AN INVESTIGATION IN THE CELLULAR MECHANISMS OF BONE REMODELING USING A HYBRID CELLULAR AUTOMATON APPROACH

A Dissertation

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by

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One of the most intriguing aspects of bone is its ability to grow, repair damage, adapt to mechanical loads, and maintain mineral homeostasis. It is generally accepted that bone adaptation occurs in response to the mechanical demands of our daily activities; moreover, strain and microdamage have been implicated as potential stimuli that regulate this sophisticated process. While researchers have made significant advances in our understanding of the bone adaptation process, there are many aspects that remain unknown. For instance, it is not fully understood how the mechanical stimulation experienced by bones influences the biochemical signaling that drives the cellular activity of remodeling. Due to the fact that evidence for bone metabolic diseases points toward the disruption of the cellular mechanisms of remodeling, such a relationship is crucial to understanding the key factors that result in pathological remodeling activity.

Over the past several decades, various theoretical and computational models have been developed to study the bone adaptation process. These computational models have primarily focused on predicting net changes in organ and tissue level bone architecture. While these simulations are able to capture phenomena such as net increases or decreases in bone volume or reorientation of tissue level structures, they do not capture cellular level details. In an attempt to ameliorate this deficiency of previous models,
more recent studies have focused on simulating the remodeling response at a single site in bone. However, few models attempt to combine models of cellular activity with the classical phenomenological remodeling paradigms.

The primary focus of this dissertation is to present a new computational framework that mechanistically models the cellular behavior involved in the bone remodeling process. This framework uniquely combines established phenomenological remodeling paradigms with cellular mechanisms to predict remodeling activity for a damaged site in bone. Biological rules were implemented to control the recruitment, differentiation, and activation of osteoclasts and osteoblasts, based on observations from histological studies. The results of this work are the first of their kind to demonstrate spatially and temporally accurate remodeling behavior at the cellular level. Furthermore, these results provide unique insights regarding key parameters that influence cellular level remodeling activity.
Dedicated to Mom, Dad, Jason, Mike, and Connie.

As a result of all your extraordinary love and support, I am able to close this chapter of my life and emerge into a brighter future.
We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

–T. S. Eliot

(Little Gidding, 1942)
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<tr>
<td>B</td>
<td>Mineralized bone</td>
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<tr>
<td>BMU</td>
<td>Basic multicellular unit</td>
<td></td>
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<tr>
<td>CA</td>
<td>Cellular automaton/automata</td>
<td></td>
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<tr>
<td>FE</td>
<td>Finite element</td>
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<tr>
<td>Fx</td>
<td>Threshold for bone fracture</td>
<td></td>
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<tr>
<td>HCA</td>
<td>Hybrid cellular automata</td>
<td></td>
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<tr>
<td>HHCA</td>
<td>Hierarchical hybrid cellular automata</td>
<td></td>
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<tr>
<td>LC</td>
<td>Lining cells</td>
<td></td>
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<tr>
<td>M</td>
<td>Bone marrow</td>
<td></td>
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<tr>
<td>M-CSF</td>
<td>Macrophage-colony stimulating factor</td>
<td></td>
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<tr>
<td>M-M</td>
<td>Michaelis-Menten</td>
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<tr>
<td>MES</td>
<td>Minimum effective strain</td>
<td></td>
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<tr>
<td>MESm</td>
<td>Minimum effective strain for modeling</td>
<td></td>
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<tr>
<td>MESp</td>
<td>Minimum effective strain for microdamage</td>
<td></td>
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<tr>
<td>MESr</td>
<td>Minimum effective strain for remodeling</td>
<td></td>
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<tr>
<td>MN</td>
<td>Mononucleated cells</td>
<td></td>
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<tr>
<td>MPS</td>
<td>Maximal principal strain</td>
<td></td>
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<tr>
<td>OB</td>
<td>Osteoblasts</td>
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<td>OC</td>
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<td>OPG</td>
<td>Osteoprotegerin</td>
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<td>--------------</td>
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<tr>
<td>OS</td>
<td>Osteocytes</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>Phosphatidylserine</td>
<td></td>
</tr>
<tr>
<td>PID</td>
<td>Proportional-integral-derivative (controller)</td>
<td></td>
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<tr>
<td>RANK</td>
<td>Receptor activator of nuclear factor κβ</td>
<td></td>
</tr>
<tr>
<td>RANKL</td>
<td>Receptor activator of nuclear factor κβ ligand</td>
<td></td>
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<tr>
<td>SED</td>
<td>Strain energy density</td>
<td></td>
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<tr>
<td>TGF-β</td>
<td>Transforming growth factor-β</td>
<td></td>
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<tr>
<td>TGF-β1</td>
<td>Transforming growth factor-β1</td>
<td></td>
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<tr>
<td>TRAP</td>
<td>Tartrate-resistant acid phosphatase</td>
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SYMBOLS

\( A_{\text{avg}}^{\text{MN}} \) Average rate of mononucleated cellular activity reported in the literature

\( A_{i}^{\text{MN}} \) Mononucleated cellular activity

\( A_{i}^{\text{OB}} \) Osteoblast cellular activity

\( A_{i}^{\text{OC}} \) Osteoclast cellular activity

\( c_{d} \) Derivative gain

\( c_{\text{form}} \) Proportional constant for formation

\( c_{i} \) Integral gain

\( c_{\text{OPG}} \) Proportional constant that represents the weight fraction of OPG in the bone matrix

\( c_{p} \) Proportional gain

\( c_{\text{resorb}} \) Proportional constant for resorption

\( c_{\text{TGF-}\beta 1} \) Constant that represents the weight fraction of TGF-\( \beta 1 \) in the bone matrix

\( d^{\text{LC}} \) Maximum lining cell communication distance

\( d^{\text{OS}} \) Maximum osteocyte communication distance

\( D \) Osteocyte signal decay constant

\( E_{i} \) Young’s modulus at a specific site \( i \)
Continuum level Young’s modulus for the $I^{th}$ submodel

Young’s modulus for each cell $i$ of the $I^{th}$ submodel

Young’s modulus of a fully dense bone

Force in the horizontal direction for the $I^{th}$ submodel

Force in the vertical direction for the $I^{th}$ submodel

Dimensionless constant for formation

Dimensionless constant for resorption

Amount of osteocyte signaling received by each lining cell $i$

Effective signal received by each lining cell $i$

Critical lining cell signaling threshold

Threshold for formation

Threshold for resorption

Total apparent density

Number of cells in the $I^{th}$ submodel

Set of all indices corresponding to lining cells

Set of indices corresponding to lining cells that are within a maximum lining cell communication distance $d^{LC}$ of the $i^{th}$ cell

Set of all indices corresponding to live osteocytes

Set of indices corresponding to osteocytes that are within a maximum osteocyte communication distance $d^{OS}$ of the $i^{th}$ cell

Penalization power

Percentage of damaged material removed
$r^\parallel$ Longitudinal axis of the resorption cavity

$r^\perp$ Transverse axis of the resorption cavity

$RS_i$ Recruitment stimulus of a CA at the discrete location $i$

$s_i^{MN}$ Substrate for mononuclear cellular activity

$s_i^{OB}$ Capacity for bone formation

$s_0$ Reduction in osteoblast capacity for formation

$S_i$ Mechanical stimulus of a CA at the discrete location $i$

$S_i^*$ Equilibrium state of a CA at the discrete location $i$

$t_i^{OB}$ Time in which the osteoclast in the $i^{th}$ cell is activated

$t_i^{OC}$ Osteoclast lifespan

$\tau_{\text{reversal}}$ Duration of the reversal period

$T_{xy}^I$ Shear force for the $I^{th}$ submodel

$U_i$ Strain energy density

$U_i^*$ Critical damage threshold

$U_{\text{crit}}^*$ Threshold for overuse

$U_{\text{max}}^*$ Threshold for disuse

$v_{\text{cell}}$ Volume of a lattice site

$V_0^{OB}$ Rate of osteoblast formation

$V_i^{OC}$ Rate of osteoclast resorption

$V_0^{OC}$ Maximum rate of osteoclast resorption

$v_{\text{resorb}}$ Total resorbed volume
$w^{LZ}$  Lazy zone width

$x_i$  Relative density at the tissue level for the $i^{th}$ element

$x_i^I$  Tissue level density distribution for each cell $i$ of the $I^{th}$ submodel

$X_I$  Apparent density at the continuum level for the $I^{th}$ submodel

$\alpha_i$  Finite vector of states defining a cell

$\gamma_i(t)$  Set of tissue types represented in the model

$\delta_{crit}$  Critical homeostatic strain

$\delta_{max}$  Maximum homeostatic strain

$\delta_{min}$  Minimum homeostatic strain

$\epsilon_X$  Maximum desired change in relative density

$\epsilon_\sigma$  Maximum desired change in stress

$\kappa_i^{OPG}$  Relative amount of OPG production

$\kappa_i^{TGF-\beta1}$  Relative amount of TGF-\beta1 available to initiate OPG production

$\tau^{MN}$  Mononuclear cellular activity period

$\tau^{OB}$  Osteoblast formation period

$\tau^{OC}$  Osteoclast resorption period

$\tau^{remo}$  Total remodeling period

$\tau^{resorb}$  Total resorption period
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CHAPTER 1

INTRODUCTION

Bone remodeling is the complex process by which old bone is replaced by new tissue. This process occurs continuously in the body and is carried out by bone cells that are regulated by numerous metabolic and mechanical factors. The remodeling process provides for various functions such as adaptation to mechanical loading, damage repair, and mineral homeostasis. In the past few decades, a great deal of attention has been focused on the study of bone biology. Researchers from a variety of fields have participated in this work, each with a broad spectrum of objectives (Burr, 2002). For instance, biologists aim at gaining insights into the impact of genetics, hormones, and drug therapies on the manipulation of the various stages of the bone remodeling process. Clinicians are searching for new methods of treating or taking preventative measures for metabolic bone diseases, such as osteoporosis. With an increasing number of osteoporotic fractures each year, engineers are seeking to improve the stability and effectiveness of bone implants over time.

Some of the earliest observations related to the adaptation of bone to its mechanical environment date back to 1638 when Galileo Galilei pointed out the mechanical implications of the shape of bones (Galilei, 1638). Currently, there are many aspects of the bone adaptation process that remain unknown; however it is predicted that the further refinement of mathematical models and computational simulations of this process will provide a means to unravel the underlying mechanisms (Huiskes, 2000).
1.1 Relevance

An extensive amount of research has been conducted on developing a relationship describing the mechanical adaptability of bone. In the past several decades, numerous computational models have been developed to simulate how the biological regulatory process of remodeling responds to changes in the mechanical environment of bone (Beaupré et al., 1990b; Carter, 1987; Cowin and Hegedus, 1976; Fyhrie and Carter, 1986b; Huiskes et al., 1987). Many of these models operate under the assumption that bone is a self-optimizing material and remodeling is triggered by various mechanical stimuli. Therefore, the required remodeling activity is determined by the deviation between the mechanical stimuli experienced and a local target mechanical stimulus. These studies most commonly employ density-based simulations to analyze trabecular bone adaptation. Typically, these remodeling algorithms have been exercised under different mechanical stimuli to demonstrate their ability to reproduce realistic trabecular patterns, such as in the structure of the proximal femur (Bagge, 2000; Fischer et al., 1996; Levenston et al., 1994). Improvements in our understanding of bone physiology and the application of this knowledge in computational models have provided a means for analyzing situations in which remodeling plays a critical role. Investigating remodeling after a hip joint arthroplasty (Doblaré et al., 2002; Huiskes et al., 1987; Kerner et al., 1999; van Rietbergen et al., 1993) or predicting trends related to systemic factors involved in bone diseases such as osteoporosis (Ruimerman et al., 2005a; van der Linden et al., 2003) are two common applications.

As our knowledge increases with respect to the cellular mechanisms involved in the bone remodeling process, improvements in the physiological basis of computational models can be undertaken. Many computational models simply predict the net turnover of bone without actually interpreting the sequence of events involved in the remodeling
process. As Huiskes (2000) indicated, the point of remodeling simulations is to simulate the key metabolic processes involved, as opposed to developing rules that result in realistic bone structures. For instance, bone remodeling is defined by an activation, resorption, formation sequence that is carried out by specialized bone cells (Robling et al., 2006). The time scale associated with a remodeling step in most models is usually too large to capture these details. One criticism of most remodeling algorithms is that they actually produce a combination of both bone modeling and remodeling in their simulations (Huiskes et al., 2000; McNamara and Prendergast, 2007; Mullender and Huiskes, 1995; Nowak, 2006b; Penninger et al., 2008; Ruimerman et al., 2005a; Tovar et al., 2006).

Bone modeling is attributed to the global changes in the architecture of the bone, as opposed to remodeling, which involves the turnover of discrete packets of bone. During modeling, formation and resorption mechanisms can act independently at individual sites in the bone, while formation follows resorption in a coupled fashion during remodeling. Few researchers have made efforts to differentiate between modeling and remodeling in their models. However, to circumvent the process of bone modeling altogether and focus on the remodeling rules alone, one can reduce the length-scale of the simulation to that of a single remodeling site. Recently, researchers have focused on the performance of their remodeling rules when applied to the surface of a single trabecular strut (McNamara and Prendergast, 2007; Mulvihill et al., 2008; Mulvihill and Prendergast, 2008). These investigations have provided new insights into the cellular level details of remodeling. Furthermore, analyzing the biological accuracy of remodeling rules for a single site can lead to improvements in continuum level models. This ideology is targeted at unraveling the unanswered questions about remodeling, rather than continuing the quest for studying the structural optimality of bone which
was inadvertently onset by “Wolff’s law”.

Mechanistic models of bone remodeling are needed to contribute to the understanding of the underlying biological activities involved in this process. A model of the cellular mechanisms involved will provide a better means to investigate the effects of various paracrine and autocrine factors (pertaining to signals dispersed locally and signals only affecting cells of the same type, respectively) on remodeling. To pursue such a model, one must first incorporate local regulatory factors which mediate the recruitment, differentiation, and activation of osteoclasts and osteoblasts, the cells responsible for resorption and formation, respectively. Currently, only a few mathematical models have been formulated to characterize the remodeling process in terms of the cellular mechanisms that are present (Komarova et al., 2003; Martin and Buckland-Wright, 2004, 2005). These models provide an excellent basis for modeling the cellular activity in the remodeling cavity; however the rules employed have no relation to any externally applied mechanical stimuli. As previously mentioned, the fundamental assumption in many bone remodeling simulations is that remodeling occurs in relation to an applied stimulus. At this time, such a connection between the cellular activity of bone cells to an applied mechanical stimulus has not been identified.

1.2 Research Objectives

Computational models of the bone remodeling process have been utilized to further our understanding of the adaptation of bone architecture to changes in its mechanical environment. The purpose of this dissertation is to develop a better understanding of the cellular communication which drives the bone adaptation process, providing further insights into the key factors that ultimately result in bone pathology. The objective of this research is to incorporate new rules that more accurately represent the bone re-
modeling process in an existing computational framework, known as the hybrid cellular automaton (HCA) algorithm (Tovar, 2004). The HCA method is a biologically-inspired algorithm capable of simulating the behavior of bone adaptation. This methodology is termed a hybrid technique because it couples global information obtained from the finite element (FE) method with the local relationships utilized by cellular automata (CA) computing.

Initially, studies were conducted on a multi-scale approach for the simulation of bone adaptation. The so-called hierarchical HCA (HHCA) framework attempts to discretize a continuum level model of bone into tissue level submodels, where HCA is applied locally to predict structural changes (Tovar, 2004). This approach is advantageous as it can capture the coupling of adaptive activity between the organ and tissue level scales. The original HHCA framework is deficient in its representation of the material behavior of the tissue level models at the continuum level. The objective for this particular investigation was to develop and implement a methodology for computing the anisotropic properties of the tissue level structures. Incidentally, it was this investigation that played a vital role in inspiring the need for a more detailed model of bone remodeling at the cellular level.

The primary focus of this dissertation is to present a new computational framework that can model the cellular mechanisms involved in the bone remodeling process by utilizing mathematical rules. The objective of modeling the cellular mechanisms involved in bone formation and resorption will be achieved by developing mechanistic mathematical rules and incorporating them in a novel HCA framework. Building off of the existing HCA framework is suitable, as the basic architecture of this method is similar to common density-based remodeling simulations (Hazelwood and Castillo, 2007; Huiskes et al., 2000; McNamara and Prendergast, 2007; Mulvihill et al., 2008;
Ruimerman et al., 2005a; Tezuka et al., 2005). While the same lattice scheme as the HCA method can be used, this new framework will differentiate between types of tissue (i.e., mineralized bone and bone marrow) and account for the activities of the cells that are involved (i.e., osteocytes, lining cells, osteoclasts, mononucleated cells, and osteoblasts).

This new framework uniquely combines existing mechanistic and phenomenological paradigms for the simulation of bone remodeling. Biological rules were implemented to connect the cellular mechanisms related to the phases of remodeling with applied mechanical stimuli, via cellular signaling. These rules control the recruitment, differentiation, and activation of the bone cells. The prominent processes for describing recruitment and inhibition of the bone cells, as reported from experimental studies, are utilized.

1.3 Overview

This dissertation is comprised of six chapters. An overview of relevant bone structure and physiology, along with a historical account of computational models of the bone adaptation process, are presented in Chapter 2. Amongst the computational models discussed, the fundamentals of the HCA methodology are presented. The HCA methodology serves as the base algorithm for the models developed in this research. In addition, a chronological summary of significant contributions to the state of the art of bone remodeling computational simulations is given to motivate the advance in modeling paradigms over the past several decades.

The original investigations conducted in this research are presented in Chapter 3 through Chapter 5. A methodology for determining the anisotropic properties of the tissue level models of the HHCA framework is developed in Chapter 3. This method-
ology is exercised on a classical simply-supported bone plate example (Weinans et al., 1992) and a cantilevered bone plate. The results of both examples are compared with previous work conducted by Tovar (2004). The following two chapters depart from continuum level simulations of bone remodeling and focus on a cellular level model which uniquely combines both phenomenological and mechanistic modeling paradigms. In Chapter 4, a set of rules that couple traditional strain-based remodeling methods with cellular mechanisms of bone resorption are developed. These rules were implemented and tested on a model of an idealized trabecular strut. A parametric study was conducted to analyze the parameters which have the greatest impact on the total volume resorbed. In Chapter 5, the aforementioned framework is extended to incorporate cellular mechanisms of bone formation. These rules were also tested on the trabecular strut model to investigate the effect of cellular level parameters on bone turnover at a remodeling site.

A summary of the original contributions, final conclusions, and recommendations for future research are presented in Chapter 6.
CHAPTER 2

LITERATURE REVIEW

Bone tissue is responsible for many different functions in the body, including structural support, mineral storage, protection of vital organs, and other physiological processes such as the formation of blood vessels. Our bones accomplish these roles while remaining light enough to allow for mobility, via muscle flexion, and durable enough to withstand day-to-day mechanical demands, by continually adapting over time. For instance, our bones are full of cracks which form and grow as a result of our daily activities (Taylor et al., 2007). If these cracks are not repaired, they could lead to failure in a very short time. The bone adaptation process provides for three major functions (Burr, 2002). First, it is a mechanism which allows the skeleton to adapt to its mechanical environment. Second, it maintains the integrity of our bones by repairing damage from repeated loading. Finally, adaptation provides a means of calcium homeostasis by storing additional mineral in the bone matrix during formation or releasing mineral through the resorption of old bone tissue.

Studying the bone adaptation process is very important as it emerges in various clinical conditions (e.g., disuse osteoporosis) and also because it affects the quality of bone in the vicinity of implants (e.g., hip joint arthroplasty) (Taylor et al., 2003). In addition, hereditary factors, hormonal changes, and an individual’s lifestyle impact the characteristics of bone adaptation (Tovar, 2004). With these factors in mind, the purpose of this investigation is to develop a better understanding of the cellular communication which
drives the bone adaptation process, providing further insights into the key factors that ultimately result in bone pathology. This section provides an overview of relevant bone structure and physiology, along with a historical review of computational models of the bone adaptation process.

2.1 Bone Structure

The term bone actually refers to a family of materials that share a common basic constituent, the mineralized collagen fibril (Weiner and Wagner, 1998). Bone is a highly complex material that offers a host of features to be studied. The structure of bone can be described in five different hierarchical levels of organization (Rho et al., 1998). As such, different structural entities within bone occur at different length scales ranging from the macrostructural level (whole bones) down to the sub-nanostructural level (elementary constituents of bone) (Fig. 2.1).

At the macrostructural level, bone can be categorized into two groups based on the degree of porosity, namely cortical and trabecular bone (Martin et al., 1998). Cortical (or compact) bone is mostly solid with a porosity ranging between 5% and 10%. This dense bone typically surrounds trabecular bone and is found in the mid-shaft of long bones (e.g., femur) or as a thin shell covering the surface of flat (e.g., pelvis) and cuboidal bones (e.g., vertebrae). Cortical bone comprises nearly 80% of skeletal mass.

Trabecular (or cancellous) bone is significantly less dense than cortical bone, with a porosity ranging from 75% to 95%. This type of bone is comprised of a series of rods and plates and has an appearance similar to that of a sponge. Trabecular bone is usually found in the end of long bones, and at the center of flat and cuboidal bones. While trabecular bone only represents about 20% of skeletal mass, it comprises some 70% of skeletal volume (Martin et al., 1998). The larger degree of porosity in trabecular bone
Figure 2.1. Hierarchical structure of bone as presented by Rho et al. (1998). This diagram illustrates various structural entities ranging from the macrostructural level (whole bones) down to the sub-nanostructural level (elementary constituents of bone).

results in a greater amount of free surfaces in contact with the cellular constituents of bone (Jacobs, 2000). For this reason, trabecular bone is more metabolically active, responsive to stimuli, and is younger on average than cortical bone (Rho et al., 1998).

At the microstructural level, the composition of cortical and trabecular structures can be observed. Cortical tissue is vascularized, with microscopic channels containing blood vessels that run longitudinal (Haversian canals) and transverse (Volkmann’s canals) to the major axis of the bone. Cortical bone is comprised of cylindrical packets of bone called osteons (Fig. 2.2). Haversian canals are located at the center of an osteon and are surrounded by concentric layers of interstitial lamellae (planar arrangements of mineralized collagen fibers). Osteons measure approximately 2-4 mm in length and 200-250 µm in diameter. These cortical structures are separated from other tissue by cement lines. The outer and inner surfaces of cortical bone are comprised of layers of lamellar bone called circumferential lamellae. These layers traverse the perimeter of the bone and form a shell around the osteonal bone.
Lamellae
Canaliculi
Haversian Canals
Volkmann’s Canals
Periosteum
Circumferential Lamellae
Osteons
Trabeculae
Interstitial Lamellae
Lamellar Structure of an Osteon

Figure 2.2. Diagram of trabecular and cortical bone tissue from Martini (1998). Cortical bone is comprised of osteons, which are cylindrical structures containing concentric rings of lamellar bone. Cement lines separate osteons from regions of tissue that has not been remodeled, known as interstitial lamellae. Cortical bone tissue also possesses channels that contain blood vessels which run longitudinal (Haversian canals) and perpendicular (Volkmann’s canals) to the long axis of the bone. Trabecular bone is comprised of an interconnected framework of rods and plates, with an underlying lamellar structure. Small cavities called lacunae can be observed throughout trabecular bone.

Microscopically, it can be observed that trabecular bone is comprised of an interconnected network of rods and/or plates. Rod-like trabecular struts are on the order of 150-300 \( \mu \)m in diameter and up to 2 mm in length (Fig. 2.2). Three different combinations of these trabecular components are usually distinguished, representing the following cellular structures: rod-rod, rod-plate, and plate-plate (Rho et al., 1998). Trabecular bone also has a lamellar structure, with newly remodeled packets of bone delineated by cement lines. Small cavities called lacunae, exist within trabecular struts. Trabecular bone does not typically contain vasculature and receives nutrients from the bone marrow that fills the non-mineralized spaces in this tissue. Wolff (1892) recognized that
trabeculae are typically oriented along the principal stress trajectories in bone.

At the sub-microstructural level, the different arrangements of collagen fiber arrays can be observed. As previously mentioned, lamellae are organized planar arrangements of collagen fiber arrays on the order of $3-7 \, \mu m$ thick. In humans, these arrays are organized in an anisotropic fashion, giving bone unique directional properties both structurally and mechanically. However, another type of bone can be distinguished by its randomly oriented collagen fiber structure, called woven bone. Woven bone is a weaker material that is rapidly formed after pathologic events occur (e.g., fracture) and eventually remodeled into the stronger lamellar bone. At the nanostructural level, the collagen fiber arrays are comprised of individual collagen fibrils. These collagen fibrils contain gaps that plate-like apatite crystals occupy. At the sub-nanostructural level, carbonated apatite crystals, type I collagen fibrils, and water comprise the main basic constituents of bone (Oyen, 2008).

2.2 Bone Physiology

Bone is living tissue that is continuously adapting and maintaining its structure throughout life. Aside from the mineralized matrix and structural features therein, bone also contains a number of specialized cells which carry out the metabolic processes necessary for meeting the demands placed on our skeleton. These cells are the bone-resorbing osteoclasts, bone-forming osteoblasts, osteocytes, and lining cells (Fig. 2.3).

2.2.1 Osteoclasts

Osteoclasts are large, multi-nucleated cells that are approximately 20-100 $\mu m$ in diameter and are derived from hematopoietic cells of the monocyte/macrophage lineage (Katagiri and Takahashi, 2002). These cells are responsible for removing old bone by
Figure 2.3. Schematic of the specialized cells within bone. Osteoclasts are large multi-nucleated cells responsible for the removal of old bone tissue. Osteoblasts are mono-nucleated cells that are responsible for forming new bone tissue. Osteocytes and bone lining cells are former osteoblasts that are trapped in the bone or attached to the bone surface, respectively. Figure adapted from www.roche.com/pages/facets/11/ostedefe.htm.

secrating acids and enzymes to break down the mineralized bone matrix; a process called resorption. A characteristic feature of osteoclasts is the ruffled border, which is surrounded by an annular sealing zone (also called the “clear zone”). The destructive chemicals used to dissolve the mineralized bone matrix are transported to the ruffled border by secretory vesicles; the sealing zone acts to contain these chemicals from affecting the surrounding areas (Martin et al., 1998). The attachment of an osteoclast to the bone surface is achieved by dynamic structures called podosomes (Hadjidakis and Androulakis, 2006). By continually assembling and disassembling these podosome structures, an osteoclast is able to move across the bone surface. Individual osteoclasts resorb bone and advance through bone tissue at rates up to 40 μm/day (Jaworski and Lok, 1972) and have an average lifespan of 12 days (Jilka, 2003).
Numerous factors are involved in the recruitment and regulation of osteoclasts. The formation of osteoclasts is supported by cells early in the osteoblast lineage that express membrane-bound receptor activator of nuclear factor κβ ligand (RANKL) and macrophage-colony stimulating factor (M-CSF) (Baron, 1993). M-CSF is a secreted cytokine that influences hematopoietic cells to differentiate into macrophages or other related cell types. RANKL is a messenger molecule that participates in osteoclast activation by binding to the receptor activator of nuclear factor κβ (RANK), which is expressed on the surface of osteoclasts.\(^1\) Over the years, several different terms have been used for RANKL, such as tumor necrosis factor related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL), and osteoclast differentiation factor (ODF) (Fuller et al., 2000). The main role of RANKL in bone is to stimulate osteoclast differentiation and activity, and to inhibit osteoclast apoptosis (or cell death) (Khosla, 2001). The activation of osteoclasts is regulated by osteoprotegerin (OPG), a secreted decoy receptor of RANKL. The presence of OPG acts as a paracrine inhibitor of osteoclast formation (Udagawa et al., 2000). Osteoclasts are of paramount importance to skeletal health as their inactivity or absence has been observed to cause potentially life-threatening pathologies, one example being osteopetrosis (Del Fattore et al., 2008).

2.2.2 Osteoblasts

Osteoblasts are cuboidal mononuclear cells that are approximately 10 \(\mu\)m in diameter. These cells share the same lineage as chondrocytes, myocytes, and adipocytes as they all are derived from a common progenitor, namely the undifferentiated mesenchymal stem cell (Katagiri and Takahashi, 2002). Proliferating osteoblast precursors are pushed toward the preosteoblast phenotype by the expression of the transcription factors, such as murine Runt-related transcription factor-2 (Runx2), distal-less homeobox-

\(^1\)RANK is a type I membrane protein that is expressed on the surface of osteoclasts.
5 (Dlx5), and msh homeobox homologue-2 (Msx2) (Robling et al., 2006). Committed preosteoblasts express type I collagen and bone sialoprotein (BSP), but require further expression of Runx2, osterix, and members of the Wnt signaling cascade to achieve a mature matrix-producing osteoblast phenotype.

Osteoblasts are responsible for synthesizing and depositing osteoid, the unmineralized organic matrix of bone. Osteoid is a low modulus material comprised primarily of type I collagen that serves as a template for the mineralized tissue that it matures into over time. Besides the collagen content of osteoid, a number of growth factors produced by osteoblasts are incorporated as well. The growth factors known to be incorporated in osteoid include transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), insulin-like growth factors (IGF), and bone morphogenic proteins (BMP) (Hadjidakis and Androulakis, 2006). Incidentally, these growth factors can be released from the matrix via bone resorption.

Osteoblasts produce osteoid at a rate of 1.4-3.0 μm/day and also participate in the mineralization process (Eriksen, 1986). These cells have many fine processes that contact neighboring cells, allowing for communication (Jones, 1974). Their lifespan can vary from a few days to around three months (Jilka, 2003). As an osteoblast matures, it becomes progressively flatter and wider and reduces its rate of osteoid production. At the end of an osteoblast’s life cycle, it can become entombed in the newly deposited osteoid as an osteocyte, die by apoptosis, or become inactive and transform into a lining cell that covers the newly quiescent bone surface (Franz-Odendaal et al., 2006).

2.2.3 Osteocytes

Osteocytes are the most abundant cellular component of the adult skeleton, comprising approximately 90-95% of all bone cells (Parfitt and Chir, 1977). As previously
mentioned, osteocytes are former osteoblasts that have ceased osteoid production and are literally buried in the bone matrix; they reside in small cavities called lacunae. These cells extend slender cytoplasmic processes (50 on average) through small channels called canaliculi (100-300 nm in diameter) (Bonewald, 2006; Manolagas, 2006). These cellular processes facilitate communication with neighboring osteocytes and cells on the bone surface (i.e., bone lining cells, osteoblasts, and/or osteoclasts), and can also extend into the bone marrow (Kamioka et al., 2001; Vääränen and Zhao, 2002). Intercellular communication is achieved via gap junctions which allow messenger molecules to be passed from cell to cell. Compared to osteoclasts and osteoblasts, osteocytes have significantly longer lifetimes (i.e., on the order of years) (Franz-Odendaal et al., 2006). This is due to the network of canaliculi providing a means for the passage of nutrients that are necessary for maintaining cell viability.

Many argue that the osteocyte is the most likely cell to serve as a transducer of signals resulting from mechanosensation in the bone tissue. Osteocytes are recognized as mechanical sensor cells because they produce prostaglandins and nitric oxide in response to mechanical stress (Chow et al., 1998; Klein-Nulend et al., 1995; Lean et al., 1995). These cells are also more sensitive to fluid flow shear stress on their cell membrane than mechanical deformation (Westbroek et al., 2000). Osteocytes have been observed to affect the cellular processes of osteoclasts and osteoblasts. For example, osteocytes produce the bone morphogenic protein sclerostin, which has been identified as a down-regulator of osteoblast activity (Poole et al., 2005). Some researchers believe that osteocytes experiencing sufficient mechanical stimuli constantly send signals to surface cells to inhibit bone resorption (Burger and Klein-Nulend, 1999). This theory is supported by experimental evidence of the arrest of osteoclast activity upon restoring the prior mechanical load to a temporarily unloaded specimen (Noble et al.,
Additionally, evidence from *in vitro* studies on bone resorption suggests that bone with osteocytes is resorbed more readily than bone devoid of osteocytes (Shimizu et al., 1990). However, at present, the true function of osteocytes in maintaining the integrity of our bones remains poorly understood (Manolagas, 2006).

### 2.2.4 Bone Lining Cells

Bone lining cells are flattened, inactive osteoblasts that lie on the quiescent (non-remodeling) surfaces of bone. These cells are the second most abundant cellular constituent of bone, covering more than 90% of endosteal surfaces in the adult skeleton (Robling et al., 2006). Like osteocytes, bone lining cells extend cytoplasmic processes and connect to each other (via surface canaliculi) and to local osteocytes, allowing them to communicate through gap junctions (Ilvesaro and Tuukkanen, 2003; Martin et al., 1998; Recker, 1992). It is believed that lining cells have some role in the activation process of bone remodeling as they respond to various chemical and mechanical stimuli (Miller and Jee, 1987). For example, a necessary step in the activation of bone resorption is the retraction of bone lining cells from the bone surface, exposing the underlying osteoid. However, an unresolved controversy exists regarding whether adaptation signals originate from bone lining cells, osteocytes, or both.

### 2.3 Bone Modeling and Remodeling

One of the most intriguing aspects of bone is its ability to adapt to changes in its mechanical environment. The adaptation process encompasses growth, damage repair, adaptation to mechanical loads, and mineral homeostasis (Burr, 2002). It is generally accepted that bone adaptation occurs in response to the mechanical demands of our daily activities; however, genes and age-related factors (e.g., post-menopausal estrogen...
deficiency in women) may impact the efficacy of this process as well. Adaptation occurs on the free surfaces in the mineralized bone matrix. According to Frost (1964), bone adaptation has been classified into two types, surface and internal remodeling. Surface remodeling, which is commonly referred to as modeling, involves bone adaptation that is related to global changes in bone geometry and reshaping of cortical surfaces. Internal remodeling, which is commonly referred to as remodeling, involves tissue level adaptation processes occurring on trabeculae and in Haversian systems. Approximately 5% of cortical bone and 25% of trabecular bone is replaced in human adults each year by remodeling (Martin et al., 1998), resulting in the renewal of the skeleton over a period of 10-15 years (Manolagas, 2006).

At the cellular level, the bone modeling and remodeling processes are quite similar. Both are based on the activity of bone-resorbing osteoclasts and bone-forming osteoblasts. Bone modeling is usually thought of as an adaptive response occurring as a result of increased stimuli (overuse) or decreased stimuli (disuse). Modeling is characterized by an inherent systemic coupling of osteoclasts and osteoblasts at different sites. As previously mentioned, modeling is responsible for global changes in bone geometry, such as during growth or local reshaping after fracture. Bone remodeling, on the other hand, is characterized by the coupled action of the bone cells at the same site. At this location, osteoclasts first resorb a cavity of bone and then osteoblasts refill the cavity with new tissue, which is separated from the native tissue by a cement line. It has been observed that remodeling targets microdamage to prevent the accumulation of microcracks in bone tissue (Burr, 2002). Remodeling also has a role in the regulation of essential minerals within the extracellular fluid (Jee, 2001). The closely coordinated efforts of the osteoclasts and osteoblasts during the remodeling process are commonly termed a basic multicellular unit (BMU) (Frost, 1986), which was previously referred to
as a bone remodeling unit (BRU) (Parfitt, 1979). In both cases of adaptation, the exact
communication between the bone cells, if any, has yet to be conclusively determined.

2.3.1 Cortical Bone Remodeling

In cortical bone, BMUs renew osteonal tissue by tunneling through the targeted
region and creating a new osteon. The elongated cylindrical cavities occupied by the
BMUs are on the order of 2 mm in length and 0.2 mm in diameter and are oriented
along the long axis of the bone (Parfitt, 1994). The typical lifespan of a cortical BMU
is 6-12 months and it can travel distances ranging from 2-6 mm. Since the lifespan of
the BMU exceeds that of the cells composing it, new osteoclasts and osteoblasts are
continually recruited to forestall the arrest of remodeling activity.

The frontal section of the cortical BMU (~0.2 mm in length) is known as the cutting
cone, which is inhabited by roughly nine osteoclasts that are resorbing the bone in front
of them (Jaworski et al., 1981). The cutting cone progresses along the longitudinal axis
of the bone at a rate of about 20-40 µm/day for a period of up to 200 days (Eriksen
et al., 1994; Parfitt, 2002). A reversal zone is located immediately behind the cutting
cone (~0.2 mm in length), where cement lines are deposited on the newly resorbed
bone surface. At the end of the BMU is the closing cone (~1.6 mm in length), which is
lined with around 2,000 osteoblasts forming bone tissue within the cavity (Jaworski and
Hooper, 1980). The entire cavity is not refilled; a Haversian canal with a diameter of 40-
60 µm remains, allowing for vasculature to pass through. The duration of the formative
period is about 140-150 days (Eriksen et al., 1994). A schematic representation of a
cortical BMU is illustrated in Fig. 2.4.
2.3.2 Trabecular Bone Remodeling

Unlike cortical bone, trabecular bone remodeling is a surface phenomenon in which renewed tissue forms scalloped interruptions in the lamellar system. This process involves the erosion of a cavity of bone, called Howship’s lacunae (Marcus, 1987), which is subsequently refilled with new tissue. A trabecular BMU measures on the order of 100 µm in length by 40-60 µm in depth, and has a typical lifespan of around 145 days (Eriksen et al., 1994; Eriksen and Kassem, 1992). While the geometry of the renewed tissue differs from cortical bone, “coupling” between the bone cells remains the same.
The trabecular remodeling process begins with resorption and lasts approximately 33-68 days (Eriksen et al., 1994). This period can be subdivided into 6-12 days of osteoclast activity, followed by 24-48 days of mononuclear cell activity; producing a cavity of about 60 µm in depth. Osteoclasts resorb bone in a direction perpendicular to the bone’s surface at approximately 2.4-6.0 µm³/µm²/day, while the much slower mononuclear cells resorb at a rate of 0.3-1.6 µm³/µm²/day (Eriksen et al., 1984b). Following resorption, a 7 day reversal period occurs in which a cement line is deposited by preosteoblast-like cells (Marcus, 1987). Finally, osteoblasts deposit osteoid in the cavity at a rate of 1.4-3.0 µm³/µm²/day over a period of 3-4 months (Eriksen, 1986). The mineralization process begins about 15 days after the onset of formation. A diagram of a trabecular BMU is illustrated in Fig. 2.5.

Figure 2.5. Schematic of a trabecular BMU from Eriksen (1986). The succession of events at a single location is as follows: (0) Exposed bone surface; (1) Osteoclast (OCL.) resorption; (2) Resorption by mononuclear (MON.) cells; (3) Appearance of preosteoblast-like (POB.) cells; (4) Early osteoid deposition by osteoblasts (OB.); (5) Late bone formation by osteoblasts after the onset of mineralization; (6) Quiescent bone surface covered by lining cells.
2.3.3 Phases of the Bone Remodeling Cycle

Bone remodeling is the dominant adaptive process in the adult skeleton. Hattner et al. (1965) found that over 96% of the bone formation processes in adult trabecular bone followed resorption at the same location. Although BMUs tunnel through cortical bone as opposed to excavating trenches on the surface of trabecular bone, the remodeling cycle follows the same progression. The remodeling process can be summarized into six phases: activation, resorption, reversal, formation, mineralization, and quiescence (Martin et al., 1998). Initially, the bone surface is covered with bone lining cells. Deviations in a local stimulus (e.g., mechanical strain and/or fatigue microcracking) trigger the activation of remodeling. Differentiated cells are recruited from precursor cells that eventually form osteoclasts. The active osteoclasts resorb bone until the resorption cycle is complete and then undergo apoptosis. This is followed by a reversal period, in which the osteoclastic activity transitions into osteoblastic activity. Once the osteoblasts have been fully activated, they begin refilling the resorption cavity with osteoid. Upon maturation of the osteoid, the collagen fibrils begin to mineralize. Full mineralization is suspected to take up to six months. Remaining osteoblasts then undergo apoptosis or differentiate into lining cells and osteocytes. The bone then returns to a quiescent state and osteocytes trapped in the newly remodeled tissue are able to support mechanotransduction for transmitting future remodeling signals. The bone remodeling process is depicted in Fig. 2.6.

2.4 Bone Mechanoregulation

It is generally accepted that bone is remodeled to adapt its structure to changes in its local mechanical environment and for repairing damage. Experimental studies have demonstrated that strain and microdamage are particularly effective in regulating the
remodeling process (Burger and Klein-Nulend, 1999; Burr et al., 1985; Lanyon et al., 1982; Lee et al., 2002; Sato et al., 2007). From a mechanical standpoint, formation is usually associated with increased strain (overuse) and resorption with decreased strain (disuse). Studies utilizing cyclic loading to create damage in canine bone have demonstrated that new remodeling sites are associated with microcracks four to six times more often than expected by chance alone (Burr and Martin, 1993; Mori and Burr, 1993). One possible explanation is that the microcracks may provide for local strain relief. Thus, the ideology of strain-based remodeling may also hold for targeting microdamage.

2.4.1 Evidence for Osteocyte Mechano-sensation

Many researchers have sought to determine how mechanosensation occurs in bone to improve our understanding of remodeling behavior. As previously mentioned, osteo-
cytes lying within the bone matrix and lining cells covering the bone surface are ideally placed for sensing various stimuli. *In vitro* studies have shown they both respond to mechanical stimuli (el Haj et al., 1990). However, it remains to be determined if the osteocytes, or lining cells, or both act as sensors. One theory is that osteocytes are constantly sending signals to lining cells, which act as signal transducers, to suppress osteoclast activity under normal stimulation. If the local strains were relaxed due to inactivity or local unloading of tissue due to microdamage, osteoclast suppression would cease allowing for resorption.

Unfortunately, the experimental observations surrounding osteocyte influence on the initiation of resorption are conflicting (Gu et al., 2005). Evidence exists for osteocytes increasing osteoclast resorption activity in organ culture (Shimizu et al., 1990) and also for the osteocytic cell line MLO-Y4 supporting osteoclast formation and activation *in vitro* (Zhao et al., 2002). However, other studies suggest that chicken calvarial osteocytes inhibit osteoclastic bone resorption (Maejima-Ikeda et al., 1997) and MLO-Y4 cells are responsible for biological activity that inhibits osteoclastic activity (Heino et al., 2002). Reconciling the differences between the aforementioned experimental studies is difficult as all of the confounding factors present are not clearly understood. For instance, these studies may not capture indirect effects as a result of the surrounding tissue *in vivo*, such as the relative increase of other supporting/inhibiting factors.

In an attempt to emphasize the aforementioned argument, observations regarding the impact of TGF-β on osteoclast activity will be exemplified. It has been observed that TGF-β supports the direct enabling and indirect inhibition of the recruitment of osteoclasts (Fox and Lovibond, 2005). As previously mentioned, osteoclast differentiation is reported as being supported by cells early in the osteoblast lineage that express RANKL and M-CSF. However, studies have shown that RANKL was unable
to induce the formation of osteoclasts in cultures of osteoclast precursors that lacked TGF-β (Fox et al., 2000; Fuller et al., 2000; Kaneda et al., 2000). In addition, it has been observed that TGF-β enables RANKL-induced osteoclast differentiation in pure populations of monocytes, suggesting that this action is a direct effect on the precursors themselves. Although TGF-β is reported to be required to enhance osteoclastogenesis (Filvaroff et al., 1999; Fuller et al., 2000), other evidence demonstrates that it not only reduces the rate of resorption by osteoclasts via the production of OPG by osteoblasts and marrow stromal cells (Murakami et al., 1998; Quinn et al., 2001; Takai et al., 1998; Thirunavukkarasu et al., 2001), but also plays a role in the apoptosis of osteoclast nuclei at relatively high concentrations (Hughes et al., 1996). As suggested by Karst et al. (2004), the effect of TGF-β on the RANKL/OPG axis is more complicated than was first appreciated; low levels of TGF-β increase RANKL production, whereas the higher concentrations, seen after TGF-β is released from the matrix during resorption, inhibit RANKL by up-regulating OPG.

From the examples given, the difficulty in unraveling the pathways by which the remodeling process is controlled is apparent. The confounding factors related to the expression of genes, growth factors, and proteins, involved in the initiation of resorption, may be more complex than anticipated. In addition, a further complication exists as meaningful measures of osteocyte activity in their native environment are currently limited. However, despite these issues, the theory of osteocytic suppression of resorption is useful when trying to explain the process of bone remodeling (Burger and Klein-Nulend, 1999).
2.4.2 Microdamage-Stimulated Remodeling

Convincing evidence has accumulated over the last two decades, indicating that remodeling serves to renew bone that was impaired by microdamage (Burr, 1993; Burr et al., 1997; Burr and Martin, 1993; Burr et al., 1985; Norrdin et al., 1998). It has been well established that fatigue microdamage results from repetitive loading in the physiological range and damage accumulation leads to the degradation of the mechanical properties of the bone matrix; a comprehensive review is presented by Burr et al. (1997). It has also been noted that microdamage is prevalent throughout bone tissue and can be observed as linear microcracks or diffuse damage (Vashishth et al., 2000).

While it is well accepted that bone remodeling provides for mineral balance, damage repair, and functional adaptation, it is not clear how compromised locations in bone are selected for remodeling. Researchers have argued that it is neither selectively nor energetically advantageous for remodeling activities to indiscriminately increase the rate of bone turnover at all skeletal sites in the event of a single damaged location (Burr, 2002). As previously mentioned, studies have indicated that remodeling activities associated with microdamage in bone is not likely to be a random phenomenon. Understanding how microdamage initiates remodeling is a key step in unraveling the process by which site-specific remodeling occurs.

A recent study showed that excessive stretching of osteocytes cultured in a three-dimensional gel led to osteocyte apoptosis as a result of microdamage. In addition, it was shown that the conditioned medium collected from these mechanically damaged osteocytes could promote a significant tartrate-resistant acid phosphatase (TRAP) positive cell induction from bone marrow cells (Kurata et al., 2007). The induction of TRAP-positive cells in their study indicated that soluble factors secreted from the damaged osteocytes were capable of regulating the initial phase of bone resorption. This
evidence does not prove that excessively stretched osteocytes secreted stimulating factors before their deaths, resulting in the increase of osteoclast differentiation; it is also possible that the supposed inhibitory factors preventing osteoclastic cell differentiation were no longer secreted due to osteocyte apoptosis, resulting in the recruitment of the TRAP-positive cells. Regardless of either of these circumstances, the fact remains that the promotion of bone resorption is associated with osteocyte apoptosis due to micro-cracking (Aguirre et al., 2006; Noble et al., 2003; Verborgt et al., 2000). This claim is further substantiated by the findings of Cardoso et al. (2009), as they observed that osteocyte apoptosis was spatially and temporally linked to bone fatigue-induced microdamage and to subsequent intracortical remodeling.

While osteocyte apoptosis is evidenced as a primary factor in the initiation of remodeling, microdamage is not its only cause. For example, Emerton et al. (2010) reported that osteocyte apoptosis due to estrogen withdrawal is linked to local remodeling activities. Local strain levels have also been observed to impact osteocyte behavior. The next section will highlight observations related to strain-stimulated remodeling activity.

2.4.3 Strain-Stimulated Remodeling

Since bone tissue is poorly innervated and cannot rely on the central nervous system to distribute signals from mechanical stimulation, bone cells must process loading information locally (Robling et al., 2006). Moreover, it remains unknown which factors of the strain environment are converted into cellular signals via mechanotransduction, leading to bone remodeling. For instance, the strains applied to whole bones in vivo are on the order of 0.04-0.3% (Rubin, 1984), while 1-10% were required to stimulate a cellular response in cell culture (Murray and Rushton, 1990). However, in a study by Wang et al. (2007) it was proposed that osteocytes can sense their mechanical en-
vironment via integrin receptors attached to the bone matrix; these attachments can increase cellular strains by up to two orders of magnitude as compared to the global strains. Another factor to consider is the fluid movement through the bone tissue upon deformation. It was found that fluid flow-induced cellular deformation is related to the amount of nitric oxide (NO) and prostaglandin E\(_2\) (PGE\(_2\)) produced by osteoclasts *in vitro*; both factors are biochemical mediators of bone formation (McGarry et al., 2005).

For the case of disuse, it is possible that a lack of mechanical loading may result in the arrest of osteocyte signaling or even apoptosis, which has the potential to inhibit the osteocytic suppression of resorption. Disuse reduces fluid flow through the canaliculari, lowering flow-induced shear stresses on the osteocyte cellular membrane and the transport of nutrients and waste products (Burger and Klein-Nulend, 1999). It has been suggested that since osteocytes derive their nutrients from canalicular fluid, mechanical loading-induced canalicular fluid flow might permit the delivery of so-called survival molecules to the osteocyte (Knothe Tate et al., 1998; Lozupone et al., 1996). Therefore, a reduction in mechanical loading has the potential to reduce osteocyte viability or even lead to apoptosis.

The promotion of bone resorption is associated with osteocyte apoptosis due to microcracking. Therefore, it is reasonable to infer that disuse-related osteocyte apoptosis is also a likely candidate for the removal of osteocytic suppression of resorption. This is supported by evidence that a reduction in loading leads to bone resorption (Gross and Rubin, 1995), while the inhibition of bone resorption is observed in mechanically stimulated bone of experimental animals (Hillam and Skerry, 1995). To investigate how osteocyte apoptosis might function to control site-specific resorption in a state of disuse, Noble and Reeve (2000) studied bone loading in rat ulnae subjected to moderate loading regimes, insufficient to cause plastic deformation and any significant microdamage.
They observed that there was an inverse relationship between osteocytes showing perceptible DNA breaks and loading, further supporting the notion that osteocyte viability decreases as mechanical loading is reduced. However, osteocyte apoptosis is not necessarily a requirement for the inhibition of the osteoclastic suppression of bone resorption in the case of disuse. For instance, depriving a bone of mechanical loading would rapidly induce osteocyte hypoxia; however upon restoring the loading it is observed that it is possible to prevent osteocyte apoptosis (Dodd et al., 1999). This is supported by the work of Noble et al. (1997), as their experiments demonstrate the arrest of resorptive activity associated with an increase in mechanical loading of previously unloaded specimens. This occurrence would be unlikely if there were no live osteocytes local to the resorptive site.

From these studies, it seems reasonable to infer that the arrest of osteocyte signaling and/or apoptosis is most likely at very high and at very low strain levels. In addition, osteocytic suppression of resorption is likely to occur at strain levels that are appropriate for normal activity of everyday existence (Noble and Reeve, 2000).

2.5 Early Works in Bone Remodeling

The concept of the mechanical implications of the shape of bones dates back to the observations by Galileo Galilei in 1638 (Galilei, 1638). Although many related observations followed, it was not until the 19th century when the idea of mechanically mediated bone adaptation was first suggested. Bell and Wyman (1902) and Bourgery (1832) recognized that cancellous bone architecture is influenced by mechanical forces and introduced the idea that the cancellous structure maximizes strength relative to the amount of material used. However, the most widely noted collaboration in the effort to uncover the mechanical influences on bone structure occurred between G. Hermann
von Meyer and Carl Culmann. Known for his work as an anatomist, von Meyer was studying the trajectories of trabecular bone in longitudinal slices of the proximal human femur and documented his observations through sketches (von Meyer, 1867). Culmann, a well-known mathematician and the father of the method of graphical statistics, analyzed von Meyer’s sketches and concluded that the trabecular architecture had very similar patterns when compared to the stress trajectories he had calculated for a curved crane (Fig. 2.7).

Culmann and von Meyer’s findings laid the foundation for the orthopaedic surgeon Julius Wolff to discover that it was not simply by chance that the trabecular architecture resembled the stress trajectories in bone. In fact, Wolff concluded that the trabecular struts were aligned along the principal stress trajectories experienced in bone, known as the trajectorial theory of trabecular alignment. Wolff (1892) hypothesized, “Every
change in the form and function of bone[s] or of their function alone is followed by certain definite changes in their internal architecture, and equally define[d] alteration in their external conformation, in accordance with mathematical laws.” This became known as “Wolff’s Law”, and is typically shortened to the concept of the “functional adaptation” of bone. Wolff’s ideas went largely unquestioned by the scientific community of the time and are often credited as the basis for adaptive bone remodeling even today (Jacobs, 1994). Wolff often wrote about the existence of mathematical rules that govern trabecular architecture, although, not being an engineer or mathematician, he never formulated a mathematical theory (Martin et al., 1998).

Roux (1895) took an interest in Wolff’s ideas and began incorporating them in his theory of the functional adaptation of biological structures and organs. Roux did not believe that the idea of functional adaptation was limited to bone. He believed that this theory could be applied to other tissues and organs in the body, such as the liver, via processes of atrophy and hypertrophy by which the functional demands necessitate an adaptive response (Jacobs, 1994). Following these works, little progress was made toward a mathematical description of bone remodeling until the emergence of high speed digital computers and computational solid mechanics. Renewed interest in the pursuit of a constitutive model of bone adaptation stemmed from the works of both Pauwels and Kummer. Amongst Pauwels’ contributions was his mathematical formulation of Roux’s functional adaptation theory (Pauwels, 1965). For this model, it was hypothesized that surface adaptation was performed to achieve an optimal stress level in bone. Kummer (1972) performed photoelastic studies on the structure of bone and constructed a set of three-dimensional stress trajectories for the proximal femur that he claimed were in agreement with trabecular orientation. He also hypothesized that internal remodeling was a regulatory response that could be characterized by a second-order control sys-
tem, with overdamped, underdamped, and critically damped modes (Kummer, 1971). Around the same time, Frost (1964) introduced one of his first mathematical descriptions of bone adaptation. This model served as the basis of his “mechanostat theory”, which is widely regarded as the seminal theory of bone remodeling.

2.6 Model Classification

Over the past several decades, various theoretical and computational models have been developed to describe the bone adaptation process. According to Hart (2001), these computational models fall into three main categories: phenomenological, optimization, and mechanistic. Each modeling technique possesses a different set of limitations and provides unique insights into the bone remodeling problem. It is important to understand the fundamental differences between each type of model to ascertain which framework best suits the objective of a particular study.

A majority of the computational models of bone adaptation that have been developed to date, have been phenomenological. The basis for a phenomenological model is to quantitatively describe an applied stimulus and the associated remodeling response. Some of the most popular stimuli utilized to drive the bone remodeling process are stress, strain, strain energy density, and damage (Burr et al., 1985; Cowin and Hegedus, 1976; Frost, 1987; Fyhrie and Carter, 1986b; Lanyon et al., 1982; Lee et al., 2002). These models can be useful for describing and predicting the outcome of bone adaptation which is especially suited to the goals of engineers and clinicians. For example, it is desirable to be able to design bone implants that integrate with the surrounding tissue and are stable throughout their life cycle (Hart and Fritton, 1997). Although phenomenological models are useful and interesting, they are limited by the fact that they do not contribute to the understanding of the biological bases for the remodeling pro-
cess. These models typically represent net remodeling behavior and do not accurately represent the activation-resorption-formation sequence which occurs. However, they are widely studied as these models can be directly applied to organ level simulations.

Several researchers have sought to explain the bone remodeling process by the application of optimization theory (Bagge, 2000; Bendsøe et al., 1995; Hollister et al., 1993; Nowak, 2006a,b; Weinans et al., 1992; Xinghua et al., 2005). The optimization approach typically utilizes a global starting assumption regarding the optimality of the bone structure; for example, bone adapts to minimize mass or to maximize strength. According to Hart (2001), these studies provide useful information related to bone as a mechanical structure, but are deficient in describing an individual’s skeletal adaptation for several reasons. First, optimization studies assume that not only is the remodeling process seeking to achieve a specific goal, but the physiological processes involved are also aimed at achieving the same goal. This assumption implies high levels of coordination between these processes, along with environmental awareness, for which strong evidence has not been discovered (Hart, 2001). A second deficiency of the optimization approach is the fact that optimization strategies focus on achieving the outcome of adaptation, while typically omitting the physiological activity associated with the required structural changes (Hart, 2001). Huiskes (2000) points out that perhaps Wolff’s law has led many to focus on the design of bone architecture, rather than how bones are maintained. He criticizes models based purely on optimization rules by stating that “There are no mathematical optimisation rules for bone architecture; there is just a biological regulatory process, producing a structure adapted to mechanical demands by the nature of its characteristics, adequate for evolutionary endurance.” While optimization models may lack biological relevance, they provide an avenue for uncovering the secrets of nature’s design process and illuminate extensions into other fields such as
structural topology optimization.

Mechanistic models are, perhaps, the most intriguing and challenging approach to modeling the bone adaptation process. The purpose of a mechanistic model is to provide a mathematical explanation for the chemical and biological mechanisms that have been observed in various stages of the remodeling process. However, for this reason, mechanistic models are the most difficult to undertake. These models require a level of understanding that surpasses the cause-and-effect predictions made by the phenomenological models and necessitate an understanding of the interplay between genes, hormones, and the mechanical environment (Hart, 2001). Mechanistic models are focused on the examination of the physiological processes that govern bone adaptation, and not on the possible mathematical rules that bone architecture might be the answer to (Huiskes, 2000). These models are sought, for example, by biologists as a means to better describe and manipulate the processes and steps in the remodeling cycle (Hart and Fritton, 1997). Few purely mechanistic models have been developed and they are typically limited in scope. Mechanistic models are the key to gaining insights into the unknown aspects of bone adaptation and maintenance.

The objective of this work is to investigate the impact of incorporating more detailed cellular mechanisms into a framework for predicting the bone remodeling process. Although a purely mechanistic model would be ideal, it is not feasible to adequately represent the cellular processes during each phase of the remodeling cycle in single model of this type. Therefore, in order to maintain the desired scope of the investigation, it is necessary to consider a model which possesses both mechanistic and phenomenological characteristics. This type of model is advantageous as cause and effect phenomenological behaviors can be used to fill information gaps between well defined cellular mechanisms.
2.7 Theoretical and Computational Modeling - State of the Art

An extensive amount of research has been conducted on developing a relationship describing the mechanical adaptability of bone. Over the past several decades, a multitude of theoretical and computational models have been proposed to explain and predict bone functional adaptation. Computational simulations are a technique that can be utilized to test hypotheses that are not easily examined experimentally, which often occurs in the case of biological processes. The goal of these simulations is to further our understanding of how bone reacts to a variety of stimuli, such as mechanical stimuli, microdamage, aging, and drug treatments. However, it remains that our understanding of bone remodeling is still a “work in progress”.

Knowledge gained from existing models has been utilized for improving implant design for added stability and fixation (Huiskes et al., 1987). Current work focusing on the cellular activity of bone adaptation has the capacity to improve tissue-engineered constructs and pharmaceutical treatments by unveiling the factors necessary for augmenting local repair mechanisms (Martin and Buckland-Wright, 2004). One significant drive behind this field of research is to improve the predictive capacity of bone remodeling simulations to provide new insights into early warning signs of bone disease.

The scope of the previous work encompasses theoretical, mechanistic, optimization, and phenomenological modeling approaches. In this section, a literature review of the most prominent bone remodeling simulations is presented. The goal of this review is to document the reasoning behind important mathematical rules being used in models today, along with those presented in this work. To preserve the continuity of the progression of previous bone remodeling research, models will be presented in a conceptual sequence rather than grouped by classification. The nomenclature presented in this section preserves the original notation utilized by the respective authors.
2.7.1 The Mechanostat Theory

The still-evolving seminal theory for describing bone adaptation, introduced by Frost (1987), is known as the “mechanostat theory”. Frost’s model originated from experiments and clinical observations about bone behavior (Frost, 1964). For instance, bone mass is suitable for its typical mechanical demands in the sense that it is over adequate, but never inadequate. From this ideology, he envisioned some mechanism(s) monitoring the mechanical usage of bone and eliciting an appropriate biological response to reduce the discrepancy between mechanical demands and bone mass. This mechanism was likened to that of a household thermostat where it would turn “ON” in response to a deviation in the mechanical usage and “OFF” in its absence, from which he coined the term “mechanostat” (Frost, 1987). The objective of this theory was to unify growth, modeling, and remodeling as a bone metabolic response to the deviation between applied strains and certain “setpoints”.

This model assumes that bone behaves as a closed loop control system in which strain setpoints trigger a bone metabolic response. Each setpoint was identified as a minimum effective strain (MES) required to trigger the corresponding adaptive response, ultimately returning the bone to a homeostatic state (Frost, 1983). These setpoints define the thresholds for remodeling (MESr), modeling (MESm), microdamage (MESp), and bone fracture (Fx). According to Frost (1987), the setpoints MESm and MESp may be “genetically determined”, and therefore vary between individuals. These setpoints may also vary with age and/or disease. For example, diseases affecting bone cells may have caused the cells to become under- or over-reactive (Frost, 1987).

The aforementioned strain setpoints are used to separate the mechanical usage windows for bone as described by Frost (1992). The disuse window (DW) occurs at low strains ranging from 0 to MESr, where bone is lost due to a decrease in remodeling bal-
ance (i.e., more bone is resorbed than refilled). The adapted window (AW), also called the “lazy zone” or “dead zone”, involves strains ranging from MESr to MESm and denotes a physiological regime where bone is in equilibrium and no adaptive response is initiated. Strains in this range have no discernable effect on bone adaptation, regardless of their frequency (Frost, 1990). The concept of a “lazy zone” was originally proposed by Carter (1984). The mild overload window (MOW) occurs between strains ranging from MESm to MESp, where net modeling activity increases bone mass through lamellar bone formation. Strains ranging from MESp to Fx denote the pathologic overload window (POW), where bone microdamage occurs more prominently and the pathologic response of woven bone formation occurs. If enough microdamage accumulates, this can cause bone to escape repair and cause/lead to a number of different types of pathologic fractures (Frost, 2004). The mechanostat theory is diagrammed in Fig. 2.8.

According to Frost (2003), the mechanostat theory predicts 32 different phenomena. However, as with all theories of bone remodeling, the mechanostat theory is not without criticism. The belief that a single unifying value of strain (or an applied stimulus) for which bone maintains homeostasis systemically is regarded as a fundamentally flawed concept (Skerry, 2006). The skeleton responds to a large variety of stimuli, of which peak strain is only one, and the strain stimulus varies throughout the body. In addition, Frost (2003) asserts that this theory is not capable of explaining why bones that receive minimal loading are not resorbed away, such as nasal bones, inner ear ossicles, and the cranial vault. He hypothesizes that the strength of these bones is likely to result from a different set of rules due to the fact that load-bearing is not their primary function. However, Carter (1984) suggests that perhaps these bones respond to significantly smaller strains (i.e., lower setpoints) as compared to load-bearing bones. Therefore, the mechanostat theory may still apply.
Figure 2.8. Diagram of Frost’s mechanostat theory for predicting changes in bone mass (due to modeling and remodeling) according to the tissue strain level. The various minimally effective strain (MES) setpoints are displayed at the bottom. These setpoints define the strain thresholds for remodeling (MESr), modeling (MESm), microdamage (MESp), and fracture (Fx). The strain span between the MESr and MESm represents the range of strains that bones normally experience. At the top, bone’s mechanical usage windows are given with their corresponding strain ranges (Frost, 1992). These are the disuse window (DW), adapted window (AW), mild overload window (MOW), and pathologic overload window (POW). Note that the strain setpoints are not given precise values due to individual variability. Figure reproduced from Frost (2003).
2.7.2 Strain Adaptive Remodeling

The theory of adaptive elasticity was developed as a thermomechanical continuum description of the bone remodeling process (Cowin and Hegedus, 1976; Cowin and Nachlinger, 1978; Hegedus and Cowin, 1976). A unique attribute of this work is that the model formulation was based on physical principles (i.e., conservation of mass, momentum, energy, and the entropy inequality). This is a two-phase model composed of a porous elastic solid which represents bone and a perfusant which represents extracellular fluid. The underlying hypothesis of this theory is that bone adaptation can be modeled by a chemically reacting porous medium in which the rate of the reaction (i.e., remodeling) is controlled by the applied strain. The strain-controlled reaction allows for mass to be transferred from the extracellular fluid phase to the bone phase and vice-versa (Cowin and Nachlinger, 1978). Remodeling was segregated into surface remodeling (i.e., changes in geometry) and internal remodeling (i.e., changes in material properties).  

Some of the basic assumptions of their model are as follows: 1) the porosity of the bone matrix depends on the ambient long-term strain history and the presence of microcracks; 2) the transfer of mass, energy and entropy occurs as a result of biochemical reactions that are mediated by bone cells; 3) the extra-cellular fluid is in contact with the blood plasma that supplies the materials for the synthesis of bone matrix; 4) the characteristic time of chemical reactions is several orders of magnitude greater than the characteristic time associated with a complete perfusion of the blood plasma in bone (i.e., the remodeling process is isothermal) (Cowin and Hegedus, 1976). Unlike Frost’s concept of remodeling turning “ON” and “OFF”, Cowin and Firoozbakhsh (1981) proposed that the rate of adaptation $U$ was proportional to the deviation between

---

2The terms surface and internal remodeling were originally introduced by Frost (1964).
the homeostatic strain $E_{ij}^0(Q)$ and the actual strain $E_{ij}(Q)$ at a location $Q$, written as

$$U = C_{ij}(\mathbf{n}, Q) \left[ E_{ij}(Q) - E_{ij}^0(Q) \right], \quad (2.1)$$

where $C_{ij}$ are surface remodeling rate coefficients which are dependent on the point $Q$ and the corresponding normal vector $\mathbf{n}$.

This model was utilized to study various aspects of cortical bone remodeling. It was shown that under the application of a uniform stress, the remodeling rules employed would drive a cylindrical bone segment with a non-homogeneous density distribution to a homogeneous density distribution (Firoozbakhsh and Cowin, 1980). Another application of this model was to theoretically analyze the internal remodeling induced in the vicinity of a medullary pin (Cowin and Buskirk, 1978). Hart et al. (1984a,b) implemented this model in an iterative numerical approach which utilized three-dimensional finite element (FE) models to evaluate local strains for arbitrary geometries. The strains were used to drive changes in geometry and material properties. In addition, Ramtani and Zidi (2001) modified this formulation to incorporate continuum damage.

More recently, Rouhi et al. (2006) proposed a new set of constitutive equations for the adaptive elasticity theory which utilized the specific surface, instead of volume fraction, and incorporated the degree of microcracking. According to their derivation, the rate of remodeling was treated as a function of the damage factor (i.e., extent of damage), but it was not related to the rate of damage production. This group also presented a mixture theory model in which chemical reactions that occur during the bone resorption process were incorporated (Rouhi et al., 2007). Their model supports the use of common stimuli for bone remodeling, as it was shown that increasing either strain energy density or hydrostatic pressure will enhance the rate of bone resorption.
2.7.3 Strain Energy Density-Based Models

Following Cowin’s adaptive elasticity, two prominent continuum models were developed. One of them was developed by Dennis Carter at Stanford University and the other by Rik Huiskes at the University of Nijmegen. In an attempt to overcome the issues associated with accounting for the directionality of strains, when using the strain tensor as the mechanical stimulus, the strain energy density (SED) was suggested as a suitable scalar feedback control variable for internal and external remodeling (Fyhrie and Carter, 1986a; Huiskes et al., 1987). Using the scalar SED as a mechanical stimulus is advantageous as it takes into account both the strain in all directions and the material properties of the tissue as well, simplifying remodeling calculations.

A theory presented by Fyhrie and Carter (1986b) assumed that bone was a locally self-optimizing structure. Their approach relates changes in trabecular bone apparent density and orientation with changes in applied stress. Therefore, the remodeling objective function \( \tilde{Q} \) was proposed as

\[
\tilde{Q}(\rho, \theta, \sigma) \geq 0,
\]

where \( \rho \) is the apparent density of the bone, \( \theta \) is the orientation of the material axes, and \( \sigma \) is the stress tensor. This objective function can be used to find the optimal orientation of the material axes and the minimum acceptable apparent density for a region of bone.

In later work, Carter (1987) extended this idea to allow for a more general treatment of the behavior of various skeletal connective tissues. This theory attempted to explain the relation between tissue mechanical stress and features of skeletal morphogenesis, growth, regeneration, maintenance, and degradation (Carter et al., 1987). By using FE models to account for the mechanical input as a regulator of bone architecture, Carter et al. (1989) realized that a single loading condition cannot be responsible for
all trabecular architecture. Therefore, they proposed that the apparent density $\rho$ was related to the effective stress $\sigma$ (scalar quantity) written as

$$\rho = K \left( \sum_{i=1}^{c} n_i \sigma_i^M \right)^{1/2M},$$

(2.3)

where $c$ is the number of loading conditions, $n_i$ represents the number of loading cycles for each effective stress $\sigma_i$, and $K$ and $M$ are constants. The effective stress used in this model was the “energy stress”, written as

$$\sigma_{\text{energy}} = \sqrt{2EU},$$

(2.4)

where $E$ is the continuum average elastic modulus and $U$ is the continuum SED.

Beaupré et al. (1990a,b) presented an extension of this work in which remodeling is a time-dependent process driven by the deviation between an attractor stress state and the effective stress stimulus.

Jacobs et al. (1997) added to Carter’s work by proposing that the goal of the adaptive response of bone was to achieve a globally efficient structure (i.e., optimal structure). In their work, a fully anisotropic material model was utilized, similar to the “free material” approach in structural optimization (Tovar, 2004; Tovar et al., 2007, 2006). This model was found to be deficient in predicting the measured material behavior of cortical bone. This is due to the fact that the anisotropic material model allowed for the alteration of the stiffness in any direction, independently from changes in other directions. Since long bones are primarily loaded longitudinally, it is likely that longitudinal stiffness changes in cortical bone would be coupled with stiffness changes in the transverse directions. It was then suggested that this type of approach may be more suited to trabecular bone, as weaker coupling may exist between longitudinal and transverse...
stiffnesses. Upon applying this technique to trabecular bone, trabecular struts meeting at oblique angles were observed; this violates the physiological assumption of perpendicular trabecular intersections. Thus, it was concluded that while the “free material” approach can obtain a highly mechanically efficient structure, the solution may not be physically obtainable by real bone due to limitations on organic construction.

Jacobs (2000) attempted to address the issues with his previous work by directly modeling trabecular architectural patterns. This involved creating a secondary FE model for each element in the primary FE model. The secondary FE models were then utilized to determine optimal trabecular patterns for each element of the primary model. This was one of the first attempts at modeling the adaptation of bone in a hierarchical fashion. While Jacobs’ work was successful at determining the optimal configuration of bone architecture, it does not consider the underlying physiological processes that occur. Therefore, this model is capable of providing insights regarding the morphology of bone, but it is limited in furthering our understanding of the adaptation process.

Another version of the SED-based remodeling paradigm was formulated by Huiskes et al. (1987). In their work, the rate of remodeling was assumed to be proportional to the difference between the actual SED $U$ and a site-specific homeostatic equilibrium SED $U_n$. In addition, this model was the first to entertain Carter’s suggestion that bone is “lazy” (Carter, 1984). That is, instead of assuming a linear relationship between the rate of bone remodeling and the remodeling variable (the SED), an equilibrium region exists. In this region, no changes in bone mass occur. This is represented as

$$
\frac{dE}{dt} = \begin{cases} 
C_e(U - (1 + s)U_n) & \text{if } U > (1 + s)U_n \\
0 & \text{if } (1 - s)U_n \leq U \leq (1 + s)U_n, \\
C_e(U - (1 - s)U_n) & \text{if } U < (1 - s)U_n
\end{cases}
$$

(2.5)
where \( E \) is the elastic modulus at the location of interest, \( sU_n \) is half the width of the “lazy” zone, and \( C_e \) is a proportional constant. Huiskes’ group developed a remodeling algorithm that utilizes a two-dimensional FE model for predicting both net internal and surface remodeling, where Eq. 2.5 is the remodeling rule. This model was applied to predict bone density changes around an idealized two-dimensional intramedullary prosthesis.

Building on the previous models, Weinans et al. (1992) used the apparent density of bone as a characterization of its internal morphology. The apparent density \( \rho \) at a particular location is an interpolation between a void (zero density) and maximally dense bone (assumed to have the density of cortical bone \( \rho_{cb} \)), via the volume fraction. Therefore, remodeling activity is transcribed into local changes in the apparent density. A generic representation for the rate of change of apparent density \( d\rho/dt \) is given as

\[
\frac{d\rho}{dt} = B(S - k), \text{ for } 0 < \rho \leq \rho_{cb},
\]

(2.6)

where \( B \) is a proportional constant, \( S = S(x, y, z) \) is the mechanical stimulus, and \( k = k(x, y, z) \) is a site-specific constant relating to the mechanical stimulus target. It was their objective to incorporate the ideas of the “effective stress” criteria into the time-dependent remodeling rule in Eq. 2.6, by utilizing the SED as the mechanical stimulus for the various daily loading conditions. In accordance with the “effective stress” criteria, the mechanical stimulus value in a region of bone was approximated as the SED per unit bone mass, \( U/\rho \). The apparent SED \( U_a \) was assumed to be the average SED for each of \( n \) loading configurations. This is written as

\[
U_a = \frac{1}{n} \sum_{i=1}^{n} U_i,
\]

(2.7)
where \( U_i = U_i(x, y, z) \) is the apparent SED for load case \( i \). Therefore, the remodeling rule for the change in apparent density \( \frac{d\rho}{dt} \) was given as

\[
\frac{d\rho}{dt} = B \left( \frac{U_a}{\rho} - k \right), \quad \text{for } 0 < \rho \leq \rho_{cb}.
\] (2.8)

This model was utilized by Weinans et al. (1992) to predict the density distribution in a two-dimensional proximal femur model. They found a density distribution similar to the one observed in an actual femur; however, no equilibrium convergence could be obtained. In fact, non-convergence was a common problem with remodeling simulations at that time. This model was also applied to a simple two-dimensional plate subject to a linearly-decreasing compressive load. The only stable solution found was one in which the elements were either empty or saturated at their maximal density.\(^3\) The distribution of material produced a discontinuous patchwork similar to that of a checkerboard and not unlike trabecular bone itself. At first, it was believed that these checkerboard patterns represented some sort of optimal microstructure, and further studies were performed to analyze the stability of these solutions (Cowin et al., 1993; Harrigan and Hamilton, 1992, 1994; Jacobs et al., 1995). However, it was shown that these checkerboard patterns were simply the result of numerical instabilities in the model (Jog and Haber, 1996; Sigmund and Petersson, 1998). This particular issue is one example of the many difficulties associated with the computational simulation of bone adaptation.

Mullender et al. (1994) proposed a unique method for overcoming this issue. Rather than simply using higher-order finite elements to smooth the discontinuities in the model (Jacobs et al., 1995) or other filtering techniques (Sigmund and Petersson, 1998),\(^3\)

\(^3\)In topology optimization, these type of solutions are termed “black and white” or 0-1 structures (Bendsøe, 1989).
they rethought the basis of their remodeling paradigm. They brought the idea that each element was considered to have one sensor that only regulates the density in that particular element into question. Bone tissue contains a vast network of osteocytes, interconnected by canaliculi, that are believed to be capable of mechanotransduction. Therefore, they proposed that bone has \( N \) osteocytes, acting as sensor cells, that are uniformly distributed throughout its volume. Each sensor cell has the ability to interpret the mechanical stimulus in a local region and, in turn, produce a remodeling signal which is released into its local environment. This remodeling signal would serve to mediate the activities of the actor cells (i.e., osteoclasts and osteoblasts). Therefore, the effective stimulus supplied to an actor cell by the \( i^{th} \) sensor cell is expressed as

\[
\Phi(x, t) = \sum_{i=1}^{N} f_i(x)(S_i - k),
\]

where \( k \) is a site-specific constant relating to the mechanical stimulus target, \( S_i = U_i/\rho_i \) is the SED per unit mass, and \( f_i(x) \) is the so-called spatial influence function of the actor cell at location \( x \). The spatial influence function is used to incorporate a decay in signal strength with increasing distance from a sensor cell. Hence, this diminishing signal is defined as

\[
f_i(x) = e^{-[d_i(x)/D]},
\]

where \( d_i(x) \) is the distance between the \( i^{th} \) sensor cell and the actor cell located at \( x \) and \( D \) is the parameter controlling the rate of signal decay, representing the distance from a sensor in which the signal strength is reduced to 36.8% of the initial value. Therefore, the rate of change of apparent density is represented as

\[
\frac{d\rho(x, t)}{dt} = \tau \Phi(x, t), \quad \text{with} \quad 0 < \rho \leq \rho_{cb},
\]

\( 46 \)
where $\tau$ is a proportional constant. The elastic modulus $E(x, t)$ at a location $x$ is calculated according to

$$E(x, t) = C\rho(x, t)^\gamma,$$

(2.12)

where $C$ and $\gamma$ are constants (Currey, 1988; Rice et al., 1988).

This model was found to be capable of synthesizing two-dimensional trabecular-like structures and was successful in predicting adaptation to applied loads and defects, such as the artificial disconnection of a trabecula (Mullender and Huiskes, 1995). An example of the trabecular adaptation results yielded by their model is displayed in Fig. 2.9. In addition, a study related to the effect of changing the mechanical set point on remodeling was performed (Mullender et al., 1998). From their analysis, the authors concluded the mechanical set point alone cannot be responsible for osteoporosis. This is due to the fact that the remodeling algorithm only predicts a loss in bone mass, not a general loss in trabecular structure. Among their various improvements to bone remodeling simulations, Mullender and Huiskes (1997) were the first to incorporate the notion of a “surface condition” in their algorithm. The “surface condition” is a constraint used to enforce that remodeling occurs in a physiological fashion, that is, changes in bone mass are only made at the bone’s surface. This is an important consideration for the biological accuracy of their remodeling algorithm and has been used by many other models as well (Huiskes et al., 2000; Penninger et al., 2008; Ruimerman et al., 2001; Smith et al., 1997; Tovar, 2004; van Oers et al., 2008a).

Following this work, Huiskes et al. (2000) developed a novel remodeling theory segregating the contributions to remodeling by osteoblasts and osteoclasts, as depicted in Fig. 2.10. In this model it is assumed that osteocytes signal osteoblasts to form bone under conditions of elevated stimulus in the bone matrix, and that osteoclasts resorb bone in areas associated with microcracks or disuse. Therefore, the total change in

47
bone mass is written as

\[ \frac{dM}{dt} = \frac{dM_{ob}}{dt} + \frac{dM_{oc}}{dt}, \]  

(2.13)

where \( \frac{dM_{ob}}{dt} \) and \( \frac{dM_{oc}}{dt} \) represent the contributions from osteoblastic formation and osteoclastic resorption, respectively (Ruimerman et al., 2001). It is assumed that osteocytes produce biochemical messengers in response to loading in their local environment. In this case, the mechanical stimulus considered is the SED rate, as this quantity may provide a pumping action to promote fluid flow through the canaliculi for signal transmission (Burger and Klein-Nulend, 1999; Cowin et al., 1991). The effective stimulus, referred to as the osteoblast recruitment stimulus (Huiskes et al., 2000;
Figure 2.10. The bone regulatory process proposed by Huiskes et al. (2000). Bone architecture is dictated by formation in response to enhanced loading and the selection of resorption sites in areas of microcracking and disuse.

Ruimerman et al., 2001), is given as

\[ P(x, t) = \sum_{i=1}^{n} f_i(x) \mu_i R_{ti}(t), \]  

(2.14)

where \( R_{ti}(t) \) is the SED rate in the location of osteocyte \( i \), \( \mu_i \) is the mechanosensitivity of osteocyte \( i \), and \( f_i(x) \) is the spatial influence function, as given in Eq. 2.10, summed over the \( n \) osteocytes within a cutoff distance \( d_{infl} \) from the location \( x \). The local change in relative bone density \( m \) is expressed as

\[ \frac{dm}{dt} = \tau(P(x, t) - k_{tr}) - r_{oc}, \text{ for } P(x, t) > k_{tr}, \]  

(2.15)

and

\[ \frac{dm}{dt} = -r_{oc}, \text{ for } P(x, t) \leq k_{tr}, \]  

(2.16)

where \( r_{oc} \) is the relative amount of bone resorbed by osteoclasts per day in the volume
considered, and $k_{tr}$ is the mechanical stimulus threshold. For this model it was assumed that a fixed amount of material was resorbed at each resorption site per iteration (i.e., $r_{oc}$ is a constant). This concept is similar to that used by Langton et al. (1998), as they considered a fixed amount of material to be turned over by a BMU at each selected surface site at every iteration. However, formation was assumed to occur in response to the local effective mechanical stimulus, as in previous models. Therefore, the amount of bone formed is proportional to the deviation between the osteoclast recruitment stimulus and the stimulus threshold.

In their work, remodeling was not only restricted to bone surface sites (i.e., “surface condition”), but resorption and formation sites were selected in a novel way. Most notably, resorption sites were chosen in a stochastic fashion. This idea stemmed from investigations showing correlations between resorption sites and osteocyte apoptosis due to microcracks, diffuse damage, and/or other unexplained factors (Burr, 2002). The probability $p$ of resorption occurring at a surface site was modeled by two different mechanisms, fatigue microcracking and disuse. In the case of microcracking (hypothesis I), microcracks due to daily activity were assumed to be equally probable at all sites. Each surface location was arbitrarily assigned a 10% probability of resorption due to microcracking for each iteration (Huiskes et al., 2000). The motivation for the spatially random distribution of microcracks and diffuse damage was drawn from observations that damage was prevalent throughout bone specimens by Vashishth et al. (2000). In the case of disuse (hypothesis II), osteoclast activation was assumed to be suppressed through cellular signaling caused by normal mechanical loading. A state of disuse would cause a decrease in signaling and result in a higher propensity for osteoclast activation (Noble et al., 1997). Therefore, the probability of osteoclast activation, due to disuse, was formulated as proportional to the stimulus error signal. The rules for
the selection of resorption sites are formulated as

hypothesis I: \( p(x, t) = 10\% \) (spatially random microdamage), \hspace{1cm} (2.17)

and

hypothesis II: \[
\begin{align*}
p(x, t) &= c[a - P(x, t)] \quad \text{if } P < a \quad \text{(strain-dependent)}, \\
p(x, t) &= 0 \quad \text{if } P \geq a,
\end{align*}
\]

(2.18)

where \( a \) is a constant related to the threshold for resorption due to disuse and \( c \) is a proportional constant. Formation was assumed to occur at locations with a sufficient amount of stimulus, as in previous models. The only restriction that was placed on formation was that, regardless of applied stimulus, if a surface site was selected for resorption to occur then resorption received priority over formation. This model was implemented in a two-dimensional simulation in which various remodeling processes, such as the reorientation of trabecular architecture upon a change in the applied loading direction, were successfully demonstrated (Huiskes et al., 2000; Ruimerman et al., 2001). This model proved that morphologically different expressions for the cellular behavior of bone growth, maintenance, and mechanical adaptation do not necessarily lead to different predictions of cell function (Ruimerman et al., 2001). The appropriate function of the bone cells is captured as a result of regulatory principles, further supporting the ideology that bone modeling and remodeling are not necessarily different from the perspective of the bone cells. Other extensions of this two-dimensional remodeling paradigm include the incorporation of cellular accommodation and microdamage by Vahdati and Rouhi (2009).

In more recent work, Ruimerman et al. (2003) extended this model to three dimensions to facilitate meaningful comparisons with real trabecular architecture and other
experimental observations. Ruimerman et al. (2003) added a unique feature to this remodeling paradigm, which involved a new method for the initiation of resorption cavities. A group of voxels (i.e., material elements), representing a realistic volume of a resorption cavity, were assumed to be resorbed by osteoclasts at each resorption location in the model. To further match the characteristics of resorption cavities, the authors consulted observations by McNamara et al. (2003) which showed that resorption cavities experience locally increased levels of SED. To match these observations, they adjusted the finite element discretization of their models to improve the resolution of the observed SED distribution. Utilizing this technique, they were successful in predicting elevated levels of SED local to the resorption cavities in their model. Thus, their representation of the stimulus distribution local to the remodeling site is more physiologically accurate.

A very similar bone adaptation paradigm was used by van der Linden et al. (2001) to explore the impact of resorption depth and formation deficit on bone loss and stiffness. The authors concluded that decreasing the formation deficit was effective in limiting the amount of bone loss, but decreasing the resorption depth was more effective in preventing loss of mechanical stiffness. To follow up these predictions, they extended their rules for predicting the effects of antiresorptive drug treatments on bone (van der Linden et al., 2003). They found that drug treatment protocols for preventing bone loss instated early on and later in the treatment regime are both effective; however, the early treatments are more effective in preserving the strength and stiffness of trabecular bone.

In another study, Ruimerman et al. (2005a) investigated the effects of simulating postmenopausal estrogen deficiency on trabecular bone architecture (Fig. 2.11). In this work it was hypothesized that estrogen deficiency could promote increases in remodeling parameters such as the osteoclast activation frequency, resorption cavity size, and
Figure 2.11. Simulated postmenopausal osteoporosis in trabecular bone by Ruimerman (2005). The homeostatic configuration (A) consisted of a remodeled lattice of trabecular bone. When increasing the osteoclast (OCL) resorption depth (B) or the osteoclast resorption frequency (C), a net bone loss was predicted. In both of these cases, a loss of trabecular thickness (Tr.Th) and trabecular number (Tr.N) was observed. When both the osteoclast resorption depth and the osteoblast formation rate (D) or the osteoclast activation frequency and the osteoblast formation rate were increased, no net bone loss was predicted.

Bone formation rate. It was found that net bone loss occurred when either the osteoclast activation frequency or the resorption cavity size was increased. In both cases, the overall trabecular thickness and trabecular number decreased. However, simultaneously increasing the osteoclast activation frequency and the bone formation rate or the resorption cavity size and bone formation rate, did not result in bone loss.

As a final note regarding this work, Ruimerman (2005) performed an analysis of various appropriate stimuli for bone remodeling. There is a wide debate over the use of physical quantities such as the SED for driving remodeling simulations. It is generally accepted that mechanical forces affect trabecular bone structure; however, the cellular
mechanisms involved in this relationship are poorly understood. In this work, several different physical quantities were applied as the mechanical stimulus in the aforementioned remodeling framework, in an attempt to examine the effect on the morphological predictions. The SED, maximal principal strain (MPS), and the volumetric strain, along with their respective spatial gradients, were utilized as mechanical stimuli. It was found that each of these stimuli was suitable for producing trabecular-like structures and for predicting adaptation. However, the SED and MPS were the only stimuli capable of reproducing the overshoot in bone mass in puberty, as found in morphological studies in pigs (Tanck et al., 2001). On the other hand, the SED and its gradient were the stimuli which produced the most homogeneous distribution of mechanical signals in their homeostatic structures. These findings are not sufficient to quell the debate over the use of mechanical signaling variables, but they provide further insight into the effectiveness of the SED in driving the remodeling process.

2.7.4 Hybrid Cellular Automata

The hybrid cellular automata (HCA) model was developed at the University of Notre Dame by Tovar (2004). This methodology is termed a hybrid technique because it couples global information obtained from the finite element method with the local relationships utilized by cellular automata (CA) computing. HCA follows the same premise as previous SED-based remodeling simulations, such as the simulation by Huiskes (2000).

By definition, CA are discrete dynamical systems that have been utilized to study idealizations of complex physical processes (Chopard and Droz, 1998). The basis for CA is that an overall global behavior can emerge from local rules acting over an automaton that possesses only local state information. A cellular automaton (CA) con-
sists of a regular lattice of cells, each described by a finite dimensional vector of states. The lattice can exist in any finite number of dimensions. CA evolve in discrete time; therefore, the state of a cell at a discrete time depends on a local rule that utilizes information from a finite number of nearby cells, known as a neighborhood. Both the local rules and neighborhoods are consistent for each site of the lattice and are applied for all generations in time. CA were brought to the attention of a wide audience in 1970, when John Conway proposed his now famous Game of Life (Gardner, 1970). One of the first studies to utilize CA for studying bone remodeling was done by Sakamoto and Oda (1995). In their work, simple rules following from Conway’s Life were used to predict the redistribution of bone tissue.

The basis for the HCA method is that the CA lattice is used to represent the connected cellular network of osteocytes in bones. Relying on the assumption that osteocytes sense the local mechanical stimulus experienced in bone, each cell of the CA lattice contains an osteocyte or a number of osteocytes, surrounded by mineralized tissue. This model assumes that bone remains locally isotropic and changes in relative density are driven by a mechanical stimulus target differential. Therefore, the state of the \(i^{th}\) cell \(\alpha_i(t)\) is defined by the relative (or normalized) density \(x_i(t)\), the mechanical stimulus \(S_i(t)\), and the error signal \(e_i(t)\), i.e.,

\[
\alpha_i(t) = \begin{pmatrix} x_i(t) \\ S_i(t) \\ e_i(t) \end{pmatrix}.
\] (2.19)

Since the relative density of each cell can vary throughout the remodeling process, changes in this parameter will result in a change in the modulus of the material. Thus, following from the work of Mullender et al. (1994) (Eq. 2.12), the modulus at a location
\( E_i(t) = E_{0i} x_i(t)^p, \)  

(2.20)

where \( E_{0i} \) is the base modulus for each cell, typically set to the modulus of fully dense bone (assumed to be equivalent to cortical bone), and \( p \) is an empirical value, typically satisfying \( 2 \leq p \leq 3 \) (Bendsøe, 1989; Currey, 1988; Rozvany and Zhou, 1991).

In this model, it is assumed that bone adapts to its mechanical environment to obtain a state of equilibrium, corresponding to a local stimulus target. Therefore, the strength of the remodeling signal is measured by the error between the effective stimulus sensed and the stimulus target

\[ e_i(t) = \bar{S}_i(t) - S^*_i, \]  

(2.21)

where \( \bar{S}_i(t) \) is the effective mechanical stimulus, which incorporates information from neighboring cells, and \( S^*_i \) is the stimulus target. The stimulus target for bone remodeling studies is defined from clinical observations. Local rules \( R \) are then used to update the material distribution in the domain, based on the magnitude of the stimulus error signal.

The set of local rules \( R \), that governs the evolution of the state of each cell of the automaton, operates according to information gathered from the cells in a prescribed neighborhood. In general, there is no restriction placed on the size of a neighborhood, only that the neighborhoods are consistent for each cell. The use of a neighborhood is similar to filtering techniques used in topology optimization to avoid numerical instabilities such as mesh dependency and checkerboarding.

As mentioned before, it is theorized that mechanical signals are detected in bone by osteocytes, which are distributed throughout the bone matrix. These osteocytes extend cellular processes in order to transmit signals to their neighbors, forming a highly
interconnected cellular network. Therefore, in the context of bone remodeling, local information gathered from neighboring cells can be viewed as the communication via the osteocytic network. In the original implementation of the HCA method, the effective mechanical stimulus sensed by each cell $\bar{S}_i(t)$ is expressed as the average of the stimuli sensed by all of the cells within the designated neighborhood

$$\bar{S}_i(t) = \frac{S_i(t) + \sum_{k \in N(i)} S_k(t)}{N(i) + 1},$$

(2.22)

where $S_i(t)$ is the state of mechanical stimulus at location $i$, $S_k(t)$ represents the mechanical stimulus sensed by the $k^{th}$ neighbor, $N(i) = \{\text{indices of neighbors of cell } i\}$, and $\hat{N}(i) = |N(i)|$ is the total number of neighbors in the neighborhood. In practice, the size of the neighborhood is typically restricted to the adjacent cells, but it can also be extended. Some common two- and three-dimensional neighborhood layouts are displayed in Fig. 2.12. In the work of Ruimerman et al. (2001), neighborhood information is also used by way of the so-called spatial influence function, given in Eq. 2.10.

The local rules $R$ utilized by the HCA framework are designed to model the process of bone functional adaptation to variations in its mechanical environment. These rules control the remodeling activities, i.e., formation and resorption in the bone. Each rule $R_i(t)$ is used to determine whether material should be added or removed, based on the strength of the remodeling signal $e_i(t)$. Thus, the local rules drive the evolution of the material distribution, which is the outcome of the remodeling process. In Tovar’s work, control-based rules and a ratio-based rule, following the principles of fully stressed design, are presented (Tovar et al., 2007). This review will only focus on the proportional, integral, and derivative (PID) control. The addition of derivative and internal control elements was a novel addition to the conventional remodeling rule.

The HCA method employs a PID control strategy whose input is the mechanical
stimulus measured for each cell and its neighbors. The purpose of this control rule is to drive the effective state of each cell to the corresponding mechanical stimulus target $S_i^*$. The reasoning behind proportional control is that it is assumed that osteoclastic or osteoblastic activity occurs in proportion to the error between a local effective mechanical stimulus and the stimulus target. Various computational models of bone remodeling use some form of proportional control in their remodeling rule (Fyhrie and Carter, 1986b; Huiskes et al., 2000, 1987; Ruimerman et al., 2005a). Integral control provides a pathway for including a sense of memory in the adaptation process. Consequently, this can be interpreted as osteocytes storing information from previous states, i.e., $e_i(t - 1)$, $\ldots$, $e_i(t - T)$. Thus, the remodeling activity is proportional to the cumulative error.

The rate of osteoblastic and osteoclastic activity depending on a prediction of the future error signal, based on the current error $e_i(t)$ and previous error $e_i(t - 1)$ signals, represents a form of derivative control. Hence, the change in relative density $\Delta x_i(t)$ for a

Figure 2.12. Common 2D ((a)–(d)) and 3D ((e)–(h)) CA neighborhoods. $\hat{N}$ depicts the number of neighboring cells.
cell at location $i$ is given as

$$
\Delta x_i(t) = c_p e_i(t) + c_i \int_0^t e_i(\tau) \, d\tau + c_d \Delta e_i(t),
$$

(2.23)

where $c_p$, $c_i$, and $c_d$ are the proportional, integral, and derivative control gains, respectively. Therefore, the material update for each cell is

$$
x_i(t + 1) = \min \left\{ \max \left\{ 0, x_i(t) + c_p e_i(t) + c_i \int_0^t e_i(\tau) \, d\tau + c_d \Delta e_i(t) \right\}, 1 \right\}. \tag{2.24}
$$

It has been observed that this PID control strategy reduces numerical instabilities and improves the convergence performance of the HCA algorithm. This approach assumes that formation and resorption are coupled. Penninger et al. (2007) extended the HCA method to utilize decoupled remodeling rules, similar to those of Huiskes et al. (2000).

The HCA method has many similarities to topology optimization techniques, although not being a formal optimization method itself (Tovar et al., 2006). In fact, Jang et al. (2009) elucidated the similarities of bone remodeling frameworks with conventional optimality criteria (OC) methods for topology optimization. Recall that this analysis began with the assumption of a stimulus equilibrium that was motivated by the physiology and occurs when the stimulus error in Eq. 2.21 goes to zero. This represents a criterion for each cell to enforce. One could reasonably ask what mathematical problem this criterion is the solution to. The answer is presented by Tovar et al. (2007), as he worked backwards from the equilibrium condition to determine the appropriate optimization formulation. It turns out to be a multiobjective optimization problem for minimizing both mass and strain energy written as

$$
\min_{0 \leq x \leq 1} f(U) + g(M), \tag{2.25}
$$
where $f(U)$ is a function of the strain energy $U$, $g(M)$ is a function of the mass $M$, and $x$ is the vector of relative densities of each cell. For the case of proportional control (i.e., $c_p \neq 0$ and $c_i = c_d = 0$), it has been shown that the HCA update in Eq. 2.24 converges to a point in the design space that satisfies the Karush-Kuhn-Tucker (KKT) optimality conditions (Penninger et al., 2009, 2010).

While the original intent of the HCA method was the study of bone adaptation, this framework has been extended to explore a broad scope of topics. Currently, HCA has also been applied to the areas of topology optimization, crashworthiness design, compliant mechanism synthesis, and design for blast mitigation (Bandi et al., 2009; Goetz et al., 2009; Mozumder et al., 2009; Patel et al., 2009a,b).

2.7.5 Cellular Level Models

One of the most prevalent criticisms of bone remodeling simulations is that the remodeling rules use lumped-parameter expressions that typically oversimplify the cellular activity that occurs. Only a few preliminary studies have attempted to incorporate descriptions of the cellular processes that occur during the remodeling cycle. Tezuka et al. (2005) developed a model based on the reaction-diffusion equations, which were originally proposed by Turing (1952) for predicting biological pattern formation. The basic Turing model utilizes two hypothetical molecules, an activator and an inhibitor, that interact with each other and diffuse independently to produce a system with positive and negative feedbacks. This system generates stable periodical patterns, known as Turing patterns. The basis for adapting this model to bone adaptation came from a previous study where it was observed that mesenchymal stem cells were forced to differentiate into osteoblasts by the action of Notch, a transmembrane protein with signaling capabilities (Tezuka et al., 2002). In these experiments, periodic cell condensation
patterns of dots and stripes were observed, leading to the realization that they were similar to Turing patterns. When a reaction-diffusion model produces a Turing pattern, the activator expresses a peak at the center of each dot or stripe, while the inhibitor has a more diffuse distribution. Therefore, a set of reaction-diffusion equations were defined to calculate the concentrations of the activator and inhibitor molecules in each element. The reaction-diffusion equations are given by

\[
\frac{dA_i}{dt} = C_1 A_i + C_2 I_i + C_A + D_A \left( \frac{d^2 A_i}{dx^2} \right) - g_A A_i + C_s S_i,
\]

(2.26)

and

\[
\frac{dI_i}{dt} = C_3 A_i + C_I + D_I \left( \frac{d^2 I_i}{dx^2} \right) - g_I I_i,
\]

(2.27)

where the concentrations of activator and inhibitor at a location \( i \) are represented by \( A_i \) and \( I_i \), respectively, \( S_i \) is the local mean von Mises stress, and the remaining parameters (\( C_1, C_2, C_3, C_A, C_I, D_A, D_I, g_A, g_I \)) are reaction-diffusion constants (Tezuka et al., 2005). In this model, local stresses act to increase the activator/inhibitor ratio, which promotes resorption and limits formation. The authors named this model “iBone” (Tezuka et al., 2003). Despite the ability of this model to mimic some cellular behavior, it is only able to predict “bulk” architectural changes at the whole bone scale and does not account for the cellular level mechanisms that drive the remodeling process.

Another interesting attempt at describing the cellular interactions of the bone remodeling cycle was developed by Komarova et al. (2003). The aim of their mechanistic model was to describe the population dynamics of bone cells in a single BMU. In their model, they assumed that osteoblasts and osteoclasts can interact via effectors (i.e., messenger molecules, transcription factors, cytokines, etc.) that are released or
activated by these cells in an autocrine or paracrine manner. They constructed a system of differential equations, employing a power law approximation as done by Savageau (1976) for highly nonlinear biochemical systems. Their formulation was stated as

$$\frac{dx_1}{dt} = \alpha_1 x_1^{g_{11}} x_2^{g_{21}} - \beta_1 x_1,$$

(2.28)

and

$$\frac{dx_2}{dt} = \alpha_2 x_2^{g_{12}} x_2^{g_{22}} - \beta_2 x_2,$$

(2.29)

where $x_1$ and $x_2$ are the number of osteoclasts and osteoblasts, $\alpha_i$ and $\beta_i$ are rate constants representing the activities of cell production and removal, and the parameters $g_{ij}$ represent the weights associated with the effectiveness of autocrine or paracrine factors derived from osteoclasts or osteoblasts. The net amount of bone resorption and formation was then assumed to be proportional to the numbers of osteoclasts and osteoblasts, respectively, exceeding steady-state levels. This model has been used to investigate the anabolic effect of parathyroid hormone on the remodeling cycle (Komarova et al., 2003), in which the authors were able to observe trends that were comparable to experimental findings. This model was modified by Moroz et al. (2006) to include the regulation of osteoclasts and osteoblasts, using a feedback loop that incorporated the stimulation of osteocytes. However, a shortcoming of these models is that they are one-dimensional in nature and they would be difficult to apply to a more accurate model of bone. In addition, the remodeling cycle is initiated and carried out solely based on prescribed initial conditions which cannot be easily translated into temporal changes in physiological activity (i.e., mechanotransduction).

In an attempt to overcome these issues, Ryser et al. (2009) presented a novel spatio-temporal model of the dynamics of a single cortical BMU for microfracture repair in
two dimensions. This model coupled expressions for the concentrations RANKL and OPG with the number of osteoblasts and osteoclasts in Eqs. 2.28 and 2.29. Their model demonstrated that a gradient of the RANKL and OPG concentrations existed across the length of the BMU, with the highest concentrations of RANKL and OPG being at the front and rear of the BMU, respectively. This observation provides an interesting insight into how BMU progression in cortical bone may be controlled.

Ruimerman et al. (2005b) began working on an extension of their previous work, in which their model was extended to the cellular scale. Representations of osteoclasts and osteoblasts were modeled to predict the dynamics of a BMU. In this model, they accounted for the osteoclast number, size, form, and position relative to the bone surface (Ruimerman, 2005). The attachment and shape of the osteoclasts was determined by using the Glazier and Graner model based on differential cell adhesion (Glazier and Graner, 1993). Therefore, the state of an osteoclast is characterized according to the amount of free energy $H_\sigma$, written as

$$H_\sigma = H_{surf} + H_{vol},$$

where $H_{vol}$ represents the potential energy associated with the volume of the cell and $H_{surf}$ is the surface energy of the osteoblast, which is a function of the surrounding tissue (Fig. 2.13). Osteoblasts were assumed to be the size of one voxel and formed bone proportional to the local stimulus sensed.

This model was extended to study BMU dynamics in cortical and trabecular bone by van Oers et al. (2008a,b). For their cortical bone simulations, the authors assumed an active resorption site was already present. They were able to study changes in osteon diameter with varying levels of strain as well as the redirection of BMU progression, resulting from decreased osteocyte signaling. They were also able to show the reorient-
Figure 2.13. Using the Glazier and Graner formalism, the contact surface energy of the osteoclast OCL1 depends on the surrounding tissues, such as marrow $h_m$, other osteoclasts $h_{ocl}$ (i.e., OCL2), and bone tissue $h_b(P)$, where $P$ is the osteoclast recruitment stimulus. Figure adapted from Ruimerman (2005).

McNamara and Prendergast (2007) presented a framework in which both strain and microdamage are utilized as remodeling stimuli. The accumulation of damage was calculated according to the method presented by Prendergast and Taylor (1994), where the damage accumulation rate was determined from an empirical relation between the local stress and the number of cycles to failure. Therefore, the local change in bone density $d\rho_j/dt$ is represented as

$$
\frac{d\rho_j}{dt} = C_1 S_{strain}^j \quad \text{if} \quad \omega < \omega_{\text{CRIT}},
$$

and

$$
\frac{d\rho_j}{dt} = C_2 S_{\text{damage}}^j \quad \text{if} \quad \omega > \omega_{\text{CRIT}},
$$
where $\omega$ is the amount of damage accumulation, $\omega_{CRIT}$ is the critical amount of damage needed to trigger damage-stimulated adaptation, $S^j_{strain}$ is the strain stimulus, $S^j_{damage}$ is the damage stimulus, and $C_1$ and $C_2$ are proportional constants. This algorithm was applied to a two-dimensional model of a single trabecular strut. Investigations were conducted to determine the critical depth of an initial resorption cavity, for which the remodeling rules would not cause the perforation of the strut (McNamara and Prendergast, 2005). They also studied the effectiveness of considering osteoclasts or bone-lining cells as mechanosensors (McNamara and Prendergast, 2007). More recently, this model was extended to three dimensions and similar investigations were performed as done for the two-dimensional model (Mulvihill et al., 2008; Mulvihill and Prendergast, 2008). It is interesting to note that critical resorption captivity depth for the three-dimensional model was 32 $\mu$m (Mulvihill et al., 2008), where it was less than 25 $\mu$m for the two-dimensional model (McNamara and Prendergast, 2005). It appears that the addition of the third dimension adds some additional stability to the model.
While scaled resorption and formation may be suitable for bone on the macroscale, it was suggested that an “ON/OFF” resorption and formation process may be better suited for individual trabeculae (Mulvihill, 2008). Therefore, Mulvihill (2008) modified their remodeling paradigm to include a mechanostat-like “ON/OFF” adaptation rule. This model was applied to the single trabecular strut, as before. It was shown that increasing the SED threshold for formation, while keeping the SED threshold for resorption constant, resulted in increased perforation of trabeculae. This is an important consequence to consider for osteoporosis, as this conclusion supports the ideology that osteoblasts become less responsive to mechanical stimuli, resulting in the loss of trabecular architecture.

Martin and Buckland-Wright (2004, 2005) mechanistically predicted osteoclast and osteoblast activities at a single remodeling site. In their model, the authors considered prominent factors affecting the cellular level processes that occur. They assumed that the cellular activity $A_c$ can be explained by using a Michaelis-Menten (M-M) formulation written as

$$A_c = \frac{V_{\text{max}} s}{s + K_m}, \quad (2.33)$$

where $V_{\text{max}}$ is the maximum velocity of the reaction, $s$ is the substrate available, and $K_m$ is the M-M constant equal to the amount of substrate when the cellular activity equals half the maximum velocity. In their work, they investigated the effectiveness of the RANK/RANKL/OPG signaling pathway on controlling bone resorption at a microsite (Martin and Buckland-Wright, 2004). They also examined the factors regulating the bone formation process, such as the impact of growth factors on osteoblast number and activity (Martin and Buckland-Wright, 2005). They were able to conduct one-dimensional simulations that closely matched histological observations of resorption depth and osteoid apposition versus time. In this thesis, three-dimensional extensions
of the ideas presented by Martin and Buckland-Wright are developed. These cellular mechanisms are uniquely connected with the existing phenomenological paradigms for the simulation of bone remodeling. Further details about this phenomenological-mechanistic model can be found in Chapter 4.

2.7.6 Other Models

From the extensive research discussed in this literature survey, one can appreciate that a wide variety of approaches to the bone remodeling problem have been undertaken. The intent of this discussion is not to mention every single work, but to provide the reader with a diverse cross-section of ideas that have been introduced over the past several decades. Here, several additional models are mentioned to round out this review.

A wide variety of stimuli and modeling techniques have been utilized to explain the bone adaptation process, in addition to those previously mentioned. Hernandez et al. (2000) developed a theoretical model that includes both mechanobiologic (i.e., applied stimuli) and metabolic influences on adaptation. Hazelwood et al. (2001) formulated a mechanistic model to characterize the dynamic behavior of BMUs in response to disuse and overload conditions. Rattanakul et al. (2003) developed a nonlinear system model of bone resorption and formation, mediated by parathyroid hormone. Lemaire et al. (2004) modeled the interactions of osteoclasts and osteoblasts as a series of chemical reactions, each associated with a set of differential equations that describe the characteristics of a particular reaction. García-Aznar et al. (2005) extended the material model for the elastic modulus (Eq. 2.12) to incorporate the stiffness loss due to microdamage. Shefelbine et al. (2005) used a fuzzy logic approach to simulate bone fracture healing. Ausk et al. (2006) presented an agent-based model for the signaling induced in osteocyte networks by mechanical stimuli. Moroz et al. (2006) presented an allosteric model
for incorporating the influences of various hormones on the cellular and molecular processes involved in remodeling. This model was extended by Wimpenny and Moroz (2007) to incorporate a feedback loop for osteocyte signals.

As previously mentioned, optimization approaches have been utilized to study bone adaptation. A common formulation for the optimization of bone structures is to minimize the total strain energy, subject to a volume constraint (Bagge, 2000; Pedersen, 2002). Nowak and Morzynski (2004) adapted this optimization paradigm to mimic trabecular bone surface adaptation. Their results were found to be similar to structures produced by conventional topology optimization methods (Nowak, 2006a,b).

2.7.7 Summary of Models

This section has encompassed a comprehensive survey of the state of the art of theoretical and computational models for the study of the bone remodeling process. While not every model was mentioned, the models discussed here have displayed the prevailing stream of ideas that have been under development in this field for the past several decades. A summary of the key concepts and advancements in the computational modeling of bone adaptation is provided in Table 2.1.
<table>
<thead>
<tr>
<th>Author</th>
<th>Model Type</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frost (1964)</td>
<td>Theoretical</td>
<td>Introduced the mechanostat theory. Bone adaptation was envisioned as a household thermostat where it would turn “ON” in response to a deviation in the mechanical usage and “OFF” in its absence.</td>
</tr>
<tr>
<td>Cowin and Hegedus (1976)</td>
<td>Phenomenological</td>
<td>Formulated a thermomechanical continuum description of bone remodeling called the theory of adaptive elasticity, where adaptation was driven by differences between the actual and homeostatic strain.</td>
</tr>
<tr>
<td>Carter (1984)</td>
<td>Phenomenological</td>
<td>Introduced the concept of a “lazy zone”, which denotes a strain range where bone is in equilibrium and no adaptive response occurs.</td>
</tr>
<tr>
<td>Hart et al. (1984a,b)</td>
<td>Phenomenological</td>
<td>Extended the theory of adaptive elasticity for use with three-dimensional FE models to calculate strains in arbitrary geometries.</td>
</tr>
<tr>
<td>Fyhrie and Carter (1986b)</td>
<td>Optimization</td>
<td>Related stress to trabecular bone orientation and apparent density, under the assumption that bone is a locally self-optimizing structure.</td>
</tr>
<tr>
<td>Carter (1987)</td>
<td>Phenomenological</td>
<td>Realized that a single applied load could not be responsible for trabecular architecture and formulated a daily stimulus history which accounted for multiple loading conditions.</td>
</tr>
<tr>
<td>Author</td>
<td>Model Type</td>
<td>Contribution</td>
</tr>
<tr>
<td>------------------------</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Huiskes et al. (1987)</td>
<td>Phenomenological</td>
<td>One of the first models to suggest that SED was a suitable scalar feedback control variable for internal and external remodeling, as it accounts for applied strain and the material properties of bone tissue.</td>
</tr>
<tr>
<td>Carter et al. (1989)</td>
<td>Computational</td>
<td>Developed a two-dimensional simulation of the proximal femur (which was non-convergent), demonstrating the need to consider multiple daily loading conditions as a single loading condition cannot be responsible for trabecular architecture.</td>
</tr>
<tr>
<td>Weinans et al. (1992)</td>
<td>Phenomenological</td>
<td>Utilized the apparent density of bone as the remodeling variable and related this parameter to the elastic modulus using a power law relation.</td>
</tr>
<tr>
<td>Prendergast and Taylor (1994)</td>
<td>Phenomenological</td>
<td>Formulated rules for predicting damage-adaptive remodeling where damage accumulation served as the mechanical stimulus.</td>
</tr>
<tr>
<td>Mullender et al. (1994)</td>
<td>Phenomenological</td>
<td>Proposed a formulation based on the idea that osteocytes act as sensor cells and interpret the mechanical stimulus in the surrounding tissue and, in turn, transmit a local remodeling signal.</td>
</tr>
<tr>
<td>Author</td>
<td>Model Type</td>
<td>Contribution</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hart and Fritton (1997)</td>
<td>Phenomenological</td>
<td>Presented a survey that encompassed relevant experimental, theoretical, and computational models for bone remodeling, as well as current issues.</td>
</tr>
<tr>
<td>Jacobs et al. (1997) and</td>
<td>Phenomenological</td>
<td>Proposed a free material approach to finding the optimal distribution of material at the whole bone scale. Later they incorporated secondary FE models to determine optimal trabecular patterns for each element of the primary model.</td>
</tr>
<tr>
<td>Jacobs (2000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner (1999)</td>
<td>Phenomenological</td>
<td>Presented a mathematical formulation for cellular accommodation, where bone cells react strongly to transients in their mechanical demands, but adjust their behavior over time to return to a steady state.</td>
</tr>
<tr>
<td>Bagge (2000)</td>
<td>Optimization</td>
<td>Derived a remodeling rate equation based on the task of maximizing stiffness in each time step of the simulation. Idealized trabecular microstructures were assumed, for which the material properties were interpolated using the homogenization method.</td>
</tr>
<tr>
<td>Huiskes et al. (2000)</td>
<td>Phenomenological</td>
<td>Developed a novel remodeling theory segregating the contributions of osteoblasts and osteoclasts. Resorption sites were chosen stochastically while formation was driven by strain.</td>
</tr>
</tbody>
</table>
TABLE 2.1

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<table>
<thead>
<tr>
<th>Author</th>
<th>Model Type</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruimerman et al. (2001)</td>
<td>Phenomenological</td>
<td>Extended the model by Huiskes et al. (2000) to three dimensions, allowing for more accurate comparisons with realistic bone structures.</td>
</tr>
<tr>
<td>van der Linden et al. (2003,</td>
<td>Phenomenological</td>
<td>Explored the impact of resorption depth and formation deficit on bone loss and stiffness. Also investigated the effects of antiresorptive drug treatments on preserving bone strength.</td>
</tr>
<tr>
<td>2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazelwood et al. (2001)</td>
<td>Mechanistic</td>
<td>Mechanistically modeled the dynamic behavior of BMUs, in response to disuse and overload conditions</td>
</tr>
<tr>
<td>Ramtani and Zidi (2001,</td>
<td>Phenomenological</td>
<td>Modified the adaptive elasticity formulation to include anisotropic continuum damage.</td>
</tr>
<tr>
<td>2002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lemaire et al. (2004)</td>
<td>Mechanistic</td>
<td>Modeled the interactions of osteoclasts and osteoblasts as a series of chemical reactions, each associated with a set of differential equations that describes the characteristics of a particular reaction.</td>
</tr>
<tr>
<td>Martin and Buckland-Wright</td>
<td>Mechanistic</td>
<td>Mechanistically modeled the activities of osteoclasts and osteoblasts at a single microsite, using a M-M formulation.</td>
</tr>
<tr>
<td>(2004, 2005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Model Type</td>
<td>Contribution</td>
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<tr>
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</tr>
<tr>
<td>Tovar (2004)</td>
<td>Phenomenological</td>
<td>Adapted the SED-based remodeling paradigm to a hybrid cellular automata framework and showed that this method is effectively a multiobjective optimization problem for minimizing total SED and mass.</td>
</tr>
<tr>
<td>Ruimerman (2005)</td>
<td>Phenomenological</td>
<td>Compared the effectiveness of the SED, maximal principal strain, and volumetric strain, along with their respective spatial gradients, as potential mechanical stimuli for remodeling.</td>
</tr>
<tr>
<td>Ruimerman et al. (2005a)</td>
<td>Phenomenological</td>
<td>Simulated postmenopausal estrogen deficiency by modifying osteoclast or osteoblast activation frequencies and resorption cavity size to predict loss of trabecular architecture.</td>
</tr>
<tr>
<td>Tezuka et al. (2005)</td>
<td>Phenomenological</td>
<td>Used reaction-diffusion equations to model the activation and inhibition of remodeling, predicting “bulk” architectural changes in bone.</td>
</tr>
<tr>
<td>García-Aznar et al. (2005)</td>
<td>Phenomenological</td>
<td>Extended the material model in their remodeling framework to incorporate the stiffness loss due to microdamage.</td>
</tr>
<tr>
<td>McNamara and Prendergast (2005, 2007)</td>
<td>Phenomenological</td>
<td>Investigated the resistance of individual trabeculae to perforation by modifying the elastic modulus and initial cavity depth. Also studied the effectiveness of osteocytes and lining cells as mechanosensors.</td>
</tr>
</tbody>
</table>
### TABLE 2.1

*Continued*

<table>
<thead>
<tr>
<th>Author</th>
<th>Model Type</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shefelbine et al. (2005)</td>
<td>Phenomenological</td>
<td>Developed a fuzzy logic approach to simulate bone fracture healing.</td>
</tr>
<tr>
<td>Moroz et al. (2006)</td>
<td>Phenomenological</td>
<td>Developed an allosteric control technique for modeling the impact of hormones on the cellular and molecular processes of remodeling.</td>
</tr>
<tr>
<td>Nowak (2006a,b)</td>
<td>Optimization</td>
<td>Extended traditional topology optimization routines to mimic trabecular bone surface adaptation.</td>
</tr>
<tr>
<td>Rouhi et al. (2007)</td>
<td>Phenomenological</td>
<td>Proposed a mixture theory model which incorporated chemical reactions that occur during the bone resorption process.</td>
</tr>
<tr>
<td>van Oers et al. (2008a,b)</td>
<td>Phenomenological</td>
<td>Simulated the dynamics of a BMU in cortical and trabecular bone. Osteoclasts and osteoblasts were explicitly modeled based on the formulation by Ruimerman (2005).</td>
</tr>
<tr>
<td>Mulvihill (2008) and Mulvihill and Prendergast (2008)</td>
<td>Phenomenological</td>
<td>Investigated the impact of reduced mechanosensitivity with age on bone turnover for a single trabecular strut. Also formulated a mechanostat-like “ON/OFF” remodeling rule.</td>
</tr>
</tbody>
</table>
CHAPTER 3
A FULLY ANISOTROPIC HIERARCHICAL HCA METHOD

Computational models of the bone remodeling process have been utilized to further our understanding of the adaptation of bone architecture to changes in its mechanical environment. It is well accepted that bone possesses a hierarchical structure, with different structural entities existing at different length scales (Rho et al., 1998). Many existing simulations of bone remodeling have been performed at the organ or tissue levels (Huiskes et al., 2000, 1987; Mullender et al., 1994; Prendergast and Taylor, 1994; Ruimerman et al., 2001; Turner, 1999; van der Linden et al., 2001). While these simulations describe the adaptation of bone at a single scale, they are not able to capture the coupling of the adaptive behavior between scales. Multi-scale approaches for the simulation of adaptation have the potential to provide new insights into the coupling of bone structural organization and adaptation, between scales.

The hybrid cellular automaton (HCA) method is a biologically-inspired algorithm capable of topology synthesis that was developed to simulate the behavior of bone remodeling as presented by Tovar (2004). This methodology is termed a hybrid technique because it couples global information obtained from the finite element (FE) method with the local relationships utilized by cellular automata (CA) computing. In an effort to accommodate the hierarchical nature of bone, the HCA methodology was extended to a multi-scale framework. This so-called hierarchical HCA (HHCA) framework attempts to discretize a continuum level model of bone into tissue level submodels, where
HCA is applied locally to predict structural changes. This approach is advantageous as it can capture the coupling of adaptive activity between the organ and tissue level scales. In addition, by discretizing the continuum model of bone into a lattice of tissue level models, a reduction in computational expense can be achieved.

The original HHCA framework is deficient in its characterization of the mechanical properties of the tissue level submodels. Isotropic material properties are calculated based on the density distribution of the tissue level structures; these properties are used to represent the mechanical behavior of the continuum level model. The isotropic properties are typically determined by scaling the modulus of fully dense bone (i.e., cortical bone) by the average density (or apparent density) of a tissue level region. This approach only considers the “apparent” behavior of the tissue level trabecular architecture (Jacobs et al., 1997). Therefore, the HHCA methodology utilizes the apparent density of each tissue level structure to update the material properties of the continuum model. This simplifying assumption is shared by several continuum level models (Beaupré et al., 1990a; Huiskes et al., 1987; Weinans et al., 1992).

In general, trabecular bone has nonlinear and anisotropic material properties. More recent continuum level models have made efforts to incorporate these properties by utilizing idealized microstructures (Bagge, 2000; Fernandes et al., 1999; Jacobs et al., 1997). However, while these idealized microstructures reflect some approximated mechanical aspects of trabecular bone, they are not capable of representing its physiological nature. It is noteworthy that the tissue level structures of the HHCA methodology result from rules for simulating the bone adaptation process. In this way, the tissue level structures represent physiologically relevant trabecular architecture. Therefore, utilizing techniques to approximate the anisotropic properties of the tissue level structures will provide a more accurate measure of the mechanical characteristics of realistic trabecular bone.
becular architecture. These properties can be used at the continuum level of the HHCA framework.

This investigation builds upon the original HHCA framework by incorporating a methodology for computing the anisotropic properties of the tissue level structures. This is done by performing numerical experiments on each tissue level structure, from which the coefficients of the stiffness tensor of each of the tissue level models can be calculated. Therefore, the stiffness tensor of each tissue level model can be utilized at the continuum scale. Adding this capability to the HHCA methodology not only increases the fidelity of the tissue level models, but provides an accurate description of the tissue level properties of bone at the organ level.

The methodology developed makes use of FE analyses to perform confined uniaxial strain tests on the tissue level structures, based on the work of van Rietbergen et al. (1996). This approach allows for the analysis of the anisotropic mechanical characteristics of a general trabecular architecture, rather than assuming an idealized microstructure. Since trabecular architecture is generally variable and inhomogeneous, this technique is better equipped to represent the properties of a continually remodeling tissue level structure. This chapter reviews the fundamentals of the HHCA framework and demonstrates the anisotropic structural analysis developed.

3.1 Hierarchical Hybrid Cellular Automata (HHCA)

The basis of the HHCA methodology is to use information from the structural adaptation of the tissue level models to define the behavior of the continuum level model of bone. Therefore, the HHCA model combines tissue level remodeling principles with a continuum level structural analysis. The HHCA methodology requires the definition of the geometry, applied load(s), and initial apparent density distribution $X(0)$ at the
continuum level of the model. The density distribution is termed as “apparent” at the continuum level because it represents an approximation of the mechanical properties of the tissue level structures. The continuum domain is then discretized into a lattice of tissue level submodels. At the continuum level, the submodels represent pieces of bone in which the apparent density is considered to be homogeneous. Typically, a lattice of identical submodels is utilized, although there is no requirement for submodel uniformity imposed by the algorithm.

Once these model parameters are defined, an appropriate FE mesh can be selected. The minimum discretization of elements necessary would be that of a one-to-one correspondence with the tissue level submodels. Recall that it is currently assumed that the behavior of the tissue level structures at the continuum level is isotropic. Therefore, no restriction is placed on increasing the mesh resolution. This concept will be revisited after the definition of the anisotropic structural analysis as additional restrictions on the FE mesh are necessary.

An initial FE analysis is conducted at the continuum level to determine the macro-mechanical properties of the structure. The objective of the continuum level analysis is to define the stress state for each of the submodels. For a two-dimensional domain, the stress state is represented using the two normal stresses $\sigma_x$ and $\sigma_y$, and the shear stress $\tau_{xy} = \tau_{yx}$. Since the stresses are not necessarily uniform throughout the continuum model, an equivalent (or average) state of stress is calculated for each submodel $I$ by sampling the stress at nine interior points (Fig. 3.1) and determining the average. Therefore, the average values of the two normal stresses and the shear stress are written as

$$\sigma_{x}^{I} = \frac{\sum_{j=0}^{8} \sigma_{x}^{j}}{9},$$  \hspace{1cm} (3.1)
Figure 3.1. Stress state sample points diagram. The stresses are sampled over nine interior points in the domain of each tissue model and averaged to approximate an equivalent state of stress.

\[
\sigma_{Iy} = \frac{\sum_{j=0}^{8} \sigma_{jy}}{9},
\]  

(3.2)

and

\[
\tau_{Ixy} = \frac{\sum_{j=0}^{8} \tau_{jxy}}{9},
\]  

(3.3)

where the superscript \( j \) corresponds to the sample points in Fig. 3.1. The equivalent stress states are applied to each submodel using distributed forces. The forces \( F_{Ix}^I, F_{Iy}^I \), and \( T_{Ixy}^I \) act in the same directions as the stresses and are applied over the cross-sectional area of the corresponding tissue level model (Fig. 3.2).

At the tissue level of the hierarchical algorithm, the HCA methodology is applied to each of the submodels to determine the required structural changes. Each submodel represents an individual cellular automaton (CA), each containing a regular lattice of cells. Typically, an identical CA lattice is used across all submodels. The tissue level density for each cell \( i \) of the \( I^{th} \) submodel \( x_i^I \) is initially assumed to be homogeneous and is determined from the apparent density at the continuum level \( X_I \), written as

\[
x_i^I = X_I.
\]  

(3.4)

In the submodels, the relationship between the Young’s modulus \( E_i^I \) and the tissue level
density $x^I_i$ for each cell $i$ is given by the power law

$$E^I_i = E_{0i} (x^I_i)^p,$$  \hspace{1cm} (3.5)

where $p$ is the penalization power and $E_{0i}$ is the Young’s modulus of mineralized tissue for the $i^{th}$ cell. In previous applications of the HCA methodology, the penalization power was chosen as $p = 3.0$ (Tovar et al., 2006).

Using the state of stress determined by the continuum level FE analysis, the HCA method finds an updated trabecular structure for each tissue level model (i.e., an updated density distribution $x^I_{i^*}$). The average tissue density of each submodel is then calculated to find the new continuum level apparent density $X_I(t + 1)$, written as

$$X_I(t + 1) = \frac{\sum_{i=1}^{N_I} x^I_{i^*}}{N_I},$$ \hspace{1cm} (3.6)

where $N_I$ is the total number of cells in the $I^{th}$ submodel. Again, this method of density averaging only accounts for an approximation of the structural properties of the tissue.
level models.

Once the apparent density distribution of the continuum model is updated, the new material properties can be calculated. The same power law relationship used for the tissue level models is applied between the continuum level Young’s modulus $E_I$ and the apparent density $X_I$ for all submodels $I$, written as

$$E_I = E_{0I}X_I^p,$$

where $E_{0I}$ is the Young’s modulus of mineralized tissue for the $I^{th}$ submodel. It is assumed the modulus of the mineralized tissue is the same at both the continuum and tissue level, i.e., $E_{0I} = E_{0i}$. This update in mechanical properties marks the end of one iteration of the HHCA framework.

The updated continuum level model will have a new stress/strain field which will affect the stress state for each tissue model. Therefore, a new FE analysis must be performed to determine the updated stress distribution in the continuum model, which is translated into an updated stress state for each tissue model. Note that the same FE mesh is typically used for every iteration of the algorithm to reduce computational cost. The HHCA methodology follows this iterative procedure until convergence is achieved with respect to both the apparent density distribution and the stress field. The convergence criterion for apparent density is defined as

$$\max\{|\Delta X_I(t)|\} < \varepsilon_X,$$  

where $|\Delta X_I(t)| = |X_I(t) - X_I(t - 1)|$ is the absolute value of the change in relative mass for submodel $I$ and $\varepsilon_X$ is the maximum desired change in relative density.
convergence over the stress field is defined as

$$\max\{|\Delta \sigma_I(t)|\} < \varepsilon_\sigma,$$  \hfill (3.9)

where $|\Delta \sigma_I(t)| = |\sigma_I(t) - \sigma_I(t-1)|$ is the absolute value of the change in the stresses $\sigma_{x}^{I}, \sigma_{y}^{I},$ and $\tau_{xy}^{I}$ for submodel $I$ and $\varepsilon_\sigma$ is the maximum desired change in stress.

A summary of the steps involved in the HHCA algorithm, depicted in Fig. 3.3, is:

Step 1. Define the geometry, loading conditions, and initial apparent density distribution $X(0)$ at the continuum level.

Step 2. Divide the continuum level model into a lattice of submodels. At the continuum level, the submodels represent pieces of bone in which the apparent density is considered to be homogeneous and behave as an isotropic material. The size of the submodels determines the detail of the trabecular structure at the tissue level and the resolution of the apparent density distribution at the continuum level. Note that the discretization of finite elements must be at least one-to-one with the submodel lattice.

Step 3. Perform a FE analysis to obtain an initial stress state for each submodel.

Step 4. Calculate an equivalent stress state for each submodel by averaging the stress values over nine interior sampling points (Fig. 3.1). These stresses are applied to the submodels by calculating corresponding distributed loads and applying them over the surfaces of the tissue model.

Step 5. Apply the HCA method locally to each submodel to determine the required structural changes. Since the calculations for a sub-model do not depend on other sub-models, this process can be done in parallel. The apparent density of the resulting trabecular architecture is used to approximate the bulk properties of the tissue models and update the material properties of the continuum level model.

Step 6. A new continuum level FE analysis is performed on the updated structure to obtain the new stress field.

Step 7. Assess if convergence has been achieved. If the change in apparent density and stress is below the desired tolerance, the algorithm is converged; otherwise, the hierarchical method continues to iterate, starting with Step 4.
Figure 3.3. Hierarchical algorithm flow chart by Tovar (2004). The HHCA method is comprised of a continuum level model which is divided into tissue level submodels. A FE analysis is performed at the continuum level to determine the equivalent stress state of each tissue model. Each submodel consists of a cellular automaton in which HCA is applied locally to determine the required structural changes via bone formation/resorption. The resulting material distribution is then averaged to obtain the new apparent density at the continuum level. The elastic properties at the continuum level are quantified using a power-law relationship between Young’s modulus and apparent density. This method iterates until convergence is achieved on both apparent density and stress.
3.2 Determination of Anisotropic Properties for Tissue Models

Incorporating the local mechanical properties of the tissue level models into the HHCA methodology requires an anisotropic structural analysis. This analysis provides detailed mechanical properties of the tissue level structures that are a more accurate representation of human trabecular bone. Utilizing these mechanical properties at the continuum level will improve the fidelity of the HHCA methodology from representing the apparent behavior of tissue level structures to representing the actual tissue behavior.

The determination of the anisotropic properties of a structure requires the computation of its stiffness tensor. For this work, bone is considered to behave like a linear elastic material (Katz and Meunier, 1987), whose mechanical behavior can be described by the generalized Hooke’s Law

\[
\sigma_{ij} = C_{ijkl} \epsilon_{kl},
\]  

(3.10)

where \( \sigma_{ij} \) is the stress tensor, \( \epsilon_{kl} \) is the strain tensor, and \( C_{ijkl} \) is the rank four stiffness tensor. The stiffness tensor of an anisotropic material consists of 21 independent coefficients in the three-dimensional case and 10 in the two-dimensional case (i.e., under the assumption of plane stress or plane strain). A two-dimensional plane strain analysis is used in this work. For the case of a two-dimensional trabecular structure, the out-of-plane stress \( \sigma_{33} \) and strain \( \epsilon_{33} \) would be meaningless since in real bone it would be unlikely that the trabecular structure would be consistent throughout the thickness of the cross-section. Therefore, plain strain was chosen to remove the dependency of the in-plane stresses on the out-of-plane strain \( \epsilon_{33} \).

Recall that under the assumption of plane strain, the out-of-plane strains are assumed to be zero (i.e., \( \epsilon_{33} = \gamma_{13} = \gamma_{23} = 0 \)). In addition, this assumption implies that
tractions cannot be applied out of the plane, therefore the out-of-plane shear stresses are also zero (i.e., \( \tau_{13} = \tau_{23} = 0 \)). In this case, Hooke’s law can be reduced to

\[
\begin{bmatrix}
\sigma_{11} \\
\sigma_{22} \\
\sigma_{33} \\
\tau_{12}
\end{bmatrix}
= 
\begin{bmatrix}
c_{11} & c_{12} & c_{13} & c_{14} \\
c_{12} & c_{22} & c_{23} & c_{24} \\
c_{13} & c_{23} & c_{33} & c_{34} \\
c_{14} & c_{24} & c_{34} & c_{44}
\end{bmatrix}
\begin{bmatrix}
\varepsilon_{11} \\
\varepsilon_{22} \\
\varepsilon_{33} \\
\gamma_{12}
\end{bmatrix}.
\]

(3.11)

To fully characterize an anisotropic material with a stiffness tensor as in Eq. 3.11, each of the 10 independent coefficients shown would need to be determined. However, it is possible to further reduce this system. Under the assumption of plane strain, the coefficient \( c_{33} \) cannot be determined because the out-of-plane strain \( \varepsilon_{33} \) is always zero. In addition, it was previously mentioned that the out-of-plane stress \( \sigma_{33} \) for a two-dimensional trabecular specimen would be meaningless. Therefore, it is not necessary to approximate the coefficients \( c_{13}, c_{23}, \) or \( c_{34} \) to characterize these two-dimensional trabecular structures. This makes it possible to reduce Eq. 3.11 to a form where the reduced stiffness tensor contains only six independent coefficients, written as

\[
\begin{bmatrix}
\sigma_{11} \\
\sigma_{22} \\
\tau_{12}
\end{bmatrix}
= 
\begin{bmatrix}
c_{11} & c_{12} & c_{14} \\
c_{12} & c_{22} & c_{24} \\
c_{14} & c_{24} & c_{44}
\end{bmatrix}
\begin{bmatrix}
\varepsilon_{11} \\
\varepsilon_{22} \\
\gamma_{12}
\end{bmatrix}.
\]

(3.12)

A system of six equations and six unknowns is needed to solve for the six independent coefficients of the stiffness tensor in Eq. 3.12. This system of equations can be obtained by performing a direct numerical analysis on each of the tissue level models (Hollister et al., 1991; Hollister and Kikuchi, 1992; van Rietbergen et al., 1996). This numerical analysis is comprised of three FE problems which are solved for three cor-
Figure 3.4. Illustration of confined strain tests. a) Analysis 1: horizontal axial strain, $\epsilon_{11} = 0.05$, b) Analysis 2: vertical axial strain, $\epsilon_{22} = 0.05$, c) Analysis 3: shear strain, $\epsilon_{12} = 0.05$. In each case, all other strains are enforced as zero.

responding confined uni-axial strain cases, as illustrated in Fig. 3.4. From each of the three analyses, it is possible to obtain the coefficients for one column of the stiffness tensor in Eq. 3.12.

For each uni-axial strain analysis, a 5% strain was applied and the boundary conditions were prescribed such that all other strains remained zero. It is important to note that this assumption will only allow for an approximation of the upper bound of the stiffness coefficients being calculated. A FE analysis was performed to obtain the corresponding normal and shear stresses for each of the three uni-axial analyses. A summary of the three analyses is:

Analysis 1:

- Boundary conditions: $\epsilon_{11}^1 = 0.05$, $\epsilon_{22}^1 = \gamma_{12}^1 = 0$

- Resulting system of equations:

\begin{align*}
\sigma_{11}^1 &= c_{11}\epsilon_{11}^1 + c_{12} \cdot (0) + c_{14} \cdot (0) \\
\sigma_{22}^1 &= c_{12}\epsilon_{11}^1 + c_{22} \cdot (0) + c_{24} \cdot (0) \\
\tau_{12}^1 &= c_{14}\epsilon_{11}^1 + c_{24} \cdot (0) + c_{44} \cdot (0)
\end{align*}

(3.13)
Analysis 2:

• Boundary conditions: $\varepsilon_{22}^2 = 0.05$, $\varepsilon_{11}^2 = \gamma_{12}^1 = 0$

• Resulting system of equations:

$$\sigma_{11}^2 = c_{11} \cdot (0) + c_{12} \varepsilon_{22}^2 + c_{14} \cdot (0)$$  
$$\sigma_{22}^2 = c_{12} \cdot (0) + c_{22} \varepsilon_{22}^2 + c_{24} \cdot (0)$$  \hspace{1cm} (3.14)  
$$\tau_{12}^2 = c_{14} \cdot (0) + c_{24} \varepsilon_{22}^2 + c_{44} \cdot (0)$$

Analysis 3:

• Boundary conditions: $\gamma_{12}^3 = 0.05$, $\varepsilon_{11}^3 = \varepsilon_{22}^3 = 0$

• Resulting system of equations:

$$\sigma_{11}^3 = c_{11} \cdot (0) + c_{12} \cdot (0) + c_{14} \gamma_{12}^3$$  
$$\sigma_{22}^3 = c_{12} \cdot (0) + c_{22} \cdot (0) + c_{24} \gamma_{12}^3$$  \hspace{1cm} (3.15)  
$$\tau_{12}^3 = c_{14} \cdot (0) + c_{24} \cdot (0) + c_{44} \gamma_{12}^3$$

Note that the superscripts in Eqs. 3.13-3.15 correspond to the analysis conducted.

Combining Eqs. 3.13-3.15 yields a system of nine equations, in six unknowns. This system appears to be overdetermined, however three equations yield redundant information. This is due to the intrinsic symmetry of the stiffness tensor. For instance, the third expression from Eq. 3.13 and the first expression from Eq. 3.15 can both be used to calculate $c_{14}$. This redundancy is present for the calculation of $c_{12}$ and $c_{24}$ as well. While mathematically the system reduces to six equations in six unknowns, numerically the stresses calculated from the FE analyses result in inconsistent equations. Thus, the off-diagonal coefficients are computed by solving a linear least squares problem $\Gamma C \approx \Sigma$ with a $9 \times 6$ coefficient matrix $\Gamma$. In a closed form the stiffness tensor
coefficients are

\[ C = \Gamma^+ \Sigma, \]  

(3.16)

where \( \Gamma^+ \) is the 6 x 9 Moore-Penrose pseudoinverse of \( \Gamma \).

3.3 Implementation of Anisotropic Structural Analysis

The computation of the stiffness tensor for each tissue model is accomplished during the anisotropic structural analysis in the updated HHCA framework (Fig. 3.5). This analysis utilizes the relative density distribution of the trabecular structures synthesized by the HCA algorithm. FE analyses are executed for each of the three uni-axial strain cases, yielding the corresponding stress distribution in the material. An averaging technique was employed to approximate the in-plane normal stresses and the shear stress. The stress was sampled at several interior points of each cell and averaged over the entire domain of the tissue model. Then, using this stress information, the individual stiffness coefficients were evaluated according to Eq. 3.16. These stiffness coefficients are then used to update the material properties of the continuum model.

Recall that the initial implementation of the HHCA methodology utilized the average density of each tissue level model to update the material properties of the continuum level model via the power law relationship in Eq. 3.7. For this method it is not necessary to have a one-to-one correspondence between the lattice of tissue level models and the FE mesh of the continuum level model since the power law relation can be applied over any region in the domain. However, when updating the material properties of the continuum level model with a stiffness tensor it becomes necessary to have a one-to-one correspondence between each tissue level model and finite element at the continuum level. This is due to the fact that the calculated stiffness tensors are only valid over the domain of each tissue level model. Thus, the stiffness tensor for each
Figure 3.5. Updated Hierarchical algorithm flow chart. This work incorporates an anisotropic structural analysis into the HHCA method to obtain a more realistic prediction of the material properties of the tissue level structures. This analysis requires the computation of the stress state for each of three confined uni-axial strain tests (Fig. 3.4). The information produced from the strain tests is then used to calculate the stiffness tensor of the tissue level structures. These stiffness tensors are used to directly update the material properties of each element in the FE mesh at the continuum level. This method iterates until convergence is achieved on both apparent density and stress.
tissue level model is used to represent the stiffness characteristics of the corresponding finite elements at the continuum level. When using the HHCA methodology with the anisotropic structural analysis update, it is necessary to ensure that the discretization of tissue level models is of the desired resolution before conducting an analysis.

3.4 Application of HHCA Methodology

The effectiveness of this approach is illustrated by applying the HHCA algorithm to two example problems, using both the apparent density and stiffness tensor methods of updating the continuum model. The first example problem deals with remodeling a plate of bone under a linearly decreasing compressive load, originally proposed by Weinans et al. (1992). The second example involves remodeling a cantilevered bone specimen. In both examples, a state of uniform strain energy density (SED) was used as the mechanical stimulus target to drive the redistribution of material in the domain.

3.4.1 Bone Plate Example

The analysis of a thin plate of bone was originally proposed by Weinans et al. (1992) and used by Tovar (2004) to illustrate the initial implementation of the HHCA algorithm. This example is comprised of a two-dimensional plate of bone having dimensions of 5 mm x 5 mm x 1/25 mm. The plate is supported from the bottom and its upper edge is subject to a compressive load that linearly decreases from a value of 50 N/mm² to 0 N/mm². The continuum domain was discretized into 5 x 5 elements as done in the original investigation by Weinans et al. (1992). This will serve as the submodel discretization for the application of the HHCA methodology. In Tovar’s work, each of the 25 submodels is discretized into a CA lattice of 25 x 25 cells, for the local HCA analysis at the tissue level. The continuum and tissue level domains are illustrated in Fig. 3.6.
The objective of this example was to drive the mechanical stimulus in the domain to a target SED of $S_i^* = 0.25 \text{ N/mm}^2$. The parameters used in this example reflect those used by Tovar (2004) to provide a comparison with results previously obtained with the HHCA algorithm.

Each tissue level model represents a 1 mm x 1 mm x 1/25 mm bone section and was discretized into a 25 x 25 CA lattice. For these submodels, a 25 x 25 FE mesh of four node linear quadrilateral elements was used. The initial state of stress calculated for the tissue models (Eqs. 3.1-3.3) is displayed in Table 3.1. For the HHCA method, each submodel is subject to a uniform stress state. This presents a subtle difficulty for the application of the local HCA method. If a uniform stress state is applied to a model with a homogeneous material distribution, an unstable equilibrium solution will occur.

The continuum domain was discretized into a 5 x 5 FE mesh of four node linear quadrilateral elements. The initial material distribution of the model was selected to be...
TABLE 3.1

BONE PLATE EXAMPLE: STATE OF STRESS FOR THE INITIAL SOLID SUB-MODELS

<table>
<thead>
<tr>
<th>Submodel</th>
<th>( X_I )</th>
<th>( \sigma_x ) [MPa]</th>
<th>( \sigma_y ) [MPa]</th>
<th>( \sigma_{xy} ) [MPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.999</td>
<td>0.000</td>
<td>-45.000</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>0.999</td>
<td>0.000</td>
<td>-45.000</td>
<td>0.000</td>
</tr>
<tr>
<td>3</td>
<td>0.999</td>
<td>0.000</td>
<td>-45.000</td>
<td>0.000</td>
</tr>
<tr>
<td>4</td>
<td>0.999</td>
<td>0.000</td>
<td>-45.000</td>
<td>0.000</td>
</tr>
<tr>
<td>5</td>
<td>0.999</td>
<td>0.000</td>
<td>-45.000</td>
<td>0.000</td>
</tr>
<tr>
<td>6</td>
<td>0.999</td>
<td>0.000</td>
<td>-35.000</td>
<td>0.000</td>
</tr>
<tr>
<td>7</td>
<td>0.999</td>
<td>0.000</td>
<td>-35.000</td>
<td>0.000</td>
</tr>
<tr>
<td>8</td>
<td>0.999</td>
<td>0.000</td>
<td>-35.000</td>
<td>0.000</td>
</tr>
<tr>
<td>9</td>
<td>0.999</td>
<td>0.000</td>
<td>-35.000</td>
<td>0.000</td>
</tr>
<tr>
<td>10</td>
<td>0.999</td>
<td>0.000</td>
<td>-35.000</td>
<td>0.000</td>
</tr>
<tr>
<td>11</td>
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<td>-25.000</td>
<td>0.000</td>
</tr>
<tr>
<td>12</td>
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<td>0.000</td>
<td>-25.000</td>
<td>0.000</td>
</tr>
<tr>
<td>13</td>
<td>0.999</td>
<td>0.000</td>
<td>-25.000</td>
<td>0.000</td>
</tr>
<tr>
<td>14</td>
<td>0.999</td>
<td>0.000</td>
<td>-25.000</td>
<td>0.000</td>
</tr>
<tr>
<td>15</td>
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<td>0.000</td>
<td>-25.000</td>
<td>0.000</td>
</tr>
<tr>
<td>16</td>
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<td>-15.000</td>
<td>0.000</td>
</tr>
<tr>
<td>17</td>
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<td>0.000</td>
<td>-15.000</td>
<td>0.000</td>
</tr>
<tr>
<td>18</td>
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<td>0.000</td>
<td>-15.000</td>
<td>0.000</td>
</tr>
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<td>0.000</td>
<td>-15.000</td>
<td>0.000</td>
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<td>0.000</td>
<td>-5.000</td>
<td>0.000</td>
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<td>-5.000</td>
<td>0.000</td>
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<tr>
<td>23</td>
<td>0.999</td>
<td>0.000</td>
<td>-5.000</td>
<td>0.000</td>
</tr>
<tr>
<td>24</td>
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<td>0.000</td>
<td>-5.000</td>
<td>0.000</td>
</tr>
<tr>
<td>25</td>
<td>0.999</td>
<td>0.000</td>
<td>-5.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>
a fully dense configuration (i.e., $X_I(0) = 0.999$ for $I \in \{1, \ldots, 25\}$). For both the density and tensor update methods, the first iteration utilized an isotropic material model for mineralized bone tissue with a Young’s modulus of 303 MPa and a Poisson’s ratio of 0.3 (Tovar, 2004). For subsequent iterations, the density approach used the power law relationship given in Eq. 3.7 with the Young’s modulus of mineralized tissue $E_{0I} = 303$ MPa and the penalization power $p = 3$. For the tensor update method, the stiffness tensor calculated for each tissue level model $C_I$ (Eq. 3.16) was used directly to update continuum model mechanical properties. The continuum level convergence parameters were selected as $\epsilon_X = 0.06$ and $\epsilon_\sigma = 12.5$ MPa, as done by Tovar (2004).

It was found that utilizing a homogeneous initial material distribution for the tissue level models resulted in an unstable equilibrium solution. For the case of homogeneous material, the stress distribution in the model was uniform. In this situation, the mechanical stimulus error for each cell will be identical over the entire CA lattice. Therefore, even when using a neighborhood averaging scheme, identical density changes will be predicted for every cell in the lattice and the density distribution will remain homogeneous. If the stimulus in the model is below the target value, the unstable equilibrium point will be a uniform distribution of intermediate density elements (i.e., $0 < x_i < 1$).

Arriving at an equilibrium solution of this kind nullifies the purpose of using the power law method for interpolating the Young’s modulus. Using a penalization power $p > 1$ facilitates the overestimation of the stiffness of high-density elements and the underestimation of the stiffness of low-density elements. This helps in driving the material in a cell to either a fully dense state or a void. Thus, in the case that the applied loading distribution is in a uniform stress state, it is necessary to use a non-homogeneous initial density distribution. It was found that small perturbations in the material distribution drove the system toward a non-homogeneous solution, as long as
the mechanical stimulus in the domain was smaller than the mechanical stimulus target (i.e., $S_i < S^*$). Therefore, in this study the cells in each tissue model were considered to be fully dense, with the exception of the central cell being set to half of the full density (i.e., $x^I_i(0) = 0.999$ for $i \in \{1, ..., 312, 314, ..., 625\}$ and $x^I_{313}(0) = 0.5$). This slight inhomogeneity in density allows the local HCA method to progress toward a stable equilibrium solution.

The local HCA analysis that was applied to the tissue level models utilized a proportional, integral, and derivative (PID) control law, with gains of $c_p = 0.10$, $c_i = 0.05$, and $c_d = 0.05$. A neighborhood size of $N = 8$ was used for calculating the effective mechanical stimulus (note that periodic boundary conditions were assumed for the neighborhoods). Convergence of the local HCA analysis was defined as a 0.1% change in overall density of the tissue model. If convergence was not achieved after 120 iterations, the local HCA algorithm was interrupted and finished.

The results for the HHCA analysis of the bone plate for both the apparent density and tensor update methods are shown in Fig. 3.7 and Fig. 3.8, respectively. The density method required three iterations to converge and the final structure had a total apparent density of $M_t = 11.4556$. The resulting structure is comparable to that found by Tovar (2004). Using the stiffness tensor update method, the HHCA algorithm required two iterations to converge and the final structure had a total apparent density of $M_t = 10.5188$. Some qualitative differences exist between the final structures for the two methods. For instance, the tissue models of the structure produced by the stiffness tensor update method do not appreciably change from the first iteration to the final iteration. However, for the apparent density update method, the horizontal struts seen in the tissue models have become skewed in some locations as the algorithm progressed, seen in Fig. 3.7c. This behavior is the result of shear forces becoming a factor in the
Figure 3.7. Iterative change in the bone plate structure using the apparent density update method. Continuum level convergence was achieved after three iterations of the HHCA method.
Figure 3.8. Iterative change in the bone plate structure using the stiffness tensor update method. Continuum level convergence was achieved after two iterations of the HHCA method.

evolution of the structure in the local HCA analyses. In terms of computational efficiency, it took 6407 FE analyses when using the apparent density update and 4324 FE analyses when using the tensor update. The stiffness tensor method required approximately 32.5% fewer FE analyses as compared to the apparent density method, primarily due to the reduction in iterations required. The results for this example are summarized in Table 3.2.

**TABLE 3.2**

**BONE PLATE EXAMPLE RESULTS SUMMARY**

<table>
<thead>
<tr>
<th>Update Method</th>
<th>Number of Iterations</th>
<th>Number of FE Analyses</th>
<th>Final Total Apparent Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent Density</td>
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<td>6407</td>
<td>11.4556</td>
</tr>
<tr>
<td>Stiffness Tensor</td>
<td>2</td>
<td>4324</td>
<td>10.5188</td>
</tr>
</tbody>
</table>
3.4.2 Cantilevered Plate Example

The second example utilized the same 5 mm x 5 mm x 1/25 mm thin plate of bone. For this analysis, the left end of the specimen was fixed and the loading condition consisted of a downward point load of 0.25 N, applied to the lower right corner of the model. The continuum domain and tissue level models were discretized into 5 x 5 elements and 25 x 25 CA lattices, respectively. The continuum and tissue level domains are depicted in Fig. 3.9. The objective of this example was to drive the mechanical stimulus in the domain to a target SED of $S_i^* = 0.02$ N/mm$^2$.

![Figure 3.9. Cantilevered plate model. The continuum domain is discretized into 5 x 5 elements (left) and each tissue model is comprised of a 25 x 25 CA lattice (right). The left end of the continuum domain is fully constrained. The loading condition consists of a downward 0.25 N point load, applied to the node in the lower right corner of the domain.](image)

An identical set of initial conditions from the bone plate example was used with the exception of $\epsilon_\sigma = 0.25$ MPa. A smaller continuum level tolerance on the change in the stress distribution was selected due to the significantly reduced stresses in the model. The initial state of stress calculated for the tissue models is shown in Table 3.3.
### TABLE 3.3

**CANTILEVER PLATE EXAMPLE: STATE OF STRESS FOR THE INITIAL SOLID SUB-MODELS**

<table>
<thead>
<tr>
<th>Submodel</th>
<th>$X_I$</th>
<th>$\sigma_x$ [MPa]</th>
<th>$\sigma_y$ [MPa]</th>
<th>$\sigma_{xy}$ [MPa]</th>
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<td>-1.944</td>
<td>10.595</td>
<td>-2.591</td>
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</tbody>
</table>
The results for the HHCA analysis of the cantilever plate for both the apparent density and tensor update methods are shown in Fig. 3.10 and Fig. 3.11, respectively. The density method required seven iterations to converge and the final structure had a total apparent density of \( M_t = 8.7956 \). Using the stiffness tensor update method, the HHCA algorithm required three iterations to converge and the final structure had a total apparent density of \( M_t = 8.0730 \). The final structures for both update methods are qualitatively similar. One significant difference was that the tissue models in the lower right corner are more dense for the density update method. Another difference was that the density approach predicted the structure of the tissue model in the upper right corner of the domain to have struts that were oriented nearly orthogonal to that of the corresponding tissue structure predicted by the stiffness tensor approach. In terms of computational efficiency, it took 17841 FE analyses when using the apparent density update and 8437 FE analyses when using the tensor update. The stiffness tensor method required approximately 52.7% fewer FE analyses as compared to the apparent density method. Again, this is primarily due to the reduction in iterations required, as seen in the previous example. These results for are summarized in Table 3.4.

### TABLE 3.4

CANTILEVER PLATE EXAMPLE RESULTS SUMMARY

<table>
<thead>
<tr>
<th>Update Method</th>
<th>Number of Iterations</th>
<th>Number of FE Analyses</th>
<th>Final Total Apparent Density</th>
</tr>
</thead>
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<tr>
<td>Apparent Density</td>
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<td>17841</td>
<td>8.7956</td>
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<tr>
<td>Stiffness Tensor</td>
<td>3</td>
<td>8437</td>
<td>8.0730</td>
</tr>
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</table>
Figure 3.10. Iterative change in the cantilever plate structure using the apparent
density update method. Continuum level convergence was achieved after seven
iterations of the HHCA method.
Figure 3.11. Iterative change in the cantilever plate structure using the stiffness tensor update method. Continuum level convergence was achieved after three iterations of the HHCA method.
3.5 Discussion

This chapter presents a method for numerically determining the anisotropic material properties of the tissue level models for the HHCA algorithm. The updated HHCA methodology is illustrated through two example problems, in which the results for both the density and stiffness tensor update methods are compared. The results demonstrate that including stiffness information in the hierarchical method improves algorithm convergence and results in a more consistent evolution of the continuum structure. It is hypothesized that these benefits result from the stiffness tensor providing a preferred orientation for stiffness characteristics of the tissue models, which influences the stress distribution at the continuum level. For both of the examples presented, the stiffness tensor update method arrived at a lighter structure and required fewer FE analyses.

The HHCA method is effective at breaking a global loading condition into a set of local loads which drive adaptation. In theory, bone follows a similar process to drive local bone adaptation to achieve the required global behavior. Unfortunately, the HHCA method suffers from not accurately representing the biological basis of the remodeling process and focuses primarily on the mechanical aspects of remodeling. The timescale for this simulation is on the order of months which is too large to make meaningful predictions about factors leading to bone pathology. A model of the cellular mechanisms of remodeling could be included as part of this framework to translate day-to-day changes in remodeling activity into the global behavior of bone. The following chapters will pursue a model of the cellular mechanisms of bone remodeling and investigate how improvements in the biological detail of the HCA method can provide further insight into the unknown aspects of this regulatory process.
A HIGH FIDELITY HCA MODEL FOR BONE ADAPTATION WITH CELLULAR RULES FOR REPRESENTING BONE RESORPTION

One of the most intriguing aspects of bone is its ability to grow, repair damage, adapt to mechanical loads, and maintain mineral homeostasis (Burr, 2002). It is generally accepted that bone adaptation occurs in response to the mechanical demands of our daily activities; moreover, strain and microdamage have been implicated as potential stimuli that regulate bone remodeling (Carter, 1984). Computational models have been used to simulate remodeling in an attempt to better understand the metabolic activities which possess the key information of how this process occurs (Burger et al., 2003; García-Aznar et al., 2005; Huiskes et al., 2000, 1987; Lemaire et al., 2004; Martin and Buckland-Wright, 2004, 2005; McNamara and Prendergast, 2005, 2007; Mullender et al., 1994; Mulvihill et al., 2008; Mulvihill and Prendergast, 2008; Prendergast and Taylor, 1994; Ruimerman et al., 2001; Tezuka et al., 2005; Tovar, 2004; Turner, 1999; van der Linden et al., 2001; van Oers et al., 2008a,b). The classical approach to modeling bone adaptation relates local changes in bone mass/density to the deviation between the local mechanical stimulus and a reference value (i.e., deviations in stress, strain, or strain energy density (SED)).

Previous organ and tissue level models have been used to predict net changes in bone architecture (Huiskes et al., 2000; McNamara and Prendergast, 2005, 2007; Mullender et al., 1994; Mulvihill et al., 2008; Mulvihill and Prendergast, 2008; Prendergast
and Taylor, 1994; Ruimerman et al., 2001; Tovar, 2004). These large-scale simulations are able to capture phenomena such as net increases/decreases in bone volume or re-orientation of tissue level structures under altered mechanical loading. However, the time scale associated with these models is on the order of months or greater. More recently, studies have focused on simulating the remodeling response at a single site in bone. Some researchers have adapted the classical remodeling paradigm to simulate net remodeling processes at the trabecular and basic multicellular unit (BMU) level (Hernandez et al., 2003; Huiskes et al., 2000; Martin, 2000; Mulvihill et al., 2008; Mulvihill and Prendergast, 2008; van der Linden et al., 2001; van Oers et al., 2008a,b); others have focused on developing rules for the cellular behavior that occurs (Martin and Buckland-Wright, 2004, 2005; Moroz et al., 2006; Ryser et al., 2009; Tezuka et al., 2005). Due to the smaller length scale of these simulations, it is possible to focus on a smaller time scale. These simulations predict remodeling activity, ranging from several days to weeks, and more accurately represent the cellular level processes that occur.

Evidence for bone metabolic diseases points toward the disruption of the cellular mechanisms of remodeling (Burr and Martin, 1989). Altering the rate of daily cellular activity can lead to bone pathologies; however, the exact change (i.e., increased osteoclast activity or decreased osteoblast activity) remains unknown. It is evident that the current trend of improvements in computational simulations of bone remodeling is progressing towards capturing cellular level detail. By capturing this level of detail, simulations can be utilized to predict physiological changes in remodeling that lead to bone pathologies. Currently, few attempts have been made to incorporate both mechanically stimulated remodeling theories with models of cellular behavior, for a single remodeling site. By combining the classical paradigm for mechanically stimulated remodeling with models of cellular behavior, it is possible to achieve a mechanistic prediction of
the cellular activity of remodeling.

The primary focus of this investigation is to model the cellular mechanisms involved in the bone resorption process. This is done by developing a new computational framework that utilizes mathematical rules to mechanistically model cellular activities. This framework incorporates potential signaling pathways that mediate remodeling cellular activity in a hybrid cellular automaton (HCA) algorithm (Tovar, 2004). Building off of the existing HCA framework is suitable, as the basic architecture of this method is similar to common density-based remodeling simulations (Hazelwood and Castillo, 2007; Huiskes et al., 2000; McNamara and Prendergast, 2007; Mulvihill et al., 2008; Ruimerman et al., 2005a; Tezuka et al., 2005). While the same lattice scheme as the HCA method can be used, this new framework will differentiate between types of tissue (i.e., mineralized bone and bone marrow) and account for the activities of the cells involved (i.e., osteocytes, lining cells, osteoclasts, mononucleated cells, and osteoblasts).

In this chapter, a new framework is presented that uniquely combines phenomenological and mechanistic paradigms for the simulation of bone resorption. This methodology connects the cellular mechanisms related to the activation and resorption phases of remodeling with applied mechanical stimuli, via cellular signaling. Mathematical rules were formulated based on prominent processes that describe the behavior of bone cells, as reported from experimental studies. These biologically based rules are implemented in the new framework to control the recruitment, differentiation, and activation of osteoclasts. This framework is exercised on an idealized model of a trabecular strut.

4.1 Cellular Signaling Paradigm

The incorporation of cellular mechanisms in a remodeling framework is a complex task that presents many challenges. There are a number of cells that participate
in the remodeling process, which communicate via gap junctions and/or other signaling pathways (e.g., by secreting various messenger molecules). To incorporate all of these activities would be computationally prohibitive with current technology, due to the level of modeling complexity, and also limited as our understanding of the remodeling process is still a “work in progress”. In addition, conflicting information exists regarding the influences of mechanical stimuli on the cells involved in the remodeling process. Furthermore, the exact biochemical signals that activate and sustain the remodeling process are not fully understood.

In the original HCA framework, tissue level simulations of bone adaptation were conducted. The computational domain was composed of a lattice of elements, containing either mineralized bone with one or more embedded osteocytes or bone marrow. In this research, when conducting simulations at the cellular level it is no longer valid for every element associated with the bone matrix to contain an osteocyte. In fact, one can account for the distribution of lining cells, osteoclasts, osteoblasts, and mononucleated cells as well. For the model developed in this investigation, \( \gamma_i(t) \) is used to differentiate between the types of tissue being represented, i.e., mineralized bone \( (B) \), bone marrow \( (M) \), lining cells \( (L) \), osteoclasts \( (OC) \), osteoblasts \( (OB) \), osteocytes \( (OS) \), and mononucleated cells \( (MN) \). Therefore, \( \gamma_i(t) \in \{B, M, L, OC, OB, OS, MN\} \).

In this signaling paradigm, osteocytes are assumed to act as mechanosensors while lining cells act as signal receptors. This paradigm was selected as osteocytes are ideally located within the bone matrix to experience a variety of mechanical stimuli and release signals that theoretically convey the demand for bone adaptation. Lining cells, in turn, are equipped and strategically located to receive signals pertaining to the need for remodeling and to either execute or mediate all four components of the activation process (Chambers, 1991; Kahn and Partridge, 1991; Parfitt, 1990). The following sections
detail osteocyte and lining cell signaling.

4.1.1 Osteocyte Mechanosensation

As previously mentioned, bone tissue contains a vast network of osteocytes, interconnected by canaliculi, that are believed to be capable of mechanotransduction. These cells are assumed to be uniformly distributed throughout the bone tissue at a density consistent with histological observations. Relying on the assumption that osteocytes can sense the mechanical stimuli in a local region, these cells have the ability to produce signals which are released into their local environment. In this investigation, the local SED experienced by an osteocyte is utilized as the mechanical stimulus driving the remodeling process. Therefore, the stimulus sensed by an osteocyte \( S_i(t) \) is written as

\[
S_i(t) = \begin{cases} 
U_i(t) & \text{if } i \in N^{OS}, \\
0 & \text{if } i \notin N^{OS}, 
\end{cases}
\]

where \( U_i(t) \) is the local SED, and \( N^{OS} \) is the set of all indices corresponding to live osteocytes, given by \( N^{OS} = \{ i : \gamma_i \text{ is an osteocyte (OS)} \} \).

4.1.2 Lining Cell Signal Reception

One of the prevailing theories for bone mechanoregulation is that osteocytes are constantly communicating with lining cells to mediate adaptation. Lining cells have been observed to both receive and deliver signals to other cells that are either on the bone surface, in the adjacent soft tissue, or trapped within the bone matrix (i.e., osteocytes) (Parfitt, 1994). Therefore, it is reasonable to assume that the osteocytes in a local region each contribute to the total signal received by the lining cells.

In this investigation, two hypotheses regarding osteocyte activity are utilized for
this signaling paradigm. First, osteocyte signals diminish with distance. This concept was originally suggested by Mullender et al. (1994), and has been incorporated in many remodeling algorithms as the so-called spatial influence function (Huiskes et al., 2000; Mulvihill, 2008; Ruimerman et al., 2005a; van Oers et al., 2008a). Second, this research assumes that osteocytes can only communicate with cells that are within a local region of influence. That is, osteocytes can only communicate with cells that are close enough to form gap junctions. Therefore, the amount of osteocyte signaling received by each lining cell $L_i(t)$ is defined as

$$L_i(t) = \begin{cases} 
\sum_{j \in N_i^{OS}} S_j(t)e^{-d(\gamma_i, \gamma_j)/D} & \text{if } i \in N^{LC}, \\
0 & \text{if } i \notin N^{LC},
\end{cases}$$

(4.2)

where $d(\gamma_i, \gamma_j)$ is the distance between the $i^{th}$ lining cell and the $j^{th}$ osteocyte, $D$ is the osteocyte signal decay constant, $N^{LC}$ is the set of all indices corresponding to lining cells, given by $N^{LC} = \{i : \gamma_i \text{ is a lining cell (LC)}\}$, and $N_i^{OS}$ is the set of indices corresponding to osteocytes that are within a maximum osteocyte communication distance $d^{OS}$ of the $i^{th}$ cell, written as

$$N_i^{OS} = \{j \in N^{OS} : d(\gamma_i, \gamma_j) < d^{OS}\}.$$  

(4.3)

Like osteocytes, bone lining cells are connected to each other via surface canaliculi, allowing them to communicate through gap junctions (Ilvesaro and Tuukkanen, 2003; Martin et al., 1998; Parfitt, 1994; Recker, 1992). If it is assumed that the lining cells communicate with other lining cells in a local region, then it follows that information from these neighboring cells can be used to determine an effective amount of the local osteocyte signaling received. In this work, the effective signal received by each lining
cell $\bar{L}_i(t)$ is modeled as a weighted sum of the signals received by neighboring lining cells in a local region. The weighting factor represents the decay in lining cell signal with distance, as with the spatial influence function for osteocyte signals. Therefore, the effective lining cell signal can be expressed as

$$\bar{L}_i(t) = \begin{cases} 
L_i(t) + \sum_{j \in N_{LC}^i} L_j(t) e^{-d(\gamma_i, \gamma_j)/D} / \left( 1 + \sum_{j \in N_{LC}^i} e^{-d(\gamma_i, \gamma_j)/D} \right) & \text{if } i \in N_{LC}, \quad (4.4) \\
0 & \text{if } i \notin N_{LC},
\end{cases}$$

where $N_{LC}^i$ is the set of indices corresponding to all the local lining cells that are within a maximum lining cell communication distance $d^{LC}$ of the $i^{th}$ cell, represented as

$$N_{LC}^i = \{ j \in N_{LC}^i : d(\gamma_i, \gamma_j) < d^{LC} \}. \quad (4.5)$$

### 4.2 Activation of Remodeling

The activation of remodeling is best described as the conversion of a region of the bone surface from a quiescent state to an active state (Parfitt, 1994). Due to the large time scales of many existing simulations, activation is not accounted for explicitly which leads to inconsistencies in the sequence of events of the remodeling cycle (Huiskes et al., 2000; Mullender et al., 1994; Prendergast and Taylor, 1994; Ruimersman et al., 2001; Tovar, 2004). This process is sometimes confused with the activation of cells or molecules; however, in a physiological sense the activation phase has four components: the selection and preparation of the remodeling site, recruitment of mononuclear preosteoclasts, budding of new capillaries (this is essential for cortical remodeling, but may not be necessary for cancellous remodeling), and attraction of pre-osteoclasts to the chosen site where they fuse into multinucleated osteoclasts (Parfitt, 1994). The exact mechanism by which the activation process is carried out is not cur-
rently known. However, bone lining cells are the most strategically located cells to either mediate and/or execute this phase of remodeling.

In this work, a new paradigm is proposed for the activation of remodeling where osteocytes and lining cells are assumed to act as mechanosensors and signal receptors, respectively. Based on the strength of the osteocyte signals, lining cells either initiate the activation of remodeling via the production of a recruitment signal or remain quiescent. The recruitment signals serve to activate the osteoblasts or osteoclasts needed to carry out the required formation or resorption activity. This paradigm differs from previous work in that the actual distribution of osteocytes, lining cells, and activated cells is accounted for in each iteration. In addition, once the appropriate cells are activated, lining cells are assumed to detach from the bone surface, exposing a target area and allowing for the attachment of the activated cells. This way, lining cells are not present to sense osteocyte signals at the surface sites that are currently undergoing adaptation. It is important to note that the time scale of this simulation is assumed to be small enough to account for the aforementioned behavior (i.e., on the order of a single day). This ideology provides for a more physiologically accurate depiction of the sequence of events in the activation process and further distinguishes this paradigm from previous models. Note that previous studies have allowed osteocyte signals to alter the remodeling behavior at each time step, owing to the fact that the time scale of their simulations was on the order of weeks and the predicted remodeling activity represented the average behavior over time.

This new paradigm is based on the same principle as the piecewise-linear mechano-regulation rule by McNamara and Prendergast (2005). While the osteocyte signals $S_i(t)$ provide for the effective signal received by lining cells $\bar{L}_i(t)$, lining cells are assumed to act as the gatekeepers for remodeling. Therefore, a recruitment stimulus $RS_i(t)$ for
The effective lining cell signal \( \bar{L}_i(t) \) depends on the SED experienced by local osteocytes due to an applied load, the osteocyte signal decay constant \( D \), the maximum osteocyte communication distance \( d^{OS} \), and the maximum lining cell communication distance \( d^{LC} \) (Eqs. 4.2-4.4). Therefore, changes in these parameters will alter the effective lining cell signals which define the bounds on the quiescent regime and the
Figure 4.1. Diagram of the cellular signaling paradigm. The upper plot displays the signaling response for a single osteocyte $S_i(t)$. The lower plot displays the recruitment stimulus $RS_i(t)$ used to activate osteoclasts and osteoblasts. The level of cellular signaling is divided into four ranges: a) Disuse, b) Lazy zone, c) Overuse, and d) Overload. If the effective lining cell signal $\bar{L}_i(t)$ is within the disuse or overuse range, the recruitment stimulus $RS_i(t)$ would initiate osteoclast or osteoblast activity, respectively. It is important to note that the upper and lower plots are not necessarily in direct correspondence with each other. The collective signaling response of osteocytes within the maximum communication distance of a particular lining cell provides for the effective lining cell signal $\bar{L}_i(t)$. For the general case, in which osteocyte signaling is not uniform, these plots will not coincide.
damage threshold of the recruitment stimulus. In their work, McNamara and Prendergast (2005) assumed that the threshold for resorption corresponded to a local strain of 1000 \(\mu\varepsilon\), while the threshold for formation occurred at 2000 \(\mu\varepsilon\). In this investigation, the threshold for resorption \(\bar{L}^{*}_{\text{min}}\) was calculated as the average signal received by a lining cell for an applied load resulting in a homeostatic strain of \(\delta_{\text{min}} = 1000 \mu\varepsilon\). Similarly, the threshold for formation \(\bar{L}^{*}_{\text{max}}\) and the critical damage threshold \(\bar{L}^{*}_{\text{crit}}\) were calculated for applied loads resulting in homeostatic strains of \(\delta_{\text{max}} = 2000 \mu\varepsilon\) and \(\delta_{\text{crit}} = 3500 \mu\varepsilon\), respectively.

4.3 Bone Resorption

A significant amount of work has been dedicated to identifying the cellular mechanisms that control resorptive activity. In this investigation, two phases of resorption are considered: Phase I) resorption by osteoclasts, and Phase II) removal of remnant collagen fibrils by mononucleated cells. A new method for modeling the daily resorption activity is presented in this section.

4.3.1 Osteoclast Cellular Activity (Phase I)

There are many factors that contribute to osteoclast regulation; however for this model only a few of the prominent processes are considered. Osteoclast differentiation is supported by cells of the osteoblast lineage that express receptor activator of nuclear factor \(\kappa\beta\) ligand (RANKL) and macrophage colony simulating factor (M-CSF) (Baron, 1993). RANKL is a messenger molecule that activates osteoclasts, while M-CSF is a secreted cytokine which influences hematopoietic stem cells to differentiate into macrophages. Proximity between osteoblastic cells and hematopoietic stem cells is required for RANKL and M-CSF to bind to their respective receptors, which are
expressed by cells of the monocyte and macrophage lineage (Martin and Sims, 2005).

For this investigation, the down-regulation of resorptive activity is assumed to occur by two mechanisms. The first negative feedback mechanism is related to the inhibition of osteoclast activation by the cytokine osteoprotegerin (OPG). It has been observed that resorptive activity decreases due to transforming growth factor-β1 (TGF-β1) induced OPG production in local stromal cells and preosteoblast-like cells (Murakami et al., 1998; Takai et al., 1998). To further substantiate this, it is known that growth factors such as TGF-β1 and insulin-like growth factor I and II are deposited in the unmineralized tissue when bone is formed (Hauschka et al., 1986). When osteoclasts resorb bone, TGF-β1 (amongst other factors) is released which causes the production of OPG by the appropriate cells local to the remodeling site. The second negative feedback mechanism for resorptive activity is related to the concentration of TGF-β1. It has been observed that osteoclasts become apoptotic at high concentrations of TGF-β1 (Hughes et al., 1996). It is not known whether the concentration of TGF-β1 is uniform throughout the bone matrix or if it accumulates locally upon resorption. In this investigation, it is assumed that the exposure to TGF-β1 over time leads to the apoptosis of osteoclasts in a period consistent with their observed lifespan.

As previously mentioned, other models have attempted to describe the cellular level mechanisms of bone resorption. Martin and Buckland-Wright (2004) developed a one-dimensional model of the resorption activity at a microsite (i.e., a single cross vertical section at a resorption site). Their model was the first to mechanistically predict resorption depth and duration. They assumed that the cellular activity during resorption could be modeled by using Michaelis-Menten (M-M) kinetics. The M-M equation has been used in other fields, such as endocrinology, for predicting cellular activity (Boonacker et al., 2002; Sunray et al., 2002). For their investigation, it was assumed that an ini-
tial concentration of RANKL exists which essentially drives the resorption process. As resorption activity proceeded, TGF-β1 induced OPG production was assumed to occur which reduced the local RANKL/OPG ratio. This is supported by experimental studies, as osteoclast activity has been found to decrease as the RANKL/OPG ratio decreases (Khosla, 2001; Murakami et al., 1998; Takai et al., 1998). Therefore, their model assumed that resorption continued until a critical concentration of TGF-β1 accumulates, resulting in osteoclast apoptosis. Thus, this model provides a mechanism which describes the osteoclast activity over time and predicts the arrest of activity in accordance with physiologically relevant factors. Unfortunately, Martin and Buckland-Wright (2004) do not address how the concentration of RANKL, necessary to begin the resorption process, is acquired or sustained.

In order to connect such a model of the cellular mechanisms of resorption to traditional remodeling simulations, a connection with the local mechanical stimulus must be established. This is essential as the fundamental assumption in many bone remodeling simulations is that remodeling occurs in relation to a local mechanical stimulus. However, this would necessitate that a correlation between the RANKL/OPG ratio and an applied mechanical stimulus exists. It has been observed that RANKL secretion is significantly increased by mechanically damaged osteocytes in a three-dimensional gel-embedded culture (Kurata et al., 2006). Unfortunately, in their study the relative production of OPG was not measured because the culture contained MLO-Y4 osteocytes, but lacked stromal cells or preosteoblasts. Another group showed that fluid-flow induced shear stress caused a transient reduction in the RANKL/OPG ratio (Kim et al., 2006). This study reported that the concentration of RANKL decreased, while that of OPG increased.

While these studies provide support for a connection between reduced local me-
chanical stimuli and the cellular mechanisms of resorption, contradictory evidence exists in the literature as well. For example, Ichimiya et al. (2007) reported that compressive stress promotes osteoclast formation through RANKL expression. This study suggests that increased mechanical stimulation could also play a role in initiating osteoclast recruitment. One noteworthy aspect is that this study used synovial cells, rather than cells of the osteocyte lineage. As a result, the relative contribution of synovial cells to osteoclastogenesis could be an additional confounding factor in their experiment. As mentioned before, osteocyte suppression of osteoclast activity occurs under normal loading and the aforementioned study does not take this activity into account.

By analyzing the information obtained from these studies, it is hypothesized that the local RANKL/OPG ratio can be up-regulated and down-regulated based on the level of mechanically induced cell signaling.

The resorption mechanism for the model developed in this work assumes that the osteoclast cellular activity $A_{i}^{OC}(t)$ can be expressed using a relation inspired by M-M kinetics, given by

$$ A_{i}^{OC}(t) = \frac{-V_{i}^{OC}(t)R_{S_{i}}(t^*)}{-R_{S_{i}}(t^*) + K_{m}^{OC}}, $$

(4.7)

where $V_{i}^{OC}(t)$ is the rate of osteoclast resorption, $t^*$ represents the time step in which the osteoclast was activated and, for this work, $K_{m}^{OC}$ is treated as a dimensionless constant. Note that it is assumed that osteoclasts initially resorb bone at the maximum resorption rate $V_{i}^{OC}(0) = V_{0}^{OC}$.

In this relation, the recruitment stimulus $R_{S_{i}}(t)$ represents the activation state of the osteoclast, which could be likened to the local RANKL/OPG concentration at that instant. Fuller et al. (1998) reported that the maximum osteoclast activity occurred at a RANKL concentration of 100 ng/ml, and half of the maximum activity occurred at a RANKL concentration of 10 ng/ml. In an effort to bring consistency between
this modeling paradigm and physiological observations, the value of the recruitment stimulus corresponding to the maximum amount of osteoclast activity was scaled to a value of -100 (note: $RS_i(t)$ is negative for osteoclast activity). In addition, constant $K_{OC}^{m}$ was given a value of -10, which represents the recruitment stimulus available when the rate of osteoclast activity is approximately half of its maximum value.

The osteoclast cellular activity $A_i^{OC}(t)$ is assumed to be down-regulated by TGF-$\beta$1 induced OPG production. It is assumed that the concentration of TGF-$\beta$1 trapped in the mineralized bone matrix is uniform, and therefore is released proportionally to the osteoclast cellular activity $A_i^{OC}(t)$. Thus, the relative amount of TGF-$\beta$1 $\kappa_i^{TGF-\beta1}(t)$ available to initiate OPG production is written as

$$
\kappa_i^{TGF-\beta1}(t) = \frac{c^{TGF-\beta1}A_i^{OC}(t)\Delta t}{v^{cell}}, \quad (4.8)
$$

where $c^{TGF-\beta1}$ is a constant that represents the weight fraction of TGF-$\beta$1 in the bone matrix, $\Delta t$ is the length of a single time step, and $v^{cell}$ is the volume of a lattice site. The concentration of TGF-$\beta$1 released would then drive the production of OPG by stromal cells and cells of the osteoblast lineage, allowing for the down-regulation of osteoclast activity. In this investigation, the relative amount of OPG produced $\kappa_i^{OPG}(t)$ is assumed to be proportional to the relative amount of TGF-$\beta$1 $\kappa_i^{TGF-\beta1}(t)$ available, written as

$$
\kappa_i^{OPG}(t) = c^{OPG}\kappa_i^{TGF-\beta1}(t), \quad (4.9)
$$

where $c^{OPG}$ is a proportional constant.

Fuller et al. (1998) reported that not only does OPG inhibit bone resorption through the inhibition of osteoclast formation, but also through the suppression of mature osteoclast activity. Therefore, for this investigation it is assumed that OPG has the effect
of reducing the rate of osteoclast resorption \( V_{i}^{OC}(t) \) at each iteration, proportional to the relative amount of OPG produced \( \kappa_{i}^{OPG}(t) \). This is written as

\[
V_{i}^{OC}(t + 1) = V_{i}^{OC}(t) - \frac{\kappa_{i}^{OPG}(t)v_{cell}}{\Delta t}.
\] (4.10)

In addition, this model also accounts for the apoptosis of osteoclasts due to TGF-\( \beta \)1. It has been reported that the average osteoclast lifespan is 12 days (Jilka, 2003). Thus, in this investigation it is assumed that continued exposure of osteoclasts to TGF-\( \beta \)1 released from the bone matrix results in apoptosis after 12 iterations.

### 4.3.2 Collagen Fibril Removal (Phase II)

In this model, a second resorption phase takes place which accounts for the removal of protruding fibrils from the newly eroded bone surface. In the body, this process is carried out by mononucleated cells (Everts et al., 2002). Very little is known about how this phase of remodeling is regulated. Therefore, for this work the mononucleated cellular activity \( A_{i}^{MN}(t) \) is assumed to be constant for each iteration. This is written as

\[
A_{i}^{MN}(t) = A_{avg}^{MN},
\] (4.11)

where \( A_{avg}^{MN} \) is the average rate of mononucleated cellular activity reported in the literature. In this investigation, it is assumed that 20% of the total volume of tissue removed by an osteoclast remains as demineralized collagen fibrils. Therefore, at a location where osteoclast activity is occurring, the substrate for mononuclear cellular activity \( s_{i}^{MN}(t) \) accumulates as

\[
s_{i}^{MN}(t + 1) = s_{i}^{MN}(t) + 0.2 \frac{A_{i}^{OC}(t)}{v_{cell}} \Delta t.
\] (4.12)
When osteoclast activity ceases, the mononucleated cells are assumed to become active and begin the removal of remnant collagen fibrils from the bone surface. The substrate for mononuclear cellular activity $s_{i}^{MN}(t)$ is assumed to decrease in accordance with the amount of material removed, given by

$$s_{i}^{MN}(t + 1) = s_{i}^{MN}(t) - \frac{A_{avg}}{v_{cell}} \Delta t. \quad (4.13)$$

Once the mononucleated cells remove the remnant collagen fibrils, the cells are assumed to vacate the bone surface. Following this phase of activity, lining cells or pre-osteoblasts are attracted to the uncovered area on the bone surface.

### 4.4 Computational Implementation

In the HCA framework, at a discrete position $i$ and time $t$, a cell is defined by a finite vector of states $\alpha_{i}(t)$ that is operated on by a set of CA rules (Tovar et al., 2006). The state of the $i^{th}$ cell in the new HCA formulation presented in this investigation is defined by using the tissue type of a cell $\gamma_{i}(t)$, the relative density $x_{i}(t)$, the local strain energy density $U_{i}(t)$, the local stimulus sensed by an osteoclast $S_{i}(t)$, the local signal sensed by a lining cell $L_{i}(t)$, and the local recruitment stimulus $RS_{i}(t)$. This can be written as

$$\alpha_{i}(t) = \begin{bmatrix} \gamma_{i}(t) \\ x_{i}(t) \\ U_{i}(t) \\ S_{i}(t) \\ L_{i}(t) \\ RS_{i}(t) \end{bmatrix}. \quad (4.14)$$
By collecting this information for each cell, the remodeling rules can be applied uniformly throughout the CA lattice.

4.4.1 Methodology

The overall structure of this new framework does not depart substantially from the original HCA methodology. A linear static structural analysis is used to obtain mechanical stimulus information throughout the model. The mechanical stimulus provides a mechanism for the initiation of local cellular activity associated with bone resorption. These structural changes are localized on the surfaces of the mineralized tissue and are effected in the model by changing the relative (or normalized) density \( x_i(t) \), where \( x_i(t) \in (0, 1] \). Therefore, the material in each cell is varied between bone marrow (\( 0 < x_i(t) \leq 0.001 \)) and fully dense bone (\( x_i(t) = 1 \)).

Since this study focuses on resorption, changes in relative density occur at locations associated with osteoclast or mononuclear cellular activity. The change in relative density due to osteoclast cellular activity is written as

\[
\Delta x_i(t) = \frac{A_{OC}^i(t)}{v_{cell}} \Delta t, \tag{4.15}
\]

where \( v_{cell} \) is the volume of a lattice site. Similarly, the change in relative density due to mononucleated cellular activity is written as

\[
\Delta x_i(t) = \frac{A_{MN}^i(t)}{v_{cell}} \Delta t. \tag{4.16}
\]

In general, the relative density of each cell can vary throughout the remodeling process. Changes in this parameter will result in a change in the mechanical properties of bone. For this investigation, it is assumed that the modulus \( E_i(t) \) at a site in the model can be
parameterized according to the power law relationship

\[ E_i(t) = E_0 x_i(t)^p, \]

(4.17)

where \( E_0 \) is the modulus of fully dense bone (assumed to be equivalent to cortical bone), and the penalization power \( p \) is an empirical value. Previous investigations typically adhere to the relation \( 2 \leq p \leq 3 \), resulting from continuum level measurements of bone apparent density and elastic modulus (Currey, 1988). It is important to note that the terms apparent density and relative density are not equivalent. In the work of Currey (1988), apparent density is a measure of the weight per unit volume of material, including voids (i.e., pore space) inherent in the material. In this investigation, the relative density is assumed to be a measure of the weight per unit volume of material of a homogeneous material. Since we are modeling bone at a much smaller scale than continuum level models, it is not necessarily valid to utilize the aforementioned range specified for \( p \). In this investigation, a value of \( p = 1 \) has been chosen as the material elements are assumed to possess no inherent microstructural features (Bendsøe and Sigmund, 1999).

The structural changes resulting from the cellular activity alter the mechanical stimulus distribution. Therefore, subsequent finite element analyses are needed to evaluate the updated mechanical stimulus distribution. This process is assumed to continue until the cellular activity ceases and the bone returns to a homeostatic condition. A summary of the steps involved in the new HCA framework is:

Step 1. Define the geometry, material properties, loading condition, and initial density distribution \( x(0) \).

Step 2. Evaluate the local strain energy density \( S_i(t) \) using a finite element analysis. This information is used to calculate the stimulus sensed by each osteocyte \( S_i(t) \) and the corresponding signals received by the lining cells \( L_i(t) \).
Step 3. Identify locations in which cellular signals are consistent with a need for remodeling activity, as determined by the recruitment stimulus $RS_i(t)$.

Step 4. Apply the cellular rules for resorption, which results in local structural changes at locations associated with the actor cells (i.e., osteoclasts or mononuclear cells).

Step 5. Update the material distribution $x_i(t+1) = x_i(t) + \Delta x_i(t)$ according to Eqs. 4.15-4.16.

Step 6. Assess if convergence has been achieved. The algorithm has converged when the cellular signaling in the bone has returned to a homeostatic state and all cellular activity has ceased; otherwise, the HCA method continues to iterate, starting with Step 2.

The new HCA framework is illustrated in Fig. 4.2.

4.4.2 One-Dimensional Comparison of Resorption Paradigms

The goal of this investigation is to embed the resorption paradigm into a three-dimensional framework for simulating the cellular activity during remodeling. However, under the assumption of an initial recruitment stimulus $RS_i(0) = RS_0$ at a location $i$, it is possible to view the one-dimensional response of the resorption rules. The one-dimensional response for the resorption paradigm is compared with the resorption model by Martin and Buckland-Wright (2004) and histological data presented by Eriksen et al. (1984b) in Fig. 4.3.

Qualitatively, the curves are similar. One significant difference is the total resorption period. The resorption period predicted by the HCA methodology is 41 days, as compared to the 43 day prediction by Martin and Buckland-Wright (2004) and 33-68 days as measured by Eriksen et al. (1984b). It should be noted that Martin and Buckland-Wright (2004) assume that two-thirds of the resorption volume is carried out by the mononuclear cells, meaning that these cells resorb a depth of 40 $\mu$m of bone tissue. This is unlikely as mononuclear cells are not equipped to secrete factors necessary for
Figure 4.2. Illustration of the HCA method for predicting the cellular mechanisms of bone resorption. This methodology employs a unique combination of phenomenological and mechanistic paradigms for the simulation of bone adaptation. While applied mechanical stimuli are responsible for the initiation of remodeling, the removal of bone is governed by cellular mechanisms that represent osteoclast and mononuclear cell behavior.
Figure 4.3. One-dimensional comparison of resorption paradigms. The resorption model presented by Martin and Buckland-Wright (2004), and the histological resorption data reported by Eriksen et al. (1984b) are depicted by the figure on the left. These curves represent the average activity of osteoclasts and mononuclear cells over the resorption period. A one-dimensional illustration of the resorption paradigm presented in this investigation is depicted in the figure on the right. This curve represents the maximum rate of osteoclast and mononuclear cell activity over the resorption period.

demineralizing bone tissue. These cells are capable of enwrapping protruding collagen fibrils in their cytoskeleton and digesting them. To the author’s knowledge, the depth of unmineralized collagen fibrils protruding from the surrounding mineralized tissue local to a resorption site has not been measured. Therefore, a more conservative estimate of mononuclear activity is utilized in this investigation, where individual mononuclear cells are assumed to have the capacity to resorb up to a depth of 10 µm of unmineralized tissue.

For this investigation, the resorption depth is simulated based on the maximum activity of a single osteoclast for a particular activation level. This ideology differs from other models in the literature. In the work of Martin and Buckland-Wright (2004), it is not ensured that the activity of a single osteoclast is being modeled. Therefore, the
depth of tissue resorbed may be accomplished by the activity of multiple osteoclasts. The same is true for the histological measurements by Eriksen et al. (1984b). Their data most likely comprises a range of osteoclast activity. This investigation presents a formulation for resorptive activity for varying levels of mechanical stimulation. The range of osteoclast activity for different levels of the initial recruitment stimulus \( RS_i(0) \) is depicted in Fig. 4.4.

4.5 Trabecular Strut Model

This new remodeling framework was applied to an idealized trabecular strut, measuring 800 \( \mu m \) in length by 150 \( \mu m \) in diameter (Fig. 4.5). The central 500 \( \mu m \) of the strut was treated as the gage section. This strut was embedded in a computational domain measuring 190 \( \mu m \) x 190 \( \mu m \) in cross-section by 800 \( \mu m \) in length. The strut...
Figure 4.5. Model of an idealized trabecular strut, measuring 800 μm in length by 150 μm in diameter. The strut is constrained at the left end, while a tensile load is applied to the right end. Note that an applied load was used as opposed to an applied displacement. While this formulation is derived from the mechanical stimulus corresponding to specified levels of strain, an applied displacement was found to be an unrealistic boundary condition. This is due to the fact that if a strain corresponding to the remodeling regime was applied, a homeostatic state could not be obtained by the addition or subtraction of bone since the applied strain is constant.
model was discretized into 10 µm x 10 µm x 10 µm elements (i.e., \( v_{cell} = 1000 \mu m^3 \)).

Therefore, the CA lattice for the computational domain was comprised of 19 x 19 x 80 elements. A fixed boundary condition was applied to the left end of the strut, and a tensile load was applied to the opposing end. Under this loading condition, the homeostatic structure experienced a strain of 1500 \( \mu \varepsilon \). The material properties for trabecular bone used in this investigation are listed in Table 4.1.

TABLE 4.1

MATERIAL PROPERTIES OF TRABECULAR BONE

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>1.2e-5 kg/mm(^3)</td>
</tr>
<tr>
<td>Young’s Modulus</td>
<td>14.9 GPa</td>
</tr>
<tr>
<td>Poisson’s Ratio</td>
<td>0.3</td>
</tr>
</tbody>
</table>

4.5.1 Cell Distribution

At this scale, it is important to consider the distribution of cells in the model. Lining cells were assumed to populate the bone surface, while osteocytes were uniformly distributed throughout the bone matrix. Mullender et al. (1996) reported osteocyte densities ranging from 12,900-18,000 cells/mm\(^3\) in human trabecular bone of the iliac crest. According to these data, the appropriate number of cells for the model used in this study is 182-254 osteocytes. For this investigation, 180 osteocytes were uniformly distributed, such that the approximate spacing between osteocytes was 30 µm (Fig. 4.6). This spacing was chosen to allow for sufficient osteocyte connectivity, as the mean canalicular length was reported to be approximately 40 µm (Boyde, 1972).

\(^1\)This discretization was chosen, in part, so that the size of an element would correspond to the size of a lacuna. Sissons and O’Connor (1977) reported mean lacunar volume to be 700-1900 µm\(^3\). Therefore, locations in the CA lattice corresponding to osteocytes could be represented as lacunae.
Figure 4.6. Illustration of the cell distribution for the idealized trabecular strut model. Lining cells (yellow) are assumed to cover the entire surface of the bone (blue). Osteocytes (red) are distributed in a uniform fashion, with an approximate spacing of 30 µm.
4.5.2 Damage Distribution

This investigation focuses on mechanistically predicting the adaptive response of bone to changes in its mechano-biological environment. Damage is prevalent throughout bone and is often the target of remodeling (Burr, 2002). However, in the current study microcracking or other forms of damage are not explicitly accounted for. To represent damage, a region of osteocytes is assumed to undergo apoptosis, thus eliminating their ability to send signals to lining cells. This is consistent with histological observations as the arrest of osteocyte signaling or apoptosis is associated with resorption (Cardoso et al., 2009). Furthermore, eliminating the signaling capacity of a group of osteocytes alters the distribution of signals that reach the bone lining cells, driving remodeling activity. Therefore, it is not necessary to induce a geometric defect as in other studies. For this study, it was assumed that all of the osteocytes within a 90 \( \mu m \times 70 \mu m \times 50 \mu m \) region were apoptotic (Fig. 4.7).

4.5.3 Cell Propagation Methods

Since this investigation employs a three-dimensional framework for the simulation of bone resorption, it is necessary to account for the propagation of cells within the model. Previous models have assumed that osteoclasts propagate along a decreasing strain gradient (Ruimerman, 2005). A recent study has demonstrated that osteocyte apoptosis plays a role in controlling the activation of resorption (Cardoso et al., 2009). Furthermore, it was previously proposed that apoptotic osteocytes attract osteoclasts, which are both responsible for resorbing the bone matrix as well as phagocytosing the dying osteocytes (Burger et al., 2003). Evidence that osteoclastic activity is directed towards apoptotic osteocytes has been observed in the growing skeleton (Bronckers et al., 1996; Elmardi et al., 1990), in relation to bone renewal (Cardoso et al., 2009;
Figure 4.7. Illustration of the initial damage distribution. In this model, damage can be uniquely represented by altering the osteocyte signaling distribution in bone. It is not necessary to insert a physical defect in the model to alter the stress/strain distribution as in previous works. A region measuring 90 µm x 70 µm x 50 µm was considered to be damaged. Therefore, all of the osteocytes within this region were considered to have become apoptotic. The lack of signaling local to the apoptotic osteocytes serves as the driving factor for initiating an appropriate remodeling response.
Verborgt et al., 2000), and under pathological conditions (Noble et al., 1997). It has been observed that the expression of phosphatidylserine (PS) on the cell membrane of apoptotic osteocytes attracts osteoclasts (Bronckers et al., 2000). Exposure of PS on osteocytic cell protrusions in canaliculi, adjacent to surfaces undergoing osteoclast activity, may attract osteoclasts to continue resorption in that direction.

In this investigation, two methods of osteoclast cellular propagation are incorporated. First, osteoclasts are allowed to propagate along a decreasing strain gradient. Second, a chemotactic gradient, dispersed in the same fashion as the osteocyte signals, is assumed to occur surrounding the apoptotic osteocytes in the model.

4.6 Computational Investigations

This investigation introduces a number of new paradigms for cellular signaling and communication, and thus it is necessary to explore the characteristics of the model. The simulations conducted for resorption are broken down into nominal and parametric studies. The nominal parameter values for resorption were selected based on those reported from literature, where available (Table 4.2).

The predictive capacity of the model was investigated by conducting a parametric study for five prominent parameters. The parameters selected were the osteocyte signal decay constant \( D \), the maximum osteocyte communication distance \( d^{OS} \), the maximum rate of osteoclast resorption \( V_0^{OC} \), the homeostatic strain under which the threshold of resorption is calculated \( \delta_{\text{min}} \), and the lifespan of an osteoclast \( t^{OC} \). Individual sensitivities were computed for five levels of each parameter (Table 4.3).

Both nominal and parametric simulations were conducted for each method of osteoclast propagation (i.e., strain and chemotactic gradients). In addition, three values for the maximum lining cell communication distance \( d^{LC} = \{0 \, \mu m, 20 \, \mu m, 40 \, \mu m\} \), based
TABLE 4.2

NOMINAL PARAMETERS FOR BONE RESORPTION SIMULATIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Values</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{avg}^{MN}$</td>
<td>0.35</td>
<td>$\mu m^3/\mu m^2/day$</td>
<td>Average rate of mononuclear cellular activity (Eriksen et al., 1984b)</td>
</tr>
<tr>
<td>$c_{form}$</td>
<td>0</td>
<td></td>
<td>Proportional constant used to scale formation activity (Note: this parameter was set to zero to render formation inactive)</td>
</tr>
<tr>
<td>$c_{resorb}$</td>
<td>-100</td>
<td></td>
<td>Proportional constant used to scale resorptive activity, based on Martin and Buckland-Wright (2004)</td>
</tr>
<tr>
<td>$c_{TGF-\beta 1}$</td>
<td>4.5e-7</td>
<td></td>
<td>Proportional constant relating the weight fraction of TGF-\beta 1 in the bone matrix to the relative concentration of TGF-\beta 1 (Mundy, 1999b)</td>
</tr>
<tr>
<td>$c_{OPG}$</td>
<td>1.23e4</td>
<td></td>
<td>Proportional constant relating the relative concentrations of TGF-\beta 1 and OPG</td>
</tr>
<tr>
<td>$D$</td>
<td>80</td>
<td>$\mu m$</td>
<td>Osteocyte signal decay constant (Mullender and Huiskes, 1995)</td>
</tr>
<tr>
<td>$d_{OS}$</td>
<td>80</td>
<td>$\mu m$</td>
<td>Maximum osteocyte communication distance, based mean canalicular length (Boyde, 1972)</td>
</tr>
<tr>
<td>$\delta_{min}$</td>
<td>1000</td>
<td>$\mu \epsilon$</td>
<td>Homeostatic strain used for the calculation of the threshold of resorption (McNamara and Prendergast, 2005)</td>
</tr>
<tr>
<td>$K_m^{OC}$</td>
<td>-10</td>
<td></td>
<td>Dimensionless M-M constant for bone resorption (Martin and Buckland-Wright, 2004)</td>
</tr>
<tr>
<td>$t^{OC}$</td>
<td>12</td>
<td>days</td>
<td>Osteoclast lifespan (Jilka, 2003)</td>
</tr>
<tr>
<td>$V_0^{OC}$</td>
<td>600</td>
<td>$\mu m^3/day$</td>
<td>Maximum rate of osteoclast resorption (Eriksen et al., 1984b)</td>
</tr>
<tr>
<td>$v_{cell}$</td>
<td>1000</td>
<td>$\mu m^3$</td>
<td>Volume of a computational cell</td>
</tr>
</tbody>
</table>
TABLE 4.3

PARAMETER VALUES FOR PARAMETRIC STUDY OF RESORPTION

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$D$ [$\mu m$]</th>
<th>$d^{OS}$ [$\mu m$]</th>
<th>$V_0^{OC}$ [$\mu m^3$/day]</th>
<th>$\delta_{min}$ [$\mu \epsilon$]</th>
<th>$t^{OC}$ [day]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>60</td>
<td>60</td>
<td>200</td>
<td>800</td>
<td>8</td>
</tr>
<tr>
<td>Level 2</td>
<td>70</td>
<td>70</td>
<td>400</td>
<td>900</td>
<td>10</td>
</tr>
<tr>
<td>Level 3</td>
<td>80</td>
<td>80</td>
<td>600</td>
<td>1000</td>
<td>12</td>
</tr>
<tr>
<td>Level 4</td>
<td>90</td>
<td>90</td>
<td>800</td>
<td>1100</td>
<td>14</td>
</tr>
<tr>
<td>Level 5</td>
<td>100</td>
<td>100</td>
<td>1000</td>
<td>1200</td>
<td>16</td>
</tr>
</tbody>
</table>

on histological data, were studied. In previous models, only the communication of osteocytes or the communication of lining cells was modeled, but not both. Inter- and intra-cellular communication between osteocytes and lining cells is likely to occur (Mullender and Huiskes, 1997). The range selected for the maximum lining cell communication distances was based on the mean length of a canaliculus and the fact that lining cells do not entirely cover the bone surface (Boyde, 1972).

4.7 Results

The framework presented in this investigation was capable of predicting the excavation of resorption cavities in a temporally accurate time period, with dimensions comparable to those reported in the literature. The following sections will detail the results for each of the simulations performed.

4.7.1 Nominal Simulation Results

As previously mentioned, simulations were conducted for each of the methods of osteoclast propagation, at three maximum lining cell communication distances, for the nominal set of parameters given in Table 4.2. In each case, the osteoclast resorption
period $\tau^{OC}$ lasted 13 days, which is comparable to the 6-12 day range reported by Eriksen et al. (1984b). The mononuclear cellular activity period $\tau^{MN}$ spanned 28-29 days, which is within the 24-48 day period observed by Eriksen et al. (1984b). Finally, the total resorption period $\tau^{resorb}$ for these simulations ranged from 40-41 days, which is consistent with the 33-68 day range reported by Eriksen et al. (1984b). These temporal results are summarized in Table 4.4.

### TABLE 4.4

**TEMPORAL RESULTS FOR NOMINAL RESORPTION SIMULATIONS**

<table>
<thead>
<tr>
<th>Osteoclast Propagation</th>
<th>$d^{LC}$ [μm]</th>
<th>$\tau^{OC}$ [days]</th>
<th>$\tau^{MN}$ [days]</th>
<th>$\tau^{resorb}$ [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotactic</td>
<td>0</td>
<td>13</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>13</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>13</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>Strain</td>
<td>0</td>
<td>13</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>13</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>13</td>
<td>28</td>
<td>40</td>
</tr>
</tbody>
</table>

While the temporal aspects of the nominal simulations are very similar, the spatial aspects of the simulated resorption cavities were varied. For the case of chemotactic osteoclast progression, the longitudinal axis of the resorption cavity $r^\parallel$ was 110 μm (for each case) and the transverse axis $r^\perp$ ranged from 110-130 μm (Fig. 4.8). These values are comparable to cavity dimensions of 100 μm in length by 40-70 μm in width, as reported by Eriksen and Kassem (1992)\(^2\). For the strain-based osteoclast progression method the cavities were significantly larger, measuring 150-190 μm along the longitudinal axis $r^\parallel$ and 130-150 μm along the transverse axis $r^\perp$ (Fig. 4.9). One should note

\(^2\)The size of a resorption cavity in trabecular bone may vary with the size of the sample specimen. The dimensions of the specimens measured were not indicated.
Figure 4.8. Illustration of the final resorption cavities for chemotactic osteoclast propagation. Increasing the maximum lining cell communication distance \( d^{LC} \) from 0 \( \mu m \) to 20 \( \mu m \) increases cavity dimensions; however, increasing \( d^{LC} \) from 20 \( \mu m \) to 40 \( \mu m \) reduces the cavity dimensions to their original size. This is as expected since increases in \( d^{LC} \) would mean that lining cell communication is increased, which will dampen out the lack of signaling from the apoptotic osteocytes.
Figure 4.9. Illustration of the final resorption cavities for strain-based osteoclast propagation. Increasing the maximum lining cell communication distance $d^{LC}$ from 0 $\mu$m to 40 $\mu$m decreases cavity dimensions.
that the resorption cavities formed with the chemotactic osteoclast propagation method are more rounded and generally deeper, as compared to the cavities obtained with the strain-based osteoclast propagation method which are shallower and span the width of the strut.

In the context of the region of prescribed damage, the chemotactic osteoclast propagation method was more effective at removing damaged tissue. The percentage of damaged material removed $p_{\text{damage}}$ was 96-98% for the chemotactic osteoclast propagation method and 85-91% for strain-based osteoclast propagation. The spatial results for the nominal resorption simulations are summarized in Table 4.5.

**TABLE 4.5**

**SPATIAL RESULTS FOR NOMINAL RESORPTION SIMULATIONS**

<table>
<thead>
<tr>
<th>Osteoclast Propagation</th>
<th>$d^{LC}$ [µm]</th>
<th>$r_{\parallel}$ [µm]</th>
<th>$r_{\perp}$ [µm]</th>
<th>$v_{\text{resorb}}$ [µm$^3$]</th>
<th>$p_{\text{damage}}$ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotactic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>110</td>
<td>110</td>
<td>5.15e5</td>
<td>98.0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>110</td>
<td>130</td>
<td>4.80e5</td>
<td>96.8</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>110</td>
<td>110</td>
<td>4.34e5</td>
<td>96.5</td>
<td></td>
</tr>
<tr>
<td>Strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>190</td>
<td>150</td>
<td>5.00e5</td>
<td>89.8</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>170</td>
<td>150</td>
<td>4.78e5</td>
<td>91.4</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>150</td>
<td>130</td>
<td>4.37e5</td>
<td>85.2</td>
<td></td>
</tr>
</tbody>
</table>

Despite the differences in resorption cavity dimensions, the total resorbed volume $v_{\text{resorb}}$ was comparable for each of the maximum lining cell communication distances $d^{LC}$ and both cases of osteoclast propagation. This is amenable to the fact that this paradigm relates the amount of cellular activity to the deviation in homeostatic osteocyte signaling. The percent difference in resorbed volume between the two methods was 2.9% for $d^{LC} = 0$ µm, 0.34% for $d^{LC} = 20$ µm, and 0.8% for $d^{LC} = 40$ µm (Fig. 4.10).
(a) Chemotactic Osteoclast Propagation

(b) Strain-based Osteoclast Propagation

Figure 4.10. History of the total volume resorbed for chemotactic osteoclastic propagation (top) and strain-based osteoclast propagation (bottom). The percent difference in the resorbed volume between the two methods was 2.9% for $d^{LC} = 0 \mu m$, 0.34% for $d^{LC} = 20 \mu m$, and 0.8% for $d^{LC} = 40 \mu m$. 

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In an attempt to illustrate resorptive activity for the nominal simulations, longitudinal and transverse cross-sections of the density distribution for the trabecular strut are displayed in Figs. 4.11-4.16. In addition, the strain distribution is displayed for the longitudinal cross-section of the strut. A strain concentration occurs at the base of the resorption cavity, with strains exceeding 3000 µε; this is consistent with the stress concentration at the base of the resorption cavity observed by McNamara et al. (2003).

4.7.2 Parametric Simulation Results

The parametric study conducted on the prominent resorption parameters was used to demonstrate the impact of each parameter on the total volume resorbed. The total volume resorbed was found to be positively correlated to the maximum rate of osteoclast resorption $V_{OC}^{0}$, the osteoclast lifespan $t^{OC}$, and the homeostatic strain under which the threshold of resorption is calculated $\delta_{min}$, and negatively correlated with the maximum osteocyte communication distance $d^{OS}$ and the osteocyte signal decay constant $D$. The sensitivities demonstrate that, for the tested parameters, increasing the homeostatic strain under which the threshold of resorption is calculated $\delta_{min}$ results in the greatest increase in resorbed volume. Likewise, decreasing the maximum osteocyte communication distance $d^{OS}$ causes the greatest decrease in the total volume resorbed. For each of the parameters, the trends were the same for each of the maximum lining cell communication distances $d^{LC}$, with the exception of $d^{LC} = 0 \, \mu m$ for the maximum osteocyte communication distance $d^{OS}$. The predicted total volume resorbed was smaller for $d^{OS} = 40 \, \mu m$ than $d^{OS} = 60 \, \mu m$; however, the predominant trend was that resorbed volume decreased as $d^{OS}$ increased. This particular anomaly results from osteocyte signals only being able to reach a few cells on the bone surface, since the communication distance is considerably small. One can observe that increasing
Figure 4.11. Resorption history for chemotactic osteoclast propagation and a maximum lining cell communication distance of $d_{LC} = 0 \mu m$. 
Figure 4.12. Resorption history for chemotactic osteoclast propagation and a maximum lining cell communication distance of $d^{LC} = 20 \mu m$. 
Figure 4.13. Resorption history for chemotactic osteoclast propagation and a maximum lining cell communication distance of $d_{LC}^{C} = 40 \mu m$. 

Day 6

Day 12

Day 18

Day 30

Day 40 (Final)
Figure 4.14. Resorption history for strain-based osteoclast propagation and a maximum lining cell communication distance of $d_{LC} = 0 \mu m$. 
Figure 4.15. Resorption history for strain-based osteoclast propagation and a maximum lining cell communication distance of $d^{LC} = 20 \, \mu m$. 
Figure 4.16. Resorption history for strain-based osteoclast propagation and a maximum lining cell communication distance of $d^{LC} = 40 \, \mu m$. 
the maximum lining cell communication distance \(d^{LC}\) helps to ameliorate this issue as lining cell communication helps to further propagate the influence of osteocyte signals.

For both osteoclast propagation methods, the trends observed for the total volume resorbed were indistinguishable. This was as expected since the propagation of osteoclasts is independent of the amount of bone they resorb, in this model. The trends for each individual parameter are shown in Figs. 4.17 and 4.18 and the combined sensitivity of all the parameters is displayed in Figs. 4.19 and 4.20.

It is important to note that the relative changes in the parameter values between levels was not uniform for this study. The parameter ranges were simply chosen to illustrate a range of behavior, based on previous studies done in the literature (McNamara and Prendergast, 2005; Mulvihill, 2008; Ruimerman et al., 2003).

4.8 Discussion

In this chapter, a new framework has been presented that uniquely combines phenomenological and mechanistic paradigms for the simulation of bone resorption. This framework was exercised on an idealized model of a trabecular strut. It was found that both methods for modeling osteoclast propagation were able to predict the resorption of a damaged region of bone in a temporally and spatially accurate manner. The results of the parametric studies demonstrate that physiological changes to the cells associated with bone remodeling (i.e., osteocytes and osteoclasts) have a greater impact on the cellular activity than signal loss with distance. This supports the notion that pathological remodeling activity can occur either due to hyperactive osteoclast activity or if changes in osteocyte sensitivity occur. However, formation mechanisms must be added to the new framework to ascertain how the alteration of resorption parameters affects the coupling between formation and resorption during the entire remodeling cycle.
Figure 4.17. Parametric study of the total volume resorbed for chemotactic osteoclast propagation.
Figure 4.18. Parametric study of the total volume resorbed for strain-based osteoclast propagation.
Figure 4.19. Combined sensitives for the parametric study with chemotactic osteoclast propagation.
Figure 4.20. Combined sensitives for the parametric study with strain-based osteoclast propagation.
The long term vision of computational models of the bone remodeling process is to explain experimental observations of bone regulation, reasonably predict the effect of drug therapies, and provide a tool for designing an individual’s treatment plan for associated bone diseases. Obtaining this objective with a computational model will decrease the current dependency on economically and socially expensive clinical trials and animal experimentation. As previously mentioned, in the past several decades numerous computational models have been developed to simulate how the biological regulatory process of remodeling responds to changes in the mechanical environment of bone (Beaupré et al., 1990b; Burger et al., 2003; Carter, 1987; Cowin and Hagedus, 1976; Fyhrie and Carter, 1986b; García-Aznar et al., 2005; Huiskes et al., 2000, 1987; Lemaire et al., 2004; Martin and Buckland-Wright, 2004, 2005; McNamara and Prendergast, 2005, 2007; Mullender et al., 1994; Mulvihill et al., 2008; Mulvihill and Prendergast, 2008; Prendergast and Taylor, 1994; Ruimerman et al., 2001; Tezuka et al., 2005; Tovar, 2004; Turner, 1999; van der Linden et al., 2001; van Oers et al., 2008a,b). One of the most prevalent criticisms of bone remodeling simulations is that the remodeling rules typically oversimplify the cellular activity that occurs. Only a few preliminary studies have attempted to incorporate descriptions of the cellular level processes
that occur during the remodeling cycle (Komarova et al., 2003; Lemaire et al., 2004; Tezuka et al., 2002).

In the previous chapter, a framework was presented that uniquely combines phenomenological and mechanistic paradigms for the simulation of bone resorption. This framework builds off of the original hybrid cellular automaton (HCA) algorithm and connects the cellular mechanisms related to the activation and resorption phases of remodeling with applied mechanical stimuli, via cellular signaling. This new methodology differentiates between various types of tissue, such as mineralized bone and bone marrow, and accounts for the activities of osteocytes, lining cells, osteoclasts, mononucleated cells, and osteoblasts. While this framework was successful at predicting bone resorption in a spatially and temporally accurate manner, its predictive capacity is limited as formation mechanisms were not included.

The primary focus of this investigation is to extend the new HCA framework to incorporate the cellular mechanisms of bone formation. In this chapter, mathematical rules for the phases of the bone remodeling processes associated with bone formation are developed and implemented into the HCA methodology. These biologically-inspired rules are consistent with the cellular signaling paradigm developed in the previous chapter and provide for the control of recruitment and activation of osteoblasts. With these rules in place, the HCA methodology provides a complete framework for simulating the remodeling process at the cellular level. This framework was utilized to investigate common theories for the onset of pathological remodeling activity, including increased osteocyte sensitivity to mechanical stimuli and increased osteoclast and osteoblast cellular activity. To examine the predictive capacity of this model, the framework was exercised on an idealized trabecular strut model.
5.1 Cellular Signaling Paradigm

The goal of the methodology is to connect the cellular mechanisms related to bone formation with applied mechanical stimuli, via cellular signaling. Therefore, this investigation employs the same cellular signaling paradigm as presented in Chapter 4. Recall that the types of tissue represented in this model are: mineralized bone ($B$), bone marrow ($M$), lining cells ($L$), osteoclasts ($OC$), osteoblasts ($OB$), osteocytes ($OS$), and mononucleated cells (MN). The cellular signaling paradigm developed in this work makes use of osteocytes as mechanosensing cells and bone lining cells as signal receptors. The mechanical stimulus sensed by osteocytes $S_i(t)$ is assumed to be the local strain energy density (SED), resulting from an applied loading condition. The osteocyte signals are transmitted to lining cells in a local region. It is assumed that osteocyte signals can only propagate to lining cells that are sufficiently close enough to establish gap junctions. The signal received by a lining cell $L_i(t)$ is assumed to be disseminated amongst lining cells in a local region; thus, an effective lining cell signal $\bar{L}_i(t)$ is determined. This effective signal is assumed to represent the propagation of osteoclast signals between adjacent lining cells.

Activation of remodeling is based on the recruitment stimulus $RS_i(t)$ for osteoclasts or osteoblasts, which is calculated from the effective lining cell signals $\bar{L}_i(t)$. The quiescent regime (i.e., lazy zone) for the recruitment stimulus $RS_i(t)$ is assumed to occur when the effective lining cell signals range from the threshold for resorption $\bar{L}^*_{min}$ to the threshold for formation $\bar{L}^*_{max}$. Therefore, if the effective lining cell signals fall beneath $\bar{L}^*_{min}$, osteocyte signals are no longer sufficient to maintain homeostasis and osteoclast activation occurs. Conversely, if the effective lining cell signals exceed $\bar{L}^*_{max}$, osteocyte signals exceed the homeostatic regime and provide for the activation of osteoblasts. Finally, if the effective lining cell signals exceed a critical damage threshold $\bar{L}^*_{crit}$, it is
assumed that the local osteocytes have been damaged and cease to signal, resulting in osteoclast recruitment. This paradigm is illustrated in Fig. 4.1.

5.2 Bone Formation

In this investigation, mathematical rules for representing the cellular mechanisms of bone formation are developed. Formation activity is divided into two stages: I) reversal (i.e., maturation of preosteoblasts), and II) osteoblast cellular activity (i.e., deposition of osteoid and mineralization). A new method for modeling the daily formation activity is presented in this section.

5.2.1 Reversal

The reversal phase of the remodeling process involves the growth in number and maturation of cells of the osteoblast lineage. It is theorized that TGF-β promotes the chemotactic attraction of osteoblasts and their precursors to the resorption site (Pfeilschifter et al., 1990). However, TGF-β has also been observed to inhibit osteoblast differentiation in vitro (Mundy, 1999c). If there is sufficient stimulation to promote formation, it is assumed that the osteoblasts are attracted to a resorption site and they begin differentiating into active osteoblasts once the mononucleated cellular activity ceases. The differentiation and activation of mature osteoblasts was observed to occur over a one to two week period (Eriksen et al., 1984a; Väänänen, 1993). For this investigation, the reversal process is modeled as a one week time delay (i.e., $t_{\text{reversal}} = 7$ days).

5.2.2 Osteoblast Cellular Activity

During the initial stages of formation, osteoblasts secrete collagen that forms the new osteoid matrix. Osteoid contains a number of growth factors, such as transform-
ing growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) (Mundy, 1999a). It is assumed that the conditions under which an osteoblast is recruited affects the overall capacity for bone formation, which is evidenced by the absence or down regulation of factors such as calcineurin (Sun et al., 2005). Therefore, this investigation utilizes the recruitment stimulus $R S_i(t)$ at a particular location to drive the initial capacity for bone formation $s_i^{OB}(0)$, written as

$$s_i^{OB}(0) = R S_i(t_i^{OB}), \quad (5.1)$$

where $t_i^{OB}$ corresponds to the time when the $i^{th}$ osteoblast is activated.

This model assumes that the osteoblast cellular activity $A_i^{OB}(t)$ can be expressed using a relation inspired by Michaelis-Menten (M-M) kinetics. In the initial phase of formation, osteoblasts primarily form osteoid. Therefore, the amount of osteoid formed by osteoblasts each day can be written as

$$A_i^{OB}(t) = \frac{V_i^{OB} s_i^{OB}(t)}{s_i^{OB}(t) + K_i^{OB}}, \quad (5.2)$$

where $V_i^{OB}$ is the rate of osteoblast formation, $s_i^{OB}(t)$ is the capacity for bone formation, and, for this work, $K_i^{OB}$ is treated as a dimensionless constant. The osteoblast capacity for osteoid synthesis was reduced at each time step to represent the limitations imposed by the gradual differentiation of the cell over time, which is accompanied by a reduction in nuclear height and protein synthesizing apparatus (Eriksen et al., 1984a). This is written as

$$s_i^{OB}(t + 1) = s_i^{OB}(t) - s_0, \quad (5.3)$$

where $s_0$ is the reduction osteoblast capacity for osteoid production in the initial phase of bone formation. Note that this model assumes that there is an ample amount of amino
acids supplied by the blood for protein synthesis.

Based on histological data, mineralization is estimated to begin when the maximum depth of osteoid in normal healthy bone reaches a depth of 16 µm (Eriksen et al., 1984a). During this stage of remodeling, osteoblasts regulate the ordered deposition of mineral by producing cytokines such as osteocalcin and bone sialoprotein (BSP), while at the same time continuing to produce new osteoid at a reduced rate (Lian et al., 1999). These additional tasks are assumed to slow osteoblast activity and are effected in the model by changing the values of the constant $K_{OBm}$ and the reduction osteoblast capacity for osteoid production $s_0$.

5.3 Computational Implementation

This investigation supplements the cellular mechanisms developed for the HCA paradigm with mathematical rules for governing the cellular behavior during bone formation. As such, CA rules can be defined to utilize the same finite vector of states $\alpha_i(t)$ given before (Eq. 4.14). This information is sufficient for applying both the rules for resorption and formation uniformly throughout the CA lattice.

5.3.1 Methodology

Fundamentally, the HCA methodology is driven by an applied mechanical stimulus. This stimulus is converted into cellular signals that exchanged between osteocytes and bone lining cells. Subsequently, these signals are utilized to determine the need for local cellular activity. The resorptive and formative activities are responsible for carrying structural changes on the surfaces of the mineralized tissue. Changes in bone mass are effected in the model by changing the relative (or normalized) density $x_i(t)$, where $x_i(t) \in (0, 1]$. Therefore, the material in each cell is varied between bone marrow
(0 < x_i(t) ≤ 0.001) and fully dense bone (x_i(t) = 1). By combining the rules for formation with the previously developed rules for re-
sorption, a complete description of the remodeling process is achieved. Changes in relative density occur at locations associated with osteoblast, osteoclast, or mononuclear cellular activity. The change in relative density due to osteoclast or mononuclear cellular activity is presented in Eqs. 4.15-4.16. The change in relative density due to osteoblast cellular activity is written as

$$\Delta x_i(t) = \frac{A_{OB}^i(t)}{\nu_{cell}} \Delta t.$$  (5.4)

Recall that the relative density of each cell can vary throughout the remodeling process. Modifying this parameter will influence the mechanical properties of bone. For this investigation, it is assumed that the modulus $E_i(t)$ uses a power law relation for parameterizing the relative density (Eq. 4.17).

The HCA paradigm begins with an initial structural analysis to determine the mechanical stimulus distribution resulting from an applied load. Following this analysis, the mechanical stimulus information is translated into cellular signals, for which the corresponding amount cellular activity is determined. The cellular activity carries out the necessary adaptive changes on the bone surface. The structural changes resulting from the cellular activity alter the mechanical stimulus distribution. Therefore, subsequent finite element analyses are needed to evaluate the updated mechanical stimulus distribution. This process is assumed to continue until the cellular activity ceases and the bone returns to a homeostatic condition. A summary of the steps involved in the new HCA framework is:

Step 1. Define the geometry, material properties, loading condition, and initial density distribution $x(0)$.
Step 2. Evaluate the local strain energy density $S_i(t)$ using a finite element analysis. This information is used to calculate the stimulus sensed by each osteocyte $S_i(t)$ and the corresponding signals received by the lining cells $L_i(t)$.

Step 3. Identify locations in which cellular signals are consistent with a need for remodeling activity, determined by the recruitment stimulus $RS_i(t)$.

Step 4. Apply the cellular rules for remodeling. This results in local structural changes at locations associated with the actor cells (i.e., osteoblasts, osteoclasts, or mononuclear cells).

Step 5. Update the material distribution $x_i(t + 1) = x_i(t) + \Delta x_i(t)$ according to Eqs. 4.15-4.16 and Eq. 5.4.

Step 6. Assess if convergence has been achieved. The algorithm has converged when the cellular signaling in the bone has returned to a homeostatic state and all cellular activity has ceased; otherwise, the HCA method continues to iterate, starting with Step 2.

The new HCA framework is illustrated in Fig. 5.1.

5.3.2 One-Dimensional Formation Paradigm

In this investigation, mathematical rules for modeling bone formation are incorporated in a three-dimensional paradigm for simulating the cellular activity during remodeling. However, the one-dimensional response can be viewed, as was done for the resorption paradigm, for an initial recruitment stimulus $RS_i(0)$ at a location $i$. The range of osteoblast activity for different levels of the initial recruitment stimulus $RS_i(0)$ is depicted in Fig. 5.2. It was predicted that under conditions of maximal osteoblast stimulation, an osteoblast is capable of accumulating a $40\mu m$ depth of bone tissue in a period of 99 days. This amount of tissue formed is consistent with the paradigm presented by Martin and Buckland-Wright (2005). In addition, the maximum lifespan predicted for an osteoblast is consistent with observations indicating that osteoblasts can live as long as 100 days (Jilka, 2003).
Figure 5.1. Illustration of the HCA method for predicting the cellular mechanisms of bone remodeling. This methodology employs a unique combination of phenomenological and mechanistic paradigms for the simulation of bone adaptation. While applied mechanical stimuli are responsible for the initiation of remodeling, the removal and replacement of bone is governed by cellular mechanisms that represent osteoblast, osteoclast, and mononuclear cell behavior.
Figure 5.2. One-dimensional illustration of the formation paradigm presented in this work, for different values of the initial recruitment stimulus \( RS_i(0) \).

5.4 Computational Investigations

This investigation introduces a framework that is capable of simulating the cellular activity during the remodeling process. To assess the performance of this model, simulations were conducted on a trabecular strut example, as presented in Chapter 4.

5.4.1 Nominal Simulations

A nominal set of parameters were utilized to evaluate the performance of the model (Table 5.1). For this study, the chemotactic osteoclast propagation method was selected. This selection was based on the results in the previous chapter which demonstrated resorption cavities with dimensions similar to those reported in the literature. The nominal simulations for this investigation were performed at three maximum lining cell communication distances, \( d^{LC} = \{0 \, \mu m, 20 \, \mu m, 40 \, \mu m\} \).
**TABLE 5.1**

**NOMINAL PARAMETERS FOR BONE REMODELING SIMULATIONS**

<table>
<thead>
<tr>
<th>Term</th>
<th>Values</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{avg}^M$</td>
<td>0.35</td>
<td>$\mu m^3/\mu m^2$/day</td>
<td>Average rate of mononuclear cellular activity (Eriksen et al., 1984b)</td>
</tr>
<tr>
<td>$c_{form}$</td>
<td>175</td>
<td></td>
<td>Proportional constant used to scale formation activity (Martin and Buckland-Wright, 2005)</td>
</tr>
<tr>
<td>$c_{resorb}$</td>
<td>-100</td>
<td></td>
<td>Proportional constant used to scale resorptive activity (Martin and Buckland-Wright, 2004)</td>
</tr>
<tr>
<td>$c_{TGF-\beta 1}$</td>
<td>4.5e-7</td>
<td></td>
<td>Proportional constant relating the weight fraction of TGF-(\beta 1) in the bone matrix to the relative concentration of TGF-(\beta 1) (Mundy, 1999b)</td>
</tr>
<tr>
<td>$c_{OPG}$</td>
<td>1.23e4</td>
<td></td>
<td>Proportional constant relating the relative concentrations of TGF-(\beta 1) and OPG</td>
</tr>
<tr>
<td>$D$</td>
<td>80</td>
<td>$\mu m$</td>
<td>Osteocyte signal decay constant (Mullender and Huiskes, 1995)</td>
</tr>
<tr>
<td>$d^{OS}$</td>
<td>80</td>
<td>$\mu m$</td>
<td>Maximum osteocyte communication distance, based mean canalicular length (Boyde, 1972)</td>
</tr>
<tr>
<td>$\delta_{\min}$</td>
<td>1000</td>
<td>$\mu \epsilon$</td>
<td>Homeostatic strain used for the calculation of the threshold of resorption (McNamara and Prendergast, 2005)</td>
</tr>
<tr>
<td>$\delta_{\min}$</td>
<td>2000</td>
<td>$\mu \epsilon$</td>
<td>Homeostatic strain used for the calculation of the threshold of formation (McNamara and Prendergast, 2005)</td>
</tr>
<tr>
<td>$K_{m}^{OC}$</td>
<td>-10</td>
<td></td>
<td>Dimensionless M-M constant for resorption (Martin and Buckland-Wright, 2004)</td>
</tr>
<tr>
<td>$K_{m}^{OB}$</td>
<td>115, 175</td>
<td></td>
<td>Dimensionless M-M constant for formation, initially (left) and during mineralization (right) (Martin and Buckland-Wright, 2005)</td>
</tr>
<tr>
<td>$s_0$</td>
<td>5, 1.5</td>
<td></td>
<td>Reduction in osteoblast capacity for osteoid formation, initially (left) and during mineralization (right)</td>
</tr>
<tr>
<td>$t^{OC}$</td>
<td>12</td>
<td>days</td>
<td>Osteoclast lifespan (Jilka, 2003)</td>
</tr>
<tr>
<td>$t^{reversal}$</td>
<td>7</td>
<td>days</td>
<td>Reversal period (Väänänen, 1993)</td>
</tr>
<tr>
<td>$V_0^{OB}$</td>
<td>180</td>
<td>$\mu m^3$/day</td>
<td>Rate of osteoblast formation</td>
</tr>
<tr>
<td>$V_0^{OC}$</td>
<td>600</td>
<td>$\mu m^3$/day</td>
<td>Maximum rate of osteoclast resorption (Eriksen et al., 1984b)</td>
</tr>
<tr>
<td>$v_{cell}$</td>
<td>1000</td>
<td>$\mu m^3$</td>
<td>Volume of a computational cell</td>
</tr>
</tbody>
</table>
TABLE 5.2

TEMPORAL RESULTS FOR NOMINAL REMODELING SIMULATIONS

<table>
<thead>
<tr>
<th>$d^{LC}$ [µm]</th>
<th>$\tau^{OC}$ [days]</th>
<th>$\tau^{MN}$ [days]</th>
<th>$\tau^{resorb}$ [days]</th>
<th>$\tau^{OB}$ [days]</th>
<th>$\tau^{remo}$ [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26</td>
<td>32</td>
<td>56</td>
<td>197</td>
<td>223</td>
</tr>
<tr>
<td>20</td>
<td>13</td>
<td>29</td>
<td>41</td>
<td>188</td>
<td>219</td>
</tr>
<tr>
<td>40</td>
<td>13</td>
<td>28</td>
<td>40</td>
<td>166</td>
<td>214</td>
</tr>
</tbody>
</table>

5.4.2 Nominal Simulation Results

The new HCA framework predicted a total remodeling period $\tau^{remo}$ ranging from 214-223 days, with the period of osteoblast formation $\tau^{OB}$ lasting 166-197 days. The formation period is comparable to the range of 100-150 days, observed by Eriksen and Kassem (1992). The temporal results for the nominal remodeling simulations are summarized in Table 5.2.

It was observed that for lining cell communication distances $d^{LC}$ less than 40 µm, bone formation occurred in areas of tissue surrounding the initial damaged region (Fig. 5.3(a) and Fig. 5.3(b)). While this behavior has not been reported in the literature for trabecular bone remodeling, this does not preclude this observation as having physical relevance as bone is being formed in regions of high strain. The remodeled strut for $d^{LC} = 40$ µm displayed localized formation only within the vicinity of the initial damaged region (Fig. 5.3(c)). The remodeling history for the nominal simulations is displayed in Figs. 5.4-5.6.

One should note that the osteoclast resorption period and the osteoblast formation period for $d^{LC} = 0$ µm were longer than the other simulations. In this case, the osteoclast resorption period is $\tau^{OC} = 26$ days. Therefore, the osteoclast resorption period $\tau^{OC}$ exceeds the osteoclast lifespan $t^{OC}$, indicating that multiple waves of osteoclast activity were necessary to carry out resorption. This results from the onset of formation
Figure 5.3. Illustration of the remodeled struts. Increasing the maximum lining cell communication distance reduces the amount of bone formed outside of the cavity (i.e., on the sides of the strut). Therefore, the lining cell communication distance $d^{LC} = 40 \mu m$ will be utilized for the rest of this investigation as bone formation is localized to the vicinity of the resorption cavity.
Figure 5.4. Remodeling history for a maximum lining cell communication distance of $d^{LC} = 0 \mu m$. 
Figure 5.5. Remodeling history for a maximum lining cell communication distance of $d^{LC} = 20 \, \mu m$. 
Figure 5.6. Remodeling history for a maximum lining cell communication distance of $d_{LC} = 40 \, \mu m$. 
Figure 5.7. History of the total strut volume during the course of remodeling. It was observed that a maximum lining cell communication distance $d^{LC} = 40 \mu m$ presented the smallest overshoot in the final strut volume. The percent increase in the total strut volume at the end of the remodeling cycle was 0.84% for $d^{LC} = 0 \mu m$, 1.10% for $d^{LC} = 20 \mu m$, and 0.03% for $d^{LC} = 40 \mu m$.

on the 16th day of the simulation, as this bone formation redistributes the loads in the model enough to induce the additional bone resorption. For simulations performed with non-zero maximum lining cell communication distances, the communication between lining cells acts to damp out the changes in the signaling distribution when formation and resorption are acting concurrently. The resorption periods recorded for these simulations were identical to those observed for resorption alone (Table 4.4).

For the nominal cases, it was observed that a maximum lining cell communication distance $d^{LC} = 40 \mu m$ presented the smallest overshoot in the final strut volume (Fig. 5.7). Therefore, $d^{LC} = 40 \mu m$ will serve as the nominal value for the maximum lining cell communication distances for the remainder of this investigation.
5.4.3 Lazy Zone Simulations

This investigation assumes that there is a correlation between the mechanical stimulation of osteocytes and the resulting level of cellular activity. If the sensitivity of the osteocytes changes with age or in circumstances of bone disease, this could impact bone turnover. Therefore, the predictive capacity of this model was exercised by analyzing three different lazy zone widths $w_{LZ}$. The width of the lazy zone $w_{LZ}$ is measured as the difference between the homeostatic strain used for the calculation of the threshold of resorption $\delta_{\text{min}}$ and formation $\delta_{\text{max}}$. Note that the nominal lazy zone width is $w_{LZ} = 1000 \, \mu\varepsilon$. The lazy zone widths $w_{LZ}$ and the corresponding resorption and formation thresholds are displayed in Table 5.3. All additional parameters were held at their nominal values.

<table>
<thead>
<tr>
<th>$w_{LZ}$ [$\mu\varepsilon$]</th>
<th>$\delta_{\text{min}}$ [$\mu\varepsilon$]</th>
<th>$\delta_{\text{max}}$ [$\mu\varepsilon$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>1200</td>
<td>1800</td>
</tr>
<tr>
<td>1000</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>1200</td>
<td>800</td>
<td>2200</td>
</tr>
</tbody>
</table>

5.4.4 Lazy Zone Simulation Results

This study demonstrated that increasing osteocyte sensitivity (via the width of the lazy zone) has the effect of increasing the total strut volume, while decreasing osteocyte sensitivity resulted in the opposite behavior (Fig. 5.8). It was found that as the lazy zone width decreased to $w_{LZ} = 800 \, \mu\varepsilon$, the increased osteocyte sensitivity resulted in a larger amount of bone resorbed followed by increased formation. This resulted
Figure 5.8. Illustration of the trabecular strut volume history for various lazy zone widths. Increasing the lazy zone width results in a decrease in total strut volume due to decreases in resorption. Decreasing the lazy zone width results in an increased osteocyte sensitivity, providing for increased resorptive and formative responses that ultimately result in an overall increase in bone volume.

in a 3% increase in total strut volume. Conversely, increasing the lazy zone width to $w_{LZ} = 1200 \, \mu \varepsilon$ decreased the osteocyte sensitivity and resulted in resorption only. In this case, the amount of resorption was reduced to a level in which the local strains due to the creation of the resorption cavity were not large enough to support bone formation. These results are consistent with the findings of Mulvihill (2008).

5.4.5 Scaling of Rates of Osteoclast and Osteoblast Activity

Some of the most interesting questions related to the onset of various bone pathologies are related to how imbalances in the remodeling process manifest themselves. In past studies, researchers have simulated the net change in bone architecture due to
changes in the amount of osteoclast and osteoblast activity. For example, Ruimerman (2005) assumed that postmenopausal estrogen deficiency could be a cause for this alteration in cellular behavior. However, it is not known whether bone loss is primarily caused by hyperactive or hypotactic osteoblast or osteoclast activity. In this framework, the maximum rates for osteoclast activity $V_{0C}^{OC}$ and osteoblast activity $V_{0B}^{OB}$ are used to control the rates of cellular activity. Thus, a ±20% change in the rate of osteoclast and osteoblast activity were analyzed (Table 5.4).

TABLE 5.4

PARAMETER SETTINGS FOR MAXIMUM RATES OF OSTEOCLAST AND OSTEOBLAST CELLULAR ACTIVITY

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{0C}^{OC}$</td>
<td>+20%</td>
<td>-20%</td>
<td>+0%</td>
<td>+20%</td>
<td>-20%</td>
<td>+20%</td>
</tr>
<tr>
<td>$V_{0B}^{OB}$</td>
<td>+0%</td>
<td>+0%</td>
<td>-20%</td>
<td>-20%</td>
<td>-20%</td>
<td>+20%</td>
</tr>
</tbody>
</table>

5.4.6 Results for the Scaling of Rates of Osteoclast and Osteoblast Activity

These simulations demonstrate situations in which both net bone gain and net bone loss occurred (Fig. 5.9). For instance, Case 1 (increased osteoclast rate), Case 4 (increased osteoclast rate and decreased osteoblast rate), and Case 6 (increased osteoclast and osteoblast rates) resulted in an overall increase in bone volume. Conversely, Case 2 (decreased osteoclast rate), Case 3 (decreased osteoblast rate), and Case 5 (decreased osteoclast and osteoblast rates) predicted a net bone loss. These results agree with those presented by Ruimerman (2005).

These simulations demonstrate some interesting sensitivities of this system. For instance, increasing the rate of osteoclast activity increases the amount of bone resorbed.
Figure 5.9. Illustration of the trabecular strut volume history for changes in the maximum rate of osteoclast activity $V_{0}^{OC}$ and osteoblast activity $V_{0}^{OB}$. 
Therefore, a deeper resorption cavity would result, leading to higher strains at the base of the resorption cavity. Regardless of the change in osteoblast activity, the model predicts an overall increase in bone volume. Thus, the signaling paradigm overestimates the need for formation.

When analyzing the cases in which the rate of resorption is reduced (Case 2 and Case 5), a net bone loss is observed. This is intuitive, as decreasing the rate of bone resorption would decrease the amount of material resorbed and a smaller cavity would result. The peak strains at the base of the resorption cavity would be smaller and therefore the stimulus provided for osteoblast activity would be reduced. However, in Case 3 the rate of resorption is unchanged and the rate of formation is reduced. In this situation, the reduction in formation leads to a net bone loss. This suggests that the down-regulation of osteoblast activity alone may be sufficient to cause bone loss.

5.4.7 Scaling of Cellular Signals

One aspect of the signaling paradigm that can impact the amount of bone turnover is the scaling of the osteocyte signals relative to the applied mechanical stimulus. From a physiological standpoint, this could represent a change in mechanosensitivity with osteocyte age or reduced canalicular fluid flow due to damaged cellular processes. The proportional constants $c_{\text{resorb}}$ and $c_{\text{form}}$ provide for the scaling between osteocyte signals and the stimulation of resorptive and formative activity, respectively. The primary focus of this portion of the investigation is to evaluate potential pathological remodeling conditions cause by changes in these parameters. Therefore, a ±20% change in the scaling constants for resorption and formation were considered (Table 5.5).
5.4.8 Results for Scaling of Cellular Signals

For each of the simulations conducted, a reduction in bone volume was observed (Fig. 5.10). One would expect that Case 4 (increased resorption scaling $c^{resorb}$ and decreased formation scaling $c^{form}$) would result in the most bone loss; however, this was not the case. The most bone loss was predicted when resorption scaling $c^{resorb}$ alone was decreased (Case 2). Interestingly, when both formation scaling $c^{form}$ and resorption scaling $c^{resorb}$ were either simultaneously increased (Case 6) or decreased (Case 5), net bone loss occurred. These results suggest that the model is quite sensitive to the up- or down-regulation of osteocyte signals for osteoblast or osteoclast stimulation, either individually or combined. Further experimental studies aiming to characterize osteocyte signaling are necessary to improve our understanding of the behavior of these scaling parameters.

5.5 Discussion

In this chapter, the addition of formation mechanisms to the new HCA framework for simulating bone remodeling was presented. This is the first framework of its kind to utilize a combination of phenomenological and mechanistic paradigms for predicting the cellular behavior of bone remodeling. This framework was exercised on an idealized

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**TABLE 5.5**

PARAMETER SETTINGS FOR RESORPTION AND FORMATION SCALING CONSTANTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c^{resorb}$</td>
<td>+20%</td>
<td>-20%</td>
<td>+0%</td>
<td>+20%</td>
<td>-20%</td>
<td>+20%</td>
</tr>
<tr>
<td>$c^{form}$</td>
<td>+0%</td>
<td>+0%</td>
<td>-20%</td>
<td>-20%</td>
<td>-20%</td>
<td>+20%</td>
</tr>
</tbody>
</table>
Figure 5.10. Illustration of the trabecular strut volume history for changes in resorption scaling $c^{resorb}$ and formation scaling $c^{form}$. Net bone loss occurred for each of the cases presented.
model of a trabecular strut. The nominal simulations conducted were able to predict the remodeling of a damaged region of bone in a temporally and spatially accurate manner. For the nominal simulations, it was observed that increasing the maximum lining cell communication distance has the effect of dampening out the overshoot in bone turnover.

Simulations were also performed for varying lazy zone widths, changes in the rates of osteoblast and osteoclast cellular activity, and also for the scaling of osteocyte signals. Bone turnover was shown to increase and decrease with corresponding changes in the lazy zone width. Increasing and decreasing the maximum rate of osteoclast and osteoblast cellular activity displayed a range of bone gain and loss, while changing the scaling of osteoclast signals primarily resulted in bone loss. One of the most notable results was that a reduction in the rate of osteoblast activity alone was able to decrease bone turnover. This result has been demonstrated for many continuum level simulations; however, these simulations typically utilized a phenomenological paradigm where formation and resorption mechanisms had some direct coupling (McNamara and Prendergast, 2005; Ruimerman et al., 2003). In this framework, the cellular activity is decoupled from the osteocyte signaling paradigm, meaning that the decline in osteoblast activity does not affect osteoclast activity. Therefore, restoring the homeostatic rate of osteoblast activity is a key factor to consider for the prevention or treatment of bone loss.
CHAPTER 6

SUMMARY

A novel framework for the simulation of the bone adaptation process is the hybrid cellular automaton (HCA) method. This biologically-inspired algorithm has been demonstrated to be effective in predicting the adaptation of trabecular bone architecture, as well as the effect of damage and other factors on bone adaptation (Tovar, 2004; Vera and Tovar, 2008). This methodology is termed a hybrid technique because it couples global information obtained from the finite element (FE) method with the local relationships utilized by cellular automata (CA) computing. In this model, FE analyses are utilized to conduct a structural analysis to obtain mechanical stimulus information, while the remodeling rules are applied to the cells of the automaton.

This dissertation focused on improving the existing HCA methodology for simulating the processes of bone remodeling, in a multi-scale framework and a cellular level framework. The initial work of this investigation focused on improving the representation of the tissue level material behavior in the hierarchical HCA (HHCA) framework. A methodology for computing the anisotropic properties of the tissue level structures of the HHCA framework was implemented and tested. As previously mentioned, it was this investigation that played a vital role in inspiring the need for a more detailed model of bone remodeling at the cellular level.

The primary focus of this dissertation was to present a new computational framework that utilizes mathematical rules to mechanistically model the cellular mechanisms
involved in the bone remodeling process. This new framework uniquely combines existing mechanistic and phenomenological paradigms for the simulation of bone remodeling. Biological rules were implemented to connect the cellular mechanisms related to the phases of the remodeling process with applied mechanical stimuli, via cellular signaling. These rules control the recruitment, differentiation, and activation of the bone cells. The prominent processes for describing recruitment and inhibition of the bone cells, as reported from experimental studies, were utilized. This model is unique in the sense that the remodeling response is mediated solely by cellular signaling, not by the incorporation of arbitrary structural defects.

6.1 Summary of Original Contributions

The original contributions of this work are presented throughout Chapters 3-5. A summary of the original contributions is as follows:

- A methodology for determining the anisotropic properties of the tissue level models for the HHCA method was developed and implemented. This methodology was demonstrated to improve the multi-scale simulation of the bone remodeling process in several ways. First, it was observed that the evolution of the continuum level bone structures was more consistent when using the anisotropic structural analysis. Second, for the examples analyzed, a reduced computational cost was achieved.

- Cellular mechanisms for resorption and formation were incorporated in the HCA paradigm. Many computational models simply predict the net turnover of bone without actually interpreting the sequence of events involved in the remodeling process. Throughout this dissertation, the necessity of improving the level of biological detail in current bone remodeling simulations has been motivated and established. In the previous chapters, rules related to cellular mechanisms involved in the remodeling process have been developed.

- A consistent description of the initiation of resorption activity for bone adaptation was formulated. It has been discussed that the arrest of osteocyte signaling and/or apoptosis is most likely to occur at very high and at very low strain levels, whereas osteocytic suppression of resorption occurs at the strain level of normal
activity. Therefore, a mechanism for resorption that targets both sites associated with microdamage and low strain (disuse) regions has been presented.

- Mathematical rules for the cellular mechanisms of bone remodeling were extended into a three-dimensional HCA paradigm. Previous investigations utilizing cellular mechanisms to drive remodeling simulations were typically limited to one-dimensional predictions.

These additions to the HCA framework significantly separate this investigation from existing remodeling simulations. The overall originality of the proposed work lies in developing a set of rules for the HCA framework that describe the relevant cellular activity for the remodeling process and have the capacity to predict effects on remodeling from the level of cellular signaling.

6.2 Recommendations for Future Research

The HCA framework presented in this investigation is the first model of its kind to combine both phenomenological and mechanistic paradigms for simulating the cellular mechanisms of bone remodeling. This model is unique in the sense that the remodeling response is mediated solely by cellular signaling, not by the incorporation of arbitrary structural defects. In addition, the rules utilized in this model have been extended for use on three-dimensional bone structures. However, this methodology has introduced a variety of new issues that have not been addressed in this dissertation. This section discusses recommendations for future research to further improve the biological accuracy of this model and broaden the scope of its application.

6.2.1 Incorporation of Microdamage

As mentioned throughout this dissertation, remodeling provides for various functions in the body such as damage repair. Convincing evidence has accumulated over
the last two decades, indicating that remodeling serves to renew bone that was impaired by microdamage (Burr, 1993; Burr et al., 1997; Burr and Martin, 1993; Burr et al., 1985; Norrdin et al., 1998). It has been well established that fatigue microdamage results from repetitive loading in the physiological range and accumulation of damage over time leads to impairment of the mechanical properties of the bone matrix (see Burr et al. (1997) for a comprehensive review). Also, it has been noted that microdamage is prevalent throughout bone tissue (Vashishth et al., 2000). As previously mentioned, a statistical correlation between remodeling sites and damaged locations was observed in histological studies (Burr and Martin, 1993; Burr et al., 1985; Mori and Burr, 1993). Numerous attempts have been made to incorporate microdamage in remodeling simulations using methods ranging from continuum damage approximations to stochastically distributing damage at each simulation time step (García-Aznar et al., 2005; Hazelwood and Castillo, 2007; Huiskes et al., 2000; McNamara and Prendergast, 2005, 2007; Ramtani and Zidi, 2001, 2002). These methods do not have the fidelity to capture the effect that microdamage has on the cell signaling that occurs during remodeling. Microdamage can rupture osteocyte processes or damage the osteocyte itself, leading to its apoptosis. Therefore, the osteocyte signal capacity would be either impaired or stopped completely.

One method for representing microdamage involves a cohesive finite element model (CFEM) approach. This technique has the ability to improve upon previous approximations of the impact of microdamage in bone. Using this method, damage is physically represented in the model so that a distribution of damage will not need to be assumed. In addition, the physiological impact of the damage on relevant structures in the bone (i.e., rupture of canalicular processes, damage coalescence surrounding osteocyte lacunae, etc.) can be assessed by the interaction of these features in the model. This
will provide new avenues for exploring the interaction of microdamage and the initial queues that drive the remodeling activation process. For these reasons, incorporating a model of the fatigue microdamage of bone in the remodeling framework presented in this investigation has a great potential for increasing the predictive capacity of our model.

6.2.2 Accurate Representation of Bone Cells

This model could be further augmented by a more accurate representation of the bone cells involved in remodeling. Despite the physical activity of the bone cells that occurs within the computational cells, a physical representation of osteoclasts and osteoblasts is not incorporated. The phenomenological models developed by Ruimerman (2005) and van Oers et al. (2008a,b) incorporate a physical representation of osteoblasts and osteoclasts. They utilize the Glazier and Graner (1993) formalism for differential adhesion and determine both the shape and attachment of each cell by utilizing energy minimization principles.

In their models, bone cells are assumed to migrate and attach to bone surfaces that receive osteocyte signals that are outside of the homeostatic signaling range. They model the strength of attachment to a particular surface by the magnitude of the osteocyte signal. In locations of low osteocyte signaling, osteoclasts are assumed to attach and resorb bone. However, osteoclasts are assumed to retract from surfaces where the osteocyte signaling levels return to the homeostatic range. Similar measures are utilized for osteoblast attachment and retraction.

Utilizing a paradigm where the cells are individually modeled makes it possible to account for both the size and number of cells acting at a remodeling site. These ideas could be further expanded to incorporate a population of precursor cells. For ex-
ample, a mathematical representation of the attachment of messenger molecules, via binding sites (e.g., RANK/RANKL binding), to osteoclast/osteoblast precursors could be modeled. This addition to the model would also provide an avenue for investigating the effect of disease- and age-related changes in the precursor cell population. Additionally, a more detailed representation of the chemotactic factors which stimulate the attraction or migration of cells to the bone surface requires further development.

6.2.3 Cyclic Loads, Cellular Accommodation, and Canalicul ar Fluid Flow

Mechanical stimulation is critical for the homeostasis and upkeep of bone architecture. It is well accepted that bones undergo cyclic loading throughout our daily activities. Despite this fact, numerous models (including the one presented in this investigation) have utilized static loading conditions. This ideology originated from previous attempts to address the multitude of daily loading cycles and conditions experienced by our bones, in a representative static loading condition (Carter, 1987; Carter et al., 1989). The consideration of cyclic loading is important as it has been proven to drive interstitial fluid flow through canaliculi (Burger and Klein-Nulend, 1999; Knothe Tate et al., 1998). The coupling of dynamic loads and fluid flow based stimulation of osteocytes may provide new insights into the impact of mechanical stimulation on bone mechanotransduction.

Along with transient loading, it has been observed that many cellular and biochemical responses to mechanical loading are transient in nature (Vahdati and Rouhi, 2009). For example, the premise of cellular accommodation is that bone cells react strongly to transients in their mechanical environment, but adjust their behavior over time to return to a steady state (Turner, 1999). One key example of this phenomenon is evidenced by the dominant forearm of a tennis player having a significantly higher BMD than the
non-dominant forearm (Ertem et al., 2009). Cellular accommodation is an important factor to consider for generalizing the cellular remodeling rules.

6.2.4 Boundary Conditions for HHCA Methodology

In this investigation, the representation of the tissue level properties of the HHCA methodology were improved by the incorporation of an anisotropic structural analysis. However, upon reanalyzing the results presented in this investigation, it was discovered that the boundary conditions that are used to translate the loads from the continuum level models to the tissue level models are not general in application. For example, the tissue level structures are assumed to be simply supported and subject to a fully stressed loading condition (Fig. 3.2). For the bone plate example, this configuration suffices as the continuum level bone plate itself is simply supported. However, for the cantilever plate example the left edge of the continuum level domain is fully constrained. Consequently, the submodels along the left edge of the domain should also share the boundary conditions imposed on the continuum level model. The current strategy for translating the applied loads from the continuum level to the tissue level does not preserve the boundary conditions for the cantilevered plate example.

A more accurate methodology for representing both the loading applied at the continuum level and the boundary conditions imposed would be to utilize the nodal displacements. The nodal displacements of the continuum level model could then be applied to the nodes along each face of the tissue level model. This strategy for coupling the continuum and tissue level models would also be able to conserve the continuity between models for a non-uniform or non-regular continuum level model discretization. In addition, this coupling strategy would allow continuity between scales for multi-grid analyses.
6.2.5 Cellular Scale for HHCA Methodology

The ultimate goal for computational simulations of the bone remodeling process is to be able to provide clinically relevant observations for better understanding the risk factors associated with bone loss or pathology. The inherent multi-scale nature of the HHCA algorithm is well suited for this task. With the ability of the HHCA methodology to span multiple length scales, the addition of a cellular level length scale would provide the biological detail that current continuum level phenomenological remodeling simulations lack. The development of such a model would have an increased capacity for planning treatment protocols for patients with bone disease or for improving the biological integration of implants or tissue constructs.

6.3 Final Remarks

The underlying goal of this dissertation was not only to challenge the existing paradigms for the simulation of bone remodeling, but to make a positive contribution to the existing state of the art. While this investigation initially focused on a multi-scale paradigm for coupling continuum level and tissue level remodeling activities, a need for a greater understanding of cellular level remodeling mechanisms was uncovered. By pursuing a unique combination of phenomenological and mechanistic modeling paradigms, a novel methodology for simulating the cellular mechanisms of bone remodeling was developed. This model was demonstrated to be able to predict remodeling at a single site in bone, in both a spatially and temporally accurate manner. The parametric analyses conducted on this model provide new observations of the sensitivities of the phases of bone remodeling to cellular level parameters that are unique to this model. Despite the lessons learned in this dissertation, a long road ahead persists in our pursuit to unravel the mechanisms of bone adaptation. In closing, it is the author’s be-
lief that the proper path to obtaining this goal lies in furthering our ability to model the cellular and molecular level mechanisms of remodeling, and not with new formulations of continuum level phenomenological simulations of bone adaptation.


Cowin, S. C., L. Moss-Salentijn and M. L. Moss. 1991. Candidates for the mechanosen-


Currey, J. D. 1988. The effect of porosity and mineral content on the Young’s modulus

of Biochemistry and Biophysics* 473(2), 147–160.

remodelling theory and applications to some problems in orthopaedic biomechanics.
*Meccanica* 37(4-5), 365–374.


Elmardi, A. S., M. V. Katchburian and E. Katchburian. 1990. Electron microscopy of
developing calvaria reveals images that suggest that osteoclasts engulf and destroy

Emerton, K. B., B. Hu, A. A. Woo, A. Sinofsky, C. Hernandez, R. J. Majeska, K. J.
Jepsen and M. B. Schaffler. 2010. Osteocyte apoptosis and control of bone resorption
following ovariectomy in mice. *Bone* 46(3), 577–583.

Eriksen, E. F. 1986. Normal and pathological remodeling of human trabecular bone:
Three dimensional reconstruction of the remodeling sequence in normals and in

Raven Press, Ltd.

of the formative site in iliac trabecular bone in 20 normal individuals employing a
243–252.

the Sandoz Journal of Medical Science* 31(2/3), 45–57.


Fox, S. W., K. Fuller, K. E. Bayley, J. M. Lean and T. J. Chambers. 2000. TGF-β1 and IFN-γ direct macrophage activation by TNF-α to osteoclastic or cytoidal phenotype. *J. Immunol.* 165(9), 4957–4963.


Huiskes, R. 2000. If bone is the answer, then what is the question? *J. Anat.* 197, 145–156.


