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Tag der mündlichen Prüfung:

To my Parents
Meinen Eltern

Analysis of Bone Remodeling An Application for Tooth Movement

Abstract

This thesis investigates a mathematical model that tries to consider most processes involved in bone formation and bone resorption. It takes the solid bone matrix and the fluid phase as bone marrow into account as well as the influences of bone cell populations on the bone remodeling cycle. The role of parathyroid hormone and calcium homeostasis and the signaling pathways between bone cells are also studied.

A complex mathematical model is derived which results in a free boundary problem as bone is constantly changing its shape and architecture. We find in the model on the macroscopic level equations for linear elasticity and Navier-Stokes equation. On the basic unit level we study equations for diffusion and transport, chemotaxis and partial differential equations for bone cell populations.

The general complex model for bone remodeling is then simplified and applied to a chosen problem in orthodontics, the movement of a tooth through bone. Tooth movement caused by braces is a possible application of our general model. Here the equations of Biot for a porous medium, the periodontal ligament, are used and combined with a free boundary. We use the homogenized system and are able to derive effective equations for the displacement and pressure.

We suggest for the analysis the Rothe method and prove in this thesis the existence of solutions for the Rothe iteration step. The full convergence proof for the free boundary problem is a problem for itself.

Zusammenfassung

Diese Arbeit untersucht durch mathematische Modellierung die Prozesse die beim Knochenumbau eine Rolle spielen, wobei sowohl der solide Anteil der Knochenmatrix, als auch der flüssige Anteil des Knochenmarks berücksichtigt werden. Darüber hinaus werden auch die Einflüsse der Knochenzellenpopulationen näher unter die Lupe genommen. Auch die Rolle des Parathormons und des Kalziumhaushalts und die Signalwege zwischen den Knochenzellen werden untersucht. Daraus entsteht ein komplexes Modell mit einem freien Randwertproblem, da Knochen sich ständig verändert. Im makroskopischen Modell finden wir partielle Differentialgleichungen, die die lineare Elastiziät beschreiben, wie auch Navier-Stokes Gleichungen. Im mikroskopischen Modell erhalten wir Gleichungen für Diffusion, Transport und Chemotaxis, aber auch partielle Differentialgleichungen, die die Knochenzellenpopulationen beschreiben.
Das allgemeine Modell wird dann vereinfacht und auf ein ausgewähltes Problem in der Kieferorthopädie angewendet, der Bewegung eines Zahnes durch den Knochen. Die Zahnbewegung ausgelöst durch eine Zahnspange ist eine mögliche Anwendung unseres allgemeinen Modells. Hier tauchen die Biot Gleichungen für ein poröses Medium auf, die auf das periodontale Ligament angewendet werden. Wir verwenden das homogenisierte System und erhalten effektive Gleichungen für die Verschiebung und den Druck.
Wir benutzen dann die Rothe Methode zur Analyse des Problem und beweisen in dieser Arbeit die Existenz von Lösungen des Rothe Iterationsschrittes. Der volle Konvergenzbeweis des freien Randwertproblems ist ein Problem an sich, da sich das Gebiet ständig verändert.

Acknowledgements

No man is an island, entire of itself
Every man is a piece of the continent, a part of the main ...
-John Donne

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Contents

1 Introduction

"What is in the marrow is hard to take from the bone."
(Irish saying)

The above stated Irish saying gives an idea of how complicated and yet so interesting the interaction between bone and bone marrow are.
Bone and its architecture has been of interest for researchers for more than a decade now. After twenty-five years of work in skeletal anatomy, adaption, and orthopaedics, Julius Wolff (1836-1902), a German surgeon, published his work on bone transformation in Berlin in 1892. Today his work is known as bone remodeling and modeling. Wolff's work and his general view of how a limb bone's morphology develops has evolved into a concept known today as Wolff's law, which is essentially the observation that bone changes its external shape and internal cancellous architecture in response to stresses acting on it.
Many contemporary investigators still ascribe to the idea that there is a Wolff's law, the fact that bone models and remodels in response to the mechanical stresses it undergoes.

Bone is a dynamic, living tissue whose structure and shape continuously changes and adjusts to changing mechanical or metabolic needs. A rigid skeleton makes it possible to support weight and ensures protection of organs and muscles. In addition bone also plays an important role in the maintenance of serum-mineral metabolism, and is considered an important component of the immune system.
There are two types of bone the compact and the cancellous bone. In this thesis we will focus on the cancellous or trabecular bone, which has a very random honeycomp structure.
Cancellous bone can be interpreted as a porous medium where we have a solid part, the mineralized bone matrix, and a fluid part, the bone marrow. Within the mineralized part we find osteocytes, osteoclasts and osteoblasts, the bone cells, that continuously change the structure and the strength of bone.

Throughout the literature many articles have been published about bone remodeling with the discussion on diverse issues. The mathematical papers either focus on detailed processes on the cell level or concentrate on the macroscopic porous structure.

Komarova (2003) develops a mathematical model that predicts a critical role for osteoclast autocrine regulation in the control of bone remodeling.
Zumsande, et al. (2011), Ayati, et al. (2010) and Lemaire, et al. (2004) analyzed mathematical models for bone remodeling, where the populations of osteoblasts, osteoclasts and osteocytes and their interactions were considered.
Kroll (2000) focused on the temporal hormonal effect of the parathormone on bone formation and resorption.
Mikelic et al. and Gilbert published various articles about the macroscopic porous structure where the system is homogenized. [37], [38], [39], [72]
We also find assorted articles about bone remodeling where the finite element method is used to analyze the system.
There are also various papers about the analysis of the Biot equations but the free boundary is neglected. Badia et al. (2008, 2009) investigated the coupling of Biot- and Navier-Stokes equations for modeling fluid-poroelastic media interaction.
The influence of calcium homeostasis on the bone remodeling process were neglected in most papers and although all articles state that the bone structure is constantly changing suprisingly, none takes the free boundary into account.

The aim of this thesis is to develop a mathematical model for cancellous bone that combines the processes involved in bone resorption and formation together with the fact that the domain of the bone constantly changes due to mechanical loading and changing metabolic needs. In our model we combine porous media with bone cell populations, signaling, piezoelectricity and influences of calcium and parathormone on the bone remodeling process.
Bone is a biosystem demanding a multiscale approach. Due to its complexity, linking the mathematical models on different scales is a challenge to mathematics which is still beyond reach e.g. for homogenization. In this investigation we derive model equations, which describe processes on the meso-scopic level, not on the cellular level, but on the level of a basic unit of a reticulated structure. The equations cover the flow, reactions, signaling, diffusion, transport und mechanics in process-depending domains.
Here we are using the approach to include in a first step all processes which might be important to understand bone remodeling, and to reduce in a second step the system to a less complex model system, including only those factors and features, which are necessary to answer the given questions. We apply our model to the porous structure of the periodontal ligament surrounding the tooth, which is adjacent to the bone. The idea for this application came up in a cooperation with Professor Dr. Lux from the orthodontic department of the Heidelberger Dental Clinic, and during the development process, there has been active exchange between his work group and the IWR.

The result of this investigation can be summarized as follows:

- Derivation of a system consisting of nonlinear partial differential equations on solution-depending domains and interfaces, modeling blood flow, the mechanics of the mineralized bone matrix, calcium and parathyroid hormone concentrations and their influence on the bone remodeling process, diffusion and transport of calcium ions and hormones as well as populations and interactions between osteocytes, osteoblasts and osteoclasts, and signaling

- Derivation and mathematical analysis of a reduced system for tooth movement through bone. The periodontal ligament is described with a mathematical model that uses the Biot equations. Our domain borders to the bone on one side and on the tooth on the other. We assume osteoblasts and osteoclasts to respond to pressure and tension directly.

- Suggestion of the Rothe method as a constructive approach of solutions. An existence proof for the discretized problem is presented. A full convergence proof for the free boundary problem will be treated in a future investigation.

The thesis is structured as follows.

Chapter two describes the biological background of bone, osteoblasts, osteoclasts and osteocytes and the substances that are involved in the bone remodeling circle. It also explains the complex process of calcium homeostasis and the role of the parathormone and their connection to bone remodeling. Bone responds to mechanical loading as well as to metabolic needs. The signaling pathways and the special role of the osteocytes, which have a sensing function, are also explained in this context.

Chapter three provides a general model for resorption and adaption of bone in response to loading and metabolic needs and the processes involved in it. It is of great interest to develop a very general model which takes all processes into account. We are then able to simplify the model and thus can neglect some of the equations in the general model. Our general model is therefore applicable to a variety of other disciplines where porous media is involved.
We consider a porous medium with fluid flow of the blood and a solid part which is the mineralized bone matrix. The blood flow can be described with Navier Stokes equations and the mechanics can be described with the equations of linear elasticity. We also consider diffusion and transport processes of calcium ions and parathormone in the fluid, in the bone matrix we also take signaling into acount. We also look at the bone cell populations and how they influence each other. Here

we find equations for processes of chemotaxis. The evolution of the free boundary is also described.
We are not able to homogenize this model because the system of equations is very big and the aim is rather to show the applicability of this model. The general model should rather be seen as a starting point which can be very useful for questions in other disciplines.
In the following chapter we show that our model can be simplified and used in orthodontics.

In chapter four of this thesis we will show that it is possible to apply the general model developed in chapter three to orthodontic tooth movement with some simplifications. We apply our model to the porous structure of the periodontal ligament which is adjacent to the bone.
When simplifying the model we will come across the Biot equations, which have been a matter of interest for a long time now. We will neglect sensing and signaling as we assume a direct influence of pressure and tension on the osteoblasts and osteoclasts.
As the system of equations is much smaller than the general model presented in chapter three we are then able to derive from the homogenized system for the periodontal ligament effective equations for the displacement and pressure. The domain has a free boundary at the bone side and a fixed but moving boundary at the side of the tooth.

Chapter five presents a mathematical analysis of the simplified model with the free boundary and the moving but fixed boundary for orthodontic tooth movement. We use the Rothe-method to discretize the system in time and prove existence of weak solutions with the theorems of functional analysis, e.g. the Lax-Milgram theorem.

In chapter six we give a short outlook of how our general model presented in chapter three could be used in other disciplines where porous media is a matter of interest. Although the system of equations is huge in the general model, it is impossible to leave out any processes as it would make the model unuseful for research in medicine or other disciplines with a slightly different question.

2 Biological background of bone

This chapter describes the structure of bone and its function in our body. As bone is constantly rebuilding this chapter also has a closer look on this phenomenon and the biological and chemical processes involved.

2.1 Bone classification

Bone is not a uniformly solid material, but rather has some spaces between its hard elements. The following figure shows the two kinds of osseous tissue, compact and cancellous or spongy bone.

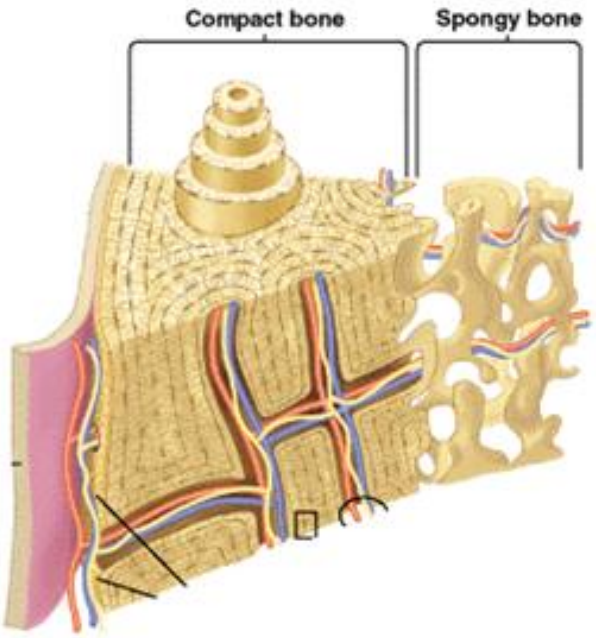

Figure 2.1: Compact and cancellous bone (www.fau.pearlashes.com)

As shown in the figure above usually both structures occur together or next to each other.

2.1.1 Compact bone

The hard outer layer of bones is composed of compact bone tissue, so-called due to its minimal gaps and spaces. Its porosity is five to thirty percent. This tissue gives bones their smooth, white, and solid appearance, and accounts for eighty percent of the total bone mass of an adult skeleton. Compact bone may also be referred to as dense bone.
We find nerves, blood vessels and osteons in compact bone. It is surrounded by the periosteum.

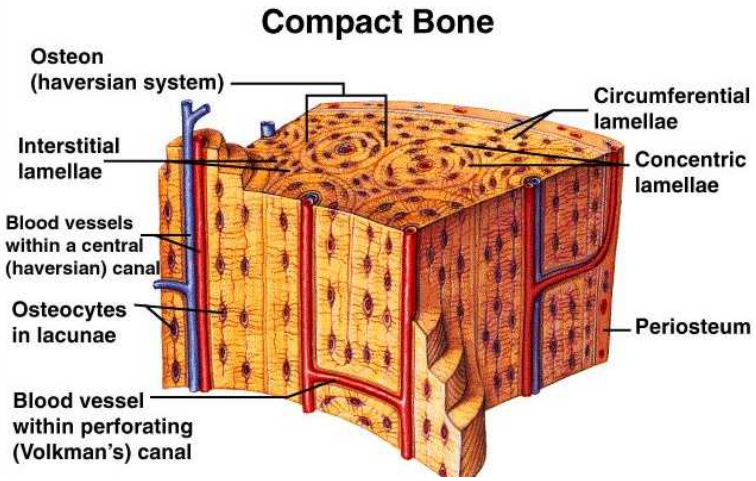

Figure 2.2: Structure of compact bone (www.fau.pearlashes.com)

2.1.2 Cancellous bone

Cancellous bone, synonymous with trabecular bone, alveolar bone or spongy bone, is one of the two structures of osseous tissue that form bones. Compared to compact bone, it has a higher surface area but is less dense, softer, weaker, and less stiff. Its porosity is thirty to ninety percent. It typically occurs at the ends of long bones, proximal to joints and within the interior of vertebrae.
Cancellous bone is highly vascular and frequently contains red bone marrow where the production of blood cells occurs. The primary anatomical and functional unit of cancellous bone is the trabeculae. These vertical and horizontal struts are oriented along force-field lines of recurrent mechanical stress.
Trabecular bone tissue fills the interior of the bone. It has a porous random network, which is composed of a honeycomb network of rod- and plate-like elements that make the overall organ lighter and allowing room for blood vessels and marrow. Trabecular bone accounts twenty percent of the total bone mass.

Bone surrounds blood in the compact bone, while blood surrounds bone in the cancellous bone.

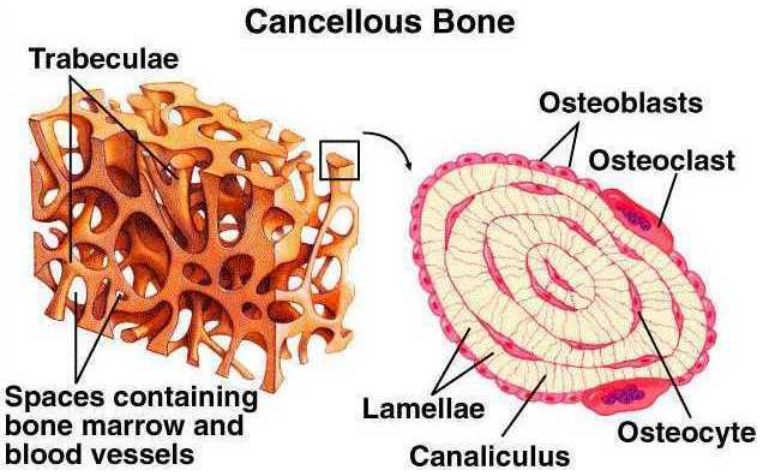

Figure 2.3: Structure of cancellous bone (www.fau.pearlashes.com)

2.1.3 Distribution of bone marrow

There are two types of bone marrow: the red marrow, which consists primarily of hematopoietic tissue, and yellow marrow, which is mainly made up of fat cells. Red blood cells, platelets and most white blood cells grow in red marrow. Both types of bone marrow contain numerous blood vessels and capillaries. Only around half of adult bone marrow is red. Red marrow is found mainly in the flat bones, such as the pelvis, sternum, ribs, vertebrae, and in the cancellous material at the ends of long bones such as the femur and humerus. Yellow marrow is found in the medullary cavity, and the hollow interior of the middle portion of long bones. (see figure 2.4)

2.2 Cellular structure

There are several types of bone cells constituting the bone. Osteoclasts and osteoblasts are located on the surface of the trabeculae whereas the osteocytes can be found inside the bone matrix. Therefore the osteoclasts and osteoblasts have direct contact to the bone marrow neighbouring them.
Figure 2.4 shows the location of the bone cells.

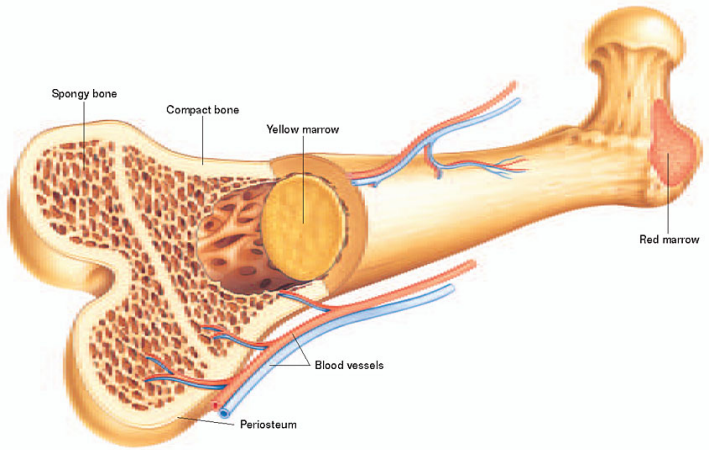

Figure 2.4: Bone marrow within cancellous bone (cooter.k12.mo.us)

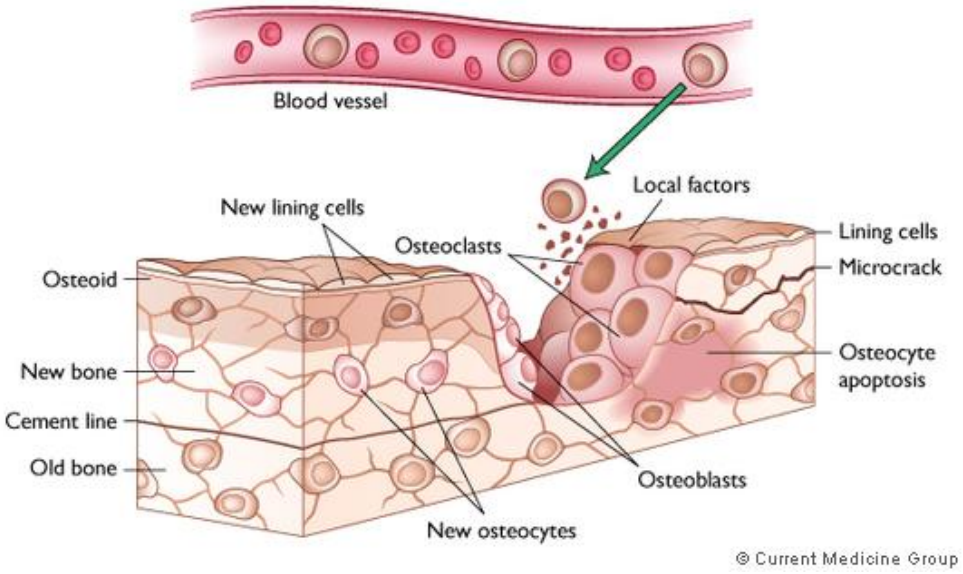

Figure 2.5: Bone matrix with bone cells (www.extra.springer.com)

2.2.1 Osteoblasts

Osteoblasts are cells that descend from osteoprogenitor cells. They are located on the surface of osteoid seams and create a protein mixture known as osteoid, which mineralizes to become bone. The osteiod seam is a narrow region of newly formed organic matrix, not yet mineralized, located on the surface of a bone. Osteoblasts also produce hormones to act on the bone itself. They cultivate alkaline phosphatase, an enzyme that has a role in the mineralization of bone, as well as many matrix proteins. Osteoblasts are the immature bone cells, which form new bone. [36]

2.2.2 Osteoclasts

Osteoclasts are the cells responsible for bone resorption or remodeling, thus they reduce the volume of the bone mass. Osteoclasts are large cells also located on bone surfaces. Osteoclasts mature and migrate to discrete bone surfaces. Upon arrival, active enzymes are secreted against the mineral substrate. They move to areas of microstructure in the bone by chemotaxis, where they then lie in a small cavity called Howship's lacunae. [36]

2.2.3 Osteocytes

Osteocytes originate from osteoblasts that have migrated and become trapped and surrounded by bone matrix that they themselves produce. The spaces they occupy are known as lacunae. Osteocytes have many processes that reach out to meet osteoblasts and other osteocytes probably for the purposes of communication. They serve different functions: formation of bone, matrix maintenance and calcium homeostasis. They have also been shown to act as mechano-sensory receptors regulating the bone's response to stress and mechanical load.
Osteocytes can be divided into osteoblastic osteocytes and osteolytic osteocytes. The first ones named carry tricalcium phosphate, which is responsible for bone growth whereas the others are able to resorb calcium from the bone matrix and are also responsible for bone resorption.
Osteocytes can accumulate or extrude calcium, depending on their microenvironment and on hormonal factors, and can therefore be considered to be ideally suited to effect rapid changes in extracellular fluid calcium concentrations. (Matthews, 1971, 589)
Osteocytes are connected to each other through small canals called canaculi. Because of these canaculi they are able to communicate with each other. The interactions between osteoclasts and osteoblasts, which guarantee a proper balance between bone gain and loss, are known as coupling.

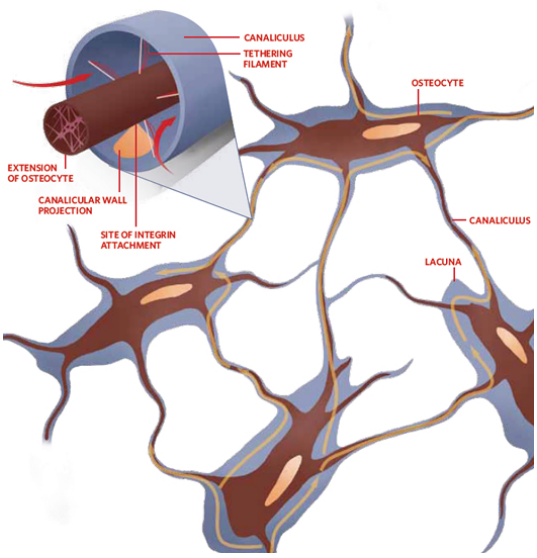

Figure 2.6: Osteocytes and their canaculi (www.the-scientist.com)

2.3 Molecular structure

Bone consists of the bone matrix, which is made up of an organic and an inorganic part. The hardening of this matrix entrapping the cells is forming bone. These cells are derived from osteoblasts and become osteocytes. The organic part, which is made of collagen, mucopolysaccharides, and non-collagenous proteins, is of less importance for our model. The organic part is also composed of various growth factors, the functions of which are not fully known. One of the main things that distinguishes the matrix of a bone from that of another cell is that the matrix in bone is hard. The inorganic part has two major components: calcium and phosphorus.

2.4 Functions of bone

Bones have several main functions: mechanical, synthetic and metabolic.

2.4.1 Mechanical

Bones serve to protect internal organs and they also provide a frame to keep the body supported. Bones with skeletal muscles, tendons, ligaments and joints

function together to generate and transfer forces so that individual parts of the body can be manipulated.

2.4.2 Synthetic

Bones also play an important part in blood production. The marrow, located within the medullary cavity of long bones and interstices of cancellous bone, produces blood cells in a process called haematopoiesis.

2.4.3 Metabolic

Bones also function as mineral storage. They act as reserves of minerals important for the body, most notably calcium and phosphorus.
The mineralized bone matrix stores important growth factors such as insulin-like growth factors, transforming growth factor, bone morphogenetic proteins and others.
The yellow bone marrow acts as a storage reserve of fatty acids.
Bone also buffers the blood against excessive pH changes by absorbing or releasing alkaline salts.
Bone tissues are also able to store heavy metals and other elements, removing them from the blood and reducing their effects on other tissues. These can later be gradually released for excretion.

There are different reasons why bone constantly remodels and changes. It basically adjusts to metabolic and mechanical needs. In the following we will have a closer look at the remodeling process and the causes for this.

2.5 Bone remodeling

Even after developmental and longitudinal growth is complete, bone keeps its ability to change its internal structure by removal of old bone and its replacement with newly formed bone in localized processes called remodeling.
Remodeling is an important property of bone that allows adaption to a changing mechanical environment. Packets of bone are removed where the mechanical demand of the skeleton is low and new bone is formed at those sites where mechanical strains are detected.

2.5.1 Stages

The bone remodeling process can be divided into four stages. Each remodeling process is initiated by an activation by which osteoblastic cells start to secrete collagenase, which removes the thin layer of unmineralized bone surface. This exposes the mineralized bone underneath to the mobile osteoclasts. During osteoclastic bone resorption, Howship's lacunae are excavated. A short reversal phase, where the cement line is formed, follows, and then bone formation normally begins. If coupling has taken place, osteoblasts deposit new bone matrix, which is initially unmineralized and called osteoid. When the osteoid thickness has reached approximately 12-15 μm, mineralization begins from the bottom. At the termination of each remodeling process, the bone surface is again covered by an extremely thin layer of non-mineralized bone and a layer of flat lining cells. The bone is again converted into a resting surface. The following figure shows the bone remodeling cycle. [45], [59],[97]

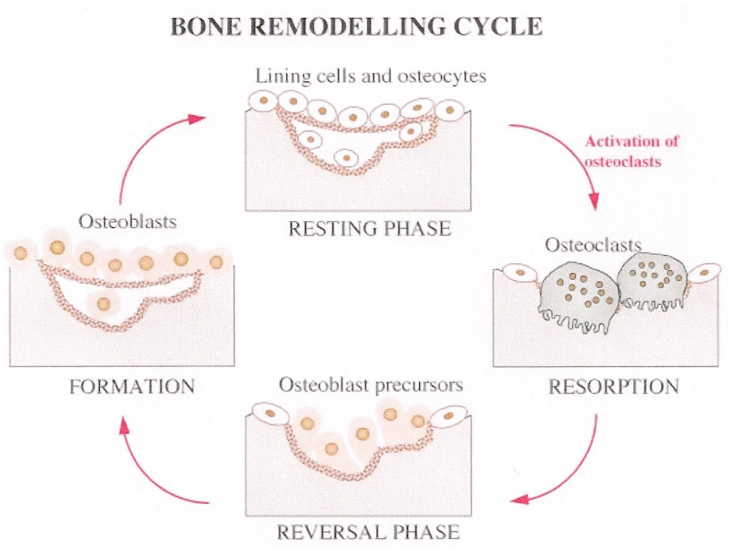

Figure 2.7: Different phases in the bone remodeling process/cycle Hill (1998)

Bone remodeling is a complex process involving a number of cellular functions and it is regulated by systemic hormones and by local factors.

2.5.2 Regulation

Many hormones affect bone growth and remodeling but bone also produces hormones thus is itself an endocrine organ.

The parathyroid hormone (PTH) regulates serum calcium levels and enhances the release of calcium from the large reservoir contained in the bones. Bone resorption, which is also called osteolysis, is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH. Stimulation is not direct since osteoclasts do not have a receptor for PTH; osteoblasts, the cells responsible for creating bone, have receptors for PTH and so PTH rather binds to these cells. Binding stimulates osteoblasts to increase their expression of substances, which can bind to osteoclast precursors. The binding stimulates these precursors to fuse, forming new osteoclasts which ultimately enhances bone resorption.
Calcitonin acts to reduce blood calcium, opposing the effects of parathyroid hormone. It inhibits osteoclast activity in bones thus causing serum calcium levels to fall.
Vitamin D is an important co-factor in the intestinal absorption of calcium, because it increases the number of calcium binding proteins, involved in calcium absorption through the apical membrane of enterocytes in small intestine.
Until the end of puberty, estrogens are needed for maturation of the skeleton. In women, after the menopause, taking supplemental estrogen slows up the bone loss that so often leads to osteoporosis. The estrogen causes the osteoclasts to self-destruct by apoptosis and in this way slows up the destruction of bone.

2.5.3 Purpose

The purpose of remodeling is to regulate calcium homeostasis, repair micro-damaged bones, which are caused from everyday stress, but also to shape and sculpture the skeleton during growth. According to Sherwood (2010), it keeps the skeleton appropriately engineered for maximum effectiveness in its mechanical uses.

Calcium homeostasis

Bone acts as reserves of minerals important for the body, most notably calcium. 99 percent of the calcium stored in our body is found in the bones.
The process of bone resorption caused by the osteoclasts releases stored calcium into the systemic circulation and is an important process in regulating calcium balance. As bone formation actively fixes circulating calcium in its mineral form, removing it from the bloodstream, resorption actively unfixes it thereby increasing circulating calcium levels. These processes occur in tandem at site-specific locations.
A constant calcium balance is essential for our body. The body tries to maintain a calcium concentration of about 2,4 mmol/l or 100mg/l in the blood.

A drop in the calcium level in the blood causes the parathyroid gland to produce

parathyroid hormone, which has the effects that calcium is released from bone and calcium is reabsorbed in the kidney.

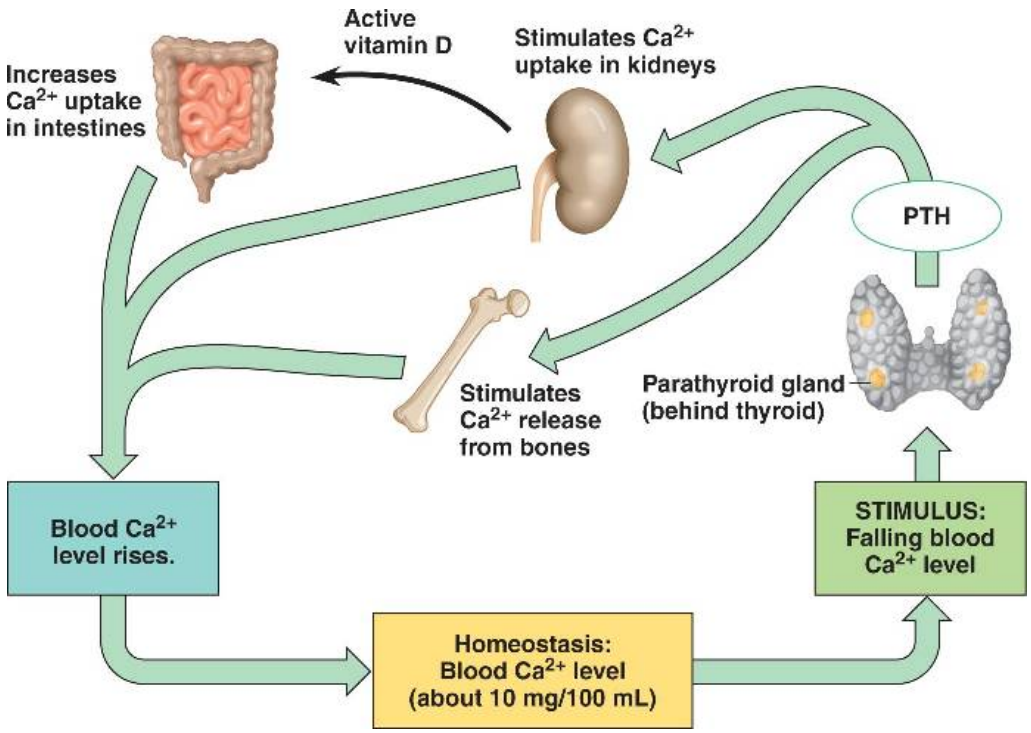

Figure 2.8: Diagrammatic representation of calcium homeostasis
http://bio1152.nicerweb.com

The regulation of the calcium household depends on different factors.
The osteocyte is considered to be very important in that it responds rapidly to stimuli. It is also anatomically capable of communicating with osteoblasts by a net of cell processes or canaculi. Calcium gains entry from the extracellular fluid, the bone marrow, between the osteoblasts. Osteoblasts continuously extrude calcium into the interstitial fluid. Osteocytes can accumulate or extrude calcium, depending on hormonal factors.
Osteolysis is a term that describes bone resorption. There are two types of osteolysis that affect bone resorption. Which of the following types occur depends on metabolic and mechanical influences. Osteocytic osteolysis does not change bone mass. Osteoclastic osteolysis on the other hand changes the bone mass. It takes place on a rather slower phase (12-24 hours). Osteoclasts break down bone and release the minerals, resulting in a transfer of calcium from bone to the blood. In a slow exchange, calcium is moved from the stable pool in mineralized bone into

the plasma by means of PTH-induced dissolution of bone.

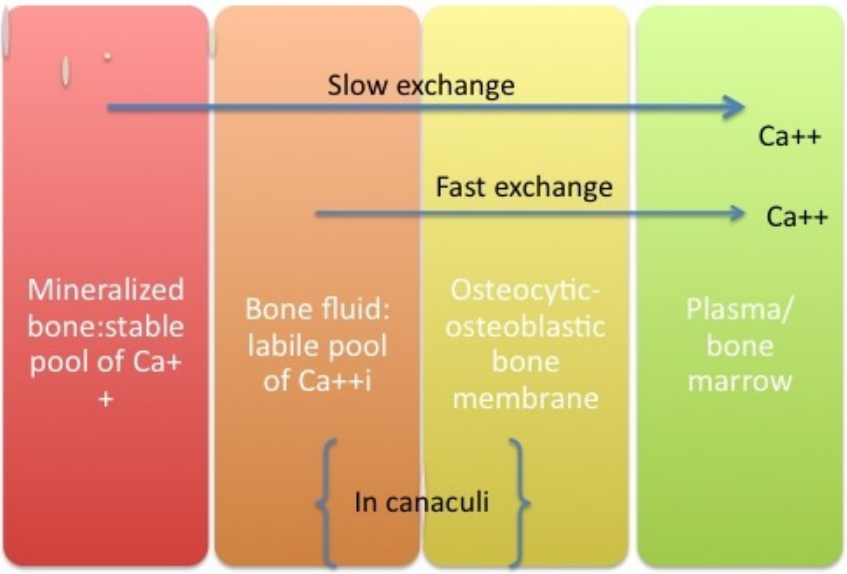

Figure 2.9: Schematic representation of fast and slow exchange of Ca++ between the bone and the plasma. In a fast exchange, Ca++ is moved from the labile pool in the bone fluid into the plasma by means of PTH activated Ca++ pumps in the osteocytic-osteoblastic bone membrane. In a slow exchange, Ca++ is moved from the stable pool in the mineralized bone into the plasma by means of PTH induced dissolution of the bone.

Bone contains such great amounts of calcium in comparison with the total amount in all extracellular fluids (about 1000 times as much) that even when parathyroid hormone causes a great rise in calcium concentrations in the fluids, it is impossible to discern any immediate effect on the bones. (Guyton, A.; Hall, J., 1996)
PTH is the main hormone involved in the fine regulation of blood calcium. It exerts its biological actions by directly influencing the function of target cells primarily in bone and kidney. The action of PTH on bone is to mobilize calcium from skeletal reserves into extracellular fluids. This process caused by PTH is called osteocytic osteolysis.
PTH stimulates the transfer of calcium from the bone fluid across the osteocytic-osteoblastic bone membrane into the plasma. The movement of calcium out of the labile pool across the bone membrane accounts for the fast exchange between bone and plasma. After calcium is being pumped out, the bone fluid is replenished with calcium from partially mineralized bone. Thus, the fast exchange of calcium does

not involve resorption of completely mineralized bone, and bone mass is not decreased. Normally this exchange is much more important for maintaining plasma calcium concentration than the slow exchange. (Sherwood, 2010)

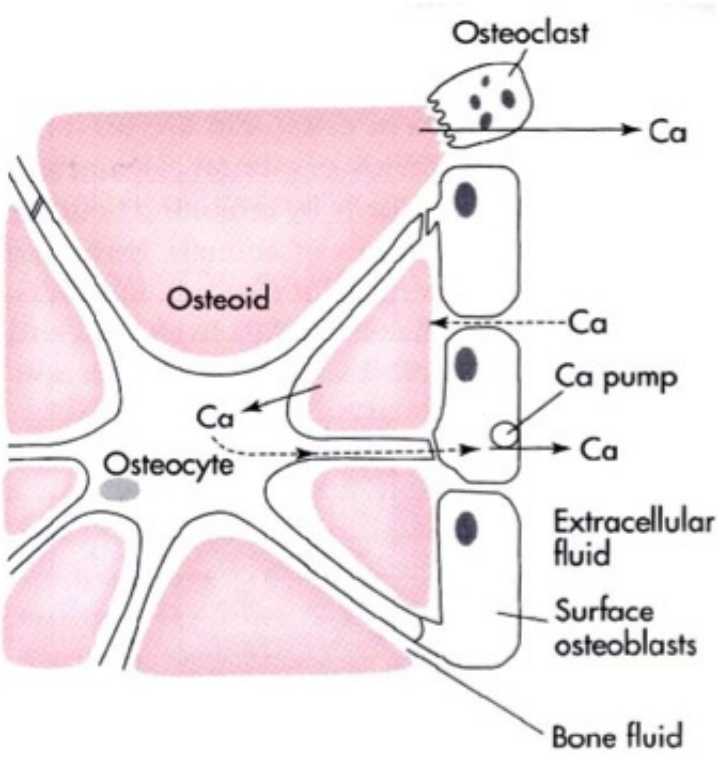

Figure 2.10: Calcium pump while osteocytic osteolysis

Only a small part of the calcium is available for this rapid phase, which takes place around 1-3 hours after the PTH stimulation.

2.5.4 Cell signaling

The actions of osteoblasts and osteoclasts are controlled by a number of chemical factors that either promote or inhibit the activity of the bone remodeling cells, controling the rate at which bone is made, destroyed, or changed in shape. The cells also use signaling to control the activity of each other.

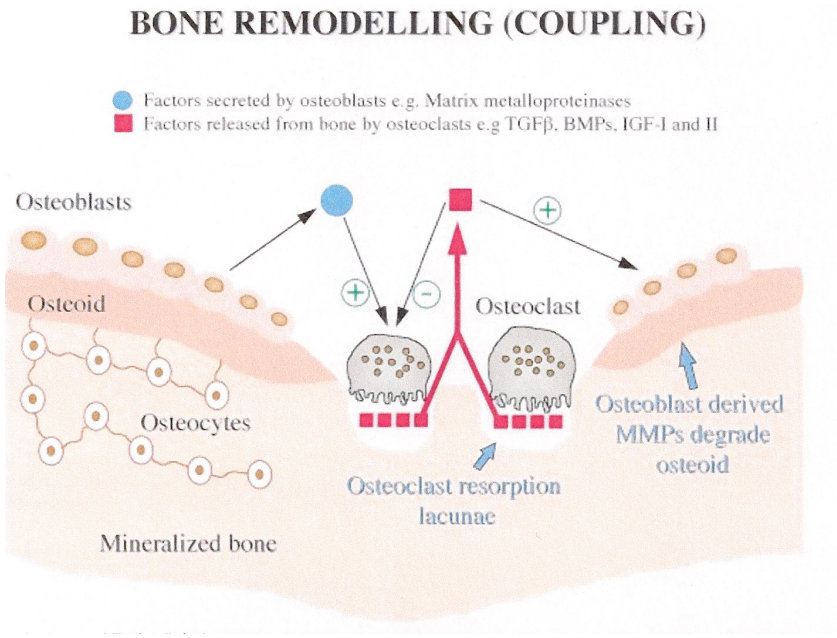

Figure 2.11: Bone remodeling (coupling). Diagrammatic representation of the coupling of osteoblastic bone resorption followed by osteoblastic bone formation with cell signaling. Hill (1998)

Osteoblast stimulation

Osteoblasts can be stimulated to increase bone mass through the increased secretion of osteoid and by inhibiting the ability of osteoclasts to break down osseous tissue.
The process of laying down new bone material by osteoblasts, is called ossification. Calcification is a process, which describes the formation of calcium-based salts and crystals within cells and tissue. It occurs during ossification. Bone building through the increased secretion of osteoid is stimulated by the secretion of growth hormone, thyroid hormone and the sex hormones such as estrogens and androgens. Osteoblasts can also be activated to secrete a number of cytokines that assist reabsorption of bone by stimulating osteoclast activity and differentiation from progenitor cells. Mainly parathyroid hormone and stimulation from osteocytes induce osteoblasts to increase secretion of RANK-ligand, which then stimulate increased reabsorption of bone by osteoclasts. These same compounds also raise the secretion of macrophage colony-stimulating factor by osteoblasts, which promote the differentiation of progenitor cells into osteoclasts, and diminishes the secretion of osteoprotegerin.

Osteoclast inhibition

The rate at which osteoclasts resorb bone is inhibited by calcitonin and osteoprotegerin.
Calcitonin is produced in the thyroid gland, and can bind to receptors on osteoclasts to directly inhibit osteoclast activity. Osteoprotegerin is secreted by osteoblasts and is able to bind RANK-L, inhibiting osteoclast stimulation.

2.6 Biomechanical control of bone remodeling

Mechanical loading has profound influences on bone remodeling. Disuse or lack of loading causes an acceleration of bone turnover, with bone resorption dominating bone formation and thus a rapid loss of bone mass. This type of bone loss is observed in astronauts who spend extended periods of time in the weightless environment of a space station or shuttle. Overuse of bone can cause damage to the tissue, which in turn stimulates bone remodeling. One of the important roles of bone turnover is to continuously replace and repair damaged bone tissue. Osteoclasts target regions of micro damage preferentially and remove compromised bone tissue. The damaged tissue is then replaced by new bone tissue. If damage accumulates faster than the tissue can be repaired, larger micro cracks may develop and propagate to form a stress fracture. (Robling, 2006, 463)
Bone as a living tissue has long been recognized to be capable of adapting its mass and structure in response to the demands of mechanical loading.
In the absence of loading, bone is lost and in the presence of loading, bone is either maintained or increased. The skeleton is unique in its ability to adaptively remodel in response to its perception of mechanical loading or lack of loading.
Bone is deposited in proportion to the compressional load that the bone must carry. For instance, the bones of athletes become considerably heavier than those of nonathletes.
The osteocyte appears to be capable of transferring the intensity of strain signals and the distribution of the strain throughout the whole bone into signals to regulate (re)modeling. (Lanyon, 1993) Adachi, Bonewald et al. claim that both the deformation of the cell and the shear stress lead to a release of a signal to the cells at the boundary of the bone.

2.6.1 Mechanotransduction

Mechanotransduction refers to a mechanism by which cells convert mechanical stimulus into chemical activity.

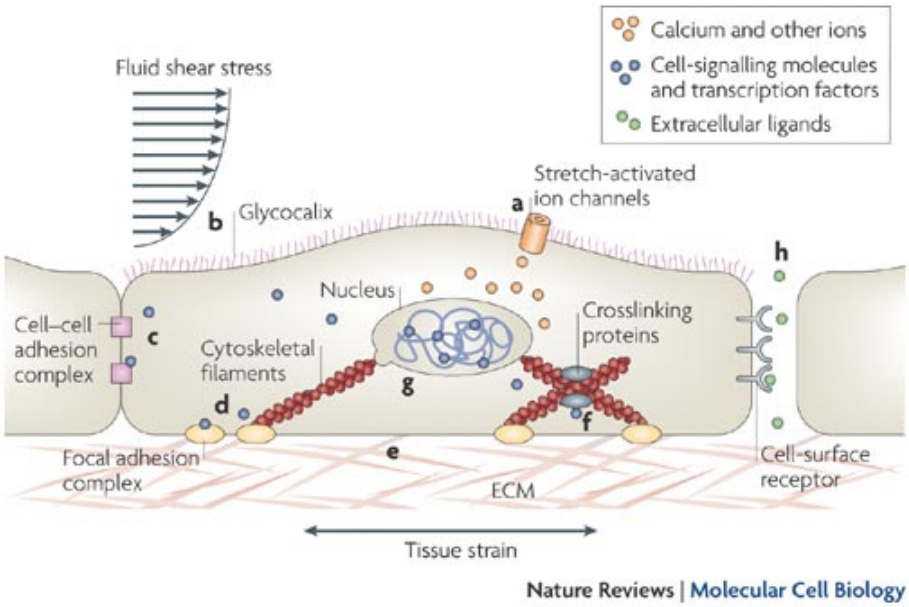

Figure 2.12: Mechanotransduction (Jaalouck, Lammerding, 2009)

Several biological factors have been proposed to act as cellular mechanosensors and are schematically shown in the cell above. a: Stretch-activated ion channels in the plasma membrane open in response to membrane strain and allow the influx of calcium and other ions. b: In special cells, the glycocalix, on the cell surface, can mediate mechanotransduction signaling in response to fluid shear stress. c,d: Cell to cell junctional receptors allow cells to probe their environments. e: Force-induced unfolding of extracellular matrix proteins, such as fibronectin, can initiate mechanotransduction signaling outside the cell. f: Intracellular strain can induce conformational changes in cytoskeletal elements such as filaments, crosslinkers or motor proteins, thereby changing binding affinities to specific molecules and activating signaling pathways. g: The nucleus itself has been proposed to act as a mechanosensor. h: Compression of the intercellular space can alter the effective concentration of autocrine and paracrine signaling molecules. (Jaalouck, Lammerding, 2009)

2.6.2 Piezoelectricity

It has not been so clear so far why calcium is moved to regions where it is needed. Piezoelectricity is a phenomenon observed in many cristalline materials. The deformation of the crystal structure produces a flow of electric current as electrons are displaced. The piezoelectric effect is created in response to force but it quickly

reaches zero. When bone is being bent areas of convexity and concavity are created. Areas of concavity are associated with negative charge and bone deposition takes place. Areas of convexity are in turn associated with positive charge and bone resorption takes place.

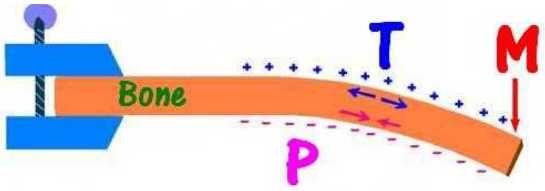

Figure 2.13: Areas of convexity and concavity on bending bone, P: pressure; T:tension; M:mass

According to (Eriksson, 1976) bone is electrically charged with respect to the extracellular fluid. "Most solids when brought into contact with aqueous medium acquire a surface electric charge. Bone is no exception. The possible charging mechanisms are ionization, ion absorption, and ion dissolution. This separation in charge between the solid phase and the liquid phase gives rise to a potential difference between the solid and the liquid, called the zeta potential." (Eriksson, 1976, 295.)
The surface of the bone is "negatively charged, so that the diffuse layer is positively charged."(Eriksson, 1976, 296)
As the calcium ions are positively charged they move towards the surface, where they pass the membrane.
Piezoelectricity in cristalline structure is shown in figure 2.13.

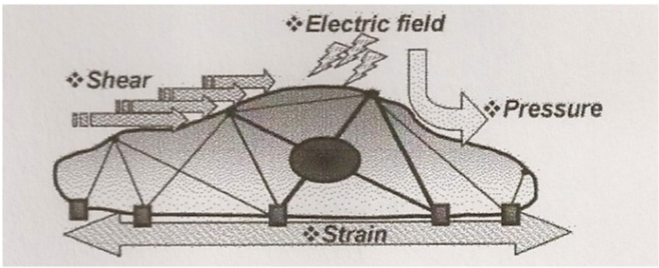

Figure 2.14: Mechanical force in the cellular environment. (Rubin, et al., 2006)

Skeletal loading generates deformation of the hard tissue with strain across the

cell's fluid. There are also shear forces through canaculi, which cause drag over cells and dynamic electrical fields because interstitial fluid flows past charged bone crystals. As osteocytes form such a structure and we also have interstitial fluid in the bone matrix, we can assume electrical fields in the mineralized bone structure. It is important to note that the piezoelectric effect is only a short term phenomenon, which perfectly explains the osteolytic calcium pump. Calcium is being shifted to areas where more strength in the bone is needed.

3 Model development

This chapter presents the differential equations that describe the biological and chemical processes involved in bone remodeling. We are studying model equations for processes in a porous elastic structure of cells. The following figure shows one cell with connected fluid and solid parts. In our model the solid is the bone matrix and the fluid is the extracellular fluid, the bone marrow.

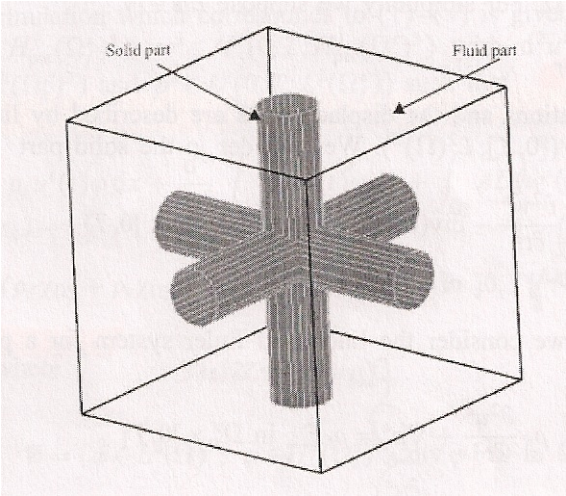

Figure 3.1: Cell with connected fluid and solid parts (Ferrin, Mikelic, 2003)

Within the solid part we find on the microscopic level also a porous medium.

3.1 Modeling assumptions

We are including the following modeling assumptions on the macroscopic level and on the unit cell level. We will only take the influences of calcium and parathyroid hormone into account. We will have to neglect the influences of the other hormones.

3.1.1 Macroscopic level

We model the blood marrow as a fluid and in the fluid we assume the following assumptions

- incompressible fluid
- Navier Stokes equation in the fluid; with the right scaling we can also use the Stokes equation (see 3.6)
- diffusion and transport of calcium and paratyroid hormone

It is important to not that he parathyroid hormone is being produced outside the domains we study. We have to have a closer look at the counterbalance of the production rate of calcium and parathyroid hormone.
The bone matrix is interpreted as a solid material and we assume the following assumptions

- mechanics of a linear elastic medium
- small deformations of structure
- mechanical properties of the solid part depend on the calcium concentration in the mineralized bone matrix, they are non linear and nonlocal in time
- coefficients change as a function of cumulated quantity of calcium concentration

Now we have a closer look at a unit cell.

3.1.2 Unit cell level

The solid part is set up by a random spongy structure which is formed by trabeculae. The solid itself can be interpreted as a porous medium as well, because in the solid part we find lacunae, which are filled with an interstitial fluid. Within the solid part we find osteocytes, one of the three bone cells. We will neglect the fluid flow in the interstitial fluid.

- calcium concentration (diffusion and transport equation)
- parathyroid hormone concentration (diffusion and transport equation)
- populations of osteocytes, osteoblasts and osteoclasts (chemotaxis)
- modeling of the signals released by the bone cells free boundary problem

The most interesting actions happen at the boundary between the solid and the fluid part. There are two types of bone cells that act within the bone remodeling process that are found at the interface between solid and fluid, namely osteoblasts and osteoclasts. Mechanical loading and calcium and PTH concentration lead to osteoblastic and osteoclastic activity on the interface between the solid and fluid phase. Chemotactic reactions also take place at the interface between the solid and the fluid. Chemical attractants are released into the fluid and attract the bone cells to become active.
The piezoelectric effect will be taken into account too because it triggers the fast exchange of calcium at the membrane.

As the boundary of the solid part is constantly changing due to the cell processes at the boundary, we assume the problem to be a free boundary problem. The following figure shows the free boundary.

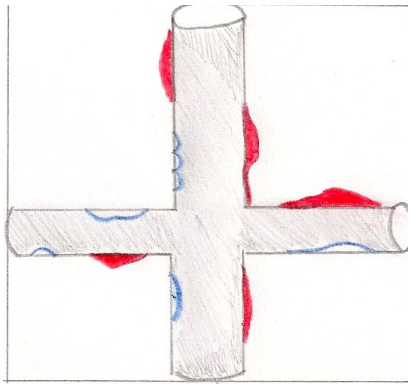

Figure 3.2: New boundary: Blue lines represent the bone resorbed by osteoclasts whereas the red part is the newly deposited bone

3.2 Domain

If we wanted to homogenize the system, it would necessary to assume a periodic arrangement of the pores. However this is not the aim here.
We suppose that the solid and fluid parts are smooth and connected.
First, we define the geometrical structure inside the unit cell $\Omega = (0,1)^3$. Our domain is time dependent as the boundary of the interface changes constantly. $\Omega_{s,t}$ represents the solid part, the bone matrix, and $\Omega_{f,t} = \Omega \backslash \Omega_{s,t}$ is the fluid part, the bone marrow. We denote the fluid-solid interface by $\Gamma_t = \partial\Omega_{s,t} \cap \partial\Omega_{f,t}$. The

boundary of the domain Ω consists of three parts

$$\partial\Omega = I \cup O \cup \bar{\Sigma}$$

where $I = \{x_1 = 0\} \times (0,1)^2, O = \{x_1 = 1\} \times (0,1)^2$ is the inlet of the domain and $\bar{\Sigma} = \cup_{j=2,3}(\{x_j = 0\} \cup \{x_j = 1\}) \times (0,1)^2$ is the outlet of the domain.
Let [0,T] denote a time interval, with T>0.
Γ_t is the most interesting part in our model. As bone is constantly changing because of the activities of osteoblasts and osteoclasts, Γ_t has to be considered as a free boundary. The following figure shows one unit cell, where we skip the index t, $\Omega_{s,t} = \Omega_s$ and for $\Omega_{f,t} = \Omega_f$.

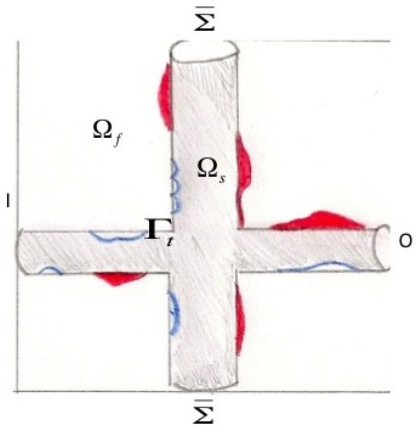

Figure 3.3: Parts of the domain in our model

3.3 Model development on the macroscopic level

On the macroscopic level we are interested in the mechanics of the solid bone matrix and the fluid flow in the bone marrow.

3.3.1 Equations for the solid bone matrix

We suppose small deformations of the cell's structure. It means that in the solid part $\Omega_{s,t}$ the equations of linear elasticity hold:

$$\rho_s \frac{\partial^2 w}{\partial t^2} - \nabla(\sigma(w)) = \rho_s F, \quad in\ \Omega_{s,t} \quad 0 \le t \le T \tag{3.1}$$

$$\sigma(w) = AD(w), \tag{3.2}$$

where w is the displacement in the solid part, ρ_s is the solid density, $\sigma(w)$ is the stress tensor and $D(w)$ is the strain tensor defined by

$$(D(w))_{i,j} = \frac{1}{2}(\frac{\partial w_i}{\partial x_j} + \frac{\partial w_j}{\partial x_i}), i, j = 1, 2, 3 \tag{3.3}$$

In the homogenous and isotropic case, the elasticity coefficients A are given with the help of Lamé's coefficients λ and μ. Another possibility is to use the Young's modulus E and the Poisson's coefficient ν. They relate to the Lamé's coefficients through

$$\begin{aligned} \lambda &= \frac{E\nu}{(1+\nu)(1-2\nu)} \\ \mu &= \frac{E}{2(1+\nu)}. \end{aligned}$$

The stress tensor has the form:

$$\sigma(w) = \lambda(\mathcal{F}((Ca)_{MBM}))\nabla \cdot (wI) + 2\mu(\mathcal{F}((Ca)_{MBM}))D(w) \tag{3.4}$$

The elasticity coefficients A depend on the concentration $(Ca)_{MBM}$. They are nonlinear and nonlocal in time; the coefficients change as a function of cumulated quantity of the calcium stored in the mineralized bone matrix.

3.3.2 Equations for the extracellular fluid (ECF)

In the fluid part, we consider the Navier-Stokes system for a viscous and incompressible fluid

$$\rho_f(\frac{\partial v}{\partial t} + (v\nabla)v) + \nabla p - \mu_f \Delta v = \rho_f F, \quad in\ \Omega_{f,t}, \tag{3.5}$$

$$\nabla \cdot v = 0, \tag{3.6}$$

where ρ_f is the fluid density, μ_f is the fluid viscosity, v is the fluid velocity and p is the fluid pressure.
We use the Navier-Stokes equation instead of the Stokes equation but we will show later that the Stokes equation can be used with the right scaling.

3.3.3 Boundary and continuity conditions

We note that the Lagrangian coordinates are used for the structure and Eulerian for the fluid. Hence, $\Omega_{s,t}$ is the reference domain and the interface between the

two media evolves with the evolution of the structure. The kinematic interface condition is the continuity of the velocity and, due to different formulations for our media, it reads

$$v(x + w(x,t),t) = \frac{\partial w}{\partial t}(x,t) \quad on\ \Gamma_t \quad 0 \le t \le T \tag{3.7}$$

The third Newton's law implies continuity of the contact forces. Expressing continuity of the contact forces at the interfaces requires introducing the fluid Langrangian configuration u^f, defined on the initial fluid configuration $\Omega_{f,t}$ and with values in $\Omega_f(t)$, which is the fluid configuration at time t. It is defined through the differential equation $\frac{\partial u^f}{\partial t} = v(u^f(x,t),t)$.Then the continuity of the normal stresses reads

$$(-pI + 2\mu_f D(v))(x + w(x,t),t) \cdot (\nabla u^f)^{-1}\nu = \sigma(w) \cdot \nu, \quad on\ \Gamma_t \quad 0 \le t \le T \tag{3.8}$$

At the exterior boundary, for every $t \in (0,T)$, we suppose:

$$(-pI + 2\mu_f D(v)) \cdot (\nabla u^f)^{-1} e_1 = (\mathcal{S}_1, \mathcal{S}_2, \mathcal{S}_3) \quad on\ I \cap \bar{\Omega}_{f,t} \tag{3.9}$$

$$A(\mathcal{F})D(w) \cdot e_1 = (\mathcal{S}_1, \mathcal{S}_2, \mathcal{S}_3) \quad on\ I \cap \bar{\Omega}_{s,t} \tag{3.10}$$

$$(-pI + 2\mu_f D(v)) \cdot (\nabla u^f)^{-1} e_1 = 0 \quad on\ O \cap \bar{\Omega}_{f,t} \tag{3.11}$$

$$A(\mathcal{F})D(w) \cdot e_1 = 0 \quad on\ O \cap \bar{\Omega}_{s,t} \tag{3.12}$$

$$v = 0 \quad and \quad w = 0, \quad on\ \bar{\Sigma} \tag{3.13}$$

For simplicity, we assume that there is no flow and no deformation for t=0, i.e.,

$$w(x,0) = \frac{\partial w}{\partial t}(x,0) = 0, \quad in \quad \Omega_{s,t} \tag{3.14}$$

$$v(x,0) = 0, \quad in \quad \Omega_{f,t}. \tag{3.15}$$

Using this continuity conditions, the complexity of our model system would increase. We will later use simpler continuity conditions.

Next, we write down the equations describing the transport of the hormones and substances and the equations for the concentrations of the bone cells and the signals they release during the bone remodeling cycle.

3.4 Model development on the unit cell level

Bone, being a major reservoir of the body calcium, is under the hormonal control of PTH (Kroll, 2000). Osteoclasts resorb bone and liberate calcium, but they

lack receptors for PTH. The preosteoblastic precursors and preosteoblasts possess receptors for PTH, upon which the hormone induces differentiation from the precursors to preosteoblasts and from the preosteoblasts to osteoblasts. The osteoblasts, consequently generate IL-6, which induces preosteoclasts to differentiate into osteoclasts (Kroll, 2000).
Thus, bone remodeling is a continuous cycle of destruction and renewal of bone that is carried out by teams of osteoclasts and osteoblasts (Marcus, 1994). Osteoclasts and osteoblasts differentiate from less mature precursors, which line bone surfaces in an inactive state. In the bone remodeling process, osteoclasts appear on a previously inactive surface of bone and then, they excavate a lacuna on the surface of cancellous bone or resorption tunnel in cortical bone. Osteoclasts are subsequently replaced by osteoblasts and finally, osteoblasts refill the resorption cavity. After osteoblasts have laid down their protein-based matrix, known as osteoid, they bury themselves in bony matrix, becoming osteocytes, or revert to an inactive cell form and line the bone surfaces as surface osteocytes or resting osteoblasts (Turner et al., 1994).
Therefore, the rate of bone deposition can be determined by the number of osteoblasts (B) while the rate of bone resorption can be determined by the number of osteoclasts (C), the balance between the number and activity of osteoblasts and osteoclasts determines whether new bone deposition or new bone resorption occurs. An excessively deep resorption space produced by osteoclasts, or an incomplete replenishment of the resorption space by the activation of osteoblasts can result in bone imbalance. If a remodeling imbalance exists after the completion of a remodeling cycle, the degree of bone loss will be exacerbated and that leads to osteoporosis (Turner et al., 1994).
The exact signals that lead to initiation of bone remodeling are yet to be defined, most likely sensors on the osteocytes are responsible for the initiation. On initiation of remodeling, osteoclasts differentiate from their monocytic precursors and resorb bone. Later, osteoblasts differentiate from mesenchymal precursors and form new bone.

Chemotaxis is the phenomenon in which bodily cells, bacteria, and other single-cell or multicellular organisms direct their movements according to certain chemicals in their environment. This is important for bacteria to find food by swimming towards the highest concentration of food molecules, or to flee from poisons. Chemotaxis is called positive if movement is in the direction of a higher concentration of the chemical in question, and negative if the direction is opposite. The term is used to denote cell movement towards or away from a chemical source, defined as positive or negative chemotaxis. The chemical is defined as chemoattractant or chemorepellent. Any cell motion that is affected by a chemical gradient that

results net propagation up a chemoattractant gradient or down a chemorepellent gradient is defined as chemotaxis.(Eisenbach, 2004) Chemotaxis is also part of the bone remodeling process because once the osteoclasts resorb bone matrix they release a signal which recruits and attracts the osteoblasts and vice versa.
The progression of bone remodeling at each site is regulated by numerous autocrine and paracrine factors. Predicting the cumulative effects of multiple factors on bone remodeling is difficult due to the large number of effectors and the multiple actions attributed to some factors. For example, transforming growth factor β(TGFβ) increases bone formation by a direct action on osteoblast differentiation. In addition, TGFβ directly activates osteoclast formation in the absence of osteoblasts, but inhibits osteoclastogenesis in co-cultures of osteoclasts and osteoblasts by decreasing expression of receptor activator of nuclear factor κB ligand (RANKL) on osteoblasts. RANKL and osteoprotegerin (OPG) are critical regulators of bone resorption, that are expressed by osteoblasts and exhibit opposite effects on osteoclasts. Whereas RANKL is a potent stimulator of osteoclasts, OPG prevents the interaction of RANKL with its receptor and inhibits bone resorption. Thus, regulation of bone remodeling is complex, involving the simultaneous actions of a number of factors that affect the formation and/or resorption of bone. (Komorova, 2003)

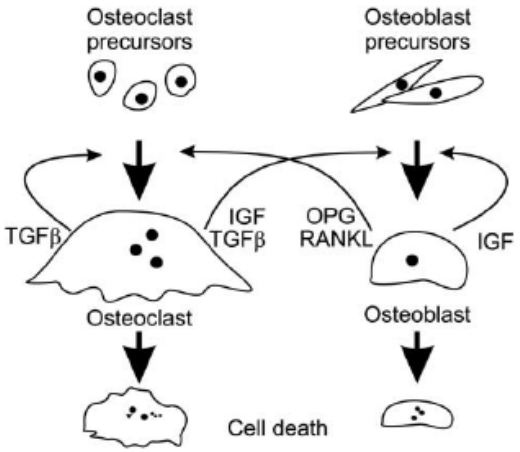

Figure 3.4: Interactions between osteoclasts and osteoblasts and the chemoattractants they release (Komarova, 2003)

The most complicated part for our model is the description of the remodeling process and the calcium homeostasis involved. The following flow chart illustrates the effects of local strain on bone formation and resorption.

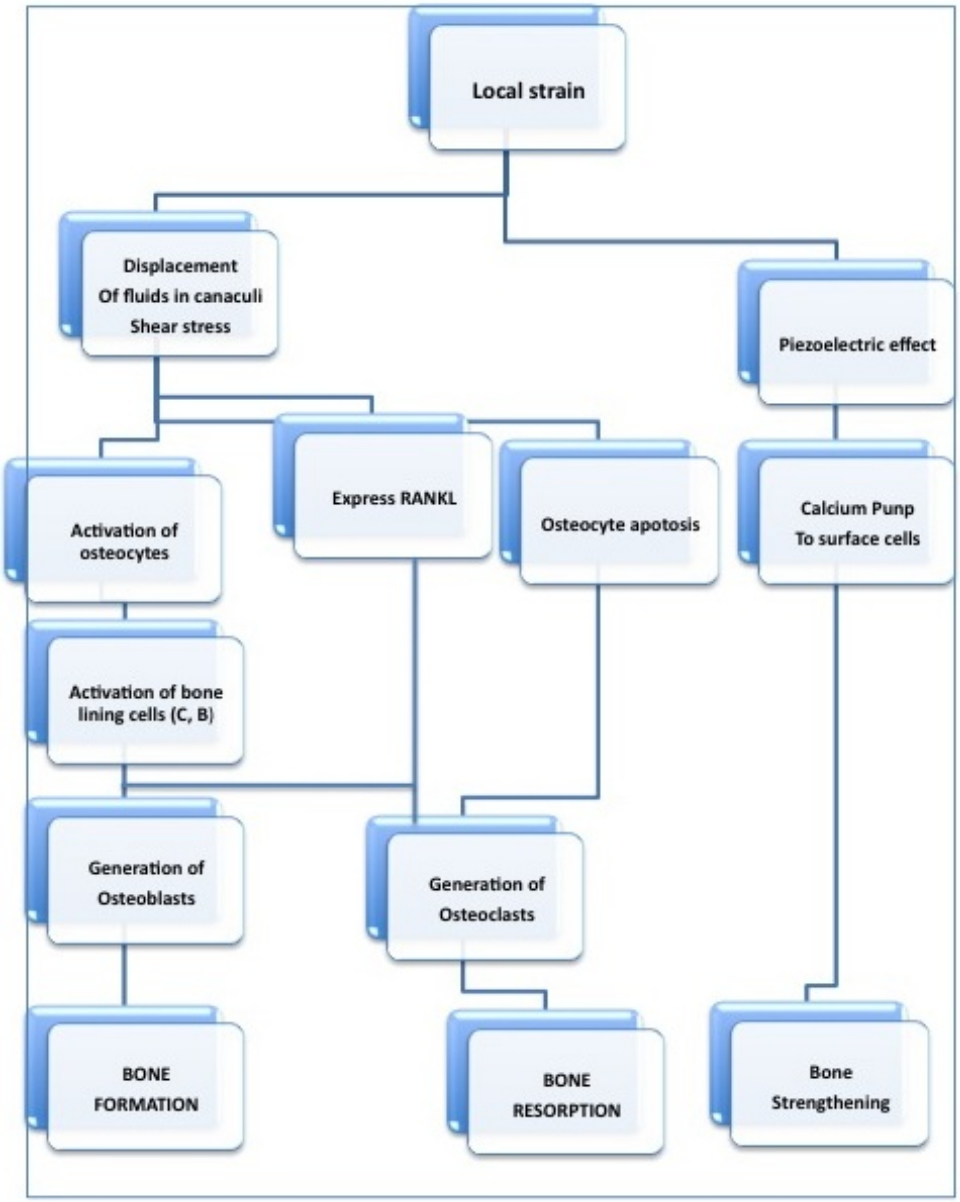

Figure 3.5: Flow chart for bone remodeling process

3.4.1 Parathyroid hormone concentration

The parathormone is secreted in the chief cells of the parathyroid glands as a polypeptide.

The parathyroid hormone and the calcium play a very important role when it comes to bone remodeling. They counterbalance each other and trigger the processes of bone resorption and bone formation.
As the blood filters through the parathyroid glands, they detect the amount of calcium present in the blood and react by producing more or less parathyroid hormone. When the calcium level in the blood is too low, the cells of the parathyroids sense that and produce more parathyroid hormone. Once the parathyroid hormone is released into the blood, it circulates to act in a number of places to increase the amount of calcium in the blood (like removing calcium from bones). If the calcium level in the blood is too high, the cells of the parathyroids produce less parathyroid hormone (or stop producing it altogether), thereby allowing calcium levels to decrease. This feedback mechanism runs constantly, thereby maintaining calcium (and parathyroid hormone) in a very narrow "normal" range. In a normal person with normal parathyroid glands, their parathyroid glands will turn on and off dozens of times per day.
Under the presence of parathyroid hormone, bones will give up their calcium in an attempt to increase the blood level of calcium. Under normal conditions, this process is very highly tuned and the amount of calcium in our bones remains at a normal high level. Under the presence of too much parathyroid hormone, however, the bones will continue to release their calcium into the blood at a rate which is too high resulting in bones which have too little calcium. This condition is called osteopenia and osteoporosis and is illustrated in the bone segment on the top which has larger "pores" and less bone mass.
When bones are exposed to high levels of parathyroid hormone for several years they become brittle and much more prone to fractures. Another way in which the parathyroid hormone acts to increase blood levels of calcium is through its influence on the intestines. Under the presence of parathyroid hormone the lining of the intestine becomes more efficient at absorbing calcium normally found in our diet.
This process takes place outside the cell in the glands which is why the equation is written as a boundary condition.

Equation for the PTH level

We find the parathyroid hormone in the bone matrix and in the bone marrow. On the boundary between the solid and the fluid phase we need continuity conditions. The equations for the rate of PTH concentration in the solid and fluid part are assumed to take the following form:

$$\frac{\partial P}{\partial t} = D_P \Delta P - v \nabla P + g_1(P, (Ca)_{ECF}) - d_1((Ca)_C, (Ca)_O, P) \quad in\ \Omega_{f,t} \quad (3.16)$$

$$\frac{\partial P}{\partial t} = D_P \Delta P + g_2(P, (Ca)_{ECF}) - d_2((Ca)_C, (Ca)_O, P) \quad in\ \Omega_{s,t} \tag{3.17}$$

$$(vP - D_P \nabla P)\chi_{\Omega_f} (\nabla u^f)^{-1} \nu = -D_P \nabla P \chi_{\Omega_s} \cdot \nu \quad on\ \Gamma_t \tag{3.18}$$

$$P\chi_{\Omega_f} = P\chi_{\Omega_s} \quad on\ \Gamma_t \tag{3.19}$$

g_1 depends on the PTH level and on the calcium level in the extracellular fluid and stands for the production rate of PTH of the parathyroid gland. The last term on the right hand side represents the fact that the hormone is removed from the system at the rate which is proportional to its current level with the removal rate constant d_1. d_1 depends on the PTH level itself, the calcium in the osteoclasts and osteocytes. Equation (3.17) describes the processes in the extracellular fluid and therefore we also find a diffusion and transport term in the equation.
Equation (3.18) represents the processes in the solid and the third equation the processes on the interface.

Boundary conditions

$$-D_P \frac{\partial P}{\partial n} = \mathcal{G}\left(\frac{1}{|O \backslash \Omega_{s,t}|} \int_{O \backslash \Omega_{s,t}} (Ca)_{ECF_O}(\tau - t) dx \right) \quad on\ I \tag{3.20}$$

$$P = P_O \quad on\ O \tag{3.21}$$

$$P = 0 \quad on\ \bar{\Sigma} \tag{3.22}$$

$$P(0) = P_0 \quad in\ \Omega \tag{3.23}$$

$\mathcal{G}$ describes the counteraction of PTH and the extracellular calcium. Active osteoclasts resorb bone and liberate calcium. Thus the calcium level will rise. Accordingly the PTH level will decrease to counterbalance the high level of calcium in the blood.
Equation (3.21) describes the fact, that the glands possess calcium-sensing receptors. Thus the amount of PTH being produced by the glands depends on the calcium level in the blood. This takes place with a time lack.

We note here also for the following equations that the functions g_i, d_i would have to be specified for the existence.

3.4.2 Calcium concentrations

Calcium is the most abundant mineral in the human body. The average adult body contains in total approximately one kilogram, ninety-nine percent in the skeleton in the form of calcium phosphate salts. The remaining one percent circulates in

the blood and other body's fluids.
The extracellular fluid contains approximately 22.5 mmol, of which about nine mmol is in the serum. Approximately 500 mmol of calcium is exchanged between bone and the extracellular fluid over a period of twenty-four hours.
Only ten to thirty percent of the calcium in the food is absorbed into the body. Calcium must be broken down by the digestive system before the body can use it. If the calcium level is too high, the kidney excretes calcium with pro-urine.
Calcium homeostasis refers to the regulation of the concentration of calcium ions in the extracellular fluid. The following figure illustrates the influences on the calcium concentration in the extracellular fluid.

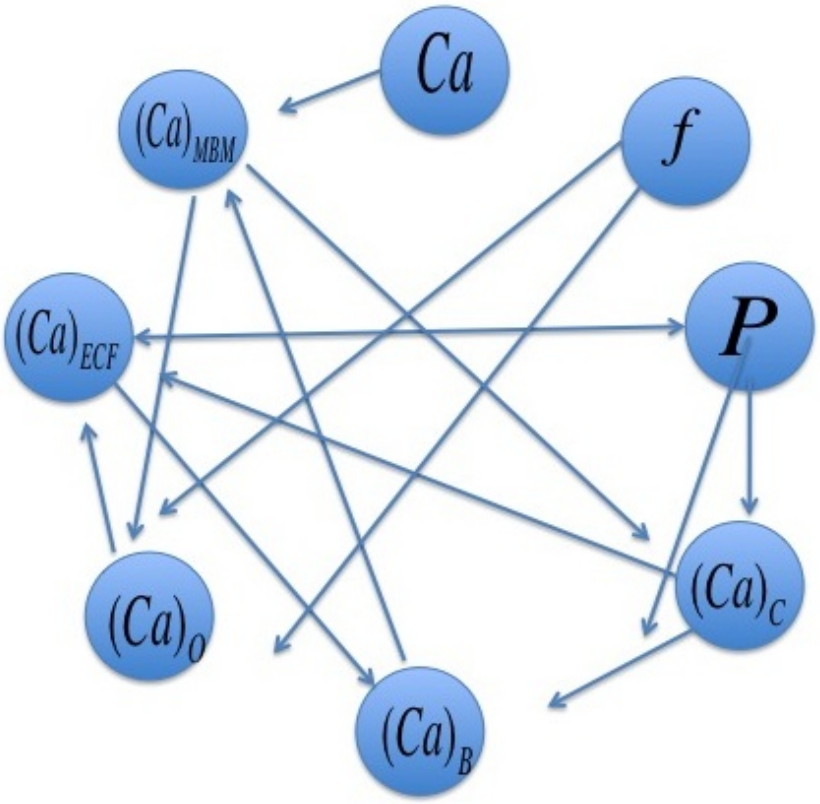

Figure 3.6: Calcium homeostasis: Influences on calcium concentration in extracellular fluid. Notations: Ca: total amount of calcium; f: force; P: PTH; $(Ca)_C$: calcium in osteoclasts; $(Ca)_B$: calcium in osteoblasts; $(Ca)_O$: calcium in osteocytes; $(Ca)_{ECF}$: calcium in extracellular fluid; $(Ca)_{MBM}$: calcium in mineralized bone matrix

Equation for the calcium level in the extracellular fluid (ECF)

The calcium is only available in the extracellular fluid and on the interface and the other boundaries.

$$\frac{\partial (Ca)_{ECF}}{\partial t} = D_{(Ca)_{ECF}} \Delta (Ca)_{ECF} - v \nabla (Ca)_{ECF} + g_3(P, (Ca)_{ECF}) - d_3((Ca)_{ECF}) \quad in\ \Omega_{f,t} \tag{3.24}$$

$$\frac{\partial (Ca)_{boundary}}{\partial t} = g_4((Ca)_C) - d_4((Ca)_B) \quad on\ \Gamma_t \tag{3.25}$$

$$-D_{(Ca)_{ECF}} \frac{\partial (Ca)_{ECF}}{\partial n} = g_5(B, (Ca)_{ECF}) \quad on\ \Gamma_t \tag{3.26}$$

$$-D_{(Ca)_{ECF}} \frac{\partial (Ca)_{ECF}}{\partial n} = g_6(P_O, (Ca)_{ECF}) \quad on\ I \tag{3.27}$$

$$(Ca)_{ECF} = (Ca)_{ECF_O} \quad on\ O \tag{3.28}$$

$$(Ca)_{ECF} = 0 \quad on\ \bar{\Sigma} \tag{3.29}$$

$$(Ca)_{ECF} = Ca_{boundary} \quad on\ \Gamma_t \tag{3.30}$$

$$(Ca)_{ECF}(0) = (Ca)_{ECF0} \quad in\ \Omega_{f,t} \tag{3.31}$$

g_i, d_i are the production and removal rates in the different domains. Equation (3.25) also involves diffusion and transport equations. Equation (3.26) describes the amount of calcium available on the interface, which depend on the number of active osteoclasts which resorb the mineralized bone matrix and liberate calcium and on the calcium pumped to the extracellular fluid by the osteocytes and on the PTH level.
Equation (3.28) represents the fact that when blood is pumped through the glands, the sensors there react to high or low calcium levels with a decreased or increased PTH secretion.
Calcium is also stored in the bone tissue.

Equation for calcium in the bone tissue

$$\frac{\partial (Ca)_{MBM}}{\partial t} = D_{(Ca)_{MBM}} \Delta (Ca)_{MBM} + g_7(O, (Ca)_{MBM}) - d_5((Ca)_C, (Ca)_O) \quad in\ \Omega_{s,t} \tag{3.32, 3.33}$$

$$-\frac{\partial (Ca)_{MBM}}{\partial n} = -g_8((Ca)_B) + d_6((Ca)_C) \quad on\ \Gamma_t \tag{3.34}$$

$$(Ca)_{MBM} = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.35}$$

$$(Ca)_{MBM}(0) = (Ca)_{MBM,0} \quad in\ \Omega_{s,t} \tag{3.36}$$

g_i represents the birth term which depends on the total amount of calcium in the body and the number of osteocytes. We also find a diffusion term in equation (3.33) because calcium can be transported by diffusion. The amount of newly formed MBM depends on the amount of calcium which the osteoblasts deposit into the bone matrix. (3.34) The bound calcium in the MBM depends on that factor and on the number of osteoblasts which mineralize the calcium and become osteocytes. The amount of bound calcium in the mineralized matrix also depends on the number of osteocytes and how much calcium is mineralized around each osteocyte. Osteoclasts resorb the bound calcium stored in the mineralized bone matrix. This fact is described by the last term on the right hand side.

Equation for calcium in the osteocytes

According to Adachi et al. (2009) and Rath et al. (2010) osteocytes respond to cell deformation and stress with an increased calcium level in the osteocyte. This increased calcium level triggers the biochemical signal to the bonecells lining the surface. The increased mineral level also correlates with the Lamé factors of the bone tissue which influence the bone mineral density.
Osteocytic osteolysis is caused by piezoelectric effect resulting in an elcetric field $\vec{E}$, where $\vec{E} = -\nabla\Phi$:

$$\frac{\partial (Ca)_O}{\partial t} = D_{(Ca)_O}\Delta (Ca)_O - div(\vec{E} \cdot (Ca)_O) +$$

$$g_9(O, (Ca)_{MBM}, (Ca)_O, F) - d_7((Ca)_{boundary}, (Ca)_O) \quad in\ \Omega_{s,t} \tag{3.37}$$

$$-D_{(Ca)_O}\frac{\partial (Ca)_O}{\partial n} = -g_{10}((Ca)_B, (Ca)_O) + d_8((Ca)_C, (Ca)_O) \quad on\ \Gamma_t \tag{3.38}$$

$$(Ca)_O = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.39}$$

$$(Ca)_O(0) = (Ca)_{O,0} \quad in\ \Omega_{s,t} \tag{3.40}$$

The first term on the right hand side of (3.37) represents the fact that the calcium level in the osteocytes depends on the deformation of the cell. The calcium in the osteocytes is taken from the calcium in the interstitial fluid. If the calcium level in the extracellular fluid is low, osteocytic osteolysis takes place, the calcium is transported in the electric field, a diffusion term also exists. The death term on the right hand side of (3.37) describes the fact that the calcium from the osteocytes is pumped out to the extracellular fluid.

Equation for calcium resorbed by osteoclasts

The amount of calcium resorbed by the osteoclasts depends on the PTH level which in turn also depends on a low calcium level in the extracellular fluid. (PTH stimulates osteoclastic osteolysis) It also depends on the strength of the signal released by the osteocytes that are transmitted to the osteoclasts at the surface.

$$\frac{\partial (Ca)_C}{\partial t} = g_{11}(P, C, (Ca)_C) - d_9((Ca)_{boundary}, (Ca)_C) \quad on\ \Gamma_t \tag{3.41}$$

$$(Ca)_C = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.42}$$

$$(Ca)_C(0) = (Ca)_{C,0} \quad on\ \Gamma_t \tag{3.43}$$

The calcium resorbed by the osteoclasts is released through the boundary into the extracellular fluid which is described by the last term on the right hand side.

Equation for calcium deposited by osteoblasts

The amount of calcium deposited by the osteoblasts depends on the signals released by osteocytes that travel to the surface and the calcium level in the extracellular fluid.

$$\frac{\partial (Ca)_B}{\partial t} = g_{12}((Ca)_{boundary}, B, (Ca)_B) - d_{10}((Ca)_{MBM}, (Ca)_B) \quad on\ \Gamma_t \tag{3.44}$$

$$(Ca)_B = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.45}$$

$$(Ca)_B(0) = (Ca)_{B,0} \quad on\ \Gamma_t \tag{3.46}$$

The birth term depends on the amount of calcium available on the boundary. The calcium deposited into the bone matrix becomes calcium in the mineralized bone matrix, which is described by the last term on the right hand side of the equation (3.44).

3.4.3 Population of bone cells and signaling

We now need equations for the osteoblasts, osteoclasts and osteocytes and the signals they send.

Equation for osteoblasts

The dynamics of the active osteoblastic population B(t) can be described by the following equation:

$$\frac{\partial B}{\partial t} = \nabla \cdot (D_B \nabla B - B\nabla\chi(S_C) - B\nabla\chi(S_O)) + g_{13}(B, S_O, P, C) - d_{11}(B) \quad on\ \Gamma_t \tag{3.47}$$

$$-D_B \partial_\nu B + B\chi'(S_C)\partial_\nu S_C + B\chi'(S_O)\partial_\nu S_O = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.48}$$

$$B = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.49}$$

$$B(0) = B_0 \quad on\ \Gamma_t \tag{3.50}$$

where g_i is the rate of production which depends on the number of osteoblasts, osteoclasts, the PTH level and the signal released by the osteocytes. PTH stimulates the reproduction of active osteoblasts (Brown, 1991; Isogai et al, 1996). PTH stimulates osteoblasts differentiation into immature osteoblasts but inhibits them into more mature cells.
The second term in (3.47) represents the diffusion term and the third term describes the influence of the chemotaxis stimulated by the chemical attractant released by the osteoclasts and the fourth term the chemotaxis stimulated by the chemical attractant released by the osteocytes.
d_i is the removal rate of the osteoblasts that either die or convert into osteocytes.
We now have a look at the signals released by the osteoblasts.

Equation for the chemical signal released by the osteoblasts

$$\frac{\partial S_B}{\partial t} = \nabla(D_{S_B} \nabla S_B) + g_{14}(B, S_B) - d_{12} S_B \quad on\ \Gamma_t \tag{3.51}$$

$$D_{S_B} \partial_\nu S_B = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.52}$$

$$S_B(0) = S_{B,0} \quad on\ \Gamma_t \tag{3.53}$$

where g_i represents the birth term, which depends on the number of osteoblasts, D_{S_B} is is diffusion coefficient of the substances that attract C, and d_i is the rate at which the signal dies.

Equation for osteoclasts

The dynamics of the osteoclastic population can be described by the following equation:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D_C \nabla C - C\nabla\chi(S_B) - C\nabla\chi(S_O)) + g_{15}(C, B, S_O, P) - d_{13}(C) \quad on\ \Gamma_t \tag{3.54}$$

$$-D_C \partial_\nu C + C\chi'(S_B)\partial_\nu S_B + C\chi'(S_O)\partial_\nu S_O = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.55}$$

$$C = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.56}$$

$$C(0) = C_0 \quad on\ \Gamma_t \tag{3.57}$$

The first term in equation (3.54) stands for the production rate which depends on the number of osteoblasts, the signal released by the osteocytes and the PTH. The reproduction of active osteoclasts requires the production of osteoclast differentiation factor (ODF) and its receptors on osteoclasts (Kroll, 2000). The more osteoclasts mean the more ODF receptors available for the reproduction of active osteoclasts, and thus the production depends on the number of active osteoclasts C at the time.
Moreover, osteoclasts precursors possess RANK, a receptor that recognizes ODF through a cell-to-cell interaction with osteoblasts, hence the rate of reproduction depends also on the number of active osteoblastic cells B(t) at the time t.
The first term describes the diffusion term and the second term represents the chemotaxis stimulated by the chemical attractant released by the osteoblasts. The next part describes the random migration of osteoclasts with random motility coefficient, as well as the directional migration in response to the spatial gradient of the chemoattractant and the signal. The chemotactic sensitivity functions $\chi(S_B), \chi(S_O)$ specify the ability of the osteoclasts to sense the attractant gradient. The last part stands for the removal rate, which depends on the osteocytes.

Equation for the chemical signal released by the osteoclasts

$$\frac{\partial S_C}{\partial t} = \nabla(D_{S_C} \nabla S_C) + g_{16}(C, S_C) - d_{14} S_C \quad on\ \Gamma_t \tag{3.58}$$

$$D_{S_C} \partial_\nu S_C = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.59}$$

$$S_C(0) = S_{C,0} \quad on\ \Gamma_t \tag{3.60}$$

where g_i represents the birth term, D_{S_C} is the diffusion coefficient of the substances that attract B, and d_i is the removal rate of the signal in the system.

Equation for osteocytes

Osteocytes compose over 90-95 percent of all bone cells in the adult skeleton and are regarded as mechanosensory cells (Adachi et al. 2009a, b), and their network system acts as the pathway of mechanical signals from the osteocytes to the cells on the trabecular surfaces (Adachi et al. 2009c). When bone is subjected to mechanical loading, bone matrix deformation produces an interstitial fluid flow in the lacuno- canalicular system (Weinbaum et al. 1994). These cells are connected to each other and cells on the bone surface through dendritic processes that occupy tiny canals called canaculi. Considering that osteocytes are sensitive to fluid flow, it is hypothesized that osteocytes respond to the fluid-induced shear stress (Weinbaum et al. 1994) and deliver its mechanical information to the surface cells by intercellular communication (Adachi et al. 2009c); as a result, bone formation and resorption are regulated.
Osteocytes originate from osteoblasts and once they are dead they are resorbed by osteoclasts which release their stored calcium.
Osteoblasts that have been trapped in the osteoids produced by other surrounding osteoblasts are called osteocytes. Osteocytes maintain bones, they play a role in controling the extracellular concentration of calcium and phosphate, and are directly stimulated by calcitonin and inhibited by PTH.
The dynamics of the population of osteocytes can be described by the following equation:

$$\frac{dO}{dt} = g_{17}(P, B, O) - d_{15}O \quad in\ \Omega_{s,t} \tag{3.61}$$

$$O = 0 \quad on\ \Gamma_t \tag{3.62}$$

$$O = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.63}$$

$$O(0) = O_0 \quad in\ \Omega_{s,t} \tag{3.64}$$

where the first term describes the influence of the PTH level on the reproduction of osteocytes (as osteocytes have PTH receptors, which triggers the osteocytic osteolysis) and the fact that osteoblasts become osteocytes. The last term represents the osteocytes that are removed from the system.

Equation for the biochemical signal released by osteocytes

Osteocytes probably do not respond directly to mechanical strain (deformation) of bone tissue, but respond indirectly to extracellular fluid flow caused by loading.

When cultured osteocytes are subjected to fluid shear stress, they release several messengers, including prostaglandins (hormones) and nitric oxide (chemical compound). (Robling et. al., 2006, 484)
Because of the strain concentrations at osteocyte lacunae, the lacunae might act as pumps that push fluid along the canaculi when the bone tissue is loaded. Fluid flow along cell bodies or processes produces drag force, fluid shear stress, and an electric potential called a streaming potential (or stress-generated potential). Each of these signals might activate bone cells, although cell culture experiments suggest that cells are more sensitive to fluid forces than they are to electric potential. The mechanical signal sensed by the osteocytes depends on the interstitial fluid pressure p, and on the fluid induced shear stress τ_p, acting on the osteocyte processes.

$$\frac{\partial S_O}{\partial t} = \nabla(D_{S_O}\nabla S_O) + g_{18}(O, F, \tau_p, S_O) - d_{16}S_O \quad in\ \Omega_{s,t} \tag{3.65}$$

$$D_{S_O}\partial_\nu S_O = 0 \quad on\ \Gamma_t \tag{3.66}$$

$$D_{S_O}\partial_\nu S_0 = 0 \quad on\ I, O, \bar{\Sigma} \tag{3.67}$$

$$S_O(0) = S_{O,0} \quad in\ \Omega_{s,t} \tag{3.68}$$

where g_i is the birth term which depends on the number of osteocytes, the shear stress, the load and the last term represents the removal rate at which the signal vanishes. Here we have a direct influence of the signals on the surface.

3.5 Free boundary problem

The most interesting and yet complex part of the model happens at the interface Γ between the bone matrix and the extracellular fluid. Bone is a living tissue that changes its shape and internal architecture in response to loading and homeostatic needs.
As the boundary of the interface between solid and fluid tissue constantly changes due to activities of osteoclasts and osteoblasts, we have to consider a free boundary problem here.
The boundary Γ separating the fluid and the solid evolves in time $\Gamma = \Gamma_t$. The evolution of Γ_t depends on the gradient betwenn the level of calcium in the extracellular fluid and the calcium available at the boundary. We denote the velocity of this free boundary by v_n and by H the curvature.

$$v_n = (\alpha\frac{\partial(Ca)_B}{\partial t} + \beta\frac{\partial(Ca)_C}{\partial t})f(H) \tag{3.69}$$

$$\frac{\partial (Ca)_B}{\partial t} = \beta_1(-\nu\nabla((Ca)_{ECF} - (Ca)_{boundary})) \quad on\ \Gamma_t \tag{3.70}$$

$$\frac{\partial (Ca)_C}{\partial t} = \beta_2(-\nu\nabla((Ca)_{ECF} - (Ca)_{boundary})) \quad on\ \Gamma_t \tag{3.71}$$

$$\partial_t S + v_n|\nabla S| = 0 \quad \Omega \tag{3.72}$$

S describes the level set function.

3.6 Weak formulation

At the interface Γ_t the following assumption holds:

$$v(x,t) = \frac{\partial w}{\partial t}(x,t) \tag{3.73}$$

Due to this continuity of velocities at the fixed reference interface Γ_t and assuming the initial displacements in the fluid to be zero, it is natural to introduce a displacement function $u : \Omega \times (0,T) \to \mathbb{R}^3$ such that

$$v = \frac{\partial u}{\partial t} \quad on\ \Omega_{f,t} \quad 0 \le t \le T \tag{3.74}$$

$$w = u \quad on\ \Omega_{s,t} \quad 0 \le t \le T. \tag{3.75}$$

We start with the variational formulation for the fluid and the solid.

3.6.1 Fluid and solid

Dimensional analysis

It makes sense to write the system with no scaling. Thus we introduce dimensionless coordinates which are defined in terms of characteristic values of the physical parameters.
Typical values of characteristic parameters are: T is the characteristic flow time, the characteristic domain size is $L = 10^{-2}m$, the characteristic size of the elastic moduli is $\Lambda = 10^9$ pascals, Poisson ratio $\nu = 0,3$, the dynamic viscosity is $\mu_f = 0,1 - 1kg/ms$ and the densities are $\rho_f = 930kg/m^3$ and $\rho_s = 2100kg/m^3$ (Currey, 2002). The characteristic cell size is $l = 2,5 \cdot 10^{-4}m$. The characteristic size of the heterogeneities is then given by $\epsilon = l\backslash L = 2.5 \cdot 10^{-2}m$.

The variational formulation which corresponds to the macroscopic equations is given in (3.75). See Clopeau, et al. (2001). It is important to note here that Clopeau et al. use the Stokes flow given in the following equation

$$\rho_f \frac{\partial u^\epsilon}{\partial t^2} - div\sigma^{f,\epsilon} = \rho_f F$$
$$\sigma^{f,\epsilon} = pI - 2\mu f \epsilon^2 D(\frac{\partial u^\epsilon}{\partial t})$$

Find $u^\epsilon \in H^1(0,T;H^1_{per}(\Omega)^n)$ with $\frac{d^2u^\epsilon}{dt^2} \in L^2(0,T;L^2(\Omega)^n)$ and $p^\epsilon \in L^2(\Omega^\epsilon_{f,t}))$ such that

$$\int_\Omega \frac{d}{dt^2}\rho^\epsilon u^\epsilon(t)\varphi\,dx + \int_{\Omega^\epsilon_{f,t}} \frac{d}{dt} 2\mu\epsilon^2 D(u^\epsilon(t)) : D(\varphi)\,dx \tag{3.76}$$
$$+ \int_{\Omega^\epsilon_{s,t}} AD(u^\epsilon(t)) : D(\varphi)\,dx - \int_{\Omega^\epsilon_{f,t}} p^\epsilon div\varphi\,dx = \int_\Omega \rho^\epsilon F\varphi\,dx,$$

where

$$\rho^\epsilon = \rho_f + \rho_s \tag{3.77}$$

and

$$u^\epsilon(0) = 0, \tag{3.78}$$
$$\frac{\partial u^\epsilon}{\partial t}(0) = 0, \tag{3.79}$$

and

$$div\frac{\partial u^\epsilon}{\partial t} = 0, \quad \Omega^\epsilon_{f,t} \quad 0 < t < T. \tag{3.80}$$

Equation (3.76) shows that the Stokes equations can be used in our model system, as the integral vanishes when $\epsilon \to 0$.

Before we start to write down the weak formulation of our problem it is important to state that we will not define the spaces for the respective testfunctions, as we will not analyze the problem analytically.

In our case we write for the weak formulation:

$$\int_{\Omega_t} \frac{d^2}{dt^2}\rho^\epsilon u(t)\varphi dx + \int_{\Omega_{f,t}} \frac{d}{dt} 2\mu_f D(u(t)) : D(\varphi) dx +$$
$$\int_{\Omega_{s,t}} A(\mathcal{F}((Ca)_{MBM} D(u(t)) : D(\varphi) dx - \int_{\Omega_{f,t}} pdiv\varphi dx =$$
$$\int_{\Omega_t} \rho^\epsilon F\varphi dx + \int_I (\mathcal{S}_1, \mathcal{S}_2, \mathcal{S}_3)\varphi dS, \quad \forall\varphi \in \quad H^1(\Omega_t) \tag{3.81}$$

where

$$\rho^{\epsilon} = \rho_f \chi_{\Omega_{f,t}} + \rho_s \chi_{\Omega_{s,t}} \tag{3.82}$$

and

$$u(x,0) = 0, \qquad \frac{\partial u}{\partial t}(x,0) = 0 \quad in\ \Omega_t \tag{3.83}$$

$$\nabla \cdot \frac{\partial u}{\partial t} = 0, \quad in\ \Omega_{f,t} \quad 0 \leq t \leq T \tag{3.84}$$

Next we look at the parathyroid hormone and calcium concentrations.

3.6.2 Parathyroid hormone and calcium

Parathyroid hormone

$$\begin{aligned}\langle \frac{\partial P}{\partial t}, \zeta \rangle = &- \int_{\Omega_t} D_P \nabla P(t) \nabla \zeta dx + \int_{\Omega_{f,t}} \frac{\partial u}{\partial t}(t) P(t) \nabla \zeta dx + \\ &\int_I \mathcal{G}\Big(\frac{1}{|O \backslash \Omega_{s,t}|} \int_{O \backslash \Omega_{s,t}} (Ca)_{ECF_O}(\tau - t) dx \Big) \zeta dS + \\ &\int_{\Omega_t} (g_1(P, (Ca)_{ECF}) \chi_{\Omega_{s,t}} + g_2(P, (Ca)_{ECF}) \chi_{\Omega_{f,t}}) \zeta dx - \\ &\int_{\Omega_t} (d_1(P, (Ca)_{ECF}, Ca_O) \chi_{\Omega_{s,t}} + d_2(P, (Ca)_{ECF}, Ca_O) \chi_{\Omega_{f,t}}) \zeta dx\end{aligned} \tag{3.85}$$

with $P = P_O$ on O.
Next we write down the variational formulations for the calcium concentrations.

Calcium

We start with the calcium in the extracellular fluid. Extracellular Calcium

$$\begin{aligned}\langle \frac{\partial (Ca)_{ECF}}{\partial t}(t), \zeta \rangle = &- \int_{\Omega_{f,t}} D_{(Ca)_{ECF}} \nabla Ca_{ECF}(t) \nabla \zeta dx + \\ &\int_{\Omega_{f,t}} (\frac{\partial u}{\partial t}(t)(Ca)_{ECF}(t)) \nabla \zeta dx + \\ &\int_I g_6(P_O, (Ca)_{ECF}) \zeta dS + \int_{\Gamma_t} g_5(B, (Ca)_{ECF}) \zeta dS + \\ &\int_{\Omega_{f,t}} g_3(P, (Ca)_{ECF}) \zeta dx - \int_{\Omega_{f,t}} d_3 (Ca)_{ECF} \zeta dx\end{aligned} \tag{3.86}$$

with $(Ca)_{ECF} = (Ca)_{ECFO}$ on O and $(Ca)_{ECF} = (Ca)_{boundary}$ on Γ_t.

Calcium in the mineralized bone matrix

$$\langle \frac{\partial (Ca)_{MBM}}{\partial t}(t), \zeta \rangle = -\int_{\Omega_{s,t}} D_{(Ca)_{MBM}} \nabla Ca_{MBM}(t) \nabla \zeta dx + \int_{\Omega_{s,t}} g_7(O, (Ca)_{MBM}) \zeta dx + \int_{\Gamma_t} g_8((Ca)_B - d_6((Ca)_C) \zeta dS - \int_{\Omega_{s,t}} d_5((Ca)_C, (Ca)_O) \zeta dx \quad (3.87)$$

Calcium in the osteocytes

$$\langle \frac{\partial (Ca)_O}{\partial t}(t), \zeta \rangle = -\int_{\Omega_{f,t}} D_{(Ca)_O} \nabla Ca_O(t) \nabla \zeta dx - \int_{\Omega_{s,t}} \vec{E} \cdot (Ca)_O div \zeta dx + \int_{\Omega_{t,s}} g_9(O, (Ca)_{MBM}) \zeta dx - \int_{\Omega_{s,t}} d_7 (Ca)_{ECF} \zeta dx - \int_{\Gamma_t} \left(d_8((Ca)_C) - g_{10}((Ca)_B) \right) \zeta dS \quad (3.88)$$

Calcium released by osteoclasts

$$\langle \frac{\partial (Ca)_C}{\partial t}(t), \zeta \rangle = \int_{\Gamma_t} g_{11}(C, (Ca)_C) \zeta dS - \int_{\Gamma_t} d_9 (Ca)_{boundary} \zeta dS \quad (3.89)$$

Calcium deposited by osteoblasts

$$\langle \frac{\partial (Ca)_B}{\partial t}(t), \zeta \rangle = \int_{\Gamma_t} g_{12}(B, (Ca)_{boundary}) \zeta dS - \int_{\Gamma_t} d_{10} (Ca)_{MBM} \zeta dS \quad (3.90)$$

Next we write down the variational formulations for the bone cells.

3.6.3 Bone cells

Osteoblasts

$$\langle \frac{dB}{dt}, \zeta \rangle = -\int_{\Gamma_t} (D_B \nabla_S B - B \nabla_S \chi(S_C) - B \nabla_S \chi(S_O)) \cdot \nabla_S \zeta dS + \int_{\Gamma_t} g_{13}(B, S_O, P, C) \zeta dS - \int_{\Gamma_t} d_{11}(O) \zeta dS \quad (3.91)$$

Osteoclasts

$$\langle \frac{dC}{dt}, \zeta \rangle = -\int_{\Gamma_t} (D_C \nabla_S C - C\nabla_S \chi(S_B) - C\nabla_S \chi(S_O)) \cdot \nabla_S \zeta dS + \int_{\Gamma_t} g_{15}(C, B, S_O, P)\zeta dS - \int_{\Gamma_t} d_{13} C\zeta dS \quad (3.92)$$

Osteocytes

$$\langle \frac{\partial O}{\partial t}(t), \zeta \rangle = \int_{\Omega_{s,t}} g_{17}(P, B, O)\zeta dx - \int_{\Omega_{s,t}} d_{15} O\zeta dx \quad (3.93)$$

Next we write down the variational formulations for the signals released by osteoblasts, osteoclasts and osteocytes.

3.6.4 Signals

Chemoattractant released by osteoblasts

$$\langle \frac{\partial S_B}{\partial t}(t), \zeta \rangle = -\int_{\Gamma_t} D_{S_B} \nabla_S S_B \nabla_S \zeta dS + \int_{\Gamma_t} g_{14}(B, S_B)\zeta dS - \int_{\Gamma_t} d_{12} S_B \zeta dS \quad (3.94)$$

Chemoattractant released by osteoclasts

$$\langle \frac{\partial S_C}{\partial t}(t), \zeta \rangle = -\int_{\Gamma_t} D_{S_C} \nabla_S S_B \nabla \zeta dS + \int_{\Gamma_t} g_{16}(C, S_C)\zeta dS - \int_{\Gamma_t} d_{14} S_C \zeta dS \quad (3.95)$$

Signals released by osteocytes

$$\langle \frac{\partial S_O}{\partial t}(t), \zeta \rangle = -\int_{\Omega_{s,t}} D_{S_O} \nabla S_O \nabla \zeta dx + \int_{\Omega_{s,t}} g_{18}(O, F, S_O)\zeta dx - \int_{\Omega_{s,t}} d_{16} S_O \zeta dx \quad (3.96)$$

3.7 Remarks

The equations (3.69)-(3.96) are modeling all processes, which are according to our research relevant for bone remodeling in general: fluid-structure interaction, combined with biochemistry, dynamics of cell population, mechano-sensing, signaling pathways, chemotaxis , ion transport and piezoelectric effects (see 3.1) This approach has the advantage, that we realize what we are neglecting if we reduce this altogether complex model system to a simpler one. Depending on the specific question to be answered by modeling and simulation reductions will be possible. Reduction will be necessary for mathematical and computational reasons, but also for the proper calibration.
We are confronted with free boundary problems, which are so far beyond reach of analytical theory, but might be accessible for computational studies. We formulated the model system in variational form, with a view to applying numerical techniques like Galerkin methods or finite elements.
Considering bone as porous structures, the derived model equations are valid on the micro-scale and the problem arises, to derive effective equations passing to a proper scale limit taken into account the small pore size. So far, such scale limits have been only studied for less complex systems, recently e.g. by Jäger et al. (2009, 2011), where just the interaction of flow, transport and reactions of chemical substances with the mechanics of solids is considered.

4 Application to tooth movement

The model presented in chapter three has a very fundamental character and there are several applications in medicine for our model. Some simplifications need to be done in order to apply our model to problems in real life. One example can be found in orthodontics.
Orthodontic tooth movement is a unique phenomenon where a solid object (tooth) is made to move through a solid medium (alveolar bone). Orthodontic treatment is possible due to the fact that whenever a prolonged force is applied on a tooth or teeth, bone remodeling occurs in the bone surrounding the tooth resulting in its movement.
Bone remodeling is a biomechanical process responsible for making bones stronger in response to sustained load-bearing activity and weaker in the absence of carrying a load. Bones are made of cells called osteoclasts and osteoblasts. Bone remodeling works like this: increase the load on a bone and osteoclasts are created which break it down in response to the load. Remove the load and osteoblasts are created which form new bony cells. Repeat the process through repetitive motion and eventually the bone density increases. Teeth are socketed in bone. Each tooth is surrounded by a periodontal ligament (PDL) which attaches it to the surrounding bone. The PDL is a sort of messenger between the teeth and surrounding bony sockets. Pressure between the PDL and bone causes the bone to create osteoclasts and breakdown the bone to restore the normal spacing between the teeth and bone. The corresponding tension on the PDL behind the movement causes the bone to create osteoblasts, effectively building new bone to fill in the difference and restore the normal spacing between teeth and bone. Teeth move through alveolar or trabecular bone whether due to the normal process of tooth eruption or due to strains generated by orthodontic appliances like braces.

4.1 Tooth movement

Adult tooth movement is a natural process. Our body has this tooth movement mechanism in place in order to keep our teeth in proper alignment.
In order to correct malpositions of teeth, they are being adjusted by braces in childhood and adolescence. This is called orthodontic tooth movement.

Orthodontic tooth movement is dependent on efficient remodeling of bone and cell to cell interactions of osteoblasts and osteoclasts.

4.1.1 Tooth structure

Teeth are surrounded by gum. Under the gum tissue the periodontal ligament (also called PDL or periodontum) encases the bottom portion of the tooth. It can be found next to the alveolar or trabecular bone. The PDL can be seen as a porous structure with fibres and fluid.

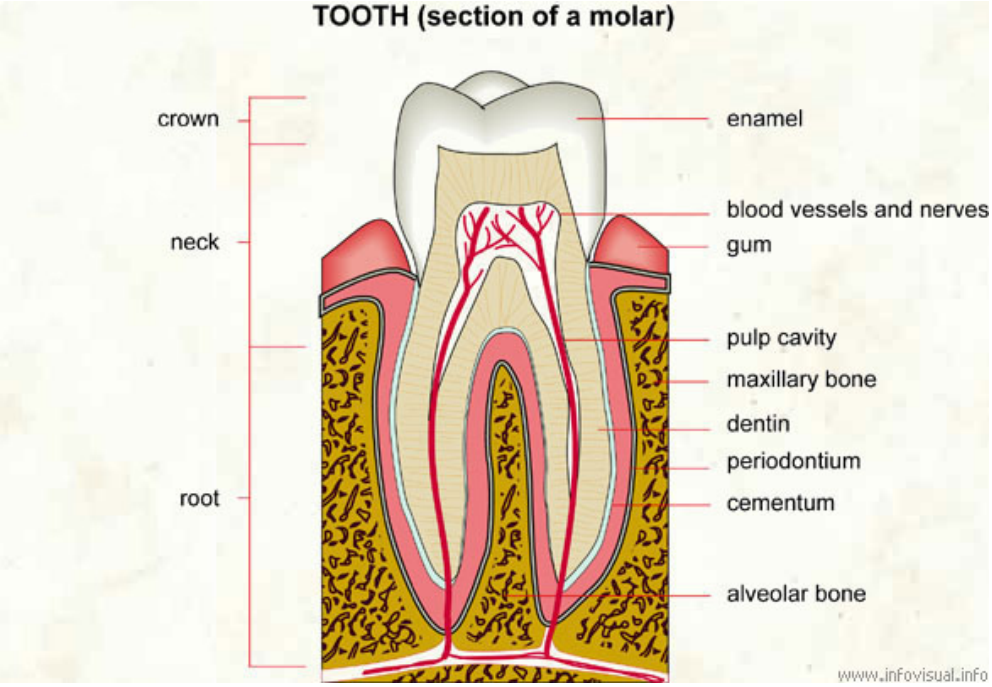

Figure 4.1: Section through a tooth (www.infovisual.info)

4.1.2 Braces

The application of braces moves the teeth as a result of force and pressure on the teeth. Braces basically consist of brackets normally made of metal or ceramic that are attached to the teeth. The arch wire which is a thin metal band runs from bracket to bracket and puts constant pressure on the teeth.

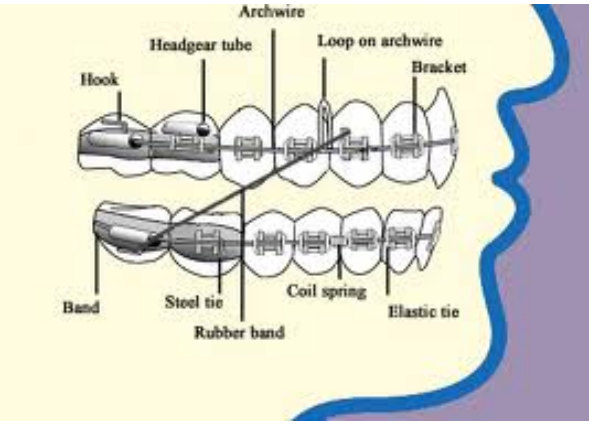

Figure 4.2: Braces on teeth

The teeth move when the arch wire puts pressure on the teeth, in response teeth move into their proper positions. The periodontal membrane stretches on one side and is compressed on the other. This loosens the tooth. The bone then grows in to support the tooth in its new position. Technically this is bone remodeling.
The following figure shows how the PDL is connected to the bone and how the bone grows into the gap.

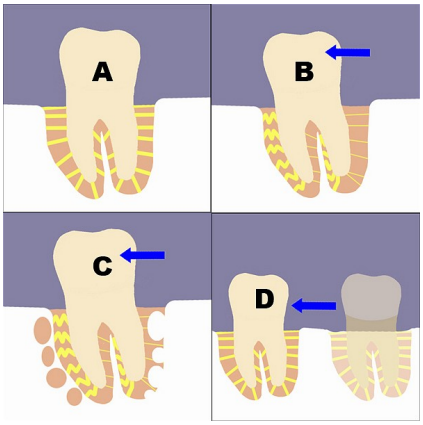

Figure 4.3: Orthodontic force on tooth

Osteoclastic activity takes place at the side where there is pressure and leads to bone resorption. Osteoblastic activity occurs at the side where there is tension, as a result we find bone formation.
The following figure shows that pressure and tension sites occur at each site, which is the case because of the rotation component of the force.

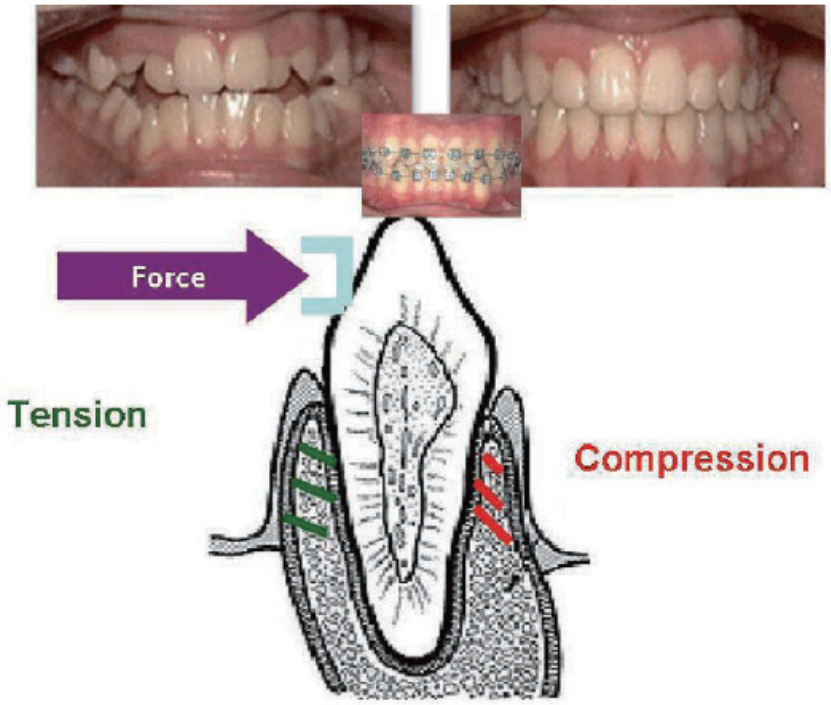

Figure 4.4: Tension and compression region in orthodontic tooth movement (sites.mc.ntu.edu.tw)

4.1.3 Theories for tooth movement

There are different theories for orthodontic tooth movement.

Blood flow theory

The blood flow theory goes back to Bien (1966). He proposed that tooth movement occurs as a result of laterations in fluid dynamics in the periodontal ligament. The contents of the periodontal ligament create a unique hydrodynamic condition resembling a hydraulic mechanism. When force of short duration is applied to a tooth, the fluid in the periodontal escapes through tiny vascular channels. When the force is removed, the fluid is replenished by diffusion from capillary walls and recirculation of the interstitial fluid.
When an orthodontic force is applied, it results in compression of the periodontal ligament on the pressure side thereby creating a favorable environment for resorption. (Singh, et. al., 2007)

The question here is though how the laterations are communicated to the osteoclasts or osteoblasts because they are the cells that build or resorb bone.

Piezoelectric theory

The piezoelectric effect occurs whenever a cristalline structure is loaded. The object is being bent and results in an electric flow.
Piezoelectric signals have two unique characteristics: a quick decay rate and the production of an equivalent signal opposite in direction, when the force is released. When the force is applied on a tooth, the adjacent alveolar bone bends. Areas of concavity are associated with negative charge and cause bone deposition. Areas of convexity with positive charge and cause bone resorption. (Singh, et. al., 2007) As the piezoelectric effect only occurs in short term loading situations it cannot be applied here to explain the tooth movement because the force applied by braces is a long term force.

Pressure tension theory

Finally Schwartz proposed the pressure tension theory in 1932 and it is the most widely accepted theory.
Whenever the tooth is subjected to orthodontic force, it results in areas of pressure and tension. The alveolar bone is resorbed whenever the root of the bone causes pressure on the periodontal ligament. New alveolar bone is deposited whenever there is a stretching force on the periodontal ligament. This is caused by alterations in the blood flow. These alterations cause formation and release of chemical messengers which then leads to the activation of osteoblasts and osteoclasts.

4.2 Mathematical model for tooth movement

In our general model the trigger for bone remodeling was on the one hand force and on the other hand calcium homeostasis. Here the situation is slightly different.

4.2.1 Modeling assumptions

In order to apply the above general model to the phenomenon of tooth movement some simplifications have to be made.

- we assume the pressure-tension theory here, we differ between compression sides where we have bone resorption and tension sides, where we find bone formation

- transport and diffusion of calcium and PTH can be neglected
- we discard the partial differential equations for the osteoblasts, osteoclasts and osteocytes

According to our modeling in chapter three we would also have to analyze the dynamics of the osteocytes, osteoblasts and osteoclasts in this situation. However discussing with the specialists of the Dental clinic in Heidelberg, we only obtained information on the osteoblasts and osteoclasts. In fact our medical partners claimed that according to experimental studies the effects only rely on the acitivity of osteoclasts and osteoblasts. The activity of osteocytes was not measurable for them. Neglecting the possible signaling of osteocytes as mecahnical sensors we model the direct influence of pressure and tension on the boundary.

- we assume the PDL to be a Biot-type material
- free boundary to the bone side
- fixed but moving boundary at the tooth side

It is important to state here that we assume a quasi-periodic structure within the PDL, although the periodontal ligament has no periodic structure.
The following figure shows the fibrous structure of the PDL.

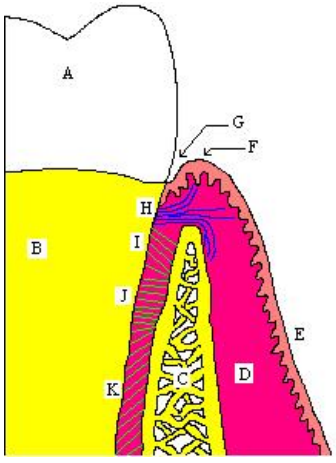

Figure 4.5: D PDL. H, I, J and K show the different kind of fibres in the PDL. C is the alveolar bone. G and F represent the gingiva. B the tooth root and A the cementum.(www.en.wikipedia.org)

4.2.2 Domains

We consider the following domains

- Ω_t represents the inside of the PDL which is a porous medium where Biot equations can be assumed and which is time dependent
- Γ_B describes the part of the boundary bordering the alveolar bone where there is either tension or compression
- Γ_B is a free boundary
- Γ_T is the part of the boundary that borders to the tooth, it has a fixed shape but moves with the tooth.
- Σ is the membrane that borders to the PDL, we can assume linear elasticity there

The following figure illustrates the descriptions from above.

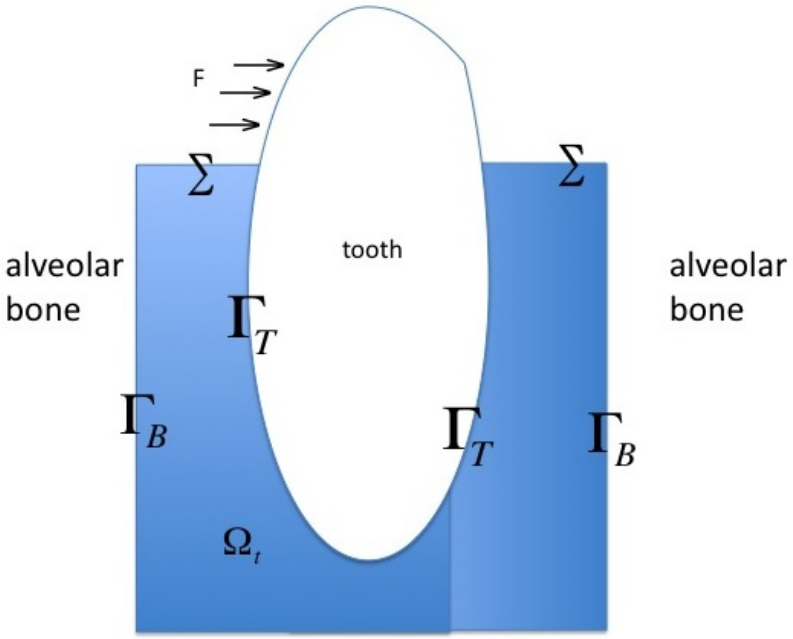

Figure 4.6: Description of the domain: blue Ω_t PDL

As it is very complicated to find equations and conditions for Σ, we should have a look at the horizontal section of a tooth, where we can neglect the membrane, in order to avoid regularity problems.

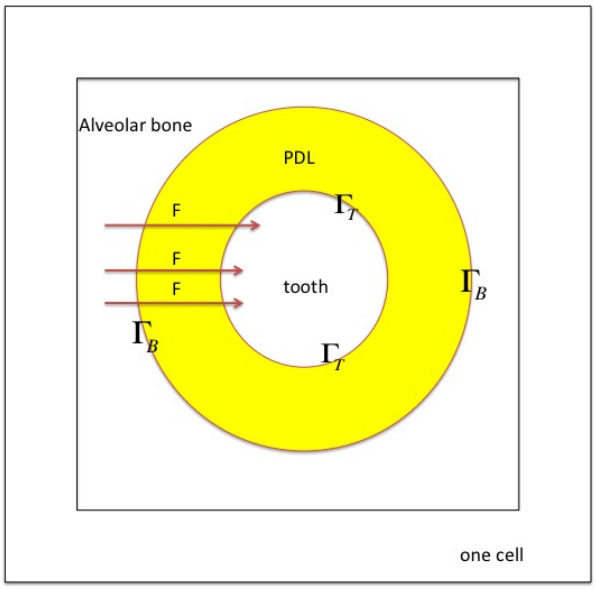

Figure 4.7: Horizontal section through the tooth

4.2.3 Mathematical model

We have to differentiate between chemoattractants depending on compression or tension. This was not the case in the other model because the piezoelectric effect covered that. The loading we look at here, is a long term loading situation. We assume that orthodontic tooth movement has the following components. We have two different solid objects, tooth and alveolar bone. The boundary of this solid objects is called the PDL.
The PDL is a heavy collagenous structure that attaches the cementum on the root surface to the dense bony plate around it (lamina dura).
Normally, the width is 0.25 mm - 0.5mm . Histologically the PDL is composed of cells, fibers, ground substance and tissue fluids. In the PDL we find cells which can differentiate into osteoblasts or osteoclasts (also called cemetoclasts) due to tension or compression situations.
The PDL space is filled with fluid, the same fluid found in all other tissues. The fluid acts as a shock absorber. When the tooth is subjected to heavy loads, a quick displacement of the tooth within the PDL space is prevented by the incompressible tissue fluid. Instead, the force is transmitted to the alveolar bone, which bends in response. The PDL is designed to resist forces of short duration. Prolonged forces will cause remodeling of adjacent bone to occur.

Equations for the PDL

We suppose that the PDL can be seen as a porous medium which occupies the domain Ω with the boundaries Γ_T and Γ_B. In the following we will neglect the boundaries and try to find a mathematical description for the behavior of the PDL. From the mathematical point of view, one can model this distribution by supposing that it is a periodic one. This periodicity can be represented by a small parameter, ϵ.
In practice, we are interested to know the global behavior of the composite material when the heterogeneities are very very small. This means that ϵ is very small, which mathematically signifies making ϵ tend to zero. The PDL can be seen as a porous media and it involves two basic elements: fluid flow and fiber deformation. Its main components are the ground substance - which is mainly fluid - and thin fibres arranged in bundles. These two components are responsible for the transmission of the forces acting on the tooth to its supporting structure. The change in fluid pressure, which is caused by fluid injection or production, alters the stress state of the PDL. The change in the stress state triggers the solid parts in the PDL to change which, in turn, affects the fluid flow processes.
The Biot theory of poroelasticity has been widely used in civic, mining and petroleum engineering, acoustic wave propagation in saturated media, and biology for several decades. We use the Biot equations to describe the behaviour of the periodontal ligament.
We formulate now the equations which model the process at the microscopic level. We assume small deformations of the cell structure. This means that in the solid part of the PDL Ω_s^ϵ the equations of linear elasticity hold.
Thus we have

$$\rho_s \frac{\partial^2 u^\epsilon}{\partial t^2} - \nabla \cdot (\sigma(u^\epsilon)) = f_s \quad in\ \Omega_s^\epsilon \tag{4.1}$$

where u^ϵ is the microscopic displacement, $D(u^\epsilon)$ is the strain tensor, and $\sigma(u^\epsilon)$ is the stress tensor given by

$$\sigma(u^\epsilon) = AD(u^\epsilon). \tag{4.2}$$

and $D(u)$ is the strain tensor defined by

$$(D(u^\epsilon))_{i,j} = \frac{1}{2}(\frac{\partial u_i^\epsilon}{\partial x_j} + \frac{\partial u_j^\epsilon}{\partial x_i}), i, j = 1, 2, 3 \tag{4.3}$$

In the homogenous and isotropic case, the elasticity coefficients A are given with the help of Lamé coefficients λ and μ. Another possibility is to use the Young's modulus E and the Poisson's coefficient ν. They relate to the Lamé's coefficients

through

$$\begin{aligned} \lambda &= \frac{E\nu}{(1+\nu)(1-2\nu)} \\ \mu &= \frac{E}{2(1+\nu)}. \end{aligned}$$

The stress tensor has the form:

$$\sigma(u^\epsilon) = \lambda \nabla \cdot (u^\epsilon I) + 2\mu D(u^\epsilon) \tag{4.4}$$

In the intercellular space Ω_f^ϵ, we consider the linearized Navier-Stokes system for a viscous and incompressible fluid. The interface between the fibers and the liquid is also linearized. At the inlet and outlet outer boundaries, we give the pressure and the shear stress. At the lateral no flow and displacement is assumed.
Now we have a closer look at the dimensions of the parameters in the equations.

Dimensional analysis for the PDL

The permeability coefficient is of order $10^{-8}/Pa \cdot sec.$ (Nyashin, 2000), the porosity $0,7$ (Bergomi, 2010), the Poisson ratio $0,45$ (Cattaneo, et al., 2005), and the Young Modulus $6,89MPa$, (Basdra, Komposch, 1997)
For the interstitial fluid in the PDL we assume the mass density of blood, which is $1025 - 1150kg/m^3$
Kanzaki, et al. (2002) found in experiments that with a compressive force of $2g/cm^2$ they find about 28 osteoclasts per square mm, whereas with a force of only $0,5g/cm^2$ we find only 12 osteoclasts per square mm in the periodontal ligament. They also showed that time plays an important role because these cell densities were found after 24 hours, but after 6 hours there were only half the size.

In its dimensionless form, the fluid-structure interaction is described by means of the microscopic displacement function u^ϵ, and the fluid pressure p^ϵ. Jäger et al. (2011) assume the following equations:

$$\frac{\partial^2 u^\epsilon}{\partial t^2} + \frac{1}{\epsilon^2}\nabla p^\epsilon = \Delta(\frac{\partial u^\epsilon}{\partial t}) \quad in\ \Omega_f^\epsilon, \tag{4.5}$$

$$\nabla \cdot (\frac{\partial u^\epsilon}{\partial t}) = 0 \quad in\ \Omega_f^\epsilon, \tag{4.6}$$

$$\frac{\partial^2 u^\epsilon}{\partial t^2} = \frac{1}{\epsilon^2}\nabla \cdot (AD(u^\epsilon)) \quad in\ \Omega_s^\epsilon, \tag{4.7}$$

$$u^\epsilon \chi_{\Omega_f^\epsilon} = u^\epsilon \chi_{\Omega_s^\epsilon} \quad on\ \Gamma^\epsilon, \tag{4.8}$$

$$(-\frac{1}{\epsilon^2}\nabla p^\epsilon I + 2D(\frac{\partial u^\epsilon}{\partial t})\cdot\nu = \frac{1}{\epsilon^2}AD(u^\epsilon)\cdot\nu \quad on\ \Gamma^\epsilon\cap\Omega_f^\epsilon, \tag{4.9}$$

$$\left(-\frac{1}{\epsilon^2}\nabla p^\epsilon I + 2D(\frac{\partial u^\epsilon}{\partial t})\right)\cdot e_1 = \begin{cases} 0 \quad on\ (\Gamma_1^\epsilon\cap\Omega_f^\epsilon), \\ \frac{1}{\epsilon^2}(\mathcal{S}_1^\epsilon,\mathcal{S}_2^\epsilon,\mathcal{S}_3^\epsilon) \quad on\ (\Gamma_2^\epsilon\cap\Omega_f^\epsilon), \end{cases} \tag{4.10}$$

$$\frac{1}{\epsilon^2}AD(u^\epsilon)\cdot e_1 = \begin{cases} 0 \quad on\ (\Gamma_1^\epsilon\cap\Omega_s^\epsilon), \\ \frac{1}{\epsilon^2}(\mathcal{S}_1^\epsilon,\mathcal{S}_2^\epsilon,\mathcal{S}_3^\epsilon) \quad on\ (\Gamma_2^\epsilon\cap\Omega_s^\epsilon), \end{cases} \tag{4.11}$$

$$\frac{\partial u^\epsilon}{\partial_t}\chi_{\Omega_f^\epsilon} + u^\epsilon\chi_{\Omega_s^\epsilon} = 0 \quad on\ \Gamma, \tag{4.12}$$

$$u^\epsilon(x,0) = 0 \quad in\ \Omega \tag{4.13}$$

$$\frac{\partial u^\epsilon}{\partial t}(x,0) = 0 \quad in\ \Omega \tag{4.14}$$

We can remark that the size of the elastic moduli and of the characteristic fluid pressure is of order $O(\frac{1}{\epsilon^2})$, whereas the viscosity forces are of order $O(1)$. This scaling corresponds to the diphasic model.

We assume that the bone cells respond directly to pressure and tension in the PDL.

Equations for the bone cell population

We also assume that the material which the osteoblasts need to form new bone is available at all times like enzymes. The osteoclasts on the other side release bone material from the compression side. We assume them to have the following form

$$\epsilon\frac{dB}{dt} = g_B(B,C,O,p) - d_B B \quad on\ \Gamma_B \tag{4.15}$$

$$\epsilon\frac{dC}{dt} = g_C(C,B,p) - d_C C \quad on\ \Gamma_B \tag{4.16}$$

The equations can be neglected due to the epsilon which will later tend to zero.

4.2.4 Variational formulation of the finite problem

The variational formulation will be the starting point for performing the homogenization limit $\epsilon \to 0$.

Find u^ϵ, satisfying for a.e. $t \in (0,T)$

$$\int_\Omega \partial_{tt} u^\epsilon \varphi dx + 2\int_{\Omega_f^\epsilon} D(\partial_t u^\epsilon(t)) : D(\varphi) dx + \frac{1}{\epsilon^2}\int_{\Omega_s^\epsilon} AD(u^\epsilon(t)) : D(\varphi) = \frac{1}{\epsilon^2}\int_{\Gamma^\epsilon} (\mathcal{S}_1^\epsilon, \mathcal{S}_2^\epsilon, \mathcal{S}_3^\epsilon)\varphi dS$$
$$\nabla \cdot \partial_t u^\epsilon = 0, \quad in\ \Omega_f^\epsilon \times (0,T)$$
$$u^\epsilon(x,0) = 0, \partial_t u^\epsilon(x,0) = 0 \quad in\ \Omega \quad (4.17)$$

for all $\varphi \in V$. The space V is defined as follows:
$V = \{\varphi \in H^1(\Omega)^3; \nabla \cdot \varphi = 0 \quad in\ \Omega_f^\epsilon\}$

4.2.5 Two-scale convergence result

Although the PDL is a fibrous medium which has different fibres, we assume the fibres to be arranged periodically. Belhadj et al. (2007) investigated filtration through a fibrous medium but the Biot equations were not considered.
In the limit $\epsilon \to 0$, the solution of the microscopic system (4.5)-(4.14) converge to the unique solution of the following homogenized system of differential equations. The effective system for the homogenized fluid-structure variables $\mathbf{u}^0, \mathbf{u}^1, p_f, \mathbf{v}, \pi^0$ consists of the homogenized equations for the structure variables

$$-Div_y\{A(t,x)(D_x(\mathbf{u}^0) + D_y(\mathbf{u}^1)\} = 0 \quad in\ \Omega \times Y_s,$$
$$A(t,x)(D_x(\mathbf{u}^0) + D_y(\mathbf{u}^1)) \cdot \nu + p_f \chi_{Y_f}(y) \cdot \nu = 0 \quad on\ \Omega_t \times \partial Y_s \backslash \partial Y,$$

$\mathbf{u}^1$ is Y-periodic,

$$-Div_x\left\{\int_{Y_s} A(D_x(\mathbf{u}^0) + D_y(\mathbf{u}^1))dy\right\} + |Y_f| p_f(t,x) = 0 \quad in\ \Omega_t$$
$$\left(\int_{Y_s} A(D_x(\mathbf{u}^0) + D_y(\mathbf{u}^1))dy - |Y_f| p_f(t,x) I\right) \cdot e_1 = \begin{cases} 0 \quad on\ \Gamma_1 \\ (\mathcal{S}_1^\epsilon, \mathcal{S}_2^\epsilon, \mathcal{S}_3^\epsilon) \quad on\ \Gamma_2 \end{cases}$$
$$\mathbf{u}^0(t,x) = 0 \quad on\ \Gamma_1,$$
$$\mathbf{u}^0(t,x) = 0 \quad on\ \Gamma_2,$$

coupled with the generalized Darcy's law for the fluid variables:

$$\Delta_y(\partial_t \mathbf{v}) + \nabla_y \pi^0 = -\nabla_x p_f \quad in\ \Omega \times Y_f,$$
$$div_y(\partial_t \mathbf{v}) = 0 \quad \Omega \times Y_f$$
$$\mathbf{v} = 0 \quad on\ \Omega \times \partial Y_f \backslash \partial Y,$$

$\mathbf{v}, \pi^0$ are Y-periodic,

$$div_x\left(|Y_f|\partial_t\mathbf{u}^0(t,x)+\int_{Y_f}\partial_t\mathbf{v}(t,x,y)dy\right)=\int_{Y_s}div_y\partial_t\mathbf{u}^1(t,x,y)dy \quad in\ \Omega$$

$$p_f=0 \quad on\ \Gamma_B,$$
$$p_f=\mathcal{P}^0 \quad on\ \Gamma_T,$$
$$\int_{y_f}\partial_t\mathbf{v}dy\cdot\nu=0 \quad on\ \Gamma_T.$$

4.2.6 Derivation of the effective equations for $\mathbf{u}, p^0$

The system is too complicated to be used directly, thus it is important to separate the fast and slow scales. Since our system is quasi-static, the decomposition calculation are simpler than in the dynamic case.
According to Mikelic and Wheeler (2011) we need the following auxiliary problems: For $i,j=1,...,3$, find the 1-periodic vector valued function $\mathbf{w}^{ij}\in H^1(Y_s)^3, \int_{Y_s}\mathbf{w}^{ij}(y)dy=0$, satisfying

$$\begin{cases} div_y\left\{A\left(\frac{e^i\otimes e^j+e^j\otimes e^i}{2}+D_y(\mathbf{w}^{ij})\right)\right\}=0 \quad in\ Y_s \\ A\left(\frac{e^i\otimes e^j+e^j\otimes e^i}{2}+D_y(\mathbf{w}^{ij})\right)\nu=0 \quad on\ \partial Y_s\backslash\partial Y \end{cases} \tag{4.18}$$

and find a 1-periodic vector valued function $\mathbf{w}^0\in H^1(Y_s)^3, \int_{Y_s}\mathbf{w}^0(y)dy=0$, satisfying

$$\begin{cases} -div_y\left\{AD_y(\mathbf{w}^0)\right\}=0 \quad in\ Y_s \\ AD_y(\mathbf{w}^0)\nu=-\nu \quad on\ \partial Y_s\backslash\partial Y \end{cases} \tag{4.19}$$

Due to the periodicity the above equations have a unique solution with regularity depending only on the smoothness of the geometry. With the assumption made, $\mathbf{w}^{ij}, \mathbf{w}^0$ are in $H^2(Y_s)^3$.

Thus, we decompose $\mathbf{u}^1$ as

$$\mathbf{u}^1(x,y,t)=p^0(x,t)\mathbf{w}^0(y)+\sum_{i,j}(D_x(\mathbf{u}^0(x,t)))_{i,j}\mathbf{w}^{i,j}(y) \tag{4.20}$$

$$\partial_t\mathbf{u}^1(x,y,t)=\partial_t p^0(x,t)\mathbf{w}^0(y)+\sum_{i,j}\frac{\partial_t(D_x(\mathbf{u}^0(x,t)))_{i,j}\mathbf{w}^{i,j}(y)}{\partial_t} \tag{4.21}$$

The cell problem corresponding to $\mathbf{v}$ is

$$\Delta\mathbf{q}^i+\nabla\pi^i=e^i \quad in\ Y_f \tag{4.22}$$
$$div_y\mathbf{q}^i=0 \quad in\ Y_f \tag{4.23}$$
$$\mathbf{q}^i=0 \quad on\ \Omega\times\partial Y_f\backslash\partial Y, \tag{4.24}$$

$\mathbf{q}^i, \pi^i$ are Y-periodic.

$\partial_t \mathbf{v}$ has the representation in terms of the $\mathbf{q}^i, \pi^i$:

$$\partial_t \mathbf{v} = \sum_{j=1}^{3} \mathbf{q}^j(y)(-\frac{p^0(x,t)}{\partial x_j}). \tag{4.25}$$

We substitute (4.25) and (4.20) and get

$$Div_x \left\{ \int_{Y_s} A \left(D_x(\mathbf{u}^0) + D_y \left(p^0 \mathbf{w}^0(y) + \sum_{i,j} (D_x(\mathbf{u}^0(x,t)))_{i,j} \mathbf{w}^{i,j}(y) \right) \right) dy \right\} +$$
$$|Y_f| p_f(t,x) = 0 \quad in \ \ \Omega$$
$$\mathbf{u}^0(t,x) = 0 \quad on \ \Gamma_T$$
$$\mathbf{u}^0(t,x) = 0 \quad on \ \Gamma_B \tag{4.26}$$

and

$$div_x \left(|Y_f| \partial_t \mathbf{u}^0(t,x) - \int_{Y_f} \sum q^j(y) \frac{\mathbf{p}^0(x,t)}{\partial_{x_j}} dy \right) =$$
$$\int_{Y_s} div_y \left(\partial_t \mathbf{p}^0(x,t) \mathbf{w}^0 + \sum_{i,j} \frac{\partial (D_x(\mathbf{u}^0(x,t)))_{i,j} \mathbf{w}^{i,j}(y)}{\partial_t} \right) dy \quad in \ \ \Omega \tag{4.27}$$

The cell problems define the effective coefficients:

$$A^H_{klij} := \left(\int_{Y_s} A \left(\frac{e^i \otimes e^j + e^j \otimes e^i}{2} + D_y(w^{ij}) \right) dy \right)_{kl} \tag{4.28}$$

$$\mathcal{B}^H := \int_{Y_s} A D_y(\mathbf{w}^0) dy, \tag{4.29}$$

$$\mathcal{C}^H_{ij} := \int_{Y_s} div_y w^{ij}(y) dy, \tag{4.30}$$

$$K_{ij} := \int_{Y_f} q^j_i(y) dy. \tag{4.31}$$

Furthermore we can state that $\mathcal{C}^H = \mathcal{B}^H$

Finally,

$$M_0 = -\int_{Y_s} div_y \mathbf{w}^0(y) dy = \int_{Y_s} A D_y(\mathbf{w}^0) : D_x(\mathbf{w}^0) > 0 \tag{4.32}$$

Now we use that

$$div_x\{(|Y_f|I - \mathcal{B}^H)\partial_t \mathbf{u}\} = (|Y_f|I - \mathcal{B}^H) : D_x(\partial_t \mathbf{u}), \tag{4.33}$$

and obtain the initial boundary problem for $\mathbf{u}, p^0$:

$$-div_x\{A^H D_x(\mathbf{u})\} + div_x\{(|Y_f|I - \mathcal{B}^H)p^0\} = 0 \quad in\ \Omega \tag{4.34}$$
$$M\partial_t p^0 + div_x\{K(-\nabla_x p^0) + (|Y_f|I - \mathcal{B}^H)\partial_t \mathbf{u}\} = 0 \quad in\ \Omega \tag{4.35}$$

, where $M = |Y_f|\kappa_{co} + M_0 = |Y_f|\kappa_{co} - \int_{Y_s} div_y \mathbf{w}^0(y)dy > 0$

In order to calculate the movement of the tooth it is important to state the tooth will move along a axis parallel to the resultant force which acts on the center of gravity of the tooth.
The shape of the tooth section can be idealized as elliptic, which means that the center of gravity is the point of intersection between the minor and major semi-axis.
On the center of gravity the force of the braces act as the resistance force of the alveolar bone.
The resultant force can be calculated as follows

$$f_{res} = \int_{A_{\Gamma_T}} f dA_{\Gamma_T} - \int_{A_{\Gamma_T}} (p_0 + AD(\sigma))dA_{\Gamma_T} \tag{4.36}$$

The resultant force describes the movement of the tooth through the bone.

$$\frac{d^2 s(t)}{d^2 t} = \frac{f_{res}}{m} \tag{4.37}$$

4.2.7 Free boundary problem

With equation (4.38) we average the boundary of the domain, which is adjacent to the bone. The following figure illustrates the averaging over the boundary.

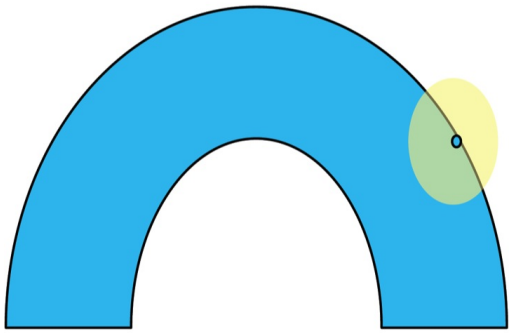

Figure 4.8: Averaging the boundary of the domain adjacent to the bone

As the osteoblasts constantly form new bone when they are active and the osteoclasts resorb bone when they are active the part of the boundary bordering to the PDL constantly changes.
The boundary Γ_B evolves in time. The evolution of the boundary Γ_B depends on the sign of the pressure on the boundary.

$$\frac{dx}{dt} = \mathcal{J}\left(\int_{\Omega_t} \rho(x(t) - y)(\sigma(y), p(y))dy\right)\nu(x(t)) \tag{4.38}$$

where $\mathcal{J}$ is a Lipschitz continuous function. x can be defined as follows $x = \xi + s\gamma(\xi)$, where ξ is the foot and s the normal coordinate.

5 Mathematical analysis of the free boundary problem

We now want to analyze the Biot system with the Rothe method. We now investigate the free boundary problem and write for $\Omega = \Omega_t$, and the index t in the other domains and boundaries.

5.1 Existence of weak solutions of the Biot system

We consider the problem

$$-div_x\{A^H D_x(\mathbf{u})\} + div_x\{(|Y_f|I - \mathcal{B}^H)\mathbf{p}\} = 0 \quad in\ \Omega_t \tag{5.1}$$

$$M\partial_t \mathbf{p} + div_x\{K(-\nabla_x \mathbf{p}) + (|Y_f|I - \mathcal{B}^H)\partial_t \mathbf{u}\} = 0 \quad in\ \Omega_t \tag{5.2}$$

$$\mathbf{u}(t,x) = 0 \quad on\ \Gamma_{B,t} \tag{5.3}$$

$$\mathbf{u}(t,x) = 0 \quad on\ \Gamma_{T,t} \tag{5.4}$$

$$\mathbf{p} = 0 \quad on\ \Gamma_{B,t}, \tag{5.5}$$

$$\mathbf{p} = \mathcal{P}^0 \quad on\ \Gamma_{T,t} \tag{5.6}$$

with the evolution of the boundary

$$\frac{dx}{dt} = \mathcal{J}\left(\int_{\Omega_t} \rho(x(t) - y)(\sigma(y), p(y))\right)\nu(x(t))$$

We will discretize the above full system in time and will show analytically that the discretized problem makes sense. We assume that the boundary of the domain is Lipschitz or C^2.

The Rothe-method uses a discretization of time. It is not possible that we assume a time interval of [0, T] to be given and divide this interval into intervals of $[t_l, t_{l+1}]$ with $t_l = h \cdot \Delta t$ and $\Delta t = \frac{T}{N} = h$. As the boundary moves it could be possible that we end up outside the domain if h is too big. Thus we start with h to be sufficiently small and make sure that we stay inside the domain.

The domains change with each time step as well. The following figure shows a cross section through the domain, where Ω_l is the domain of the periodontal ligament at time l. On the left the cross represents the tooth and the line represents the bone. Ω_{l+1} is the domain at the time step $l+1$. It is important to note that the domains must stay inside the domain Ω_t. Thus, we start with a sufficiently small h to ensure that we stay inside the domain.

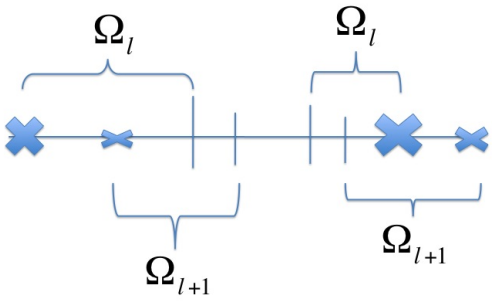

Figure 5.1: Crossection through the domains

We now have a closer look at the domain of the bone. The tooth could be illustrated equivalently.

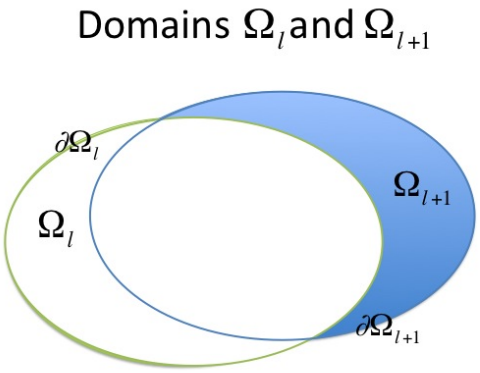

Figure 5.2: Bone domain in the Rothe Method

The following PDEs are valid in Ω_l, the functions u_l and p_l fulfil the PDEs only in Ω_{l-1}. We continue u through zero and p through P_0.

The solution u shall be approximated at time t_l by $u(t_l) \approx u_l \in L^2(\Omega_l)$. Let $t_0 = 0$ and $t_1 = h$. Using finite forward discretization we get

$$-\nabla_x A^H D_x u_{l+1} + (|Y_f| I - \mathcal{B}^H)\ \nabla \cdot\ p_{l+1} = 0 \qquad in\ \Omega_l$$

For simplicity, we set $E = (|Y_f| I - \mathcal{B}^H)$ and $A^H = A$ get

$$-\nabla_x A D_x u_{l+1} + E\ \nabla \cdot\ p_{l+1} = 0 \tag{5.7}$$

and

$$M\frac{p_{l+1} - p_l}{h} + \frac{div_x((|Y_f| I - \mathcal{B}^H)u_{l+1}) - div_x((|Y_f| I - \mathcal{B}^H)u_l)}{h} - \nabla_x K \nabla_x p_{l+1} = 0$$

With the above simplifications:

$$\begin{aligned} M\frac{p_{l+1} - p_l}{h} + \frac{div_x(Eu_{l+1}) - div_x(Eu_l)}{h} - \nabla_x K \nabla_x p_{l+1} &= 0 \qquad in\ \Omega_l \\ \mathbf{u}(t,x) &= 0 \qquad on\ \Gamma_{B,t} \\ \mathbf{u}(t,x) &= 0 \qquad on\ \Gamma_{T,t} \\ \mathbf{p} &= 0 \qquad on\ \Gamma_{B,t} \\ \mathbf{p} &= \mathcal{P}^0 \quad on\ \Gamma_{T,t} \end{aligned} \tag{5.8}$$

We assume that we know u_l, p_l and show that we can calculate u_{l+1} and p_{l+1} from that. (5.8) can be simplified because u_l, p_l are known.

$$M\frac{p_{l+1}}{h} + \frac{div_x(Eu_{l+1})}{h} - \nabla_x K \nabla_x p_{l+1} = M\frac{p_l}{h} + \frac{E div_x u_l}{h}$$

We now multiply with h and get

$$M p_{l+1} + E\ div_x\ u_{l+1} - h\ \nabla_x K \nabla_x p_{l+1} = f_l \tag{5.9}$$

where $f_l = E\ div_x\ u_l + M p_l$.

We also need to discretize the movement of the boundary:

$$\frac{x_{l+1} - x_l}{h} = \mathcal{J}\left(\int_{\Omega_t} \rho(x_l(t-y)(\sigma(y), p(y))dy\right)\nu(x_l(t))$$

5.1.1 Weak formulation of the discretized Biot system

Let the Hilbert spaces V_1 and V_2 such that:

$$V_1 = \{\varphi \in (H^1(\Omega_l))^2 : \varphi = 0 \quad on\ \Gamma_B, \varphi = 0 \quad on\ \Gamma_T\},$$
$$V_2 = \{\phi \in (H^1(\Omega_l))^2 : \phi = 0 \quad on\ \Gamma_B, \phi = \mathcal{P}^0 \quad on\ \Gamma_T\}$$

We multiply the equations (5.7) and (5.9) with the test functions $\varphi \in V_1$ and $\phi \in V_2$ respectively and integrate over Ω_l, to get

$$\int_{\Omega_l} AD_x u_{l+1} : \nabla\varphi + \int_{\Omega_l} E\ \nabla\cdot\ p_{l+1}\ \varphi = \int_{\partial\Omega_l} A(\nabla u^{l+1} + (\nabla u^{l+1})^*) \cdot \nu\varphi \quad \forall\varphi \in V_1 \tag{5.10}$$

with $Du_{l+1} = \frac{1}{2}((\nabla u_{l+1}) + (\nabla u_{l+1})^*)$, where * stands for the transpose matrix, we get

Lemma 1:

$$\int_{\Omega_l} A(\nabla u_{l+1} + (\nabla u_{l+1})^*) : \nabla\varphi + \int_{\Omega_l} E\ \nabla\cdot\ p_{l+1}\varphi = \int_{\partial\Omega_l} A(\nabla u^{l+1} + (\nabla u^{l+1})^*) \cdot \nu\varphi \quad \forall\varphi \in V_1 \tag{5.11}$$

and

$$\int_{\Omega_l} p_{l+1}\ \phi + \int_{\Omega_l} div\,(Eu_{l+1})\,\phi - h\int_{\Omega_l} K\Delta p_{l+1}\phi = \int_{\Omega_l} f_l\phi + h\int_{\partial\Omega_l} K\nabla p^{l+1} \cdot \nu\phi \quad \forall\phi \in V_2 \tag{5.12}$$

Using the divergence theorem and using Green's formula we get

Lemma 2:

$$-\int_{\Omega_l} Eu_{l+1} \cdot \nabla\phi + \int_{\Omega_l} p_{l+1}\phi + h(K\nabla p_{l+1}\nabla\phi) = \int_{\Omega_l} f_l\phi - \int_{\partial\Omega_l} Eu^{l+1} \cdot \nu\phi + h\int_{\partial\Omega_l} K\nabla p^{l+1} \cdot \nu\phi \quad \forall\phi \in V_2 \tag{5.13}$$

We take the testfunction out of V_2.

We have to be careful with the spaces V_1 and V_2 because they have to be inside Ω_t.

We introduce the bilinear forms a, b, and c as follows and define them over Ω:

$$a(u,v) := \int_\Omega A(\nabla u + (\nabla u)^*) : \nabla v$$
$$b(v,p) := \int_\Omega E\ \nabla \cdot\ p\ v$$
$$c(p,q) := \int_\Omega [p\ q + h\ K\nabla p \nabla q]$$

and

$$r_1(u,v) := \int_{\partial\Omega} A(\nabla u + (\nabla u)^*) \cdot \nu v$$
$$r_2(f_l,q) := \int_\Omega f_l q$$
$$r_3(u,p,q) := -\int_\Gamma Eu \cdot \nu q + h \int_\Gamma K\nabla p \cdot \nu q.$$

The weak formulation of our problem is: find $(u_{l+1}, p_{l+1}) \in V_1 \times V_2$ such that:

$$a(u_{l+1},\varphi) + b(\varphi,p) = r_1 \qquad \forall \varphi \in V_1,$$
$$-b(u_{l+1},\phi) + c(p_{l+1},\phi) = r_2 + r_3 \qquad \forall \phi \in V_2$$

That is,

Lemma 3:

$$a(u_{l+1},\varphi) + b(\varphi,p_{l+1}) = r_1 \qquad \forall \varphi \in V_1, \tag{5.14}$$
$$b(u_{l+1},\phi) - c(p_{l+1},\phi) = -r_2 - r_3 \qquad \forall \phi \in V_2 \tag{5.15}$$

We will show that the system (5.14)-(5.15) has a unique solution.

We now investigate the bilinear forms introduced above.

5.1.2 Continuity and coercivity of the bilinear forms

Definition 1: *The bilinear form* $a(\cdot,\cdot) : V_1 \times V_1 \to \mathbb{R}$ *and the bilinear form* $b(\cdot,\cdot) : V_1 \times V_2 \to \mathbb{R}$ *are continuous provided that positive constants* β *and* γ *exist such that:*

$$|a(u,\varphi)| \leq \beta \|u\|_{V_1} \|\varphi\|_{V_1} \qquad \forall u, \varphi \in V_1.$$

and

$$|b(u,\varphi)| \leq \gamma \|u\|_{V_1} \|\varphi\|_{V_2} \qquad \forall u \in V_1, \varphi \in V_2.$$

Definition 2: *The bilinear form* $a(\cdot,\cdot) : V_1 \times V_1 \to \mathbb{R}$ *is coercive provided that a positive constant* α *exists such that:*

$$|a(\varphi,\varphi)| \geq \alpha \|\varphi\|^2_{V_1} \qquad \forall \varphi \in V_1.$$

Theorem: *If the bilinear form* $a(\cdot,\cdot) : V_1 \times V_1 \to \mathbb{R}$ *is continuous and coercive,* $c(\cdot,\cdot) : V_2 \times V_2 \to \mathbb{R}$ *is continuous and coercive, and* $b(\cdot,\cdot) : V_1 \times V_2 \to \mathbb{R}$ *is continuous then for every* $f \in V_1'$ *and* $g \in V_2'$

$$\begin{aligned} a(u,\varphi) + b(\varphi,p) &= (f,\varphi) \\ b(u,\phi) - c(p,\phi) &= (g,\phi) \end{aligned}$$

has a unique solution (u,p).

For the proof of the above theorem we need the following Theorem:

Lax-Milgram Theorem
Assume that
$B : H \times H \to \mathbb{R}$ is a bilinear mapping, for which there exist constants $\alpha, \beta > 0$ such that

$$(i) \qquad |B[u,v]| \leq \alpha \|u\| \|v\| \qquad (u, v \in H)$$

and

$$(ii) \qquad \beta\|u\|^2 \leq B[u,u] \qquad (u \in H)$$

Finally, let $f : H \to \mathbb{R}$ be a bounded linear functional on H.
Then there exists a unique element $u \in H$ such that

$$B[u,v] =< f, v >$$

for all $v \in H$.

Proof. We introduce
$x := \begin{pmatrix} u \\ p \end{pmatrix} \qquad y := \begin{pmatrix} \varphi \\ \phi \end{pmatrix}$
and define for x in $V_1 \times V_2$ the following norm

$$\|x\|^2_{1,\Omega,\alpha} = \|u\|^2_{1,\Omega} + \alpha\|p\|^2_{1,\Omega}$$

where α is a positive constant.
Moreover we define another big bilinear form by subtracting the above two:

$$d(x,y) = a(u,\varphi) + b(\varphi,p) - b(u,\phi) + c(p,\phi)$$

$d(x,y)$ is not symmetric, but coercive

$$d(x,x) = a(u,u) + c(p,p),$$

which yields

$$\begin{aligned} d(x,x) &\geq \alpha_a\|u\|^2_{1,\Omega} + \alpha\frac{\alpha_c}{\alpha}\|p\|^2_{1,\Omega} \\ &\geq min(\alpha_a, \frac{\alpha_c}{\alpha})\|x\|^2_{1,\Omega,\alpha} \end{aligned}$$

Our above system of bilinear forms is equivalent to the following variational formulation

$$(*) \qquad d(x,y) = k(y) \qquad y \in V_1 \times V_2$$

where $k(y) = f - g$.
$\Rightarrow$ is clear through adding the equations, but $\Leftarrow$ not so obvious. With
$y_1 := \begin{pmatrix} \varphi \\ 0 \end{pmatrix} \qquad y_2 := \begin{pmatrix} 0 \\ \phi \end{pmatrix}$

$(*)$ can be o a problem with a homogenous Dirichlet boundary. Find $w = x - x^* \in V_1 \times V_2$, such that

$$d(w, y) = \tilde{k}(y) := k(y) - d(x^*, y) \qquad \forall y \in V_{1,0} \times V_{2,0}$$

with arbitrary $x^* = \begin{pmatrix} u^* \\ p^* \end{pmatrix} \in V_1 \times V_2$. The coercivity of $d(.,.)$ in $V_1 \times V_2$ together with the continuity of the bilinear forms $a(.,.), c(.,.), b(.,.)$ secures the solvability of the variational problem due to the Theorem by Lax-Milgram. □

In order to use the above theorem in our problem, we now have to show that the bilinear forms $a(\cdot,\cdot)$ and $c(\cdot,\cdot)$ are continuous and coercive and the bilinear form $b(\cdot,\cdot)$ is continuous on the respective spaces, hence there exist unique solutions u and p of the problem.
Let's consider $a(\cdot,\cdot), c(\cdot,\cdot)$ and $b(\cdot,\cdot)$ as definded before and we show that the assumptions of the theorem are fulfilled.
Recall that:

$$V_1 = \{\varphi \in (H^1(\Omega_t))^2 : \varphi = 0 \quad on\ \Gamma_B, \varphi = 0 \quad on\ \Gamma_T\},$$
$$V_2 = \{\phi \in (H^1(\Omega_t))^2 : \phi = 0 \quad on\ \Gamma_B, \phi = \mathcal{P}^0 \quad on\ \Gamma_T\}$$

Continuity and coercivity of $a(\cdot,\cdot)$

First we look at the continuity.

Continuity of $a(\cdot,\cdot)$

$$|a(u,\varphi)| = \left| \int_{\Omega_l} A\nabla u : \nabla\varphi + A\nabla u^* : \nabla\varphi \right|$$

Using the triangle inequality

$$|a(u,\varphi)| \leq \left| \int_{\Omega_l} A \sum_{i,j} \frac{\partial u_i}{\partial x_j} \cdot \frac{\partial \varphi_i}{\partial x_j} \right| + \left| \int_{\Omega_l} A \sum_{i,j} \frac{\partial u_j}{\partial x_i} \cdot \frac{\partial \varphi_i}{\partial x_j} \right|$$

Thus

$$\begin{aligned} |a(u,\varphi)| &\leq \alpha{**}\|\nabla u\|\|\nabla\varphi\| + \alpha{**}\|\nabla u\|\|\nabla\varphi\| \\ |a(u,\varphi)| &\leq 2\alpha^{**}\|\nabla u\|\|\nabla\varphi\| \end{aligned}$$

Hence

$$|a(u,\varphi)| \leq 2\alpha^{**}\|\nabla u\|_1\|\nabla\varphi\|_1$$

Hence $|a(u,\varphi)|$ is continuous.

Now we show the coercivity of $a(\cdot,\cdot)$.

Coercivity of $a(\cdot,\cdot)$

$$a(u,\varphi) = \int_{\Omega_l} A(\nabla u + \nabla u^*) : \nabla\varphi$$

and

$$\begin{aligned}(\nabla u + \nabla u^*) : \nabla\varphi &= \nabla u : \nabla\varphi + \nabla u^* : \nabla\varphi \\ &= \frac{1}{2}[\nabla u : \nabla\varphi + \nabla u^* : \nabla\varphi^* + \nabla u^* : \nabla\varphi + \nabla u : \nabla\varphi^*] \\ &= \frac{1}{2}(\nabla u + \nabla u^*) : (\nabla\varphi + \nabla\varphi^*)\end{aligned}$$

We also recall that the strain is

$$D(u) = \frac{1}{2}(\nabla u + \nabla u^*),$$

and

$$a(u,\varphi) = \int_{\Omega_l} 2A(\frac{1}{2}(\nabla u + \nabla u^*)) : (\frac{1}{2}(\nabla\varphi + \nabla\varphi^*)).$$

Now,

$$a(\varphi,\varphi) \geq \alpha^* \int_{\Omega_l} (D(u))^2$$

(Cioranescu and Donato, p. 191)

Korn's inequality (Ciarlet, p. 291): Let $\Omega \subset \mathbb{R}^3$ be an open bounded set with piecewise smooth boundary. In addition, suppose $\Gamma_0 \subset \partial\Omega$ has positive two-dimensional measure. Then there exists a positive constant $c = c(\Omega,\Gamma_0)$ such that:

$$\int_\Omega D(v) : D(v) \geq c\|v\|_1^2 \qquad \forall\ v \in H^1_\Gamma(\Omega).$$

We assumed that the measure on the boundaries Γ_T, Γ_B are positive, then from the Korn's inequality $a(\cdot,\cdot)$ is coercive.

$$a(\varphi,\varphi) \geq \alpha\|\varphi\|_1^2 \qquad \forall\varphi \in (H^1(\Omega_t))^2. \tag{5.16}$$

Moreover, the bilinear form $a(\cdot,\cdot)$ is symmetric. (See Appendix)

Now we show the continuity of $b(\cdot,\cdot)$.

Continuity of $b(\cdot,\cdot)$

Recall that

$$b(\varphi,p) := \int_{\Omega_l} E(\nabla p)\varphi$$

hence

$$\begin{aligned} |b(\varphi,p)| &\leq \|E\nabla p_{l+1}\|\|\varphi\| \\ &\leq \epsilon\|p\|_1\|\varphi\|_1 \quad \forall p \in H^1(\Omega) \text{ and } \varphi \in (H^1(\Omega))^2. \end{aligned} \tag{5.17}$$

We show now the continuity and coervitiy of $c(\cdot,\cdot)$.

Continuity and coercivity of $c(\cdot,\cdot)$

We start with the continuity.

Continuity of $c(\cdot,\cdot)$
We have

$$c(p,\phi) := \int_{\Omega_l} [p\ \phi + hK\nabla p\nabla\phi]$$

thus,

$$\begin{aligned} |c(p,\phi)| &\leq \|p\|\ \|\phi\| + h\kappa\|\nabla p\|\|\nabla\phi\| \\ &\leq max(1,h\kappa)\|p\|_1\|\phi\|_1 \qquad \forall p,\phi \in H^1(\Omega_l). \end{aligned} \tag{5.18}$$

Thus c is continuous.

Coercivity of $c(\cdot,\cdot)$
Now,

$$\begin{aligned} c(\phi,\phi) &= \int_{\Omega_l} \phi^2 + hK(\nabla\phi)^2 \\ &\geq \|\phi\|^2 + h\kappa\|\nabla\phi\|^2 \\ &\geq min(1,h\kappa)\|\phi\|_1^2 \qquad \phi \in H^1(\Omega_l). \end{aligned} \tag{5.19}$$

Thus c is coercive.

Corollary: *The bilinear form $a(\cdot,\cdot) : V_1 \times V_1 \to \mathbb{R}$ is continuous. If the measure of the boundaries Γ_B, Γ_T are positive, then $a(\cdot,\cdot)$ is coercive. The bilinear forms $c(\cdot,\cdot) : V_2 \times V_2 \to \mathbb{R}$ is continuous and coercive, and $b(\cdot,\cdot) : V_1 \times V_2 \to \mathbb{R}$ is continuous. Hence (5.14)-(5.15) has a unique weak solution (u, p)*

Using the previous corollary we can now prove existence of the weak solutions with Rothe's method.

In the following part we will sketch the proof for the convergence. It is not possible to show uniqueness as it is complicated because of the moving and changing domain.

5.2 Convergence

We now have a look at the Rothe sequences $u^n(x,t)$ and $p^n(x,t)$ in the space $H^{1,2}(I, H^{1,2}(\Omega))$.
The Rothe functions are

$$u^n(x,t) = u_l + (t - t_l^n)\frac{(u_{l+1}^n - u_l^n)}{h_n}, \quad in\ I_{l+1}^n = [t_l^n, t_{l+1}^n],$$
$$p^n(x,t) = p_l + (t - t_l^n)\frac{(p_{l+1}^n - p_l^n)}{h_n}, \quad in\ I_{l+1}^n = [t_l^n, t_{l+1}^n].$$

Proposition:

(u^n, p^n) is pre-compact in $L^2(I, L^2(\Omega)) = L^2(I \times \Omega)$ and

$$u^{n_j} \to u \qquad u \in L^2(I, H^{1,2}(\Omega)$$
$$p^{n_j} \to p \qquad p \in L^2(I, H^{1,2}(\Omega)$$

for a proper chosen subsequence.
For this we need to show that u^n, p^n are equicontinuous with respect to n.

For the convergence proof we would need the following estimates. Treating the convergence of Rothe functions to a solution of the differential equations and the

analysis in the case of free interfaces is a challenge for future investigations.

We need to show that

$$h\sum_{j=1}^{n}\|\delta u_{l+1}^{n}\|^2 \leq const$$

which means

$$h\sum_{j=1}^{n}\|\frac{u_{l+1}^{n}-u_{l}^{n}}{h}\|^2 \leq const$$

Equivalently with p:

$$h\sum_{j=1}^{n}\|\delta p_{l+1}^{n}\|^2 \leq const$$

which means

$$h\sum_{j=1}^{n}\|\frac{p_{l+1}^{n}-p_{l}^{n}}{h}\|^2 \leq const$$

It is possible to show this for a fixed domain, but for a free boundary there are problems when integrating by parts. We will derive in the following the estimates for the fixed domain, also to illustrate, where the difficulties in the case of free boundaries arise.

5.2.1 A priori estimates

Here we assume the boundary to be fixed and write now Ω for the fixed domain. For the approximate solutions of the fixed domain we can state the following

Lemma 4:

$$\begin{aligned}
\|u_{l+1}\|^2_{L^2(\Omega)} &\leq const \qquad (1)\\
\|\nabla u_{l+1}\|^2_{L^2(\Omega)} &\leq const \qquad (2)\\
\|p_{l+1}\|^2_{L^2(\Omega)} &\leq const \qquad (3)\\
h\|\nabla p_{l+1}\|^2_{L^2(\Omega)} &\leq const \qquad (4)
\end{aligned}$$

First we recall our problem with homogeneous boundary and initial conditions.

$$\begin{aligned}
-\nabla_x A D_x u_{l+1} + E\nabla\cdot p_{l+1} = 0 \qquad (1)\\
\frac{M}{h}(p_{l+1}-p_l)+\frac{E}{h}(div_x u_{l+1} - div_x u_l) - \nabla\cdot K\nabla_x p_{l+1} = 0 \qquad (2) \qquad (5.20)
\end{aligned}$$

The weak formulation of this problem is: find $u_{l+1} \in V_1^*$ and $p_{l+1} \in V_2^*$, where V_1^* and V_2^* are the spaces from 5.1.1 with homogenous boundary conditions, such that

$$-\int_\Omega \nabla A D_x u_{l+1} : \varphi + \int_\Omega E\ \nabla \cdot\ p_{l+1}\varphi = 0 \quad \forall \varphi \in V_1^* \tag{5.21}$$

$$\int_\Omega M(p_{l+1} - p_l)\phi + \int_\Omega E(\nabla \cdot u_{l+1} - \nabla \cdot u_l)\phi + \int_\Omega hK\nabla p_{l+1} \cdot \nabla\phi = \int_\Omega hb_{l+1} \cdot \phi, \quad \forall \phi \in V_2^*. \tag{5.22}$$

Now we set $\phi = p_{l+1}$, and assume that p vanishes at the boundary.

$$\int_\Omega M\big(\frac{1}{2}|p_{l+1}|^2 - \frac{1}{2}|p_l|^2 + \frac{1}{2}|p_{l+1} - p_l|^2\big) + h\int_\Omega K\nabla p_{l+1}\nabla p_{l+1} + (*) \leq \int_\Omega \alpha h b_{l+1}^2 + \beta h p_{l+1}^2 \tag{5.23}$$

Now we have a closer look at (*):

$$\begin{aligned}(*) &= \int_\Omega E(\nabla u_{l+1} - \nabla u_l)p_{l+1} \\ &= -\int_\Omega E(u_{l+1} - u_l)\nabla p_{l+1}\end{aligned}$$

Using (5.21) with $\varphi = u_{l+1} - u_l$ we get

$$(*) = -\int_\Omega \nabla A D_x u_{l+1} : (u_{l+1} - u_l) \tag{5.24}$$

$$= -\int_\Omega A D_x u_{l+1} : \nabla(u_{l+1} - u_l) \tag{5.25}$$

$$= \int_\Omega 2AD(u_{l+1}) : D(u_{l+1} - u_l) \tag{5.26}$$

Getting from (5.24) to (5.26) is only possible if integrating by part is possible, which is not in the case in the case of a free boundary, since the equation for u_{l+1}

holds only in Ω_l. We assume a fixed boundary and continue.

$$(*) = \frac{1}{2}\int_\Omega 2AD(u_{l+1}) : D(u_{l+1}) - \frac{1}{2}\int_\Omega 2AD(u_l) : D(u_l) + \frac{1}{2}\int_\Omega 2AD(u_{l+1}-u_l) : D(u_{l+1}-u_l)$$

Now by summing from 0 to l we get

$$\frac{1}{2}(Mp_{l+1}, p_{l+1}) - \frac{1}{2}(Mp_0, p_0) + \frac{1}{2}\sum_{k=0}^{l} M(p_{k+1}-p_k)(p_{k+1}-p_k) + h\sum_{k=0}^{l}(K\nabla p_{l+1}, \nabla p_{l+1}) + \frac{1}{2}(2AD(u_{l+1}), D(u_{l+1})) - \frac{1}{2}(2AD(u_0), D(u_0)) + \frac{1}{2}\sum_{k=0}^{l} 2AD(u_{k+1}-u_k) : D(u_{k+1}-u_k) \leq \frac{1}{\epsilon}h\sum_{k=0}^{l} b_{k+1}^2 + \epsilon\beta h\sum_{k=1}^{l+1}\|p_k\|^2 \quad (5.27)$$

Now we can show the a priori estimates from Lemma 4 because M is bounded

$$\begin{aligned} \|p_{l+1}\|^2 &\leq const_0 + \epsilon const_1 h\sum_{k=1}^{l+1}\|p_k\|^2 \\ \|p_{l+1}\|^2 &\leq const \end{aligned}$$

$const_0$ depends on ϵ.

The other estimates follow from inequality (5.27).

Now we multiply (5.21) with $l+1$ respectively l with testfunctions $u_{l+1}-u_l$ and obtain by subraction

$$\int_\Omega 2AD(u_{l+1}-u_l) \,:\, D(u_{l+1}-u_l) + \int_\Omega E\nabla(p_{l+1}-p_l)(u_{l+1}-u_l) \,=\, 0 \quad (5.28)$$

Multiplying (5.22) with $p_{l+1} - p_l$ and we obtain

$$\int_\Omega |p_{l+1} - p_l|^2 + \int_\Omega E\nabla(u_{l+1} - u_l)(p_{l+1} - p_l) + h\int_\Omega K\nabla p_{l+1}\nabla p_{l+1} - h\int_\Omega K\nabla p_{l+1}\nabla p_l = \int_\Omega hb_{l+1}(p_{l+1} - p_l) \leq \frac{1}{2}h^2\int_\Omega |b_{l+1}|^2 + \frac{1}{2}\|p_{l+1} - p_l\|^2 \quad (5.29)$$

Add (5.28) and (5.29) and obtain with partial integration

$$\frac{1}{2}\int_\Omega \|p_{l+1} - p_l\|^2 + \frac{1}{2}h\int_\Omega K\nabla p_{l+1}\nabla p_{l+1} - \frac{1}{2}h\int_\Omega K\nabla p_l\nabla p_l + \frac{1}{2}h\int_\Omega K(\nabla p_{l+1} - \nabla p_l)\cdot(\nabla p_{l+1} - \nabla p_l) + \int_\Omega 2AD(u_{l+1} - u_l) : D(u_{l+1} - u_l) \leq h^2\int_\Omega |b_l|^2 \quad (5.30)$$

Sum up from $k = 0$ to l and obtain by using Poincaré's inequality and Korn's inequality

$$\sum_{k=0}^{l} \|p_{k+1} - p_k\|^2 + \sum_{k=0}^{l} \|(u_{k+1} - u_k)\|^2 \leq const \cdot h \quad (5.31)$$

Using well-known compactness theorems we get for the problem with fixed boundaries convergence of subsequences. Furthermore, it can be shown with standard arguments that the limit satisfies the original equations in a weak sense. Since also the solutions are unique, one obtains convergence. Since we are here interested in the free boundary problem, and since we only intended to illustrate the critical points arising in the derivation of the required estimates, we refrain from presenting a full proof for the case of a fixed boundary.

6 Discussion and Outlook

To investigate the influences of loading, resulting shear stress, calcium, and parathyroid hormone concentrations on bone formation and bone resorption this thesis developed a model for bone remodeling and a possible application for this model in dentistry.

We described the bone as a solid material filled with fluid bone marrow and considered both mechanical and homeostatic influences on the porous structure. Bone is constantly changing its shape and mineral content due to changing stress conditions and homeostatic needs. The most challenging and yet interesting part of the model is the description of this phenomenon. Thus the domain where our problem is formulated is time dependent with a free boundary.

Our model developed in chapter three has a very fundamental character and is the first that considers not only the porous structure with population of bone cells but also the chemical signaling and the calcium and parathormone concentration in bone remodeling and the free boundary. We derived a number of partial differential equations which combined Navier Stokes and elasticity equations with partial differential equations that describe the bone cell populations of osteoblasts, osteoclasts and osteocytes which control and regulate the bone metabolism. As bone cells communicate and influence each other, we also involved equations for the chemical reactions like chemotaxis and equations for movement and transport due to the piezoelectrical effect. As many complex processes are involved and considered, we ended up with a huge system of equations.
This first, very complex model was presented in chapter three. A free boundary problem was formulated in weak sense. But we were unable to prove existence of weak solutions because the system of equations is too complex. Even simpler sub-problems are challenges to current research.
With regard to possible applications in medicine, the model was kept on a rather fundamental level. Hence, due to the biological complexity of hemeostasis, some limitations exist. The most striking one is that the dependence of phosphates and hormones on bone remodeling were neglected.
In order to apply the fundamental model to problems in medicine it is inevitable to conduct some simplifications by means of reducing the number of equations. The choice of the appropriate equations depends on the research questions embodied

in the study.

In chapter four we were able to apply our general model to a problem in dentistry. As we were interested in tooth movement, the calcium metabolism and parathormone exchange was of minor interest for us. Following the concepts of our partners in medicine, we only considered the activity of the osteoblasts and osteoclasts, assuming that they react directly to the mechanical forces. We also assumed that the populations are in a quasi steady state depending on the local stresses. The generation and degradation of bone are functions of the size of the cell populations. Therefore we assumed that the velocity of the moving surface of the bone is a functional of the local stresses. The role of the bone cells is assumed to be similar to those of enzymes in chemical reactions. We described the periodontal ligament bordering the trabecular bone as a Biot type material with a free boundary and a moving, but fixed boundary on the tooth side. We formulated effective equations for the dynamics of the Biot fluid and the dynamics of the free, respectively moving boundary, using concepts and results of homogenization.

The bio-mechanics of the periodontal ligament is of great interest in medical research. The model developed here can help to derive valuable information for orthodontics. To our knowledge, free boundary problems for Biot-fluids have not been mathematically treaded so far. In chapter five we proved the existence of the Rothe step of the discretized problem.
It is challenging

- to prove convergence of the Rothe method of the free boundary problem. Here the derivation of the necessary a-priori estimates of the solutions of the Rothe iteration is an important step,
- to consider a model system in three dimension, where an additional interface, closing the ligament and connecting tooth and bone, has to be considered. Here new problems in modeling and analysis are arising,
- to prove the uniqueness of solutions to the free boundary problem,
- to develop numerical algorithms and simulate the model equations in realistic situations.

The next research steps could be

- a priori estimates for u and p are needed to prove convergence
- to homogenize the model for the trabecular bone
- numerical analysis of the free boundary problem

Our general model could also be used in studies where the research questions are of rather pharmaceutical character.

Osteoporosis, a disease where the bones become porous and the risk of fracture increases dramatically is of great interest to researchers who constantly try to improve the treatment of this disease. The goals are to stop or slow down bone loss and prevent bone fractures with medicines that strengthen bone. The parathyroid hormone plays a very important role in treatment of osteoporosis, "Human parathyroid hormone was approved in 2004 for the treatment of severe osteoporosis." (Cranney, et al. 2006) Rattanakul and Lenbury (2003) investigated the bone response to PTH and estrogen therapy. As our model considers the influence of parathyroid hormone on bone formation and the mineral content of bone, it could be valuable for simulations of medical treatments in this field.

Our model could also be applicable to other research disciplines where porous media is involved and where we find interactions between substances at the boundaries or transport of substances in porous media. Bio tissues and life in Bio-porous media could also be a possible application.

Setting up a rather comprehensive mathematical model system for bone remodeling, taking into account most recent empirical results, was rather time consuming and challenging to mathematical modeling. As usual at the interface between life sciences and mathematics more detailed questions are arising to mathematical research.

List of Abbreviations and Appendix

Below, the notations used throughout the manuscript are listed. They are subdivided into the chapters they are used in.

Notations used in chapter 3

$\Omega_{s,t}$: solid part of the domain, changes in time

$\Omega_{f,t}$: fluid part of the domain, changes in time

Γ_t: free boundary, interface between solid and fluid part

I: Inlet of the boundary

O: outlet of the boundary

Σ: upper part of the boundary

w: displacement of the solid part

f: force

ρ_s: solid density

$\sigma(w)$: stress tensor in the solid

$D(w)$: strain tensor

λ, μ: Lamé coefficients

E: Young modulus

ν: Poisson coefficient

v: fluid velocity

ρ_f: fluid density

μ_f: fluid viscosity

p: fluid pressure

$\sigma(v)$: stress tensor in the fluid

$D(v)$: strain tensor in the fluid

$\vec{E}$: electric field

Φ: potential

H: curvature

S: level set function

MBM: mineralized bone matrix

INF: interstitial fluid in the canaculi

ECF: extracellular fluid, bone marrow

g_i: birth constants or functions

d_j: death or removal constants or functions

$(Ca)_{MBM}$: level of bound calcium in MBM

$(Ca)_{INF}$: level of calcium in interstitial fluid

$(Ca)_{ECF}$: level of free calcium in extracellular fluid

$(Ca)_{boundary}$: calcium available at the boundary

$(Ca)_O$: calcium in the osteocytes

$(Ca)_C$: calcium resorbed by osteoclasts

$(Ca)_B$: calcium deposited by osteoblasts

P: level of PTH

B: number of active osteoblasts

C: number of active osteoclasts

O: number of osteocytes

F: load

τ_p: shear stress caused by interstitial fluid flow/pressure

S_C: chemical attractant released by osteoclasts

S_B: chemical attractant released by osteoblasts

S_O: stimulus released by osteocytes

$\mathcal{F}$, $\mathcal{G}$: functions

φ, ζ: testfunctions

Notations used in chapter 4

P: pressure

T: tension

Ω: continuation of the domain of the PDL

Ω_t: changing domain of the PDL

Ω_s: solid part of the PDL (fibres)

Ω_f: fluid part of the PDL

Γ_B: boundary bordering on the alveolar bone, free boundary

Γ_T: boundary bordering on the tooth, moving but fixed shaped

ρ_s: density of the skeleton

ρ_f: density of the fluid in the pores

v: fluid velocity

q: filtration velocity

p_f: fluid pressure

u: displacement of the porous structure

λ, μ: Lamé coefficients of the PDL

$\sigma(u)$: stress tensor in the PDL

$D(u)$: strain tensor (membrane)

E: Young modulus (Biot)

ν: Poisson ratio (Biot)

u_T: tooth displacement

x: displacement of the free boundary

A_{Γ_T}: Area of boundary Γ_T

$\mathcal{J}$: function

B,C, O: osteoblasts, osteoclasts and osteocytes

φ, ϕ: testfunctions

u^0: macroscopic displacement

u^1: microscopic displacement

f_{res}: resultant force on the center of gravity of the tooth

$s(t)$: movement of the tooth

m: mass of the tooth

Appendix

$$\nabla u : \nabla v = \sum_{i,j} \frac{\partial u_i}{\partial x_j} \cdot \frac{\partial v_i}{\partial x_j},$$
$$\nabla \cdot u = \sum_i \frac{\partial u_i}{\partial x_i}$$

Symmetry of $a(\cdot,\cdot)$:

$$a(u,\varphi) = \int_\Omega A(\nabla u + \nabla u^*) : \nabla \varphi$$

and

$$(\nabla u + \nabla u^*) : \nabla \varphi = \frac{1}{2}(\nabla u + \nabla u^*) : (\nabla \varphi + \nabla \varphi^*).$$

Therefore

$$\begin{aligned}
a(u,\varphi) &= \int_\Omega \frac{1}{2} A(\nabla u + \nabla u^*) : (\nabla \varphi + \nabla \varphi^*) \\
&= \int_\Omega \frac{1}{2} A(\nabla u : \nabla \varphi + \nabla u : \nabla \varphi^* + \nabla u^* : \nabla \varphi + \nabla u^* : \nabla \varphi^*) \\
&= \int_\Omega \frac{1}{2} A(\nabla \varphi : \nabla u + \nabla \varphi^* : \nabla u + \nabla \varphi : \nabla u^* + \nabla \varphi^* : \nabla u^*) \\
&= \int_\Omega \frac{1}{2} A(\nabla \varphi + \nabla \varphi^*) : (\nabla u + \nabla u^*) \\
&= \int_\Omega A(\nabla \varphi + \nabla \varphi^*) : \nabla u \\
&= a(\varphi, u).
\end{aligned}$$

Hölder's inequality:
Let $1 < p, q < \infty$ such that $\frac{1}{p} + \frac{1}{q} = 1$. Then if $u \in L^p(\Omega), v \in L^q(\Omega)$, it follows that $uv \in L^1(\Omega)$ and

$$\int_\Omega |u(x)v(x)|dx \leq \|u\|_{L^p(\Omega)} \|v\|_{L^q(\Omega)}.$$

Young's inequality:
Let $1 < p, q < \infty$ such that $\frac{1}{p} + \frac{1}{q} = 1$. Then

$$ab \leq \frac{a^p}{p} + \frac{b^q}{q} \qquad \forall a, b \geq 0.$$

Poincaré-Inequality
Let $\Omega \subset \mathbb{R}^n$ be an open, connected, bounded subset. Then there exists a constant C (dependent on Ω) such that

$$\int_\Omega |u|^2 \leq C \int_\Omega |\nabla u|^2 \qquad \forall u \in H^{1,2}(\Omega).$$

Korn's inequality: Let $\Omega \subset \mathbb{R}^3$ be an open bounded set with piecewise smooth boundary. In addition, suppose $\Gamma_0 \subset \partial\Omega$ has positive two-dimensional measure. Then there exists a positive constant $c = c(\Omega, \Gamma_0)$ such that:

$$\int_\Omega D(v) : D(v) \geq c\|v\|_1^2 \qquad \forall\ v \in H^1_\Gamma(\Omega).$$

List of Figures

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