Modeling the Long Term Effects of Alendronate on Bone Mass Preservation of
the Femur with Articular Surface and Total Hip Replacements

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by
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ABSTRACT

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Calculating femoral bone density changes after hip arthroplasty is of interest to researchers and clinicians for predicting the longevity of the prosthetic implant and the surrounding bone. Recently clinicians have been administering bisphosphonate drugs in an attempt to reduce the bone resorption due to stress shielding caused by these implants. Current strain-adaptive computational models with bisphosphonate treatment don't predict the long term effects or look at treatment with hip resurfacing implants. The main goal of this study was to create and validate a computer model of the human femur incorporating a bone remodeling algorithm based on biological remodeling processes and bisphosphonate drug treatment. A secondary objective was to then create various bisphosphonate drug treatment scenarios and evaluate differences in bone density, damage, and activation frequency. Experimental studies were used to validate the model and the effects of bisphosphonates. A finite element model created from a CT scan of a cadaveric femur, a bone remodeling algorithm, and a bisphosphonate algorithm were incorporated into the model with loading conditions representative of walking and stair climbing. The model was allowed to evolve from an initial state of homogenous density to a steady state

form with a density similar to that of the femur. Reduced loading representative of decreased muscle forces were applied to the steady state form to simulate preoperative conditions of a patient with hip osteoarthritis. Both a femoral hip resurfacing component and an uncemented, tapered stem were then integrated in the computer model representative of a postoperative state. Bisphosphonate treatment was applied to both the preoperative and postoperative states in several scenarios after untreated simulations. Bone loss was predicted over a six year postoperative period for both implants and varying treatments. Femoral bone loss in bisphosphonate treatment scenarios matched results seen clinically. Bone volume fraction (BVF) showed little change between one year preoperative to one year postoperative Alendronate treatment and one year postoperative Alendronate treatment for a specific implant type. Both treatment scenarios increase the BVF over no treatment. Pretreating with Alendronate appears to help against femoral neck fracture. This study successfully created a three-dimensional finite element model able to simulate long term effects of the remodeling process in bone with Alendronate treatment. The results show an importance of treatment timing for both types of implants especially when potentially requiring a revision surgery.

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1. Introduction

1.1. Purpose

A primary concern following total hip arthroplasty is the bone loss in the proximal femur [1, 2]. Part of the bone loss is due to stress shielding, where the implant takes up a majority of the load applied and transfers it to distal bone, creating lower than normal strains on the surrounding bone in the proximal aspect. This bone experiencing lower strain remodels, and decreases the bone density for that area increasing the periprosthetic fracture risk and contributing to implant loosening [3-5]. This decrease of bone density means less bone stock and other options for revision surgery [6].

Newer uncemented, tapered, titanium stems have shown less bone loss over long-term than similar uncemented straight stems [7, 8]. In addition, metal-on-metal hip resurfacing retains bone stock in the proximal aspect of the femur, making it easier to convert to a total hip arthroplasty in revision surgery [9]. This is especially important for younger patients with hip osteoarthritis who may need several revision surgeries. Resurfacing arthroplasty is also believed to maintain a more natural loading state in the proximal femur. Recently a group of drugs called bisphosphonates have been administered in conjunction with hip arthroplasty [10, 11]. Normally used to help prevent bone mineral density loss in osteoporosis, bisphosphonates are being used in an attempt to prevent the bone loss in the proximal aspect of the femur after hip arthroplasty.

Computer models that accurately simulate bone remodeling could be useful in comparing bone loss following arthroplasty surgeries with

bisphosphonate treatment because it's not always possible to accurately measure bone mass density changes clinically. Existing computer models don't incorporate the underlying biological process of a basic multicellular unit that is responsible for bone's adaptation in response to environmental loading changes while looking at the long term bisphosphonate effects. Existing models also do not look into modeling the effects with the use of a surface replacement arthroplasty.

The goal of this project is to integrate bisphosphonate drug treatment into a computer model with a bone remodeling algorithm based on the biological remodeling process to explore the problem of bone loss following hip arthroplasty. The objectives of this study are to: (1) validate the implementation of a previously developed computer model into the current study, (2) implement bisphosphonate code into the model, (3) perform and validate long term computer simulations to study the mechanisms of bone loss in the proximal aspect of the femur for an uncemented tapered stem and a resurfacing component under the effects of Alendronate, and (4) evaluate different Alendronate treatment scenarios.

1.2. Bone Structure

Bone is a dynamic tissue made of collagen, water, hydroxyapatite mineral, proteoglycans, and noncollagenous proteins that constantly adjusts to its mechanical and physical environment through changes in the microscopic architecture and composition [12]. The nonmineralized space in bone contains marrow which is a tissue composed of nerves, blood vessels, and other cells.

The remaining bone is mineralized and split into two different types determined by porosity. Most bone tissue is either very low porosity or very high porosity. The low porosity bone is known as compact bone while the high porosity is known as trabecular bone.

Compact bone forms the cortex for long bones and has a porosity of 5-10%. The pores are categorized as either Haversian canals, Volkmann's canals or resorption cavities. Haversian canals align with the long axis of bone and contain the nerves and capillaries. Volkmann's canals also contain capillaries, and are transverse canals which connect Haversian canals to each other and to the outside of bone. Resorption cavities are the spaces temporarily made by osteoclasts during bone remodeling.

Trabecular bone is normally found at the end of long bones as well as flat bones and cuboidal bones and has a porosity of 75-95%. The pores are filled with marrow and the bone matrix forms struts called trabeculae that often seem randomly arranged. Important features of both types of bone can be seen in

Figure 1-1.

Figure 1-1 shows important features of a typical long bone [12].

Both types of bone contain two major bone tissue types. Lamellar bone is highly organized and slow forming bone, consisting of layers called lamellae which create a matrix of collagen fibers and minerals. This calcified matrix surrounds the Haversian canals in concentric rings which is also called an osteon. Woven bone is poorly organized and quick forming bone where the matrix of collagen fibers and minerals is more randomized.

1.3. Bone Remodeling

Within the cortex of bone, basic multicellular units (BMUs) initiate osteonal bone remodeling. BMUs are the coupling of osteoclasts and osteoblasts working in teams with a central Haversian canal providing the pathway for capillaries to supply needed nutrients which can be seen in **Figure 1-2**. BMUs are activated by a stimulus such as damage or disuse. Osteoclasts are multinucleated cells formed from monocytes that resorb bone. The osteoclasts demineralize bone with acid and dissolve collagen with enzymes [12]. Normally it takes about three weeks to resorb the bone perpendicular to the path of the BMU. Osteoblasts are mononuclear cuboidal cells that differentiate from mesenchymal cells. Osteoblasts produce the organic portion of the bone matrix [12] and refilling the resorption space takes about three months but may take up to six months to completely mineralize. During the remodeling process, osteoblasts can be buried inside cavities, called lacunae, in the newly formed bone and can become osteocytes. Osteocytes communicate to each other and other osteoblasts through tunnels called canaliculi. The whole remodeling process maintains existing bone or changes the porosity, and can realign the trabeculae of trabecular bone.

Figure 1-2 shows the coupling action of both osteoclasts and osteoblasts which make up a BMU [13].

1.4. Osteoporosis

Osteoporosis is defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk [14]. Most notably, the vertebra, hip and wrist bones become porous and weak, making them susceptible to fracture after minimal forces or pressure. The underlying mechanism is an imbalance between an increased resorption of bone and decreased formation of bone, and normally presents itself in low trauma fracture, backache, height loss, spinal deformity, or in radiological bone mineral density [15]. An example of bone microarchitectural deterioration can be seen in **Figure 1-3**.

Figure 1-3 shows scanning electron micrographs to show the structure of L3 vertebra in a 31 year old woman (top) and in a 70 year old woman (bottom) [15].

Some risk factors of osteoporosis include sex and race, age, early menopause, family history of osteoporosis, lack of estrogen, poor calcium intake, smoking, heavy alcohol or caffeine consumption, and a lack of exercise [16-18]. Women are at most risk due to a lower peak of bone mass, an increased bone loss at menopause, and a higher life expectancy [15]. The risk for a fracture

increases dramatically with age, decreasing the lifespan and increasing the mortality rate [15].

The treatment of osteoporosis is based upon bone mineral density in the spine and proximal femur using a dual energy x-ray absorptiometry (DXA). To be diagnosed with osteoporosis, a bone mineral density of 2.5 or more standard deviations away from the normal peak bone mass must be observed. DXA is used primarily because it is fairly inexpensive, involves low radiation exposure, and can measure bone density accurately in areas where fractures are the most common [17].

Ideally, people want to prevent osteoporosis by optimizing their skeletal bone mass throughout life, and to keep bone mineral density levels as close to peak levels as possible. Doing this can be accomplished by taking actions aimed at the risk factors outlined above. Therapeutic options now exist for those who are diagnosed with osteoporosis. Some of these options include bisphosphonates, raloxifene and hormone replacement therapy, strontium ranelate, and parathyroid hormone peptides.

1.5. Bisphosphonates

Bisphosphonates are related to pyrophosphate in which the oxygen bridge is replaced by a carbon with various side chains. They were developed and used in the treatment of bone disease after being discovered that they effectively control calcium phosphate formation and dissolution as well as mineralization and bone resorption in vivo. Bisphosphonates bind strongly to the bone mineral, hydroxyapatite, which explains the mode of action for the drug. Deposits form

where bone mineral is exposed to surrounding fluids, especially areas of bone formation and resorption. The release of bisphosphonates in the body is primarily when the bone is being resorbed again. Otherwise, due to the chemical backbone of bisphosphonates (P-C-P group) being enzymatically resistant seen in **Figure 1-4**, the body is unable to metabolize the compound and they are excreted by the kidneys without alteration. The charge and the size of the bisphosphonate limits the penetration through different cellular membranes [19].

Figure 1-4 shows the common bisphosphonate chemical backbone.

Effects of bisphosphonates can be separated into several categories. At the tissue level, bisphosphonates reduce bone turnover by decreasing both bone resorption and bone formation. Since there is a negative balance at each BMU, a decrease in the turnover leads to a decrease in bone loss. There isn't evidence of reduction of osteoblast activity at each site however, so the amount of bone formed at each BMU is not decreased, but increased. Also, after a decreased turnover, newly formed bone has more time to complete mineralization since there's less chance of it being remodeled. Both these create an increase in the amount of bone in humans. At the cellular level, the final target of bisphosphonates is the osteoclast. Different ways of reducing

resorption by the osteoclast include inhibition of recruitment to the bone surface, inhibition of activity at the bone surface, shortening of the lifespan, or alteration of the bone mineral in ways which reduce the rate of dissolution. At the molecular level, it's possible bisphosphonate action on a cell surface or bisphosphonate uptake by the cell interacts with an enzyme or other molecule, affecting cellular metabolism [19].

The potency of bisphosphonates depends on the side chains connected to the backbone, and typically are separated into either a nitrogenous groups or a non-nitrogenous group. Those with a nitrogen side group are considered to be the most potent. One example of a potent bisphosphonate is Alendronate (commercially known as Fosamax). Alendronate ($C_4H_{12}NO_7P_2Na \cdot 3H_2O$) is considered a first line option and normally taken orally when fasting, however it can be taken intravenously as well [15]. Some adverse effects include upper gastrointestinal intolerance [20] as well as auditory, visual, and olfactory hallucinations [21]. The chemical structure of Alendronate can be visualized in

Figure 1-5.

Figure 1-5 shows the chemical formula for Alendronate

1.6. Osteoarthritis

Osteoarthritis is the most common type of arthritis, estimated in 12.1% of the adult population and about 20% of people above the age of 65 will be at high risk in the year 2030 [22]. Before 1986 osteoarthritis was regarded as a degenerative disease involving articular cartilage and subchondral bone but it has become viewed as a syndrome with many complex etiologies [23]. Osteoarthritis is currently characterized physiologically by focal areas of damage to the articular cartilage, changes in the subchondral bone, as well as synovitis and capsular thickening [23]. Radiographs help to see the joint space, as seen in **Figure 1-6**, and changes of subchondral bone but people with severe radiographic change can still be symptom free. Symptoms normally include pain, stiffness after activity, popping, and swelling of the joint. Women are at higher risk than men and the risk increases with age as well. Therapies for osteoarthritis include lifestyle modification and pharmacological treatment before the long term solution of a joint surgery [22, 23].

Figure 1-6 shows a radiograph of a patient with hip osteoarthritis.
<http://chicopmr.org/pain/images/hip-xray-osteoarthritis.jpg>

1.7. Hip Arthroplasty

Hip arthroplasty is the artificial replacement of the joint which connects the pelvis to the femur. In order to recreate the ball and socket joint, both the femur and acetabulum have parts surgically removed. On the femur, the head and part of the neck is removed in order to fit a metal stem into the medullary canal which can be seen in **Figure 1-7**.

Figure 1-7 shows the removed parts of the femur to incorporate a total hip replacement [24].

On top of the stem sits a metal ball, normally composed of cobalt chromium, to replicate the femur head. A small part of the acetabulum is removed in order to fit a metal cup lined with ultra-high molecular weight polyethylene (UHMWPE) for the replicated femur head to fit into. This cup can be seen in **Figure 1-8**.

When early metallic implants made of cobalt chrome started to be used, femur designs used bone cement made of polymethylmethacrylate (PMMA) to help secure the fixation. While the cement did initially aid in fixation of the

femoral implant, the interfaces of the cement with both bone and implant failed, leading to high loosening rates [25] causing further damage to the bone.

Due to the high loosening rates, uncemented implants were used more. Using a larger diameter stem with a press fit into the bone created a strong fixation and solved the problem with the bone cement. Unfortunately, the new design structure of the stem with increased size and high stiffness caused stress shielding. To address the high stiffness, more flexible titanium stems with a proximally porous coating to allow for bone to grow into the stem were used and determined to lead to less bone resorption compared to the cobalt chrome with extensive porous coating [26, 27]. The stem used in this study, seen in **Figure 1-8**, is an uncemented, tapered, titanium stem which has shown less bone loss long term than similar uncemented straight stems.

Even with improvements in fixation and in the bearing of surfaces, total hip arthroplasty did not have encouraging results for all patients. Articular surface replacement became popular due to a larger demand from younger, more active patients [28] for the preservation of bone stock as well as less stress shielding in the proximal femur because of the possible need for revision operations [29]. Resurfacing the femur involves removing part of the femur head and covering it with a hemispherical shell with a short stem as seen in **Figure 1-9**. Early material for articular surface replacement by Smith-Petersen tried using glass, due to its inertness, and viscaloid, which ended up causing too much foreign body response [30] before a cobalt chrome alloy was introduced later. Resurfacing in the 1970's started using a metal stem with a polyethylene

acetabular cup but long term studies showed high failure rates [29] due to loosening which caused wear debris, initiating a foreign body response [31]. Within the past 10 years, resurfacing has become even more popular due to better manufacturing techniques [32]. The new components use metal femoral and acetabular parts, reducing the wear and failure rates [32], however there are some concerns about the implantation procedure and fracture risk of which the mechanism is unknown [33]. It also is not possible to measure bone mineral density changes within the femoral head and certain regions of the femoral neck using DXA scans. These metal on metal implants have demonstrated short term success [29] but much about the wear debris and long term success are still unknown.

Figure 1-8 shows the Biomet Taperloc stem (left) and Depuy ASR femoral component (right) that were used in this study. Radiographs of an implanted hip resurfacing component (top right) and an uncemented, tapered stem (bottom right). Acetabulum components can be seen in both radiograph images [34].

Figure 1-9 shows the resurfaced femur (top) with an ASR implant (bottom) [24].

Recently, bisphosphonates like Alendronate have been used with hip replacements to help against stress shielding. The bisphosphonates are used in order to preserve the bone mass of the femur, however their anti-resorptive action may lead to increases in fatigue microdamage.

1.8. Previous Remodeling Simulations

Many algorithms to explain the architecture and properties of bone have been developed based on the observations by Wolff which resulted in his hypothesis known today as “Wolff’s Law” [35]. Wolff states that bone has the adaptive property to change its architectural shape and external form in response to mechanical stimuli, limited to certain mathematical rules. Since modeling rates slow down significantly more compared to remodeling rates when reaching skeletal maturity [12], most algorithms focus on predicting bone changes due to remodeling.

Cowin et al. created an algorithm for the adaptive process of bone describing it as an elastic material which adapts structurally to an applied loading [36]. This model maintains a level of bone strain through either modeling or remodeling processes to adjust the density of cortical bone. Taking this adaptive elasticity model further, Huiskes created an algorithm that would model or remodel bone in order to maintain a constant level of strain energy density [37]. A schematic of this algorithm can be seen in **Figure 1-10**.

Figure 1-10 shows a schematic representation of the adaptive remodeling program integrated with finite element method (FEM) code. The feed-back control variable is the difference between the actual strain energy density (SED), the apparent strain energy density U , and homeostatic SED, U_n .

Implementing this algorithm with a prosthesis used in total hip arthroplasty, the effects of stress shielding on bone loss based upon the loaded implant was modeled two-dimensionally. They created a set threshold for homeostatic strain energy density, and an increase or decrease outside this range results in bone gain or loss, respectively. The two dimensional model then incorporated these effects by modeling straight stem implants of increasing diameter subjected to loading in a straight bone shaft. The model representation created was adequate enough to describe the three-dimensional structural integrity of the bone. The study also helped predict the effects of stem rigidity and degree of fixation related to stress shielding as can be seen in **Figure 1-11**.

Figure 1-11 shows predicted bone loss around varying stem sizes using the strain adaptive algorithm created by Huiskes et al. [37]

Continuing with this work, Huiskes et al. [38] looked at a two-dimensional model to describe the post-loosening mechanical behavior of surface replacements. The cup was modeled with linear beam elements in the frontal plane and spanning beam elements in the medial and lateral sides that corresponded to a solid model showing equivalence. A bi-linear stress-strain behavior, low elastic modulus, and gap elements were used to model the fibrous tissue. The results indicate that high failure rates are correlated indirectly with the implant design to implant loosening and the propagation of bone resorption and fibrous tissue formation. This suggested that the ability of these implants to obtain a stable post-loosening configuration is an important design criterion for the long-term survival.

Furthering the algorithm use, Huiskes et al. [39] looked at the relationship between stress shielding and bone resorption around total hip stems and the effects of flexible materials in a three-dimensional model. They found flexible stems reduce stress shielding and bone resorption but they increase the proximal surface stresses. The findings also supported the hypothesis that resorption processes are an effect of bone adaptation to stress shielding and individual variations in bone reactivity and mechanical bone quality may account for the individual differences found in experiments.

Another algorithm created by Beaupre et al. [40] determined the net resorption and formation by taking the difference between the stimulus and the tissue attractor state. The attractor state is the level of daily loading necessary to maintain bone at a known density. They use a time dependent approach for modeling and remodeling, taking into account the amount of bone surface area both osteoclasts and osteoblasts can work. The model uses local signals which don't necessarily lead toward global optimization. Each bone site optimizes its own environment instead of towards the structure as a whole. This means during normal aging, local changes made by modeling and remodeling never stop, indicating the model never converges just like actual bone. However, the rate of change will diminish as each site reaches the attractor state. A diagram of their remodeling code can be seen in **Figure 1-12**.

Figure 1-12 shows a block diagram representation of bone remodeling with multiple feedback loops created by Beaupre et al. driven by local, not global signals [40].

A three-dimensional, iterative model by Van Rietbergen et al. [41] used the site formulation theory as well. This theory assumes the treated bone with an implant attempts to normalize its stress-strain patterns to the same value as the untreated bone [37]. They also incorporate Martin's theory [42] that says bone apposition and resorption can occur only at free bone surfaces. Bone mass is regulated by elastic strain energy per unit mass, and when the difference between the treated bone and untreated bone reaches a certain threshold, no remodeling takes place and the model converges. More recently, Gupta et al. [43] uses this adaptive bone remodeling theory to assess the short term risk of femoral neck fracture (1-2 years) and long term risk of failure of fixation (5 years) of a cemented resurfacing femoral head. Results showed strain shielding in the femoral head with a 50-90% reduction in bone density in the superior femoral head region and elevated strains of 0.50 – 0.80% generated in the superior

femoral neck. These high strains only occurred in a small fraction of bone indicating a low risk of fracture post-surgically and the strains were considerably reduced after bone remodeling leading to an even smaller chance of fracture.

Peter et al. [44] takes a remodeling algorithm and adds in bisphosphonate treatment. The model developed takes into account bone inhomogeneity and bone transverse isotropic symmetry by using relative density and an anisotropy tensor. For this short term simulation, the bone density is linked to the mechanical stimulus in a linear relation and the tensor is kept constant. To simulate the drug, the resorption parameters are affected with the formation parameters kept constant.

1.9. Remodeling Algorithm

The remodeling algorithm used in this study was developed by Hazelwood et al. [45] and models the activity of basic multicellular units (BMUs) responsible for resorbing and depositing bone through activation by both disuse and fatigue microdamage. A schematic of this algorithm can be seen in **Figure 1-13**.

Figure 1-13 shows a schematic representation of the bone remodeling algorithm developed by Hazelwood et al. Remodeling is activated by disuse and damage and the porosity is determined from the activation frequency history [45].

The model can adapt its porosity over time in local areas of disuse or damage throughout the entire bone since it simulates BMU behavior. In the remodeling code, the rate change in porosity ($\dot{p}$) is the difference between the resorbing and refilling rates.

$$\dot{p} = Q_R N_R - Q_F N_F \quad (1)$$

The resorption rate ($Q_R N_R$) is the product of the resorption rate per BMU (Q_R) and the number of resorbing BMUs/area (N_R). Similarly, the refilling rate ($Q_F N_F$) is the product of the refilling rate per BMU (Q_F) and the number of refilling BMUs/area (N_F). The number of BMUs resorbing and refilling varies as a

function of BMU activation frequency. The resorption ($Q_R = A/T_R$) and refilling

($Q_F = A/T_F$) rates are calculated by the average area resorbed or refilled per

BMU (A) divided by the resorption or refilling time period (T_R, T_F respectively).

Net bone resorption occurs during disuse and initially during microdamage

removal. Activation frequency (f_a) is defined as the sum of the activation

frequency due to disuse ($f_{a(disuse)}$) and the activation frequency due to damage

($f_{a(damage)}$), multiplied by the specific surface area (S_A). The specific surface

area is the free internal surface area per unit volume that's available for

remodeling and uses normalized values between 0 and 1.

$$f_a = (f_{a(disuse)} + f_{a(damage)}) S_A \quad (2)$$

Damage (D) is defined as a crack length per area of bone. The rate of

fatigue damage is described as the difference in fatigue damage formation ($\dot{D}_F$)

and removal ($\dot{D}_R$) rates.

$$\dot{D} = \dot{D}_F - \dot{D}_R \quad (3)$$

The fatigue damage formation rate ($\dot{D}_F$) is assumed to be proportional to the product of the strain (s_i) raised to a power (q) and the loading rate (R_{Li}) summed over n loading conditions [46].

$$\dot{D}_F = k_D \sum_{i=1}^n s_i^q R_{Li} = k_D \varphi \quad (4)$$

In this equation, φ represents the summation term and is known as the mechanical stimulus and k_D is the damage rate coefficient. The exponent q balances the relative importance between strain magnitude and the number of loading cycles and in the case of this study, a value of 4 is used based on previous research [40, 45, 46].

If we assume damage and BMUs are random throughout the bone, then the fatigue damage removal rate ($\dot{D}_R$) would equal the product of damage (D) and the area fraction resorbed per day ($f_a A$) where A is the cross sectional area of a BMU. However in the model, it is assumed damage actually initiates BMU activation which means the damage removal rate would be greater than random remodeling. Since the rate would be greater, a specificity factor (F_s) was included.

$$\dot{D}_R = D f_a A F_s \quad (5)$$

Disuse for the model is defined as a level of mechanical stimulus (φ) below the equilibrium stimulus (φ_e). To model the effects of disuse, BMU activation frequency is increased when below a given stimulus threshold and the refilling rate is reduced as well [47]. The relationship between activation frequency due to disuse and activation frequency due to damage are assumed sigmoidal which enables activation frequency calculation. Once calculated, the number of resorbing and refilling BMUs can be determined, followed by the rate of change in porosity (Eq. 1).

1.10. Bisphosphonate Algorithm

The bisphosphonate effects for this study are modeled according to code implemented by Nyman et al [48, 49]. This treatment reduces activation frequency [19, 50-52] as well as the resorption cavity size [19, 51-53] to account for Alendronate. The potency of suppressing the activation frequency is a function of the number of resorbing BMUs.

$$(6) \quad P = P_{max}(1 - e^{-\tau_s N_R})$$

where P_{max} is the maximum suppression coefficient, τ_s is the rate of suppression coefficient, and N_R is the number of resorbing BMUs. Both variables reflect the dosage and structure of the bisphosphonate. Nyman incorporated this bisphosphonate code into a two-dimensional model for knee arthroplasty to investigate the long-term effects to minimize proximal bone loss and found bisphosphonate treatment to slow the rate of bone loss by 42% after one year as seen in **Figure 1-14** [48].

Figure 1-14 shows that the rate of bone loss after total knee arthroplasty below the tibial tray is slower when bisphosphonate effects are simulated than without treatment [48].

1.11. Finite Element Analysis Modeling

Algorithms can be integrated into finite element models that have a variable modulus as a function of bone density because changes in strain drive the remodeling process. Previously, studies have been performed to examine postoperative changes in femoral bone density to evaluate effects of different muscle groups on the remodeling process as well as changes following hip arthroplasty [43, 54, 55]. Deuel improved the current three-dimensional femur models by implementing the remodeling algorithm by Hazelwood et al. in order to incorporate the biological mechanism of remodeling to study changes in bone density following total hip and hip resurfacing arthroplasty procedures.

The previous simulations using this algorithm were performed with a two-dimensional model by Hazelwood and Mizumoto [56]. The model was created

from a radiograph and used joint reaction and abductor muscle forces which originally started in a homogenous bone density distribution. With the remodeling algorithm, the model was allowed to evolve until reaching a steady state condition. Bone loss predictions by the model were consistent with the measurements clinically found after surgery.

Similarly, Nyman et al. [57] incorporated the remodeling algorithm into a two-dimensional finite model of the tibia to investigate bone loss following total knee arthroplasty (TKA). The model predicted most bone loss to happen during the first six months following surgery which was also consistent with clinical findings.

1.12. Current Model

The femur model created by Deuel et al. [34] was created from a CT scan, using a LightSpeed QXi CT scanner, (GE Healthcare, Milwaukee, WI) of a male cadaveric femur with soft tissue removed. Mimics (Materialise USA, Ann Arbor, MI) was used to create the initial two-dimensional surface mesh from the scan which was then imported into Patran (MSC Software Corporation, Santa Ana, CA) and converted into a three-dimensional mesh using second order tetrahedral elements. A convergence study was then performed using a simplified loading scheme of hip joint and abductor forces to compare principle strains and displacements and enable an appropriate mesh density selection. The finite element solver Abaqus (Simulia, Providence, Rhode Island) was used for all analyses.

Two similar meshes of the native femur were created to allow the removal of elements for both the resurfacing implant and tapered stem. For the native femur used in the tapered stem model, the finite element mesh consisted of 45,691 elements and 63,986 nodes and for the resurfacing implant the mesh consisted of 29,175 elements and 41,723 nodes. This original model consisted of a solid mesh with elements having homogeneous material properties based on experimentally measured values of cortical bone.

Three load cases during the single stance phase of walking and stair climbing were used in the model for hip joint contact and muscle forces. These cases included the loading during heel strike and toe-off phases of normal walking and maximum forces during stair climbing. Normal activity levels of patients with normal functioning total hip replacements included 5000 daily loading cycles during walking and 20 daily cycles for stair climbing. Using a body weight of 836 N based on the weight of a typical patient undergoing total hip arthroplasty surgery, magnitudes and directions of hip joint and abductor muscle forces were calculated to determine appropriate joint loading angles during walking and stair climbing as can be seen in **Figure 1-15**. Only the gluteus medius, gluteus minimus, adductor longus, adductor brevis, psoas, vastus lateralis, and the vastus medialis muscle groups were used because they have previously demonstrated to be the most significant influence on strain distribution and remodeling. The distal region of the femur model was constrained rigidly above the femoral condyles.

<i>Force</i>	<i>Force Magnitude at Load Case (% body weight)</i>		
	I	II	III
1. Hip joint	250	250	270
2. Gluteus medius	84	84	101
3. Gluteus minimus	41	40	40
4. Vastus lateralis	76	-	101
5. Vastus medialis	-	-	202
6. Psoas	-	19	-
7. Adductor brevis	10	10	10
8. Adductor longus	23	23	23

Figure 1-15 shows anterior (a) and posterior (b) views of hip joint contact and muscle force magnitudes applied to the model as a percentage of body weight (BW = 836 N) for three separate load cases: I. heel-strike phase of walking; II. toe-off phase of walking; III. stair climbing. Force application points represent the approximate centers of distributed loads [34].

The hip replacement models used are a 49 mm resurfacing femoral component (ASR, DePuy, Warsaw, Indiana) and an 11 x 142 mm uncemented, titanium, tapered femoral stem with a 32 mm cobalt chrome head (Taperloc, Biomet, Warsaw, Indiana). With the remodeling algorithm, the models evolved under loading from its initial homogenous material state until the remodeling porosity, damage, and activation frequency reached steady state values. Data

from a comparative experimental study between hip resurfacing versus total hip arthroplasty were then used to validate the computational finite element model [24].

After validation, the model simulated reduced loading conditions due to pain and loss of function because of hip osteoarthritis. Hip joint contact and muscle force magnitudes were decreased by 6% and the number of loading cycles was reduced by 20% as well. One year of this reduced loading was used to describe the preoperative state due to hip osteoarthritis. Following the preoperative state, either the hip resurfacing or tapered stem components were introduced to the model. Reduced loading continued for 3 months postoperatively and then returned to normal but with a continued reduction in loading cycles by 10% until one year postoperatively. The remodeling simulation was run for a total of 2 years postoperatively and changes in bone density were compared between the resurfacing and tapered stem implants using seven regions of interest defined by Gruen et al. which can be seen in **Figure 1-16** [25].

Figure 1-16 shows the seven sections around the femoral component for evaluation [25].

Deuel et al. found a 5% mean loss in bone density across all Gruen zones (GZ) over the one year preoperative period. Implantation of the total hip replacement showed bone loss most prominent in region 7 with a 24% loss of bone volume fraction (BVF) at two months and remained approximately 25% after two years. Damage levels decreased rapidly during the initial postoperative period and activation frequency increased, indicating strain shielding. Bone resorption was also observed in zones 6 and 7 and stabilized at about two years. A reduction in BVF of 8% was observed in region 5 and damage levels increased over the two years suggesting increased remodeling from damage. Reductions in BVF of 4% or less were observed in all the other zones. Changes in the BVF

over the two year period for the total hip replacement can be seen in **Figure 1-17**.

Figure 1-17 shows the percentage change in BAF (bone area fraction, equivalent to BVF assuming normal stereologic conditions [58]) versus postoperative time for the seven Gruen zones in the total hip replacement [34].

For the resurfacing implant, small amounts of transient bone loss occurred in all regions within the first two months and nearly returned to preoperative levels after two years. The maximum loss of BVF in all zones was about 2% or less. Reductions in bone density were most notable in the superolateral and inferomedial regions of the femoral head. The inferior region of the femoral neck showed a transient BVF loss with density decreasing rapidly in the first two months and then increasing over the next two years, but not returning to preoperative levels. Damage levels were high and still increasing, but at a decreased rate in this area. Changes in the BVF over the two year period for the articular surface replacement can be seen in **Figure 1-18**.

Figure 1-18 shows the percentage change in BAF (bone area fraction, equivalent to BVF assuming normal stereologic conditions [58]) versus postoperative time for the seven Gruen zones in the articular surface replacement [34].

Using this model and incorporating the bisphosphonate code can give a better understanding of the long term effects of the femur with both hip replacement and drug interactions. The aim of the experiment is to incorporate both of these effects into a user subroutine combined with the finite element model to compare changes in femoral bone density, activation frequency, and damage between types of hip implants as well as drug regimens. The trends this information will show can help physicians decide which type of hip replacement to use bisphosphonate drugs with and when to administer the drugs.

2. Methods

2.1. Model Recreation

For the current study, the first step was to recreate the finite element model simulation by Deuel et al. [34]. This model contained a user material subroutine (Appendix A) in Abaqus which allowed the model to adapt to different loading conditions mimicking how bone changes to its loading environment. The algorithm developed by Hazelwood et al. [45] models BMUs which are responsible for the resorption and formation of bone after being activated by both disuse and fatigue microdamage. This allows adaptation of porosity over time in localized areas of disuse or damage. Porosity in the model can be defined as the void volume fraction with bone volume fraction (BVF) equal to $1 - \text{porosity}$. Increases in damage and loading may result in increased porosity and decreased density, or BVF, during the lag period. Several small changes were made to the existing user material subroutine enabling Abaqus to run properly in our laboratory.

2.2. Model Incorporation and Validation

The model for this experiment included the implants described previously. The initial mesh was created from a CT scan of an intact cadaveric femur and a convergence study was performed to select the correct mesh density. Originally, the intact model was allowed to evolve under loading from its initial homogenous state until porosity, damage, and activation frequency reached steady state values, defined by a change of less than 5% over a period of 30 days. The steady state intact model was validated through clinical experimentation by Deuel

et al [34]. The steady state intact model then was subjected to reduced loading conditions lasting for one year, which resulted in the preoperative model. Next, either the resurfacing or total hip replacement was introduced to the model, resulting in the postoperative model. Load magnitudes were returned to normal after three months, but still with a slight reduction in loading cycles until one year after surgery. After recreating the preoperative and postoperative finite element models, we validated our current running simulation through Gruen zone comparisons to results obtained by Deuel et al [34] as well as those obtained clinically at one and two years.

2.3. Alendronate Code

Using the algorithm by Nyman et al. [49] as described previously (section 1.10), a maximum suppression coefficient ($P_{\max}$) of 1.0 and a rate of suppression coefficient (τ_s) of 5 reduces activation frequency by a percentage P . Adding in a reduction in the resorption area by 3/13 observed previously by Chavassieux et al [50], the complete Alendronate treatment was simulated, corresponding to 10 mg of Alendronate daily [48] or 70 mg weekly [59, 60]. Simulations with these values give similar results to that observed by dual-energy x-ray absorptiometry over 7 years in the spines of postmenopausal women who were treated with 10 mg of daily Alendronate [59].

2.4. Alendronate Treatment Scenarios

When implementing the Alendronate treatment, we wanted to look at differences in treatment times and the results following termination of treatment. Each simulation ran for a total of six years postoperatively for either the

resurfacing hip or total hip arthroplasty models and was compared to mean data from experimental studies. Six years was chosen in order to compare results with Arabmotlagh et al [59] for long term Alendronate effects. A list of the various treatment simulations can be seen in **Table 2-1**. These different treatments were then compared between each other, between the different types of implants, and between the non-treatment scenario by looking at differences in damage, activation frequency, and porosity at specific regions (the Gruen zones) of the femur. The main comparisons were between the postoperative models having no treatment, one year of treatment, and six years of treatment and between the models with one year of postoperative treatment with either no preoperative treatment or with a full year of preoperative treatment.

Table 2-1 shows the different treatment scenarios for preoperative and postoperative models. Treatment scenarios were used for both total hip and surface hip replacements. The main scenarios being compared are the postoperative results with a year of treatment for each preoperative model treatment.

Preoperative Model Treatment (1 year)	Postoperative Model Treatment (6 years total)
No Alendronate	Six years with no Alendronate
	Six years of Alendronate
	First year with Alendronate
One year of Alendronate	First year with Alendronate

2.5. Model Implementation

Models were run on a Dell Precision 490 (N-series) computer (Dell, Round Rock, Texas) with Red Hat Linux (Red Hat, Raleigh, North Carolina) using Abaqus version 6.7 (Simulia, Providence, Rhode Island). In order to run a postoperative model, a text file holding all the state variables is created from the last step of the preoperative model and is called for in the user material

subroutine to initialize the postoperative simulation. The code, created by Deuel et al, is shown in Appendix B. In order to extract results from our models we use two files in conjunction. The executable file reads in an .isv file that contains the model file where we want to extract results, the new file name containing the results, the starting and stopping steps we want to extract results from, and the list of elements in the desired Gruen zone that we want data from. The executable then takes all this information and formats data for activation frequency, porosity, and damage. This file also allows us to determine the step interval to extract from. The extracting executable file can be seen in Appendix C, and the .isv file can be seen in Appendix D.

3. Results

3.1. Validation

The reduced loading conditions representative of preoperative changes due to hip osteoarthritis resulted in a 1% mean bone density loss over all GZ over one year. Further loss of femoral bone density resulted after implementing the tapered stem into the model. The most prominent bone loss occurred in GZ 7, seen in **Figure 3-1**, with about a 24% BVF loss within two months, and remaining around 25% after two years.

Figure 3-1 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the total hip replacement validation run. The reference BVF baseline is taken from the day of surgery.

Damage levels for this zone initially decreased rapidly, seen in **Figure 3-2**, while activation frequency increased, seen in **Figure 3-3**, indicating an area of strain shielding.

Figure 3-2 shows the postoperative damage in the seven Gruen zones for the total hip replacement validation run.

Figure 3-3 shows the postoperative activation frequency in the seven Gruen zones for the total hip replacement validation run.

A reduction in BVF of about 8% could also be viewed in GZ 5. During this time period, damage levels in this zone continued to increase suggesting that the losses in density weren't due to stress shielding, but instead due to an increase of remodeling from damage removal in this area. All other reductions in bone density were significantly less in other regions, with a loss of 4% or lower in all other GZ. The distal end of the stem had slightly higher losses seen in GZ 3 and 4.

After implementing the resurfacing implant into the model a small amount of bone loss occurred over all GZ within the first two months following implantation, however bone density values nearly returned to preoperative levels by the end of the two year period with a maximum BVF loss under 2% for all GZ. These changes can be seen in **Figure 3-4**.

Figure 3-4 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the articular surface replacement validation run. The reference BVF baseline is taken from the day of surgery.

Comparing our results to clinical data, we validated our model at one and two year postoperative time. These studies all used dual energy X-ray absorptiometry (DEXA) to measure the small changes in bone mass. At one year, there were no apparent differences in the percent BMD change found when comparing our results to Nishioka et al. [61] seen in **Figure 3-5**. Visual inspections of the standard deviation results obtained by Nishioka et al. were used for this determination since the values were not given.

Figure 3-5 shows a comparison between BMD change results obtained clinically by Nishioka et al. [61] and our experimental data one year postoperatively for a THR. There were no apparent differences in any GZ.

Comparing to Nakamura et al, [62] after one year there were no significant differences in BMD changes after one year postoperatively following THR surgery in GZ 3, GZ 4, and GZ 5, but the model overpredicted the BMD changes in GZ 1 (p-value = 0.037), GZ 2 (p-value = 0.010), GZ 6 (p-value = 0.018) and GZ 7 (p-value = 0.003) as seen in **Figure 3-6**.

Figure 3-6 shows a comparison between BMD results obtained clinically by Nakamura et al. [62] and our experimental data one year postoperatively for a THR. There were statistical similarities in GZ 3, GZ 4, and GZ 5 and significant differences in GZ 1 (p-value = 0.037), GZ 2 (p-value = 0.010), GZ 6 (p-value = 0.018) and GZ 7 (p-value = 0.003).

After one year, there were no significant differences in the percent BMD change compared to the results of Arabmotlagh et al. [63] as seen in **Figure 3-7**.

Figure 3-7 shows a comparison between BMD change results obtained clinically by Arabmotlagh et al. [63] and our experimental data one year postoperatively for a THR. There were no significant differences.

Looking at results from Nakamura et al. [62] once again after two years postoperative, there were no significant differences in BMD changes after two years postoperatively following THR surgery in GZ 1, GZ 3, GZ 4, and GZ 5, but the model again overpredicted the BMD changes found in GZ 2 (p-value = 0.027), GZ 6 (p-value = 0.028), and GZ 7 (p-value = 0.039) which can be seen in **Figure 3-8**.

Figure 3-8 shows a comparison between BMD results obtained clinically by Nakamura et al. [62] and our experimental data two years postoperatively for a THR. There were statistical similarities in GZ 1, GZ 3, GZ 4, and GZ 5 and significant differences in GZ 2 (p-value = 0.027), GZ 6 (p-value = 0.028), and GZ 7 (p-value = 0.039).

Comparisons of the model results with those from literature confirm the validity of the model used in the current study. While there were significant differences in some regions between our experimental results and those of Nakamura et al, [62] the clinical data is almost fifteen years old. The model results were statistically similar to the results from the most current research groups. Looking at the values from these clinical experiments, the success with the newer clinical studies shows more bone being retained which could be attributed to the advancement of hip prosthesis in the last fifteen years. With current clinical results being similar to our computer simulated model, this allowed us to evaluate the long term effects of joint replacement as well as the effects with Alendronate treatment.

3.2. Long Term Implant Effects

Both total hip and articular surface replacement models were run postoperatively for a total of 6 years. For the total hip replacement, reductions in BVF continued until about four years postoperatively. After four years, GZ 7 maintained about a 30% BVF change, seen in **Figure 3-9**, due to stress shielding. Reductions in BVF continued in GZ 5 for three years and then maintained a BVF loss of about 13%.

Figure 3-9 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the total hip replacement six years postoperatively. The reference BVF baseline is taken from the day of surgery.

While damage levels off for GZ 2-6, it continues to rise for GZ 1 and 7 throughout the six year period, seen in **Figure 3-10**.

Figure 3-10 shows the postoperative damage change in the seven different Gruen zones for the total hip replacement six years postoperatively.

Activation frequency leveled off for all GZ at three to four years postoperatively as seen in **Figure 3-11**. The sharper increases for activation frequency occurred in the distal regions of the stem implant (GZ 3-5) while the damage also increased, indicating the decrease in porosity is due to the increased remodeling due to damage occurring in these regions.

Figure 3-11 shows the activation frequency in the seven different Gruen zones for the total hip replacement six years postoperatively.

For the articular surface replacement the BVF maintained the levels seen from the validation run. All GZ BVF changes remained under 2% and can be seen in **Figure 3-12**.

Figure 3-12 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the articular surface replacement six years postoperatively. The reference BVF baseline is taken from the day of surgery.

Damage levels in GZ 1 increased rapidly throughout all six years postoperatively, seen in **Figure 3-13**, while the other GZ didn't show any significant change.

Figure 3-13 shows the postoperative damage change in the seven different Gruen zones for the articular surface replacement six years postoperatively.

Overall, activation frequency only showed a slight increase in GZ 1 over the six year period, seen in **Figure 3-14**. The sharp increase in damage, and relatively stable porosity and activation frequency suggest the damage is a result of increased strains and the mechanical stimulus.

Figure 3-14 shows the activation frequency in the seven different Gruen zones for the articular surface replacement six years postoperatively.

3.3. Preoperative Alendronate Effects

Implementing Alendronate treatment one year preoperatively for the total hip replacement model led to an increased BVF of 6% in GZ 1 at the end of the preoperative period, seen in **Table 3-1**. Other GZ didn't experience a significant change.

Table 3-1 shows the preoperative end state porosity change for the total hip replacement between no Alendronate treatment and one year of Alendronate treatment.

THR Preoperative			
	BVF (%)		
Gruen Zone	No Treatment	Treatment	% Difference
1	55%	49%	6%
2	6%	5%	0%
3	5%	5%	0%
4	6%	7%	0%
5	8%	9%	-1%
6	11%	10%	1%
7	6%	6%	0%

Alendronate treatment one year preoperatively with the articular surface replacement led to an increased BVF of 11% in GZ 1 at the end of the preoperative period, with smaller increases in all other regions as well, seen in **Table 3-2**.

Table 3-2 shows the preoperative end state porosity change for the articular surface replacement between no Alendronate treatment and one year Alendronate treatment.

ASR Preoperative			
	BVF (%)		
Gruen Zone	No Treatment	Treatment	% Difference
1	57%	46%	11%
2	7%	6%	1%
3	7%	6%	1%
4	7%	6%	1%
5	8%	6%	2%
6	12%	9%	3%
7	7%	6%	2%

3.4. Postoperative THR Alendronate Treatment Effects

Continuous Alendronate treatment starting one day postoperatively and lasting for all six years resulted in constant BVF gains for GZ 1 seen in **Figure 3-15**. At the end of six years, GZ 1 had gained 23% BVF. The only other region to show gains was GZ 6 at 2%. Gruen zone 7 lost about 3% BVF while every other region lost less than 1% BVF.

Figure 3-15 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the total hip replacement six years postoperatively with continuous Alendronate treatment. The reference BVF baseline is taken from the day of surgery.

Continuous treatment for 6 years postoperatively curbed damage across all GZ by year three as seen in **Figure 3-16**. This is due in part to the decrease in resorption area caused by Alendronate, which helps improve bone balance, decreasing the microdamage further. This increased bone balance increases bone volume, and the strain and mechanical stimulus decline, decreasing damage formation. The diminished mechanical stimulus also increased remodeling activity over time due to the disuse response.

Figure 3-16 shows the postoperative damage change in the seven different Gruen zones for the total hip replacement six years postoperatively with continuous Alendronate treatment.

Activation frequency remained relatively the same across GZ 2-6, while GZ 1 showed slight gains and GZ 7 increased the most as seen in **Figure 3-17**. The increase in activation frequency of GZ 7 and decrease in damage over the six years still show the prevalence of stress shielding.

Figure 3-17 shows the activation frequency in the seven different Gruen zones for the total hip replacement six years postoperatively with continuous Alendronate treatment.

For a total hip replacement with Alendronate treatment starting one day postoperatively and lasting one year, BVF loss was not as severe as the non treated model. Significant BVF reduction occurred after treatment had terminated in year one. At the end of six years, a decrease in BVF for GZ 1 reached 26% and BVF reached a 7% reduction in GZ 5 as seen in **Figure 3-18**.

Figure 3-18 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the total hip replacement six years postoperatively with one year postoperative Alendronate treatment. The reference BVF baseline is taken from the day of surgery.

Damage in GZ 7 decreased throughout the six year postoperative period while damage in GZ 1 slightly increased as seen in **Figure 3-19**. The first year saw damage peak for GZ 2-6 while it leveled off starting in year two.

Figure 3-19 shows the postoperative damage change in the seven different Gruen zones for the total hip replacement six years postoperatively with one year postoperative Alendronate treatment.

Activation frequency for GZ 1 and 7 increased during the first year while all other GZ decreased as seen in **Figure 3-20**. During the second year, only GZ 1 decreased in activation frequency and by year three the activation frequency was stable for all GZ. Sharp increases in activation frequency with concurrent decreases in damage suggest some level of stress shielding for all regions but GZ 1.

Figure 3-20 shows the activation frequency in the seven different Gruen zones for the total hip replacement six years postoperatively with one year postoperative Alendronate treatment.

Using the preoperative Alendronate treatment for one year combined with one year postoperative Alendronate treatment, only GZ 1 shows significant change with an 8% BVF increase over a no treatment scenario at the end of one year as can be seen in **Figure 3-21**. After treatment one year postoperatively, GZ 7 has reduced BVF by about 29% and GZ 5 has reduced BVF by about 6%.

Figure 3-21 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the total hip replacement six years postoperatively starting Alendronate treatment one year preoperative and ending one year postoperative. The reference BVF baseline is taken from the day of surgery without preoperative treatment to visually compare the differences at postoperative time 0 with pretreatment.

Damage levels after one year postoperatively start to increase constantly in GZ 1 as seen in **Figure 3-22**. In all other regions, damage remains fairly constant after one year. During the first year, only GZ 7 sees a decrease in damage.

Figure 3-22 shows the postoperative damage change in the seven different Gruen zones for the total hip replacement six years postoperatively starting Alendronate treatment one year preoperative and ending one year postoperative.

Activation frequency for GZ 1 and 7 increased during the first year while all other GZ exhibited decreased activation frequency as seen in **Figure 3-23**. During the second year, GZ 1 decreased in activation frequency, GZ 6 stayed about the same, and all other GZ exhibited increased activation frequency. The first year GZ 7 increased in activation frequency while decreasing in damage, demonstrating stress shielding. After the second year, GZ 7 saw a gradual decrease in activation frequency.

Figure 3-23 shows the activation frequency in the seven different Gruen zones for the total hip replacement six years postoperatively starting Alendronate treatment one year preoperative and ending one year postoperative.

3.5. Postoperative ASR Alendronate Treatment Effects

Continuous Alendronate treatment for six years postoperatively with the articular surface replacement led to an increase of BVF of 26% for GZ 1 by the end of the six years as seen in **Figure 3-24**. An increase in BVF of 3% was also seen in GZ 6. All other GZ remained stable throughout the six year period.

Figure 3-24 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the articular surface replacement six years postoperatively with continuous Alendronate treatment. The reference BVF baseline is taken from the day of surgery.

The continuous treatment helped curb damage levels across all GZ by year three, seen in **Figure 3-25**. Damage in GZ 1 peaked in year one and asymptotically decreased towards zero.

Figure 3-25 shows the postoperative damage change in the seven different Gruen zones for the articular surface replacement six years postoperatively with continuous Alendronate treatment.

Activation frequency over the six years increased for GZ 1 and also increased more gradually for GZ 6 as seen in **Figure 3-26**. All other GZ experienced little activation frequency change.

Figure 3-26 shows the activation frequency in the seven different Gruen zones for the articular surface replacement six years postoperatively with continuous Alendronate treatment.

Postoperative BVF changes with treatment starting the day of surgery and ending after one year remained pretty stable throughout the six year period as seen in **Figure 3-27**. Initially GZ 1 showed a 3% increase in BVF but declined to 1% at the end of six years. All other GZ experienced losses of less than 2% over the six year period.

Figure 3-27 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the articular surface replacement six years postoperatively with one year postoperative Alendronate treatment. The reference BVF baseline is taken from the day of surgery.

Damage levels for the one year postoperative articular surface replacement model stayed constant with the exception of GZ 1, as seen in **Figure 3-28**. Damage levels in GZ 1 gradually increased over the entire six year period.

Figure 3-28 shows the postoperative damage change in the seven different Gruen zones for the articular surface replacement six years postoperatively with one year postoperative Alendronate treatment.

Activation frequency also remains pretty constant for the entire six years after one year postoperative Alendronate treatment to the articular surface replacement model, as seen in **Figure 3-29**.

Figure 3-29 shows the activation frequency in the seven different Gruen zones for the articular surface replacement six years postoperatively with one year postoperative Alendronate treatment.

Using the preoperative Alendronate treatment for one year and continuing treatment for one year postoperatively mainly affected the BVF in GZ 1 seen in **Figure 3-30**. The BVF for GZ 1 increased to 13% in year one before decreasing to less than a 1% gain over the six year period. All other GZ had a decrease in BVF over the six year period of less than 2%.

Figure 3-30 shows the postoperative bone volume fraction changes in the seven different Gruen zones for the articular surface replacement six years postoperatively starting Alendronate treatment one year preoperative and ending one year postoperative. The reference BVF baseline is taken from the day of surgery without preoperative treatment to visually compare the differences at postoperative time 0 with pretreatment.

Damage levels for this scenario remained constant throughout the six years for GZ 2-7 as seen in **Figure 3-31**. A constant increase in damage for GZ 1 started after year one and continued for the whole simulation.

Figure 3-31 shows the postoperative damage change in the seven different Gruen zones for the articular surface replacement six years postoperatively starting Alendronate treatment one year preoperative and ending one year postoperative.

Activation frequency for the one year preoperative Alendronate treatment with one year postoperative treatment stayed fairly constant for most GZ seen in **Figure 3-32**. A small decrease for GZ 1 happened after year one but then remained constant for the following years.

Figure 3-32 shows the activation frequency in the seven different Gruen zones for the articular surface replacement six years postoperatively starting Alendronate treatment one year preoperative and ending one year postoperative.

4. Discussion

Bisphosphonate drugs such as Alendronate have recently been administered in conjunction with a hip arthroplasty [10, 11]. These drugs are being used in an attempt to prevent the bone loss in the femur as a result of the implant and surgical procedure. In this study we attempted to directly compare the long term effects bisphosphonates had on both total hip and articular surface replacements using a 3-D finite element model of the femur with an adaptive bone remodeling algorithm incorporating Alendronate treatment. Our results showed the success of creating a long term total hip and articular surface replacement model treated with Alendronate.

Clinically, with dual-energy X-ray absorptiometry measurements, it's been shown most bone loss occurs in the first few months after THR surgery and reveals little change after the first postoperative year. Alendronate treatment could change this effect.

In one study mentioned earlier (section 3.1), Arabmotlagh et al. [63] monitored patients for one year postoperatively that had undergone a total hip replacement surgery and measured the bone mineral density (BMD) change using dual-energy x-ray absorptiometry (DEXA). In this experiment one group received a placebo, another group received 10mg/day of oral Alendronate for ten weeks, and another group received 20mg/day for five weeks. After one year, the group with the placebo helped validate our model since there were no significant differences when compared to our results. However, this clinical experiment also lasted a total of six years. When comparing the placebo group to our computer

model results after six years, GZ 1, GZ 2, GZ 6, and GZ 7 were statistically similar while GZ 3 – 5 had significant differences (p-values = 0.035, 0.012, 0.001 respectively) as seen in **Figure 4-1**.

Figure 4-1 shows a comparison between results obtained clinically by Arabmotlagh et al. [63] and our experimental data six years postoperatively for a THR with no Alendronate treatment. Statistical similarities were found in GZ 1, GZ 2, GZ 6, and GZ 7 and significant differences were seen in GZ 3 (p-value = 0.035), GZ 4 (p-value = 0.012), and GZ 5 (p-value = 0.001).

The results of the experimental treatment group that received the 10 mg/day for ten weeks were fairly consistent to the results from this computational study after one year of treatment. At the end of one year, the percent change of BMD of our experimental study was consistent with the clinical results, with one significant difference in GZ 7 (p-value = 0.004), seen in **Figure 4-2**. This discrepancy is largely due to our model still being under Alendronate effects at this time (one year).

Figure 4-2 shows a comparison between results obtained clinically by Arabmotlagh et al. [63] and our experimental data one year postoperatively for a THR with one year postoperative Alendronate treatment. All regions were statistically similar except one significant difference seen in GZ 7 (p-value = 0.004).

After six years with the postoperative Alendronate treatment scenarios by Arabmotlagh et al. compared with the one year treatment from ours, there were no significant differences found, as can be seen in **Figure 4-3**.

Figure 4-3 shows a comparison between results obtained clinically by Arabmotlagh et al. [63] and our experimental data six years postoperatively for a THR with one year postoperative Alendronate treatment.

Another study by Nishioka et al. [61] in which we used to validate our model also evaluated the effects of Alendronate on bone loss caused by stress shielding after total hip arthroplasty in Japanese patients. The Alendronate was administered orally at 5 mg/day for one year and measured a change in bone mineral density ratio using DEXA scans. All model results after one year were within the range of these clinical results as seen in **Figure 4-4**. Again, visual inspection of the standard deviation results obtained by Nishioka et al. [61] were used for this determination since the values were not given.

Figure 4-4 shows a comparison between results obtained clinically by Nishioka et al. [61] and our model data one year postoperatively for a THR with one year postoperative Alendronate treatment.

Comparisons to both studies by Arabmotlagh et al. [63] and Nishioka et al. [61] showed significant similarities clinically to the results of the current study. While treatment scenarios, patient bone anatomies, and differing hip implants are some of the differences between our study results and the clinical results, we are still able to gain a confidence our models are working and predicting bone changes correctly. The total hip replacement results acted as a validation for our model and led to an acceptance for our surface replacement results. Figures showing the BVF distribution on the bone can be seen in Appendix E for one year postoperative and in Appendix F for six years postoperative.

An interesting observation occurs between the runs with preoperatively treated bone to the bone with no preoperative treatment. While initially bone with

the pretreatment has a higher BVF, especially in GZ 1, after postoperative treatment the change in BVF between the scenarios was minimal. Damage on the other hand has some significant long term differences. After the conclusion of Alendronate treatment, the pretreated bone had a greater increase of damage over the six year period with both types of implants for GZ 1. At the end of the six years, the damage was about double that of the bone treated at the start of surgery in GZ 1 with little change in other GZs. The implications here are that there is no benefit to pretreating a patient with Alendronate for bone in the Gruen zones, and that it might actually be worse in the long run for fracture risk in GZ 1 due to the damage buildup. This could be due to increased time exposure before stopping treatment causing a more brittle bone susceptible to damages after one year when both the loads are returned to normal and treatment stops at the same time.

At the end of six years we can draw some comparisons between all the different scenarios we ran. With regards to BVF, there is little change between one year preoperative to one year postoperative Alendronate treatment and one year postoperative Alendronate treatment for a specific implant type, while both treatment scenarios seem to increase the BVF over no treatment. However, when comparing between different implant types, the ASR had higher BVF for all GZs. This is expected since the GZs are defined around a THR stem and for an ASR, the GZ are distal to the implant. These comparisons can be seen in **Figure 4-5**.

Figure 4-5 shows the bone volume fraction (BVF) change comparisons after six years for the major treatment scenarios. The reference BVF baseline is taken from the day of surgery without preoperative treatment.

After six years postoperative time, we could also compare damages between the different Alendronate treatment scenarios. Pretreatment for both the THR and ASR had a large impact on the damages in GZ 1. Damages in the distal GZs were higher with the THR while damages in the proximal GZs had more damage with an ASR given the same treatment scenario. Treatment scenarios with the THR seemed to decrease the damage for GZ 3, 4, and 5. These damage comparisons can be seen in **Figure 4-6**.

Figure 4-6 shows the damage for the major treatment scenarios after six years.

One finding by Deuel et al. [34] showed high levels of strain adjacent to the rim of the ASR, similar to Watanabe et al [64]. In the study by Watanabe et al. stress shielding was observed in the femoral neck, leading to a suggestion that the losses in bone density due to stress shielding in combination with areas of stress concentration around the implant could lead to fracture following hip resurfacing. With our simulations, the effects of Alendronate treatment scenarios could be compared for the area around the ASR rim as well. Looking at the strains without any Alendronate treatment we can see a sharp increase right after implantation with the values steady about three years postoperative. With treatment starting the day of surgery the strain lowers, and with pretreatment strain lowers even more, closer to normal levels. The differences in strain

around the ASR rim can be seen in **Figure 4-7** and pictures of the strain can be seen in Appendix F.

Figure 4-7 shows the differences in strain adjacent to the ASR rim for the different treatment scenarios.

Damage follows a similar pattern to the strain with the different treatment scenarios seen in **Figure 4-8**. Alendronate treatment drastically reduces the damage level when being compared to no treatment. Pretreating with Alendronate seems to show the best damage reduction value.

Figure 4-8 shows the differences in damage adjacent to the ASR rim for the different treatment scenarios.

Interestingly, the BVF adjacent to the rim increased with Alendronate treatment. Pretreating also seemed to increase the BVF even more, as seen in **Figure 4-9**. With this information, it seems as if the Alendronate helped even out the imbalance of bone resorption to reformation. This helped decrease the damage in the rim area and maintain lower strain values with the increase of bone density in the area.

Figure 4-9 compares the BVF percentage adjacent to the ASR rim for the different treatment scenarios.

Previous models incorporating this bisphosphonate code [48, 49] maintained continuous treatment and never looked at the effects after treatment had stopped. The bisphosphonate code is either turned on or off, with no lingering effects. However, drugs still remain in the body even after a person has stopped the intake. The half life of Alendronate in humans is estimated to be about ten years in length [65]. The current code for bisphosphonates needs to add in a function over time related to the potency to decrease the effects of bisphosphonates to correspond with the half life. While the long term results still fit to clinical numbers, the simulation could become more accurate with this implemented.

There are also some limitations to the bone model itself in our study. A model from the CT scan of the cadaveric bone had an unknown loading history, and comparisons between the clinical and experimental bone density changes occurred under estimated loading conditions which may not have been representative of the individual. Also, the identical loading conditions were used for the models of both hip resurfacing and total hip replacements, even though the patient population for resurfacing is generally younger and more active. Patterns of bone loss were consistent with other clinical and computational studies however. A limitation with the user material subroutine to our model is that bone remodeling is a complex process affected by skeletal loading as well as metabolic and hormonal activities and these factors aren't accounted for. Loading changes from the native state following surgery is the most likely factor contributing to the remodeling rates though. The implants in the model are also fully bonded to the surrounding bone immediately following implantation, which has the potential of allowing greater load transfer to the proximal aspect of the femur than occurs for the total hip replacement clinically.

Even with all these limitations we were able to show the pretreatment of Alendronate compared to starting treatment the day of surgery may not have much of an impact on long term bone density for the Gruen Zones. Damage seems to double with pretreatment compared to no treatment for GZ 1. The resurfacing implant caused more damage to the proximal GZs while the total hip replacement caused more damage to the distal zones around the implant stem. When looking around the resurfacing rim however, pretreatment seems to show

big changes in the damage, strain, and bone density values when compared to no treatment and treatment starting the day of surgery. The implication is that pretreatment may help prevent femoral neck fracture.

Future experiments might want to investigate if offsetting the termination of Alendronate and the return of full force loads would help decrease the damage accumulation rate. Also, the addition of the Alendronate half life to better simulate long term drug effects on the bone might provide higher accuracy. Additionally, modeling hormonal effects and implementing them into the user material code could improve the model simulations. A more complete muscle force set could be added to the femur model as well. While the primary muscles involved in stress patterns for the proximal aspect of the femur were used, other muscles such as the quadriceps and iliotibial band have been shown to have more of an effect on diaphyseal strains [66]. The loading conditions for the model were also applied under an ideal implant state while implanting into an actual human will not have the perfect surgical positioning, for example the implant may not always have the same neck length as the native femur. Diseases like cancer could also be factored into the model in the future. Radiation effects on bone remodeling and bone properties could be observed as well. As newer drugs are produced and more information about remodeling is discovered, these effects can then be modeled and compared using this simulation. The user material subroutine could also be used for other bones with implants to determine similar effects with bisphosphonate treatments and whether certain treatment scenarios provide any long term benefits.

Bibliography

1. Masri, B.A., E.L. Masterson, and C.P. Duncan, *The classification and radiographic evaluation of bone loss in revision hip arthroplasty*. Orthop Clin North Am, 1998. **29**(2): p. 219-27.
2. Harris, W.H., et al., *Extensive localized bone resorption in the femur following total hip replacement*. J Bone Joint Surg Am, 1976. **58**(5): p. 612-8.
3. Bryan, J.M., et al., *Altered load history affects periprosthetic bone loss following cementless total hip arthroplasty*. J Orthop Res, 1996. **14**(5): p. 762-8.
4. Pritchett, J.W., *Femoral bone loss following hip replacement. A comparative study*. Clin Orthop Relat Res, 1995(314): p. 156-61.
5. Sumner, D.R., et al., *Functional adaptation and ingrowth of bone vary as a function of hip implant stiffness*. J Biomech, 1998. **31**(10): p. 909-17.
6. Murphy, S.B. and J. Rodriguez, *Revision total hip arthroplasty with proximal bone loss*. J Arthroplasty, 2004. **19**(4 Suppl 1): p. 115-9.
7. Parvizi, J., et al., *Primary total hip arthroplasty with an uncemented femoral component: a long-term study of the Taperloc stem*. J Arthroplasty, 2004. **19**(2): p. 151-6.
8. Schmidt, R., et al., *Osteodensitometry after total hip replacement with uncemented taper-design stem*. Int Orthop, 2004. **28**(2): p. 74-7.
9. Schmalzried, T.P., *The optimal metal-metal arthroplasty is still a total hip arthroplasty: in opposition*. J Arthroplasty, 2006. **21**(4 Suppl 1): p. 77-9.
10. Wilkinson, J.M., et al., *Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial*. J Bone Miner Res, 2001. **16**(3): p. 556-64.
11. Shanbhag, A.S., C.T. Hasselman, and H.E. Rubash, *The John Charnley Award. Inhibition of wear debris mediated osteolysis in a canine total hip arthroplasty model*. Clin Orthop Relat Res, 1997(344): p. 33-43.
12. Martin, R.B., D.B. Burr, and N.A. Sharkey, *Skeletal tissue mechanics*. 1998, New York: Springer. xiv, 392 p.
13. Hadi, T.M.A., *Bone turnover, osteocyte apoptosis, and the basic multicellular unit: a quantitative study of the rabbit tibial mid-diaphysis*. 2007, UC Davis: Davis, CA.
14. Raisz, L.G., *The osteoporosis revolution*. Ann Intern Med, 1997. **126**(6): p. 458-62.
15. Poole, K.E. and J.E. Compston, *Osteoporosis and its management*. BMJ, 2006. **333**(7581): p. 1251-6.
16. Abbott, T.A., 3rd, B.J. Lawrence, and S. Wallach, *Osteoporosis: the need for comprehensive treatment guidelines*. Clin Ther, 1996. **18**(1): p. 127-49; discussion 126.
17. Amarshi, N., J.A. Scoggin, and S. Ensworth, *Osteoporosis: Review of guidelines and consensus statements*. American Journal of Managed Care, 1997. **3**(7): p. 1077-1084.

18. Peter Pietschmann, M.R., Wolfgang Sipos, Katharina Kersch-Schindl, *Osteoporosis: An Age-Related and Gender-Specific Disease - A Mini-Review*. Gerontology, 2009. **55**: p. 3-12.
19. Rodan, G.A., *Mechanisms of action of bisphosphonates*. Annu Rev Pharmacol Toxicol, 1998. **38**: p. 375-88.
20. Semih Aki, N.E., Ulku Akarirmak, Fikret Tuzun, Merih Eryavuz, Serap Alper, Oktay Arpacioğlu, Fatma Atalay, Vural Kavuncu, Siren Kokino, Omer Kuru, Kemal Nas, Onder Ozerbis, Gursoy Savas, Omer Faruk Sendur, Derya Soy, Gulseren Akyuz, *Gastrointestinal Side Effect Profile Due to the Use of Alendronate in the Treatment of Osteoporosis*. Yonsei Med J, 2003. **44**(6): p. 961-967.
21. Coleman, C.I., K.A. Perkerson, and A. Lewis, *Alendronate-induced auditory hallucinations and visual disturbances*. Pharmacotherapy, 2004. **24**(6): p. 799-802.
22. Katz, W.A., *Nonpharmacologic Approaches to Osteoarthritis*. American Journal of Lifestyle Medicine, 2007. **1**(4): p. 249-255.
23. Kidd, B.L., *Osteoarthritis and joint pain*. Pain, 2006. **123**(1-2): p. 6-9.
24. Deuel, C.R., et al., *Alterations in femoral strain following hip resurfacing and total hip replacement*. J Bone Joint Surg Br, 2009. **91**(1): p. 124-30.
25. Gruen, T.A., G.M. McNeice, and H.C. Amstutz, *"Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening*. Clin Orthop Relat Res, 1979(141): p. 17-27.
26. Bobyn, J.D., et al., *Producing and avoiding stress shielding. Laboratory and clinical observations of noncemented total hip arthroplasty*. Clin Orthop Relat Res, 1992(274): p. 79-96.
27. Huiskes, R., *The various stress patterns of press-fit, ingrown, and cemented femoral stems*. Clin Orthop Relat Res, 1990(261): p. 27-38.
28. Daniel, J., P.B. Pynsent, and D.J. McMinn, *Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis*. J Bone Joint Surg Br, 2004. **86**(2): p. 177-84.
29. McMinn, D., et al., *Metal on metal surface replacement of the hip. Experience of the McMinn prosthesis*. Clin Orthop Relat Res, 1996(329 Suppl): p. S89-98.
30. Smith-Petersen, M.N., *Arthroplasty of the Hip: A New Method*. The Journal of Bone and Joint Surgery, 1939. **21**: p. 269-288.
31. Bell, R.S., et al., *A study of implant failure in the Wagner resurfacing arthroplasty*. J Bone Joint Surg Am, 1985. **67**(8): p. 1165-75.
32. Shimmin, A., P.E. Beaulé, and P. Campbell, *Metal-on-metal hip resurfacing arthroplasty*. J Bone Joint Surg Am, 2008. **90**(3): p. 637-54.
33. Cossey, A.J., et al., *The nonoperative management of periprosthetic fractures associated with the Birmingham hip resurfacing procedure*. J Arthroplasty, 2005. **20**(3): p. 358-61.
34. Deuel, C.R., *Development of an Adaptive 3-D Model of the Human Femur to Simulate Bone Remodeling Following Hip Resurfacing and Total Hip Arthroplasties*, in *Mechanical Engineering*. 2007, University of California Davis: Davis. p. 95.

35. Wolff, J., *Das Gesetz der Transformation der Knochen*. 1892: Hirschwald, Berlin.
36. S. C. Cowin, D.H.H., *Bone Remodeling I: Theory of Adaptive Elasticity*. Journal of Elasticity, 1976. **6**(3): p. 313-326.
37. Huiskes, R., et al., *Adaptive bone-remodeling theory applied to prosthetic-design analysis*. J Biomech, 1987. **20**(11-12): p. 1135-50.
38. Huiskes, R., et al., *Post-loosening mechanical behavior of femoral resurfacing prostheses*. Clin Mater, 1990. **6**(1): p. 37-55.
39. Huiskes, R., H. Weinans, and B. van Rietbergen, *The relationship between stress shielding and bone resorption around total hip stems and the effects of flexible materials*. Clin Orthop Relat Res, 1992(274): p. 124-34.
40. Beaupre, G.S., T.E. Orr, and D.R. Carter, *An approach for time-dependent bone modeling and remodeling-application: a preliminary remodeling simulation*. J Orthop Res, 1990. **8**(5): p. 662-70.
41. Van Rietbergen, B., et al., *ESB Research Award 1992. The mechanism of bone remodeling and resorption around press-fitted THA stems*. J Biomech, 1993. **26**(4-5): p. 369-82.
42. Martin, R.B., *The effects of geometric feedback in the development of osteoporosis*. J Biomech, 1972. **5**(5): p. 447-55.
43. Gupta, S., A.M. New, and M. Taylor, *Bone remodelling inside a cemented resurfaced femoral head*. Clin Biomech (Bristol, Avon), 2006. **21**(6): p. 594-602.
44. Peter, B., et al., *Peri-implant bone remodeling after total hip replacement combined with systemic alendronate treatment: a finite element analysis*. Comput Methods Biomech Biomed Engin, 2004. **7**(2): p. 73-8.
45. Hazelwood, S.J., et al., *A mechanistic model for internal bone remodeling exhibits different dynamic responses in disuse and overload*. J Biomech, 2001. **34**(3): p. 299-308.
46. Martin, B., *A theory of fatigue damage accumulation and repair in cortical bone*. J Orthop Res, 1992. **10**(6): p. 818-25.
47. Frost, H.M., *On rho, a marrow mediator, and estrogen: Their roles in bone strength and "mass" in human females, osteopenias, and osteoporoses - insights from a new paradigm*. Journal of Bone and Mineral Metabolism, 1998. **16**(2): p. 113-123.
48. Nyman, J.S., et al., *Predictions on preserving bone mass in knee arthroplasty with bisphosphonates*. J Arthroplasty, 2006. **21**(1): p. 106-13.
49. Nyman, J.S., et al., *A theoretical analysis of long-term bisphosphonate effects on trabecular bone volume and microdamage*. Bone, 2004. **35**(1): p. 296-305.
50. Chavassieux, P.M., et al., *Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis*. J Clin Invest, 1997. **100**(6): p. 1475-80.
51. Eriksen, E.F., et al., *Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis*. Bone, 2002. **31**(5): p. 620-5.

52. Chavassieux, P.M., et al., *Effects of alendronate on bone quality and remodeling in glucocorticoid-induced osteoporosis: a histomorphometric analysis of transiliac biopsies*. J Bone Miner Res, 2000. **15**(4): p. 754-62.
53. Mashiba, T., et al., *Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles*. Bone, 2001. **28**(5): p. 524-31.
54. Turner, A.W., et al., *Computational bone remodelling simulations and comparisons with DEXA results*. J Orthop Res, 2005. **23**(4): p. 705-12.
55. Bitsakos, C., et al., *The effect of muscle loading on the simulation of bone remodelling in the proximal femur*. J Biomech, 2005. **38**(1): p. 133-9.
56. Hazelwood, S. and Y. Mizumoto, *Abductor muscle impairment and recovery may affect bone loss around hip implant stems.*, in *American Society of Biomechanics 2001 Annual Meeting*. 2001: San Diego, CA.
57. Nyman, J.S., et al., *Long stemmed total knee arthroplasty with interlocking screws: a computational bone adaptation study*. J Orthop Res, 2004. **22**(1): p. 51-7.
58. Parfitt, A.M., et al., *Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee*. J Bone Miner Res, 1987. **2**(6): p. 595-610.
59. Greenspan, S.L., et al., *Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis*. Journal of Bone and Mineral Research, 2002. **17**(11): p. 1988-1996.
60. Schnitzer, T., et al., *Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis*. Aging Clinical and Experimental Research, 2000. **12**(1): p. 1-12.
61. Nishioka, T., et al., *Alendronate inhibits periprosthetic bone loss around uncemented femoral components*. J Bone Miner Metab, 2007. **25**(3): p. 179-83.
62. Nakamura, K., *Measurement of periprosthetic bone mineral density after cementless hip arthroplasty by dual energy X-ray absorptiometry: Longitudinal and cross-sectional evaluation*. Journal of Orthopaedic Science, 1996(1): p. 113-122.
63. Arabmotlagh, M., et al., *Changes of femoral periprosthetic bone mineral density 6 years after treatment with alendronate following total hip arthroplasty*. J Orthop Res, 2009. **27**(2): p. 183-8.
64. Watanabe, Y., et al., *Biomechanical study of the resurfacing hip arthroplasty: finite element analysis of the femoral component*. J Arthroplasty, 2000. **15**(4): p. 505-11.
65. Marx, R., et al., *Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, Treatment*. Journal of Oral and Maxillofacial Surgery, 2005. **63**(11): p. 1567-1575.

66. Szivek, J.A., J.B. Benjamin, and P.L. Anderson, *An experimental method for the application of lateral muscle loading and its effect on femoral strain distributions*. Med Eng Phys, 2000. **22**(2): p. 109-16.
67. Nantel, J., et al., *Gait patterns after total hip arthroplasty and surface replacement arthroplasty*. Arch Phys Med Rehabil, 2009. **90**(3): p. 463-9.

Appendix A User Subroutine

```
subroutine sdvini(statev,coords,nstatv,ncrds,noel,npt,  
* layer,kspt)  
c  
c include '/usr/apps/abaqus/6.7-3/site/aba_param_dp.inc'  
c  
c character*80 fname  
c dimension statev(nstatv),coords(ncrds)  
c dimension jelarr(110000,2),sdvvarr(110000,105)  
c integer kflag  
c save kflag,sdvvarr,jelarr  
c  
c write(*,*) 'kflag = ', kflag  
c if (kflag.eq.0) then  
c  
c     fname='/home/thryce/bmu/taperloc_preop_bis.txt'  
c     intpts=106124  
c  
c     open(unit=300,file=fname,status='old')  
c  
c  
c     do i=1,intpts  
c         read(300,310) jelarr(i,1),jelarr(i,2),(sdvvarr(i,j),j=1,105)  
310     format(i5,1x,i2,1x,4f12.9,1x,e12.6,1x,3f10.6,1x,100f9.6)  
c     end do  
c  
c     kflag=1  
c     write(*,*) 'Finished reading .txt file'  
c end if  
c  
c if (noel.le.26531) then  
c     if ((noel.gt.19694).and.(noel.le.26531)) then  
c         krownum=((noel-2)*4)+npt  
c     else if (noel.le.19694) then  
c         krownum=((noel-1)*4)+npt  
c     end if  
c  
c     do k2=1,105  
c         statev(k2)=sdvvarr(krownum,k2)  
c     end do  
c else  
c  
c initialize porosity  
c  
c
```

```

statev(1)=0.05
c statev(1)=0.20
c
c initialize minimum principal strain for first,
c second, and third steps
c
statev(2)=0.0
statev(3)=0.0
statev(4)=0.0
c
c initialize damage potential
c
statev(5)=0.0
c
c initialize equilibrium damage
c
statev(6)=0.03662944
c
c initialize number of refilling and resorbing BMUs
c
statev(7)=0.0
statev(8)=0.0
c
c initialize activation frequency for trif days
c
do k=9,nstatv
statev(k)=0.00670
end do
end if
close (unit=300)
return
end
c
c
c
c
c
c
subroutine umat(stress,statev,ddsdde,sse,spd,scd,
* rpl,ddsddt,drplde,drpldt,
* stran,dstran,time,dtime,temp,dtemp,predef,dpred,bone,
* ndi,nshr,ntens,nstatv,props,nprops,coords,drot,pnewdt,
* celent,dfgrd0,dfgrd1,noel,npt,layer,kspt,kstep,kinc)
c
include '/usr/apps/abaqus/6.7-3/site/aba_param_dp.inc'
c
character*8 bone

```

```

dimension stress(ntens),statev(nstatv),ddsdde(ntens,ntens),
* stran(ntens),dstran(ntens),props(nprops),s(3),ps(3)
integer trif,tr,ti,tf,lstr
real kb,kc,kd,kr,nf,nr,nfexist,nreexist,do,sa,modulus,nu,
* tstep,minprin,rl1,rl2,rl3,phi,shearmod,bulkmod,lambda,samax,
* q,pi,fs,dt,facur,famax1,famax2,fao,rc,rh,dexist,area,ddotform,
* ddotrep,dcurrent,fadivsa,fa,ab,ac,qb,qc,phc,qnet,dp,maxprin,
* maxmag
c
c elastic properties
c   write(*,*) 'step = ', kstep

c
c
c   if (statev(1).lt.0.097267787) then
c     modulus=23440*(1-statev(1))**5.74
c   else
c     modulus=14927*(1-statev(1))**1.33
c   endif
c
c   nu=props(1)
c
c   specify props for titanium
c   if (noel.gt.26531) then
c     modulus=114000
c     nu=0.33
c     spd=3
c     scd=75.
c     sse=0.8
c   end if
c
c   bulkmod=modulus/(3*(1-2*nu))
c   shearmod=modulus/(2*(1+nu))
c   lambda=bulkmod-2*shearmod/3
c
c elastic stiffness
c
c
c
c
c   ddsdde(1,1)=2*shearmod+lambda
c   ddsdde(2,2)=2*shearmod+lambda
c   ddsdde(3,3)=2*shearmod+lambda
c   ddsdde(4,4)=shearmod
c   ddsdde(5,5)=shearmod
c   ddsdde(6,6)=shearmod
c   ddsdde(1,2)=lambda

```

```

        ddsdde(1,3)=lambda
        ddsdde(2,1)=lambda
        ddsdde(2,3)=lambda
        ddsdde(3,1)=lambda
        ddsdde(3,2)=lambda
    c
    c initialize stress for the current step
    c
        do k1=1,ntens
            stress(k1)=0.0
        end do
    c
    c calculate stress
    c
        do k1=1,ntens
            do k2=1,ntens
                stress(k2)=stress(k2)+ddsdde(k2,k1)*(stran(k1)+dstran(k1))
            end do
        end do
    c
    c proceed through remodeling algorithm for elements defining bone
    c
    c
    c
    c calculate minimum and maximum principle strains
    c
    c transform current steps to tstep to define first, second, and
    c third steps of input file
    c
    c store maximum magnitude principle strain as state variable for each step
    c
        if (kstep.eq.1) then
            if (noel.eq.1) then
                if (npt.eq.1) then
                    write(*,*) 'calculating strains'
                endif
            endif
        endif
    c
    c
        if (noel.le.26531) then
            do k1=1,ntens
                s(k1)=stran(k1)+dstran(k1)
            end do
            lstr=2
            call sprinc(s,ps,lstr,ndi,nshr)

```

```

        if (abs(ps(1)).ge.abs(ps(2))) then
            maxmag=ps(1)
        else
            maxmag=ps(2)
        endif
c
        tstep=abs((real(kstep))/3-int(kstep/3))
        if ((tstep.gt.0.2).and.(tstep.lt.0.5)) then
            statev(2)=maxmag
        else if ((tstep.gt.0.5).and.(tstep.lt.0.8)) then
            statev(3)=maxmag
        else if (tstep.lt.0.2) then
            statev(4)=maxmag
        endif
c
c
c
c
c specify activation frequency at equilibrium
    fao=0.00670
c
c
c calculate time for resorptive phase of remodeling cycle, tr
c calculate time for reversal phase of remodeling cycle, ti
c calculate time for refilling phase of remodeling cycle, tf
c calculate total time of remodeling cycle, trif
c
    tr=25
    ti=5
    tf=64
    trif=tr+ti+tf
c
c initialize the existing number of refilling and resorbing BMUs
c specify existing number of refilling and resorbing BMUs
c
    if (kstep.eq.1) then
        if (noel.eq.1) then
            if (npt.eq.1) then
                write(*,*) 'calculating BMUs'
            endif
        endif
    endif
endif
c
c
    if (kstep.eq.1) then
        statev(7)=fao*tf
    
```

```

        statev(8)=fao*tr
    endif
    nfexist=statev(7)
    nrexist=statev(8)
c
c *****
c
c
c proceed through porosity update after the third step
c
c
c
c     if ((kstep.ne.1).and.(tstep.lt.0.2)) then
c
c calculate damage potential
c store damage potential as state variable
c calculate rate of damage formation
c calculate rate of damage repair
c calculate current day damage
c store current day damage as state variable
c
c specify equilibrium damage
c initialize existing damage
c specify existing damage
c
c     do=0.03662944
c     dexist=statev(6)
c
c specify coefficients for damage formation equation and
c             activation frequency equations
c
c     kd=40.2
c     kd=185000.
c     kr=-1.6
c     kb=13000000.
c     kb=65000000000.
c     kc=0.0000004325
c     kc=0.0000000000938
c
c
c
c specify loading rate for load case 1, rl1, load case 2, rl2,
c             and load case 3, rl3
c specify exponent for damage formation equation
c
c     if (kstep.le.270) then
c         rl1=2000.
c         rl2=2000.

```

```

        rl3=16.
    else if ((kstep.le.1095).and.(kstep.gt.270)) then
        rl1=2250.
        rl2=2250.
        rl3=18.
    else
        rl1=2500.
        rl2=2500.
        rl3=20.
    endif
c      q=2.89
c      q=4
c
c
c specify value for pi
c specify repair specificity factor
c specify time step
c
        pi=3.1415926535897932385
        fs=5.0
        dt=1.0
c
c specify current day activation frequency
c specify max activation frequency/max specific surface area
c
        facur=statev(9)
c      famax1=2.15
c      famax1=0.50
c      famax2=4.15
c      famax2=1.15
c      samax=4.1905
c
c specify cement line radius
c specify haversian radius
c
        rc=0.095
        rh=0.020
c
c
c
*      phi=((abs(statev(2)))**q)*rl1+((abs(statev(3)))**q)*rl2
        +((abs(statev(4)))**q)*rl3
        statev(5)=phi
        if (statev(1).le.0.20) then
            area=pi*rc**2
        else

```

```

        area=0.5*pi*rc**2
    endif
    ddotform=kd*phi
    ddotrep=dexist*facur*area*fs
    dcurrent=dexist+(ddotform-ddotrep)*dt
    if (dcurrent.ge.800) then
        dcurrent=800
    endif
    statev(6)=dcurrent
c
c
c update current activation frequency
c calculate specific surface area
c add in potency for bisphosphonate treatment
c update activation frequency by a reduction of P
c
    fadivsa=(fao*(famax1/samax))/(fao+(famax1-fao)
*
        *exp(kr*famax1*(dcurrent-do)/do))
    if (dcurrent.lt.do) then
        fadivsa=(fao/samax)*(dcurrent/do)
    endif
    sa((((28.8*statev(1)-101)*statev(1)+134)*statev(1)
*
        -93.9)*statev(1)+32.3)*statev(1)
c
    if (phi.lt.0.000000865) then
    if (phi.lt.0.0000000001875) then
        fadivsa=fadivsa+(famax2/samax)/(1+exp(kb*(phi-kc)))
    endif
    fa=fadivsa*sa
    if (kstep.le.1092) then
        P=1*(1-exp(-5.0*nrexis))
        fa=(1-P)*fadivsa*sa
    endif
c
c update activation frequency history
c
    do k1=trif+9,10,-1
        statev(k1)=statev(k1-1)
    end do
c
c store current activation frequency as state variable
c
    statev(9)=fa
c
c add in bisphosphonate reduction to trabecular bone
c calculate daily amount of bone added per refilling BMU
c calculate daily amount of bone removed per resorbing BMU

```


c include decreased resorption after specified time
c include less refilling on trabecular surfaces in disuse
c

```

ac=area
  if (kstep.le.1092) then
    if (statev(1).gt.0.20) then
      ac=area*(10/13)
    endif
  endif
  if (statev(1).le.0.20) then
    area=pi*(rc**2-rh**2)
  endif
ab=area
qb=ab/tf
qc=ac/tr
  if (statev(1).gt.0.20) then
    if (phi.lt.0.0000000001875) then
      qb=(0.5+0.5*phi/0.0000000001875)*ab/tf
    endif
  endif
endif

```

c
c calculate number of refilling BMUs for current day
c calculate number of resorbing BMUs for current day
c store number of refilling and resorbing BMUs as state variables
c

```

nf=nfexist+(statev(tr+ti+9)-statev(trif+9))*dt
nr=nrexist+(statev(9)-statev(tr+9))*dt
  if (nf.lt.0.0) then
    nf=0.0
  endif
  if (nr.lt.0.0) then
    nr=0.0
  endif
statev(7)=nf
statev(8)=nr

```

c
c calculate net amount of bone added per day
c

```

phc=0.04432132964
qnet=(qb*nf)-(qc*nr)
  if (statev(1).le.0.20) then
    qnet=(qb*nf)-(1-phc)*(qc*nr)
  endif

```

c
c calculate change in porosity
c update porosity

```

c      dp=-qnet*dt
      statev(1)=statev(1)+dp
c
c      specify limits for porosity
c      check porosity against limits
c      specify state variables to plot
c
c      write(*,*) 'delta porosity = ', dp
c      write(*,*) 'final porosity = ', statev(1)
c      write(*,*) 'activation freq = ', statev(9)
c      write(*,*) 'damage = ', statev(6)
      ulim=0.99
      blim=0.05
      if (statev(1).ge.ulim) then
        statev(1)=ulim
      else if (statev(1).le.blim) then
        statev(1)=blim
      endif
    endif
    spd=statev(1)
    sse=statev(9)
    scd=statev(6)*(0.95/(1-statev(1)))
c      spd=statev(5)
c      sse=modulus
c      scd=statev(6)
c      spd=statev(2)
c      sse=statev(3)
c      scd=statev(4)
  endif
  return
end

```

Appendix B Extracting Results

```
C=====
C=====
C
C This program extracts state variables from a .fil file
C
C Reference Abaqus Standard User's Manual Volume 1 Sections 5.1.2,3
C and Abaqus Example Problems Manual Section 11.1.3 V6.3
C=====
C=====
C
C Define variables and arrays
C
  SUBROUTINE ABQMAIN
    INCLUDE '/usr/apps/abaqus/6.7-3/site/aba_param_dp.inc'
    CHARACTER*80 FNAME, FOUT
    DIMENSION STVAR(200)
    DIMENSION ARRAY(513),JRRAY(NPRECD,513),LRUNIT(2,1)
    EQUIVALENCE (ARRAY(1),JRRAY(1,1))
C
C Name output file and results file
C
  WRITE(*,*) 'ENTER OUTPUT FILENAME'
  READ(*,*) FOUT
  WRITE(*,*) 'ENTER .FIL FILENAME WITHOUT .FIL EXT'
  READ(*,*) FNAME
C   FNAME="
C
C Open output file
C
  OPEN(UNIT=400,FILE=FOUT,STATUS='NEW')
C
C Intiliaze ABAQUS interface with FORTRAN
C See Abaqus manual section 5.1.3 version 6.3
C
  NRU=1
  LRUNIT(1,1)=8
  LRUNIT(2,1)=2
  LOUTF=0
  CALL INITPF(FNAME,NRU,LRUNIT,LOUTF)
  JUNIT=8
  CALL DBRNU(JUNIT)
C
C Read records from the results file (*.fil).
```

```

C
DO 100 K1=1,99999999
  CALL DBFILE(0,ARRAY,JRCD)
C    write(*,*) 'jrcd', jrcd
  IF (JRCD.NE.0) GO TO 110
C
C Get record key for current line.
C
  KEY=JRRAY(1,2)
C    write(*,*) 'KEY= ',KEY
C
C Retrieve element and int point # from element header record (key=1)
C See Abaqus manual section 5.1.2 version 6.3 for keys
C
  IF (KEY.EQ.1) THEN
    JEL=JRRAY(1,3)
    JPNT=JRRAY(1,4)
C
C Retrieve solution dependent state variables (key=5)
C
    ELSE IF (KEY.EQ.5) THEN
      DO I=1,105
        STVAR(I)=ARRAY(I+2)
      END DO
      WRITE(400,80) JEL,JPNT,(STVAR(J),J=1,105)
80    FORMAT(I5,1X,I2,1X,4F12.9,1X,E12.6,1X,3F10.6,1X,100F9.6)
    END IF
100  CONTINUE
110  CONTINUE
C
  CLOSE (UNIT=400)
  STOP
  END

```

Appendix C Extracting File

```
C=====
C=====
C
C The program extracts the state variables from a bone adaptation
C model for given region per 75 days into a text file.
C
C=====
C=====
C
C Define variables and arrays
C
  INCLUDE '/usr/apps/abaqus/6.7-3/site/aba_param_dp.inc'
  CHARACTER*80 FNAME, OUTNAME
  INTEGER NOELEM, JELDUM, JCT, INCSTART, INCSTOP, LAST
  REAL NOSTV
  DIMENSION JELEM(1000), STVAR(1000), AVGSTV(1000)
  DIMENSION ARRAY(513),JRRAY(NPRECD,513),LRUNIT(2,1)
  EQUIVALENCE (ARRAY(1),JRRAY(1,1))
C
C Open input file and read in results file, number of elements in group
C of interest, and list of element numbers making up group.
C
  OPEN(UNIT=300,FILE='taperlocpostopgruen1.isv',STATUS='OLD')
  READ(300,500) FNAME
  PRINT *, FNAME
  READ(300,500) OUTNAME
  PRINT 502, 'Output file is ', OUTNAME
  READ(300,501) INCSTART
  PRINT 503, 'Start increment is ',INCSTART
  READ(300,501) LAST
  PRINT *, LAST
  READ(300,501) NOELEM
  PRINT 503, 'Number of Elements in Group = ', NOELEM
  DO 15 L=1,NOELEM
    READ(300,501) JELDUM
    JELEM(L)=JELDUM
15  CONTINUE
500  FORMAT(A)
501  FORMAT(I)
C
C Open output file
C
  OPEN(UNIT=400,FILE=OUTNAME,STATUS='NEW')
```

```

C
C Check to see if input file was read correctly.
C
502 FORMAT(A20,A20)
503 FORMAT(A30,I)
    DO 16 L=1,NOELEM
        PRINT *, 'ELEM #', JELEM(L)
16 CONTINUE
C
C Intilize ABAQUS interface with FORTRAN
C
    NRU=1
    LRUNIT(1,1)=8
    LRUNIT(2,1)=2
    LOUTF=0
    CALL INITPF(FNAME,NRU,LRUNIT,LOUTF)
    JUNIT=8
    CALL DBRNU(JUNIT)
C
C Heading for output file
C
    WRITE (400,104) 'step', 'fa', 'porosity', 'damage'
104 FORMAT(1X, A4, T6, A7, T17, A9, T27, A8)
C
C Call the desired steps from which data is extracted.
C
C Loop through calls of step number (e.g. 150,300,450,600)
C
    NSTEP=INCSTART
    INCSTOP=LAST
    NINC=0
    DO 2000 J10=1,50
        IF (NSTEP.GT.INCSTOP) GO TO 2001
        K=1
        JCT=0
        CALL POSFIL(NSTEP,NINC,ARRAY,JRCD)
C        WRITE(*,*) 'JRCD = ', JRCD
        WRITE(*,*) 'STEP ', NSTEP
C
C Set state variables equal to zero.
C
    NOSTV=3
    DO J=1,NOSTV
        STVAR(J)=0.0
    END DO
C

```

```

C Read records (element, state variables) from the results
C file (*.fil). Cover a maximum of 10 million records.
C
      DO 1000 K100=1,10000
      DO 1000 K1=1,9999
C          WRITE(*,*) 'K100 ', K100
C          WRITE(*,*) 'K1 ', K1
          CALL DBFILE(0,ARRAY,JRCD)
C          write(*,*) 'jrzd', jrzd
          IF (K.GT.NOELEM) GO TO 1001
C
C Get record key for current line.
C
      KEY=JRRAY(1,2)
C      write(*,*) 'KEY= ',KEY
C
C Retrieve element number form record line
C
      IF (KEY.EQ.1) THEN
          JEL=JRRAY(1,3)
          JPT=JRRAY(1,4)
C
C
C
      ELSE IF (KEY.EQ.14) THEN
C          write(*,*) 'JEL= ',JEL
C          write(*,*) 'JELEM= ',JELEM(1)
          IF (JEL.EQ.JELEM(K)) THEN
              DO I=1,NOSTV
                  STVAR(I)=STVAR(I)+ARRAY(I+2)
              END DO
C          WRITE(*,*) 'ELEM #', JEL
C          WRITE(*,*) 'INTEG #', JPT
C          WRITE(*,*) 'ARRAY ',ARRAY(3)
C          WRITE(*,*) 'VARIA ',STVAR(1)
              K=K+1
          END IF
      END IF
1000  CONTINUE
1001  CONTINUE
C
C Calculate the average state variables for all integration points.
C
C
      DO L=1,NOSTV
          AVGSTV(L)=STVAR(L)/(NOELEM)

```

```
        END DO
C      WRITE(400,504) NSTEP, (AVGSTV(J),J=1,NOSTV)
504    FORMAT(I5,1X,F9.6,1X,F9.6,1X,F9.6)
        NSTEP=NSTEP+1092
2000 CONTINUE
2001 CONTINUE
        CLOSE (UNIT=400)
        STOP
        END
```


Appendix D ISV File

taperloc_postop
taperlocpostopgruen12250.txt
1092
2184
20
19734
19738
19877
20406
20486
20497
20519
20523
20529
20533
20565
21104
21199
21205
21240
21241
21845
21948
21958
21991

Appendix E One Year Porosity Pictures

Figure E-1 shows porosity for the total hip replacement one year postoperatively for no biphosphonate treatment (left), treatment starting day of surgery (middle), and treatment starting one year preoperatively (right).

Figure E-2 shows porosity for the articular surface replacement one year postoperatively for no biphosphonate treatment (left), treatment starting day of surgery (middle), and treatment starting one year preoperatively (right).

Appendix F Six Year Porosity Pictures

Figure F-1 shows porosity for the total hip replacement six years postoperatively for treatment starting day of surgery (left) and treatment starting one year preoperatively (right).

Figure F-2 shows porosity for the articular surface replacement six years postoperatively for treatment starting day of surgery (left), and treatment starting one year preoperatively (right).

Appendix G Six Year Strain Pictures

Figure G-1 shows the strain adjacent to the articular surface replacement rim six years postoperatively for no treatment (top), treatment starting day of surgery (middle), and treatment starting one year preoperatively (bottom).