CHAPTER 1

Mechanobiology of bone regeneration and bone adaptation to achieve stable long-term fixation of endosseous implants

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Abstract

The success or failure of the clinical application of endosseous implants lies in the adequacy of the host to establish and maintain osseointegration. Although the success rate for implants is generally high, failures still occur. Mechanical loading has been identified as an important factor for both early and late biological failure. These phenomena are studied here by means of a representative member of the endosseous implants family: the oral implants. Early biological failure is a process of bone regeneration that has mostly been studied during fracture healing in long bones. Different theoretical models aim to describe these observed processes and employ different mechanical and biological parameters to drive the regeneration process. Several of these models were implemented to simulate the process of peri-implant tissue differentiation in an in vivo bone chamber. Qualitative agreements can be noted between the numerically predicted and experimentally observed tissue patterns in the chamber. Late biological failure has often been attributed to inappropriate implant loading. Numerous animal experiments show a distinct influence of the various types of loading on bone adaptation. Theoretical models aim to capture these observations in mathematical expressions. From an anatomical finite element model the peri-implant only part of the marginal bone loss could be related to overload. To further explore the relation between marginal bone resorption and overload one of the theoretical models was implemented. A redistribution of the peri-implant bone stresses caused by the removal of peri-implant tissue experiencing overload put a hold on the marginal bone resorption.
1 Introduction

The use of implant-supported oral prostheses for the treatment of partially and fully edentulous patients has nowadays grown into a viable alternative to removable dentures. Implants are installed into the jaw bone tissue and transfer the occlusal loads, exerted on the prosthesis to the surrounding bone. The key to a successful clinical application of oral implants lies in the establishment and maintenance of a direct connection between the implant surface and the surrounding bone tissue, without any intervening fibrous tissue layer. This is commonly termed osseointegration [1]. However, most definitions of this term remain rather vague with respect to the actual histological, physico-chemical and mechanical nature of the implant-bone interface in case of osseointegration. In most cases direct implant-bone contact is judged on a light microscopic examination of the interface, but electron microscopic studies have revealed that the implant-bone interface is much more heterogeneous at the ultrastructural level [2].

Although the clinical outcome for different commercial implant systems is in general highly successful [3], failures still occur. Failures can be divided into mechanical failure and biological failure. While a mechanical failure refers to fracture of an implant component, mostly due to fatigue, a biological failure can be defined as the inadequacy of the host to establish or to maintain osseointegration. The inability to establish osseointegration during the healing phase can be regarded as an early failure, whereas the inability to maintain the achieved osseointegration, under functional conditions, may be considered a late failure. Clinically, lack of osseointegration is generally characterized by implant mobility. A fibrous tissue layer may have developed at the interface with the mobile implant. Biological failure may also be associated with excessive marginal bone loss (i.e. bone loss around the implant neck (cf. fig. 1)), although the implant may remain clinically stable.

Figure 1: Röntgenograms of orals implant with excessive marginal bone loss. The crater-shaped bone defect is clearly visible (arrows).
The conservation of the marginal bone plays a crucial role in the long-term clinical success of an implant.

1.1 Early biological failure

Early implant failure can be defined as the inadequacy of the host to establish osseointegration. The bone regenerative processes at the bone implant interface are strongly influenced by the initial surface properties of the implant and the mechanical environment at the site.

Kasemo and Lausmaa [4] described the biological and chemical interactions that take place at the interface of a (bio)material, starting from the nanometer scale up to the macroscopic level. They argued that the interaction of the (bio)material surface and the biological environment is determined by the chemical composition, the (micro)structure and the topography of the surface. These are, in turn, controlled by the history (manufacturing, cleaning, environmental contamination, sterilization) of the (bio)material. Apart from its chemical composition, the implant surface can strongly vary in terms of microstructure and morphology, which are partly determined by the grain structure of the underlying metal, and partly by the oxidation conditions. When the implant is brought into the biological tissue a complex cascade of chemical and biological reactions take place at different spatial and time scales. After the initial hydration of the surface, biomolecules (like proteins) adsorb to the surface. It is likely that the nature of the biomolecule layer has an influence on the cell type that proliferates at the implant surface.

It is well accepted that mechanical factors play a role in bone regeneration, although the exact nature remains unknown. Many groups tried to qualify and quantify the exact contribution of the mechanical loading to tissue differentiation and bone regeneration, either by means of animal experiments [5–8] or numerical simulations [9–19]. One common result of these studies is that severe implant loading in the early stages of the regenerative process will lead to the establishment of a fibrous tissue layer around the implant, preventing osseointegration taking place.

Section 2 deals in greater detail with the topic of bone regeneration. It starts with an overview of the biology involved in bone regeneration. Next, a series of theoretical models describing the process of bone regeneration is presented, followed by the application of several of these models in the simulation of the peri-implant tissue differentiation in an in vivo bone chamber.

1.2 Late biological failure

Considering late biological failures two major etiological factors were suggested: infection and mechanical loading. Several clinical studies investigated the relation between oral hygiene (plaque accumulation) and marginal bone loss, but contradictory results were reported [20, 21]. Based on a study of Esposito et al. [3] it seems that plaque is not an important etiological factor for marginal bone loss in
case of machined ("smooth") implant surfaces, like e.g. the Brånemark implant. However, for implants with a rougher surface, plaque-induced marginal bone loss could play a more important role, since the rough surface may promote plaque accumulation.

A number of animal experiments showed that overload can lead to excessive marginal bone resorption or even complete loss of osseointegration [22–24]. This does not however prove that the same is true in a clinical situation. A number of clinical studies hypothesized that marginal bone loss can be correlated with unfavorable prosthesis design and parafunctional habits (clenching, bruxism), both possibly leading to overload [21, 25, 26]. The risk of excessive marginal bone loading due to high bending moments was recognized by many authors. However in none of these clinical studies where excessive marginal bone loss was observed were the implant loads actually quantified.

In contrast to this overload theory, others suggested underload (disuse atrophy) to be responsible for marginal bone decrease. Pilliar et al. [27] reported bone loss around the smooth collar of endosseous implants that were installed in dog mandibles. They argued that due to the lack of retention, stresses cannot be transferred to the bone around the collar, resulting in disuse atrophy of the marginal bone.

Section 3 takes a closer look at the influence of mechanical loading on bone adaptation. It starts with a general description of the functional adaptation of bones based on the results from animal experiments throughout the years. This is followed by a summary of the theoretical models which have been established to describe the observations of the experiments. Finally, two case studies are discussed that aim to gain insight into the biomechanics of oral implants and to verify some of the hypotheses that relate mechanical loading to peri-implant bone responses.

2 Bone regeneration

Bone regeneration is a complex process encountered for instance in fracture healing and implant osseointegration. The course of this process is influenced by many parameters such as the size of the trauma, the mechanical nature of the regenerative site, the nature of the surrounding tissue etc. Two major types of regenerative processes can be discerned: direct and indirect healing [17]. Bone will regenerate in a direct way when there is little or no loading of the injured site (e.g. cortical defects, rigidly fixated fractures). The defect will ossify via intramembranous bone formation without any external callus formation. Indirect or secondary bone regeneration is characterized by a rapid stabilization of the trauma site. The formation of a callus ensures a rapid restoration of the mechanical integrity. After this quick initial repair, a long period of remodeling eventually returns the bone to its original shape.

The complex character of bone regeneration has mostly been studied during fracture healing of long bones. Therefore, this section starts with an overview of the biology of fracture healing. This is followed by a summary of theoretical models that aim to describe the influence of different mechanical and biological parameters.
Computational Modeling of Tissue Surgery

on the process of fracture healing. In the case studies some of these models were implemented to simulate the process of peri-implant tissue differentiation inside an *in vivo* bone chamber.

### 2.1 Biology of fracture healing

Secondary fracture healing can be roughly divided in three overlapping phases: the inflammatory, reparative (including soft and hard callus formation) and remodeling phase [28, 29]. The initial stage of fracture healing is characterized by an acute inflammatory reaction. Following bone injury, the cortical bone/periosteum and surrounding soft tissues are torn, and numerous blood vessels are ruptured. This blood rapidly coagulates to form a clot enclosing the fracture area. The haematoma has inherent angiogenic and osteogenic potential [30, 31]. As a consequence of the vascular damage, the fracture site becomes hypoxic. Osteocytes at the fracture line become deprived of their nutrition and die. Severely damaged periosteum and marrow as well as injured surrounding tissues contribute necrotic tissue to the region. This necrotic material elicits an immediate inflammatory response: acute inflammatory cells and polymorpho-nuclear leukocytes are recruited to the fracture site, followed by macrophages. Concomitantly, fibroblasts, mesenchymal progenitors and endothelial cells also invade the haematoma and later replace it with connective tissue and (fibro-) cartilage. The inflammatory response is associated with pain, heat, swelling and release of several growth factors and cytokines that have important roles in subsequent healing [32, 33]. For instance, the inflammatory reaction may stimulate mesenchymal cell proliferation at the site of injury and induce angiogenesis, thus playing a key requisite role in the repair process [28].

The inflammatory stage is closely followed by the reparative phase which in its turn can be divided into two phases. During the first reparative phase, fibrous tissue forms and mesenchymal cells proliferate and differentiate, either into chondrocytes that will mature towards hypertrophy (i.e. endochondral ossification, forming mainly the internal callus), or directly into osteoblasts that deposit bone (i.e. intramembranous ossification, predominantly creating the external callus). The mechanisms that control the behavior of each individual cell at this stage are largely unknown, but are likely to derive from the cell’s microenvironment. For instance, a major determinant is believed to be the extent of vascularization, with variations in oxygen tension affecting the preference to form either cartilage or bone. As such, this first reparative phase is characterized by the formation of a callus composed of (fibro-) cartilage in areas that are distant from the vasculature and of immature, woven bone predominantly in subperiosteal areas. As the immature callus envelopes the bone ends, stability of the fracture increases.

The second phase of repair is characterized by the replacement of the cartilaginous callus scaffold with bone, in a process indistinguishable from endochondral bone formation except for its lack of organization. This occurs largely concomitant with the remodeling of the already newly formed bone. Hard callus tissue, consisting of mineralized bone matrix, is produced by osteoblasts that receive enough
oxygen and are subjected to the proper mechanical stimuli. The bone ends gradually become enveloped by a bone callus mass, immobilization of the fragments becomes more rigid through this internal and external hard callus formation, and eventually a clinical “union” is achieved.

In the middle of the reparative phase, the remodeling phase begins with osteoclastic resorption of unnecessary, poorly placed or inefficient parts of the callus and the formation of new haversian systems and trabecular bone. During this final phase of the healing process, the large fracture callus is replaced by secondary bone; the size of the callus is reduced to that of the pre-existing bone at the damage site, and the vascular supply reverts to a normal state. This remodeling takes place for a prolonged period of time, constantly refining the bony architecture to match the mechanical needs of the skeleton. The end result of remodeling is regenerated bone that, if it has not returned to its original form, has been altered so that it may best perform the function demanded of it.

2.2 Mathematical models

The first theoretical models to describe the mechanoregulation of skeletal tissue differentiation were introduced by Pauwels [16]. He recognized that physical factors cause stress and deformation of the mesenchymal cells and that these stimuli could determine the cell differentiation pathway. He hypothesized that deviatoric stresses, which are always accompanied by strain in some direction and thus a change in cell shape, stimulate the formation of fibrous connective tissue. Hydrostatic stresses on the other hand are a specific stimulus for the formation of cartilaginous tissue. A specific stimulus for the formation of bone, however, is not present in the theory of Pauwels. According to Pauwels, bony tissue proceeds on the basis of a rigid framework of fibrous tissue, cartilage or bone [16]. Some years later, the concept of interfragmentary strain (IFS) was developed by Perren [17] and Perren and Cordey [18]. They proposed that a tissue, with a certain failure strain, cannot be formed in a region that experiences strains higher than this level. This means that a fracture gap can only be filled with a tissue capable of sustaining the IFS without failure. The IFS concept provides a theoretical basis for evaluating fracture treatment strategies, but is not applicable for bone regeneration in general, since it disregards the structural and mechanical heterogeneity of the fracture callus. Building on the theories of Pauwels [16], Perren [17] and Perren and Cordey [18], many research groups have formulated a theoretical model relating tissue differentiation to mechanical loading. Carter and co-workers [10, 11] specifically discussed the importance of cyclic tissue loading and proposed a mechanical stimulus that takes into account the local stress or strain history. The stress acting on the regenerating tissue is described in terms of hydrostatic stress and distortional strain. Direct bone formation is permitted in regions experiencing low hydrostatic stresses and low distortional strains. Carter, however, never provided any values for stimuli that favors bone formation. Claes and Heigele [12] combined the result of their finite element analyses of the mechanical stimuli on ossifying surfaces during fracture healing with a histological analysis of a real callus geometry. From this, they derived a quantitative mechanoregulatory
model relating magnitudes of hydrostatic pressure and principal strain to the bone formation process. Intramembranous bone formation occurred at the regenerating bone surface for hydrostatic pressures smaller than 0.15 MPa, while endochondral bone formation occurred when the compressive hydrostatic pressure exceeded this threshold. The above mentioned theories all considered tissues as solid elastic materials. Prendergast et al. [19] proposed a mechanoregulatory model for tissue differentiation, based on a poroelastic (biphasic) behavior of the tissues. Maximal distortional strain and relative fluid velocity constitute the stimulus that controls the differentiation process. High values of both solid strain and fluid velocity favor fibrous tissue formation, while intermediate values lead to cartilaginous tissue. Bone can only be formed if the values are sufficiently low. Huiskes et al. [13] quantified the upper and lower limits of the mechanical stimulus for the different tissue phenotypes, which yielded a mechanoregulatory diagram for tissue differentiation. The model was extended to include mesenchymal cell migration (by means of a diffusion equation), as a first step to incorporate the underlying cellular processes [34, 35]. Carter [36] defined mechanobiology as the study of how mechanical or physical conditions regulate biological processes. At the same time, it is clear that the influence of mechanical loading on tissue differentiation is mediated by other factors, like vascularization or the presence of biochemical agents. The previously described mechanoregulatory models hardly incorporate any biological parameters – apart from Lacroix and Prendergast – and treat the interaction between mechanical loading and tissue differentiation in a more phenomenological way. In contrast, Bailón-Plaza and van der Meulen [9] developed a mechanistic model for fracture healing which approaches the differentiation process from an exclusively biological point of view. In their model, they incorporate the differentiation and proliferation of the different cell types that play a role in fracture healing and the regulation of these processes by means of growth factors. In a recent study [37] they integrated the concepts of Carter et al. [11] into their model for the mechanoregulation of ossification. Such an integrated approach seems highly promising for a better understanding of mechanobiological processes and for the establishment of models that have a more quantitative predictive value.

2.3 Case studies

The predictive value of a model can only be assessed by comparison with in vivo data. Moreover, it would be interesting to compare different theoretical models by applying them to the same, well-defined problem. The following case studies discuss the simulation results of two mechanoregulatory models developed by Prendergast et al. [19] and Claes et al. [12] and of the biological model developed by Bailón-Plaza and van der Meulen [9] when implemented to simulate the peri-implant tissue differentiation in an in vivo bone chamber [38–40].

The repeated sampling bone chamber methodology was developed to investigate the exact role of the mechanical environment on the bone adaptive response around titanium implants. This is not easy because of the difficulty of isolating the implanted material and its surrounding tissues and protecting it from external...
Computational Modeling of Tissue Surgery

Figure 2: Picture and composition-drawing of the bone chamber. After insertion of the outer bone chamber (1) in the rabbit’s proximal tibia, there is a healing period of six weeks during which bone ingrowth via the perforations (2) in the wall is inhibited by a teflon inner chamber (7). After six weeks this inner chamber is removed and replaced with an inner chamber (3), a teflon bearing (5) and an implant (6).

influencing factors. In addition, the ruling mechanical conditions should be well-controlled. A bone chamber which contains a central test implant, was implanted in the proximal tibia of New Zealand white rabbits (fig. 2). Via perforations, bone grows into the bone chamber. An actuator allows a well-controlled mechanical stimulation of the test implant. After an experiment, the content of the bone chamber can be harvested and subjected to a variety of analyses. Consecutively, a new inner bone chamber structure with a central test implant can be inserted in the outer bone chamber structure and a new experiment can start. Pilot studies lead to an acceptable surgical protocol and showed the applicability of the methodology. The methodology offers the possibility to study tissue differentiation and bone response around titanium implants under well-controlled mechanical conditions, protected from external influences [41]. Repeated sampling of the bone chamber allows the conducting of several experiments within the same animal at the same site, thereby excluding subject- and site-dependent variability [42]. In addition, it reduces the number of required experimental animals.

2.3.1 Mechanoregulatory models

The mechanoregulatory models developed by Prendergast et al. [19] and Claes et al. [12] both consider mechanical factors to be the determinants of the differentiation process. Based on the values for strain, stress or fluid flow, they predict certain tissues (bone, cartilage, fibrous tissue) to be formed or pathways (intramembranous vs. endochondral bone formation) to be followed.

2.3.1.1 Materials and methods

A 2D axisymmetric finite element (FE) model of the tissue inside the chamber was created (fig. 3). For both theoretical models the entire chamber is filled with granulation tissue at the start of the simulation.

In the model developed by Prendergast et al. [19] and Huiskes et al. [13] the tissues are treated as biphasic (solid and fluid constituents) and the mechanical stimulus for tissue differentiation is defined in terms of relative fluid velocity and maximal distortional strain. Depending on the value of the stimulus, a favoured
tissue phenotype ((im)mature bone, cartilage, fibrous tissue) is predicted. A simple diffusion law (eqn (1)) is assumed to describe the migration of mesenchymal cells throughout the chamber. $D$ represents the diffusion coefficient, $n$ the cell density and $t$ represents time.

$$D \nabla^2 n = \frac{dn}{dt}.$$  \hspace{1cm} (1)

Using a rule of mixtures [34] the biphasic material properties are adjusted every iteration step depending on the predicted phenotype and the local concentration of mesenchymal cells. This process is continued until a stable configuration in the chamber is obtained. Figure 4 (top) shows the flowchart of the numerical simulation, table 1 contains the material properties of the different tissues.

In the mechanoregulatory model of Claes et al. [12] the major principal strain and hydrostatic stress are the determinants of the differentiation process. Based on their value either soft tissue formation or endochondral or intramembranous bone formation takes place. Again, the material properties of each element are updated every iteration step until a stable configuration is reached (fig. 4, bottom).

### 2.3.1.2 Results and discussion

There are several ways to validate a model. A comparison between the simulation outcomes and the results of an animal experiment can be performed in a qualitative way (e.g. comparison of the tissue types) or a quantitative way (e.g. comparison of measured and calculated reaction forces on the implant). The influence on the simulation outcome of the parameters that cannot be validated experimentally can be assessed by means of sensitivity analyses. The mechanoregulatory models described above are validated in all three ways.
Figure 4: Flow-chart of simulation process for the mechanobiological models of Prendergast et al. [19] (top) and Claes et al. [12] (bottom).

Table 1: Material properties [43] of the tissues used in the simulations of the model developed by Prendergast et al. [19] and Huiskes et al. [13].

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Granulation tissue</th>
<th>Fibrous tissue</th>
<th>Cartilage</th>
<th>Immature bone</th>
<th>Mature bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young’s modulus</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1000</td>
<td>6000</td>
</tr>
<tr>
<td>(MPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisson’s ratio</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Permeability</td>
<td>$10^{-14}$</td>
<td>$10^{-14}$</td>
<td>$5 \times 10^{-15}$</td>
<td>$10^{-13}$</td>
<td>$3.7 \times 10^{-13}$</td>
</tr>
</tbody>
</table>
Figure 5: Top: histological sections taken from 2 animals at 3 different heights in the bone chamber (height indicated in bottom right figure). Bottom: results of the simulations with the models of Prendergast et al. [19] (left) and Claes et al. [12] (right).

Figure 5 shows the simulation result (upper left) and the histological sections taken at three different heights in the bone chamber from two rabbits. The animals were loaded twice a week for 12 weeks with an implant-displacement of 30 µm (1 Hz, 400 cycles) the first six weeks, followed by another six weeks of loading with an implant-displacement of 50 µm (1 Hz, 800 cycles).
Table 2: Numerically calculated forces needed to impose the required implant displacements.

<table>
<thead>
<tr>
<th>Imposed displacements</th>
<th>Numerically calculated forces</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model of Prendergast et al. [19]</td>
</tr>
<tr>
<td>30 µm</td>
<td>123 N</td>
</tr>
<tr>
<td>60 µm</td>
<td>30 N</td>
</tr>
<tr>
<td>90 µm</td>
<td>21 N</td>
</tr>
</tbody>
</table>

Changing the boundary values for the fluid flow stimulus (30 and 90 µm/s instead of 3 and 9 µm/s), the simulation predicts the formation of a layer of fibrous tissue at the implant interface, almost no cartilage formation and (im)mature bone formation in the main part of the chamber. The results from the experiments show those same tissue types (bone and fibrous tissue) in the bone chamber. The spatial distribution of the tissue phenotypes at the implant interface varies from animal to animal. The forces needed to impose the required displacement of the implant were measured during the experiments and calculated during the FE simulations. The results in table 2 are from an experiment where all animals were loaded with four different loading conditions (0, 30, 60 and 90 µm – 1 Hz, 800 cycles) that were applied twice a week during six weeks. The simulation results are reasonable for the higher displacements; they are in the same order of magnitude as the experimentally measured forces. For the 30 µm loading condition though, the simulations predict the entire chamber to be filled with mature bone, requiring high forces (>100 N) to ensure the displacement of the implant, whereas the experimental measurements indicate that only low forces (20 N) are required in reality.

The sensitivity analyses show that the fluid flow has a direct influence on the degree of maturation of the bone in the chamber and a considerable indirect effect (through the biphasic nature of the tissues) on the strain values and hence the differentiation patterns in the bone chamber. The number of loading cycles applied per iteration step (e.g. one period of a sine function instead of 800 periods) has no influence on the predicted tissue phenotypes. Variations in the diffusion rate ($D$ in the diffusion eqn (1)) do not influence the outcome of the simulations, only the computational time to reach a converged situation in the bone chamber (i.e. application of additional iteration steps does not alter the tissue phenotype configuration in the chamber).

Changing the boundary values in the model of Claes et al. [12] (3.75% and 11.25% strain and 0.75 MPa hydrostatic pressure instead of 5% and 15% and 0.15 MPa) gives rise to the simulation results represented in fig. 5 (upper right) and table 2. Comparing to the results obtained with the model of Prendergast et al. [19], similar trends are obtained, although quantitative differences can be noticed. The sensitivity analyses indicate that the strain is responsible for the formation of the layer of fibrous tissue at the implant interface and the value of the hydrostatic
stress mainly determines the character of the ossification process (endochondral vs. intramembranous).

### 2.3.2 Biological model
The mathematical model of tissue differentiation by Bailón-Plaza and van der Meulen [9] is schematically represented in fig. 6. This model describes the spatiotemporal evolution of seven quantities: cell densities (mesenchymal cells, chondrocytes, osteoblasts), extracellular matrix densities (connective/cartilage and bone matrix) and growth factor concentrations (chondrogenic and osteogenic) by means of a system of seven coupled partial differential equations of the taxis-diffusion-reaction (TDR) type. This model accounts for many of the important events in fracture healing including haptokinetic and haptotactic mesenchymal cell migration depending on the matrix densities, space-limited cell proliferation as well as environment-dependent cell differentiation, growth factor and matrix production and degradation.

#### 2.3.2.1 Materials and methods
Figure 7 shows the simplified 2D model of the tissue in the bone chamber. A time-limited inflow of mesenchymal cells and growth factors, via prescribed concentration values, through the chamber perforation in the outer wall and the bottom, (cf. the markings on the upper and left domain boundary, respectively, in fig. 7) is assumed. The bottom boundary of the domain is
Figure 7: 2D model of the entire bone chamber (top – numbers cf. fig. 2) and simplified model of the tissue inside the chamber.

The seven concentrations appearing in the mathematical model are nonnegative. This qualitative property of the solution should be inherited by numerical approximations of the concentrations and hence must be obeyed by the algorithms employed. Reliable numerical methods for TDR models have been investigated extensively by Gerisch [44]. The techniques developed there are adapted to the specific system at hand. The general approach taken is the method of lines (MOL) which consists of three substeps.

- Selection of a spatial grid. With each grid cell, for each of the seven quantities a time-dependent (spatial) average concentration value is associated. The aim of the following two steps is the computation of the temporal evolution of these average concentrations.

- Spatial discretization, i.e. approximation of the spatial derivatives of the PDE system in all grid cells by using the average concentration values in neighboring grid cells (finite differences/finite volumes approach). This leads to the so called MOL-ODE, that is a system of coupled ordinary differential equations (ODEs) describing the temporal evolution of the average concentrations in the grid cells. One important characteristic of the selected spatial discretization is the requirement that the resulting ODE admits only nonnegative solutions whenever the initial data is nonnegative. The requirement leads to conditions on the discretizations employed for taxis, diffusion, and reaction terms. These are easily met for the reaction terms (point wise evaluation) and the discretization of the diffusion...
term (standard second-order central differences). However, the discretization of
the taxis term is not straightforward under these conditions and upwinding tech-
niques with nonlinear limiter functions (van Leer limiter) are employed in order
to satisfy them. A detailed discussion of the spatial discretization can be found
in [44].

• Time integration of the MOL-ODE. Due to the enormous size of the MOL-
ODE this calls for efficient numerical techniques. ODE systems arising from the
discretization of PDEs involving diffusion terms are so-called stiff systems and
and call for implicit time integration schemes. Such a method is implemented in the
efficient and reliable code ROWMAP [45] which is used in our simulations.

2.3.2.2 Results and discussion

The results of the simulations with the biological
model are not yet validated with specific histomorphometrical and immunohisto-
chemical analyses of the tissues in the bone chambers at different stages in the
experiment, therefore the values of the parameters of the model are assumed to be
the same as in [9] and sensitivity analyses are performed to assess the influence of
these assumptions on the final outcome.

After three days, the mesenchymal cells have spread throughout the entire cham-
ber, describing a steep moving front (fig. 8, top). Under the influence of the chon-
drogenic growth factor, the cells start differentiating into chondrocytes that fill the
entire chamber with a fibrous tissue/cartilage ECM by day five. Hereafter, the endo-
chondral replacement starts. Chondrocytes are replaced by osteoblasts describing
again the same steep moving fronts. A bony ECM is laid down and by day ten, the
entire chamber is filled with bone. Figure 8 (middle and bottom) shows the vari-
ation of both the fibrous tissue/cartilage and the bone ECM throughout the entire
simulation. Moderate changes to the values of the boundary and initial conditions

Figure 8: Simulation results for the model of Bailón-Plaza and van der Meulen [9].
Change over time of mesenchymal cell density ($c_m$, top), density of carti-
lage and fibrous tissue ECM ($m_c$, middle) and density of bone ECM
($m_b$, bottom).
have no influence on the simulation results. A too low value for the mesenchymal cells at the boundaries will lead to a bone chamber filled with cartilage ECM and a too low level of the initial ECM values will cause a delay or an arrestment in the differentiation process. Setting the initial value of the chondrogenic growth factor to zero causes intramembranous bone formation, filling the chamber with bone in four days. When the initial value of the osteogenic growth factor is set to zero, the endochondral replacement is prohibited from taking place hence no bone is formed. Not only the values of the boundary and initial conditions may determine the outcome of the process, the values of the model parameters also play an important role. Changing the values of the parameters involved in describing the cell differentiation and replacement causes a delay or an arrestment in the differentiation process. Changes in the values of the parameters that describe the formation and degradation of the ECM cause smoothening of the steep moving fronts by which all the processes run through the chamber.

3 Bone adaptation

The mechanical environment of the peri-implant tissue is not only important for the establishment of the osseointegration, but also for the maintenance thereof. Both over- and underload conditions have been shown to induce marginal bone loss and affect the osseointegration [21–27].

This sections starts with an overview of the experimental data gathered over the years that aims to provide a better understanding of the process of functional bone adaptation. This is followed by a summary of mathematical models that have been established based on these experimental data. Finally two case studies are presented that aim to gain insight into the biomechanics of oral implants and to verify some of the hypotheses that relate mechanical loading to peri-implant bone responses.

3.1 Animal experiments and observations

The observation that bone geometry and structure seem to be “optimally” adapted to its mechanical environment was already made by Galileo in 1638 [46]. It was however only in the second half of the 19th century that the first theories of bone adaptation emerged, when Karl Culmann, Hermann von Meyer and Julius Wolff compared the trabecular arrangement with the principal stress trajectories in a homogeneous bone. Especially Wolff became famous with his “Law of bone transformation” – later known as “Wolff’s Law” – published in 1892 [47], in which he proposed a number of axioms related to growth and adaptation of bone tissue. Wolff stated that “every change in the form and function of bones or of their function alone is followed by certain definite changes in their internal architecture, and equally definite secondary alterations in their external conformation, in accordance to mathematical laws”. Today, it is clear that Wolff’s law is in fact a poorly defined law and that many of his concepts proved to be erroneous. A description of the historical context of bone adaptation can be found in [48].
Speaking about bone adaptation involves different aspects that can be described as [49]:

- The optimization of strength with respect to weight.
- The alignment of trabeculae with principal stress trajectories.
- Self-regulation of bone structure by cells responding to a mechanical stimulus.

This paragraph focuses on the last aspect. The word “adaptation” will be used here to designate modeling as well as remodeling in response to (changes in) mechanical loading. Other frequently encountered terms in literature about bone adaptation are “external remodeling” and “internal remodeling” [50]. The first refers to a change in outer bone geometry, either achieved by a movement in- or outward of the periosteum or endosteum (or both). The latter designates the change in bulk density of trabecular bone, the change in porosity of cortical bone and the change in orientation of the individual trabeculae.

The idea of self-regulation was introduced by Roux in 1881 [51], who hypothesized that organisms have the possibility to adapt to changes in their environment. Applying this to bone he stated that cells can either form or resorb bone tissue according to variations of a functional (mechanical) stimulus. The question was and still is: which mechanical stimulus? In vitro experiments have pointed out that cell cultures from the osteoblast lineage can respond to strain [52]. Fluid flow seems another important regulator of (osteocytic) cell activity [53]. Fluid flow may interact with the osteocytes, either by inducing shear deformation by means of electrical signals. The latter stems from the fact that the extracellular matrix in bone has a net negative electrical charge so that the extracellular fluid (which can be considered as an electrolyte) will develop a diffuse double layer of positive charges. When the solid matrix is deformed, the fluid will start to flow, thereby giving rise to streaming currents and streaming potentials, which may interact with the osteocytes [54]. The formation of micro-cracks is also suggested as another stimulus that could directly trigger a cellular response [55–57]. During in vivo experiments it is not possible to monitor the mechanical stimuli at the cellular level. Since osteoblasts and bone lining cells are attached to bone surfaces, it is reasonable that they will “feel” the deformation of the bone surface (although the in case of osteocytes, the relation between macroscopic bone deformation and cellular deformation seems far from straightforward). Therefore, many researchers have concentrated on the measurement of strain (by means of strain gauges) on the periosteal surface of (mostly long) bones during different levels of activity in animals [58–62].

Interestingly, for all the different animals and bones, peak strains were found between 2000 and 3000 µε. These results sustain the hypothesis that bone adaptation takes place in order to control the level of maximum strains during function. The work of Hylander [59] is of particular interest for the field of implant dentistry, since he is the only one that performed measurements on the (macaque) mandible. He found peak strains of 2200 µε during biting.

Ulthoff and Jaworski studied the effect of disuse on bone tissue by immobilizing one of the forelimbs in either growing [63, 64] or older dogs [65]. In case of growing dogs they found a loss of bone mass of about 50% after 32 weeks, involving
resorption at the periosteal, endosteal and intracortical envelopes. When the forelimbs were mobilized again, 65–70% of the lost bone mass was recovered within 28 weeks. For the older dogs bone loss primarily occurred at the endosteal surface and through increased intracortical porosity. The capacity to recover the bone loss seemed lower for older dogs, recovering only 40%. Lanyon et al. [61] looked at the effect of increased bone loading in the radius of mature sheep, by removing the ulna (i.e. ulnar osteotomy), so that the radius must carry the entire load in the forelimb. They observed woven bone formation at the periosteal perimeter, which was most intense at the side adjacent to the osteotomised ulna. At this side, the woven bone was also secondary remodelled. However, this was not the side of the radius that experienced the largest increase in bone strains due to the ulnar osteotomy. Even more surprisingly, the strain level after adaptation had dropped below the strain level before osteotomy. These findings seem conflicting with the idea that the strain magnitude controls the adaptive response of bone. In order to try to explain their results, Lanyon et al. [61] argued that alterations in the “normal” strain distribution may play a role as well in the bone adaptive response. Lanyon and co-workers performed another series of highly interesting animal experiments with adult turkeys, in which the shaft (diaphysis) of the ulna was isolated and loaded via pins that were surgically inserted. In this way, they had much more control over the different parameters of tissue loading, since the ulna only experienced the experimentally applied loads. They performed several experiments in which they studied the effect of strain magnitude, the daily number of load cycles and the effect of static versus dynamic loading. When no loading was applied, bone loss was observed in the form of endosteal resorption and an increase in intracortical porosity. Compressive static loading up to 2000 $\mu$ε generated the same results, but when the same compressive loading magnitude was applied dynamically (100 cycles per day, 1 Hz) an increase in cross-sectional area with 24% was observed, primarily from periosteal woven bone formation [66]. The same regime of 100 cycles per day and a frequency of 1 Hz – but now in a bending mode – was considered to study the effect of peak strain magnitude [67]. They found a linear relation ($R^2 = 0.69$) between peak strain magnitude and (increase in) cross-sectional area. Calculating the intercept with the x-axis (i.e. zero increase), it seemed that for the applied cyclic load a deformation of 1000 $\mu$ε was enough to maintain bone mass. Higher strains caused bone formation, while lower strains were associated with bone resorption. In order to assess the influence of the number of daily loading cycles, a bending load was applied at a frequency of 0.5 Hz that produced a peak strain of 2050 $\mu$ε. The number of loading cycles was 4, 36, 360 and 1800 [62]. Only 4 cycles were sufficient to maintain bone mass. For the other regimes, similar bone increases by means of woven bone formation were observed, indicating that the adaptive response was an all-or-nothing phenomenon and not a linear response to the number of cycles. Another parameter that seems to have an effect on the bone adaptive response is the loading frequency. McLeod and Rubin [68] used the same isolated adult avian ulna model and varied the frequency between 1 Hz and 30 Hz for different peak strain magnitudes. For all strain magnitudes, the amount of bone formation increased with increasing frequency. At 30 Hz, the minimum strain that was necessary to maintain bone mass was 300 $\mu$ε,
while in case of 1 Hz, this value increased to 1200 με. Moreover the sensitivity to an increase in strain magnitude was much higher for higher frequencies. A number of conclusions can be drawn from these animal experiments:

- Bone loading needs to be dynamic in order to maintain (or increase) bone mass. If only static loads are applied, resorption seems to occur.
- The bone adaptive response is not only sensitive to strain magnitude, but also to strain rate (frequency). A change in strain distribution may as well play a role.
- A limited amount of daily load cycles is sufficient to maintain or even increase bone mass. If bones are completely immobilized, disuse atrophy (resorption) takes place.
- Functional adaptation is different in mature versus growing bone.

Based on the in vivo measurements, different regions of strains have been defined that correspond to different adaptive responses in weight-bearing bones. Frost [69] has termed this the bone “mechanostat”:

- Disuse atrophy: below a certain strain value, resorption due to disuse is initiated. Different values have been proposed by different authors, ranging between 10 με [67], 50 με [65] and 200 με [70].
- Physiological load: comprises the range between disuse and mild overload: in this range bone tissue is in homeostatic equilibrium. Other terms that have been used to describe this region are “lazy zone” or “dead zone”.
- Mild overload: the strains are between 2000 and 4000 με. Peak strains that are encountered in this region can trigger an increase in bone mass (bone formation). Frost [69] suggested that there is a “minimum effective strain” that has to be exceeded in order to have a net bone formation.
- Pathologic overload: above a certain strain irreversible bone damage takes place, either by fatigue or by creep (or both). A strain value of 4000 με has been proposed as the lower limit of this region.

The described animal experiments were all carried out in load-bearing bones. Other bones in the skeleton, like e.g. the skull merely have a protective function and bone adaptive principles do not seem to be applicable here. In those bones the anatomy seems to be dictated by genetic and inherent physiological conditions. Moreover, the bone adaptive responses may be different in the vicinity of “special” tissues, like the periodontal ligament, that surrounds natural teeth. Orthodontic forces, which are static, are capable of translating and rotating teeth through the bone tissue by the induction of local bone resorption and formation (although even in this case a dynamic occlusal loading component is present). Bertram and Swartz [42] critically discussed the animal experiments of the 1970s and 1980s that studied bone adaptation. Based on the disuse experiments of amongst others Uthoff and Jaworski [63–65] they argued that there are prominent differences in the response of growing versus mature bone to the removal of functional load. It seems that mature animals are less sensitive to disuse. Moreover, the amount
of resorption in case of immobilization appears to be dependent on anatomical location as well: for mature dogs, Jaworski et al. [65] found a reduction in cross-sectional area of 40%, 10% and 3% for respectively the metacarpus, the radius and the humerus. Bertram and Swartz [42] mentioned that complete removal of loads could also interfere with other factors – like calcium regulating hormones, blood flow, oxygen and nutrient levels, pH – that are important for bone maintenance, so that mechanical load has only an indirect effect on disuse atrophy. In order to induce increased bone loading, many researchers performed an osteotomy of one of the paired limb bones (e.g. [61]). Bertram and Swartz focused attention on the fact that the surgical intervention itself can trigger an osteogenic response, even at anatomical locations that are far removed from the osteotomy. Such systemic reactions were observed by Bab et al. [71], who found increased bone formation at the mandibular condyle of rats, when bone marrow was removed from the tibia. As a consequence, it may not be possible in practice to distinguish the osteogenic effect of increased loading from the effect of surgical trauma. Therefore, one of the most elegant experiments that has demonstrated the bone adaptive response to dynamic loading are the experiments with the isolated adult avian ulna model, as developed by Lanyon and co-workers. In their experiments a control animal was included, that was subjected to the surgical protocol, but remained unloaded. For this animal, no possible osteogenic response to the surgery was observed, at the same time demonstrating that the bone formation encountered in the loaded animals are indeed attributed to the applied dynamic loading. To conclude this paragraph, it is important to notice that mechanical load is clearly not the only influencing factor. Nutrition (calcium deficit) and hormonal aspects are as important and can interfere with the effects of a change in loading conditions.

3.2 Mathematical models

For more than two decades researchers have tried to capture bone adaptive responses into mathematical laws. By implementing these “adaptive rules” into a feedback system that makes use of finite element modeling to calculate the local mechanical stimulus, the observed changes in bone geometry, density and/or orientation can be simulated or even – if possible – predicted. Two different approaches have emerged:

- strain-adaptive rules
- damage-based rules.

It must be noted that the existing theories concentrate on the prediction of bone resorption and formation below the range of pathologic overload. None of the theories reported in literature has incorporated pathological overload.

The founders of the strain-adaptive rules were Cowin and Hegedus [72], who developed their theory of adaptive elasticity. The adaptive rules are based on the assumption that bone tissue that is mechanically loaded, aims at an equilibrium level of strain, called the homeostatic strain level. The mechanical stimulus that drives the adaptive response is then calculated as the difference between actual and homeostatic strain. In case of external remodeling (cf. definitions previously
mentioned) the equation can be written as:

$$\frac{\partial X}{\partial t} = C_{ij} \left( \varepsilon_{ij} - \varepsilon_{ij}^0 \right), \quad (2)$$

where $X$ is the surface position of either the periosteum or endosteum, $\varepsilon_{ij}$ is the actual strain tensor and $\varepsilon_{ij}^0$ is the homeostatic strain tensor. $C_{ij}$ is a matrix of site-specific external remodeling rate constants. For internal remodeling a similar equation can be written, but now the change in (isotropic) elastic modulus $E$ (assuming that continuum mechanics is valid) must be considered

$$\frac{\partial E}{\partial t} = C'_{ij} \left( \varepsilon_{ij} - \varepsilon_{ij}^0 \right), \quad (3)$$

Again, $C'_{ij}$ is a matrix of internal remodeling rate constants. Instead of defining one threshold that determines the limit between bone resorption and bone formation, two threshold values can be defined as well in order to include a “lazy zone”. Others, like Carter et al. [73] defined a different mechanical stimulus, called the daily stress stimulus $\phi$, which is a magnitude-weighted summation of individual products of effective stress magnitude $\bar{\sigma}_i$ and daily count $n_i$ for multiple activity types of similar magnitude, given by:

$$\phi = \left[ \sum_{\text{day}} n_i \bar{\sigma}_i^m \right]^{1/m}. \quad (4)$$

The effective stress is defined as a fictitious stress, corresponding to a uniaxial stress and strain state that produces the same elastic strain energy density $U$ as the real three-dimensional stress and strain state:

$$U = \frac{\bar{\sigma}^2}{2E} = \frac{1}{2} \sum \sigma_{ij} \varepsilon_{ij}, \quad (5)$$

where $E$ is the (isotropic) elastic modulus and $\sigma_{ij}$ and $\varepsilon_{ij}$ are the stress and strain components respectively. Again, in order to simulate adaptive responses, a reference valued for $\phi$ must be defined. Carter and co-workers [73–75] applied the concept of the daily stress stimulus to calculate bone density distributions, starting from a homogeneous distribution. In this way, they did not distinguish between cortical and trabecular bone. One of the biggest problems in the previous equations is that a number of empirical constants must be determined. In practice, this is done by calibrating the model to animal experimental data.

Prendergast and Taylor [76] developed an alternative theory, based on damage accumulation. As was already mentioned, the formation of microcracks has been proposed to be responsible for the initiation of remodeling. Instead of assuming that bone aims at a constant level of a strain-based parameter, one could assume that the level of damage throughout the bone must remain constant. If bone is overdamaged, then new bone must be added to avoid that damage accumulation would cause fracture. Similarly, if the damage level drops below a certain level,
then bone mass is removed to reach an optimal level of damage. As to the latter, one could argue that a bone is inefficiently organized when the factor of safety for fracture is too large. Indeed, in that case the metabolic cost of maintaining the bone tissue would not be optimized with respect to the risk of fracture. Therefore the damage theory could be interpreted as an optimization of strength. The damage-based theory assumes that there is an equilibrium level damage of damage $\omega_E$. Suppose that the actual level of damage is $\omega$, then the stimulus for bone adaptation $\Delta \omega$ is calculated as:

$$\Delta \omega = \omega - \omega_E.$$  \hfill (6)

In the case of external remodeling eqn (6) can be rewritten as

$$\frac{\partial X}{\partial t} = C\Delta \bar{\omega},$$  \hfill (7)

where $C$ is a rate constant that has to be determined. Equation 7 relates the apposition or resorption rate at the periosteal or endosteal envelopes to the total amount of damage in the bone. Mori and Burr [57] have observed increased remodeling in the direct vicinity of microcracks. Martin et al. [70] argued that one of the most important tasks of remodeling is the repair of damaged bone tissue. However, this does not prove that the presence of internal cracks can trigger a modeling response at the periosteum or endosteum.

### 3.3 Case studies

Although many researchers have suggested the important role of mechanical loading in the long-term success of oral implants, there is still a lack of quantitative data on peri-implant bone tissue loading during function. A rabbit experiment was set up to study the peri-implant bone response to cyclic loading [24, 77, 78]. At the same time, an individualized, image-based FE model was created, in order to calculate the bone stresses and strains during this cyclic loading experiment, and to relate them to the observed bone response (case study 3.3.1). The results of this finite element model only give an insight into the “initial” stress and strain distribution, i.e. before any marginal bone loss has taken place. In order to fully understand the role of mechanical loading in peri-implant bone response, it is necessary to simulate the changes in bone geometry and/or density and study their influence on stresses and strains. Therefore, a computer algorithm was programmed that simulates overload-induced bone resorption (case study 3.3.2).

#### 3.3.1 Animal study

The aim of the study presented below was to verify whether “excessive” implant load can lead to increased (marginal) bone loss or even complete loss of implant fixation by comparing animal experimental data with data obtained from FE analyses.

#### 3.3.1.1 Materials and methods

A rabbit experiment was set up, in which a cyclic transverse force was applied to a screw-shaped titanium implant (self-tapping Brånemark implant) that was bicortically fixed in the part of the tibial diaphysis. No
trabecular bone was present around the implants. Ten rabbits were included in the study and per rabbit a test (loaded) and a control (unloaded) implant were installed in the left tibia.

All implants were allowed to heal subcutaneously for 6 weeks, after which the cyclic loading experiment was started. A cyclic pulling force with amplitude of 14.7 N (1.5 kg) was manually applied perpendicular to an aluminium beam that is mounted on top of the abutment (total length of beam + abutment is 50 mm). In order to control the force amplitude in each cycle, two strain gauges were attached to the outer surface of the beam to register the either tensile or compressive bending strain. Since both strain gauges were mounted opposite to each other at the same distance of the applied force, only the sign of the measured strain is different. This configuration allowed the compensation of the strain signal for possible fluctuations in temperature. The frequency of the manually applied cyclic load was approximately 1 Hz. During the first week of the loading experiment 90 cycles per day were administered. During the second week the number of daily cycles was increased to 270, so that the total duration of the animal experiment could be shortened (in order to prevent an inflammatory reaction of the skin to manipulation of the loading device).

After animal sacrifice histomorphometrical analyses of all test and control implants were performed. One ground section was prepared in the middle of each implant parallel to the load direction (sagittal plane). For one randomly selected rabbit a μCT scan (Skyscan 1072) was taken from the test implant before section preparation. This allowed the assessment of the bone response around the entire implant (and not only in the loading plane) and the creation of an individualized, μCT-based FE model of the implant and the part of the tibia that was scanned.

Solid models were created in a computer-aided design (CAD) programme (Unigraphics) for both the bone and the implant. The μCT data was used to derive the correct anatomy and the correct position of the implant relative to the tibia. The solid model of the implant was created, based on known dimensions of the self-tapping Brånemark implant (length 10 mm, diameter 3.75 mm). For the solid model of the tibia a medical image processing programme (Mimics) was used to derive contours (polylines) that describe the outer and inner surface of the cortical bone. The contours were imported in Unigraphics, where surfaces were fitted to these contours. Once the solid models were obtained, the position of the implant solid model was aligned with the correct position of the implant, as determined from the μCT data. A Boolean operation was performed to create the implant insertion hole in the tibia. Tetrahedral meshes (four-noded tetrahedral elements) were created within Unigraphics for both solids (fig. 9). Orthotropic elastic properties were applied to the cortical bone [79] (table 3). Titanium was modeled as isotropic with a Young’s modulus of 110 GPa and a Poisson ratio of 0.3.

Nonlinear, static contact analyses were performed, using the MSC.Marc/Mentat FE programme. In a first series of analyses a finite interfacer tensile strength was used, resulting in relative motion between the implant and the bone when tensile stresses exceed the tensile strength. Although exact values for the tensile strength of the implant-bone interface in case of “smooth” titanium are lacking, it can be
Figure 9: FE meshes for implant and bone.

Table 3: Elastic orthotropic properties of cortical bone, used in the FE model according to Ashman et al. [79]. The 1-direction is the radial direction of the tibia, 2-direction the circumferential direction and 3-direction the axial direction.

<table>
<thead>
<tr>
<th>Young’s modulus [GPa]</th>
<th>Shear modulus [GPa]</th>
<th>Poisson’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_1$</td>
<td>$E_2$</td>
<td>$E_3$</td>
</tr>
<tr>
<td>12.8</td>
<td>15.6</td>
<td>20.1</td>
</tr>
</tbody>
</table>

estimated to be of the order of 0.5–1 MPa, based on literature values for other biomaterials and surface roughness [80]. Additionally, an analysis was performed with a fully-bonded interface (infinite strength), preventing any relative motion.

The nodes at the outer proximal and distal boundaries of the bone mesh were fully constrained. Loading conditions, corresponding to the force amplitude in the cyclic loading experiment, were applied (lateral force 14.7 N, bending moment 73.5 Ncm).

### 3.3.1.2 Results and discussion

The µCT scan of the test implant revealed the occurrence of marginal bone resorption in the loading plane, but not in a direction, perpendicular to it. As can be appreciated from fig. 10, bone craters were formed at both the proximal (“tensile”) and the distal (“compressive”) side.

As to the finite element analyses, relative motion occurs at the proximal (i.e. “tensile”) side of the implant neck for all considered values of finite interfacial tensile strength (1, 5 and 10 MPa). As a result, only large compressive forces are developed between the implant neck and the bone at the distal side. This is reflected in the equivalent strain distribution, shown in fig. 11: large equivalent strains (more
Figure 10: µCT image of a test implant in a sagittal plane (i.e. loading plane (left) and a medio-lateral plane (right)). The direction of force application is also indicated.

Figure 11: Equivalent strain distribution in the case of a finite interfacial tensile strength of 1 MPa: sagittal (left) and transverse (right) cross-section. Other finite strengths (5, 10 MPa) yield the same results.

than 4000 µε) occur at the distal side of the implant neck, while at the proximal side much smaller strains (1100 µε) exist. The equivalent (Von Mises) strains encountered around the implant neck in a medio-lateral cross-section are much lower than at the distal side (around 2000 µε). They are the result of normal tensile strains in the proximo-distal direction, occurring medially and laterally from the implant neck.

For an infinite interfacial strength the maximum strains are smaller: equivalent strains proximally and distally from the implant neck amount to 2500 µε. Since tensile stresses can now be transferred as well, a much more symmetric equivalent strain distribution is obtained.

Since a value of 10 MPa seems to strongly overestimate the actual interfacial tensile strength of a “smooth” machined titanium surface, it is likely that relative
motion occurred during the cyclic loading experiment. Therefore, the strain distribution in fig. 11 must be regarded as more representative for the peri-implant bone tissue loading than the strain distribution in case of an infinite interfacial strength, which implies that only the distal side experienced high strains. Nevertheless, histomorphometrical analysis of all test implants did not show any statistically significant difference in crater depth, crater width or marginal bone contact between the proximal and distal sides. At both sides a continuing process of bone resorption (Howship’s lacunae) was observed. For the marginal bone resorption at the distal (“compressive”) side it seems reasonable that overload caused the excessive marginal bone loss, since strains were calculated that even exceeded 4000 µε. Frost [81] considered this to be the threshold for pathologic overload, although this value might not be that absolute. Possibly, due to the high bone stresses and strains microcracks were formed at the distal side, which in turn activated osteoclasts to resorb bone tissue [57]. However, looking at the strain values at the proximal side (1100 µε), neither overload nor underload (disuse atrophy) seem to be a plausible explanation. One could hypothesise that relative motion also plays a role in the observed bone response. Previous animal experiments have indeed shown that relative motion can interact with tissue differentiation processes around endosseous implants [7]. At the moment, it is not clear whether relative motion can also interfere with osteoclastic activity in “mature” bone. The relative displacements (“gaps”) at the proximal side were in the range of 10–15 µm. This is an order of magnitude smaller than the relative motion, encountered in the experiments of Søballe et al. [7]. Again, it is not clear if such small relative displacements can play a significant role in bone adaptive/resorptive processes. Besides, since relative (tangential) displacement is also taking place at the medial and lateral sides of the implant neck – although to an even smaller extend – one could also expect marginal bone resorption to be present at these sides. This could not be detected in the µCT scan of the test implant.

### 3.3.2 Simulation of marginal bone resorption

The results of the finite element model discussed above only give insight into the “initial” stress and strain distribution, i.e. before any marginal bone loss has taken place. In order to fully understand the role of mechanical loading in peri-implant bone response, it is necessary to simulate the changes in bone geometry and/or density and study their influence on stresses and strains. Therefore, a computer algorithm was programmed that simulates overload-induced bone resorption.

#### 3.3.2.1 Materials and methods

In order to study the interaction between a change in marginal bone level and a change in stress state a simple iterative feedback algorithm was developed that relates pathological overload to bone resorption (fig. 12). When the average effective stress in an element exceeded a pre-defined threshold value, this element was removed in order to simulate overload-induced bone resorption. This process was repeated until a new equilibrium geometry (no more overload) or until complete loss of osseointegration (no equilibrium) was obtained.
The iterative feedback algorithm was applied to a finite element model of a single cylindrical implant, surrounded by a cylindrical cortical bone volume (fig. 13). Cortical bone was modeled as isotropic \((E = 15.5 \text{ GPa}, \nu = 0.31)\) [82]. A fully bonded interface was assumed between bone and implant. The same load amplitude and direction as in the rabbit experiment was applied. Nodal displacements on the
outer cylindrical surface were fully constrained. Eight-noded hexahedral elements were used for the mesh.

A first simulation was performed with equivalent Von Mises stress as the effective stress. It must be remarked that Von Mises stress is only physically meaningful for isotropic materials and should not be used to characterize the stress state in case of anisotropic materials – like cortical bone [83, 84]. For the purpose of this study the use of Von Mises stress is acceptable, since only qualitative results are of interest here. The simulation only considered bone resorption due to pathological overload. Other adaptive responses (resorption due to disuse, formation due to mild overload) were not yet included. Moreover no attempt was made to simulate resorption as a function of time.

3.3.2.2 Results and discussion  Overload-induced marginal bone resorption was initiated at the marginal bone edge in the loading plane. For an overload threshold of 31 MPa (in terms of Von Mises stress) resorption was arrested and a new equilibrium geometry was found, as depicted in fig. 14. Resorption (removal of elements) did not progress around the entire implant, but was limited to bone regions in or near the loading plane. The total decrease of the marginal bone level in the loading plane amounted to 1 mm. When a smaller value for the overload threshold was chosen, no equilibrium was established. Again, resorption was initiated in the loading plane, but progressed in the circumferential direction until a complete ring of elements was removed at the marginal bone edge. Subsequently, resorption advanced in the axial direction towards the implant apex along the entire implant surface until all bone at the implant surface was lost. This situation can be considered as a complete loss of osseointegration due to overload.

Due to the simplicity of the finite element model and the simulation algorithm quantitative results are of minor importance. However qualitative trends are still

![Figure 14: Marginal bone decrease for the equilibrium configuration. The Von Mises stress distribution (in MPa) is also shown.](image-url)
valid. Figure 15 illustrates the change in stress distribution and stress values when marginal bone resorption takes place. It demonstrates that when overload-induced resorption is initiated in the loading plane, the maximum stresses at the marginal bone level decrease in the loading plane, while they increase in the plane perpendicular to it. These results suggest that a shift in stress transfer occurs during resorption. In the new equilibrium configuration the bone in the plane perpendicular to the loading direction carries a larger portion of the applied load than in the initial configuration. Once the stresses in the loading plane drop below the threshold, resorption is arrested. As long as the (increased) stresses in the plane perpendicular

![Stress distributions](image)

Figure 15: Bone stress distribution in the loading plane (top) and the plane perpendicular to it (bottom) for the initial bone geometry (“start”) and the new equilibrium geometry (“end”). Stresses are evaluated along a straight line in the nodes at the implant-bone interface. Results were obtained for an overload threshold of 31 MPa.
to the loading plane do not exceed the threshold, resorption will not be initiated at this side. This situation was encountered for an overload threshold of 31 MPa (or larger). When resorption is initiated in the plane, perpendicular to the loading plane (either due to a lower overload threshold or due to a higher implant load), it cannot be arrested anymore. This results in a complete loss of osseointegration, as was encountered for thresholds, smaller than 31 MPa.

These results indicate that overload-induced marginal bone resorption can be arrested as long as initiation of resorption is limited to the loading plane. In reality resorption might be arrested by other mechanisms as well, e.g. densification ( stiffening) of peri-implant bone. The simulation algorithm must further be elaborated to also include these adaptive responses.

4 Conclusion

This chapter described the different causes of failure that might occur in the clinical application of oral implants. A mechanical failure refers to the fracture of an implant component whereas a biological failure refers to problems with the osseointegration.

When an implant fails shortly after implantation, this is usually due to the unsuccessfulness of the osseointegration. The mechanics and the biology of the peri-implant site seem to play a major role herein. The complex process of bone regeneration is described by means of its most studied example: fracture healing in long bone. The theoretical models that aim to simulate the above described process of bone regeneration were divided into mechanoregulatory and biological models, depending on the parameters they employ to drive the differentiation process. The mechanoregulatory models predict fibrous tissue formation when the mechanical stimulus (strain, stress, fluid flow) has a high value (corresponding to a severe loading of the fracture zone or implant). The case studies presented in Section 2 described the application of different mechanoregulatory and biological models for the prediction of peri-implant tissue differentiation in an \textit{in vivo} bone chamber. There were qualitative agreements between the numerically predicted and experimentally observed tissue phenotypes in the chamber. Additional histological analyses of samples, harvested at different phases in the regeneration process are needed however to be able to quantify these results.

Late biological failure mostly occurs due to inappropriate implant loading. Numerous animal experiments were conducted to describe the influence of the different aspects of loading (magnitude, frequency, duration) on bone adaptation. Theoretical models try to capture these phenomena into mathematical expressions. The first case study discussed in Section 3 compares the peri-implant bone stresses and strains measured during a controlled loading animal experiment with those same variables calculated from an anatomical FE-model. Marginal bone loss occurring during the experiment could only partially be related to overload. The second case study further explored the relation between marginal bone resorption and overload by implementing a theoretical model for bone adaptation. A redistribution of the
peri-implant bone stresses during the adaptation process put a hold on the marginal bone resorption.

All of the theoretical models presented in Sections 2 and 3 are situated on a continuum level. The mechanical variables employed by the mechanoregulatory models are the tissue stress, strain, strain energy density or the fluid flow velocity. The biological model bases the tissue differentiation on the concentration of cells and growth factors and on ECM densities. However, the processes of bone regeneration and bone adaptation are becoming more and more understood although the exact influence of the mechanical factors and their interaction with the biochemical regulatory pathways is not yet fully unravelled. While these subcellular processes are being investigated from the biological point of view, the theoretical models also need to bring these processes into account and aim to generate mechanistic models that incorporate both mechanical and biological factors on a subcontinuum level. Only then, theoretical models really can contribute to a better understanding of the experimentally observed phenomena and help to gain insight into the mechanisms that are very hard to investigate experimentally.

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32 Computational Modeling of Tissue Surgery


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