Osteoarthritis or OA, especially in the knee, is a common disease in elderly people but also in athletes that have suffered a trauma, e.g. anterior cruciate ligament rupture. Currently, OA cannot be cured, but its risks can be estimated and minimized. This thesis aims to develop a novel, computational model of the subject’s knee that could, in future, be used by doctors as a diagnostic tool to evaluate the risk of post-traumatic OA before and after surgical operations.
KIMMO HALONEN

Validation and application of computational knee joint models

Finite element modeling analysis

Publications of the University of Eastern Finland
Dissertations in Forestry and Natural Sciences
No 187

Academic Dissertation
To be presented by permission of the Faculty of Science and Forestry for public examination in the SN201 in Snellmanin Building at the University of Eastern Finland, Kuopio, on 2nd October 2015, at 12:00 o’clock.

Department of Applied Physics
ABSTRACT

Osteoarthritis (OA) is a joint disease in which the structure of articular cartilage slowly changes, which results in slow degeneration. First the collagen fibril network starts to deorganize, the proteoglycan content decreases and the water content increases. Next, the cartilage starts to crack and eventually wears away, at which point the knee joint has to be replaced with a prosthesis. Since the treatment options for OA are currently very limited, prevention of OA would be the most cost-efficient method to deal with it.

Even though the exact cause of OA is unknown, the disease is believed to be a combination of inflammatory, biological and mechanical changes in the articular cartilage. Excessive stresses in the articular cartilage have been shown to lead to the development of OA as the mechanical structure of articular cartilage is damaged. The cause of abnormal stresses in the cartilage might be a result of the subject’s natural gait pattern, an injury (e.g. anterior cruciate ligament (ACL) rupture) or a surgical operation (e.g. osteotomy, ACL reconstruction).

The direct measurement of stresses in the knee joint is not possible in vivo. However, finite element (FE) modeling enables the estimation of stresses and strains in a human knee joint during e.g. walking or standing, which are the two most frequent daily activities for the joint. In FE modeling the geometry is discretized into small elements and the loads and moments acting on the knee joint are implemented through boundary conditions. With the use of motion analysis the subject-specific gait pattern can be recorded and implemented into the model. A validated, patient-specific FE model would enable the evaluation of OA risk in the knee joint before and after surgical operations.

In the present study, the knee joint was first imaged with a magnetic resonance (MR) scanner. Different tissues such as articular cartilage, menisci, patellar cartilage, ligaments and muscles were segmented from the MR images. The tissues were then transformed into solid geometry, meshed (i.e. divided into finite elements) and
given their material properties. In the first methodological study, the gait was implemented as rotations and translations obtained from literature. Five different material properties for the articular cartilage were compared during dynamic and static loading. In the second study, the strains in the articular cartilage were experimentally determined during static loading (standing) and compared to the model. In the third study, the gait of the subject was determined using skin markers and a camera system in a motion laboratory. The gait was implemented into the model as moments and translational forces and the femoral rotations of the model were compared to the measured rotations. Also the stresses, strains and pore pressures were evaluated in the patellar cartilage. In the fourth study, the effect of ACL rupture, single bundle and double bundle ACL reconstruction on knee joint motion was evaluated.

The results of the first study emphasized the importance of arcade-like fibril network structure on dynamic tissue response and the effect of proteoglycans on tissue response during static loading. While fibril volume density was shown to have an effect on stresses and strains in extreme scenarios, the depth-wise variation in real cartilage is too small to have an effect on the simulations. In the second study the cartilage was observed to deform most right after the introduction of load (half of body weight), but continued to deform up to the 30 minute mark. The simulated strains matched the observed strains surprisingly well considering the material parameters were not subject-specific. The third study highlighted the importance of including the patella in moment and force driven FE models. As expected, arcade-like collagen fibril network reduced fibril strains in superficial and deep zones compared to homogeneous model while the compressive strains were highest at all depths in the model with the very early OA. In the fourth study, the model with anterior cruciate ligament (ACL) deficiency showed similar increased laxity to clinical findings. The results emphasized that rather than the choice of technique, the stiffness and pre-strain of the graft determine the success of the reconstruction.

In conclusion, the present study takes a step to create a new di-
agnostic tool for the pre- and post-operational assessment of stresses and strains in a human knee joint. This study is a part of the progress in diagnostic imaging where the focus is shifting from structural imaging of the knee joint to functional imaging and consequently, prevention of diseases. With over 100 million patients in Europe alone, OA a substantial burden to economy in terms of treatment costs and losses to productivity. With the public aging the need for prevention is even more urgent. A validated, patient-specific FE model of the knee joint would help doctors assess the risk sites for OA.

Medical Subject Headings: Biomechanical modeling; Finite element method; Articular cartilage; Meniscus; Knee; Ligament, Collagen fiber; Proteoglycan; Anterior cruciate ligament; Reconstruction; Graft; Stress; Strain; Pore pressure;

Yleinen suomalainen asiasanasto: Biomekaaninen mallintaminen; pienelementtimenetelmä; nivelrusto; nivelkierukka; polvi; nivekside; kollageenisäie; proteoglykaani; eturistiside; korjaus; siirre; jännitys; venymä; nestepaine;
Preface

This study was carried out during the years 2011-2015 in the Department of Applied Physics at the University of Eastern Finland. First, I would like to thank my supervisors: Associate professor Rami Korhonen, my main supervisor, has been the main driving force behind my research, giving invaluable insight into the process of scientific thinking while making sure the research is always grounded in reality. Rami has always represented the modeling aspect of my research support. Dean Jukka Jurvelin, for encouraging and representing the empirical aspect of my research along with Juha. Professor Juha Töyräs for guidance in the experimental parts of my study, connections to the hospital and general encouragement. I thank all three supervisors for their contributions to this thesis. Also for hiring me.

Special thanks go to my colleague, Dr. Mika Mononen, for extensive help in technical difficulties with Abaqus. Your magical touch caused the ‘reverse demo effect’, i.e. the problem ceased to exist when you came to look at it. I doubt this thesis would have been possible without your help.

I wish to also thank the referees who reviewed my thesis: Dr. Guoan Li and Dr. Jeffrey Weiss.

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I wish to thank my parents Jorma and Pirjo Halonen, and my little brother Tommi for your support during my studies.

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Kimmo Halonen
Kuopio, 03.10.2015
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>2D</td>
<td>Two-dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>A</td>
<td>Anterior bundle of PCL</td>
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<tr>
<td>AM</td>
<td>Antero-medial bundle of ACL</td>
</tr>
<tr>
<td>ACL</td>
<td>Anterior cruciate ligament</td>
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<tr>
<td>BW</td>
<td>Body weight</td>
</tr>
<tr>
<td>C</td>
<td>Central bundle of PCL</td>
</tr>
<tr>
<td>C3D8</td>
<td>Continuum element type with 8 nodes</td>
</tr>
<tr>
<td>C3D8P</td>
<td>Continuum element type with 8 nodes and porosity</td>
</tr>
<tr>
<td>C3D20R</td>
<td>Continuum element type with 20 nodes and 8 integration points</td>
</tr>
<tr>
<td>C3D20RP</td>
<td>Continuum element type with 20 nodes, 8 integration points and porosity</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTa</td>
<td>Computed tomography arthrography</td>
</tr>
<tr>
<td>FE</td>
<td>Finite element</td>
</tr>
<tr>
<td>FEM</td>
<td>Finite element modeling</td>
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<tr>
<td>FRPE</td>
<td>Fibril-reinforced poroelastic</td>
</tr>
<tr>
<td>FRPVE</td>
<td>Fibril-reinforced poroviscoelastic</td>
</tr>
<tr>
<td>GRF</td>
<td>Ground reaction force</td>
</tr>
<tr>
<td>LCL</td>
<td>Lateral collateral ligament</td>
</tr>
<tr>
<td>MCL</td>
<td>Medial collateral ligament</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>PCL</td>
<td>Posterior cruciate ligament</td>
</tr>
<tr>
<td>PL</td>
<td>Postero-lateral bundle (in ACL), Posterior-longitudinal bundle (in PCL)</td>
</tr>
<tr>
<td>PML</td>
<td>Posterior meniscofemoral ligament (in PCL)</td>
</tr>
<tr>
<td>PO</td>
<td>Posterior-oblique bundle of PCL</td>
</tr>
<tr>
<td>POR</td>
<td>Pore pressure</td>
</tr>
<tr>
<td>TE</td>
<td>Time of echo</td>
</tr>
<tr>
<td>TR</td>
<td>Time of repetition</td>
</tr>
<tr>
<td>T</td>
<td>Tesla (unit of magnetic flux density)</td>
</tr>
</tbody>
</table>
SYMBOLS

\( B_0 \) External magnetic field in MRI
\( \eta \) Viscous damping coefficient
\( C \) Ratio of primary collagen fibrils to secondary fibrils
\( \varepsilon \) Strain
\( \dot{\varepsilon} \) Time derivative of strain
\( \varepsilon \) Void ratio
\( E_0 \) Dynamic elastic modulus
\( E_m \) Non-fibrillar matrix modulus
\( E_\varepsilon \) Fibril network modulus
\( F \) Deformation tensor
\( G \) Shear modulus
\( I \) Unit tensor
\( J \) Jacobian determinant
\( K \) Bulk modulus
\( k_0 \) Initial permeability
\( k \) Permeability
\( k_s \) Spring constant
\( M \) Material constant
\( n^f \) Fluid fraction
\( p \) Fluid pressure
\( S \) Von Mises stress
\( \sigma_e \) Effective solid stress
\( \sigma^f \) Stress of fibrillar part
\( \sigma^{nf} \) Stress of non-fibrillar part
\( \sigma^s \) Solid matrix stress
\( \nu_m \) Poisson’s ratio
\( z \) Normalized tissue depth
LIST OF PUBLICATIONS

This thesis consists of a review of the author’s work in the field of biomechanical modeling of the human knee joint and the following selection of the author’s publications:


Throughout the thesis, these papers will be referred to by Roman numerals.
AUTHOR’S CONTRIBUTION

The publications in this dissertation are original research papers on simulation and experimental studies of tissues in the human knee joint. The author has been the main contributor to each method presented in the publications and carried out all of the data analyses and simulations. The author conducted all the simulations and experimental measurements and imaging measurements, apart from the motion analysis and related inverse and forward dynamics analyses, which were carried out in University of Jyväskylä, Jyväskylä, Finland and University of Technology, Lappeenranta, Finland. The author has been the main writer of each paper.
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Articular cartilage is a lubricating, load bearing tissue found in diarthrodial joints. The structure of articular cartilage is complex, consisting of chondrocytes and an extracellular matrix (ECM) [1–3]. Depending on the depth, approximately 60-80% of the wet weight of articular cartilage consists of interstitial water [2]. The second largest constituents of cartilage are type II collagen fibers (70% of dry weight) and proteoglycans (20-30%) [2]. Chondrocytes occupy 1-5% of the volume of articular cartilage [4]. The collagen fibers form an organized network that resists dynamic deformation as well as swelling [5, 6]. In early osteoarthritis (OA), the collagen fibril network starts to disorganize and the proteoglycan content decreases. The cartilage surface starts to fibrillate, after which cracks start to form. Eventually the cartilage wears away, causing pain and hindering joint movement [3]. OA, especially in the knee, causes a major strain on health care, with approximately 34% of people over the age of 60 suffering from the disease in the United States [7].

As the cartilage lacks blood vessels, its self-healing capabilities are very limited. Currently OA can be treated to limited degree, ranging from opioid pain treatment and glucosaminoglycan/chondroitin sulfate injections in the early stages of OA [8] to total knee replacement in late stages [9]. In addition to the high cost of surgical operation, the knee prosthesis has an expected lifespan of 10-20 years [10, 11]. Because of these reasons the most cost-efficient treatment would be prevention of the disease.

The exact mechanisms of OA onset and development are unknown. However, abnormal stresses and strains in articular cartilage have been shown to greatly increase the risk of OA [3,12,13]. These stresses can be a result from the patient’s abnormal walking pattern especially when paired with obesity [14] or a consequence of an injury [15,16]. Specifically a rupture in the anterior cruciate ligament (ACL) has been shown to greatly increase the risk of
Kimmo Halonen: Validation and application of computational knee joint models

OA [15–17]. While the patients with reconstructed ACL showed nearly restored knee function [15], the outcome is dependent on the success of the surgery.

In cadavers, the contact stresses can be measured [18–20]. Due to ethical reasons, the direct assessment of stresses in the knee articular cartilage of a living human is not possible. Thus, an indirect method is needed. Finite element (FE) method allows the simulation of stresses and strains in the knee joint during daily activities, such as walking [21–23]. In this method, the knee joint geometry is first obtained from magnetic resonance (MR) images, from which the different tissues are segmented. The tissues are divided into small (finite) elements and the solution is approximated iteratively. Before the application of any computational model, validation is needed. Examples of the types of knee joint model validation include material validation and motion validation. Material validation in the knee consists of the development of a theoretical material model and comparing it to actual response of the knee cartilage. Motion validation requires determining the patient’s knee motion in a motion laboratory and comparing it to simulated rotations and translations. A validated model can then be used for applications, such as simulating the effects of joint disorders on the knee cartilage or the outcomes of surgical operations.

This study aims to develop a realistic model of a knee joint for the simulation of stresses and possible failure sites in cartilage. In study I, the effects of different types of theoretical cartilage tissue models on the simulated depth-dependent stresses and strains during gait (walking) and at equilibrium (standing) were investigated. In study II, the test subject’s knee was imaged during static loading and the deformation of tibial cartilage was compared with the predictions based on the FE model. In study III, the subject’s gait was analyzed in a motion laboratory. The gait was simulated using moments and forces in the FE model and the resulting rotations and translations were compared with those measured in the motion analysis. Subject-specific quadriceps forces and a patellar cartilage with depth-dependent characteristics were implemented.
Introduction

for the first time. Finally, in study IV, the effect of ACL rupture as well as several ACL reconstruction techniques on the stresses and strains in tibial cartilage surface were investigated.

This study contributes to the shift in diagnostic imaging, from conventional structural imaging to imaging of the function of the joints, evaluation of the effects of surgical operations and assessment of possible failure sites. This could provide medical doctors with a novel diagnostic tool to assess, e.g., the outcome of surgical knee operations pre- and post-operatively. If successful, the prevention of OA would greatly benefit the patients as well as reduce the burden the disease causes to healthcare.
Kimmo Halonen: Validation and application of computational knee joint models
2 Anatomy and function of the knee joint

Human knee joint (Figure 2.1) is a complex structure consisting of soft tissues and three bones: femur, tibia and patella. The soft tissues include ligaments, tendons, menisci, muscles and articular cartilages.

2.1 BONES

2.1.1 Anatomy

Femur is an asymmetrically shaped bone that attaches to the hip at its proximal end [24]. There are two condyles in the distal end of femur: lateral and medial, with medial being more prominent than the lateral. Tibia has lateral and medial plateaus with which the femur articulates. The medial tibial plateau is almost flat, while the lateral has a convex shape. These two plateaus are covered with articular cartilage and are in contact with the femoral condyles. The plateaus are separated by a spine, which the anterior horn of lateral and medial menisci as well as the anterior cruciate ligament are attached to [24]. In the anterior side of the tibia, there is a tubercle for the insertion of patellar tendon. Patella is a sesamoid bone that articulates with the trochlea of the distal femur. Like femur and tibia, the contacting surface of patella is covered with articular cartilage. The articulating surface is divided into a medial and a lateral facet, with the lateral side being wider in the lateral-medial direction but smaller in the anterior-posterior direction. [24].

2.1.2 Biomechanics

The bones consist of two distinctive phases: cortical bone and trabecular bone. Cortical bone forms the outer layer of bones and is
highly organized and very stiff. Trabecular bone forms the inside of the bones and is porous in structure. Trabecular bone is also softer than the cortical bone. The primary function of bones is to provide a rigid base structure of the body, one the muscles attach to through tendons. Bones also absorb some of the loads due to their elastic nature [25]. The elastic modulus (representing bone stiffness) and ultimate stress vary depending on the subject’s age. For example, in human femur the elastic modulus varies between 17 GPa (ages 20-29) and 15.6 GPa (ages 80-89), and ultimate stress between 140 MPa and 120 MPa. The bone can withstand high loads, especially in axial direction, but very low strains: the ultimate strain is only a few percents, 3.4% in femur [26].

Figure 2.1: Anatomy of the human right knee joint, coronal view. Ligaments and muscles have been omitted for clarity.

2.2 LIGAMENTS

2.2.1 Anatomy

The knee has four primary ligaments; anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), lateral collateral ligament (LCL) and medial collateral ligament (MCL) (Figure 2.2), and one secondary ligament, the anterolateral ligament (ALL) [24, 27]. The
Anatomy and function of the knee joint

Origin of ACL is in the medial femoral condyle at the posterior aspect of the intercondylar notch. The direction of the ACL is in the anterior, distal and medial direction toward the tibia, where it is attached. The ACL is both vasculated and innervated. Upon close inspection, the ACL consists of two bundles, the antero-medial (AM) and posterior-lateral (PL) bundles [24,28].

Out of all the ligaments, PCL has the largest cross-section and provides approximately 95% of the total restraint to posterior tibial translation. The origin of PCL is in the medial femoral condyle at the posterior aspect of the intercondylar notch. Its insertion site is in the posterior intercondylar fossa of the tibia, just posterior to the lateral meniscus [24]. Although the PCL is characterized as a continuum of fibers [29,30], its structure can be divided into five bundles: anterior (A), central (C), posterior-longitudinal (PL), posterior-oblique (PO) and posterior meniscofemoral ligament (PML), which attaches to the lateral meniscus [31].

LCL has its origin in the posterior part of lateral femoral epicondyle, just above the popliteus and insertion site in the proximal tibia, on the lateral fibular head. The LCL is a strong, round, fibrous cord that functions as a major static support against varus moments [24].

The origin of MCL is in the medial side of the knee, on the medial femoral epicondyle, near the instant center of rotation of the knee. The surface of the MCL consists of parallel and oblique components [24,32]. The parallel, thick fibers extend from the medial femoral epicondyle to the medial surface of tibia. The oblique fibers are more posterior and have their origin in the medial epicondyle but blend with the posteromedial joint capsule. The MCL acts as a primary support against valgus moments in the knee. It also resists the external rotation of the tibia [24].

The existence of ALL was first reported in 1879, but mostly ignored until Claes et al. (2013) showed that the ligament is present in approximately 97% of people [27]. The ALL has its origin in the lateral femoral condyle just anterior of the origin of LCL. Its insertion site is in the proximal tibia, just posterior to Gerdy’s tubercle. Not
much is known about ALL, but some preliminary results suggest the ligament has only a minor role in resisting forces in a healthy knee and ACL reconstructed knee, but the contribution is elevated in an ACL deficient knee [33].

In addition to the primary ligaments, the knee also contains smaller ligaments. Out of these the lateral and medial patellofemoral ligaments (LPFL and MPFL, respectively) have been included in the FE model used in studies I-IV (See Materials and methods, page 43). As the names imply, the LPFL and MPFL are located in their respective sides in the lateral and medial sides of the knee. The LPFL originates in the lateral side of the femur and attaches to the lateral side of the patellofemoral ligament [34]. The MPFL has its origin in the soft tissues of adductor magnus tendon and superficial MCL, and attaches to the medial side of the patellofemoral ligament [32]. The patellofemoral ligaments contribute to the stabilization of the patella [35].

2.2.2 Biomechanics

The function of ligaments is to stabilize the knee by resisting forces and moments. The ligaments are very stiff in tension compared with cartilage or meniscus (and soft in compression). This is due to the fact that 90% of the ACL is composed of collagen fibers, and 10% consisting of elastic fibers entangled in a mucopolysaccharide ground substance [36]. Ligaments are viscoelastic material. However, their material properties in knee joint models are usually described with linear stiffness and ultimate load of a ligament (approximately 242 N/mm and 2160 N for ACL, respectively) [37, 38] due to the dynamic nature of knee loading. The cruciate ligaments are the most important static stabilizer of the knee against anteroposterior translation of the femur with respect to tibia [24, 28]. The ACL and PCL account for more than 80% of the resistance at flexion angles from 30° to 90° [39]. In ACL, the PL bundle experiences highest loads at full extension, under an anterior tibial load. The forces the AM bundle experiences increase as a function of flexion angle up to 60° and decrease after that, but remain lower compared
Anatomy and function of the knee joint

with the PL bundle forces [40]. Under rotatory loads, the PL loads are higher at 15° and lower at 30° than the AM bundle [40]. The PCL provides approximately 95% of the total restraint to posterior tibial translation. The main function of LCL and MCL is to resist varus and valgus moments, respectively [24].

Figure 2.2: Primary ligaments in the human knee joint. Left: coronal view. Dashed line indicates the position of the sagittal plane. Right: sagittal view.

2.3 MENISCI

2.3.1 Anatomy

The lateral and medial menisci are crescent-shaped tissues situated in their corresponding sides between the femoral condyle and tibial plateau [41]. The meniscus is a structurally complex tissue comprised of cells, specialized ECM constituents and region-specific innervation and vascularization. The primary constituent of meniscus is water (72% of wet weight), while the rest consists mostly of the ECM and cells. Collagen fibers (mainly type I) take majority of the dry weight (70-80% depending on the region), followed by proteoglycans (17%), and other glycoproteins (1%) [42]. The me-
dial meniscus is noticeably larger than the lateral one. Though they both are semi-lunar shaped with a wedge-like crosssection, the lateral meniscus varies in size, shape, thickness and mobility compared with the medial meniscus [41]. The lateral meniscus also covers a larger portion of the tibial plateau (75-93% of the lateral plateau) compared with the medial meniscus (51-74% of the medial plateau) [43].

The main stabilizing ligaments of the menisci are the medial collateral ligament, transverse ligament, meniscofemoral ligaments and the attachments to tibia at the anterior and posterior horns [41]. The meniscofemoral ligaments, also known as Humphrey and Wrisberg ligaments, connect the posterior horn of the lateral meniscus to the location near the insertion site of the PCL. Only 46% of people have both of these ligaments, but 91-100% of people have at least one of them [31, 44].

At birth, the meniscus is fully vascularized. However, as the tissue ages the vascularization begins to subside. At 10 years of age, only 10-30% of vessels are present in the meniscus, and in adults only the peripheral 10-20% of menisci have blood vessels and nerves [43]. It is critical to note that only this vascularized, innervated area at the outer edges of the meniscus has the capability of healing [42].

The shape of the menisci are congruent with the femoral condyles, helping to distribute the loads exerted on the knee by increasing the size of the contact area. In the case of total meniscectomy, the contact pressure in the tibial articular cartilage is increased by 100-235% [19, 45]. Due to this, in the case of meniscus injuries, the prevalent trend in meniscus repair is to preserve as much of the tissue as possible [46, 47].

### 2.3.2 Biomechanics

The main role of the menisci is load bearing and distribution in the knee joint [48]. Furthermore, it has been demonstrated that the menisci provide shock-absorbing capability to the knee, as meniscectomized knees show a reduction of 20% in shock-absorption [49].
Anatomy and function of the knee joint

The uppermost layer of the menisci has been shown to behave isotropically, with radially and circumferentially oriented samples having tensile moduli of 48 and 71 MPa, respectively [50]. This direction-dependency in modulus is primarily due to collagen fiber orientation. The middle meniscal portion, which covers the vast majority of the axial thickness of the meniscus, has a tensile modulus of over two magnitudes greater (198 MPa) than the radially oriented samples (2.8 MPa) [48]. The tensile stiffness of meniscus also varies spatially: the tensile modulus in posterior two-thirds of the medial meniscus is significantly smaller than in the anterior one-third of the medial meniscus or the whole lateral meniscus [51]. Compared to i.e. articular cartilage, the stress-strain curve of the meniscus is more linear, with small toe and yield regions [52]. The human meniscus is much less stiff in compression than tension, with aggregate modulus and permeability in the range of 0.11 – 0.41 MPa and 1.8 – 2.0 × 10⁻¹⁵ m⁴N⁻¹s⁻¹, respectively [48].

2.4 MUSCLES

2.4.1 Anatomy

In the anterior side of the knee, the quadriceps muscle group controls the extension of the knee [24]. The four constituents of the quadriceps are as follows: rectus femoris, vastus lateralis, vastus intermedius and vastus medialis. The origin of rectus femoris is in the anterior inferior iliac spine. It narrows down to a tendon 5-8 cm above the patella [24]. The true insertion site of the rectus femoris is into the tibial tubercle, but conventionally its insertion site is considered to be in the patella [53]. Being the largest muscle in the quadriceps muscle, the vastus lateralis has its origin at the proximal part of the intertrochanteric line and extends to halfway down the linea aspera on the femur. The vastus medialis can be divided into two parts: the vastus medialis obliquus and the vastus medialis longus. Its origin is in the medial side of the femur and insertion in the quadriceps tendon. Vastus intermedius has its origin in the anterior and lateral shaft of the femur. The insertion site of the vas-
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tus intermedius forms the deepest layer of the trilaminar superior border of the patella. Vastus medialis and lateralis contribute to the middle layer, and the rectus femoris contributes to the superficial layer of the trilaminar patellar border [24].

The flexion and internal rotations of the knee are strongly controlled by the pes anserinus muscles, which are the sartorius, gracilis and semimembranosus muscles. These muscles are located in the medial side of the knee. Also in the medial side is the medial head of the gastrocnemius. The lateral side contains the biceps femoris, iliotibial band and lateral gastrocnemius muscles [24, 54].

2.4.2 Biomechanics

The primary function of muscles is to move the body by contracting. They also provide stability and shield vital organs from damage. Muscles attach to bones via tendons. Muscle functions can be tested by measuring the force they can produce by using resistance-based measurements. The electrical activity of muscles can be examined using electromyography (EMG) [55, 56], although the relationship between EMG activity and muscle output is not clear due to redundancy in muscle recruitment [56]. In EMG the electric potential in muscles is measured using electrodes attached to the skin. Muscle coordination during activities such as walking is captured using motion analysis [56].

2.5 ARTICULAR CARTILAGE

Human articular cartilage (Figure 2.3) is an avascular [57] tissue that behaves like a sponge; exuding water when compressed and draining water in after the pressures is released. Articular cartilage consists of chondroctes and the extracellular matrix (ECM) [2, 6]. The ECM can be further divided into tissue fluid, fibrillar and non-fibrillar parts [6].
2.5.1 Tissue fluid

The fluid phase consists of interstitial water and mobile ions. The water is distributed unevenly throughout the depth of the cartilage, with 80% of the cartilage wet weight in the superficial zone and 65% in the cartilage-bone interface [2, 58]. This fluid contains small proteins, metabolites, gases and a high concentration of cations to balance the negatively charged proteoglycans [58]. The large concentration of negative charges causes an electrical imbalance, which in turn causes osmotic pressure in the tissue (the Donnan effect [6]). The collagen network acts as a counterbalancer to the influx of tissue fluid, resisting the Donnan osmotic pressure associated with the proteoglycans [59]. The incompressible fluid helps the cartilage absorb impact loads.

2.5.2 Fibrillar part

Collagen fiber network

In healthy articular cartilage, the fibrillar part consists of an organized, mainly type II collagen (90-95%) fiber network, with each
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fiber consisting of primary and secondary fibrils [6]. Other collagen types in articular cartilage include type VI, IX, X and XI [6, 58]. Collagen fibers take approximately 60% of the dry weight of articular cartilage [6]. Collagen fibers are long, rope-like structures that have a high tensile strength but almost no compressive stiffness [6]. They also behave in a viscoelastic manner. The main function of the collagen network is to resist tensile forces [6] and instantaneous deformation [5]. The collagen network also contributes to the cohesiveness of the articular cartilage by trapping the large proteoglycan molecules in its meshwork [6].

Near the cartilage surface (superficial zone), the collagen fibers are oriented parallel to the surface. In humans, collagen concentration is lowest close to the surface, which itself has a higher density of collagen [60]. This dense and organized layer of collagen fibrils gives the superficial zone a greater tensile stiffness and strength than the deeper zones [6]. It also affects the movement of molecules through the surface of cartilage [6]. In vitro studies have shown this zone to also have an important contribution to the compressive behavior of articular cartilage [61].

Below the surface, in the middle zone, the fibers start to arc towards the bone and are larger in diameter than in the superficial zone. This zone can be 2-3 times thicker than the superficial zone [6, 62]. Recent evidence suggests that the middle zone has a major contribution to resisting shear forces caused by joint movement [63].

In the deep zone, the fibers are perpendicular to the cartilage-bone interface [1] and are largest in diameter [6]. Their concentration is also highest in the deep zone in humans [60]. The collagen fibers pass into the tidemark, which is a thin basophilic line that can be seen on light microscopic sections of decalcified articular cartilage [6].

Split-line patterns are another characteristic of the collagen fiber network. If pierced with an ink stained needle, the cartilage stretches the resulting hole in a certain direction, shaping a line. In macroscopic scale, these lines show a pattern resembling the directions in
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which the collagen fibers are aligned along the surface [64].

2.5.3 Non-fibrillar part

Proteoglycans

The proteoglycans can be divided into two major classes: large aggregating molecules \(\text{aggrecans}\) and smaller proteoglycans including \(d\text{EcoRIn},\) biglycan and fibromodulin [6]. Cartilage also contains large non-aggregating proteoglycans. They may represent degraded aggrecans as they resemble aggrecans in structure and composition [6]. Aggrecan molecules take up most of the interfibrillar space in the cartilage matrix [6]. Large aggregating proteoglycans take approximately 90% of the proteoglycan mass, with large non-aggregating proteoglycans taking 10% and small nonaggregating proteoglycans approximately 3%. In articular cartilage, majority of the aggrecans associate noncovalently with hyaluronic acid and link proteins to form proteoglycan aggregates [6, 58].

Proteoglycans are large macromolecules with a protein core and one or more glycosaminoglycan chains. These chains are long, unbranched polysaccharide chains consisting of repeating disaccharides that contain an amino sugar [6, 58]. Each disaccharide unit has at least one negatively charged carboxylate or sulfate group so the glycosaminoglycans form long strings of negative charges. Proteoglycans and noncollagenous proteins are either bound or mechanically entrapped within the collagen network [6]. Proteoglycan content is lowest in the superficial zone and increases as a function of cartilage depth, the highest concentration being in the deep zone near the calcified cartilage [6]. The concentration of proteoglycans varies also with patient’s age and health [6].

The negative charges attract cations in the tissue fluid while repelling other negative charges and negatively charged molecules [6]. The ionic imbalance in the tissue fluid causes swelling in cartilage, counterbalanced by the tensile resistance of the collagen network. Proteoglycans mainly contribute to fluid flow in cartilage [5] (although the collagen network also contributes [65–67]) and stiff-
ness in mechanical equilibrium [68].

**Chondrocytes**

Chondrocytes are the only cell type that exists in articular cartilage [6]. Occupying only approximately 1% of the volume of adult human articular cartilage, chondrocytes are highly specialized cells that regulate the macromolecular content of articular cartilage [6]. Having all the organelles necessary for matrix synthesis, chondrocytes synthesize various macromolecules, including proteoglycans. Chondrocytes organize the collagens, proteoglycans and noncollagenous proteins and glycoproteins into a complex, organized cartilage structure [6]. The cells respond to changes in the matrix composition [6] as well as external stresses. Chondrocytes are surrounded by a *pericellular matrix* and do not form direct cell-to-cell contact with other chondrocytes [6]. The pericellular matrix has a high concentration of proteoglycans and also contains noncollagenous matrix proteins and collagens (mainly type VI collagen [69]).

The uppermost layer of superficial zone is void of chondrocytes. Just below the uppermost layer, chondrocytes have a flattened ellipsoid shape and orient themselves parallel to the surface just like collagen fibers. In this layer, the chondrocytes synthesize matrix that has a high concentration of collagen and a low concentration of proteoglycans relative to the other cartilage zones [6,58]. In the middle zone, the chondrocytes take a spheroidal shape and synthesize a matrix that has larger diameter collagen fibrils and higher concentration of proteoglycans. However, the water and collagen concentrations are lower than in the superficial zone [6]. In the deep zone, the chondrocytes are aligned in columns that run perpendicular to the surface [58]. The rate at which chondrocytes synthesize appears to be in response to the structural needs of the cartilage matrix, possibly including the loading of the cartilage detected by the cells [6,58]. In adults, the repairing capability of chondrocytes is very limited. Therefore they are unable to repair damage induced to the cartilage due to overweight or abnormal loading. Therefore it would be crucial to prevent any damage to the cartilage.
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2.5.4 Biomechanics

An essential part of the mechanical response of the articular cartilage is the dynamic between swelling of proteoglycans and the constraints the collagen fiber network exerts on the swelling [70]. The response to long-term loading is also tied to the fluid flow through cartilage. Under impact loading, cartilage is very stiff (but softer than meniscus) and behaves as an incompressible, elastic material because the fluid has no time to flow and collagen fibers are stretched [70]. At equilibrium, the aggregate modulus of articular cartilage is typically in the range of 0.5 – 0.9 MPa and Young's modulus in the range of 0.45 – 1 MPa [6, 71]. These equilibrium properties are primarily controlled by proteoglycans. Permeability ranges between $10^{-15}$ and $10^{-16}$ m$^4$/Ns [70].

Cartilage can withstand mechanical contact stresses of 15 to 20 MPa during daily activities such as walking or climbing stairs. These stresses, experienced over short time periods of less than a second, can lead to small cartilage compressive strains of about 1 – 3%. During long term loading, the stresses can be as high as 3.5 MPa and strains as high as 35 – 45% [6]. Cartilage loading is necessary: immobilization or reduced loading can cause substantial decreases in matrix synthesis and content, and result in softening of the tissue. On the other hand, high impact loads or strenuous exercise loading can cause cartilage degeneration [6,72].
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3 Knee joint disorders and their evaluation

3.1 JOINT DISORDERS AND OSTEOARTHRITIS

Knee joint disorders are a collection of trauma-induced disabilities, defects acquired at birth as well as diseases. Common trauma-induced disorders include ACL rupture and meniscus damage, both of which are often present in the damaged knee [73,74]. Meniscal lesions are very common, with annual incidence of 66 reported per 100,000 inhabitants in the United States [75] and 9 or 4 (male, female respectively) per 10,000 in Denmark [76]. Sports are involved in more than a third of all cases. These injuries usually involve cutting or twisting movements, hyperextension or actions of large forces [41]. Meniscal tears are accompanied by ACL tearing in over 80% of cases [73,74]. Natural defects include knee malalignment, a condition where a substantial portion of body weight is loaded on either lateral or medial side of the knee. Malalignment is associated with osteoarthritis (OA), both with the development and progression [77]. The most common knee joint disease is osteoarthritis, which can either develop in its own or post-traumatically, e.g. as a result of the aforementioned disorders. Out of these knee joint disorders, the focus of this thesis is on ACL rupture and osteoarthritis.

3.1.1 ACL rupture and reconstruction

With over 250,000 incidents in the US every year, the ACL rupture is one of the most common injury types [78]. The vast majority of these injuries are sports related and concern active 15 to 44 year-old people [79]. A knee with ACL rupture becomes less stable with increased tibial translation in the anterior direction and increased tibial rotation in the interior direction [80,81]. Furthermore, this instability may cause clinical symptoms such as meniscal tears [82] and...
damage to articular cartilage [83]. In fact, ACL deficiency greatly increases the risk of OA in the knee [15–17, 84–86], especially if meniscal injury is also present [16, 82, 85].

ACL reconstruction is a surgical technique in which a graft tissue is harvested either from the patient (autograft) or a donor (allograft) and used to replace the severed ligament [87]. The graft is harvested either from central patellar tendon or from gracilis and semitendinosus tendons [86–89]. A meta-analysis showed that the choice of graft has no significant effect on the outcome [89]. Two common techniques are used: the single bundle and double bundle reconstruction method. In single bundle reconstruction a tunnel is drilled through both femur and tibia. The graft is inserted through the tunnel, tightened and fixed with special screws. Double bundle reconstruction mimics the AM and PL bundles of a healthy ACL by using two bundles made from the harvested graft [87]. It has been hypothesized that the anatomical resemblance would result in reduction of graft failures [90]. Single bundle reconstruction is still the default technique [91], but the double bundle technique is becoming more common. Despite its increasing popularity, in a meta-analysis double bundle was shown to yield no clinically significant differences in joint laxity compared with single bundle technique [87]. Unfortunately, the risk of OA is still increased in the ACL reconstructed knees compared with healthy knees [86, 92–95].

3.1.2 Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease in which articular cartilage starts to degenerate and eventually wears away, causing pain and limiting joint mobility [6]. Although the exact cause of OA is not known, overloading of the cartilage has been shown to substantially increase the risk of OA [96, 97]. The disease progresses in three overlapping stages: cartilage matrix damage or alteration, chondrocyte response to tissue damage, and the decline of the chondrocyte synthetic response and progressive loss of tissue [98–100].

In the first stage, the collagen architecture starts to disorganize, along which the macromolecular framework of the cartilage matrix
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is disturbed or altered at the molecular level, and the water content rises. Usually the proteoglycan concentration decreases in the superficial layer [98–101]. These factors increase the permeability of cartilage and decrease its stiffness [3,6].

In the second stage, the chondrocytes detect the tissue damage and react to it by changing their anabolic and catabolic activity. The repair response, or increased synthesis of matrix macromolecules, may last for several years and in a very few instances, restore the tissue. Although rare, some studies have reported that altering the joint’s mechanical environment, e.g., by osteotomy can stimulate the restoration of an articular surface [102–104]. However, a failure to do so results in the third stage, in which the loss of articular cartilage progresses and a decline in chondrocytic activity is observed [6]. The cartilage starts to crack and eventually wears away. As the cracks grow deeper, the superficial tips of the fibrillated cartilage tear and fragments of the cartilage are released into the joint space [6]. Simultaneously, enzymatic degradation of the cartilage matrix further reduces the cartilage volume further [105,106]. Also, extensive bone remodeling and sclerosis takes place in the subchondral bone [3], as well as the formation of fibrous, cartilaginous and bony prominences called osteophytes [6].

Symptoms of OA include joint pain, restriction of joint motion, crepitus with motion, joint effusions and deformity [6]. Most common occurrences of OA are in the foot, knee, hip, spine and hand joints [107]. Even though OA concerns all tissues of the synovial joint, including articular cartilage, synovium, subchondral and metaphyseal bone, joint capsules, ligaments and muscles, the primary changes occur in articular cartilage [101,108].

3.2 IMAGING OF JOINT DISORDERS AND OSTEOARTHRITIS

The knee joint condition and health of cartilage and other tissues can be determined invasively or non-invasively. Arthroscopy is an invasive method in which the joint is examined from the inside.
The health of the cartilage can be assessed by palpation, indentation or by inserting a probe with a catheter inside into the knee cavity of the patient. The probe can be a camera to image the surface of cartilage or, possibly in the future, an ultrasonic transducer, allowing the surgeon to image the inner structure of the cartilage. However, arthroscopy carries the usual downsides of invasive techniques, such as a high cost and risk of infections. Therefore, non-invasive techniques such as radiography (X-rays) and MRI are preferred. It should also be noted that due to the invasive nature of arthroscopy, it is never conducted as the first means to assess the state of cartilage. On the other hand, the knee is thoroughly inspected arthroscopically before an ACL reconstruction [88, 109, 110] or in case of chondral or meniscal injury [109].

3.2.1 Radiography

Radiography is still the predominant imaging technique for the structural assessment of OA [111–113]. Traditional x-rays are unable to image the cartilage due to its similar attenuation coefficient with the synovial fluid (Figure 3.1). However, OA can be detected indirectly by the assessment of osteophytes, subchondral sclerosis, subchondral cysts, and joint space narrowing [112]. In the standard procedure, the patient stands on both feet in front of a vertically tilted x-ray tube and the knee is imaged in coronal plane [114]. The image is scored based on predetermined criteria such as joint space narrowing, osteophyte size, and level of bone attrition [115]. Different features need to be studied with equal importance, which is best done by directly measuring the distribution and size of each feature [116]. The advantages of radiography include low cost and availability [112, 115, 117, 118].

3.2.2 Magnetic resonance imaging

In evaluation of articular cartilage defects, magnetic resonance imaging (Figure 3.1) is superior to radiography as it is able to assess the health and thickness of the cartilage directly [119–121]. In addition
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Figure 3.1: Imaging of the knee joint using X-ray or fluoroscopy, contrast enhanced CT, and MRI.

to cartilage lesions, MRI is also used for the assessment of meniscal tears [122] and ACL ruptures [123, 124]. Generally, the MR signal can be weighted by proton density (which relates to water in the tissue), $T_1$ or $T_2$ by choosing TR and TE conveniently [125]. While there are dozens of pulse sequences, the most commonly used for clinical cartilage imaging are based on T2-weighed fast spin-echo (FSE) [126] and gradient-recalled echo (GRE) sequences [127] or proton density weighting [128], with or without fat suppression. Fast-spin echo sequences use refocusing $90^\circ$ pulses that allow high-resolution images to be acquired in a very short time period. The multiple refocusing pulses produce a magnetization transfer effect in the articular cartilage, which decreases its signal intensity. This phenomenon does not occur in the synovial fluid, which enables a sharp contrast between cartilage and synovial fluid as well as improves the conspicuity of chondral effects [129]. However, the refocusing pulse cancels the effect of field inhomogeneities, which are desired in $T_2'$ images.

In GRE sequence the signal is refocused without cancelling the $T_2'$ effects by applying two gradient pulses: first dephases the magnetization proportionally to its time integral, and the second rephases it [130]. In proton density weighting, the signal is proportional to the water content, which decreases from surface to the deeper layer [131]. Fat suppression is a method that allows the cartilage to show up bright against dark bone. Fat suppression is based on
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the inherently different resonance frequencies of protons in water and fat [131, 132]. When a presaturation pulse is applied to this frequency, protons are saturated, which results in a lower signal compared with the other tissues [133]. While the images without fat suppression are accurate, the fat suppression allows the detection of changes in the subchondral bone marrow signal [129]. Novel MRI methods allow the structural assessment of articular cartilage, e.g. collagen architecture with $T_2$ weighted MR imaging [134, 135] or fixed charge density distribution with $^{23}$Na MR imaging [136].

3.3 MOTION ANALYSIS

Although a myriad of activities involving the knee joint are performed daily, the two most common ones are standing and walking (gait). Simulation of standing is fairly straightforward as only the patient-specific stance has to be accounted for. Gait is far more complex to simulate. Walking pattern varies from patient to patient [137] and is affected by knee joint disorders such as ACL rupture [138, 139] and OA [137, 140].

There are two approaches to motion analysis in terms of finding individual muscle forces: forward and inverse dynamics. Forward dynamics calculates the motion based on a predicted muscular activation. While being attractive in terms of modeling a myriad of activities, the forward dynamics approach is a very computationally costly optimal control problem that requires a demanding optimization to make the model work [55, 141]. Inverse dynamics, on the other hand, computes muscle activation based on known motion. This causes restrictions on the model, but makes it computationally more efficient. The computation is done by minimizing an objective function, which is effectively the assumed criterion of the recruitment strategy of the central nervous system, and is a function of muscle forces. The minimization is done with respect to all unknown forces, i.e. muscle forces and joint reaction forces [141]. The inverse dynamics method has some limitations, as it is sensitive to inaccuracies in the various input parameters. The errors arise from
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estimating body segment parameters, joint parameters, skin movement artifacts, noise on skin-mounted marker data or force plate calibration [142].

The most common method to capture the gait motion is by using multiple cameras to capture the movement of retroreflective markers placed on anatomic landmarks. The markers are assigned an arbitrary mass and the center of mass and the inertia tensor of this cluster of points are calculated [143]. Using the inverse dynamics method, the joint forces and moments are then calculated [144,145].

By using dozens of markers, the effect of skin movement under one marker on the center of mass of the whole system is minimized. The marker-based system allows a substantial reduction to the error caused by the non-rigid body movement [143].

An alternative to the marker-based method is the dual fluoroscopy method, where two X-ray fluoroscopes are positioned nearly perpendicularly to each other, so that the beams intersect at the location of the knee. The subject walks on a treadmill at a constant pace while the knee is imaged. The projected images are matched with a 3D geometry of the bones and the rotations and translations are determined from a set point, usually the rotation center of the femur, i.e. midpoint between the epicondyles [146,147]. The method eliminates the error caused by skin movement, which makes it superior to the marker-based method.

3.4 LIMITATIONS IN CURRENT EVALUATION OF JOINT DISORDERS

Despite the advances in the diagnostics of joint disorders, some limitations exist. Radiography has good specificity [112] and reproducibility [118] but low sensitivity for cartilage loss [112], especially in the early stages of OA [117]. In order to acquire reproducible results, the positioning of the leg needs to be highly standardized and ideally fluoroscopically verified [148,149]. In addition, it has been shown that radiography is only able to produce relatively accurate results in the medial compartment of the knee in the detection of
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OA [150], and it cannot differentiate between femoral and tibial cartilage loss. Although traditional radiography is unable to directly detect changes in cartilage, contrast-enhanced computed tomography (CECT) and its clinical application, delayed CT arthrography, have been shown to be able to diagnose cartilage injuries and degeneration [151, 152]. In addition, novel cone beam CT (CBCT) scanners (Figure 3.1), dedicated to musculoskeletal imaging, are able to image joints during weight-bearing and non-weight-bearing modes [153,154].

Even though MRI has exceptional specificity and sensitivity in cartilage imaging when compared with radiography, the method is not without several downsides. The biggest downside is its high cost: novel MR scanners run at prices of 1-2 M€. Due to the relatively long TR times of some tissues, the image acquisition times are long compared with radiography [120].

In motion analysis, the skin marker based method is prone to errors in the measurement of very small motions, such as the internal-external rotation, abduction-adduction or mediolateral translation. Even though the center-of-mass method reduces the error caused by the movement of skin and soft tissues, it affects the measurement of the small movements [143, 155, 156]. Dual fluoroscopy, on the other hand, is a very expensive method as it requires two fluoroscopes as well as proper facilities that meet the requirements for the use of radiation. Due to the limited space, the activities the system is able to measure are limited to treadmill gait, stair ascent/descent and lunge. In addition, as the walking speed increases the error of the measured motions also increases [146]. Dual fluoroscopy also causes a high radiation dose on the subject.

These methods enable the assessments of OA symptoms and in some cases, possible risks of OA, but are unable to estimate the stresses the cartilage goes through during various types of loading. For that purpose, simulation is needed.
4 Computational modeling of the human knee joint

4.1 KNEE JOINT MODELS

Computational modeling of the knee is a new branch of diagnostics that aims to assess the knee’s possible failure sites that could be susceptible to damage, and consequently, OA. Musculoskeletal modeling considers the human body as a framework of rigid bodies controlled by muscle activation. Using either forward dynamics (muscle forces causing knee motion) or inverse dynamics (observed knee motion is caused by muscle forces) the dynamics of a joint can be determined [145]. These models, however, do not investigate the stresses and strains in the tissue level. Finite element models (FE or FEM for FE method) are used for that purpose. Knee joint models, specifically those utilizing the FE method, have been shown to be able to simulate stresses in the human knee [157–159]. Earliest FEM studies date back to 1970s, when the method was used to estimate stresses and strains in the femur [160, 161]. Bendjaballah et al. (1995) [157] published one of the earliest articles featuring a fully three-dimensional FE model of the knee joint, that featured cartilages modeled as linearly elastic solids as well as menisci with circumferential fibers. Guoan Li et al. (1999) [162] introduced their model, that had a substantially more refined mesh and non-linear springs representing ligaments. Articular cartilage was modeled as linear elastic solid. Donahue et al. (2002) [158] developed a knee joint model to assess the effect of bony deformations and constrained rotations on the contact behavior of articulating surfaces. Again, the cartilage was modeled as linearly elastic. However, the menisci were defined as transversely isotropic elastic to simulate the anisotropy in menisci caused by the circumferential collagen fibers.
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Peña et al. (2006) [163] included hyperelastic and transversely isotropic ligaments with prestrain in their model. The model also included patellar cartilage and patellar tendon. Cartilages were once again modeled as homogeneous, linearly elastic and isotropic. In addition to hyperelastic material, the ligaments are commonly modeled as linear or non-linear springs [157, 164–166]. The first model to use fibril-reinforced material for cartilage in a knee joint geometry was Shirazi et al. (2008) [164], which was followed by studies like Gu et al. (2011) [167]. Mononen et al. (2012) [168] even included split-line patterns in their 3D knee joint model.

4.2 MATERIAL MODELS OF ARTICULAR CARTILAGE AND MENISCUS

For articular cartilage and meniscus, multiple different material models have been designed in the past, including linear elastic, biphasic, transversely isotropic (poro)elastic to fibril-reinforced biphasic models. The linear elastic model can simulate contact pressures fairly well, but not much else. Linear elastic material is usually implemented into the knee model when the main focus is not on cartilage or the main parameters being investigated are contact pressures and small deformations. Considering those parameters, the linear elastic model behaves similarly to the biphasic model [169], which consists of a solid phase and a fluid phase [170]. The biphasic linear elastic models of cartilage are able to simulate experimentally measured data from confined compression [170, 171]. However, in unconfined compression, the model cannot account for the time-dependent stress-relaxation response of cartilage [172] and has difficulty explaining creep indentation results for short time periods [173]. Cohen et al. (1998) [174] presented a transversely isotropic model that could fit the data from creep indentation and unconfined compression experiments.

Two poroviscoelastic models have been introduced in literature: first of which defines the solid matrix as viscoelastic in shear deformation [175], and the second both in shear and bulk deforma-
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The material was able to model lateral displacements and reaction forces simultaneously. Also the modeling unconfined compression and *either* indentation or confined compression was possible at the same time. However, the model lacks the anisotropy and compression-tension non-linearity of the cartilage, which likely explains why the experiments could not be conducted simultaneously.

Transversely isotropic poroelastic model is able to simulate lateral displacements and realistic reaction forces, but not both at the same time. The model is also not ideal for confined compression [177]. Conewise elastic model [178] has the same properties in in-plane compression and tension, but takes into account the compression-tension non-linearity of the tissue into account, while still being linear. However, like the transversely isotropic poroelastic model, the conewise linear elastic model cannot account for the lateral displacements and reaction forces at the same time [177]. These models do not account for the non-linear compression-tension behavior of collagen fibers, which was later taken into account in fibril-reinforced models.

Fibril-reinforced biphasic models, namely Le Ping Li et al. in 1999 [179], Korhonen et al. in 2003 [68] (fibri-reinforced poroelastic, FRPE), and Wilson et al. in 2004 [180, 181] (fibril-reinforced poro-viscoelastic, FRPVE) and Li et al. (2004) again [182] (FRPVE), consider a fluid phase and a solid phase, which consists of a fibrillar and non-fibrillar part. The fibril-reinforced biphasic model allows the simulation of cartilage deformation simultaneously in multiple loading conditions. Many researchers have started to incorporate the material in their 3D knee models [154, 164–168, 183–185].

### 4.2.1 Poroelastic biphasic theory

The poroelastic biphasic theory for porous materials was first published by Biot in 1941 [186] and later introduced for cartilage by Mow et al. in 1980 [170]. It assumes an intrinsically incompressible, linearly elastic solid matrix and a separate, also incompressible fluid phase. The only time-dependent feature in the theory is the

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fluid flow. The total stress $\sigma^{\text{tot}}$ is given by the sum of solid matrix stress $\sigma^s$ and fluid stress $\sigma^f$ [170,187,188]:

$$\sigma^{\text{tot}} = \sigma^s + \sigma^f,$$  \hspace{1cm} (4.1)

where $\sigma^s$ and $\sigma^f$ are defined as

$$\sigma^s = -\varphi^s p I + \sigma^e,$$  \hspace{1cm} (4.2)

$$\sigma^f = -\varphi^f p I,$$  \hspace{1cm} (4.3)

and therefore

$$\sigma^{\text{tot}} = \sigma^e - p I,$$  \hspace{1cm} (4.4)

where $\varphi^s$ is solid volume fraction, $\varphi^f$ fluid volume fraction, $p$ fluid pressure, $I$ identity tensor and $\sigma^e$ effective elastic stress. The fluid flow through a surface $J$ is considered to follow Darcy’s law [187]:

$$J = A k \frac{\Delta p}{h},$$  \hspace{1cm} (4.5)

where $A$ is the surface area through which the fluid flows, $k$ permeability of the solid, $\Delta p$ the hydrostatic pressure difference between the sides and $h$ the thickness of the perfused tissue. As the tissue deforms, the fluid flows out, which changes the porosity of the solid phase. The permeability $k$ is therefore considered to be porosity-dependent [189]:

$$k = k_0 \left( \frac{1 + e}{1 + e_0} \right)^M,$$  \hspace{1cm} (4.6)

where $k_0$ is the initial permeability, $e$ void ratio, $e_0$ initial void ratio and $M$ material constant. Void ratio is the ratio of fluid to solid material:

$$e = \frac{n^f}{n^s},$$  \hspace{1cm} (4.7)

where $n^f$ is the fluid fraction and $n^s$ the solid fraction.
4.2.2 Transversely isotropic material

Given the highly anisotropic structure of articular cartilage and meniscus, simple isotropic elastic or poroelastic material is unable to capture most of the characteristics of the tissue. Transversely isotropic model mimics the compression-tension nonlinearity by assigning direction-dependent elastic moduli. In a transversely isotropic material, the effective stress in the solid is given by [190,191]:

\[
\sigma^e = \begin{bmatrix}
\sigma_{11} \\
\sigma_{22} \\
\sigma_{33} \\
\sigma_{12} \\
\sigma_{13} \\
\sigma_{23}
\end{bmatrix} = \begin{bmatrix}
\frac{1}{E_L} & \frac{-v_{LT}}{E_T} & \frac{-v_{TT}}{E_T} & 0 & 0 & 0 \\
\frac{-v_{LT}}{E_T} & \frac{1}{E_T} & \frac{-v_{LT}}{E_L} & 0 & 0 & 0 \\
\frac{-v_{TT}}{E_T} & \frac{-v_{LT}}{E_L} & \frac{1}{E_T} & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{1}{G_L} & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{1}{G_L} & 0 \\
0 & 0 & 0 & 0 & 0 & \frac{1}{G_T}
\end{bmatrix} \begin{bmatrix}
\varepsilon_{11} \\
\varepsilon_{22} \\
\varepsilon_{33} \\
\varepsilon_{12} \\
\varepsilon_{13} \\
\varepsilon_{23}
\end{bmatrix}, \quad (4.8)
\]

where \( E_L \) and \( E_T \) are the longitudinal and transverse Young’s moduli, respectively, \( G_L \) the longitudinal shear modulus, and \( v_{LT}, v_{TT} \) and \( v_{TL} \) are the Poisson’s ratios that give the strain in the longitudinal direction for a transverse stretch and transverse direction for a longitudinal stretch, respectively. The transverse shear modulus \( G_T \) is defined as

\[
G_T = \frac{E_T}{2(1 + v_{TT})}. \quad (4.9)
\]

Due to symmetry the following holds true:

\[
\frac{v_{LT}}{E_L} = \frac{v_{TL}}{E_T}. \quad (4.10)
\]

Therefore in a transversely isotropic material, only five parameters are independent: \( E_L, E_T, v_{LT}, v_{TT} \) and \( G_L \). If the material is biphasic, permeability \( k \) (equation 4.6) is also independent from other parameters [191].
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4.2.3 Fibril-reinforced poroviscoelastic material

In fibril-reinforced poroelastic (FRPE) and poroviscoelastic (FRPVE) materials, in addition to the fluid phase and solid phase, the solid phase consists of a fibrillar part and a non-fibrillar part [191]. The stress of the tissue ($\sigma_{\text{tot}}$) is therefore a sum of the fibrillar stress ($\sigma_f$), non-fibrillar stress ($\sigma_{nf}$) and fluid pressure ($p$) [180,181,192]:

$$\sigma_{\text{tot}} = \sigma_{nf} + \sigma_f - p I$$ \hfill (4.11)

$$\sigma_{\text{tot}} = \sigma_{nf} + \sum_{i}^{N} \sigma_i^f - p I , \hfill (4.12)$$

where ($\sigma_i^f$) is the stress of a single fibril ($\sigma_f$ in the derivation below).

Fibrillar matrix

In the FRPE material, the stress of the fibrillar network ($\sigma_f$) is usually defined as [179]

$$\sigma_f = \frac{1}{2} E_f \varepsilon_f^2 + E_0^f \varepsilon_f , \hfill (4.13)$$

where $\varepsilon_f$ is the tensile strain of the fibrils, and $E_f$ and $E_0^f$ are constants. Collagen fibrils are considered to have no resistance to compression, i.e. for $\varepsilon < 0, E_f = 0$.

In the FRPVE material, the viscoelastic fibrils are modeled as a system consisting of an elastic spring (with spring constant $E_0$) parallel with a series of a non-linear spring (with constant $E_0^f$) and a dashpot (damping coefficient $\eta$) (Figure 4.1) [180,181,192].

The stress of one fibril is derived as follows:

$$\sigma_f = E_0 \varepsilon_f + \eta \dot{\varepsilon}_f , \hfill (4.14)$$

$$\sigma_f = E_0 \varepsilon_f + \eta (\dot{\varepsilon}_f - \dot{\varepsilon}_e) , \hfill (4.15)$$

where $\dot{\varepsilon}$ denotes the time derivative of strain. In addition,
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Figure 4.1: Schematic depiction of the linear spring (with spring constant $E_0$) parallel to a series consisting of a non-linear spring (with constant $E_\varepsilon$) and a dashpot (damping coefficient $\eta$). $\varepsilon_f$ denotes fibril strain, $\varepsilon_e$ and $\varepsilon_\nu$ denote the strain experienced by the non-linear spring and the dashpot, respectively.

\[
\varepsilon_e = \frac{\sigma_e}{E_\varepsilon}, \quad \text{and} \quad \varepsilon_\nu = \frac{1}{2\varepsilon_e} \sigma_e.
\]

\[
\varepsilon_f = \sigma_f - E_0 \varepsilon_f. \tag{4.18}
\]

Inserting equations 4.16, 4.17 and 4.18 into equation 4.15 yields the final form for the fibril stress:

\[
\sigma_f = -\frac{\eta}{2\sqrt{(\sigma_f - E_0 \varepsilon_f)E_\varepsilon}} \sigma_f + E_0 \varepsilon_f + \left( \frac{\eta E_0}{2\sqrt{(\sigma_f - E_0 \varepsilon_f)E_\varepsilon}} \right) \dot{\varepsilon}_f. \tag{4.19}
\]

Similarly as for the elastic fibrils, equation 4.19 is only true for $\varepsilon_f > 0$ (and $\sigma_f = 0$ if $\varepsilon_f \leq 0$). The model used in this thesis takes into account the primary (organized, arcade-like) and secondary (randomly organized) collagen fibrils [193,194] by defining
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\[ \sigma_{f,p} \text{ (stress of primary fibrils) and } \sigma_{f,s} \text{ (stress of secondary fibrils) as well as the depth-dependent fibril volume fraction } \rho_z: \]

\[ \sigma_{f,p} = \rho_z C \sigma_f \tag{4.20} \]
\[ \sigma_{f,s} = \rho_z \sigma_f, \tag{4.21} \]
\[ \rho_z = \frac{C}{\rho_z C} \sigma_{f,p} \tag{4.22} \]

where C denotes the relative density of primary fibrils with respect to the secondary fibrils.

**Non-fibrillar matrix**

The non-fibrillar matrix is considered as either elastic according to Hooke’s law or Neo-Hookean hyperelastic material [192]. For an elastic material, the stress is given by Hooke’s law:

\[ \sigma^{nf} = K \epsilon^{nf}, \tag{4.23} \]

where \( K \) is the stiffness matrix. For the Neo-hookean non-fibrillar matrix, the stress of the nonfibrillar part \( \sigma^{nf} \) is given as:

\[ \sigma^{nf} = K \ln \left( \frac{J}{J_0} \right) I + \frac{G}{J} (F \cdot F^T - J^2 I), \tag{4.24} \]

where \( J \) is the determinant of the deformation tensor \( F \), \( K \) the bulk modulus and \( G \) the shear modulus. \( K \) and \( G \) are defined as

\[ K = \frac{E_m}{3(1 - 2\nu_m)}, \tag{4.25} \]
\[ G = \frac{E_m}{2(1 + \nu_m)}, \tag{4.26} \]

where \( E_m \) is the Young’s modulus and \( \nu_m \) the Poisson’s ratio. Permeability \( k \) of the non-fibrillar matrix can be considered to be either constant or porosity-dependent similarly as in equation 4.6.
Finite Element Method

Complex behavior of soft and hard tissues in the joint cannot be solved analytically. Finite element method offers an iterative way to approximate how a material behaves. In FEM, the object geometry is divided into small (finite) elements, which are given material properties (see Materials and methods, page 43). The corners of these elements are called nodes, which are typically given displacements or forces (either fixed or several degrees of freedom). The solution is then interpolated between the nodes using polynomial base functions, which may be linear, quadratic or higher order [195]. The investigated material (see above) dictates the differential equations needed to be solved.

Consider a simple, second order differential equation [196, 197]:

\[-u''(x) + q(x)u(x) = f(x), \quad 0 < x < 0\]  
\[u(0) = 0\]  
\[u(1) = 0\]

The aim is to find an approximate solution in the form of

\[u(x) \approx u_h(x) = \sum_{i=1}^{N} \alpha_i \phi_i(x),\]  

where \(\alpha_i\) are unknown constants and \(\phi_i\) are known base functions. In the FEM, this is done by considering a residual function in the form of

\[r = -u'' + qu - f,\]  

and requiring that \(r = 0\) in a weak sense [196–198], e.g. we get

\[\int_{0}^{1} r(x)v(x)dx = 0,\]  

where \(v\) is a test function. Equation 4.32 can be written in the form
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\[ \int_0^1 (-u'' + qu - f)v(x)dx = 0, \quad (4.33) \]

and by using partial integration [196, 197]

\[ \int_0^1 (u'v' + quv)dx - \int_0^1 u'v = \int_0^1 f v dx. \quad (4.34) \]

Because \( v(0) = v(1) = 0 \), the middle term vanishes and we are left with a variational problem (i.e. Galerkin method [196, 197, 199, 200]): how to find \( u \) so that

\[ a(u, v) = F(v) \quad (4.35) \]

and

\[ a(u, v) = \int_0^1 (u'v' + quv)dx, \quad (4.36) \]

\[ F(v) = \int_0^1 f v dx. \quad (4.37) \]

This variational problem is equivalent with equation 4.27, which means that function \( u \) is the solution to the equation 4.27 only if \( u \) is the solution to the variational equation (equation 4.35) and vice versa. The solution to the variational equation is approximated by inserting the approximation \( u_h = \sum_{l=1}^N \alpha_l \phi_l \) (equation 4.30) and choosing the test functions \( \phi_j \) so that

\[ a(u_h, v_j) = F(\phi_j) \quad \text{for all} \quad j = 1, 2, \ldots, N \quad (4.38) \]

\[ \Leftrightarrow \int_0^1 \left( \sum_{l=1}^1 \alpha_l \phi_l^j \phi_j + q \sum_{l=1}^1 \alpha_l \phi_l \phi_j \right) dx = \int_0^1 f \phi_j dx. \quad (4.39) \]

Equation 4.39 can be rearranged as

\[ \Leftrightarrow \sum_{l=1}^1 \int_0^1 \left( \phi_l^j \phi_j^l + q \phi_l \phi_j \right) dx \alpha_l = \int_0^1 f \phi_j dx \quad (4.40) \]
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Figure 4.2: One-dimensional example of the finite element method. The analytical solution \( y = -3x^2 + 3x \), blue, of a differential equation and FEM approximation (green). Elements (black, red) consist of linear base functions.

and written as

\[
\sum_l k_{jl} \alpha_l = b_j \quad \text{for all } J = 1, 2, \ldots, N \tag{4.41}
\]

or

\[
K \alpha = b, \tag{4.42}
\]

where

\[
K = k_{jl} = \int_0^1 (\phi'_l \phi'_j + q \phi_l \phi_j) \, dx, \tag{4.43}
\]

\[
b = b_j = \int_0^1 f \phi_j \, dx, \tag{4.44}
\]

\[
\alpha = (\alpha_1, \alpha_2, \ldots, \alpha_N)^T. \tag{4.45}
\]

By solving \( \alpha = K^{-1}b \), the final solution for the initial equation 4.27 in the investigated is the element approximation.
The matrix $K$ is called stiffness matrix and $b$ the load vector [196, 199]. The equation 4.42 is solved numerically. The investigated area is divided into small elements, defined by nodes. Each node has a base function $\phi_l$ that is chosen so that it has the value 1 at the node and 0 in other nodes. Because the base function has the value 1 at the nodes, equation 4.46 is reduced to just $u_h = \sum_{l=1}^{N} \alpha_l \phi_l$ at the nodes. Base functions $\phi_l$ are usually chosen to be linear functions (Figure 4.2) in order to make the matrix $K$ sparse and therefore minimize the number of integrals needed to be solved. In higher dimensions, the investigated area is divided into triangles or quadrangles (in two dimensions) and tetrahedrons or hexahedrons (in three dimensions) [196, 198].

A base element is transformed into the investigated element by making a variable substitution. During this substitution, the base function of the investigated element is transformed into the base function of the base element, e.g. $[0, 1]$. Using a numerical integration method, e.g. Gauss quadrature, the solutions can be calculated for the base element, to which the arbitrary element was transformed into [196]. The precision of the solution is controlled using convergence criteria for different parameters [200].

### 4.4 MODEL VALIDATION AND APPLICABILITY

Before application of any biomechanical model, there has to be model validation or verification [201]. The biomechanical behavior of tissue level model is typically validated using in vitro or in situ tests. Generally, the model is first applied to cartilage plugs harvested from human cadavers or animals (such as bovine, porcine, rabbit) [202]. Typical in vitro experimental protocols include unconfined compression [172, 175, 203–205] and confined compression [175, 188, 202, 204, 206, 207]. In unconfined compression, the surface and bottom of the plug is fixed and the plug is compressed,
allowing the cartilage to expand at the sides [172, 203–205]. In confined compression, the cartilage is not allowed to expand but has to deform in a confined space [202, 206]. Typical test protocols include creep and relaxation tests [188, 202–207]. Other *in vitro* tests include optical measurement of deformation either by observing fluoroscopically stained chondrocytes [207] or the expansion of the cartilage plug [208].

*In situ* tests are conducted without disturbing the cartilage structure and without removing cartilage from bone. Indentation is an example of an *in situ* test [175, 204, 209–211]. In indentation testing the tip of a probe is pressed against the cartilage, while the probe measures the force at which the cartilage resists compression. The FRPVE material used in this study has been validated in several studies using unconfined and confined compression data as well as indentation testing [175, 180, 181, 192].

Relevant to this thesis, *in vivo* tests can be conducted with a patient or a healthy test subject. Non-invasive *in vivo* tests include MRI, CT, motion analysis and fluoroscopy. Tissues and bones in the subject’s can be segmented from MR and CT images and the simulated deformation of articular cartilage can be compared with those observed in CT/MR images. The gait motion of the test subject as well as forces and moments can determined in a motion laboratory. The subject’s gait can then be simulated using the forces and moments as input, and compare the resulting rotations and translations to those observed during the motion analysis. A validated, patient-specific model could help assess the possible risk sites in cartilage associated with alterations to the knee by surgical operations such as ACL reconstruction. This new diagnostic tool could provide surgeons with a means to assess the outcome of surgical operations before and after the procedure.
5 Aims

In this thesis, the FRPVE material is implemented into 3D models of knee joints. Depth-dependent characteristics of articular cartilage, including PG and collagen distribution along with collagen fiber architecture, are incorporated into the model. The process towards a realistic model starts from a methodological study with motion data obtained from literature, and evolves into a more patient-specific model with complex knee joint geometry and force and moment driven input data. The model is validated against experimental imaging and motion analysis data, and applied to assess the outcomes of various ACL reconstruction techniques.

The specific aims of this thesis are:

1. To investigate depth-dependent stresses and strains in articular cartilage during simulated gait and under static loading of the knee joint. Five models, ranging from homogeneous to highly depth-dependent characteristics are compared.

2. To measure in vivo deformation of articular cartilage using cone beam CT and compare them to the simulated strains in the model.

3. To implement the patient-specific forces and moments acting on the knee and patella. The depth-dependent stresses and strains in the patellar articular cartilage during gait are studied.

4. To study the effect of ACL rupture and various ACL reconstruction techniques on the stresses and strains in the tibial articular cartilage during patient-specific gait.

This study will take a step towards a new diagnostic tool for the assessment of possible risks sites in the knee cartilage as well as to assess the outcomes of surgical operations.
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6 Materials and methods

6.1 MODEL GEOMETRY AND PARAMETERS

6.1.1 Segmentation from MR images

In study I the left knee of a healthy 61-year-old male (weight = 100 kg) was imaged with a MR scanner (GE Signa Twin-Speed 1.5 T clinical scanner, GE Healthcare, Milwaukee, WI, USA) using a fast spoiled gradient echo sequence (TR = 26.7 ms, TE = 6.7 ms, flip angle = 20°, slice thickness = 1.5 mm, matrix size = 512 × 512, in-plane resolution = 0.27 mm). In studies II-IV, the imaged subject was a healthy 28 year-old male (weight = 82 kg), whose left knee was imaged using a clinical 3.0 T MR scanner (Philips, Best, The Netherlands) (Figure 6.1). The pulse sequence was 3D fast spin-echo (VISTA) with in-plane resolution = 0.5 mm, slice thickness = 0.5 mm, TR = 1300 ms, TE = 32.3 ms. The workflow from MR images to the FE model is presented in Figure 6.1.

In all studies the femoral and tibial articular cartilages as well as menisci and the insertion points for ACL, PCL, LCL and MCL were segmented from the MR images using Mimics software (v.12.3 in study I, v. 15.01. in studies II-IV, Materialise, Leuven, Belgium). In studies III and IV, patellar cartilage and insertion points for quadriceps tendon and patellar tendon were also segmented. In study IV, the full insertion sites of ACL and PCL were segmented from the images with the help of two experienced orthopedists. In study I, the segmented tissues were first imported into SolidWorks v. 2008 SP2.1 (SolidWorks Corp., Concord, MA, USA) and transformed into a solid geometry before importing into Abaqus v.6.10-EF1 (Simulia, Providence, RI, USA). In studies II-IV the segmented sections were imported straight into Abaqus v.6.12-3 (Dassault Systèmes Simulia Corp., Providence, RI, USA).

In study I the femoral and tibial cartilages (Figure 6.2) were meshed with the element type C3D20RP for dynamic loading (i.e.
gait) and C3D8 for mechanical equilibrium analysis (i.e., standing). C3D20RP is a three-dimensional (3D) hexahedral continuum element with 20 nodes and reduced number of integration points (8 instead of the 20 in C3D20P) and porosity. C3D8 is a 3D hexahedral continuum element with 8 nodes and 8 integration points. The menisci were meshed with the element type C3D20R, a 3D hexahedral continuum element with 20 nodes and 8 integration points but no porosity. In study II C3D20RP was used for all tissues and in studies III and IV the element type C3D8P (like C3D8 but with porosity) was used for all tissues.

6.1.2 Material parameters

In all studies, femoral and tibial articular cartilages were defined as FRPVE (Tables 6.1 and 6.2). In addition, patellar cartilage was implemented into the model as FRPVE in studies III and IV. Arcade-like collagen fiber architecture with split-lines was implemented into the cartilages in all studies.

In study I, the depth-wise distribution of PGs was simulated with the non-fibrillar matrix modulus $E_m$, calculated from the data of Schinagl et al. [207]. The depth-wise fibril volume density $\rho_z$ was obtained from the data of Saarakkala et al. [60]. Fluid fraction was also considered depth-dependent [2]:

$$n^f = 0.8 - 0.15z,$$

where $z$ is the normalized depth of the articular cartilage (0 being the surface and 1 the cartilage-bone interface). The complete list of parameters used in study I is presented in Table 6.1.

In study I, the menisci were defined as transversely isotropic elastic during the gait: the Young’s modulus was set as 20 MPa in the axial and radial directions and as 140 MPa in the circumferential direction [158, 212]. The in-plane and out-of-plane Poisson’s ratios were set to 0.2 and 0.3, respectively, and in-plane shear modulus was 57.7 MPa.

In study II-IV, the menisci were defined as FRPE (Table 6.2).
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The direction of the collagen fibers were defined as circumferential at all depths of the menisci due to the number of depth-wise element layers: assigning radial or randomly oriented fibers would have exaggerated the thickness of the radial layer, which is only $150 - 200 \mu m$ thick [213]. The list of material parameters used in studies II-IV are listed in table 6.2.

No ligaments were included in the model of study I. Instead, the effect of muscles and ligaments was included in the gait input, which used rotation, translation and axial force data taken from...
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Figure 6.2: Development of finite element models and meshes from study I to study IV.

literature [147, 214], as well as during long term standing (mechanical equilibrium). In studies II and III the ligaments were modeled as linear springs with the following stiffness $k$: 201 Nmm$^{-1}$, 258 Nmm$^{-1}$, 114 Nmm$^{-1}$ and 134 Nmm$^{-1}$ for ACL, PCL, LCL and MCL, respectively [37]. In study IV, non-linear spring elements were used for the ligaments in order to cause a prestrain of 5% for ACL and PCL and 4% for LCL and PCL [215], respectively, at 0 mm displacement. In studies III and IV, the quadriceps tendon and patellar tendon were also defined as a set of linear springs with a combined stiffness of 545 Nmm$^{-1}$ and 475 Nmm$^{-1}$, respectively [216]. In those studies, the LPFL and MPFL were modeled using truss elements without compressive stiffness. The elastic mod-
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ulus was defined as 17 MPa for LPFL and 19 MPa for MPFL [217]. Poisson’s ratio was set as 0.499 for both.

The bones were considered rigid in all studies. Four anchor points (simulating the meniscal attachments) were defined, one for each meniscal horn, and a set of linear springs with a total stiffness of 2000 Nmm$^{-1}$ [158, 212]. In study II, because the lateral anterior horn was observed to nudge anteriorly when the load was applied, a non-linear spring in the lateral anterior horn was used to replicate this translation.

6.1.3 Boundary and loading conditions

All models consisted of three fundamental modeling phases or steps (not to be confused with the physical step of gait): in the first step (duration = 0.1 s), the articulating surfaces were brought into light contact. In Abaqus, in order to achieve convergence a direct contact between two surfaces has to be first introduced using displacement instead of forces. Then, in step two (duration = 0.1 s) the femur is rotated into the position the knee is at the beginning of gait (as opposed to the initial position the knee was during MR imaging). Simultaneously, the joint forces acting on the joint are implemented. Finally, in step 3 (duration varies depending on the type of simulation), the time-dependent forces, moments, rotations and/or translations are applied. Depending on the type of simulation, either ‘soils’ option or ‘static’ option was used for the step for time-dependent or equilibrium analysis, respectively.

The forces, moments, rotations and translations of the knee were applied through a reference point determined in the midpoint between the epicondyles of femur (also known as the rotation center, Figure 6.2) [219]. This was done by coupling the cartilage-bone interface to the reference point.
Table 6.1: Material parameters for the FRPVE material used in different models in study [2, 60, 67, 180, 181, 207, 218].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
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<td>0.11</td>
<td>-0.84</td>
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<td>0.46</td>
<td>0.46</td>
<td>0.46</td>
<td>0.46</td>
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<td>$E_\varepsilon$ (MPa)</td>
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<td>673</td>
<td>673</td>
<td>673</td>
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<td>$k_0$ ($\times 10^{-15}$ m/Ns)</td>
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<td>-0.15</td>
<td>0.8</td>
</tr>
<tr>
<td>Fibril orientation</td>
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<td>Parallel to surface</td>
<td>Parallel to surface</td>
<td>Parallel to surface</td>
<td>Parallel to surface</td>
</tr>
<tr>
<td></td>
<td>- middle zone Parallel to surface Arcing to surface</td>
<td>Arcing to surface Arcing to surface</td>
<td>Arcing to surface Arcing to surface</td>
<td>Arcing to surface Arcing to surface</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- deep zone Parallel to surface Perpendicular to surface</td>
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<td>Perpendicular to surface Perpendicular to surface</td>
<td>Perpendicular to surface Perpendicular to surface</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: Homogeneous, with collagen fibers parallel to surface at all depths
Model 2: Arcade-like collagen fibers
Model 3: Arcade-like collagen fibers, depth-dependent PG distribution
Model 4: Arcade-like collagen fibers, depth-dependent fibril volume density distribution
Model 5: Arcade-like collagen fibers, depth-dependent PG and fibril volume density distribution
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6.2 SIMULATIONS

6.2.1 Effect of depth-wise tissue characteristics

In study I, the effects of depth-wise characteristics of the FRPVE cartilage material were studied during dynamic loading (gait) and at mechanical equilibrium (long-term standing). Five models with different depth-wise properties were created:

1. Homogeneous model with collagen fibers parallel to surface at all depths
2. Inhomogeneous model with arcade-like collagen fiber architecture
3. Inhomogeneous model with arcade-like fibers and depth-wise PG distribution
4. Inhomogeneous model with arcade-like fibers and depth-wise fibril volume density distribution
5. Inhomogeneous model with arcade-like fibers and depth-wise PG and fibril volume density distributions

Femoral and tibial cartilages were meshed to have four element layers (layer 1 representing the superficial zone, layer 4 the deep zone near cartilage-bone interface), and the PG [207] and fibril volume density [60] distributions were averaged at their respective bulk depths and implemented into the corresponding element layer (see Table 6.1 for the exact values). The fibril volume density distribution was normalized so that the average of the values in all four element layers was 1 (same as the homogeneous fibril volume density in models 1-3). Maximum principal stresses, strains, pore pressures and contact pressures were evaluated during gait. Von Mises stresses, axial strains and pore pressures were determined in the contact area at different depths during the first peak force of gait, while Von Mises stresses and axial strains were determined at equilibrium.
Finally, a parametric study was done on the PG and fibril volume density distributions (Table 7.1) to emphasize the effect of these distributions in extreme cases. The gradient of fibril volume density distribution was allowed to vary from 0.89 in the surface all the way to 10 in the deep zone, while $E_m$ was allowed to vary from 0.11 MPa in the surface to 10 MPa in the deep zone. Again, the depth-wise Von Mises stresses, axial strains and pore pressures (only during gait) were determined at the contact area.

In study III, the effects of collagen fiber architecture was investigated by creating three models (Figure 6.3):

1. Homogeneous
2. Arcade-like
3. Early OA

The homogeneous and arcade-like models were similar to models 1 and 2 in study I: in the homogeneous model, the fibers were parallel to surface at all depths, while the arcade-like model had superficial fibers parallel to surface, arcing fibers in the middle and perpendicular fibers in the deep zone. The early OA model had randomly oriented fibers in the superficial zone to mimic the deterioration of the collagen architecture observed in the earliest stages of OA [6]. The split-line patterns were defined in the superior-anterior direction according to Bae et al. (2007) [220]. Fibril strains, compressive strains and maximum principal stresses in the patellar cartilage were determined during the stance phase of gait.

### 6.2.2 ACL rupture and the effects of reconstruction techniques

The objective of study IV was to assess the outcome of ACL reconstruction in terms of knee joint motion and deformation patterns of the tibial articular cartilage. The same mesh for femoral and tibial cartilages as well as menisci was used as in study III, but patellar cartilage was meshed more sparsely in order to improve convergence. For the healthy ACL, the AM and PL bundles were defined
Materials and methods

Figure 6.3: Finite element model used in study III. (a) Sagittal and coronal views of the model. In order to account for the quadriceps force acting on the knee joint, a force of equal magnitude was applied to a point coupled to the reference point (midpoint between the epicondyles of femur). (b) Left: Different depth-wise fibril architectures used in the model. Right: Split-line pattern in the patellar cartilage surface. Coronal view from the posterior direction.

separately using the non-linear spring element SPRINGA. For the PCL, five bundles were defined using the same spring elements: A, C, PL, PO and PML. Six models were created:

1. Healthy ACL
2. ACL rupture
3. Single bundle reconstruction
4. Double bundle reconstruction
5. Single bundle, weakened graft
6. Single bundle, less graft prestrain

The model with healthy ACL consisted of the normal knee joint geometry (Figure 6.4), including the normal AM and PL bundles of the ACL and their anatomical insertion sites. As the name implies, the model with ACL rupture had ACL completely removed. Two ACL reconstruction techniques were simulated: single bundle and double bundle techniques. In both models insertion sites of the graft were positioned with the help of two orthopedists. The diameter of the graft (and in double bundle technique, diameter of a bundle) was approximately 6-8 mm. The grafts were modeled as gracilis/semitendinosus grafts with a stiffness of 715 Nmm\(^{-1}\) [221]. Several studies [89,222] have reported no significant differences between the outcomes of patellar tendon grafts and gracilis/semitendinosus grafts, therefore only gracilis/semitendinosus graft stiffness was used in the simulations. In order to study the effect of graft stiffness and pretension, in the model with weakened graft the graft stiffness was defined the same as the healthy ACL (201 Nmm\(^{-1}\) [37]). To study the effect of prestrain (and consequently, pretension), in the model with less graft prestrain the effect of post-operative graft loosening, as reported by [223], was simulated by reducing the prestrain of ACL graft from 5% [215] to 2%.

Reaction forces in the tibial cartilage-bone interface and maximum principal strains in the tibial surface were determined during gait. In order to highlight differences between models, subtraction images of maximum principal strains, fibril strains, pore pressures and maximum principal stresses were created by subtracting the values of the healthy joint model from those in other models. Finally, the mean values of these parameters in the contact area were plotted as a function of time during the gait.
Table 6.2: Material parameters for the FRPVE material used in different models in studies II-IV [2, 41, 67, 218, 224, 225]. The patellar fibril orientation presented here is the healthy patellar cartilage model in study III. $E_m =$ non-fibrillar matrix modulus, $E_0 =$ initial fibril network modulus, $E_\epsilon =$ strain-dependent fibril network modulus, $v_m =$ Poisson’s ratio of the non-fibrillar matrix, $\eta =$ damping coefficient, $k_0 =$ initial permeability, $M =$ material constant for void ratio dependent permeability, $n_f =$ fluid fraction, $z =$ normalized depth, $C =$ density ratio of primary fibrils to secondary fibrils.

<table>
<thead>
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<th>Studies II-IV</th>
<th>Studies III &amp; IV</th>
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</thead>
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<td>Tibial cartilage</td>
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<tr>
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<td>$\eta$ (MPas)</td>
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<td>1062</td>
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<td>1</td>
</tr>
<tr>
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<td>18</td>
</tr>
<tr>
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<td>15.64</td>
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<tr>
<td>$n_f$</td>
<td>$0.8 - 0.15z$</td>
<td>$0.8 - 0.15z$</td>
</tr>
<tr>
<td>$C$</td>
<td>12.16</td>
<td>12.16</td>
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</table>

Fibril orientation
- superficial zone       | Parallel to surface | Parallel to surface | Circumferential to surface | Parallel to surface |
- middle zone             | Arcing              | Arcing              | Circumferential to surface | Arcing              |
- deep zone               | Perpendicular to surface | Perpendicular to surface | Circumferential to surface | Perpendicular to surface |
Figure 6.4: (a) Finite element model used in study IV. As with previous studies, the bones are modeled as rigid. (b) Tibial insertion sites of healthy ACL (red) and healthy PCL (blue). The attachments of double bundle reconstruction bundles are circulated and labeled as AM (A) and PL (P). The attachment of single bundle reconstruction is in cyan. Axial view from the superior direction. (c) Femoral insertion site of healthy ACL (red) and attachments of double bundle reconstruction (A and P) as well as the single bundle (cyan). Sagittal view from the medial direction. (d) Femoral insertion site of healthy PCL (blue). Sagittal view from the lateral direction.

6.3 EXPERIMENTS - MODEL VALIDATION AND INPUT

6.3.1 Computed tomography arthrography

The aim of study II was to determine the in vivo deformation of articular cartilage in a knee joint using contrast enhanced CT arthrography (CTa) during long term loading and compare the strains to the simulated strains in the FE model. An isotonic contrast agent solution of ioxaglate-based Hexabrix® (53% of the total volume) and distilled water (47% of the total volume) was prepared to match the osmolarity of synovial fluid (300 mOsm/L) in the knee joint [226].
Materials and methods

A commercial cone-beam CT (Verity®, Planmed, Finland) with a voxel size of 0.2 × 0.2 × 0.2 mm was used to image the left knee of the subject. First, the knee was imaged with light contact (12.8 ± 2.8 of the body weight, BW) between the cartilages (referred to from now on as reference stack), then immediately after introducing a load of approximately half of body weight (47.1 ± 2.3% of BW). After that the weight was held constant and the knee was imaged at 1, 5 and 30 min after the initial contact. Preliminary tests showed 30 min was the last time point in which the surfaces of the articular cartilages were distinguishable. During the imaging, half of the subject’s BW was suspended by harnesses attached to the surface (Figure 6.5). The subject held a quick-release lever that allowed the instantaneous increase of load from light contact to half of BW. The force under volunteer’s foot was monitored in real time using a custom-made Python program and Nintendo Wii Balance Board®.

The femoral and tibial cartilages as well as menisci were segmented from the CTA images (Figure 6.5) in Mimics v.15.01. The cartilage-cartilage interface was determined to be in the halfway point of the contrast agent film between articulating surfaces in the tibio-femoral contact. The image stacks were manually co-registered in Analyze v.10.0 (Biomedical Imaging Sources, MN) by rotating the stacks so that the edges of the tibia bone in the reference stack matched in all of the stacks at other time points of creep. The local cartilage thicknesses were determined in Matlab v. R2012a by calculating the closest euclidian distance between nodes in the surface and cartilage-bone interface [119]. The mean strains were calculated at each time point and compared to the model. In addition, the displacement of the menisci during the creep was determined.

Similarly to study I, in study II the effect of material parameters on the creep response was investigated by varying the stiffness of the collagen fiber network, non-fibrillar matrix modulus, permeability and fluid flow boundary conditions (Table 7.1). In the case of fluid flow boundary conditions, the fluid was allowed to flow through non-contacting surfaces in the reference model by defining
pore pressure $P = 0$ at non-contacting nodes, and was inhibited in the parametric study.

### 6.3.2 Motion analysis

Study III focused on validating the joint movement as well as investigating the importance of patella and quadriceps forces in the simulation of knee joints. The aim was to first determine the subject’s gait pattern, then determine the forces and moments acting on the knee and use them as input for the model. Analysis of the subject’s gait was conducted in Department of Biology of Physical Activity, University of Jyväskylä, Jyväskylä, Finland, and the multibody analysis in Laboratory of Machine Design, Lappeenranta University of Technology, Lappeenranta, Finland. The subject’s height, weight, length of the leg and diameter of the knee and ankle were measured. 34 retro-reflective skin markers were placed anatomical landmarks according to the instruction of Plug-in Gait full body model (Vicon, Oxford, UK). Four additional markers were placed on the anterior side of the thigh, two markers on the anterior side of the tibia, one marker to the medial knee joint line and one marker to the patella. The subject walked along a 10 m track at self-selected speed (1.7 m/s). A ten-camera system (Vicon T40, Vicon) and a force platform (AMTI OR6-6, Advanced Mechanical Technology, Watertown, MA, USA) were used to record marker positions and ground force (GRF) data synchronously at 500 and 1500 Hz, respectively.

A multibody musculoskeletal modeling was conducted in Lappeenranta University of Technology using LifeMOD (LifeModeler, San Clemente CA, US) virtual human modeling plug-in and general purpose MD Adams simulation software (MSC Software, Newport Beach, CA, US) [227–229]. From this data and analysis, knee joint moments, translational forces, and corresponding rotations and translations were acquired (Figure 6.1). In addition, quadriceps forces during the stance phase of gait were determined using an inverse dynamics driven biomechanical modeling according to Brechter et al. (2002) [230]. For this analysis, the moment arms of
Table 6.3: Parametric investigations of studies I and II. $E_m = \text{non-fibrillar matrix modulus}$, $E_0 = \text{initial fibril network modulus}$, $E_\varepsilon = \text{strain-dependent fibril network modulus}$, $\nu_m = \text{Poisson's ratio of the non-fibrillar matrix}$, $\eta = \text{damping coefficient}$, $k_0 = \text{initial permeability}$, and $\rho_z = \text{fibril volume density}$.

<table>
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<tr>
<td>$k_0$ ($\times 10^{-15}$ m$^3$/Ns)</td>
<td>4</td>
<td>1.74</td>
</tr>
</tbody>
</table>

Fluid flow: No (non-contact surfaces)
the patella and femur were determined from the MR images around the epicondylar axis of femur, which is also the axis of knee rotation [231].

The final input for the FE analysis consisted of the extension-flexion rotation, varus-valgus and internal-external moments as well as translational forces in axial, anterior-posterior and lateral-medial directions. The rotations, moments and translational forces were implemented into the model as boundary conditions. The rotations resulting from the moment and force input were compared to the rotations measured in the motion analysis as well as the dual fluoroscopy data by Kozanek et al. (2009) [147]. In addition, the reaction forces in lateral and medial tibial cartilages as well as at the surface of the patellar cartilage were investigated.
Materials and methods

Figure 6.5: (a) Experiment setup in study II. The subject wore harnesses that suspended 50% of the body weight while standing on one leg. The force under the leg was monitored in real time using Nintendo Wii Balance Board® and displayed on the laptop screen using a custom made Python program. (b) Deformation in lateral tibial cartilage before the load (‘No contact’), immediately after application of the load (‘Contact 0 min’) and after 30 minutes (‘Contact 30 min’).
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7 Results

The most important results of studies I-IV are summarized in this chapter. For details and rest of the results, see 'Original publications'.

7.1 MODEL VALIDATION AND PARAMETRIC STUDIES

7.1.1 Cartilage deformation in vivo

In the CTA measurements of study II, the medial meniscus stayed nearly stationary during the experiment (Figure 7.1a). On the other hand, the anterior horn of the lateral meniscus shifted in the anterolateral direction when the load was introduced. 80% of the in vivo strains in the tibial cartilage were observed immediately after the introduction of the load. However, cartilage continued to deform up to the 30 minute time point (Figure 7.1b). Immediately after loading the peak strains were 24% and 29% in lateral and medial tibial compartments, respectively. At 30 minutes, the peak strains were 30% and 39% in the lateral and medial compartments, respectively.

The first minute of the creep was simulated and the measured mean strains in the contact area were compared with the simulated ones (Figure 7.1c). The reference model slightly underestimated the observed mean strains, while the other model with the reduced fibril stiffness gave the best match. The parametric study showed that the fibril stiffness shifted the creep curve the most (Figure 7.2), while change in the non-fibrillar matrix modulus changed the slope of the curve the most. In the 30 minute simulation with a load of 50 N, changes to fibril stiffness values still substantially affected the creep curve: high fibril network stiffness reduced mean strains by 27% while low fibril network stiffness increased them by 11% at 30 min of creep. At 30 minutes, the increase in non-fibrillar modulus caused a reduction of 31% in the mean strains. Change in the initial permeability and fluid flow boundary conditions (fluid ei-
ther allowed or prohibited to flow through cartilage surfaces) had minimal effect on the both short term and long-term strains.

Figure 7.1: (a) Position of the menisci during the experiment in study II. (b) Strains in the tibial cartilage immediately after the introduction of a load of 50% BW, then 1, 5 and 30 minutes after that. The position of the menisci are marked with the colored lines. (c) Average strains in the medial and lateral tibial cartilage surfaces.

7.1.2 Knee joint motion

In study III, the inclusion of patella and quadriceps forces caused a substantial decrease in the range of internal-external tibial rotation. The level of the internal-external rotation matched the measured rotation well, and the shape of the internal-external rotation was congruent with the literature data as well (Figure 7.3a-c). In the
Results

Figure 7.2: Parametric investigation in study II. Effect of collagen fiber network stiffness (a), non-fibrillar matrix modulus (b), permeability (c), and fluid flow boundary conditions (d) on the mean strains of tibial articular cartilage.

varus-valgus rotation, the patella and quadriceps forces showed a minimal effect.

Quadriceps forces caused an increase of up to 160% in the total tibial cartilage reaction forces during the first 20% of the stance phase of gait (Figure 7.3d-e). Peak reaction forces in the lateral and medial tibial plateaus were 860 N and 1700 N, respectively. Between 50% and 100% of the stance, differences in the reaction forces between the models were reduced. The combined peak tibial reaction force at medial and lateral compartments was 2560 N (3.2 × BW), while the peak patellar reaction force was 688 N (at 20% of the stance) (Figure 7.3f).

Figure 7.4 shows the tibial translations and rotations relative to femur compared with data obtained from literature [147, 232, 233]. The data has been shifted to start from 0 for easier comparison. The simulated translations are in accordance with the literature apart from medial-lateral translation in the study by Kozanek et al.
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(2009), where the literature values are substantially lower during the first 50% of stance and elevated during the last 50% of stance, compared with the model. In the rotations, the curves from the model follow the same trends as the literature data.

7.1.3 Effect of depth-wise tissue properties and OA

In study I, the arcade-like collagen fiber orientation in the knee joint cartilage reduced maximum principal strains and contact pressures in the cartilage surface during the whole stance phase of gait, with the peak differences seen during the second peak force (80% of the stance phase of gait), compared with the homogeneous model. The

![Figure 7.3: Simulated, measured and literature values for the tibial rotations (a)-(c) in study III. (a) Extension-flexion rotation. (b) Internal-external rotation. (c) Varus-valgus rotation. Reaction forces in the (d) lateral tibial plateau, (e) medial tibial plateau and (f) patellar cartilage surface.](image)
Results

- Effect of both fibril volume density distribution and PG distribution on strains and contact pressures was minimal during the dynamic loading (gait). However, in mechanical equilibrium the depth-wise distribution of PGs caused a substantial increase in axial strains at the superficial zone and a decrease at the deep zone (Table 7.1). As with gait, in equilibrium the effect of fibril volume density distribution on the axial strains was minimal.

The parametric study showed that an extreme, nonphysiological gradient in fibril volume density affected the tissue response during dynamic loading, as the Von Mises stresses and Pore pressures were increased at all depths by up to +50%. The depth-wise strains decreased substantially, especially in the deep zone near cartilage-bone interface, where they decreased by up to −52%. In equilibrium, the most extreme, non-physiological distribution increased the Von Mises stresses in the deep zone. However, even then the effect on axial strains in equilibrium was minimal. The
depth-wise PG distribution showed the opposite effect: during dy-
namic loading, its effect on the stresses, strains and pore pressures
was again negligible, but in equilibrium, a more steep gradient in-
creased depth-wise strains in the superficial zone by up to +16% and
reduced them in the deep zone by up to −86%.

In study III, the arcade-like collagen architecture substantially
increased maximum principal stresses (Figure 7.5), particularly in
the middle zone of the patellar cartilage, compared with the homo-
geneous model with collagen fibers parallel to surface at all depths.
The model with early OA changes (superficial fibrillation) showed
increased compressive strains in the superficial and middle zones
and decreased stresses and fibril strains especially in the middle
zone.

Figure 7.5: Maximum principal stresses at different depths of the patellar cartilage in
homogeneous (collagen fibers parallel to surface at all depths), inhomogeneous (arcade-like
fibers) and osteoarthritic models (randomly oriented fibers in the superficial zone). Study
III.
Table 7.1: Depth-wise comparison of Von Mises stresses, axial strains and pore pressures during the second peak force (80%) of gait cycle and at equilibrium (load = 150 N) in study I. Values are averaged from the integration points of 5 elements located at the area with peak contact pressure. Layer 1 corresponds to the superficial zone, Layer 4 the deep zone near the cartilage-bone interface.

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Model 1: Homogeneous, with collagen fibers parallel to surface at all depths
Model 2: Arcade-like collagen fibers
Model 3: Arcade-like collagen fibers, depth-dependent PG distribution
Model 4: Arcade-like collagen fibers, depth-dependent fibril volume density distribution
Model 5: Arcade-like collagen fibers, depth-dependent PG and fibril volume density distribution
7.2 ACL RUPTURE AND RECONSTRUCTION

In study IV, the ACL rupture caused an increase of up to 542% in tibial anterior translation during the first 50% of the stance phase of gait (Figure 7.6). The peak translation occurred during the heel strike, while the lowest increase in translation was between the ipsilateral heelrise and contralateral heelstrike. ACL rupture also caused an increase in the lateral tibial translation as well as elevated internal tibial rotation. No difference in the translations and rotations of the knee between the single and double bundle models were seen. The model with the reduced ACL graft stiffness provided the best match with the healthy joint model, followed closely by the model with the reduced pre-strain of the graft.

![Figure 7.6: Simulated tibial translations (a)-(c) and rotations (d)-(f) with respect to femur during the stance phase of gait (study IV). Subject-specific moment and force driven gait was implemented into six models: healthy knee joint with ACL intact, with ACL rupture, with single bundle ACL reconstruction, with double bundle ACL reconstruction, single bundle ACL reconstruction with softer graft, and single bundle ACL reconstruction with reduced graft pre-strain. Due to the input, the flexion-extension rotations are identical across all models.](image)

During the first peak force of gait (20% of stance), the ACL rup-
Results

ture caused a shift in the contact area in the posterior direction and consequently, increased strains in some areas and decreased strains in others. The peak maximum principal strain was actually increased compared with the healthy knee joint model (17.8% vs. 13.8%). However, the reaction forces as well as average contact pressures, maximum principal strains, fibril strains, pore pressures and maximum principal stresses calculated over the contact area were all reduced compared with the healthy knee joint model (Figure 7.7). The maximum difference between the healthy joint model and the model with ACL rupture was in average pore pressures, which were decreased by up to 80%.

Both the single bundle and double bundle ACL reconstruction techniques produced similarly elevated strains and stresses in the tibial cartilage surface compared with the healthy knee joint model. The maximum difference compared with the healthy joint model was in the single bundle model, in fibril strains, which were increased by up to 79%. Maximum difference between the single bundle and double bundle models was in 12% in the maximum principal stresses. The models with the reduced ACL graft stiffness and pre-strain produced stress and strain patterns most similar to those in the healthy knee. A closer look at the mean contact pressures, strains and stresses showed that the model with the reduced graft stiffness provided the best fit with the healthy ACL model: the maximum difference between the healthy joint model and the model with the reduced pre-strain was 37% in the average contact pressures, and for the model with the weakened graft, the maximum difference was 10%, in average maximum principal stress.
Figure 7.7: Average values at the contact area of the medial tibial compartment of a healthy joint model, ACL rupture model and ACL reconstruction models in study IV. (a) contact pressures, (b) maximum principal strains, (c) fibril strains, (e) pore pressures and (f) maximum principal stresses in the medial tibial cartilage surface during the stance phase of gait. The values are averaged at the contact area nodes of the healthy joint model as a function of time.
8 Discussion

Previous chapters described the fundamental theory and anatomy behind the FE knee model and how the experiments (used to validate the models) and simulations were conducted, as well as the results of these investigations. In the following sections, the meaning and significance of these results are discussed.

8.1 VALIDITY OF THE MODELS

In the CTa measurements of study II, the majority of cartilage deformation occurred during the first few seconds, but the cartilage continued to slowly deform up to the 30 minute mark. This is consistent with the results of Hosseini et al. (2010) [234], who reported similar in vivo creep response for cartilage. However, unlike Hosseini et al., who measured the cartilage thickness indirectly by determining the distance between bones, in this study the local tibial cartilage thickness was assessed directly from tibial cartilage surface to cartilage-bone interface. The results suggest that, in a real knee joint, the cartilage may never reach mechanical equilibrium. During the experiment, only the anterior horn of the lateral meniscus moved from under the load when the 50% of BW was applied, while the medial meniscus stayed nearly stationary. This is in accordance with earlier findings suggesting that the anterior horn of the lateral meniscus is less susceptible to mechanical damage compared with the posterior horn of the medial meniscus [235].

The model was able to match the observed average strains surprisingly well, especially since the material parameters for the articular cartilage were obtained from bovine studies [2, 67, 224] and thus were not subject-specific. Rather than pursuing the best fit, the focus was on the mechanisms controlling the creep. The model was also able to capture the translation of the lateral meniscus in the anterior direction that was observed in the experiment.
The simulated femoral rotations matched well with those observed in the motion analysis of study III. The simulated internal-external rotations highlight the importance of including the patella and quadriceps forces in moment and force driven models, as the model with the patella produced a substantially better match with the observed rotations. In knee joint models, if no quadriceps force data during gait is available however, the results suggest a rotation and translation based input should be used instead of forces and moments. The inclusion of quadriceps forces caused a total peak reaction force of $3.2 \times \text{BW}$ through the tibiofemoral contact (at 20% of the stance phase of gait), which is in accordance with the results of Bergman et al. (2014) [236], who reported a force of $3.2 \times \text{BW}$ at 20% of the stance phase of gait. The reaction forces in the patellar cartilage surface were also consistent with those reported by Huberti and Hayes (1984) [237].

It is well known that ACL rupture causes a substantial increase in anterior tibial laxity and internal tibial rotation at the beginning of the stance phase of gait [80, 81]. This exact phenomenon was seen in the model with the ACL rupture in study IV. In addition to these increased motions, an increase in lateral tibial translation was observed, which could possibly contribute to the increased peak stresses and strains observed in the medial tibial plateau. Concerning the ACL reconstruction’s ability to restore knee motion close to healthy levels, minimal differences between the single bundle and double bundle ACL reconstruction techniques were observed, which is in accordance with experimental results [87].

8.2 IMPORTANCE OF MATERIAL PROPERTIES

8.2.1 Static loading

Under physiological load, changes in the collagen fiber network caused the most drastic change in the initial creep of study II. However, as the creep advanced, the effect began to diminish, which is in accordance with studies suggesting that the collagen network primarily controls the dynamic response of cartilage [5,68,209,238],
shown here in the knee, to our knowledge, for the first time. Change in the non-fibrillar matrix (simulating mainly the effect of PGs) modulus altered the creep rate the most, although the effect was substantially lower than the effect of the collagen fiber network, especially considering a 10-fold increase in the modulus in the parametric study. Due to excessive strains in the superficial zone, the load was reduced to 50 N for the 30 minute simulation. The simulation showed that in the knee joint, the increased non-fibrillar matrix modulus caused a substantial decrease in mean strains at 30 minutes. As the PGs have been shown to mainly contribute to the equilibrium response of articular cartilage, the results were in accordance with experimental laboratory studies [68, 209, 239].

Neither a change of 12 orders of magnitude to permeability nor the prohibition of fluid flow out of the cartilage had an effect on the creep during the first minute of creep, but both had a substantial effect during the 30 minute simulation. In the knee, the vast majority of tibial cartilage surface is compressed by femoral cartilage and menisci [240]. Due to this the pore pressure distribution was uniform throughout the depth and width of the cartilage under the contacting areas, causing the creep behavior to initially arise primarily from a redistribution of fluid within cartilage and collagen viscoelasticity. A closer inspection revealed that only after 20 minutes of creep the fluid velocity increased substantially through the free surfaces. The results suggest that fluid flow boundary conditions are not an important factor when considering models of short term loading, which was also suggested by Gu and Li (2011) [167].

8.2.2 Gait loading

In study I, the gait cycle simulation emphasized the importance of the arcade-like collagen architecture on the stresses and strains in articular cartilage during dynamic loading. This is in accordance with experimental studies reporting that the collagen network modulates the dynamic response of cartilage [5, 68, 209, 238, 239]. Based on the results, the collagen architecture seems to be more important than the fibril volume density, which was shown to have a
negligible effect during both dynamic and static loading. This is most likely due to the low depth-wise variation [60], a point that was highlighted by the parametric study: the fibril volume density has a substantial effect on the stresses and strains during dynamic loading, but only if implemented unrealistically into the model.

In the knee cartilage, the effect of PGs was shown to be almost non-existent during dynamic loading but substantial in static loading, which is in accordance with the experimental laboratory studies [68, 209, 239], suggesting that the PGs mainly contribute to the equilibrium response of the cartilage. Varying the PG gradient caused an increase in the superficial axial strains during static loading, which is a result from the increased stiffness of the deep zone. The results suggest that when simulating the dynamic loading of a knee joint, the arcade-like collagen architecture should be taken into consideration. However, the depth-wise fibril volume density and PG distributions may be omitted.

During gait, patellar cartilage undergoes substantial shear forces. Results of study III suggest that the middle zone plays an important role in resisting shear forces in the patellar cartilage. This is in agreement with experimental results suggesting that the depth-wise collagen fiber orientation causes the depth-dependent shear modulus and energy dissipation of cartilage, and that the middle layer controls cartilage response to shear forces [63]. Compared with the arcade-like model, the model mimicking fibrillation of collagen network in very early OA showed reduced fibril strains and maximum principal stresses in the superficial and middle zones. Consequently, compressive strains were substantially elevated in those zones of the OA model. Results suggest that, during the very early stages of OA, substantial changes in the patellar tissue response occur during walking, and the changes are concentrated on the middle zone. This is also consistent with experimental results [63], suggesting that altered energy absorption of shear forces in the middle zone of the patellar cartilage may expose cartilage to further damage and progression of OA.
8.2.3 Optimization of ACL reconstruction techniques and graft properties

In study IV, the ACL rupture model showed the same altered joint motion that has been reported in clinical studies [80, 81]. ACL rupture model also showed a consistent trend of decreased mean reaction forces, stresses and strains in the medial tibial cartilage compared with the healthy joint model. However, the local stresses could be increased or decreased. The elevated peak values in the posterior medial tibial cartilage could expose the site to an elevated risk of OA [241]. All ACL reconstruction models showed a movement pattern similar to the healthy joint model, with the single bundle model with weakened (softer) graft stiffness providing the best match. Even though the single bundle ACL reconstruction model produced marginally higher values than the double bundle ACL reconstruction model, both the distributions and quantitative mean values in reaction forces, stresses and strains were consistently and similarly elevated in both models, compared with the healthy joint model. This is again in agreement with the literature data [87], suggesting that the choice of reconstruction technique may not determine the outcome of the reconstruction.

It is well known that patients with ACL deficiency have a high risk of post-traumatic OA [15, 242]. Many mechanisms are thought to contribute to the development of post-traumatic OA, including the damage to articular cartilage and subchondral bone occurring at the time of the ACL injury [243]. However, the results of this thesis suggest that the change in contact area could also contribute to the disease. Experimental studies show that in the knee, the stiffness of tibial articular cartilage varies depending on the site. Specifically, the cartilage is softest at areas that experience high loads, and stiffer elsewhere, e.g., under the menisci [19, 244, 245]. The results indicate that in cases where the ACL is not reconstructed, the forces the cartilage goes through are lowered due to the lack of ACL, but the contact area changes. This shift causes the stiffer areas of cartilage - that are normally less loaded - to experience abnormal stresses due to their differing mechanical properties, which in turn increases the
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risk of OA. On the other hand, in the case of ACL reconstruction, the results show that due to the high stiffness of the ACL graft (compared with the healthy ACL), the cartilage is still exposed to elevated stresses. This, again, could increase the risk of OA, even though the motion of the knee would be restored back to healthy levels.

The best match with the healthy joint model, in terms of joint motion, distribution and values of stresses, was provided by the single bundle model with weakened graft stiffness. Though not as good, the second best fit was with the single bundle reconstruction with reduced pre-strain of the graft. To see if the double bundle reconstruction technique would yield better results than the weakened single bundle with the modulated graft properties, an additional simulation was conducted with a weakened double bundle graft. The model showed a good match with the healthy knee joint, similarly as the weakened single bundle model. The results indicate that rather than the choice of technique, the graft stiffness and pre-strain play a major role in restoring the function of the knee.

It is known that the graft loses some of its tension immediately after the surgery, which results in increased laxity in the anterior-posterior direction [80]. According to a cadaveric study by Arnold et al. (2005) [223] the graft loses 46% of its tension after 1500 extension-flexion cycles. The results of this study emphasize the importance of the final tension the graft ends up with - therefore it is beneficial for the function of the knee that the graft is initially over-tensioned as it relaxes after the operation.

8.3 LIMITATIONS

Some limitations have to be noted. In studies I and II, the physiological forces exerted onto the joint caused excessive strains in the superficial zone, which prevented the simulation of the full equilibrium (or 30 minutes static loading in study II). In study I the ‘static’ option was used to simulate the equilibrium response. In study II, because of this and the fact that 80% of the observed max-
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imum strains occurred during the first few seconds after the application of the load, only the first minute of creep was simulated with physiological loads. To study the long-term effects of different parameters on the creep, the 30 minute simulation was done with a force of 50 N. The conclusions from the 50 N simulation were consistent with the conclusions drawn from the 1 minute simulation of physiological loading - only the absolute values would differ.

In study III, while the level of the internal-external rotation (in the model with the patella and quadriceps forces) matched the measured ones, there were some differences in the shape of the internal-external rotation. This is likely due to the limitation of the camera-based motion capture method, which is prone to errors arising from the skin and soft tissue movement [155, 156]. This effect is most prominent in the internal-external rotations that are, by nature, very small. Therefore a fluoroscopy study by Kozanek et al. (2009) [147] was included as a reference. The shape of the rotations in the model with the patella matched the literature data well, differences arising likely from subject-specific factors. Furthermore, a similar implementation of the gait data into the FE model as presented here was done recently [246].

It is well known that patients with a ruptured ACL adapt their gait, specifically many develop a pattern called quadriceps avoidance [138,247,248]. Because the only a healthy subject was used, the model does not take into account the altered forces and moments after the incidence of ACL rupture. The reason is that it would be difficult to conduct an experiment in which the subject is modeled before and after undergoing a rupture and reconstructive surgery.

In study I, the effect of ligaments was implemented using rotation and translation based input obtained from literature [147]. Due to this the knee motion was not subject-specific. However, because the objective was to conduct a methodological study that focuses on the depth-wise characteristics of articular cartilage and not a realistic simulation of gait, one can argue the input is sufficient. In studies II-IV, the ligaments were modeled as linear springs instead of solids, using ligament stiffnesses obtained from literature [37].
In the static loading used in study II the use of linear springs is justified due to the stationary nature of the simulation. However, in gait studies (III and IV), the model may not represent the nonlinear, viscoelastic properties of ligaments accurately [249]. However, the joint motion observed during the motion analysis showed a good agreement with the simulated joint motion. Further, as the focus of studies III and IV was on the stresses the cartilages experience, and not the ligaments, the decision to use linear springs to model ligaments can be considered justifiable.

In all of the studies, only one subject was investigated. However, given the methodological nature of this thesis, the focus is on validating the model and investigating the effects of different parameters (such as cartilage properties, quadriceps forces, patella) on the model response before applying it for further clinical studies with more subjects. Furthermore, the mechanisms investigated in this thesis, which can only be studied through modeling, should not depend on joint geometry or other variables. The exact values of stresses and strains would vary from subject to subject, but the conclusions would not change [250].

Finally, despite all the advantages FE modeling of the knee joint brings, there are currently several issues that prevent its use in clinical practice. The crux of the problem is time, as all stages of modeling are time-consuming, limiting their use in clinical applications. All modeling begins from acquiring the geometry, which is typically done by manually segmenting the tissues from MR image stacks. For clinical practices, the segmentation needs to be automated. The next step, meshing, is also very time consuming and difficult to automate if using hexahedral elements (such as in this thesis). It is common to have to manually cut the edges of the tissues to achieve a functioning mesh, a process that is difficult for the computer. The gait input is currently semi-automated, usually needing manual processing in noise-reduction. Even after obtaining the geometry, mesh and motion input, it takes time to make the model work and get the simulation results. The model calculation is very demanding in terms of computing resources: on a fairly
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powerful computer a full gait cycle can take over 16 hours, although the process could be optimized by altering the material code. To be feasible in clinical practice, the segmentation, meshing, model creation and analysis should all be automatic or semiautomatic and instantaneous.
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9 Summary and conclusions

In this thesis, fibril-reinforced poro(visco)elastic materials were implemented into articular cartilages as well as menisci in three-dimensional, subject-specific FE models of knee joints. The \textit{in vivo} deformation of articular cartilage was determined during static loading using CTa imaging, and the strains were compared to the subject-specific model. Motion analysis was used to determine the rotations, translations, forces and moments in the subject’s knee, and were then compared to the model. The effect of the architecture of collagen fibers and depth-wise distributions of collagen and PG contents of tibial and patellar cartilage were investigated during gait and static loading. Finally, the moment-driven gait model was used to assess the outcomes of different ACL reconstruction techniques. The main conclusions of these studies can be summarized as follows:

1. Collagen fiber architecture controls the dynamic response of articular cartilage \textit{in vivo}. During dynamic loading, the effect of both the depth-wise fibril volume density distribution and PG distribution on the stresses and strains in the cartilage is negligible. However, during static loading the PG distribution plays a major role and should be considered in simulations of static loading.

2. In an intact knee, the vast majority of cartilage deformation occurs within the first few seconds after the application of the load, but the cartilage continues to deform slowly and may never reach mechanical equilibrium \textit{in vivo}. Collagen fibril stiffness modulates the initial creep response, but the effect of PGs increases as the creep advances. Permeability and fluid flow boundary conditions have a negligible effect on the initial response, but more substantial effect in later stages of creep (post-20 min).
3. The moment and force driven model is able to replicate the observed rotations of the subject’s knee during gait. As the patella and quadriceps forces play a major role in resisting the rotations, especially the internal-external rotation, they should be included in force and moment driven models of knee joints. In the patellar cartilage, the middle zone plays a major role in resisting shear forces during gait.

4. When the ACL rupture is introduced, the moment and force driven model shows a substantial increase in anterior tibial translation and internal rotation, similarly to clinical findings. The ACL rupture reduces reaction forces, strains and stresses in the tibial cartilage, but increases peak local stresses compared with the healthy joint model. All investigated ACL reconstruction techniques show similar capability to restore the movement of the joint close to the healthy knee joint model. Between the single bundle and double bundle reconstruction techniques, only minor differences in joint function or stresses and strains was seen. Rather than the choice of technique, the graft stiffness and pre-strain seem to modulate the outcome of the ACL reconstruction.

In conclusion, the work presented in here takes a step towards a novel diagnostic tool for the assessment of possible failure sites in the human knee. Ultimately, a validated model could provide a means to assess the outcome of treatments (e.g. weight loss) or surgical procedures (e.g. ACL reconstruction), and it could be then used in clinical decision making.

9.1 FUTURE

The modeling process has several issues that future studies will need to solve. Those are for instance: a reliable automatic segmentation of tissues from MR images, ligament tissue properties, patient-specific physiological loading conditions as well a selection of different functional activities. Time-wise, the need for manual
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segmentation is currently the most demanding process if the material model is simple. While patient-specific tissue properties may never be acquired, in future studies the ligaments should be modeled as solids rather than linear springs, with more accurate viscoelastic material models. Ideally, the patient’s gait should be captured using dual fluoroscopy to minimize motion artifact resulting from skin movement. Although gait is the default physical activity to be simulated, the research will eventually expand to other activities such as stair-climbing or lunge.
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Osteoarthritis or OA, especially in the knee, is a common disease in elderly people but also in athletes that have suffered a trauma, e.g. anterior cruciate ligament rupture. Currently, OA cannot be cured, but its risks can be estimated and minimized. This thesis aims to develop a novel, computational model of the subject’s knee that could, in future, be used by doctors as a diagnostic tool to evaluate the risk of post-traumatic OA before and after surgical operations.