , and not at other locations. This is demonstrated, for example, in Fig. 9b, which shows that the width at half-peak in the percent change in $I_{\min}$ is independent of A . Thus, we identify A as a parameter that amplifies the response of the mechanosensory system (osteocytes) that senses the effect of the loading. We note that A is a conjugate of the pseudo-time t , so that increasing A (for fixed t) or t (for fixed A) are equivalent, and hence the gain parameter, when set in appropriate units of time, will be able to differentiate between different time courses of loading. We also observe that the growth response begins to saturate for large A .

The second parameter, ϕ_{ref} , affects the adaptation in a different way than A . As ϕ_{ref} decreases, not only is there an increase in the rate of adaptation response at a certain location, but also an expansion of the domain over which adaptation occurs. This is illustrated in Fig. 10, which shows that the width at half-peak in the percent change of $I_{\min}$ increases as ϕ_{ref} decreases. Thus, we identify ϕ_{ref} as the parameter that quantifies the response of the mechanosensory system, which triggers bone growth.

Our parametric study shows that similar adaptation response can result from different combinations of the gain and threshold-sensitivity parameters. The threshold-sensitivity parameter ϕ_{ref} can be determined uniquely based on the threshold strain for adaptation and the loading history (depending on the number of bouts of loading, as pertaining to this study). We have also seen that the growth-timestep and the gain parameter A are convolved. Thus, in order to establish a unique value of A , the growth-timestep needs to be calibrated. More experimental results quantifying the growth of the periosteal surface over time (say the growth of bone per day or week) would permit one to obtain a unique value for the gain parameter A .

The validation of the numerical results obtained in this study with experiments, for certain chosen parametric values, can help shed more light on the biomechanical relevance of these two parameters of the growth law. It is well known that most of the cell types sense and respond to their mechanical environment by reorganizing their cytoskeleton.^{13,30} Reorganization of the cytoskeleton changes the cell's sensitivity, and hence its response, to the mechanical environment. Since osteocytes are widely considered to be the sensor cells in a bone matrix, any changes in the external loading conditions alter its mechanical environment, which can result in a change in mechanosensitivity. In the experiments of Robling *et al.*,³⁴ more growth was observed when the load cycles were divided into four bouts, while maintaining the magnitude and frequency of loading the same. Cellular desensitization, due to continuous loading, resulted in lower growth, whereas cellular resensitization, due to the rest periods, was attributed to the improved bone adaptation response.

We have shown that the numerical model can predict the re-sensitization of osteocyte cells associated with the separated bouts by decreasing only the threshold-sensitivity parameter ϕ_{ref} from 3×10^4 to 1×10^4 , while maintaining $A = 1 \times 10^{-10}$ fixed (Fig. 7). Based on this

observation, we see that the adaptation response of bone as a result of cellular level stimulation (desensitization and re-sensitization) can be captured in the numerical model through the threshold-sensitivity parameter ϕ_{ref} alone. Thus, the threshold-sensitivity parameter ϕ_{ref} is a quantitative measure of the mechanosensitivity of the osteocytes to their extracellular mechanical environment. Also, since the threshold-sensitivity changes from 3×10^4 to 1×10^4 for the two cases of loading with one bout and with four bouts, respectively, we can deduce that the threshold-sensitivity is a function of the loading history.

The gain parameter A amplifies the growth for a given value of the threshold-sensitivity parameter ϕ_{ref} . We have shown that a variation in the gain parameter A does not result in the expansion of the adaptation region, a characteristic effect of changes in threshold-sensitivity. Thus the gain parameter is not a measure of the mechanosensitivity of the osteocytes, but rather it must be a measure of other biological parameters that can amplify the adaptation response such as the amount of osteoblastic or osteoclastic activation by the osteocyte, the amount of available nutrients for bone formation, etc. We have shown that the value of the threshold-sensitivity used is consistent with the threshold strains observed previously. A biologically consistent value for the gain parameter A could be determined from an experiment by measuring the rate of bone surface expansion, e.g., using fluorochrome labels, and fitting the results of such an experiment to the growth law.

Since the model parameters incorporate biological information about the cellular mechanical environment and the current health status of the bone tissue (and body as a whole), more experiments are needed to quantify these parameters, for the model to be used as a predictive tool. For example, experiments can be designed to quantify the growth response to different diets, drugs, diseases, and other factors, and these experiments can inform the numerical model on how the growth law parameters are affected for each of these biological parameters. While the threshold-sensitivity parameter is a convenient way to quantify the biomechanical status of the osteocyte, we need more experiments both at the lengthscale of the bone and at the lengthscale of the osteocyte cell itself to obtain a better understanding of process of mechanotransduction of the osteocyte and subsequent bone adaptation. Though some cellular level mechanical models already exist in literature,^{19,44} there is no clear experimental evidence connecting the mechanosensitivity of the osteocyte cells to the bone adaptation response at the cellular lengthscale. These are some of the open issues that still remain to be addressed.

We have shown that the effects of magnitude and bouts of bending load on cortical bone adaptation in rats can be modeled using of one of the simplest of material models (isotropic, linear elastic material model) and a simple adaptation law, to a good degree of accuracy. The only discrepancies between model predictions and experimental data were seen near the proximal and distal ends of the ulna. These can be attributed to osteophyte (bone spur) formation, which is a pathological process and was observed in the experiments of Robling *et al.*³⁴ Since osteophyte formation is not due to adaptation, we cannot expect the model to predict this elevated growth near the ends of the ulna.³⁴

An important requirement for the onset of bone adaptation is the presence of dynamic loads, rather than static loads, as pointed out by a number of researchers.^{5,9,37,39,41} It has also been shown that cyclic loading in synergy with cellular stimuli (such as growth factors) result in much higher adaptation response.¹⁸ One of the main shortcomings of our model is that using strain energy density as the stimulus precludes modeling of the effect of frequency, number of load cycles (dynamic loads), and the time between the bouts of loading on the adaptation response. A time dependent stimulus and a coupled material model are required to describe the effects of dynamic loads. It has been observed that the load induced fluid flow in cortical bone is dependent on frequency.^{23,24,38} This can be a direct addition to the mathematical

model described herein, with flow-based stimuli in addition to strain energy density, by use of a poroelastic material model, for example, to include the effects of time-dependent parameters such as loading frequency and number of load cycles on the adaptation behavior, which constitutes our current work in progress.

CONCLUSIONS

We have successfully developed a numerical framework to simulate the process of external bone adaptation with respect to applied mechanical loading, using a homogeneous, isotropic material model for the cortical bone and a simple remodeling law. The implementation of the numerical framework is very general and can accommodate readily different material models and mechanical stimuli. We have used the external bone adaptation algorithm to simulate the bone growth on complicated bone geometry, generated from micro-CT data of the rat ulna. We have explored the individual effects of the two parameters in the remodeling law, gain and threshold-sensitivity, on the cortical bone adaptation behavior. We found that with an increase in gain, the rate of bone growth was amplified. Decreasing the threshold-sensitivity resulted in expansion of the adaptation region of the rat ulna, in addition to amplification of bone growth rate. We also observed that by decreasing the threshold-sensitivity parameter in the remodeling law we can model the effect of increased bone growth due to loading of the bone in multiple bouts, as observed in the experiments of Robling *et al.*³⁴ The model presented here is one of the first attempts at numerical simulation of external adaptation of cortical bone using FE on realistic bone geometry. Since the numerical model is based upon a number of assumptions, further improvements such as a time dependent mechanical stimulus, coupled constitutive model, and more quantitative, experimental data can be included in the framework that can lead to better understanding of the phenomenon of bone adaptation and its dependence on different loading parameters.

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FIG. 1.

The finite element model of the rat ulna constructed from micro computed tomography images. The mesh contains 62,789 nodes and 37,000 elements. A compressive load of 9 N is applied to the right end (proximal end) and a node at the left end (the distal end) is fixed.

FIG. 2.

Demonstration of the smoothing procedure on a circular cylinder. (a) $w=1$ (local data only) produces a jagged surface. (b) $w=0$ (local information about the stimulus is lost) leading to rippled surfaces. (c) $w=0.5$ produces a smooth surface.

FIG. 3.
Flowchart of the external adaptation algorithm.

FIG. 4. Strain energy density contour plots of (a) original ulna and (b) adapted ulna. Grey regions denote elements with strain energy density greater than $1.1 \times 10^5 \text{ J/m}^3$. We can clearly see that the strain energy density is reduced in the adapted ulna, due to the added bone.

FIG. 5.

Comparison of the overlay plots of the rat ulna midshaft from simulation (left) and experiments of Robling *et al.*³⁴ (right). The dotted line on the left corresponds to the original bone and the solid line corresponds to the grown bone cross section in the simulation. The red line on the right corresponds to the original bone and the outer dark green solid line corresponds to the grown bone cross section in the experiments. The experiments lasted 16 weeks.

FIG. 6.

Plot showing the percent change in the geometric properties of cross-sections ($I_{\max}$, $I_{\min}$ and area) between the original and grown ulna after 20 timesteps for the baseline values of parameters A and ϕ_{ref} .

FIG. 7.

Comparison of the percent change in the minimum principal moments of inertia $I_{\min}$ between the original and adapted ulna from external bone adaptation simulations and experiments of Robling *et al.*³⁴ The error bars shown for the experimental data correspond to one standard deviation. $\Delta I_{\min}$ is the change in the minimum moment of inertia between the original and adapted ulna and $I_{\min}^0$ is the minimum moment of inertia of the original ulna.

FIG. 8.

Plots showing the (a) effect of timesteps on the percent change in $I_{\min}$ and (b) variation of peak of percent increase in $I_{\min}$ with number of timesteps on the external bone adaptation simulation. $\Delta I_{\min}$ is the change in the minimum moment of inertia between the original and adapted ulna and $I_{\min}^0$ is the minimum moment of inertia of the original ulna.

FIG. 9.

Plots showing the (a) effect of gain A on the percent change in I_{min} and (b) variation of peak value of percent increase in I_{min} and width at half peak with respect to A on the external bone adaptation simulation. ΔI_{min} is the change in the minimum moment of inertia between the original and adapted ulna and I_{min}^0 is the minimum moment of inertia of the original ulna.

FIG. 10.

Plots showing the (a) effect of sensitivity ϕ_{ref} on the percent change in I_{min} , and (b) variation of peak value of percent increase in I_{min} and width at half peak with respect to sensitivity on the external bone adaptation simulation. ΔI_{min} is the change in the minimum moment of inertia between the original and adapted ulna and I_{min}^0 is the minimum moment of inertia of the original ulna.