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Tissue-level Remodeling Simulations of Cancellous Bone Capture Effects of *In Vivo* Loading in a Rabbit Model

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Abstract

The adaptation of cancellous bone to mechanical stimuli occurs throughout normal skeletal growth and aging, as well as in response to surgery, disease and device implantation. Previously we developed an *in vivo* cancellous loading model in the distal lateral femur of the rabbit. In response to daily *in vivo* loading for four weeks, bone mass increased, trabeculae thickened and the apparent modulus of the underlying cancellous bone increased. Here, we simulated our prior *in vivo* rabbit loading experiment using a cell-based tissue remodeling algorithm (Mullender et al. 1994) and compared the results to the *in vivo* experimental data published previously. Cancellous bone tissue was added or removed from the surface of trabeculae in regions of high and low mechanical stimulus, respectively. To examine the effect of material properties on mechanically regulated adaptation, we implemented both a homogeneous material model and a model where the relative density of tissue was lower for new and surface bone tissue compared to interior tissue. The simulations captured the changes in histomorphometric parameters and mechanical properties measured in the *in vivo* experiment illustrating the ability of computational simulations to predict the effect of mechanically regulated adaptation on cancellous bone histomorphometry and apparent modulus.

Keywords

cancellous bone; functional adaptation; bone remodeling; finite element model

Introduction

Functional adaptation of the skeleton to mechanical loading has been examined for over a century, starting with von Meyer and Wolff in the late 1800's (von Meyer, 1867; Wolff, 1986). Changes to the *in vivo* loading of the skeleton can be caused by total joint replacements, osteoporosis or osteoarthritis. The long-term effect of these changes on

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cancellous bone depends on the ability of the bone tissue to remodel the trabecular architecture to bear the new loads. Animal models have helped to better characterize the skeletal response to mechanical loading and relate this response to physical load parameters (van der Meulen & Huiskes, 2002).

Mathematical rules and relationships have been suggested to quantitatively explain the skeletal response to mechanical loading (Cowin and Hegedus, 1976; Fyhrie and Carter 1986; Huiskes et al., 1987). Computational models provide the capability to implement these mathematical theories of bone adaptation for many different load cases and remodeling parameters. Early computational models of cancellous bone adaptation primarily focused on tissue-level apparent density changes within a fixed two-dimensional geometry, e.g., the proximal femur (Beaupré et al., 1990; Carter et al., 1987; Weinans et al., 1992). Bone density was increased or decreased due to external loading based on whether a local mechanical stimulus, such as strain energy density, was greater or less than a reference stimulus level. Resulting density distributions were qualitatively similar to those found in normal bones or following adaptation to implants.

The load-bearing capability of cancellous bone depends not only on bone mass but also on the architecture of the trabeculae (Goulet et al., 1994), which is not considered in continuum-level simulations. A cell-based approach for tissue-level remodeling of cancellous bone was proposed by Mullender *et al.* in which the trabecular architecture is adapted by reshaping the rods and plates of the trabeculae (Mullender et al., 1994). Similar to the continuum-level models, bone tissue density increased or decreased depending on whether the local stimulus was greater or less than a reference value, and in addition, the trabecular architecture responded to loading. The mechanical stimulus was sensed by a network of cells distributed throughout the bone. Physiologically, the sensor network represented osteocytes, and bone tissue was added and removed by osteoblasts and osteoclasts, respectively. These cell-based models were implemented for idealized geometries. For example, analyses of two-dimensional structures with this algorithm produced trabecular-like architectures with the ability to reorient depending on the orientation of applied loads (Mullender and Huiskes 1995) (Fig. 1). Hypothetical bone loss during osteoporosis was also simulated in three-dimensions (Mullender et al., 1998).

Cancellous bone adaptation occurs on the surface of trabeculae (Burket et al. 2013). Therefore, surface-based algorithms may predict *in vivo* behavior better than density-based methods. Surface-based remodeling algorithms, in which bone tissue is added or removed only at the trabecular surface, have been implemented to simulate hypothetical loading of cancellous bone and to model the structural changes around a fixation screw in vertebrae (Adachi et al., 2001; Tsubota et al., 2003). More recently, surface-based algorithms have been used to simulate *in vivo* bone adaptation due to controlled mechanical loading of caudal vertebrae in mice (Schulte et al., 2011, 2013). These surface adaptation simulations, however, either did not include mechanical feedback or modeled the tissue properties of cancellous bone as homogeneous. Mineral crystallinity of cancellous bone has a spatial dependence, with less crystalline mineral present on the outer perimeter of trabeculae and more mature mineral located farther from the surface (Paschalis et al., 1997; Burket et al. 2013). Similar increases of tissue density with depth from trabecular surface were measured

in cancellous bone by microcomputed tomography (microCT) (Morgan et al., 2002; Bourne and van der Meulen 2003). Inhomogeneous distributions of isotropic material in cancellous bone affected apparent modulus measurements from finite element analyses (Jaasma et al., 2002; van der Linden et al., 2001). However, these studies used hypothetical distributions for the material properties, and the impact of inhomogeneous properties on adaptation simulations is unknown.

Combined surface- and cell-based adaptation models have not been used previously to simulate both load and control outcomes from *in vivo* loading experiments. Therefore, the goal of this study was to implement a tissue level, surface adaptation algorithm to simulate an *in vivo* loading experiment. We previously developed an implantable device to apply controlled loads to cancellous bone *in vivo* in the distal condyle of the rabbit femur. The daily application of 1 MPa loads with this device for 4 weeks increased bone volume fraction, trabecular thickness, and mean intercept length in the direction of applied loading in the cancellous tissue directly below the loading device relative to paired control limbs without loads applied (van der Meulen et al., 2006). Additionally, increased cancellous apparent modulus and altered strain distributions were present in finite element models created from the microCT data (van der Meulen et al., 2009). To better understand the tissue response, we applied computational bone remodeling algorithms to our experimental data. We hypothesized the cell-based tissue remodeling approach of Mullender *et al.* (1994) would capture our experimental behavior. We further hypothesized that the presence of lower mineralization in newly formed surface tissue would be integral to simulating cancellous behavior in this adaptation experiment.

Including this work in an issue of the *Journal of Biomechanics* dedicated to Rik Huiskes is quite fitting for both scientific and personal reasons. While mechanistic cellular models of bone adaptation were discussed by many researchers, Rik truly brought bone adaptation models to the cellular level and implemented these approaches. Here we took the long overdue step to apply these models to *in vivo* data. When this research was initiated, nearly two decades ago, technology was quite different. We did not have a microCT scanner of our own in 1997. The initial microCT scans for this project were performed at the Orthopaedic Research Laboratory of the University of Nijmegen in collaboration with Dr. Harrie Weinans who was in Nijmegen, as was Rik. Tim Morgan, the first author here, was a graduate student at the time and traveled to the Netherlands to scan after our initial shipment was opened by customs, resulting in the loss of samples. Once there, of course, he had the pleasure of meeting Professor Huiskes. Personally, Rik was a scientific tie to my motherland, and I met him during a formative period of my professional life. Around 1990, two research groups were primarily active in the development of computational bone adaptation, that of my graduate mentor Dennis Carter at Stanford University and that of Rik Huiskes. I got to know most of the authors in this issue during those years. Rik invited me to the Nijmegen laboratory dinner at the Orthopaedic Research Society meeting every year, and I visited his lab several times in conjunction with visits to see family. He very much enjoyed discussing the process of science. I remember discussing what differentiated scientists versus engineers. Rik truly identified with the former, and I was honored that he considered me a scientist as well.

2. Methods

Computer simulations of *in vivo* cancellous bone adaptation were performed using an iterative tissue-level, surface remodeling algorithm (Fig. 2). The tissue-level stimulus was calculated using finite element models developed from scans of experimental specimens from contralateral control limbs. The results of the *in vivo* adaptation experiments have been reported separately (van der Meulen et al., 2006). Both loaded and control loading scenarios were simulated. The tissue-level mechanical stimulus was sensed by a network of osteocytes distributed throughout the bone tissue (Mullender et al., 1994). Bone adaptation was then simulated by adding or removing tissue on the surface of trabeculae in the region of high and low mechanical stimulus, respectively.

2.1 In Vivo Loading Model (van der Meulen et al. 2006)

Previously controlled, compressive loads were applied directly to cancellous bone *in vivo* for 4 weeks using an implantable loading device applied to the distal lateral femoral condyle of rabbits (van der Meulen et al., 2006). The device consisted of a stationary base attached to the lateral femoral condyle with two bicortical screws, a movable loading core and a top (Fig. 3). The cortical shell beneath the loading core was removed to expose the underlying cancellous bone, and daily compressive loads were applied to the cancellous bone by rotating the top percutaneously. Devices were implanted in left and right femora; the device in the right limb was used to apply loads and the left limb used as a contralateral control. Upon completion of the 4-week experiment, the limbs were scanned by microCT at 19 μm isotropic voxel resolution. In this study, we used microCT data from paired limbs ($n=5$ rabbits) of experimental specimens loaded to 1 MPa of compressive force, 50 cycles/day at 0.5 Hz for four weeks and their contralateral controls ($n=5/\text{group}$). This experimental group experienced the greatest anabolic response *in vivo*, compared to groups loaded at 1 MPa for 10 and 25 cycles per day. The procedure was approved by the Hospital for Special Surgery IACUC.

2.2 Finite Element Models

MicroCT scans from the paired contralateral control limbs of loaded rabbits were used to develop the models. Simulated bone remodeling was performed using the cancellous morphology obtained by microCT at the conclusion of the *in vivo* loading experiment for a 3.6 mm cubic volume of interest centered below the loading device. For all models, the control limb morphology was used as the simulation starting point and comparisons were made to data for the experimental limbs. 3D finite element meshes were created by directly converting each voxel in the microCT scans into 8-noded linear brick elements (Hollister et al. 1994; van Rietbergen et al. 1995). To reduce the number of degrees of freedom in the finite element models, the microCT data were coarsened prior to conversion to finite elements. Coarsening was performed by averaging blocks of 27 adjacent voxels in $3\times3\times3$ regions into single elements, resulting in finite element edge lengths of 57 μm . A global threshold was used to separate bone from marrow voxels, and all voxels that did not share a face with the primary structure were removed. Additionally, bone voxels were classified as interior or surface voxels with surface bone voxels sharing at least one face with a marrow voxel.

Two sets of material properties were implemented. The first, Sim_{homogenous}, modeled all bone tissue as homogenous with a Young's modulus of 10 GPa. The second, Sim_{surface}, used an inhomogeneous material model and assigned a 15% lower relative density to new and surface bone tissue compared to interior tissue. A cubic relationship between relative density and Young's modulus was assumed with 10 GPa assigned to elements with relative density of 1.0 (Currey 1988). Therefore, surface and interior elements in the Sim_{surface} models had a Young's modulus of 6.1 GPa and 10 GPa, respectively. In both material models, a Poisson's ratio of 0.3 was used.

Boundary conditions were applied to simulate the control and loaded specimens from the *in vivo* experiment. Normal cage activity was simulated by applying 1 MPa compressive pressures to two faces of all models, excluding the lateral face (Fig. 4). The load applied by the device was simulated by adding a 1 MPa pressure on the lateral face of loaded specimens. The distal, posterior and medial faces of the finite element models were constrained from displacing out of their respective planes for both control and loaded specimens.

For the finite element analyses performed to determine the mechanical properties after the bone remodeling simulations, the trabecular tissue was modeled as linear elastic, isotropic, and homogeneous with a Young's modulus of 10 GPa and Poisson's ratio of 0.3 (ABAQUS 6.3, HKS, Pawtucket, RI). A single material model was used for all mechanical property analyses to isolate any differences in apparent modulus or tissue-level strains to the trabecular architecture generated by the different simulations.

2.3 Bone Remodeling Algorithm

Bone remodeling was simulated using the osteocyte regulatory approach of Mullender et al. (1994). Each finite element was assumed to have one osteocyte located at the element center. The mechanical stimulus at each location was determined by nearby osteocytes, and the influence of the stimulus on nearby cells decreased exponentially with distance to each osteocyte (Eq. 1, Mullender et al., 1994):

$$f_i(x) = e^{-(d_i(x)/D)}$$

At location x , each osteocyte, i , had a spatial influence function, $f_i(x)$, that exponentially decreased with distance, $d_i(x)$, between osteocyte i and location x . The parameter D determined the distance at which the effect of each osteocyte reached 36.8% (e^{-1}), and was set to 1.2 times the finite element width (Mullender et al. 1998). For each element, the mechanical stimulus was calculated with Eq. 1 for osteocytes within a $13 \times 13 \times 13$ element cubic region centered at the location of interest.

Cancellous bone remodeling was simulated by adding or removing tissue on the surface of trabeculae in regions of high and low mechanical stimulus, respectively. Strain energy density was used as the mechanical stimulus, and thresholds of 0.05 and 0.20 MPa were used for low and high strain energy density regions, respectively. These thresholds were determined by simulating control and loaded bone adaptation for one specimen with various

low and high thresholds. The thresholds chosen yielded the largest increase in bone volume fraction of the loaded simulation while maintaining the bone volume fraction of the control simulation to within 1% of the value from the *in vivo* experiment. Bone remodeling iterations were continued until both the number of elements and the total apparent density changed less than 1%. All finite element analyses were performed in ABAQUS (Version 6.3, HKS, Pawtucket, RI), bone remodeling equations solved in Matlab (Version 6.1, The Mathworks, Inc., Natick, MA), and a shell script was used to run the processes.

2.4 Outcome Measurements

Cancellous bone histomorphometry and mechanical properties were calculated for each cancellous bone sample at the end of the remodeling iterations. Histomorphometric measures included bone volume fraction (BV/TV), direct trabecular thickness (Tb.Th), direct trabecular separation (Tb.Sp), mean intercept length (MIL), and architectural anisotropy. Additionally, we determined changes in mean intercept length (MIL) in the direction of applied loading during the experiment. MIL-3 was defined as the mean intercept length in the lateral direction calculated from the MIL ellipsoid.

To assess the effect of bone remodeling on the mechanical properties of cancellous bone located beneath the loading device, we calculated the tissue-level strains and apparent modulus in the direction of experimental loading with finite element analyses (van der Meulen et al., 2009). Apparent modulus was calculated by simulating a uniaxial compression test in which the surface of the bone specimen adjacent to the loading core was displaced -0.5% and the opposite surface was constrained from displacing out of plane and fixed at a point to prevent rigid body motions. The apparent modulus was calculated as the total reaction force divided by the apparent cross-sectional area. Strains in the tissue were calculated following the application of a 1 MPa compressive load per unit area as in the *in vivo* experiment. Minimum principal strains were calculated at the element centroids for the central 3.4 mm cubic portion of each bone specimen. The central portion was selected to minimize artifacts from elements with boundary conditions applied to the nodes. To compare values across specimens, minimum principal strains were stratified into three levels based qualitatively on strain magnitudes. Low, medium, and high strains were defined as having absolute value less than 500 microstrain, 500 – 1,500 microstrain, and greater than 1,500 microstrain, respectively.

2.5 Statistical Analysis

Paired t-tests were used to compare histomorphometric parameters, apparent moduli in the direction of applied loading, and tissue level strains of the control and loaded specimens in each of the three remodeling groups (Experiment, Sim_{surface}, Sim_{homogeneous}) (StatView Version 5.01, SAS Institute Inc., Cary, NC). Multiple paired t-tests with Bonferroni correction were used to compare control and loaded specimens between the three groups. An alpha value of 0.05 was considered significant.

3. Results

3.1 Histomorphometry

On average both simulations showed architectural changes similar to those observed experimentally, and the changes were best captured by the inhomogeneous material simulation (Fig. 5, Table 1). Cancellous bone adaptation with homogenous material properties (Sim_{homogeneous}) resulted in significant increases in BV/TV, and MIL-3, and a reduction of architectural anisotropy with *in vivo* loading relative to control specimens. However, the increased Tb.Th seen experimentally was not present. When surface and new bone tissue were simulated with a 15% lower density, significant increases were present in BV/TV, Tb.Th, and MIL-3 with no significant change in Tb.Sp. Additionally, architectural anisotropy was significantly reduced for loaded specimens in the simulations.

While general trends of histomorphometric parameters were similar between experimental and simulated cancellous bone adaptation, the ability to capture the changes for individual specimens varied. During the experiment, loading in Specimen 5 increased BV/TV, Tb.Th, and MIL-3 and decreased Tb.Sp and architectural anisotropy. Both simulations resulted in the same change with loading compared to the control. However, the trends for individual specimens differed between the two simulations. For example, in the experiment Specimen 3 had increased Tb.Th with loading, and Tb.Th was predicted to increase with Sim_{surface} but decrease with Sim_{homogeneous}. Furthermore, the two material models predicted different values for the histomorphometric parameters that were significantly increased by loading *in vivo*: BV/TV, Tb.Th, and MIL-3 (Table 1)). Histomorphometric parameters for control specimens from the two material models were not significantly different.

3.2 Mechanical Properties

Experimental femurs loaded daily had significantly higher apparent modulus in the loading direction compared to contralateral controls (Fig. 6 and Table 2). Simulated bone adaptation also significantly increased the mean apparent modulus of loaded specimens. Individually, Specimen 1 in the experimental group had a lower increase in modulus with *in vivo* loading compared to the other specimens. In both simulations the increase in modulus with loading for this specimen was also less than for the other four specimens. Control specimens simulated with Sim_{surface} and Sim_{homogeneous} were not different. However, the modulus values for loaded specimens were significantly different for the two material models in the simulations.

The change in cancellous bone histomorphometry with controlled loading in the *in vivo* experiment resulted in a microstructure with reduced minimum principal strains under 1 MPa of compressive loading. Loaded experimental femurs had a significantly smaller percentage of high level tissue strains and a significantly larger percentage of low level strains compared to controls (Fig. 7). On average, both simulation groups also had a smaller percentage of high level strains and a larger percentage of low level strains in loaded specimens compared to controls; however, these differences were not significant. Medium level strains in loaded limbs in the Sim_{homogeneous} simulation group were significantly higher than controls. The percentage of elements with low strains differed significantly between the

experimental loaded and the Sim_{homogeneous} loaded specimens. Additionally, the fractions of low and high strains differed between the two material models.

4. Discussion

Cancellous bone adaptation following *in vivo* loading was captured with a computational, surface-based tissue level remodeling algorithm (Mullender et al. 1994). Both simulation approaches captured the experimentally-observed relative mean changes in bone mass and architecture with applied loading. Trabecular thickness changes were captured more accurately when new and surface tissue were modeled with a 15% lower relative density than interior bone tissue. The change in bulk stiffness of the tissue with loading was also captured; however, the tissue level strain changes were not replicated in the simulations.

While capturing mean trends by computational simulations of cancellous bone adaptation is desirable, greater value lies in predicting individual absolute behavior, particularly since individual specimen-specific geometry was used. However, predictions for individual specimens varied, as did the agreement between two simulation approaches. For individual specimens all possibilities were present: both simulations predicted different behavior than what was measured experimentally, or one simulation predicted the same response to loading as seen in the experiment while the other did not. These deviations between the two material models differed significantly between the loaded specimens for the three histomorphometric parameters that were significantly affected by mechanical loading in the *in vivo* experiment. Recently, several studies have shown the benefit of examining local strains (Lambers et al., 2011) or visually examining locations of bone formation and resorption on individual specimens (Schulte et al., 2013; Levchuk et al., 2014). Any future work with this computational algorithm would also include these additional outcome parameters.

An advantage of the computer simulations is that the same initial architecture can be used for the loaded and control boundary conditions. Previous analyses of explanted femurs showed no mean left-right differences; however, large variability existed (van der Meulen et al., 2006). This variability would be removed by using the same specimen architecture for control and loaded simulation cases, as was implemented here. However, the true initial geometry of the loaded limbs was not known, so the use of the final architecture of the control limbs for the simulations is a limitation. Using the identical initial conditions for both loaded and control cases may explain the relative lack of morphological variability in the simulations compared to the experimental data.

While capturing the mean changes in histomorphometry and mechanical properties with loading measured in the *in vivo* experiment, the simulations have several limitations. A single static boundary condition based on load magnitude was used to simulate the experimental loading. The architecture of the cancellous bone is likely influenced by the range of loading the femur experienced throughout the animal's lifetime. Incorporating a daily loading history would allow for quantitative comparisons of different loading protocols and different daily activity levels of the animals. Similarly, the cyclic nature of the loading was not captured with these simulations. Adaptation was driven entirely by the strain

stimulus, independent of the number of applied cycles and duration of loading. A single pair of low and high thresholds of strain energy density was used to determine whether bone was added or removed. Parametric analyses of these thresholds and examination of other mechanical stimuli, such as minimum principal strain or stress, could improve the correspondence with experimental data. The choice of these many experimental parameters may also contribute to the lack of individual correspondence between the experimental data and simulations. Limited data exist upon which to base these choices, either for the group or individually, so the reasonable correspondence between the models and experiments is a strength.

The cancellous architecture was approximated with hexahedral finite elements. Use of hexahedral elements is advantageous for mesh creation and mesh adaptation during the remodeling iterations. However, the surfaces are not smooth, and errors in local strain along the surfaces of trabeculae may affect the remodeled architecture. The exponential osteocyte sensing function used in the remodeling algorithm served to smooth the mechanical stimulus and reduced the errors in the strain field due to the discretization of the architecture.

To our knowledge, this study is the first to simulate an entire *in vivo* experiment with known, controlled loading including an inhomogenous material model and reporting changes in both histomorphometry and mechanical properties of the control and loaded specimens. Earlier three-dimensional simulations made qualitative comparisons to *in vivo* experimental data but did not simulate specific experiments (Adachi et al. 2001; Mullender et al. 1998; Tsubota et al. 2003). When *in vivo* mechanical loading experiments were modeled, previous simulations did not include mechanical feedback (Schulte et al., 2011) or only used homogenous material properties and did not simulate control specimens or measure the change in mechanical properties with loading (Schulte et al., 2013). More recently, computer simulations of trabecular bone adaptation to several loading and treatment regimens accurately captured changes in static histomorphometry measured *in vivo* (Levchuk et al., 2014). However, a homogenous material model was used, and the effects of remodeling on mechanical properties were not examined. While different simulation parameters were implemented across these distinct models, taken together, these studies show the improved capability of computer simulations to capture cancellous functional adaptation. True predictive experiments are now needed.

In summary, we have implemented a surface-based cancellous bone adaptation algorithm and compared simulated results with an *in vivo* loading experiment. Applied loading significantly altered histomorphometry and apparent modulus in the *in vivo* experiment that was captured in simulated adaptation. Differences in tissue-level strain distributions from 1 MPa of applied pressure between control and loaded specimens were also similar between the experimental and simulated adaptation specimens. Variations in individual specimen behavior between the two simulation methods demonstrated the importance of the material model in adaptation simulations. The inhomogenous material model that included 15% less stiff tissue on the surface better matched the experimental results. The cell-based remodeling approach of Mullender et al. (1994) used for the simulations was appropriate for modeling the *in vivo* experiment and examining the effect of mechanically-regulated adaptation on cancellous architecture and apparent modulus.

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Figure 1. Two-dimensional simulation of tissue-level remodeling of cancellous bone. Initial architecture adapts to similar loads applied at 0 or 30 degrees, resulting in trabecular struts aligned with load direction. Adapted from Mullender & Huiskes (1995).

Figure 2.

Flowchart for computational tissue-level cancellous bone remodeling. The initial cancellous architecture was based on microCT scans of the contralateral control limbs from 4-week *in vivo* loading experiments. In the experiment, limbs were loaded at 1 MPa for 50 cycles/day, 5 days/week (van der Meulen et al. 2006). The scans were coarsened and directly converted into finite element meshes. Loads were applied and adaptation was simulated using the osteocyte regulatory approach of Mullender et al. (1994). The final morphology predicted by the simulations was compared to the results from the *in vivo* experiment.

Figure 3. Schematic of *in vivo* loading device attached to distal femur of the rabbit, and representative cancellous specimen isolated from the volume of interest beneath loading core.

Figure 4.

Boundary conditions for adaptation simulating control and loaded cases. Control boundary conditions compressively loaded specimens in the anterior and distal directions simulating normal cage activity. Loaded specimens received an additional 1 MPa pressure on the lateral surface simulating the applied pressure from the loading device during the *in vivo* experiment.

Figure 5. Paired histomorphometry (individual, paired values) for experimental and simulated cancellous bone adaptation. Experimental data from four week *in vivo* loading experiment. Simulations modeled adaptation to control and loaded boundary conditions using initial morphology of control specimens from adaptation experiments.

Figure 6.

Both simulations predicted the increase in the apparent modulus in the loading direction following adaptation to *in vivo* loading. Individual values shown and pairs indicated. Experimental data from four week *in vivo* loading experiment. Simulations modeled adaptation to control and loaded boundary conditions using initial morphology of control specimens from adaptation experiments.

Figure 7.
Effect of applied loading on low, medium, and high tissue level minimum principal strains (mean + standard deviation) for experimental and simulated cancellous bone adaptation. *
p < 0.05 between control and loaded specimens

Table 1

Both simulations predicted increases in the BV/TV and MIL-3 of cancellous bone with *in vivo* loading, similar to the significant changes measured experimentally. The values of BV/TV, Tb.Th and MIL-3 predicted by the homogeneous simulations were lower than those predicted for a heterogeneous tissue modulus. Mean (SD) histomorphometry of loaded and control cancellous bone specimens during *in vivo* experiment and simulated bone remodeling.

	Experiment		Sim _{surface}		Sim _{homogeneous}	
	Control	Loaded	Control	Loaded	Control	Loaded
BV/TV (%)	19.6 (5)	33.2 (10) *	25.9 (2)	30.8 (2) *, +	22.1 (1)	25.4 (1) *
Tb.Th (µm)	155 (20)	226 (40) *	241 (20)	275 (40) *, +	226 (20)	248 (30)
Tb.Sp (µm)	654 (140)	619 (170)	760 (90)	779 (120)	829 (30)	870 (140)
MIL-3 (µm)	184 (20)	267 (50) *	243 (30)	292 (40) *, +	230 (20)	266 (40) *
Architectural Anisotropy	1.51 (0.1)	1.44 (0.2)	1.49 (0.1)	1.29 (0.1) *	1.46 (0.1)	1.28 (0.1) *

* p < 0.05, Control vs Loaded.

+ p < 0.05, Sim_{surface} Loaded vs Sim_{homogeneous} Loaded.

Table 2

Both simulations predicted increases in the BV/TV and MIL-3 of cancellous bone with in vivo loading, similar to the significant changes measured experimentally. The values of BV/TV, Tb.Th and MIL-3 predicted by the homogeneous simulations were lower than those predicted for a heterogeneous tissue modulus. Mean (SD) histomorphometry of loaded and control cancellous bone specimens during in vivo experiment and simulated bone remodeling

Apparent Modulus	Control	Loaded
Experiment	163.8 (103)	444.3 (260) *
Sim _{surface}	175.1 (102)	583.5 (106) *
Sim _{homogeneous}	136.8 (59)	421.9 (89) *

*
p < 0.05, Control vs Loaded.