MECHANRO-REGULATION OF MANDIBULAR BONE DEVELOPMENT AND PERI-IMPLANT OSSEOINTEGRATION

A Dissertation Presented

by

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Abstract

Bone remodeling and bone healing are both complex biological processes that involve well-coordinated cellular activities. Mechanical loading is believed to influence the cellular responses during the development, maintenance, adaptation, and repair of bone. The works contained within this dissertation are aimed to investigate that the role of mechanics plays in the (1) mandibular bone development, (2) bone remodeling around dental implant, and (3) bone healing around dental implant. Regulatory algorithms of bone remodeling and bone healing are implemented in the finite element models.

In the first part of this work, the mandibular bone is shown to be determined by bone adaptation to external loading due to the daily activities. The density distribution of mandible is predicted to form a tubular structure similar to the observations in the medical images. Such bone architecture is known to provide bone the optimum strength to resist bending and torsion during mastication while reducing the bone mass. In addition, lack of the mechanical stimulation is shown to cause bone loss following edentulism.

The second part of this work shows that bone remodeling takes place due to the biomechanical alteration caused by dental implantation. In comparison to the long implants, the short implants are better for conserving the biomechanical state induced by the natural tooth in the surrounding bone. In addition, the short implants are predicted to lead to lower interfacial bone loss at high loads in the long term, while the long implants cause a more consistent level of bone loss for different load levels.
The final part of this work investigates the effect of immediate loading on the peri-implant bone healing. Applying higher load on the dental implant is demonstrated to impede the development of bone tissue and result in incomplete osseointegration. The region underneath implant apex is always found to experience high fluid stimulus that induces the development of soft tissue. A continuous layer of soft tissue grows along the smooth surface of threadless implant as a result of high distortional stimulus. The thread design redistributes the interfacial load and prevents the development of continuous high distortional stimulus.
Acknowledgement

I would like to express my deepest gratitude and respect to Professor Sinan Müftü. His advice and support are the effective stimuli that have been directing me throughout the research process. This dissertation would not have been possible without him.

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1.1 Dental implant treatment

Global demographics is forecasted to follow a fast trend toward an aging population (Howse 2012). Figure 1.1 shows the predictions of the percentage of aging population in selected countries for 2050. Health problems become a main concern for an aging community. Tooth loss, for example, is a common problem for the elderly. Table 1.1 lists the selected countries with prevalence of tooth loss of the elderly (Petersen 2004).

Figure 1.1 Percentage of aging population (65+ years) in selected countries (Howse 2012).
Table 1.1 Prevalence of edentulism in the elderly population, reported for some selected countries (Petersen 2004).

<table>
<thead>
<tr>
<th>Region</th>
<th>% tooth loss</th>
<th>Age group</th>
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<tbody>
<tr>
<td><strong>Africa</strong></td>
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<tr>
<td>Gambia</td>
<td>6</td>
<td>65+</td>
</tr>
<tr>
<td>Madagascar</td>
<td>25</td>
<td>65-74</td>
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<td><strong>The Americas</strong></td>
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<tr>
<td>Canada</td>
<td>58</td>
<td>65+</td>
</tr>
<tr>
<td>USA</td>
<td>26</td>
<td>65-69</td>
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<td><strong>Eastern Mediterranean</strong></td>
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<td>Egypt</td>
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<td>65+</td>
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<td>Lebanon</td>
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<td>64-75</td>
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<td>Saudi Arabia</td>
<td>31-46</td>
<td>65+</td>
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<td><strong>Europe</strong></td>
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<td>Albania</td>
<td>69</td>
<td>65+</td>
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<td>Austria</td>
<td>15</td>
<td>65-74</td>
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<td>Bosnia and Herzegovina</td>
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<td>65+</td>
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<td>Bulgaria</td>
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<td>Denmark</td>
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<td>Finland</td>
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<td>United Kingdom</td>
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<td>65+</td>
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<td><strong>South-East Asia</strong></td>
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<td>India</td>
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<td>Indonesia</td>
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<td>Sri Lanka</td>
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<td>Thailand</td>
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<td><strong>Western Pacific</strong></td>
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<td>Cambodia</td>
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<td>China</td>
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<td>Malaysia</td>
<td>57</td>
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<td>Singapore</td>
<td>21</td>
<td>65+</td>
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Conventional treatments for patients who suffer from missing tooth or teeth include fixed dental bridge and removable dentures. A fixed dental bridge is supported by the teeth
as abutments. The preparation of teeth abutment usually involves recounting of the adjacent healthy teeth. As a result, part of the enamel is removed to accept the crowns. The attachment of a removable denture is even poorer; such a denture is simply placed on the gum tissue; however, some devices can be bonded or clipped onto the remaining teeth. Without the proper attachment and support, it is difficult to keep the removable denture in place, and slippage of the device is likely to occur due to the cyclic muscle contraction during chewing and speaking.

A dental implant system can be separated into three components: the implant, the abutment; and the prosthesis. Dental implants are metal anchors that are surgically inserted into the jaw bone and provide convenient supporting function for various dentures and also enable single tooth replacements. Dental implants therefore reduce/eliminate the need to use the healthy teeth as bridge abutments, and provide anchoring functionality for patients with severe edentulism. The abutment is a post that retains a prosthesis, and it is attached to the implant. Two types of attachment designs, screw-in and tapered interference fit, are commonly used between the abutment and the implant (Bozkaya and Müftü 2003). Typically, a dental implant is made of titanium or titanium alloy (Ti-6Al-4V) (Lemons and Dietch-Misch 1999), due to its biocompatibility, and proven ease of osseointegration.

In modern dentistry, the goal of treatment is not only to restore the patient to normal speech and masticatory function, but also to provide a natural and aesthetically acceptable appearance. In the case of conventional restorations, lack of sound foundation in the bone site significantly affects the functionality and life of the restoration. Moreover, associated bone loss following tooth extraction may cause serious shrinkage (bone loss) in
the jawbone resulting in potential changes in jaw function, and even in facial contour. Such failure of bone maintenance is likely attributed to the lack of mechanical stimulation in bone. In that regard, dental implant treatment is considered to have therapeutic advantage over conventional treatments since the mechanical stimulation can be delivered by the implant itself. The placement of implant into the bone also provides the direct support to the prosthesis; as a result, retention, position and function of prosthesis are greatly improved. In addition, patients can benefit from other broader advantages including occlusal awareness, improved phonetics, maintenance of facial expression and improved psychological health (Misch 1999).

1.2 Masticatory system

The main functions of masticatory system are chewing, swallowing and speech. Masticatory system is composed of the teeth, the maxilla, the mandible, the ligaments, the muscles and the temporomandibular joint (TMJ) (Müftü and Müftü 2006). Here, brief introduction of teeth, masticatory muscles and TMJ is provided in the following sections.

1.2.1 Teeth

Human dentition comprises 32 teeth (Fig. 1.2). They are arranged in a row on both the maxillary (upper) dental arch and mandibular (lower) dental arch. According to the functions, the teeth can be classified into four types, incisors, canines, premolars and molars (Dunn and Shapiro 1975; Müftü and Müftü 2006). The incisors have wedge-shaped crowns. The sharp biting edge is designed to provide effective cutting and shearing. In humans, canines mostly function as incisors, but are longer and stronger than incisors. They are the only teeth in the dentition with single cusp that can firmly hold and grasp the
Figure 1.2 Dental arches. Modified from Dunn (1975).

food. The premolars have the function of the canines and molars. They are considered the transitional teeth during mastication. The food is crushed into small sizes before being transferred from canines to the molars. The molars are located in the poster regions of both dental arches. Molars have relatively large biting surfaces with multiple cusps and grooves, which enable effective crushing and grinding of the food.

1.2.2 Masticatory muscles

The masticatory muscles are those that move the mandible in order to perform the act of chewing. These muscles are divided into the depressors and the elevators (Hiatt and Gartner
Figure 1.3 Masticatory muscles. a Temporials, b Masseter, c Medial pterygoid and d Lateral pterygoid. Modified from Okeson (2003).

2000). The depressors including the digastric, the suprhyoid, and the infrahyoid muscles are mainly involved during jaw closing and swallowing (Müftü and Müftü 2006). The elevators including the temporalis, the masseter, the medial pterygoid, and the lateral pterygoid muscles that are responsible for jaw closing are considered the primary muscles of mastication (Muscolino 2005).

The temporalis is formed by fan-shaped muscle fibers, which orients from the temporal fossa of the temporal bone and pass through the zygomatic arch (Fig. 1.3a). These muscle fibers converge and attach as a tendon on the coronoid process. The masseter has a superficial layer and a smaller deep layer (Fig. 1.3b). The superficial layer of masseter originates from the anterior two-thirds of inferior margin of zygomatic arch and inserts
Figure 1.4 Lateral view of bones and bony landmarks of the head. Modified from Muscolino (2005).

into the inferior external surface of the ramus (Figs. 1.4-1.5). The deep layer of masseter originates from the posterior one-third of inferior margin and inserts into the superior external surface of the ramus (Figs. 1.4-1.5). Medial pterygoid (Fig. 1.3c), which is also called internal pterygoid is anatomically and functionally a counterpart to the masseter
Figure 1.5 Inferior view of bones and bony landmarks of the head. Modified from Muscolino (2005).

(Hiatt and Gartner 2000). It is originates from pterygoid fossa of sphenoid bone and connects to inferior internal surface of the ramus (Figs. 1.4-1.5). The lateral pterygoid (Fig. 1.3d) has two muscle bundles. The superior portion originates from the sphenoid bone and attaches to the capsule and articular disk of temporomandibular joint (Figs. 1.4-1.5). The
Figure 1.6 Schematic representation of TMJ. **a** The articular disk and its connecting tissues. **b** The capsular ligament. **c** The temporomandibular ligament. **d** The stylomandibular and sphenomandibular ligaments. Modified from Okeson (2003).

inferior portion originates the lateral pterygoid plate and inserts into the neck of condyle (Figs. 1.4-1.5).

### 1.2.3 Temporomandibular joint

The TMJ enables the articulation of mandible with respect to the skull. It is composed of the mandibular condyle, the articulating surface, the articular disk, the ligaments and the muscles (Fig. 1.6). There are five ligaments, the collateral ligament, the capsular ligament, the temporomandibular ligament, the sphenomandibular ligament, and the stylomandibular ligament, in the TMJ as shown in Fig. 1.6. The function of ligaments is to guide the movement of the mandible in order to prevent the excessive movements (Müftü and Müftü 2006). The temporomandibular disk is located between mandibular condyle and
the articulating surface. The disk is a compact, dense and fibrous connective tissue containing a mesh of collagen fibers with interstices filled with proteoglycans (Hiatt and Gartner 2000; Müftü and Müftü 2006). The collagen fibers can maintain the shape of the disk during loading. The elastin fibers within interstices assist to recover the form after unloading.

1.3 Bone

Bone enables the body to function as a structure by resisting a large fraction of the external loads that it experiences. Bone also serves as a mineral reservoir which allows minerals that are critical to physiological function, such as calcium and phosphate, to be stored and transferred between the skeleton and the bloodstream. In general, bone is mainly composed of water, collagen, hydroxyapatite $[\text{Ca}_{10}\text{(PO}_4)_{6}\text{(OH)}_2]$, and small amount of other nutrients and cells. The collagen, a structural protein, organizes itself into fibers which account for the strength of the bone (Martin et al. 1998).

1.3.1 Porosity

Porosity is the void volume fraction of the bone. Based on the porosity, bone can be classified into two types, compact bone (cortical bone) with low porosity (5-10%) and cancellous bone (spongy or trabecular bone) with high porosity (75-95%) (Martin et al. 1998). The bone matrix of cancellous bone usually forms in rod and/or strut like structures with approximately 200 µm in diameter. The orientation of these rods, called trabeculae, has a random appearance, but in some locations organized arrays are observed. The interconnected pores within cancellous bone are occupied by bone marrow, which provides negligible structural support, but functions as the main source of blood cells.
Figure 1.7 Stereologic methods for porosity measurement. a Two dimensional method. $A_V$ is the area of void. $A_T$ is the total area of the image. b One dimensional method. $L_V$ is the length of line section that falls on the void. $L_T$ is the total length of the test line. c Zero dimensional method. $P_V$ is the number of points that fall on the voids. $P_T$ is the number of total points over the image.

Cortical bone, a dense bone matrix, usually forms a shell (cortex) that is filled with cancellous bone and marrow. Such macroscale organization is common in long bones, and the mandible. Cortical bone can also exist along a tubular shaft in the mid-section of long bones (Carter and Beaupré 2001). The pores of the cortical bone consist of canals approximately 50 µm in diameter in which nerves and blood vessels propagate.

The measurement of porosity is usually performed by the means of stereology, which is a method to estimate variables of a three-dimensional (3D) body while only the two dimensional (2D) sections of the solid body are available (Martin et al. 1998). There are three ways to quantify the void volume fraction from the 2D histologic sections of bone. The first method is a 2D technique, which divides the total void area ($A_V$) by the entire area ($A_T$) of the bone specimen (Fig. 1.7a). The second method is the one dimensional technique that a test line is randomly placed on the image (Fig. 1.7b). Fractional length of the line section that fall on the voids is measured. Finally, a set of grid points is placed on the image.
and the points that fall on the voids are counted (Fig. 1.7c). This can be called zero dimensional technique. While more tests are accumulated, all these measurements are expected to approach to the real porosity, void volume fraction (Odgaard 2001).

1.3.2 Bone density

The porosity of cancellous bone displays the complexity to determine the bone volume. Two types of volumes are considered. One is the volume of mineralized bone tissue and the other is the total volume of bone specimen including the bone tissue and the pores (Galante et al. 1970). Therefore, two expressions of bone density result from different considerations of bone volume. The true bone density or the density of bone tissue is the bone mass per volume of mineralized bone tissue. Carter and Hayes (1977) suggested that the true densities of cancellous bone and cortical bone are similar. This suggestion supports Wolff’s statement about the cortical bone that it is simply dense cancellous bone tissue. Another commonly used variable to describe bone density is the apparent density, which is defined as the bone mass divided by the total volume of bone specimen (Martin et al. 1998). Assuming the density of bone tissue is a constant value, the apparent bone density is the volume fraction of bone tissue multiplied by the density of bone tissue. The magnitude of apparent bone density depends on the distribution of pores throughout the bone or the porosity (Rice et al. 1988).

1.4 Bone remodeling

Bone growth is accomplished by two modes, intramembranous ossification and endochondral ossification. The flat bones such as skull, scapulae and pelvis, are formed by intramembranous ossification, where bone formation cells, osteoblasts, create bone
Formation of limb bones is completed by endochondral ossification, where cartilage is formed first and replaced by bone. Unlike bone growth mostly occurring in the early age of skeletal development, bone remodeling is a process of continuous cellular activities to replace aged, injured and dead bone. The remodeling process consists of three principal stages named activation, resorption and formation, and it is carried out by basic multicellular units (BMUs) that consist of about 10 osteoclasts and several hundred osteoblasts (Fig. 1.8). Normally, osteoclasts, bone cells responsible for resorption, are inhibited by osteoprotegerin (OPG), which is a protein secreted by osteoblasts as inhibitory signal (Carda et al., 2005). The osteoclastic resorption is signaled by the circulating parathyroid hormone and locally secreted receptor activator nuclear kappa-b ligand (RANKL), which binds to RANK receptors on the membrane of osteoclasts (Marx 2007). In addition to OPG, osteoblasts also secrete RANKL so that the activation of osteoclasts and the amount of resorption are regulated.

When remodeling is activated, osteoclasts are first recruited to bone surface and start to excavate the bone by releasing hydrochloric acid to dissolve the inorganic matrix, and collagenases to break down the organic matrix (Marx 2007). A tunnel with
approximately 200 µm in diameter and 300 µm long is excavated at the rate of 40 µm/day (Martin et al. 1998). Following the resorption, there is a reversal phase before the initiation of formation. A cylindrical space in the tunnel can be observed and the length of this region varies with the lag between the resorption and formation.

During bone resorption, some bone morphogenetic proteins (BMPs) and insulin-like growth factors (IGFs) are released as active cytokines (growth and differentiation factors), which induce the differentiation of stem cells into osteoblasts (Marx, 2007). Bone formation is conducted by the osteoblasts, which refill the space with unmineralized bone matrix, osteoid, at a rate of about 1-2 µm/day (Martin et al., 1998). As the osteoblastic activity continues, a tunnel with 40-50 µm in diameter called Haversian canal is left for the transportation of the nutrients to bone cells. Finally, the bone matrix deposited by osteoblasts is mineralized and turns into Haversian system, osteon. Osteoclastic activity restores to quiescent condition under the influence of osteoblasts, and bone is maintained until the aging or diseased bone triggers the secretion of RANKL by osteoblasts (Marx, 2007).

1.5 Bone adaptation
In addition to biologic influences, mechanical factors contribute significantly to bone regeneration. Bone’s ability to adjust its internal architecture and external form, based on mechanical loads that it experiences was proposed by Wolff (1892; 1986) following numerous observations. The possible mechanism of bone adaptation to mechanical loading requires the existence of a physiological control system that involves sensor, transducer, comparator and feedback functions (Hart 2001; Hart et al. 1984). Frost’s mechanostat hypothesis suggested that minimum effective strain is the control signal regulating bone
remodeling (Frost, 1987). Frost identified four strain ranges that he called windows that cause distinctly different bone response. In the adapted window, the bone density is maintained. Strain levels fall in this window as the normal daily activities are carried out. Increased external loading that cause a slight increase in bone strain levels defines the mild overload window. In this window, bone formation takes place and the bone density increases. Further increased strain levels that eventually cause faster accumulation of micro damage than that can be repaired by remodeling defines the pathologic overload window. On the other hand, when the bone is persistently exposed to low strain levels, defined as the disuse window, net bone loss (bone atrophy) is observed. Frost based this mechanostat hypothesis on empirical data, however, he neither clearly defined the strain measure, nor the exact strain values for the “windows.” Nevertheless, his work along with Wolff’s observations was influential in the works of next generations of researchers.

Several mathematical models have been formulated to model the bone response to mechanical stimuli starting in 1970’s. The common thread of these mathematical formulations is: to quantitatively describe the functional adaptation of the bone; to predict

**Figure 1.9** Bone adaptation rules.
the bone adaptation by numerical simulation; to come up with therapeutically beneficial ideas (Hart 2001). The fundamental idea of bone remodeling theory is that bone requires a certain level of mechanical stimulus to maintain the bone strength. This remodeling equilibrium state also named homeostatic state or lazy zone is assumed to be determined by a preset value of reference stimulus (Fig. 1.9). While the change of external loading causes a new mechanical state that falls outside of the equilibrium state, bone adaptation takes place through bone resorption and bone formation in order to restore the homeostasis.

These theories are separated into two categories, external (re)modeling and internal remodeling (Frost 1964; Cowin et al. 1978; 1979). External (or surface) remodeling indicates bone is only added or removed at the periosteal and endosteal surfaces and results in changes of shape. Several hypotheses (Frost 1964; Basset 1965; Weinbaum et al. 1994) were developed accordingly to explain the phenomenon that abnormally curved bones due to fractures tend to straighten themselves. In addition, growth of diaphyseal cross section was simulated by assuming that surface remodeling takes place on the inner (endosteal) or outer (periosteal) circumference of an annular area (Cowin and Firoozbakhsh 1981; van der Meulen et al. 1993).

Internal remodeling can be further subdivided into two groups: trajectory theory and density theory. The trajectory theory suggests that trabeculae align themselves in the directions to resist the external loading. Weinans et al. (1992) showed one of the first models that trabecular like struts are self-developed in a 2D rectangular bone plate. Jang and Kim (2008) applied the topology optimization to simulate the trabecular trajectory of a proximal femur. Density theory focuses on the changes to the porosity of trabecular bone
as a function of time. Finite element models were introduced by Carter et al. (1987) and Huiskes et al. (1987) to solve this problem. Remodeling algorithms of Carter et al. (1987) and Huiskes et al. (1987) are implemented in Chapter 2 and 3, respectively. Density distributions of proximal femur predicted by the models of both Carter et al. and Huiskes et al. have shown good agreement with the experimental observations (Carter et al. 1989; Weinans et al. 1992).

Although the development of bone adaptation theories is based on Wolff's law, it should be noted that many have argued Wolff's view of trabecular architecture. Wolff observed that many trabeculae cross at right angles and further attributed this phenomenon as a result of the trajectories of principal stresses (Bertram and Swartz 1991). Cowin (2001) pointed out that the comparison between the trabecular orientation of cancellous bone and the stress trajectories in a homogeneous isotropic elastic material is the false premise of Wolff's law. Therefore, the contemporary investigators should rather learn the philosophical statement or the conceptual idea of Wolff's law than accept its rigid form.

1.6 Bone (Fracture) healing

Bone (fracture) healing is a process of skeletal tissue regeneration triggered by trauma such as fracture or surgical osteotomy that causes physical disruption of the mineralized tissue matrix, death of cells and interruption of blood supply (Carter and Beaupré 2001). Three biological phases, inflammatory, reparative and remodeling phases, are normally observed in fracture healing (Martin et al. 1998).

The inflammatory response begins immediately as extravascular blood cells aggregate and form hematoma due to the rapture of blood vessels following trauma. In
addition to the immobilization of the fracture by swelling and pain, an important task of this initial phase is to activate cells responsible for healing. Molecular and active mediators including inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6), and growth factors such as platelet-derived growth factors (PDGF) and transforming growth factors (TGF) are released from the hematoma to regulate the fracture healing and cellular response (Prendergast and van der Meulen 2001). Bone healing involves complicated cellular events, but each step is predicted based on previous events. It’s similar to other biologic cascade involving a series of cellular activities that cannot be recovered once a mistake is made. Clinically, many fractures that do not heal in the expected time span or fail to heal are caused by the defect during the process.

During the reparative phase, pluripotential mesenchymal stem cells (MSC) appear to the healing site and then differentiate into chondrocytes and osteocytes which proliferate and generate the reparative callus (Prendergast and van der Meulen 2001). To rapidly repair the damaged bone, both intramembranous ossification and endochondral ossification are activated simultaneously. The reparative phase completes when the bony union is achieved and the strength of the broken bone is restored. The final phase of healing is bone remodeling which gradually restores the original shape and internal architecture of the bone to improve mechanical efficiency.

1.7 Mechanobiology of tissue regeneration

A crucial stage of bone healing or skeletal regeneration is the differentiation of MSC into cells that form different tissues. The differentiation pathway (Fig. 1.10) that results in final phenotype is believed to be greatly influenced by the mechanical stimuli (Carter and Beaupré 2001; van der Meulen and Prendergast 2000). Pauwels (1980) postulated the idea
Figure 1.10 Connective tissue cells differentiate from the MSCs in response to local mechanical and biomechanical stimuli. Modified by Van der Meulen and Prendergast (2000) from Caplan (1994).

that the differentiation pathway is regulated by the mechanical stress and strain invariants of hydrostatic (dilatational) stress and octahedral shear (distortional) stress through the observation of differentiation pattern and mechanical loading in the fracture callus. The conclusion of his finding can be schematically illustrated in Fig. 1.11, which suggests high hydrostatic stress favors the development of cartilage, while the fibrous tissue is the product of high shear. There is no specific stimulus determined for the bone formation; in addition, ossification occurs when soft tissue is stable and stiff enough to provide the suitable mechanical environment for the primary remodeling, formation of woven bone, followed by the secondary remodeling, formation of lamellar bone.

Following Pauwels, Carter et al. (1988) introduced a model where cyclic hydrostatic stress history and cyclic shear stress history account for the tissue differentiation.
**Figure 1.11** A schematic representation of Pauwels’ hypothesis of the mechano-regulatory tissue differentiation. Modified by Weinans and Prendergast (1996) from Pauwels (1980).

Furthermore, the model indicated the fact that bone formation cannot take place without sufficient vascular supply. In a later model, Carter et al. (1998) proposed a more generalized model that replaces the shear stress with the principal tensile strain due to the prospect that biological events are often related to the change in shape of the cells and deformation of the local matrix. The maximum principal strain was assumed to be important for the intramembranous ossification and also in controlling synthesis of type I collagen (Carter and Beaupré 2001), which is the predominant collagen in bone (Martin et al. 1998). A phase diagram illustrating this model is shown in Fig. 1.12. Carter et al. employed the linear elastic finite element model to predict the tissue differentiation pattern at the bone implant interface, fracture, distraction osteogenesis and chondrogenesis in repair (Carter et al. 1998; Loboa et al. 2001; Loboa et al. 2005; Giori et
Figure 1.12 A schematic representation of Carter's hypothesis of the mechano-regulatory tissue differentiation (Carter and Beaupré 2001).

Claes and Heigele (1998) presented the first model that quantified the thresholds (Fig. 1.13) of various tissue formation in terms of local stress and strain by comparing the experimental data from animal histology and finite element analysis, which simulated fracture callus as a hyperelastic material. Their hypothesis suggests that intramembranous bone formation occurs as strains smaller than approximately $\pm 5\%$ and hydrostatic pressure smaller than $\pm 0.15\text{MPa}$. Compressive pressure that is greater than $-15\text{MPa}$ and strains smaller than $\pm 15\%$ stimulates endochondral ossification. All other conditions lead to the development of fibrous tissue or fibrocartilage.

A poroelastic model taking into account the stimuli contributed by both solid and fluid phases of the tissue was proposed by Prendergast et al. (1997). A biophysical stimulus comprised of two deformation measures, shear strain and flow velocity, were assumed to regulate the differentiation pathway. High level of this stimulus is associated with the
**Figure 1.13** A schematic representation of Claes and Heigele's hypothesis of the mechano-regulatory tissue differentiation. Modified by Isaksson (2007) from Claes and Heigele (1998).

fibroblast differentiation, intermediate stimulus is in favor of chondrocyte differentiation and low stimulus promotes the osteoblast differentiation as shown in Fig. 1.14. This model is implemented in Chapter 4 in order to study peri-implant bone healing.

**1.8 Motivation**

Successful implant treatment is highly dependent on *osseointegration*, a bone integration process termed by the Swedish orthopedic surgeon, Brånemark, after extensive experimental studies (Misch and Misch 1999). Osseointegration begins with the rapid growth of random and unorganized woven bone soon after surgical implantation, if the relative motion between the implant and the adjacent bone can be minimized (Adell et al. 1981). This initial bony structure is maintained by bone remodeling and bone adaptation, during which woven bone is slowly replaced by more organized, lamellar bone. Adaptation
of bone morphology in response to functional loads continues throughout life (Schenk and Buser 1998).

To assess quality and quantity of bone in the healing site, several studies have been conducted. Qualitative assessment of the bone implant interface can be evaluated by medical imaging technology such as radiography or computed tomography (CT). However, care should be taken as the patients could be exposed to substantial radiation dosage on a regular basis over the healing period. Resonance frequency analysis also serves as a non-destructive test which relates the implant stability or osseointegration to interfacial stiffness (Hz), but the credibility of this method still needs to be further investigated (Schliephake et al. 2006; Sul et al. 2001).

Quantitative studies usually involve implant retrieval. Measurement of removal torque during the retrieval is a straight forward technique, and the magnitude is interpreted as the strength of the interfacial connection between bone and implant.

Figure 1.14 A schematic representation of Prendergast’s hypothesis of the mechano-regulatory tissue differentiation (Prendergast et al. 1997).
Histomorphometric evaluation is another quantitative study. Histologic sample is prepared by cutting the bone-implant retrieval into thin slices so that the observation of bone implant interface can be performed via high magnification microscope. Histologic images are captured and digitized in order to quantify the bone implant contact (BIC) fraction, which determines the length of the region that bone directly connects to implant over the total implant contour. Both approaches provide useful measures to inspect the stability of the bone implant interface. However, systematic evaluation is very difficult to establish by such in vivo experiments, due to their time consuming nature and more serious concerns about ethical issues. Hence, the development of a computational model that can avoid drawbacks raised by experiments may be an alternative to study bone implant stability.

Finite element (FE) method has been applied to implant dentistry to assess the stress field altered by the placement of dental implant in the bone including effects of various implant designs (Bozkaya et al. 2004; Faegh and Müftü 2010) and various clinical scenarios (Chou et al. 2010; Van Oosterwyck et al. 2002). In these studies, material properties of the bone are assumed to be constant, and bone strength is evaluated by comparing maximum displacements, stress or strain predicted in the simulation with either excessively high or inadequately low load levels that result in pathologic bone loss.

However, either the initial phase of bone regeneration or the later phase of bone remodeling during osseointegration is a dynamic cellular process that continuously governs quality and quantity of peri-implant bone tissue. The assumption of constant material properties is inadequate to represent peri-implant bone. Developing
computational models that account for how mechanics regulates dental implant induced bone development and bone remodeling is the aim of this research.

1.9 Thesis organization

The development of mandibular bone structure as a result of mastication and jaw open and close cycles, and the long term bone loss following various edentulism scenarios are demonstrated in Chapter 2. Peri-implant bone remodeling in response to the different biomechanical states caused by the natural tooth and the dental implant is evaluated in Chapter 3. The effect of immediate loading on the peri-implant bone healing is investigated by implementing a mechano-regulatory tissue differentiation model in Chapter 4. The summary of conclusions drawn from Chapter 2, 3 and 4, and the future works are presented in Chapter 5.
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Influence of Mastication and Edentulism on Mandibular Bone Density

2.1 Introduction

During mastication, the mandible is subjected to the external loads including masticatory muscle forces, reactions on the teeth and reactions on the temporomandibular joints (TMJ) (Müftü and Müftü 2006). Successful masticatory function depends on a harmonious relation between these forces. Research on the biomechanics of the mandible has been divided into two streams: Maximum bite forces and contact pressure in the TMJ during clenching were determined by static analyses (Prium et al. 1980; Osborn and Baragar 1985; Koolstra et al. 1988); Dynamic analyses to predict the trajectory of mandible movement, condyle position and maximum jaw open during the jaw open and close cycles were carried out by Koolstra and van Eijden (1997; 1999). In all of these studies the mandible was assumed to be rigid.

In general, bone morphology is influenced by the inherent genetic factors that account for the differences in the size of bones between individuals. The acquired mechanical environment is believed to be another significant factor that contributes to the changes in the external form and internal architecture of the bone in response to the changes of functional loading, as suggested by Wolff (1986). Based on extensive
observations, Wolff proposed the law of bone remodeling where he qualitatively described that bone remodeling is regulated by certain mathematical rules. This hypothesis has interested investigators to formulate and examine more rigorous bone remodeling rules that simulate bone adaptation to various mechanical functions (Frost 1990; Cowin and Hegedus 1976; Carter et al. 1987; Huiskes et al. 1987). Bone remodeling models have been demonstrated to be valid for studying the bone density distribution of the femur with finite element (FE) method (Carter et al. 1987; Huiskes et al. 1987). This, not only qualitatively validates the mathematical model, but also shows the potential of using similar approaches to investigate bone remodeling in the femur due to the alteration of biomechanical environment caused by the use of orthopedic implants (Huiskes et al. 1987; Orr et al. 1990). The prediction of bone morphology in the femur has become the benchmark problem for testing newly proposed computational algorithms of bone remodeling (Doblare et al. 2002; Zhu et al. 2005; Jang et al. 2008).

Based on the successful predictions of bone morphology in long bone community, same approaches have been used to investigate the effects of dental implants on peri-implant bone remodeling (Chou et al. 2008, 2012; Crupi et al. 2004; Li et al. 2007; Lian D et al. 2011; Lin C-L et al. 2010; Lin D et al. 2010). However, Lin et al. (2009) indicated the need to show the applicability of bone remodeling algorithms to model dental bone. To the best of our knowledge, works of Reina et al. (2007) and Perez et al. (2010) are the only studies in the open literature that show good agreement between the predicted bone density distribution, obtained by using their long-bone remodeling algorithm, with the corresponding CT scans of the mandible. The first goal of the present study is to show that the bone remodeling algorithm purposed by Beaupre et al. (1990) can be used to predict
the mandibular bone structure in response to the functional loads such as mastication, speech and involuntary open-and-close cycles. To this end the biomechanical factors that determine the development of mandibular bone density in the algorithm are explored numerically. In addition the effects of various edentulism scenarios on long term bone loss are investigated.

2.2 Materials and methods

2.2.1 Finite element model

A three-dimensional (3D) FE model of the mandible is prepared by using the medical image processing software, Mimics 13.1 (Materialise, Plymouth, MI). Segmentation is performed on each CT slice to distinguish densities between various tissue types based on radiodensities. The complete 3D volume of the teeth and the mandible are rendered by stacking the 2D contours. The final model is meshed with 4-node tetrahedral elements by 3-Matics, a meshing module of Mimics. Upon a mesh convergence study, the global element length is chosen to be 1 mm due to consideration of the computational effort. The FE model comprises of 16 teeth meshed with 11760 nodes and 49518 elements, and the mandible meshed with 41938 nodes and 196844 elements. Panagiotopoulou et al. (2011) showed that periodontal ligament has little effect on the biomechanical analysis of mandible, as its effects on the strain distribution are confined to close proximity of the teeth. Based on this finding, in this initial study, the periodontal ligament is not included in the current model, but it should be included in the follow-on studies.

An empirical power-law relationship is used to relate the apparent bone density to its elastic modulus as follows (Beaupre et al. 1990),
Initially, the bone is assumed to have a homogenous density (0.5 g/cm³) distribution. Elastic modulus of teeth is set to be 20 GPa (Anusavice 2003). Poisson’s ratio is 0.3 for bone and teeth, and both are assumed to behave in a linear elastic and isotropic manner (Bozkaya et al. 2004; Chou et al. 2010; Faegh and Müftü 2010).

\[
E = \begin{cases} 
2042\rho^{2.5}, & \rho \leq 1.2\ g/cm^3 \\
1798\rho^{3.2}, & \rho > 1.2\ g/cm^3 
\end{cases} \tag{2.1}
\]

The disk at the TMJ is not directly modeled, but its behavior is approximated by attaching spring elements with elastic modulus of 6 MPa and Poisson’s ratio of 0.4 (Beek 2000) to the surface of condyles in all directions. All springs are constrained in all degrees of freedom. Loads acting on the FE model include mandibular flexure and muscle forces. Mandibular flexure due to jaw opening and closing is simulated by applying a small displacement along the \( y \)-direction on both condyles (Fig. 2.1). Muscle forces are determined by a static model of mastication which is explained in detail in the following.
Table 2.1 Maximum muscle tension according to Osborn and Baragar (1985), and coordinates of attachment points on mandible and skull for the masticatory muscles considered in this study. Only half of the model in positive y-direction is listed, with the other half symmetrical.

<table>
<thead>
<tr>
<th>Max tension (kg)</th>
<th>Attachment points on mandible (mm)</th>
<th>Attachment points on skull (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Msa</td>
<td>14.0</td>
<td>28.5130</td>
</tr>
<tr>
<td>Msp</td>
<td>13.0</td>
<td>7.5917</td>
</tr>
<tr>
<td>Mdp</td>
<td>9.0</td>
<td>6.3605</td>
</tr>
<tr>
<td>Pma</td>
<td>8.0</td>
<td>20.9447</td>
</tr>
<tr>
<td>Pls</td>
<td>12.0</td>
<td>1.6906</td>
</tr>
<tr>
<td>Plu</td>
<td>13.0</td>
<td>3.2027</td>
</tr>
<tr>
<td>Tv</td>
<td>27.0</td>
<td>31.9769</td>
</tr>
<tr>
<td>Toa</td>
<td>17.0</td>
<td>28.5326</td>
</tr>
<tr>
<td>Top</td>
<td>16.0</td>
<td>26.7552</td>
</tr>
<tr>
<td>Di</td>
<td>11.0</td>
<td>67.1799</td>
</tr>
</tbody>
</table>

section. In general, the bite force acting on a tooth can be due to the reaction force resulting from the contact between two teeth, or between a tooth and bolus of food. By constraining the contact points of the teeth, the bite forces can simply be represented as the reaction
Table 2.2 Locations of bite forces on different teeth. Only half of the model in positive y-direction is listed. (Units are in mm).

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st incisor</td>
<td>84.2592</td>
<td>2.6962</td>
<td>-44.1738</td>
</tr>
<tr>
<td>2nd incisor</td>
<td>81.8360</td>
<td>7.6099</td>
<td>-43.7000</td>
</tr>
<tr>
<td>Canine</td>
<td>77.9431</td>
<td>12.5835</td>
<td>-42.8298</td>
</tr>
<tr>
<td>1st premolar</td>
<td>71.8997</td>
<td>17.1181</td>
<td>-43.9110</td>
</tr>
<tr>
<td>2nd premolar</td>
<td>63.7967</td>
<td>16.2554</td>
<td>-41.1827</td>
</tr>
<tr>
<td>1st molar</td>
<td>52.9877</td>
<td>18.1871</td>
<td>-41.8510</td>
</tr>
<tr>
<td>2nd molar</td>
<td>42.5019</td>
<td>21.0057</td>
<td>-42.9288</td>
</tr>
<tr>
<td>3rd molar</td>
<td>32.2598</td>
<td>23.1073</td>
<td>-41.2803</td>
</tr>
</tbody>
</table>

forces at the contact points. The origin of Cartesian coordinate system is placed at the center of two condyles as shown in Fig. 2.1. The sagittal plane lies on the x-z plane, the frontal plane lies on the y-z plane, and the occlusal plane lies parallel to the x-y plane. The coordinates of the muscle attachment points on the mandible and skull, and the locations of the bite forces on different teeth are given in Tables 1 and 2, respectively.

2.2.2 Static model of mastication

During chewing and/or clenching, the external forces acting on the mandible are generated by various muscle groups (Prium et al. 1980). Forces are transferred to the mandible through the teeth and the joint reaction forces on the TMJ. In this work a static model of mastication proposed by Osborn and Baragar (1985) is used to determine the muscle forces applied on the mandible as a result of bite forces (constraints) on the teeth. Static
equilibrium, when the mandible is subjected to muscle forces ($\vec{F}_m$), bite forces ($\vec{F}_b$) and joint reactions ($\vec{F}_j$), is expressed as follows,

$$\sum_{i=1}^{N_m} \vec{F}_m^i + \sum_{i=1}^{N_b} \vec{F}_b^i + \sum_{i=1}^{N_j} \vec{F}_j^i = 0 \quad (2.2)$$

$$\sum_{i=1}^{N_m} \vec{r}_m^i \times \vec{F}_m^i + \sum_{i=1}^{N_b} \vec{r}_b^i \times \vec{F}_b^i + \sum_{i=1}^{N_j} \vec{r}_j^i \times \vec{F}_j^i = 0 \quad (2.3)$$

where $N_m$, $N_b$ and $N_j$ are the total number of muscles, teeth and joints, and $r_m$, $r_b$ and $r_j$ indicate the length of the moment arm for muscle forces, bite forces and joint reactions.

Muscle groups activated during mastication considered here are divided into 13 symmetrical muscles on each side of the mandible including the superficial anterior (Msa), superficial posterior (Msp), deep anterior (Mda), and deep posterior (Mdp) masseter; the medial anterior (Pma), and medial posterior (Pmp) pterygoid; the lateral superior (Pls), lateral upper (Plu) and lateral inferior (Pli) pterygoid; the oblique anterior (Toa), vertical (Tv), oblique posterior (Top) temporalis; and the digastric (Di) (Müftü and Müftü 2006). For a specific bite force, there are many combinations of muscle forces and joint reactions that would satisfy the equilibrium Eqs. (2.2-2.3), as the system is over determined. However, muscles are only able to produce tension forces. The force applied by a muscle $i$, $\vec{F}_m^i$, is limited by a maximum force, $\vec{F}_{m,max}^i$, specific to that muscle, which depends on its cross-sectional area (Prium et al. 1980). The magnitude of muscle forces are, therefore, constrained as follows,

$$0 \leq |\vec{F}_m^i| \leq |\vec{F}_{m,max}^i| \quad (2.4)$$
Moreover, only the compressive joint reaction forces are admissible,

\[ 0 \leq |\vec{F}_i| \]  

(2.5)

The values for all the muscle groups are listed in Table 1. In addition, Osborn and Baragar assumed that mastication is performed in a way that minimizes the total muscle forces. Under such assumptions, the problem of finding the muscles forces becomes a linear optimization problem involving Eqs. (2.2-2.5). A MATLAB script involving \textit{linprog} function was developed for this study.

2.2.3 Remodeling algorithm

Beaupre et al. (1990) developed a mathematical model that simulates the bone adaptation as a result of daily loading history. The remodeling stimulus ($\psi$), which characterizes the number of loading cycles and the daily bone stress is defined as follows,

\[ \psi = \left( \sum_{i=1}^{N} n_i \sigma_i^m \right)^{1/m} \]  

(2.6)

where the exponent ($m$) is an empirical constant that is set to be 4 to weigh the relative contribution of the number of loading cycles ($n_i$) and the tissue level effective stress ($\sigma$) for a specific load type-i. At the tissue level, the stress state develops within the mineralized bone tissue, while the continuum level stress is determined from the FE calculations. The effective stress at the continuum level is defined as,

\[ \vec{\sigma}_c = \sqrt{2EMU} \]  

(2.7)
where $E$ and $U$ are elastic modulus and strain energy density at the continuum level. The continuum level stress and the tissue level stress are related as follows,

$$
\bar{\sigma} = \left( \frac{\rho_{cb}}{\rho} \right)^2 \bar{\sigma}_e
$$

(2.8)

where $\rho_{cb}$ is the maximum density of the fully mineralized bone tissue with zero porosity (e.g. cortical bone), and $\rho$ is the apparent density of the bone.

The driving force of the bone remodeling is the difference ($\psi - \psi_{AS}$) between the remodeling stimulus and the attractor stimulus ($\psi_{AS}$). The nonlinear remodeling law is represented as follows,

$$
\dot{r} = \begin{cases} 
\frac{c_1[\psi - \psi_{AS}(1-w)]}{c_2[\psi - \psi_{AS}(1+w)]} & \text{for } \psi < \psi_{AS}(1-w) \\
0 & \psi_{AS}(1-w) \leq \psi \leq \psi_{AS}(1+w) \\
\frac{c_1[\psi - \psi_{AS}(1-w)]}{c_2[\psi - \psi_{AS}(1+w)]} & \psi > \psi_{AS}(1+w)
\end{cases}
$$

(2.9)

where $\dot{r}$ is the surface remodeling rate (µm/day), $c_1$ and $c_2$ are the bone formation and bone resorption constants, and $w$ is the width of dead zone, where the remodeling difference is not great enough to trigger either bone resorption or formation. The value of 0.02 (µm/MPa) is used for formation constant, $c_1$ (Beaupre et al. 1990). Resorption constant, $c_2$, is set to be three times greater than formation constant, $c_1$, to represent bone resorption is a faster process than bone formation (Weinans et al. 1992; Martin et al. 1998). The width of dead zone is set to be 0.25 (Beaupre et al. 1990). Equation (2.9) characterizes the bone remodeling that occurs on the bone surface. The internal bone remodeling, change of bone density ($\dot{\rho}$), is related to the surface remodeling rate as follows,
\[ \dot{\rho} = k S_v \rho \dot{\rho} \]  

(2.10)

where \( k \) is the fraction of local area which is actively remodeling, \( \rho \) is the density of the bone tissue that is being remodeled, and \( S_v \) is the bone-specific surface introduced by Martin (1984) to quantify the available remodeling surface of a bone volume (Fig. 2.2). By combining Eqs. (2.9-2.10) the internal bone remodeling can be solved with forward time integration as follows,

\[ \Delta \rho = k S_v \rho \dot{\rho} \Delta t \]  

(2.11)

where \( \Delta \rho \) is the change in bone density during an integration step \( \Delta t = 30 \) days. Bone density variation is between 0.05 and 1.92 g/cm\(^3\), according to Carter et al. (2001). The bone remodeling algorithm is written by using APDL in FE software ANSYS (Canonsburg, PA).

**Figure 2.2** Bone-specific surface as a function of bone apparent density adapted from Beaupre et al. (1990).
2.3 Results

Osborn and Baragar (1985) considered a simultaneous bilateral pattern during mastication, meaning that the food contacts the teeth (e.g., 1st molars) symmetrically with respect to the sagittal (x-z) plane. Manns et al. (1988) reported that most people use the alternate bilateral mastication pattern, in which the food is switched to the opposite side after several unilateral bites. This pattern was modeled in this work. The solutions obtained from the static mastication model contain the required magnitudes of total 26 muscle force vectors and 2 joint reactions for specific bite force on tooth. Muscle recruitment patterns of biting and non-biting sides for bite forces located on different teeth were computed as described above, and they are shown in Figs. 2.3 and 2.4, respectively.

Results show that digastric muscle is never activated in all simulations. This is reasonable as digastric muscle is considered to be responsible for jaw opening not closing/clenching. In general, it is seen that in order to increase the biting force, muscles that have been recruited initially increase activity level. Eventually, the load capacity of the muscle is saturated and other muscle groups are activated to induce even greater biting force. Although the muscle recruitment patterns are very distinct from one another, similar patterns are shown on both biting and non-biting sides when the bites take place in the anterior region, where incisors are close to symmetry plane.

In order to investigate whether the bone remodeling algorithm would predict a realistic bone density distribution, occlusal loads and mandibular flexure is applied to a bone with uniform density ($\rho = 0.5 \text{ g/cm}^3$) with the shape of the mandible obtained from the CT scan.
Figure 2.3 Muscle recruitment patterns and joint reaction (Jr) of the biting side required to generate the bite forces on a 1st incisor, b 2nd incisor, c canine, d 1st premolar, e 2nd premolar, f 1st molar, g 2nd molar, and h 3rd molar.
Figure 2.4 Muscle recruitment patterns and joint reaction (Jr) of the non-biting side required to generate the bite forces on (a) 1st incisor, (b) 2nd incisor, (c) canine, (d) 1st premolar, (e) 2nd premolar, (f) 1st molar, (g) 2nd molar, and (h) 3rd molar.
Changes of bone density at different time steps are presented in Fig. 2.5 showing that bone density is continuously redistributed until an equilibrium state is reached. Prominent remodeling activities are predicted within the first 360 days, and only slight densification can be noticed from 360 to 900 days. The change of total mandible mass over time is characterized as,

$$\text{convergence} = \frac{\int \Delta \rho \, dv}{\int \rho \, dv} \times 100\%$$  \hspace{1cm} (2.12)$$

The curves in Fig. 2.6 show the convergence history of simulated bone remodeling of mandible. The change is reduced to less than 1 % after 210 days and less than 0.5 %
Figure 2.6 History of convergence shows that the error is reduced to less than 1% after 210 days and less than 0.5% after 330 days.

after 330 days. In this study, the remodeling period is set to 900 days, which is enough to ensure the equilibrium.

Effects of parameters on bone remodeling are investigated by performing a parametric study on attractor stimulus \( \psi_{AS} \), and loading conditions including magnitude of bite force \( \bar{F}_b \), daily cycles of bite force \( n_{bf} \), magnitude of mandibular flexure \( d_{mf} \), and daily cycles of mandibular flexure \( n_{mf} \). Cross sections at the incisor \((x-y)\) plane, premolar \((y-z)\) plane and molar \((y-z)\) plane areas of mandible (Fig. 2.7a) are selected for the investigation of the bone density distribution at equilibrium. A normal case is determined so that parameters used can yield realistic density distribution by comparing the predicted results with CT scans (Table 2.3 and Figs. 2.7b-c). The base line parameters are indicated as the normal case in Table 2.3. Each parameter is modified -50% and +200% of the normal case (Table 2.3). Corresponding bone density results after 900 days of remodeling are shown in Fig. 2.8.
Figure 2.7  

**a** Locations of cross sections taken from the mandible.  
**b** CT scans taken from the same locations.  
**c** Cross-sectional density distribution after 900 days of bone remodeling for the normal (base line) case. From left to right: 1st incisor, 2nd premolar, 1st molar and 2nd molar.

Perturbing the attractor stimulus $\Psi_{AS}$ has more significant effects on the bone remodeling than the loading parameters do. Low attractor stimulus induces great bone densification, and only small regions appear to become cancellous bone. On the other hand, bone loss is observed at premolar and molar regions, and the outer cortical layer fails to form around the mandible.

Recalling that the bite force is the contact reaction on the tooth as a result of masticatory muscles acting on the jaw, the magnitude of bite force is related to the
Table 2.3 Parametric study on a attractor stimulus ($\Psi_{AS}$), b bite force ($\bar{F}_b$), c daily cycles of bite force ($n_{bf}$), d mandibular flexure ($d_{mf}$), and e daily cycles of mandibular flexure ($n_{mf}$).

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<td>$\Psi_{AS}$ (MPa/day)</td>
<td>$\bar{F}_b$ (Kg)</td>
<td>$n_{bf}$ (cycles/day)</td>
<td>$d_{mf}$ (mm)</td>
<td>$n_{mf}$ (cycles/day)</td>
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</table>

activation level of masticatory muscles as shown in Fig. 2.3 and Fig. 2.4. The study show that the thickness of cortical layer is reduced for low bite forces; and as expected increased cortical layer thickness and cancellous layer density is predicted for high levels of bite forces. Figure 2.8 also shows that the magnitude of bite forces has larger influence on bone remodeling than the daily bite cycles.

It is found that the daily cycles of bite force is a less influential parameter that changes density level of the cancellous bone especially at the incisor region of high case. Similar to parameters related to biting, the effect of magnitude of mandibular flexure is more noticeable than that of daily cycles of mandibular flexure. Moreover, it is seen that the anterior region is more sensitive to the mandibular flexure than posterior region by
Figure 2.8 Parametric study of cross-sectional bone density distribution after 900 days of bone remodeling. a Attractor stimulus ($\psi_{AS}$), b bite force ($\bar{F}_b$), c daily cycles of bite force ($n_{bf}$), d mandibular flexure ($d_{mf}$), e daily cycles of mandibular flexure ($n_{mf}$). From left to right: 1st incisor, 2nd premolar, 1st molar and 2nd molar.
observing the density levels at the incisor region. Either low magnitude or low cycles of mandibular flexure impedes the development of cortical bone at the chin region.

Complete edentulism and three partially edentulous scenarios including bilateral posterior, unilateral posterior, and bilateral anterior edentulism are simulated by removing all premolars and molars, unilateral premolars and molars, and all incisors, respectively. Partially edentulous cases are selected according to the classification system by Kennedy (1928). Edentulism induced bone remodeling is simulated for 120 months following 900 days of bone development of the normal case. Changes of total bone mass over time for various edentulous scenarios are shown in Fig. 2.9. Complete edentulism causes the most bone loss. The level bone loss is reduced for scenarios with lower number of missing teeth. The long term cross-sectional bone density distributions of various edentulism scenarios are illustrated in Fig. 2.10. For the completely edentulous case, significant cancellous bone loss is predicted in the molar region. Bone resorption occurs at certain spots of cortical bone including alveolar ridge. As a result, there is no longer a dense bone layer

**Figure 2.9** History of mandibular bone loss of various edentulous scenarios.
Figure 2.10 Cross-sectional bone density distribution of different edentulous scenarios after 120 months of bone remodeling. a Complete edentulism, b bilateral posterior edentulism, c unilateral posterior edentulism, d bilateral anterior edentulism. From left to right: 1st incisor, 2nd premolar, 1st molar and 2nd molar.

surrounding the mandible. Similar bone loss patterns, reduced bone density in the molar region and in the alveolar ridge, are also found, but they are less significant in the cases of bilateral and unilateral posterior edentulism. Bilateral anterior edentulism shows only minimal influence on the bone loss.

2.4 Discussion

In this study, Osborn and Baragar’s static mastication model (1985) was used to predict the muscle activity due to unilateral bite-forces that occur during alternate bilateral mastication. The predicted magnitude of muscle force is limited by its maximum load
delivery capacity (Prium et al. 1980). The maximum possible bite forces predicted in this study are compared with the data reported in literature in Fig. 2.11a. In the study of Osborn and Bargar (1985), four bite locations (1st incisor, 1st premolar, 1st molar and 3rd molar) were selected to simulate simultaneous bilateral mastication. The maximum possible bite force predicted is the summation of bite forces on two sides. Koolstra et al. (1988) also purposed an optimization model to study unilateral mastication. Although the variation between studies can be observed possibly due to the anatomical differences between specimens, generally, the maximum possible bite force is greater in the molar region than the incisor region. This prediction agrees with the common biting pattern for which hard food is usually crushed by the posterior teeth. Tortopidis et al. (1998) measured higher bite force when force transducer is placed more posteriorly, and suggested that these data are partly because of the lever effect of mandible and partly because of the reduced inhibitory effect of nociception, a sensory mechanism that detects potential damage to tissue. In addition, Koc et al. (2010) indicated lower unilateral bite forces as compared to bilateral bite forces. Similar results can be seen when present prediction is compared to bilateral bite by Osborn and Baragar (1985) in Fig. 2.11a, except for the bite location at 1st molar.

Maximum joint reaction ($\hat{F}_j$) is compared with data reported by Koolstra et al. (1988), in Figs. 11b-c. An average value of 50 kg was reported by Osborn and Baragar (1985). Both studies observed a similar trend that maximum joint force on the biting side decreases when the bite location moves toward posterior region, and the biting location is less influential to maximum joint force on the non-biting side. It is also predicted that maximum joint force is higher on the non-biting side than on the biting side, and same remark is reported in literature (van Eijden 2000; Hylander 1984; Hart et al. 1992).
Figure 2.11 Comparison between present results and results reported in literature (Koolstra et al. 1988; Osborn and Baragar 1985). a Maximum possible bite force \((F_b)\) b joint force \((F_j)\) on biting side and c joint force \((F_j)\) on non‐biting side due to bite force acting on different teeth, 1st incisor \((I_1)\), 2nd incisor \((I_2)\), canine \((C)\), 1st premolar \((PM_1)\), 2nd premolar \((PM_2)\), 1st molar \((M_1)\), 2nd molar \((M_2)\), and 3rd molar \((M_3)\).

Actual chewing is a more complex dynamic process. However, muscle forces computed show fair approximation of loading conditions and remodeling stimuli which result in realistic prediction of bone density distribution. The mandible is initially assumed
to have an unrealistically low, uniform density distribution of \( \rho = 0.5 \text{ g/cm}^3 \) with a mass of 40 g. After 900 days of bone adaptation to masticatory loads, a tubular structure develops and the mass of mandible increases to 76.15 g (Fig. 2.6), which is similar to the experimental data, 80.18 g for dry weight and 90.85 g for wet weight, reported by Zhang et al. (2002).

The fundamental idea of bone remodeling theory is that bone adapts to the change of external loading by altering bone morphology in order to restore the homeostasis. Attractor stimulus \((\psi_{\text{AS}})\) determined in Eq. (2.9) represents the homeostatic condition in terms of daily stresses. Beaupre et al. (1990) suggested that no single remodeling path can be applicable for all bones. For example, skull should have a very low attractor stimulus and little or no resorption phase so that it can maintain the bone mass while only experiencing minimal loads. In the study of bone remodeling of femur, Beaupre et al. (1990) estimated the attractor stimulus of 50 MPa/day for bone maintenance. Reina et al. (2007) indicated that mandible does not bear loads as high as the femur so that the attractor stimulus of mandibular bone should be a low value. This is in agreement with our prediction that lower attractor stimulus of 15 MPa/day is an appropriate value to simulate bone remodeling of mandible.

The parametric study on loading conditions shows that the morphology of mandible can be explained by biomechanical function. The predicted bone density distribution forms a curved beam with a dense outer shell structure, where the surface region of mandible turns into cortical bone layer and the inner section is filled with cancellous bone. Thicker and denser cortical layer is developed as an adaptive response to torsion and bending that are mainly experienced by the mandible during mastication. Increased loading magnitude
and cycles stimulate bone formation activity, and less significant bone formation is the result of lacking remodeling stimulation. During incision and mastication, mandibular flexure caused by lateral transverse bending, vertical bending in coronal plane and dorsoventral shear together is recognized as the main biomechanical function affecting the bone morphology of chin (Hylander 1984; Dobson and Trinkaus 2002). This study shows the development of denser bone at the chin region is affected by the mandibular flexure, which is assumed to represent the medial transverse bending during jaw opening. Experimental studies have been conducted to quantify the medial mandibular flexure by measuring the change of intraoral width between two teeth. The change of width between two 1st molars was reported to range between 0.02 and 0.8 mm (McDowell and Regli 1961; DeMarco and Paine 1974; Chen et al. 2000). The intraoral width change due to values of mandibular flexure we applied in this study is well within this limit.

Load transfer between implant and peri-implant bone is a crucial parameter that directs the bone failure and adaptive response of bone (Bozkaya et al. 2004; Chou et al. 2010; Faegh and Müftü 2010; Faegh et al. 2011). Studies have identified the significant effects of mandibular flexure on the development of high stress at the bone implant interface (Fischman 1990; Zarone et al. 2003; Nokar and Naini 2010). However, mandibular flexure is usually not taken into account in the literature (Crupi et al. 2004; Li et al. 2007; Lin C-L et al. 2010; Lin D et al. 2010) simulating dental implant induced bone remodeling due to the intricate muscle activation, complicated geometry of full jaw and the common understanding that dental implant is designed primarily to endure bite force. Neglecting these long range loads causes underestimation of the stress or strain in the peri-implant bone and the remodeling stimuli thereof. As a result, excessive bone loss due to
underloading might be incorrectly predicted. In studies of modeling overloading resorption (Crupi et al. 2004; Li et al. 2007; Lin C-L et al. 2010), prediction could be merely a small portion of more catastrophic bone loss.

In addition, the effects of edentulism and the resulting reduction of muscular loading on mandibular bone loss are investigated. As a result of teeth loss, direct contact between mandibular and maxillary teeth is lost. This results in either reduced number of bites leading to less frequent recruitment of the masticatory muscles, or redistribution of the biting patterns, leading to altered muscle activation scenarios. In either case, modification of masticatory function alters the biomechanical equilibrium established by the normal masticatory activities and steers the bone remodeling mechanism into bone resorption phase.

As stated previously, unilateral bites require harmonic cooperation of the masticatory muscles at biting and non-biting sides. Unilateral edentulism causes muscle loading deficit not only on the biting side but also on the non-biting side. This explains bone resorption occurs on both sides of mandible in the unilateral edentulous case. Another interesting prediction of this work is the development of a thin dense layer around some of the extraction sockets, which behave as defects in the whole structure with respect to the homeostatic equilibrium state established for the fully dentate mandible. Thus the remodeling stimulus experienced by the bone tissue results in bone formation. Cardaropoli et al. (2003), and Araujo and Lindhe (2008) reported remodeling activity around the extraction socket, where woven bone is replaced with lamellar bone in a process is called corticalization.
2.5 Conclusions

Mandibular loading due to mastication, speech and involuntary open-and close activities are modeled by using a static model of the muscle forces and flexure of the mandible, respectively. A bone remodeling theory that was originally developed to study the density distribution of proximal femur was used to study the morphology of mandible in response to functional loads. It was shown that mandibular bone morphology is determined by function. The overall mandibular bone density distribution results in a tubular structure, which is known to provide the bone increased strength to resist bending and torsion during mastication. It was also shown that the development of dense bone at the chin region is affected by the mandibular flexure. The model also verified that reduced loading due to various types of edentulism results in clinically observed bone density change patterns. This work indicates the applicability of long bone remodeling theory to the mandible.
References


Bozkaya, D., Müftü, S., Müftü, A., 2004. Evaluation of load transfer characteristics of five different implants in compact bone at different load levels by finite element analysis, Journal of Prosthetic Dentistry 92, 523-530.


Later Stage of Osseointegration: Peri-Implant Bone Remodeling

3.1 Introduction

Use of dental implants has become an effective treatment modality to restore partial and/or complete edentulism in recent decades (Romeo et al. 2004). Traditional delayed placement protocol requires implant to remain submerged for a healing period which may take up to several months before the installation of abutment and prosthesis for functional loading (Brånemark et al. 1977). Advances in implant technology and continuous clinical research have evolved new treatment concepts, such as early and immediate functional loading, which reduce the treatment time and increase patients’ comfort during healing (Romanos 2005). In case the implant is placed in an extraction sockets, a gap may occur due to the incongruence of dental implant with the bony socket walls. Botticelli et al. (2004; 2008) demonstrated that such marginal defect can be resolved by new bone formation during healing. Depending on the extent of hard and soft tissue changes following tooth loss, various site preparation techniques may be utilized to enhance mechanical stability of an implant and esthetics. The use of bone graft to cover the peri-implant gap is often necessary (Misch 1999).
It is shown that long term implant stability is related to the quality of surrounding bone as a result of peri-implant bone remodeling (Schenk and Buser 1988). The remodeling process is carried out by basic multicellular units through the interplay between osteoclastic and osteoblastic cell functions that lead to bone resorption or bone gain. The hypothesis of bone remodeling induced by mechanical stimulation, which was first suggested by Wolff (1986), has been generally accepted and became the basis of various mathematical models for predicting bone morphology and density. Bone remodeling theories distinguish between external remodeling, where bone is added or removed at the periosteal and endosteal surfaces resulting in changes of shape, and internal remodeling characterized by changes in apparent bone density (Cowin and Van Buskirk 1978; 1979). Strain, stress and strain energy density have been suggested as the remodeling stimuli (Cowin and Hegedus 1976; Carter et al. 1987; Frost 1987; Huiskes et al. 1987). Two well known remodeling theories introduced by Carter et al. (1987) and Huiskes et al. (1987) have been incorporated into finite element analysis to mathematically model the density distribution of proximal femur. These remodeling theories have also been used to study bone remodeling around orthopedic implants (Huiskes et al. 1987), and the bone structure of other bone regions, such as acetabulum, proximal tibia, metacarpal and calcaneus (Carter and Beaupré 2001).

Numerous clinical and histologic studies have been carried out to understand osseointegration in order to improve dental implant designs, surfaces and surgical protocols. Developing mathematical models of dental bone remodeling can help uncover biomechanical factors controlling short and long term survivability of implant treatments. Recently, Lin et al. (2009) suggested that long bone remodeling theories can be applicable
to study the bone remodeling in dental implant treatments. Renia et al. (2007) and Lin D. et al. (2010) simulated the mandibular bone remodeling with and without a dental implant, respectively, and both showed significant consistency with clinical evaluations. Occlusal overload is attributed to be a major cause of marginal bone loss, which was demonstrated in literature by including the condition of overload resorption in the remodeling theories (Crupi et al. 2004; Li et al. 2007; Lin C.-L. et al. 2010). Lian et al. (2010) and Chou et al. (2008) showed long term peri-implant bone density pattern similar to the observation of animal study by Watzak et al. (2005). A common thread in these studies is the assumption of homeostatic remodeling stimulus having a constant value, independent of location. This implies that bone remodels toward a homogenous biomechanical field, despite the fact that the biological environment (i.e. the cells and the nutrients) among bone sites is inhomogeneous.

In this study, we hypothesize that bone remodeling is regulated by the site specific homeostatic remodeling (attractor) stimulus, which must be similar to that induced by a natural tooth in its supporting structures. The effects of various biomechanical factors including implant dimensions, implant designs, magnitude of occlusal load, and properties of osteogenic bone grafts on peri-implant bone remodeling are investigated.

3.2 Materials and methods

3.2.1 Bone remodeling algorithm

Bone remodeling depends on mechanotransduction where the effect of external loading induces biochemical activity in the basic multicellular units, which eventually result in the bone density adjustments. Various remodeling stimuli have been suggested to initiate this
response. Huiskes et al. (1987) proposed the remodeling stimulus $S$ to be strain energy per unit mass,

$$S(\vec{r}, t) = \frac{u(\vec{r}, t)}{\rho(\vec{r}, t)}$$  \hspace{1cm} (3.1)$$

where $u$ is the strain energy density and $\rho$ is the apparent bone density, $t$ is time and $\vec{r}$ is the position vector in the bone.

Bone remodeling rate is expressed in terms of bone density change, and it is a non-linear function of the remodeling stimulus (Huiskes et al. 1987),

$$\frac{d\rho}{dt} = \begin{cases} 
A_f \left[ S - (1+s)K \right]^2 & S \geq K(1+s) \\
0 & K(1-s) < S < K(1+s) \\
A_r \left[ S - (1-s)K \right]^3 & S \leq K(1-s)
\end{cases}$$  \hspace{1cm} (3.2)$$

where $K(\vec{r})$ is the attractor stimulus representing the homeostatic loading conditions of the bone, $A_f$ and $A_r$ are formation and resorption coefficients and $s$ is a coefficient that represents the width of the dead zone. The thresholds of bone formation and bone resorption are $K(1+s)$ and $K(1-s)$, respectively. Remodeling stimuli that fall within the dead zone do not evoke bone remodeling. However, if the bone is subjected to a mechanical stimulus that is larger than the threshold value of $K(1+s)$, bone density and elastic modulus increase over time. Conversely, if the mechanical stimulus is lower than the threshold value of $K(1-s)$, the bone density and elastic modulus are reduced. Clinical studies show that bone loss takes place at a faster rate than bone formation. Thus the exponents 2 and 3 are used in Eq. (3.2) for formation and resorption, respectively (Huiskes et al. 1987). Carter and
Hayes (1977) show that the elastic modulus of bone is a function of the bone apparent density as follows,

$$E = C \rho^3$$  \hspace{1cm} (3.3)

where $C = 3.79$. The unit of the elastic modulus $E$ is GPa, if $\rho$ is in g/cm$^3$. Equation (3.2) is solved iteratively by the forward Euler time integration as follows,

$$
\rho_m^j = \begin{cases} 
\rho_m^{j-1} + A_r \Delta t \left[ S_m^{j-1} - K (1 + s) \right]^2 & S_m^{j-1} \geq K (1 + s) \\
0 & K (1 - s) < S_m^{j-1} < K (1 + s) \\
\rho_m^{j-1} + A_f \Delta t \left[ S_m^{j-1} - K (1 - s) \right]^3 & S_m^{j-1} \leq K (1 - s)
\end{cases}
$$  \hspace{1cm} (3.4)

where $j$ indicates the time iteration level and $m$ indicates the spatial location in the finite element representation of the discretized bone. The remodeling constants, $A_r$ and $A_f$, can be combined with time step, $\Delta t$, as a single time integration parameter, $A \Delta t$, the value of which was chosen as $1 \times 10^{-11}$ after extensive numerical tests to ensure convergence. The width of dead zone, $s$, was set to be 0.75 according to literature (Huiskes et al. 1992).

In order to determine the site specific attractor stimuli, $K(\rho)$, the strain energy per unit mass of bone induced by the occlusal force acting on a natural tooth was first computed. The effect of the periodontal ligament was neglected in this study but should be considered in future studies. The interstitial space due to the incongruence of dental implant with extraction socket was assumed to be occupied by the bone graft in the computational model. The implant was assumed to be in full contact with the bone graft. A constant value $K_g$ was assigned to represent the attractor stimulus of the bone graft. This parameter is treated as the potential of bone graft to induce bone remodeling.
Figure 3.1 Flow chart of the bone adaptation algorithm.

The remodeling algorithm used in this work is presented schematically in Fig. 3.1. Bone remodeling is driven by the difference between the local remodeling stimulus $S$ due to the bone-implant-prosthesis complex and the site specific homeostatic stimulus $K(\bar{r})$. Bone density around the dental implant continuously adapts to equalize the remodeling stimuli to the homeostatic stimuli.

3.2.2 Finite element model

A planar X-ray computed tomography (CT) image of the mandibular premolar region that is representative of the buccal-lingual plane was digitized by using the medical imaging software, Mimics version 12 (Materialise, Leuven, Belgium), and then was extruded to a thickness of 80 mm in the mesial-distal direction, to represent a 3D segment of mandible (Fig. 3.2). A three dimensional (3D) model of the 2nd premolar was created according to the same set of CT scan images. The morphology of the extraction socket was determined by removing the premolar from the model. This leaves a void in the bone that conforms to the root form of the 2nd premolar as shown in Fig. 3.2. In addition, five implant designs including 3 long
Figure 3.2 Schematic finite element models of bone-tooth and bone-implant-prosthesis complexes. Occlusal load ($F_o$) is applied at the angle of $\theta = 11$ degrees, measured from the implant axis.

Figure 3.3 Various implant designs used in this analysis. The units are given in millimeters. (about $3.5 \times 11$mm) implants and 2 short (about $5 \times 5$mm) implants were modeled based on commercially available designs (Fig. 3.3).
The remodeling algorithm presented in Fig. 3.1 was implemented into the commercial available finite element analysis software package, ANSYS version 11 (Canonsburg, PA), by using its script language. Bone implant and bone tooth complexes were imported into this modeling environment. Ten-node tetrahedral solid elements were used to discretize the bone, the tooth and the implants. For the sake of computational efficiency, symmetry boundary condition was applied to the mesial side of buccal-lingual plane. The modeled mandibular segment was constrained in all degrees of freedom at the distal side of buccal-lingual plane. The density of the finite element mesh was increased near the bone-implant interface, where significant remodeling activities are expected. Approximately 95,122 elements and 67,307 nodes were used to mesh the long implant system, and 89,475 elements and 63,583 nodes were assigned to the short implant system. These numbers were determined based on the numerical experiments and authors’ past studies (Bozkaya et al. 2004; Chou et al. 2010; Faegh and Müftü 2010). All materials were assumed to be linear-elastic, homogenous and isotropic. Material properties of the implant, the cortical bone, the cancellous bone, the tooth and the prosthesis are obtained from literature (Van Oosterwyck et al. 1998; Misch and Bidez 1999; Bozkaya et al. 2004; Anusavice 2003) as listed in Table 3.1.

Autologous bone harvested from the surgical patient is considered the ideal graft material due to its inherent osteogenic benefits (Hoexter 2002; Marx 2007). Such graft directly forms bone as a result of transplanted bone cells (Misch 1999). To study the effect of graft properties on bone remodeling, the material property of bone graft was varied in the range between cancellous bone to cortical bone.
Table 3.1 Material properties used in the analysis

<table>
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<th>Young's modulus (GPa)</th>
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</tr>
<tr>
<td>Cortical bone</td>
<td>13.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Cancellous bone</td>
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<tr>
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</tr>
<tr>
<td>Bone graft</td>
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</tr>
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</table>

Magnitude of occlusal load generated during mastication varies among individuals and it depends on chewing scheme, food texture, jaw movement and alignment of antagonistic teeth (Rodriguez et al. 1994; Mornegurg and Proschel 2003). Axial load acting on the posterior teeth and on the implant supported prosthesis was reported in the range of 390 to 880 N and 42 to 412 N, respectively (Stanford and Brand 1999). The lateral component of the occlusal load was found to be less than 100 N (Brunski 1997). Considering the physiological range of force magnitude reported above and the existence of both axial and lateral loads during occlusion, loading conditions in this study were simulated by three load levels, 100, 300 and 500 N, applied on the tooth or crown at the 11 degrees from the implant axis.

3.3 Results

The iterative change of bone modulus, induced by bone remodeling around a short implant, is presented in Fig. 3.4. The color contours show that most of the predicted remodeling process was completed by the first 50 iterations and no significant remodeling activity took
Figure 3.4 Iterative changes of elastic modulus distribution around a dental implant. No significant remodeling activities are predicted after 50 iterations. History of average bone stimulus, $S_{\text{ave}}$, shows acceptable convergence has been achieved.

place between 50th and 100th iterations. The average bone stimulus, $S_{\text{ave}}$, as a function of iteration number (Fig. 3.4) is defined as,

$$S_{\text{ave}} = \frac{1}{N_{\text{total}}} \sum_{i=1}^{N_{\text{total}}} S_i$$  \hspace{1cm} (3.5)

where $N_{\text{total}}$ is the total number of bone elements, and $S_i$ is the remodeling stimulus of the $i$th bone element. The history of average bone stimulus showed remodeling equilibrium was represented well by 100 iterations. Therefore, in this study, the total number of iterations was set to 100.

Distribution of the equilibrium remodeling stimulus for a natural tooth is presented in Fig. 3.5a. It is clear that the effect of the biting force on remodeling stimulus is high in the close proximity of the tooth. This equilibrium stimulus $S(\vec{r})$ is then used as a location dependent attractor stimulus $K(\vec{r})$ for the rest of the simulations that involve implants. Remodeling stimuli of the bone is calculated when a short implant is placed in the
Figure 3.5 a Attractor stimuli distribution of a bone tooth model. b Attractor stimulus of bone graft is assigned to the grey region. c Initial remodeling stimuli distribution of a bone implant prosthesis model. d Remodeling stimuli distribution of a bone implant prosthesis model at equilibrium state.

Due to the aforementioned mismatch between the implant size and the socket diameter and shape, bone grafting is necessary as shown in the grey volume (Fig. 3.5b). Bone eventually replaces the graft, both in vivo and in the computer implementation. The computational bone remodeling algorithm requires assignment of elastic properties, $E_g$ and, $\nu_g$, and attractor stimulus, $K_g$, to the graft region. The effects of the initial values of these variables are presented later. Nevertheless, for this short implant, the stimulus $S(\vec{r})$ distribution, in the first step and at remodeling equilibrium (Fig. 5c-d) are very similar to that of the natural tooth.

The bone graft around the implant was initially assumed to contain a layer of cortical bone in contact with the implant crest and the rest of the implant body was surrounded by cancellous bone (Fig. 3.6). The attractor stimulus of the graft was chosen as
Figure 3.6 Initial elastic modulus distribution of bone shows cancellous region surrounded by a layer of cortical bone. Non-uniform elastic modulus distributions of bone are predicted at equilibrium state under various conditions.
constant, $K_g = 0.5 \text{ J/kg}$. For the rest of the bone, the attractor stimulus was the site dependent value $K(\tilde{r})$ computed for the natural tooth under the oblique bite force, as described above. Three load levels, 100, 300, and 500 N, were evaluated for the effect of occlusion on bone remodeling. For each load, the $K(\tilde{r})$ value was computed separately using the natural tooth model. The predicted bone elastic modulus ($E$) distributions at the equilibrium state (100 iterations) due to various load magnitudes are presented in Fig. 3.6.

For the case in which the implant is subject to 100 N occlusal load, elastic modulus distribution in the sub-cortical region remains intact for both of the modeled short implants, except near the implant body. It is seen that the bone density increases around the threads of the short implants, and connects the implants to the cortical region, resulting in increased stability. However, stress shielding causes reduction in bone density within the implant threads. The thread design also makes a difference as it can be seen in the comparison of short-1 and short-2 implants. All three long implants stimulate the bone in their apex region and cause a substantial volume of bone to attain cortical bone properties. In contrast the crestal and sub-crestal region of the bone for the long implants experience bone density reduction and bone loss. The extent of this reduction and loss also depends on the implant contour and the thread shape as can be observed for all long implants.

Several characteristics were observed when the occlusal load was increased. Generally, the extent of bone loss in the cortical region increased, more dense bone developed at both the implant crest and apex. In particular, region of total bone loss (grey region) grew in the cases of long-1 and long-3 implants, but the long-2 and short implants did not induce the same phenomenon. Short implants did not alter the biomechanical
Figure 3.7 Effect of occlusal load $F_o$ on the percent interfacial bone loss (IBL) for the five implant designs as $K_g = 0.5$ J/kg.

The effect of external load is represented in terms of the relative amount of interfacial bone loss (IBL) with respect to a fully osseointegrated scenario for each implant type (Fig. 3.7). The IBL indicates the relative surface area of the implant where the bone density was reduced to zero due to remodeling. This figure shows a distinct difference between the short and the long implant groups, where the short implants are better in preventing IBL at higher loads, and the long implants have a more consistent IBL response at different load levels.

The effects of the initial value of the attractor stimulus $K_g$ of the graft region on the outcome of bone remodeling were also investigated. It was observed that the remodeling stimulus of the bone around a natural tooth varies between 0.1 to 0.5 J/kg (Fig. 3.4a). Based
Figure 3.8  

a Effect of attractor stimulus of graft $K_g$ as $F_o = 100$ N, b effect of attractor stimulus of graft $K_g$ as $F_o = 300$ N, c effect of attractor stimulus of graft $K_g$ as $F_o = 500$ N, d effect of elastic modulus of graft, $E_{gr}$, on the percent interfacial bone loss (IBL) for the five implant designs.

On this observation, three different $K_g$ values, 0.1, 0.2, and 0.5 J/kg, were assigned to the graft region (Fig. 3.5b). The results at remodeling equilibrium are presented in terms of the IBL as a function of $K_g$ for occlusal loads of $F_o = 100$, 300 and 500 N (Fig. 8a-c). These three figures show that, in general, high IBL at remodeling equilibrium correlates with high
initial $K_g$ values, and that less IBL is predicted with increasing levels of loads on the implant. The implant length also adds to this behavior in a non-linear manner: the short implants appear to lose considerably lower amounts of interfacial bone at the high levels of loading, whereas the long implants appear to be relatively less sensitive to the load levels in terms of their IBL amounts.

In order to evaluate the effects of the elastic modulus of the bone graft on remodeling, three different elastic modulus values $E_g = 2, 7.5$ and $13$ GPa, were considered, while the attractor stimulus of the graft and the occlusal load were chosen as $K_g = 0.5$ J/kg and $F_o = 100$ N, respectively. The results are presented in terms of IBL (Fig. 3.8d), where it is seen that the IBL increases if the graft stiffness is high.

### 3.4 Discussion

Osseointegration begins with the rapid bone healing, and the initial bony structure is maintained by bone remodeling and bone adaptation. Bone healing is a process of skeletal tissue regeneration that is triggered by trauma such as fracture or surgical osteotomy that causes physical disruption of the mineralized tissue matrix, death of cells and interruption of blood supply (Carter and Beaupré 2001). During bone healing, skeletal tissue is originated by the proliferation and differentiation of pluripotential mesenchymal stem cells. The differentiation pathway that results in final phenotype is at least partially influenced by the mechanical loads (van der Meulen and Prendergast 2000; Carter and Beaupré 2001). While mathematical models of tissue differentiation have been developed (Lacroix and Prendergast 2002), this phase of bone healing is not modeled here. The work presented here considers the maintenance phase of bone remodeling, which is mathematically represented by the remodeling theory of Huskies et al. (1987). This and
other bone remodeling theories have been used to predict bone density change around dental implant systems, and the remodeling of mandible in response to other prosthodontics treatments (Crupi et al. 2004; Li et al. 2007; Reina et al. 2007; Chou et al. 2008; Lin et al. 2009; Lian et al. 2010; Lin D. et al. 2010; Lin C.-L. 2010). Field et al. (2010) showed correlation between the observed (X-ray) and computed the change of mandibular bone density, in a combined, longitudinal clinical and numerical study of mandibular bone remodeling induced by a fixed partial denture. Lin D. et al. (2010) showed similarities between computed and observed bone density changes for remodeling around dental implant systems.

Bone remodels around osseointegrated implants. In a histomorphometric study in dogs, Coelho et al. (2009) showed high levels of osteoactivity near the implant surface. Peri-implant bone remodeling is triggered by the geometric and material differences between a natural tooth and a dental implant. Bone density gradually adapts to the new conditions by minimizing the difference between the current and the reference remodeling stimuli. It was assumed, in this work, that the homeostatic reference stimulus is site specific, and that its value should be similar to that caused by the natural tooth. This hypothesis has been used to simulate the stress shielding and bone resorption around hip prostheses (Huiskes et al. 1992; Weinans et al. 1993). The present work shows that for short implants, remodeling is localized around the implant, and decays with increasing distance away from implant surface. Short implants are predicted to keep the bone density distribution closer to that of the natural tooth.

This work also showed that increasing the load on the implant results in decreased levels of interfacial bone loss, and this is accompanied with increase of bone density near
the implants’ apex. This effect has a strong dependence on implant length and type, and is the result of a few factors working together. Most important of these is the fact that bone remodeling redistributes the bone density to provide better anchoring in order to counteract increased level of loads, resulting in lower IBL.

Bone densification was predicted around the apical region of implants. The extent of bone remodeling around a short implant considerably differed from a long implant. For the long implants modeled in this work, the load is directly transferred to the deeper regions of the cancellous bone; this causes relatively high remodeling stimulus $S$ to develop, resulting in increasing bone density near the implant apex. On the other hand, for the short implants, the difference between the homeostatic stimulus $K$ and the remodeling stimulus $S$ is confined to a more localized region near the apex of the implant, resulting in a more moderate increase in bone density. These effects are clearly the result of implant dimensions, and morphology. Current predictions, especially for the short implants, showed a certain degree of resemblance to observations reported in histologic studies. Watzak et al. (2005) investigated effects of designs and surface modifications of dental implants on peri-implant bone, and showed a layer of peri-implant cortical bone with dense bone regions oriented toward the pre-existing bone. Schenk and Buser (1988) suggested that thread tips promote bone growth due to the role of implant treads for load transfer from implant to surrounding bone. Although the present work predicts several similarities, differences with respect to clinical observations exist due to the biological aspects.

Bone grafting is an acceptable and necessary technique for socket preservation, sinus and ridge augmentation (McAllister and Haghighat 2007). Biomechanical studies
showed initial implant stability is improved when the implant is secured by better quantity and quality of graft materials (Tepper et al. 2002; Fanuscu et al. 2004; Inglam et al. 2010). On the other hand, long term implant stability should depend on overall bone remodeling, and remodeling within the bone graft (Gosain et al. 1999; Xu et al. 2005). The result presented in this work show that peri-implant bone remodeling is sensitive to the initial quality of graft material. Lowering the elastic modulus of the grafted region to the level of cancellous bone (2 GPa) resulted in relatively less resorption, whereas increasing it to the level of cortical bone (13.7 GPa) induced relatively more resorption. This result is attributed to the nature of bone remodeling, where a stiffer graft material causes lower level of strain that results in a lower level of remodeling stimulus $S$, and thus the bone is shielded into the resorption region of Eq. (3.2). This work thus shows that relatively low graft stiffness is in favor of interfacial bone to experience adequate remodeling stimulus. This finding is in agreement with Inglam et al. (2010) who investigated effect of graft stiffness on load sharing, and suggested that bone graft with stiffness of 2 GPa demonstrates the optimal load sharing characteristics with respect to bone graft with stiffness of 11 GPa.

In addition to mechanical properties of graft material, the attractor stimulus assigned, $K_g$, to the graft region, which is assumed to represent the osteogenic potential, was also seen to be influential in peri-implant bone remodeling. Bone graft in this model could only represent osteogenic graft materials as the attractor stimulus is related to a mechanical signal that can be sensed by osteoblasts. This work showed that lower values of $K_g$ lead to a higher level of bone formation and thus lower interfacial bone loss.
In general, the outcome of bone grafting is difficult to predict due to a variety of factors involved in the mechanism of healing, including absence of infection, soft tissue closure, defect morphology, space maintenance, healing time, graft immobilization, supply of blood, growth factors, collagen, and calcium phosphate (Misch 1999). It should also be mentioned that by assuming full contact between the implant surface and the graft, the problem is simplified with respect to clinical scenarios. Amount of initial contact between the implant and the graft material is another variable that can be investigated and that could potentially influence the outcome of osseointegration. Apparently, a non-site specific constant, $K_g$, similar to attractor stimulus defined in aforementioned literature (Crupi et al. 2004; Li et al. 2007; Reina et al. 2007; Chou et al. 2008; Lin et al. 2009; Lian et al. 2010; Lin D. et al. 2010; Lin C.-L. 2010) is insufficient and needs to be further explored. Nevertheless, the choice of $K_g$ based on the observation of overall stimuli around a natural tooth, used in this preliminary work, seems to be a fair approximation. The computational predictions presented here are also limited by the other simplifications made in this study. In particular, the application of occlusal load in FE model compared to the regular mastication was greatly simplified. To determine the loading conditions of the jaw during mastication involves the activity level of each muscle and constraints of temporal-mandibular joint.

3.5 Conclusions

The computational bone remodeling work presented shows distinct differences between the bone maintenance characteristics of short and long implants. Short implants are predicted to conserve the mechanotransductive signaling environment of the natural tooth, whereas the long implants are not. It is also found that the short implants are better in preventing the interfacial bone loss at the high loads and the long implants have a
consistent level of bone loss at different load levels. In this work the effects of bone graft properties on long term bone maintenance were also studied. It is predicted that, in the long term bone grafts with relatively low elastic modulus in combination with high loads lead to lower levels of interfacial bone loss.
References


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Early Stage of Osseointegration: Peri-Implant Bone Healing

4.1 Introduction

The standard protocol of a two-stage dental implant surgery introduced by Brånemark (1983) requires submerged dental implants to be covered by soft tissue for a healing time of three to six months. The second stage surgery is necessary to uncover the dental implants for the placement of prostheses. It would be of great interest for the patients and surgeons if a new protocol that considerably shortens the treatment duration and even reduces the number of appointments can be developed. This idea underlies the emergence of immediate loading protocols in which restoration is performed at the time of implant surgery (Misch et al. 2004). Clinical studies have documented satisfactory survival rate of immediately loaded implants (Chiapasco et al. 1997; Testori et al. 2004; Donati et al. 2008). However, it is also indicated that the failure rate is relatively high when the conditions of recipient site are compromised (Lekholm 2003); when the implant is placed in the high loading region such as molar site (Rocci et al. 2003; Romanos and Nentwig 2006); and when a single implant is used instead of splinted implants (Malo et al. 2003).
A successful dental implant treatment relies on maintaining the stability of the implant within the host bone site. This condition is achieved through osseointegration, which can be defined as a direct connection established between bone and dental implant (Branemark 1983). The trauma to the bone caused by implant placement triggers a process known as bone healing (Carter and Beaupré 2001, Davies 2003). Tissue regeneration involves a reparative phase, where mesenchymal stem cells differentiate into different progenitor cells, and result in the development of different skeletal tissues such as fibrous tissue, cartilage tissue, and bone tissue (Prendergast and van der Meulen 2001). During the peri-implant bone healing, osteoprogenitor cells derived from bone marrow and endosteal bone surfaces migrate to the healing callus. They proliferate and differentiate into osteoblasts, which then begin to lay down new bone on the existing bone surface or on the implant surface (Davies 2003). Random and unorganized woven bone forms as a scaffold to bridge the gap at a relatively rapid rate (Schenk and Buser 1998). The loading condition should be well controlled throughout the process for successful bone formation. Otherwise, soft tissue develops and provides minimal mechanical stability. This can lead to implant loosening, which is recognized as a common cause of implant failure (Huiskes et al. 1997).

The initially developed bony structure is later replaced by more organized lamellar bone through bone remodeling to achieve long term implant stability (Schenk and Buser 1998). Unlike the healing process, bone remodeling is a slow and continuous cellular process involving interplay between bone removal and bone growth by osteoclasts and osteoblasts, respectively. During this phase, the biomechanical environment that provides moderate mechanical stimulation is believed to be beneficial to bone growth (Frost 1987).
While the biological process at the bone implant interface was revealed by extensive experimental studies, numerical simulation can further provide interpretation and explanation of the underlying mechanisms. Most of the previous work focused on investigating the effects of biomechanical factors on the mechanical state around dental implant including implant and abutment designs, bone morphology and loading conditions (Bozkaya et al. 2004; Chou et al. 2010; Faegh and Müftü 2010; Perez et al. 2012). Others evaluated long term peri-implant bone evolution in response to mechanical loading by incorporating a bone remodeling algorithm into computer simulations (Crupi et al. 2004; Li et al. 2007; Chou et al. 2008; 2012; Lin et al. 2009). Only few studies made contributions to the modeling of healing around dental implants (Ambard and Swider 2006; Amor et al. 2009; Moreo et al. 2009; Vanegas-Acosta et al. 2011). These studies evaluated peri-implant healing from the point of view that tissue regeneration is a complex biological process involving a cascade of coordinated cellular events and the interaction of biochemical compounds (Bailon-Plaza and van der Meulen 2001) without considering the influence of functional loads on bone healing. In order to investigate the effect of immediate loading on the peri-implant bone healing, the mechano-regulatory tissue differentiation model proposed by Huiskes et al. (1997) and Prendergast et al. (1997) is adopted in this study.

4.2 Materials and methods

4.2.1 Bone healing algorithm

Biphysical stimuli with both solid and fluid loading components have been proposed as the regulators of the tissue differentiation pathway (Prendergast et al. 1997). Huiskes et al. (1997) defined a healing stimulus $S$ that governs tissue differentiation by taking into account the distortional strain ($\gamma$) and the interstitial flow velocity ($v$) as follows,
where \( a = 0.0375 \) and \( b = 3 \text{ µm/s} \) are empirically determined constants. Depending on the value of healing stimulus \( (S) \), cells inside the callus are able to differentiate into different phenotypes. High stimulus \( (S > 3) \) is associated with the development of fibrous tissue. Intermediate stimulus \( (1 < S < 3) \) is in favor of chondrocyte differentiation, which forms fibrous cartilagenous tissue. Low stimulus \( (S < 1) \) promotes the osteoblast differentiation and results in woven bone. At very low stimulus \( (S < 0.2667) \), mature (cancellous) bone instead of immature (woven) bone is generated.

Mechanisms with which the mesenchymal stem cells spread out within the healing callus involve migration and proliferation. These mechanisms are complex and unclear. Lacroix and Prendergast (2002) assumed random and nondirectional movement of cells resulting in the net effect that cells advance into regions with lower cell concentration. Such a description of cell distribution can be modeled by the diffusion equation as follows,

\[
D \nabla^2 n_{\text{cells}} = \frac{dn_{\text{cells}}}{dt}
\]

where \( n_{\text{cells}} \) is the local cell concentration and \( D \) is a diffusion constant. For numerical implementation \( D \) is determined so that the entire healing callus reaches the maximal cell concentration after a preset healing time (Lacroix and Prendergast 2002).

As the production of new tissue depends on the temporal evolution of mesenchymal cell concentration, at a given time the healing compartment will simultaneously have callus
### Table 4.1 Material properties used in the study (Misch and Bidez 1999; Geris et al. 2003)

<table>
<thead>
<tr>
<th></th>
<th>Young’s modulus (MPa)</th>
<th>Poisson’s ratio</th>
<th>Permeability (m⁴/Ns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>113 × 10³</td>
<td>0.3</td>
<td>NA</td>
</tr>
<tr>
<td>Callus tissue</td>
<td>0.2</td>
<td>0.17</td>
<td>10⁻¹⁴</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>2</td>
<td>0.17</td>
<td>10⁻¹⁴</td>
</tr>
<tr>
<td>Cartilage tissue</td>
<td>10</td>
<td>0.17</td>
<td>5 × 10⁻¹⁵</td>
</tr>
<tr>
<td>Immature bone</td>
<td>1000</td>
<td>0.3</td>
<td>10⁻¹³</td>
</tr>
<tr>
<td>Cancellous bone</td>
<td>6000</td>
<td>0.3</td>
<td>3.7 × 10⁻¹³</td>
</tr>
<tr>
<td>Cortical bone</td>
<td>20 × 10³</td>
<td>0.3</td>
<td>10⁻¹⁷</td>
</tr>
</tbody>
</table>

and differentiated tissue. Therefore, a rule of mixture is used to account for the local material property in this transient state as follows,

\[
E_{\text{new}} = \frac{n_{\text{cells}}}{n_{\text{max}}} E_{\text{tissue}} + \frac{n_{\text{max}} - n_{\text{cells}}}{n_{\text{max}}} E_{\text{callus}}
\]  

(4.3)

where \(E_{\text{new}}\) is the local elastic modulus of the new tissue, \(n_{\text{cells}}\) is the local cell concentration determined by Eq. (4.2), \(n_{\text{max}}\) is the maximal cell concentration, \(E_{\text{tissue}}\) is the elastic modulus determined by the mechano-regulatory models described in Eq. (4.1), \(E_{\text{callus}}\) is the elastic modulus of callus tissue. The local material properties including the Young’s modulus, Poisson’s ratio and permeability are determined by the rule of mixture. Table 4.1 lists the material properties used in this study. In addition, a gradual change of material properties toward the phenotype is assumed in the process. To avoid numerical instability caused by too much change between consecutive iterations, Lacroix and Prendergast (2000) suggested a numerical smoothening scheme that takes into account material properties predicted from previous \(N\) iterations as follows,
where $N = 5$ is used in this study. One iteration $i$ is defined as one day (Laxroix and Prendergast 2000).

4.2.2 Finite element model

A 2D axisymmetric configuration that consists of a dental implant, the surrounding cortical and cancellous bone regions, and the osteotomy gap is modeled by finite element analysis (Fig. 4.1). Osteotomy gap is assumed to be filled with callus tissue. The dental implant is modeled with 4-node quadrilateral structural elements. All tissues are modeled with 4-node coupled pore-pressure mechanical solid elements with radial $r$ and axial $z$ deformations and one pore-pressure degree of freedom at each node. Intersection of the lower boundary of the bone and the symmetry axis is constrained in both directions. Otherwise the lower boundary is constrained in the $z$ direction. The liquid pressure at the top boundary of the healing callus and the cortical bone is set to be ambient ($p = 0$). Cell diffusion takes place in the healing callus, and the cells originate from the surrounding bone tissue. These boundary conditions are illustrated in Fig. 4.1. As load is applied on top of the implant, the computed biphysical stimuli determine the tissue phenotypes in the healing callus. The material properties of healing tissue are updated iteratively according to the tissue phenotype and cell population during the healing period of 28 days. Unless otherwise specified, diffusion constant $D$ is determined by assuming that progenitor cells fully distribute throughout the healing callus within 14 days; the implant is subjected to 10 µm displacement; and the osteotomy gap size is set to be 0.2 mm. The process is simulated
Figure 4.1 A 2D axisymmetric finite element model consists of a screw thread dental implant, the cortical bone region, the cancellous bone region, and the osteotomy gap.

Figure 4.2 Flow chart of peri-implant bone healing simulation.
by using the script developed in APDL in FE software ANSYS (Canonsburg, PA). The flow chart of the simulation is illustrated in Fig. 4.2. Parametric studies are performed to investigate the effects of cell migration rate, magnitude of applied displacement and the size of osteotomy gap on bone healing. In addition to screw thread design, a threadless implant and three threaded designs are considered.

4.3 Results

Due to the nonlinear nature of the poroelasticity simulation the computational effort involved in the solution is extensive. A mesh convergence study is performed in order to find a balance between solution convergence and computational time. Element sizes of 0.03, 0.035, 0.04 and 0.05 mm are selected to mesh the healing callus. Bone implant contact (BIC), which is a common measure of the osseointegration in histomorphometric analysis by quantifying the direct bone contact with an implant is evaluated (Gottlander and Albrektsson 1996). Here, bone volume fraction (BV) of the healing callus is also computed.

![Figure 4.3](image)

**Figure 4.3** Bone implant contact (BIC), bone volume fraction (BV), and computational time in the mesh convergence study.
Figure 4.4 Tissue types predicted in mesh convergence study with element size of a 0.03. b 0.035. c 0.04. d 0.045 mm. Implant displacement: 10 µm. Osteotomy gap size: 0.2 mm. Cell migration rate: 14 days.

The effects of the element size on the BIC and BV, and computational time are presented in Fig. 4.3. It is seen that the element size has a small effect on the final BV and BIC values whereas the computational time increases more than threefold as element size is reduced. Contours in Fig. 4.4 illustrate the final tissue distribution in the healing compartment predicted by using different element sizes. Element size of 0.035 mm is selected for this study as the tissue development around the implant collar and implant apex converge at this value (Fig. 4.4b).

Transient results of the tissue types predicted on days 7, 14, 21 and 28 are presented in Fig. 4.5. On day 7, a relatively small amount of immature bone tissue develops around the implant collar and apical threads, whereas most of the healing callus is still occupied by the cartilage tissue. The distribution of tissue types remains similar on day 14 except that the amount of bone tissue is reduced. On day 21, most cartilage tissues are
Figure 4.5 Transient results of tissue differentiation for a healing period of 28 days. Displacement: 10 µm. Osteotomy gap size: 0.2 mm. Cell migration period: 14 days.

replaced by the immature bone and the previously developed immature bone turns into mature cancellous bones. No significant tissue differentiation is observed between day 21 and day 28. During 28 days of healing period, only callus and fibrous tissues appear below the implant apex.

Effects of cell migration rate on the transient results are compared by plotting BV and BIC with respect to the healing period in Fig. 4.6. Four cell migration rates, 7, 14, 21 and 28 days, are chosen by adjusting the $D$ value in Eq. (1) for cells to fully distribute within the osteotomy. It’s clear that the major differentiation of bone tissue occurs after the completion of cell migration. The cell migration rate does not significantly influence BV, but the delayed migration rate decreases BIC at the end of healing period.

Effects of the magnitude of applied displacement on the bone healing are shown in Fig. 4.7a for 5 and 20 µm of implant displacement. It is seen that the lower value (5 µm) results in the development of bone tissue. In contrast, soft tissue appears as a result of
higher displacement (20 µm). In order to understand the roles of distortional strain and interstitial flow velocity in the healing, stimuli induced by the two different levels of displacement are separately demonstrated as solid and fluid parts in Figs. 4.7b-c. In the case of low displacement, the overall distortional stimulus remains low in the healing callus. However, fluid stimulus is found to be high underneath the implant apex, where soft tissue develops. In the case of high displacement, similar phenomenon is observed underneath the implant apex. Additionally, a clear band of soft tissue develops in the implant periphery that can be correlated to the high distortional stimulus.

Figure 4.8 illustrates the effects of osteotomy gap size on the bone healing and the associated distribution of stimuli. Models with osteotomy gap size of 0.1 mm and 0.3 mm are generated. More soft tissue develops due, not only, to increased distortional stimulus at the implant surface, but also increased fluid stimulus throughout the healing compartment when the osteotomy gap is reduced to 0.1 mm. Increased osteotomy gap to
Figure 4.7 Effects of displacement magnitude on bone healing. a Predicted tissue types. b Distribution of solid stimuli. c Distribution of fluid stimuli. Osteotomy gap size: 0.2 mm. Cell migration period: 14 days
Figure 4.8 Effects of osteotomy gap size on bone healing. a Predicted tissue types. b Distribution of solid stimuli. c Distribution of fluid stimuli. Implant displacement: 10 µm. Cell migration period: 14 days.
0.3 mm leads to lower solid and fluid stimuli promoting bone healing in the implant periphery. High fluid stimulus is always observed underneath the implant apex regardless of the size of osteotomy gap.

In order to evaluate the effects of implant threads on the bone healing, a threadless implant contour, and contours with square, buttress and screw shaped threads are analyzed (Fig. 4.9). In general, a large part of the smooth surface of threadless implant is covered by a continuous layer of soft tissue, and the ingrowth of bone tissue between threads is observed for the threaded implants. Crest regions, root regions and sloping sides of implant threads have various effects on the tissue development. Soft tissues develop around the crest regions of the threads. Same as the smooth surface of threadless implant, the crest regions of threaded implants have surfaces parallel to the direction of applied displacement, in which high distortional strain level is susceptible to occur. However, the root regions of square threads, which also have surfaces parallel to the direction of applied displacement, do not induce high distortional strain levels. Growth of bone tissues at these regions results in direct contact with the implant. Interestingly, predicted tissue patterns and stimulus levels adjacent to the horizontal sides of square threads and buttress threads are similar. High fluid stimulus level underneath the horizontal sides of buttress-1 and square threads causes the development of soft tissue. The development of bone tissue is observed in the region above the horizontal sides of buttress-2 and square threads. Differences between BV levels for different threaded designs are insignificant, but lower BIC levels are predicted for the threadless implant and buttress-1 threaded implant.
Figure 4.9 Effects of implant designs on bone healing. a Predicted tissue types. Arrows indicate crest regions with distortional stimulus greater than 1. b Distribution of solid stimuli. c Distribution of fluid stimuli. Implant displacement: 10 µm. Osteotomy gap size: 0.2 mm. Cell migration period: 14 days.
4.4 Discussion

Unlike failure of orthopedic implants, which usually occur in the long term due to stress shielding induced bone resorption (Huiskes et al. 1987), peri-implant healing during the early stage of osseointegration is an essential determinant to the fate of dental implants. In fact dental implants immediately loaded with functional loads could easily run into the risk of unsuccessful osseointegration due to excessive implant mobility. Davies (2003) suggested that peri-implant healing is a process of de novo skeletal tissue regeneration which is similar to the fracture healing involving tissue differentiation by a cascade of cellular activities. Proper implant stability and successful implantation can be determined by clinical and radiography examinations, but limited information about the relation between healing process and associated biomechanical factors can be explored by this method. Alternatively, mathematical models can provide insight into this problem. However, only few studies investigate the role of growth factors in the evolution of cellular activities during peri-implant bone healing (Ambard and Swider 2006; Amor et al. 2009; Moreo et al. 2009; Vanegas-Acosta et al. 2011). Lacroix and Prendergast (2002) investigate the effects of fracture gap size and loading on fracture healing by using mechano-regulatory model (Prendergast et al. 1997, Huiskes et al. 1997) taking into account differentiation pathway as a result of mechanical stimulation. The algorithm was implemented to simulate bone ingrowth of glenoid component of the shoulder arthroplasty (Andreykiv et al. 2005) and the effect of porous implant surface on bone ingrowth (Liu and Niebur 2008). In addition, experiments involving implantation of bone chamber into the proximal tibia of rabbit were performed to assess the validity of the numerical simulation (Geris et al. 2003, 2004). Similar bone ingrowth patterns in certain regions were observed
in experiment as in simulation. The study presented here applies the same algorithm to simulate the influence of immediate loading on bone healing for dental implant systems.

Bone marrow within bone tissue is recognized as the main source of mesenchymal stem cells (Davies 2003). Current study assumes that mesenchymal stem cells are recruited from surrounding bone tissue as it was also assumed by previous studies (Geris et al. 2003, 2004; Lacroix and Prendergast 2002; Liu and Niebur 2008). The presence of mesenchymal stem cells in the healing callus is prerequisite to the initiation of tissue differentiation. Cells may disperse by proliferation and migration (Perez and Prendergast 2007). Experiments have shown both random and directed cell movement (Sengers et al. 2007). Simplifying cell population migration as a diffusive process is based on the random cell movement, but Geris et al. (2003) pointed out that the perturbation caused by the applied displacement on the dental implant may result in the presence of mesenchymal stem cells throughout the healing callus. Similar to the prediction of Geris et al. (2003), in our simulations the differentiation patterns remained alike in the end of healing period. Two bone formation phenomena, contact osteogenesis and distance osteogenesis, are characterized during peri-implant healing (Davies 2003). In contact osteogenesis, implant surface is colonized by bone cells and newly formed bone proceeds toward the surrounding bone. In contrast, distance osteogenesis shows that new bone is laid down on the surface of surrounding bone resulting in bone growth toward implant. Due to the assumption of diffusive cell movement, gradient of cell density decreases from surrounding bone to implant surface. As a result, predicted bone formation pattern is similar to the distance osteogenesis.

In this study the geometry of the bone around dental implant is simplified by a 2D axisymmetric model. Without considering mandibular flexure occurring during jaw
movement and the lateral component of the bite force, vertical displacements varied between 5 and 20 µm were applied. Bone healing was demonstrated to depend strongly on the levels of applied displacement. It was shown that high level of applied displacement promotes the development of soft tissue while the low level of displacement increases the amount of bone formation. Excessive relative micromotion at the bone implant interface has been reported to prevent or delay bone formation. However, the maximum allowable amount of interfacial micromotion is still not clear (Liu and Niebur 2008). In vivo animal studies report that relative motion in 20-150 µm range is tolerated for bone formation (Bragdon et al. 1996; Szmukler-Moncler et al. 2000; Leucht et al. 2007). In this study soft tissue formation underneath the implant apex is predicted and this is shown to be due to high level of fluid stimulus. Similar to our finding Leucht et al. (2007) reported that osteoblast differentiation fails in this region. High mechanical stimulus, effective strain in their study, is indicated as the reason of the failure.

Schenk and Buser (1998) pointed out two major advantages of implant threads. First, the implant threads improve implant stability to avoid excessive interfacial micromotion. Second, the implant threads affect the load transfer from implant to surrounding tissue, and the bone tissue is observed around implant threads. Misch and Bidez (1999) indicated that a threadless implant with long smooth surface is at risk of bone loss, which is attributed to inadequate load transfer. Our previous study also demonstrated that bone formation is less active on the smooth surface in the long term bone remodeling (Chou et al. 2008). In the present study, greater distortional strain was found at the bone implant interface which prevented bone formation during initial healing phase. The introduction of thread designs of dental implants provides more surface area that allows
more bone contact and enhances implant stability through macro-level interlocking as predicted bone development inside the groove regions. More importantly, load transfer characteristic diverted by the proper thread designs can result in favorable biomechanical state of bone development (Faegh and Müftü 2010). The magnitude of normal and shear loads carried by the dental implant can be easily altered by varying thread angles. Predictions show that interfacial distortional strain profile is redirected so that the continuously long development of soft tissue that reduces BIC and osseointegration is avoided.

4.5 Conclusions

Previously developed fracture healing model is adopted to investigate peri-implant bone healing due to immediate loading. Applying higher load on the dental implant is demonstrated to impede the development of bone tissue. Instead, a great amount of soft tissue appears in the healing callus resulting in incomplete osseointegration. The region underneath implant apex is always found to experience high fluid stimulus that induces the development of soft tissue. Threaded implants show superior capability to enhance bone development than a threadless implant. Thread designs redistribute the interfacial load to prevent continuous soft tissue from developing on the implant surface.
References


Liu, X., Niebur, G.L., 2008, Bone ingrowth into a porous coated implant predicted by a mechano-regulatory tissue differentiation algorithm, Biomechanics and Modeling in Mechanobiology 7, 335-344.


5.1 Influence of mastication and edentulism on mandibular bone density

Mandibular bone structure is shown to be determined by the adaptation of bone to external loading due to the daily activities. These include mastication, speech and involuntary open and close cycles. Assuming a daily stress state that maintains the bone strength exists as the attractor stimulus, remodeling of bone is simulated by a mathematical model that controls the change of bone density as a function of the relative differences from this state. The bone remodeling algorithm is implemented into a three-dimensional finite element model of the mandible, obtained by computerized tomography (CT) images of a human mandible. Masticatory muscle activation during clenching is modeled by static analysis using linear optimization; other loading conditions are approximated by imposing mandibular flexure. The conclusions of this study are summarized as follows,

- The predicted bone density distribution results in a tubular structure similar to the observations in medical images.
- Such bone architecture is known to provide the bone optimal strength to resist bending and torsion during mastication while reducing the bone mass.
• Bone resorption following edentulism is predicted as a result of lack of remodeling stimulation.

• Current study demonstrates mandibular bone morphology is determined by function, and the bone remodeling algorithm developed for the long bones is applicable to the mandible.

5.2 Later stage of osseointegration: peri-implant bone remodeling

Peri-implant bone remodeling as a response to biomechanical factors including implant size and contour, magnitude of occlusal load, and properties of osteogenic bone grafts is studied. A bone remodeling algorithm is incorporated into the finite element method, where bone remodeling takes place as a result of the biomechanical alteration caused by dental implantation, and continues until the difference between the homeostatic state and the altered state is minimized. The site-specific homeostatic state is based on the model consisting of a natural tooth. Three long (11 mm) implants and two short (5 mm) implants are investigated. A three dimensional segment of the mandible is constructed from a CT image of premolar region. The extraction socket is filled with bone graft. The conclusions of this study are summarized as follows,

• Generally, the areas between the implant threads are prone to bone resorption.

• Bone graft materials that are relatively stiff and that have high equilibrium stimulus values are predicted to result in increased bone loss.

• Short implants are better for conserving the mechanotransductive signaling environment of the natural tooth than the long implants.
• Short implants are predicted to lead to lower interfacial bone loss at high loads in the long term, while long implants have a more consistent level of bone loss for different load levels.

• It is also predicted that in the long term, bone grafts with relatively low elastic modulus lead to lower levels of interfacial bone loss.

5.3 Early stage of osseointegration: peri-implant bone healing

The role of immediate loading on the peri-implant bone healing for dental implants is investigated by using numerical simulation. A mechano-regulatory model that takes into account both solid and fluid effects on tissue differentiation during fracture healing is adopted. Diffusion of pluripotent stem cells into the healing callus is modeled. A two-dimensional axisymmetric model consisting of dental implant, healing callus tissue and host bone tissue is constructed for finite element analysis. Poroelastic material properties are assigned to the healing callus and bone tissue. The conclusions of this study are summarized as follows,

• Applying higher load on the dental implant is demonstrated to impede the development of bone tissue. Instead, a great amount of soft tissue appears in the implant periphery resulting in incomplete osseointegration.

• Region underneath implant apex is always found to experience high fluid stimulus that induces the development of soft tissue.

• A continuous layer of soft tissue develops along the smooth surface of threadless implant as a result of high distortional stimulus.
Thread design redistributes the interfacial load and prevents the development of continuous high distortional stimulus.

- Ingrowth of bone tissue between the threads is observed.

**5.4 Future works**

Following Wolff's *law of bone remodelling* (1896; 1986), Many regulatory rules were proposed in order to describe the bone adaptation to function. Frost's mechanostat hypothesis suggested different bone remodeling activities in response to different effective strain levels (Frost 1987; 2003). Carter et al. (1987) and Huiskes et al. (1987) incorporated bone remodeling models into finite element analysis for studying the bone density distribution of the femur. On the other hand, theories of tissue differentiation were developed separately from the bone remodeling. Pauwels (1980) hypothesized that tissue differentiation pathway is regulated by the hydrostatic stress and octahedral shear stress. Carter et al. (1988) considered cyclic hydrostatic stress and shear stress into the differentiation model. Claes and Heigele (1998) suggested the thresholds of tissue development in terms of principal strain and hydrostatic pressure. Prendergast et al. (1997) proposed a poroelastic model taking into account both solid and fluid stimuli for the tissue differentiation.

Algorithms of bone remodeling and bone healing have been independently developed in the past few decades. Current research on bone healing and bone remodeling was separated into two parts based on the observation that osseointegration begins with peri-implant bone healing, which is followed by the bone remodeling (Schenk and Buser 1998). However, while bone healing is taking place in the healing callus, the intact bone
tissue, which is the bone region without being traumatized during osteotomy, should be simultaneously undergoing bone remodeling. As a result, a new algorithm that combines bone healing and bone remodeling should better predict osseointegration. The possible working algorithm is illustrated schematically in Fig. 5.1.

**Figure 5.1** Flow chart of combined peri-implant bone healing and peri-implant bone remodeling simulation.
References


