

Automated Image Analysis of High-field and Dynamic Musculoskeletal MRI

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Abstract

Abnormal knee biomechanics and injury to the menisci and posterior cruciate ligament (PCL) have been shown to increase the risk of developing knee osteoarthritis (OA). Recent advances in magnetic resonance (MR) imaging introduced methods for *in-vivo* quantitative measurement of meniscus and ligament morphology and biochemical integrity (water distribution and mobility) as well as 3D knee kinematics. Recent investigations have demonstrated the value of these imaging techniques for quantification of the morphology (meniscus volume, subluxation and tibial coverage) and T_2/T_2^* properties of the knee menisci and PCL for assessment of early changes associated with pre-osteoarthritic degeneration, or tissue health and function post-surgery. Likewise, quantitative measurements of knee kinematics such as patellar shift, tilt and cartilage contact areas from kinematic MR images have been used to study the etiopathogenesis of pain and cartilage degradation in relation to abnormal knee function.

Although these techniques can enhance assessments of the menisci, PCL and knee function, there is currently no efficient method to extract these measurements from the MR images. Current methods require significant time and resources from experts to perform manual analyses, which limits clinical applicability.

In this thesis, we develop and validate a set of novel image analysis algorithms allowing the automated segmentation and quantitative analysis of the morphology and biochemistry of the medial meniscus (MM), lateral meniscus (LM) (Aim 1) and PCL (Aim 2) from MR images of the knee joint, and the automated estimation of several important kinematic measurements (cartilage contact mechanisms, bone tracking) of the knee joint from kinematic MR images (Aim 3).

An active-shape-model approach driven by a template matching process was developed to segment the MM and LM from MR images of the knee joint (*Aim 1*). Experimental MR datasets included images from patients with ligament and meniscus injuries (3T clinical scans) or knee OA (3T research scans) and healthy subjects (7T MR scans). Extensive validation was performed against expert manual segmentations using the Dice similarity index (DSI), a measure of spatial overlap. The results indicated that the automated method obtained accurate and robust segmentations of the MM and LM in all the MR datasets (mean DSI between 74.5–84.3% for the MM and 76.5–85.1% for the LM). Quantitative measurements of the 3D morphology (volume, subluxation and tibial coverage) and biochemical composition (T_2 -properties) of the MM and LM were automatically estimated from the segmentation volumes. Good correlations were achieved between measurements derived from the automated and manual segmentations of the menisci ($r \ge 0.7$). Statistical comparison of these quantitative values across clinically relevant groups of patients with variable knee pathologies obtained results in agreement with the literature.

A multi-atlas patch-based method was used to automatically segment the PCL in T_2 -maps from healthy and pathological knee joints (Aim 2). Quantitative validation of the method against expert manual segmentations performed in T_2 -maps of healthy knee joints demonstrated good accuracy (mean DSI 74.5%). Qualitative inspections showed good PCL segmentation results in T_2 -maps from pathological knee joints. Correlations between the PCL T_2 -relaxation values derived from the automated and manual segmentations were moderate to strong (r > 0.74).

In-vivo 3D knee kinematics was evaluated automatically from MR images of the joint acquired at six different degrees of knee flexion ("quasi-static" 3D) and in active motion (dynamic 2D+t) (Aim 3). The method extended an existing approach to segment the knee bones and cartilages from MR images of the joint at full extension. Two registration-based schemes were developed to align bone and cartilage segmentations throughout the quasi-static and dynamic MR sequences. Automated segmentations obtained throughout the quasi-static MR sequences were validated quantitatively against manual segmentations. Results showed good segmentation accuracy (mean DSI above 88.4% for the bones and above 68.1% for the cartilages). Cartilage contact kinematics as well as quantitative measurements of patellar tilt and shift were estimated using features extracted automatically from the reconstructed bone surfaces. The cartilage contact areas derived from the automated and manual segmentations showed good spatial agreement (mean DSI above 84.0%). The correlations between quantitative measurements estimated using the manual and automated segmentations were $0.46 \le r \le 0.93$, with most correlations being moderate to strong (> 0.60). Active knee kinematics estimated from the dynamic MR sequences was evaluated qualitatively.

The automated MR image analysis algorithms can accurately and reliably evaluate the morphology and T_2 relaxometry of the knee menisci and PCL. This represents a considerable technical advance towards clinical applicability of quantitative MR evaluation of these structures and can facilitate clinical studies. The results obtained from the automated analysis of kinematic MR images demonstrate its potential. However, further technical improvements in image acquisition and analysis are required before possible clinical applicability.

Declaration by Author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications During Candidature

Peer-Reviewed Journal Articles

[Paproki 2014] Paproki A., Engstrom C., Chandra S.S., Neubert A., Fripp J., and Crozier S. Automated segmentation and analysis of normal and osteoarthritic knee menisci from magnetic resonance images - data from the Osteoarthritis Initiative. *Osteoarthritis and Cartilage*. 2014 Sep 30;22(9):1259-70.

[Yang 2015] Yang Z., Fripp J., Chandra S.S., Neubert A., Xia Y., Strudwick M., Paproki A., Engstrom C., and Crozier S. Automatic bone segmentation and bone-cartilage interface extraction for the shoulder joint from magnetic resonance images. *Physics in medicine and biology*. 2015 Feb 21;60(4):1441.

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[Yang 2014] Yang Z., Fripp J., Engstrom C., Chandra S.S., Xia Y., Paproki A., Strudwick M., Neubert A., and Crozier S. Automatic Bone Segmentation for Shoulder MRI using Statistical Shape Models. *International Society for Magnetic Resonance in Medicine, 22nd Scientific Meeting & Exhibition.* 2014 (p. 4308).

Publications Included in this Thesis

Although none of the publications produced during this research work were used in their entirety, significant portions were utilised throughout the chapters of this thesis. In particular, parts of the publications produced were utilised in the following chapters:

- Chapter 4 [Paproki 2014]
- Chapter 5 [Paproki 2014]
- Chapter 6 [Paproki 2016b]

For all the listed publications, individual contributions from all the authors are provided below.

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Contributions by Others to the Thesis

Prof. Stuart Crozier, as primary supervisor, obtained funding for the research and substantially contributed in the conception and design of the studies, the analysis and interpretation of the research data and provided critical revisions for this thesis.

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List of Abbreviations

- T_E Echo Time, page 29
- T_R Repetition Time, page 29
- ACL Anterior Cruciate Ligament, page 2
- ASM Active Shape Model, page 83
- BCI Bone-Cartilage Interface, page 117
- BLOKS Boston-Leeds Osteoarthritis Knee Score, page 52
- CNR Contrast to Noise Ratio, page 30
- CPC Cine phase contrast, page 42
- CT Computer Tomography, page 27
- CV Coefficient of Variation, page 55
- DESS Dual Echo Steady State, page 36
- DSI Dice similarity index, page 60
- EM-ICP Expectation Maximisation Iterative Closest Point, page 93
- FISP Fast Imaging with Steady Precession, page 35
- FLASH Fast Low Angle Shot, page 35
- GAG GlycosAminoGlycan, page 15
- GLM(s) Grey Level Model(s), page 83
- GRE Gradient-Echo, page 30
- ICC Intraclass Correlation Coefficient, page 51
- ICP Iterative Closest Point, page 72

ITK	Insight Registration	Toolkit, page 9	0
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- JSN Joint space narrowing, page 26
- K/L Kellgren & Lawrence, page 26
- KOSS Knee Osteoarthritis Scoring System, page 51
- LM Lateral Meniscus, page 14
- MASD Mean Absolute Surface Distance, page 98
- MM Medial Meniscus, page 14
- MOAKS MR imaging Osteoarthritis Knee Score, page 53
- MOST The Multicenter Osteoarthritis Study, page 61
- MSK Musculoskeletal, page 1
- NCC Normalised Cross Correlation, page 96
- NMI Normalised Mutual Information, page 48
- NMV Net Magnetisation Vector, page 28
- OA Osteoarthritis, page 1
- OAI Osteoarthritis Initiative, page 83
- PCA Principal Component Analysis, page 94
- PCL Posterior Cruciate Ligament, page 2
- PD Proton Density, page 29
- PDM Point Distribution Model, page 94
- PFPS Patellofemoral Pain Syndrom, page 24
- RF Radio Frequency, page 29
- rOA Radiographic Osteoarthritis, page 26

List of Tables

- SNR Signal to Noise Ratio, page 30
- SPRI Steadman Philippon Research Institute, page 86
- SSD Sum of Squares Difference, page 46
- SSM(s) Statistical Shape Model(s), page 83
- T Tesla, page 39
- TSE Turbo Spin-Echo, page 33
- UQ The University of Queensland, page 86
- WE Water Excitation, page 37
- WORMS Whole-Organ Magnetic Resonance Imaging, page 51

Chapter 1

Introduction

Contents

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This chapter presents an overview of the research contained within the thesis. In particular, a brief overview of the key medical and technical motivation and background is presented, before the research problem and justification are detailed. This then leads to the presentation of the scope and specific aims of the PhD work, followed by details regarding the contribution of the research to the musculoskeletal imaging field. An outline of the thesis document is provided at the end of the chapter as a guide to the reader.

1.1 Background Information

1.1.1 Clinical Motivation

Musculoskeletal (MSK) injuries and disorders are one of the most common causes of pain in the human body and can lead to severe physical disability [BJD 2016]. Joint conditions such as osteoarthritis (OA) affect several hundred million people worldwide, with an estimated prevalence of 10% in men and 13% in women over the age of 60 years [Zhang 2010b]. OA is a complex, multi-factorial disease leading to a progressive loss of articular cartilage, changes in peri-articular joint tissues, bone deformations such as osteophytes and inflammation in synovial joints [Johnston 1997]. The most commonly affected load bearing joint is the knee joint, and symptoms of knee OA include pain, swelling, stiffness of the joint and abnormal range of motion or grinding while moving. In most cases, these debilitating symptoms result in restrictions in activity levels predisposing to a premature sedentary lifestyle.

Recent studies have demonstrated that acute or chronic injury of the knee menisci or the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) represent a significant risk factor for development of this degenerative joint disease [Englund 2004, Simon 2015, von Eisenhart-Rothe 2012, Levy 2012]. Current hypotheses suggest that alterations in the normal biomechanical functions of these structures, which protect the articular cartilage from high focal stress and provide stability to the knee joint, may alter the loading mechanisms of the joint and initiate or promote cartilage wear. Likewise, abnormal patellar motion resulting in patellofemoral pain syndrome (PFPS) has been associated with increased risks of patellofemoral OA development as a result of elevated stress on the articular cartilage [Utting 2005]. The morphological, biochemical and biomechanical factors involved in the underlying etiopathogenesis of knee OA, however, remain unclear and are still a topic of ongoing research [Sharma 2016, Varady 2016].

New developments in quantitative magnetic resonance (MR) imaging have generated considerable clinical interest for the design of methods to study the morphology and biochemical composition of the medial meniscus (MM), lateral meniscus (LM) and PCL in relation to knee injuries and OA [Wirth 2010, Wenger 2013], as well as for the assessment of *in-vivo* 3D knee kinematics using dynamic MR imaging (e.g., contact mechanisms between cartilages [Borotikar 2012]). These measurements offer avenues to study early pathophysiological changes associated with pre-osteoarthritic degeneration (e.g., reorganisation of the extracellular matrix of the meniscus affecting normal function [Juras 2014, Zarins 2010]); assess the structural integrity of the menisci and ligaments post-surgery (e.g., healing properties of the tissues [Chu 2014, Biercevicz 2014a, Wilson 2016]); or investigate abnormal bone tracking or contact mechanisms in PFPS [Pal 2013] or in ligament-deficient patients [Barrance 2006] for predicting subsequent risks of cartilage wear.

1.1.2 Technical Motivation

Quantitative measurements of the morphology and biochemistry of the MM, LM and PCL from MR images usually require their precise identification from MR images, a process called segmentation.

Likewise, in order to evaluate the *in-vivo* kinematic characteristics of the knee joint from MR images, the articulating bones and cartilages are usually segmented.

Segmentation of these soft-tissue structures from MR images is challenging due to their complex morphology (high curvature, thin), shape variability within the population, variability in contrast characteristics (i.e., demarcation with surrounding tissues) and various artifacts commonly found in MR images (e.g., partial volume effects, susceptibility artifacts). For these reasons, the segmentation is traditionally performed manually by an experienced radiologist or semi-automatically by a highly trained observer. These methods are not only expertise-intensive but are very time-consuming and often require subjective interpretations of individual structures in unclear areas of the MR images, which impacts upon the reproducibility and repeatability of subsequent quantitative measurements and limits the clinical applicability of quantitative MR imaging.

Advances in medical image processing algorithms provide avenues to facilitate quantitative MR analyses through automated image segmentation and the estimation of robust and reproducible morphological, biochemical and kinematic measurements from the segmentation volumes. If successfully implemented and validated, these methods lend themselves for analyses of large-scale datasets and clinical investigations into early knee OA, and will likely facilitate translation of quantitative MR imaging into routine clinical examinations.

Currently, there are no fully-automated methods that allow the cost-efficient segmentation and quantitative analysis of the pathological knee menisci or healthy and pathological PCL from MR images of the knee joint. Similarly, no fully-automated method has been proposed to facilitate analyses of the bone and cartilage kinematics from MR images of the knee joint in motion.

A review of the literature shows that:

- Previous automated segmentation methods for the menisci were designed to segment healthy knee joints from cartilage-specific MR sequences not utilised in routine clinical examinations [Fripp 2009, Zhang 2013];
- Accuracy and sensitivity of quantitative measurements estimated from automated segmentations of the individual MM and LM in MR images has not been investigated;
- No thoroughly validated method for automated segmentation of the PCL from MR images has been proposed and the field remains mostly unexplored;
- Accuracy and sensitivity of automated T_2 -mapping of the PCL has not been investigated;

• Automated segmentation and analysis of kinematic MR images of the knee joint is not available.

1.2 Research Aims and Challenges

This PhD thesis addresses the shortcomings listed in the previous section with the development and thorough validation of novel image-processing algorithms to facilitate quantitative analyses of MR images of the human knee joint. The automated algorithms allow the three-dimensional (3D) segmentation, visualisation and quantitative analysis of the knee menisci and PCL from structural and biochemical MR images of the knee joint in healthy and pathological states. A method to facilitate the estimation of *in-vivo* kinematic descriptors of joint motion (e.g., bone motion trajectory and contacts between articular cartilages) from MR images of the healthy knee joint with variable degrees of flexion (quasi-static) or in active motion is also implemented.

Specifically, the major objectives of this thesis revolved around the following areas:

1. Meniscus

- Automated segmentation of the menisci (MM, LM) from cartilage-specific or routine clinical MR images of the healthy and pathological knee joint;
- Quantitative measurement of the morphology of the MM and LM from the segmentation volumes of these fibrocartilaginous structures;
- Estimation of the biochemical properties (water mobility) of the MM and LM using T₂map MR images;

2. Posterior cruciate ligament

- Automated PCL segmentation from biochemical MR images;
- Accurate estimation of the biochemical properties of the PCL using T_2 -mapping;

3. Knee joint kinematics

- Automated segmentation of the articulating bones and cartilages of the knee joint from 3D MR images;
- Estimation of *in-vivo* knee motion from dynamic and quasi-static MR images;

• Measurement of several important kinematic parameters (e.g., patellar shift, tilt and cartilage contact-areas) from the estimated motion.

To achieve this, the three aims detailed in the following sections have been developed.

Aim 1. Automated segmentation and quantitative analysis of the menisci from MR images of healthy and pathological knee joints

Aim 1.1 Automated segmentation of the knee menisci from MR images

Accurate segmentation of the knee menisci is important for subsequent quantitative measurements of the morphology and biochemistry of these fibrocartilaginous structures (**Aim 1.2**). Robust automated segmentation is problematic due to the inherent complexity of the meniscal shape (millimetre thin crescent-shaped structures) and variability within the population. The quality of the MR images (e.g., noise, spatial resolution, tissue contrast) is another factor impacting upon the complexity of the segmentation task as intensity inhomogeneities may appear within menisci, and the surrounding tissues may feature similar signal intensity as the menisci (e.g., ligaments and fat). Pathologies such as acute tears or OA will often exacerbate these challenges and increase the difficulty of the task.

The proposed automated segmentation algorithm will utilise recent advances in model based segmentation in order to identify the individual MM and LM from MR images of the knee. The method will be robust to the changes occurring within the menisci in common pathologies. The software will be ideally suited to segment MR images acquired with pulse sequences commonly used in clinical studies and routine diagnostic imaging of the menisci. Resulting segmentations will be validated by comparison against expert manual segmentations.

Aim 1.2 Automated estimation of quantitative measures of the menisci

Quantitative analyses of the MM and LM from MR images offer avenues to acquire information on early degeneration associated with pathologies and the health of these cartilaginous tissues. Current analysis techniques estimate subjective semi-quantitative scores from X-rays or MR images, which lack sensitivity for detection of subtle changes. Existing fully-quantitative MR analyses rely on manual segmentations, limiting current practice to clinical studies with small populations. Evaluating the accuracy of quantitative MR measurements estimated from automated segmentations is desired, yet unknown.

Several algorithms will be developed for the estimation of clinically important morphological parameters related to knee OA, including meniscal volume, subluxation and tibial coverage. The automated analysis of the biochemistry of the menisci will also be investigated by transfer of the anatomical information obtained in **Aim 1.1** onto typical MR pulse sequences sensitive to water content and collagen content and organisation such as T_2 -mapping. The accuracy will be evaluated by comparing quantitative measurements obtained from automated and expert manual segmentations.

Aim 2. Automated segmentation and quantitative analysis of the PCL from MR images

The PCL is an important intra-articular ligament for stabilising and controlling motion of the human knee joint. Automated segmentation of the PCL from MR images of the knee joint offers avenues for quantitative diagnosis of this commonly injured structure in both pre- and post-clinical management (e.g., repair). This is challenging due to the large variability of shapes of the PCL among the population, variable appearance features in MR images as a result of knee positioning and the similarity of the PCL signal intensity with the surrounding menisci and ACL. While the contiguous ACL is also crucial for knee joint stability, this aim was developed as part of a research study focusing on the PCL [Wilson 2016], with expert manual assessments and clinical data collected for this ligament in a rigorously pre-screened cohort.

In this thesis, an atlas based segmentation procedure is used for identification of the PCL from T_2 map images of the knee joint in healthy and pathological subjects. The atlas will contain MR images characterising sufficient variability of PCL configurations for robust segmentation of this ligament in MR images of the extended knee joint. The segmentations obtained will be used to estimate the T_2 properties of the PCL in healthy and pathological cohorts. The method will be validated by comparison of the automated results to expert manual analyses.

Aim 3. Automated segmentation and quantitative analysis of kinematic MR images of the knee joint

Aim 3.1 Automated segmentation and estimation of knee motion from kinematic MR images

Kinematic MR imaging of the knee joint offers avenues to facilitate the diagnosis of the origin of pains not easily observable in a patient at rest or in analyses of altered bone and cartilage biomechanics in the knee. However, this imaging technique generates large amounts of data which are difficult to visualise and analyse efficiently. Automating the analysis process with the development of algorithms for bone and cartilage segmentation, model reconstruction and estimation of knee motion will likely facilitate clinical studies investigating the kinematic factors involved in knee pathologies. This is challenging as acquisitions are usually tailored to specific setups such as large bores and open-coils in various MR systems and are prone to strong motion and inhomogeneity artifacts, while generating MR images with relatively low signal contrast and spatial-resolution.

The implemented model- and registration-based method will allow the automated identification of the articulating bones and cartilage plates of the knee joint from structural MR images and the estimation of knee joint motion from (1) quasi-static 3D MR images of the knee in different angles of flexion and (2) real-time 2D dynamic MR images of the moving knee. The method will be robust to the various artifacts found in kinematic MR images. Validation of the experimental results of knee motion estimated from the quasi-static MR images will be performed by comparison of the resulting segmentation volumes against manual segmentations performed for all available knee flexion angles. At this stage, validation of *in-vivo* knee motion obtained from the dynamic MR images is performed qualitatively.

Aim 3.2 Automated estimation of quantitative parameters from 3D model reconstructions incorporating motion information

Quantitative analysis of knee kinematics via parameters such as contact areas between the cartilages of the knee or tracking of the bones can provide useful information on abnormal biomechanics of the knee. These can potentially help predict subsequent risks of cartilage wear or articular pathologies. To date, these measurements have been obtained from tracking of manual segmentations of the knee structures in the kinematic images, which is time consuming and limits the reproducibility of the measurements.

The algorithms developed will allow the estimation of several important kinematic parameters from reconstructed knee models incorporating motion information, including cartilage contact areas and patellar tilt/shift. Parameters estimated from quasi-static MR images will be carefully validated for accuracy against parameters estimated from the manual segmentations of the 3D quasi-static MR images. As this stage, parameters estimated automatically from dynamic MR images will be qualitatively evaluated.

1.3 Contributions of the Thesis

The major contributions of this PhD thesis revolve around the development and validation of the following automated image analysis algorithms:

1. Automated segmentation of the MM and LM

A fully-automated algorithm for the segmentation of the individual MM and LM from MR images of the knee joint is presented. The method is the first one to be extensively validated on both (1) MR images typically acquired in routine clinical examination of the menisci and those acquired for research into knee OA and on (2) MR images of the pathological knee joint (mixture of acute ACL and meniscal injury and knee OA disease status). Applicability of the method on novel 7T MR images is also demonstrated.

2. Automated estimation of quantitative measurements describing the morphology and biochemical composition of the MM and LM

Automated image and surface processing algorithms for the evaluation of important morphological (volume, tibial coverage and subluxation) and biochemical (regional T_2 -mapping) parameters of the MM and LM of the knee are presented. This study is the first to evaluate and report the accuracy of quantitative parameters of the menisci fully-automatically estimated from MR images (from segmentation to parameter extraction). Results obtained from the extensive validation suggest that the developed method is suitable for application in clinical studies to facilitate analyses and promote objective measurements. It also provides a significant advance towards the utilisation of quantitative MR imaging of the menisci into routine clinical MR examinations to support standard qualitative assessment of MR images.

3. Automated segmentation and analysis of the PCL

An automated method allowing the segmentation of the PCL from biochemical T_2 -maps of the knee joint is presented. This study is the first to carefully validate an automated segmentation algorithm for the PCL. The results reported offer a baseline for comparison in future automated PCL segmentation experiments. The accuracy of the PCL T_2 -parameters estimated from automated segmentations is also reported for the first time by comparison to measurements estimated from manual segmentations. The method provides a promising alternative to manual methods for quantitative MR analysis of the PCL in clinical studies.

4. Automated segmentation and quantitative analysis of kinematic MR images of the knee
joint

A method allowing the fully-automated segmentation and quantitative analysis of kinematic MR images of the knee joint is presented. Specifically, the method combines the anatomical information automatically extracted from structural MR images with the kinematic information provided by dynamic and quasi-static MR images in order to estimate knee motion and extract kinematic parameters such as cartilage contact areas and patellar tilt/shift. This is the first study to present a fully-automated pipeline for evaluation of *in-vivo* 3D knee kinematics from MR images of the knee joint. Experimental results of accuracy are reported for the quasi-static experiment.

1.4 Organisation of the Thesis

The thesis is organised as follows:

Chapters 2 provides background information regarding the anatomy and biochemistry of the knee structures of interest for this thesis and provides an overview of MR imaging of knee joint. An introduction to medical image segmentation is also provided.

Chapter 3 presents a review of the literature related to quantitative MR analyses of the morphology and biochemistry of the knee menisci and PCL, followed by an overview of the current methods utilised in clinical research to study *in-vivo* knee kinematics from MR imaging technologies.

Chapter 4 details the segmentation approach developed to allow the automated, robust and accurate segmentation of the knee menisci from MR images using an active shape model approach (*Aim 1.1*).

Chapter 5 presents the methodology utilised to quantify the morphology (volume, subluxation and tibial coverage) and biochemistry of the knee menisci from the segmented MR images and validate the accuracy the measures (*Aim 1.2*).

Chapter 6 presents the methodology utilised to obtain segmentations of the PCL from MR images and to estimate biochemical information from the segmented anatomy (*Aim 2*).

In Chapter 7, the methodology utilised to estimate quantitative measures automatically from kinematic MR images is presented (*Aim 3.1, 3.2*). The final chapter provides a general discussion on the results obtained by the various automated algorithms and presents the limitations and interesting avenues for future work on this project.

Finally, Chapter 8 closes this thesis with a general summary and discussion of the research.

Chapter 2

Background

Contents

2.1	Anatomy and Physiology of the Knee Joint
2.2	Basic Kinematics of the Knee Joint
2.3	Knee Malfunction, Degeneration and Disorders
2.4	Magnetic Resonance Imaging of the Human Knee Joint
2.5	Medical Image Segmentation 43

The first section of this chapter presents general background information on the anatomy, biochemical composition and function of several important structures of the human knee joint. A focus on specific components such as the knee menisci and posterior cruciate ligament relevant to the research of this thesis is made along with a brief description of other associated structures such as the knee bones and cartilages. The knee joint pathologies that directly motivate the present research are then described.

The second part of this chapter provides an overview of static and dynamic magnetic resonance imaging, with a focus on the description of the pulse sequences commonly used for investigation and clinical diagnosis of the knee joint. The final section of the chapter gives an introduction to medical image segmentation.

2.1 Anatomy and Physiology of the Knee Joint

The human musculoskeletal (MSK) system is composed of skeletal muscles, tendons, ligaments, cartilages (soft-tissues) and bones (hard-tissues) which provide support and allow movement of the body. The bones within the axial and appendicular skeletons have a number of functions including support, shape, protection of internal organs, mineral storage and provide a system of levers to allow a spectrum of motion of the limbs and body segments. The skeletal muscles, connected to the bones via tendons, allow skeletal movement and locomotory activities by way of concentric, eccentric and isometric contractions, applying direct forces on the bones (pulling or pushing).

The MSK system is articulated through a variety of immobile (e.g., cranial sutures), semi-mobile (e.g., joint formed by two vertebrae) and freely mobile (e.g., knee) joints, which connect two or more bones together. A "typical" synovial (diarthrosis) joint is composed of a set of articulating bone surfaces, a fibrous joint capsule (encapsulating synovial membranes and fluids), ligaments, hya-line/articular cartilages and, depending on the joint, other connective tissue structures such as the knee menisci or shoulder labrum.

The knee joint is a synovial joint that connects the femur, tibia and patella bones and articulates the leg (Fig. 2.1). It is the largest synovial joint in the human body and one of the most complex joint to understand functionally due to the large number of structures interacting together to allow the motion of three inter-dependant articulations: (1) the articulation between the patella and the femur (patellofemoral), (2) the articulation between the surface of the medial tibial plateau and the medial femoral condylar surface (medial tibiofemoral) and (3) the articulation between the surface of the lateral tibial plateau and the lateral femoral condylar surface (lateral tibiofemoral). The knee bears a great majority of the body weight and is considered a modified hinge joint due to the tibiofemoral articulation which allows the knee to bend and enables walking. The articulating bone surfaces are separated by connective soft tissues that protect them from shocks and frictions. This includes a thin layer of articular cartilage covering the articulating surface of the bones, the menisci and the cruciate ligaments.

2.1.1 Bones

The knee joint incorporates the articulating surfaces of three bones: the femur, the tibia and the patella (also called the knee cap).

The **femur** is the longest and strongest bone of the human body. The superior portion of the femur consists of a large spherical head which forms a ball-and-socket type joint with the deep acetabular fossa of the hip bone while the inferior portion forms a modified hinge joint with the tibia and the patella. The inferior posterior compartment of the femur exhibits two semi-spherical bony eminences called the medial condyle and the lateral condyle. The femoral condyles are separated by the inter-condylar fossa (Fig. 2.1(b)) and act as two separate articulations with the shallow, concave plateau



Figure 2.1: Anatomy of the knee joint structures relevant to this research (reconstructed from manual segmentations of MR imaging data). (a) a simple 3D model of the knee joint from *(left)* anterior and *(right)* posterior views showing the patella, proximal tibia and distal femur (medial and lateral condyles). The bones and cartilages are displayed in black and white, respectively. The knee menisci and cruciate ligaments are displayed in yellow and red, respectively. (b) shows a 3D model of the articular cartilages of the patella, femur and tibia within the knee joint. (c) shows a 3D model of the medial and lateral menisci. (d) shows shows a 3D model of the anterior and posterior cruciate ligaments.

surfaces of the tibia. Of the two femoral condyles, the medial condyle is larger than the lateral condyle due to the larger compression loads transmitted from the upper body as a result of a centre gravity being medial to the knee structure. The inferior anterior portion of the femur has a concave shape called the trochlear groove that accommodates well with the patella bone and allows sliding motion of this bone vertically along the patellar surface of the femur situated between the two condyles.

The **tibia** bone is the second largest bone in the human body. It runs down the lower leg together with the smaller, lateral fibula and forms a gliding joint with the talus bone of the foot. The superior portion of the tibia is separated into two areas, called the medial and lateral tibial plateaus (or condyles). The upper surface of the tibial plateau is covered by a thin layer of articular cartilage and the medial and lateral menisci. The separation between the two plateaus is referred to as the intercondylar area of the tibia. This region provides attachment points for the intra-articular soft-tissue structures of the knee, including the cruciate ligaments and the menisci.



Figure 2.2: Structure of the knee menisci. (a) shows the red-red, red-white and white-white zones of the meniscus, which are named after the vascularisation of the structure. (b) shows a cross-section of the meniscus which highlights the different layers of collagen fibres: (1) the superficial layer, (2) the lamellar layer and (3) the main layer. (a) is adapted without permission from [Makris 2011]. (b) is adapted without permission from [Petersen 1998].

The **patella** is the final functional bone of the knee joint and the largest *sesamoid* bone¹ of the MSK system. It is embedded within the patellar tendon, which runs down from the quadriceps muscle and attaches anteriorly to the tibial tuberosity. The patella has a circular-triangular shape and the posterior region facing the femur is covered by articular cartilage which allows smooth vertical gliding of the patella along the trochlear groove of the femur.

2.1.2 Articular Cartilages

Like most articulating joints, the bone surfaces of the human knee joint are covered by a 2mm to 4mm thick layer of articular cartilage that is organised as a dense extracellular matrix [Fox 2009]. The articular cartilage in the knee joint is commonly described as four individual cartilage plates consisting of the patellar, femoral, medial tibial and lateral tibial cartilage plates (Fig. 2.1 (b)). In healthy knee joints, cartilage tissue covers the entire articular region and provides a smooth surface which allows the bones to move easily against each other without causing damage to the underlying subchondral bone. They also provide flexibility and support to the joint motion, absorb shocks and resist compression loads to lessen the impact on the knee bone.

2.1.3 Knee Menisci

The medial meniscus (MM) and lateral meniscus (LM) of the knee joint are two crescent-shaped fibrocartilaginous structures located between the femoral cartilage and the medial tibial and lateral tibial cartilages (Fig. 2.1 (d)). In adults, the LM is generally 32 - 35mm long, with a maximum width

¹Sesamoid: Embedded in a ligament or tendon.

situated between 25 - 30mm, while the MM approximates a length of 40 - 46mm and a width of 26 - 28mm [McDermott 2004]. Their cross-section is triangular, with a flat inferior surface laying on the tibial cartilage plates and a concave superior surface matching the spherical shape of the femoral cartilage.

Acting as a cushioning layer between the articular cartilage plates of the tibiofemoral joint, their normal function is crucial for healthy knee biomechanics [Seedhom 1974]. In particular, with their high flexibility and rubbery texture, the menisci allow the knee joint to dissipate kinetic energy and assume a role of shock-absorber during gait cycles [Kelly 1990]. Through increased medial and lateral contact areas between articular cartilages, they facilitate the transmission and repartition of compression loads and protect the cartilage from high focal stress [Kelly 1990, Makris 2011]. The menisci are also important for joint stability and congruity [Tummala 2012], with anterior and posterior horns and meniscofemoral ligaments firmly attached to the tibial plateau, and a triangle-shaped inner part accommodating well the femoral condyles. They have also been attributed the role of providing nutrition to the articular cartilage and participating to the joint lubrication process [Fox 2012].

Biochemically, the menisci are composed primarily of water (70%), a complex matrix of collagen fibres (22%) and various glycosaminoglycans (GAG, 6%), DNA fibres (2%), glycoproteins (<1%) and elastin (<1%) [Fox 2012]. Each meniscus can be separated circumferentially into three zones called the white-white (innermost), the white-red (middle) and the red-red (outermost) zone [Makris 2011]. The red-red zone is the most vascularised zone and the one with the strongest ability to heal (see Fig. 2.2(a)). The cross-section of the meniscus can be further split into three different layers based on the organisation of the collagen fibres (Fig. 2.2(b)) [Petersen 1998]. In the deeper layer (layer (*3*)), the fibres are oriented circumferentially (i.e., parallel to the periphery) which allows transfer and spread of longitudinal compression loads into circumferential hoop stresses [Fox 2012]. Sparse radial fibres are intertwined within the circumferential fibres to provide better structural integrity (arrowheads in Fig. 2.2(b)). In the superficial layer (layer (*1*)), thin fibres are intertwined randomly to create a smooth surface resembling cartilage that lowers friction between the menisci and adjacent structures during joint motion. The fibres of the lamellar layer (layer (*2*)) are oriented more radially to maintain the shape and structural integrity of the menisci under stress.

2.1.4 Anterior and Posterior Cruciate Ligaments

The ACL and the PCL are two intracapsular ligaments situated between the femur and the tibia (Fig. 2.1(d)). The ACL originates anteriorly from the intercondylar eminence of the tibia, runs upward and is attached to the inner-posterior aspect of the lateral femoral condyle [Flandry 2011]. Typically, the ACL in adults is between 26mm - 38mm long, the average width is 11mm and its length changes by less than 2.5mm during flexion/extension of the knee joint [Goldblatt 2003]. Structurally, it is composed of two bundles called the anteromedial and posterolateral bundles which are arranged parallel at full knee extension and twisted at increasing levels of knee flexion. The main function of the ACL is to resist forces exerted by the knee joint to prevent the tibia from sliding excessively forward with regards to the femur, to provide rotational stability and restrain varus, valgus motion² and hyperextension of the knee joint [Goldblatt 2003, Bonasia 2011].

Running crossways with the ACL, the PCL originates from the posterior intercondylar eminence of the tibia and is attached to the inner-anterior medial femoral condyle. The PCL averages approximately 38mm in length and 13mm in width and is separated into two bundles called the anterolateral and the posteromedial bundles [Goldblatt 2003]. These bundles provide most of the restraining forces (95%) to posterior translation of the tibia with regards to the femur and, similarly to the ACL, provide secondary restraint to varus, valgus stress and external rotation [Goldblatt 2003, Bonasia 2011].

Both the ACL and PCL are composed primarily of type I collagen (90%) and approximately 10% type III.

2.1.5 Other Important Knee Structures

The knee joint possesses additional ligaments that are not central to this research and as such they will only be briefly described in this section as their location within the knee joint may have a secondary influence on the performance of the image-processing algorithms presented in this thesis.

The patellar tendon (or quadriceps tendon) attaches the quadriceps muscles to the patella bone. It allows extension of the knee joint by applying pulling forces from the quadriceps onto the patella. The patellar tendon continues down the patella as a ligament and is attached to the anterior portion of the tibial tuberosity. The patella is also connected to the femur and the tibia medially and laterally through the patellofemoral ligaments and the patellotibial ligaments (which together are commonly

²Varus/Valgus: motion resulting in an increased or decreased distance between the femur and the tibia in the medial or lateral compartment.



Figure 2.3: Additional important structures of the knee. (a) shows the tibial-plateau of the knee joint as visualised in the transversal plane. It shows the knee menisci as well of the meniscomeniscal and the collateral ligaments. (b) shows the ligaments involved in the patella biomechanics, including the patellar tendon and ligament, as well as the medial and lateral retinaculum (medial and lateral patello-tibial ligament and patellofemoral ligaments). (a) is adapted without permissions from [Pagnani 1995, Greis 2002]. (b) is adapted without permission from [Flandry 2011].

referred to as the medial and lateral retinaculum). The tendon and the three ligaments keep the patella bone in a firm position and guide the trajectory along the femoral trochlear groove during flexion and extension of the knee articulation.

The medial and lateral collateral ligaments extend from the medial and lateral aspects of the femoral condyles and are attached to the tibia and the fibula respectively. The medial collateral ligament, as it runs through the side of the knee capsule, attaches itself to the medial meniscus, reducing its movement and increasing risks of injury. Both ligaments provide support to the extended knee joint and have a role of stabiliser, restraining lateral or rotational motions between the femur and the tibia.

The transverse (or meniscomeniscal) ligament connects the anterior horns of the MM and LM and prevents excessive anterior-posterior extrusion of the horns with regards to the tibia. The *Humphrey* and *Wrisberg* ligaments (also called anterior and posterior meniscofemoral ligaments) originate from the posterior horn of the lateral meniscus and are attached to the inner surface of medial condyle of the femur. They run upward anteriorly and posteriorly to the PCL and may play a minor role in secondary restrain of posterior tibial translation (especially suspected after rupture of the PCL).

The anatomy and physiology of these important structures can be observed in Fig. 2.3.

2.2 Basic Kinematics of the Knee Joint

The knee joint is the most complex joint of the human MSK system. Comparatively to other joints, the distance between the articulating bones is larger, allowing more degrees of freedom of movement, and multiple ligaments and fibrocartilaginous structures are involved in the motion. The joint can be separated into two separate articulations: (1) the patellofemoral articulation between the femur and the patella, and (2) the tibiofemoral articulation between the femur and the fibrace on the description of the basic kinematic characteristics of these two articulations. Qualitative descriptions of the biomechanics will be provided rather than quantitative analyses of the forces involved in the motion, which go beyond the scope of this thesis.

2.2.1 The PatelloFemoral Joint

The patellofemoral articulation can be classified as a 'saddle' type of joint (or sellar joint). During knee flexion and extension, the convex shape of the posterior surface of the patella (see Fig. 2.4(a)) slides along the concave shape of the trochlear groove of the femur under the pulling, restraining and reaction forces of the quadriceps and hamstring muscles and ligaments, the medial and lateral retinaculum (Figure 2.3(b)) and the anatomical constraints provided by the shape of the bones and cartilages. Throughout knee flexion, the patella undergoes a lateral shift and a slight longitudinal rotation (called patellar tilt, $12 - 15^{\circ}$) that displaces the medial facet posteriorly in comparison to the lateral facet.

At full extension, the patella is not always in contact with the trochlear groove. Contact may occur between $10 - 20^{\circ}$ of knee flexion depending on the length of the patellar tendon. Initial contact occurs with the inferior surface of the patellar cartilage and moves upward during flexion. Under $60 - 75^{\circ}$ of knee flexion, the contact area is shaped as a long band extending from the margin of the medial facet of the patella to that of the lateral facet. When the flexion reaches roughly 90° , the contact area splits into two regions as the patella is in contact with both the medial and the lateral condyles of the femur, separated by the deep intercondylar fossa (Fig. 2.4(b & c)). In deep knee, flexion the lateral condyle of the femur is nearly fully covered while the patella is barely in contact with the inner aspect of the medial condyle as a result of the lateral shift and tilt of the patella [Schindler 2011, Andrish 2015].

Functionally, the patellofemoral articulation is commonly referred to as the extensor mechanism of the knee joint. When contracting, the quadriceps muscles will apply pulling forces onto the patella



Figure 2.4: Important factors involved patellofemoral kinematics. (a) shows different posterior shapes commonly exhibited by the patella bone, with the medial and lateral facets marked as M and L. (b) shows the interaction of the patella with the trochlear groove of the femur under 90° and over 90°. (c) shows the contact-areas between the patella and femur at various degrees of knee flexion (the patella is displayed in a flipped position to show the contact area). (a & b) are adapted from [Andrish 2015] without permission and (c) is adapted without permissions from [Schindler 2011].

bone through the tendon and onto the tibia through the patellar ligament. By increasing the moment arm of the tendon-ligament complex (i.e., distance from the axis of rotation of the knee joint), the patella enhances the quadriceps extensor mechanisms. Acting as a lever, the presence of the patella allows flexion and extension of the knee with a lesser amount of forces from the quadriceps muscles (up to 50% less reported in the literature [Schindler 2011, Andrish 2015]). The patella also prevents dislocation of the extensor mechanism by guiding the trajectory of the patellar tendon and ligament along the trochlear groove of the femur.

2.2.2 The tibiofemoral Joint

The tibio femoral joint can be further divided into two condyloid articulations. The medial and lateral femoral condyles form hinge-like articulations with the medial and the lateral plateaus of the tibia. The primary angular motion of the tibiofemoral joint is flexion-extension around the femoral condyles and in the sagittal plane. It is accompanied, to a lesser extent, by secondary motion including internal and external rotations of the tibia and the femur as well as varus and valgus motion. The approximate range of knee flexion involved in various daily activities is provided in Table. 2.1. For ease of interpretation,



Figure 2.5: (a) shows the projection of the condyle centroids onto the tibial plateaus. This illustrates the roll back of the femur on the tibia to allow for a larger range of motion. (b) shows the trajectory of the centroid of the contact area between the femur and the tibia across a 120° knee flexion. (c) illustrates the posterior displacement of the contact areas between the femur and the tibia throughout flexion. (a) is adapted without permission from [Scarvell 2004] and (b) and (c) are adapted without permissions from [Bingham 2008].

the following description will consider the tibia bone fixed, with the femur moving relative to the tibia (somewhat comparable to the motion occurring during a squatting exercise).

The axis of rotation for flexion and extension of the knee can be simplified as the axis passing through the centre of the spherical medial and lateral condyles of the femur. From 0° to approximately 30° the femoral condyles simply roll onto the medial and lateral tibial plateaus, displacing the contact areas between the femoral cartilage and the medial and lateral tibial cartilages posteriorly (Fig. 2.5(a)). Considering the smaller articular surface of the tibia comparatively to that of the femur, if rolling was the only motion occurring, the femur would run out of tibial space to roll onto early during the knee flexion and the range of motion would be strongly limited. Therefore, after $25 - 30^{\circ}$ of knee flexion, simultaneous rolling and anterior gliding of the femur onto the tibial plateaus occur to compensate for the posterior displacement. The anteroposterior translation of the femur with respect to the tibia then becomes negligible (illustrated in Fig. 2.5(a), where the centroids of the femoral condyles does not translate posteriorly after 30°). This gliding motion is permitted by the intervention of the ACL, PCL and to some extent that of the knee menisci [Scarvell 2004].

During flexion, posterior rolling of the femur onto the tibia will create a tension in the ACL which will then resist posterior translation. During extension, the anterior rolling of the femur onto the tibia will tense the PCL, and the resistance of the ligament will limit anterior translation onto the tibial plateau. While the knee menisci slightly deform during flexion, the strong attachment of their roots



 Table 2.1: Range of (angular) motion of the knee for different activities.

Figure 2.6: Classification and illustration of the different types of tears commonly found in meniscus injury. Adapted without permission from [Wadhwa 2016].

onto the tibia and their tensile strength contributes and provides further resistance to anterior and posterior translation by conferring an *uphill* anatomy for the femur to roll onto during flexion and extension.

2.3 Knee Malfunction, Degeneration and Disorders

The knee health can be altered acutely by trauma or chronically through degenerative disorders such as OA. The health of the knee can also be compromised by an imbalance that may impact upon normal biomechanics and increases the focal stress on the articular cartilage. Such imbalance can be a consequence of an acute injury or simply caused by a muscle, tendon or ligament weakness. In this section, we will shortly review several of the most common injuries and disorders affecting knee which have had an impact or motivated the present research.

2.3.1 Meniscal Tear

Meniscal tears are among the most common injuries of the knee and may be the consequence of an acute trauma (very common in sports) or degenerative processes (myxoid degeneration) [Wadhwa 2016]. Considering the vascularisation of the menisci (i.e., only the periphery of the menisci us is supplied with blood), only tears situated in the outer third circumferential portion of the menisci have the potential to heal. The ability to heal will also differ between individuals and with age. As illustrated in Fig. 2.6, Meniscal tears can be classified into different categories based on their morphology: transversal (or horizontal), radial and longitudinal. A tear can be small, large or complex and can create a meniscus *flap* or *handle*. A flap occurs when a small portion of the meniscus becomes loose and is displaced from its original position. The flap is usually unstable and can move more or less freely. In some cases, a complex longitudinal tear can create a handle shape within the meniscus, in which case the tear is called a bucket-handle tear.

The crucial function of the menisci in knee biomechanics has been presented in section 2.1.3 and 2.2.2. Meniscal tear, by altering the organisation and integrity of the collagen fibres, will result in altered biomechanics of the knee. A torn meniscus will have less ability to resist compression loads and spread weights on a larger articular cartilage surface. The increased focal stress on the cartilage may result in the apparition of micro-lesions and activate the maladaptive immune response involved in knee OA. Overall, a loss of integrity of the extra-cellular matrix of the menisci has been indicated as a strong determinant within the multi-factorial aetiology of knee OA [Hunter 2006, Englund 2009].

Symptoms of a meniscus tear include pain (as the structure is innervated circumferentially in the vascular region [Mine 2000]), swelling, loss of range of motion and sensation of locking or that the knee 'gives-way'. After physical examination by a physician and elimination of other possible causes of knee pain using X-ray imaging, a meniscus tear is usually diagnosed using MR imaging. The reported sensitivity of MR imaging (spin-echo pulse sequence, see section 2.4.2) in the detection of meniscal tears varied between the MM and the LM and between studies but ranged between 72–93% [Nikolaou 2008, Chambers 2010, Subhas 2012]. When the cause of pain is not identified using MR imaging, arthroscopic surgery³ is performed and may detect a small meniscal tear.

Fifty years ago, total meniscectomy (i.e., complete removal of the meniscus from the knee) was the best solution to treat a meniscal injury. However, considering the consequences of a missing meniscus on the subsequent health of the articular cartilage and the knee joint in general [Fairbank 1948],

³Arthroscopy/Arthroscopic surgery: small incision and insertion of an endoscope to capture images

recent treatment techniques opted for solutions more conservative of the meniscus tissue. Partial meniscectomy has been commonly used as an alternative to total meniscectomy; however, current strategies involve maintaining the meniscus tissue intact and repairing the lesions when possible [Makris 2011, Turman 2008]. Significant research on tissue transplant and regeneration is also underway to replace damaged tissue instead [Makris 2011]. Often the best treatment strategy is influenced by the location and size of the tear. A small tear in the red zone of the meniscus may not require surgery and heal with rest. A large tear in the same zone will require surgery and often heal well. A tear extending to the red-white zone has less ability to heal and surgery may not work. Finally for a tear situated completely within the red-white or white zone, repair is not usually performed and partial meniscectomy of the damaged zone is preferred.

2.3.2 ACL and PCL Injuries

Rupture or tearing of a cruciate ligament is another very common type of knee injury. In acute form, injuries usually occur as a result of a knee trauma (sport injury or car accident) while they are found in chronic form in the knee of patients with OA [Hill 2005]. Clinically, ligament injuries are classified into grades, such that in *grade I* the fibres are elongated (loose ligament) without tear, in *grade II* the fibres are partially torn, in *grade III* the ligament is ruptured and finally in *grade IV* both the ACL and the PCL are ruptured. The ACL and PCL will rarely be partially torn and the majority of acute injuries entail complete rupture.

Symptoms of a cruciate ligament injury include pain on the outside and back of the knee, swelling, limited range of movement, instability of the knee and the feeling that joint can 'give-out' at times. The ACL is more often injured than the PCL. Acute injuries can be diagnosed with X-ray if the ligament tore off a piece of bone at the time of injury, although MR imaging provides a more reliable means to detect partial tears. A high sensitivity (ranging from 86-100%) has been reported for the detection of acute injuries [Kam 2010, Crawford 2007, Razak 2015], but chronic injuries are still problematic to diagnose and arthroscopy remains the gold standard for detection of subtle degenerations [Servant 2004].

Injury to a cruciate ligament is not always treated surgically and the choice usually depends on the level of activity of the patient and the type of injury [Buss 1995]. If surgery is required, ligament reconstruction (i.e., replacement of the ligament with a graft) is usually performed over repair due to the poor healing capacity of the ACL and the PCL [Howe 1991, Johnson 1992]. Recent advances in tis-



Figure 2.7: Illustration of differences in patella tracking in patients with and without PFPS. *(left)* shows the patellar tilt, as measured by the angle around the patellar longitudinal axis. *(middle)* shows the patellar spin about the anterior-posterior axis. *(right)* shows the lateral subluxation (shift) of the patella in the medial-lateral direction. In the proposed graphs, * and ** show two-way analysis of variance group differences (condition × flexion angle) with p < 0.05 and p < 0.01, respectively. Adapted without permission from [Wilson 2009b].

sue engineering and regenerative medicine have however renewed interest in repair techniques, which may provide opportunities to conserve normal ligament function [Kiapour 2014]. This is important as a loss of normal intra-articular knee ligament function (especially the ACL) has been associated with frequent secondary injury to other knee structures and development of knee OA [Hill 2005].

2.3.3 Patellofemoral Pain Syndrome

Patellofemoral pain syndrome (PFPS) is another common knee problem encountered by clinicians which accounts for 30% of all injuries reported in sport clinics and 10%-20% of all lower-extremity injuries [DeHaven 1986, LaBella 2004]. Besides blunt trauma, abnormal tracking of the patella bone can cause patellofemoral pain. It occurs when the patella strays away from the trochlear groove of the femur during knee flexion. It has been shown to alter contact mechanisms in the patellofemoral joint and to increase joint stress by reducing the surface area of contact between the patellar and femoral cartilages (increased focal stress) [Heino 2002].

The aetiology and pathogenesis of PFPS is not well understood and multiple predisposing factors have been proposed, including muscle weakness, overuse, excessive weight, genetic predisposition or abnormal bone alignment (e.g., inward, outward or backward bowing of the leg, differing leg-length, external tibial torsion or lateral position of the tibial tubercle where the patellar ligament is attached), although many patients may not show any apparent reason [Kannus 1999, LaBella 2004].

Symptoms include cracking, grating or catching of the knee and anterior knee pain (where the patella and the femur meet) that tends to get worse with exercise or prolonged sitting. The most common diagnosis of PFPS is physical examination [Post 1999]. Standard X-ray and MR imaging are useful to rule out other possible sources of knee pain but provide little addition to physical ex-



Figure 2.8: X-ray image of a right knee *(left)* without radiographic signs of OA, *(middle)* with severe lateral compartment tibiofemoral OA and *(right)* with severe medial compatment tibiofemoral OA. Green arrows point out the areas with reduced joint space width caused by cartilage loss and meniscus extrusion, and the yellow arrows point out subchondral bone deformations (osteophytes).

aminations. Alternatively, MR imaging of joint motion has shown good sensitivity in determining excessive patellar tilt and lateral shift (characteristic features of PFPS, see Fig. 2.7), and could potentially improve diagnoses [Witoński 1999]. Unfortunately, kinematic MR imaging is tailored to specific acquisition setups and is still experimental.

The treatment of PFPS is highly dependent on the factors causing pain and it is therefore paramount to accurately identify the origin of the syndrome. Non-surgical treatment (e.g., physical therapy, muscle strengthening, orthopaedic insoles, knee brace) has been shown to be effective for 75% to 84% of the patients [LaBella 2004]. When conservative approaches fail, arthroscopy may provide insights on the causes of pain and surgery such as ligament reconstruction or release may be performed.

The association between PFPS and increased risks of patellofemoral OA development is still being debated [Thomas 2010]. However, it is hypothesised that individuals suffering from PFPS may exhibit higher levels of focal stress on the patellar and femoral articular cartilages which may accelerate cartilage wear and activate the maladaptive repair responses involved in knee OA.

2.3.4 Knee Osteoarthritis

Osteoarthritis is the most common degenerative knee condition and alters the whole knee joint including the bones, cartilages, ligaments and muscles. OA affects mainly the elderly population (over 65 years) although it can be found in younger individuals. The *Australian Institute of Health and Welfare* has reported that one in thirteen Australian suffers from OA (1.8 million) and the cost associated with OA was estimated at 1.6 billion Australian dollars [AIHW 2016]. Symptoms differ between individuals and the affected joint, but for the knee, it will commonly be associated with pain, stiffness, swelling and a limited range of motion. Overall, OA disrupts the normal function of the knee and can be very debilitating.

Knee OA is characterised by the gradual loss of articular cartilage, stiffening and deformation of subchondral bone tissue (e.g., formation of bone osteophytes) and tearing of intra-articular soft-tissues, especially the knee menisci, ACL and PCL. A strong research focus of knee OA has been on cartilage loss and it has been extensively utilised for clinical diagnosis and assessment of disease progression. Although the aetiology of osteoarthritis is still unclear, known risk factors for the development of this degenerative joint disease include genetic predisposition (primary OA), and increased mechanical stress on the joint as a result of excess weight, repetitive loading tasks, abnormal joint alignment and injury to important biomechanical structures of the knee such as the ACL, PCL and the menisci (secondary OA).

Traditional diagnosis involves the acquisition of an X-ray for a patient seeking medical advice following knee pain and the identification of biomarkers of knee OA such as joint space narrowing⁴ (JSN) or osteophytes. In particular, in clinics and research into knee OA, the severity and progression of the disorder is usually assessed using semi-quantitative grades such as medial and lateral JSN scores or composite grades such as the well accepted Kellgren & Lawrence (K/L) grade [Kellgren 1957]. A description of the composite K/L grading system is provided in Table 2.2. This system is used throughout this thesis to characterise the severity of knee OA (or a composite grade very similar) and will be referred to as radiographic OA (rOA). X-ray images from a normal and two pathological knee joints are provided in Fig. 2.8.

MR imaging is likely a more sensitive technique for early detection and precise tracking of the degeneration pathways of OA. It allows imaging of all the soft-tissue structures of the knee including the articular cartilage and thus provides opportunities to evaluate cartilage loss with great precision. It can also detect anomalies commonly associated with OA of the knee joints, including synovitis, bone marrow lesions and meniscus or ligament tears.

There is currently no treatment to stop of the progression of the OA. Current strategies to lessen the burden of knee OA include pain management, weight loss, reduction of the loads applied on the affected joint as well as physical therapy to maintain joint mobility and strengthen the muscles respon-

⁴Joint space narrowing: reduction of the space between the femur and the tibia

Grade	Diagnostic	Condition
0	no rOA	No radiographic features of OA are present
Ι	possible rOA	Possible signs of JSN and osteophytic lipping
II	mild rOA	Definite osteophytes and possible JSN
III	moderate rOA	Multiple osteophytes, definite JSN, sclerosis
IV	severe rOA	Large osteophytes, advanced JSN, severe sclerosis

Table 2.2: Kellgren & Lawrence grading system for knee rOA [Kellgren 1957]

sible for joint stability (i.e., minimise the impact of abnormal biomechanics). In the case of advanced knee OA, total knee arthroplasty may be required to reduce the pain and disability.

As OA develops over a decade, early detection currently provides the best opportunity to delay the onset of the symptoms through management plans and physical therapy [Chu 2012]. Accurate quantitative analysis of cartilage morphology from MR images could provide useful information on subtle changes in cartilage thickness prior to the onset of the symptoms. Newer biochemical MR imaging sequences measuring water content and collagen content and organisation (e.g., T_2 -, $T_{1\rho}$ mapping) may also provide a sensitive means to detect the molecular changes occurring within the soft-tissues of the knee joint such as the menisci prior to irreversible tissue damage.

2.4 Magnetic Resonance Imaging of the Human Knee Joint

2.4.1 Introduction

Non-invasive structural imaging of the knee has played an increasingly important role in the prevention, diagnosis and treatment of common knee injuries and disorders. Three imaging modalities, including radiography (or X-Ray), computed tomography (CT) and MR imaging have stood out as suitable and variably sensitive means to assess the origin of knee pain and injuries. Of these three imaging modalities, MR imaging is the most promising technology to study and diagnose the knee joint. In comparison to X-ray and CT imaging, MR imaging has several advantages, including multiplanar capabilities (i.e., 3D imaging with flexible slice orientation), no exposition to ionising radiations and excellent soft-tissue contrast for the whole knee joint, including articular cartilages, cruciate ligaments and menisci.

Although conventional MR imaging of the knee joint is often sufficient to assess the most common anomalies and their likely origin, several subtle disorders or acute pains are more easily diagnosed in



Figure 2.9: Sagittal MR image of a left knee $(0.365 \times 0.365 \times 0.699mm, 384 \times 384 \times 160)$. From left to right, the knee is observed in the sagittal, coronal and axial plane. MR image from the Osteoarthritis Initiative (OAI) [Peterfy 2008].

motion. Therefore, there has been a growing interest in the assessment of knee motion from kinematic MR imaging technologies (i.e., acquisition of the images of the knee joint in motion). These can be useful for the detection of various anomalies related to knee malfunction including knee snapping (jerky movements of the knee during flexion originating from an hypermobility of the medial meniscus, lesions in the ACL or PCL or patellar instability), the detection of a small meniscal tear (i.e., apposed edges separating under stress during flexion), PFPS, and joint locking or stiffness resulting from a malfunctioning meniscus or cruciate ligament.

In the following paragraphs, a review of MR imaging is provided. The basic principles of conventional MR imaging are first detailed, followed by a description of the MR pulse sequences commonly utilised to diagnose and study the knee joint. An introduction to dynamic MR imaging is finally presented.

2.4.2 Conventional Magnetic Resonance Imaging

2.4.2.1 Basic Principles of MR Imaging

MR imaging is a cross-sectional imaging modality relying on the *nuclear magnetic moment* of atom nuclei. The magnetic moment of an atom nucleus originates from the spin of the protons which induces a magnetic field. Under the presence of a strong homogeneous magnetic field B_0 , these moments (referred to as spins) will be randomly reoriented in the same $(spin + \frac{1}{2})$ or opposite $(spin - \frac{1}{2})$ direction as B_0 and start to "wobble" at a frequency defined by $\omega_0 = B_0 \times \gamma$, where γ is the gyromagnetic ratio of the atom. The cumulative magnetic field strength created by the spins, known as the net magnetisation vector (NMV) (i.e., difference in number of $+\frac{1}{2}$ spins and $-\frac{1}{2}$ spins), then generates a detectable MR signal. In this state, the spins are *in-phase* and at *equilibrium*.

By applying a brief radio-frequency (RF) pulse B_1 , the NMV can be "pushed away" from the direction of B_0 . In an ideal MR system, when the B_1 pulse is switched off, the NMV then returns to equilibrium through two relaxation processes, each taking place at different speed. T_1 -relaxation (spin-lattice or longitudinal relaxation) is the time required for the NMV to realign with B_0 . T_2 -relaxation (spin-spin or transversal relaxation) relates to the dephasing of the spins with respect to each other. As a result of B_0 field inhomogeneity, which increases the rate of dephasing, the effective T_2 measured (T_2^*) is usually much faster than the theoretical T_2 .

The MR scanner can then measure an MR signal using a receiver coil. This MR signal has an intensity proportional to the number of protons participating in the creation of this signal (a parameter called proton-density (PD)) and dependant of the T_1 and T_2 properties of the tissues imaged. MR imaging aims at measuring these parameters using the atom of hydrogen (¹*H*). A careful weighting of T_1 , T_2 and PD allows to achieve high contrast between the different tissues of the knee joint. In order to weight these tissue characteristics, the MR pulse sequences used to image the knee joint need to be parametrised carefully using the echo-time (T_E), the repetition-time (T_R) and the flip angle. T_E corresponds to the time between the RF pulse B_1 and the signal echo (resulting from the application of a refocusing RF pulse in spin-echo and gradients sequences of different polarity in gradient-echo sequences). T_R corresponds the time between application of consecutive B_1 RF pulses. The flip angle corresponds to the amount of rotation applied by the RF pulse to the NMV.

Longitudinal magnetisation regains equilibrium faster in fat than water, and a difference in relaxation can be detected with a short T_R . This difference cannot be detected with long T_R . Therefore, T_R relates to T_1 and affects intensity in T_1 -weighted MR images. When the T_E is long the difference in T_2 decay can be detected, which is not the case at short T_E . T_E thus relates to T_2 affects signal intensity in T_2 -weighted MR images. When T_1 and T_2 cannot be detected (i.e., long T_R and short T_E), the signal measured is mainly affected by the quantity of protons participating in the MR signal, thus PD-weighting is achieved.

The localisation of the MR signal received is detected using orthogonal magnetic field gradients. The slice-selection gradient defines the target area of the RF pulse excitation. The phase-encoding gradient gradually shifts the phase of the spinning protons to allow the MR scanner to detect and encode the variable phase of the spins. Finally, the frequency-encoding gradient (or readout gradient) gradually shifts the frequency of the spins in a direction orthogonal to the slice- and phase-encoding gradients. As the MR scanner has knowledge of the amplitude and direction of the slice-, phase-and frequency-encoding gradients, it can calculate the precise location and amplitude of the received

signal. When received, these raw information are stored in the *k-space* matrix and the final image is obtain by applying a Fourier transform to the k-space matrix.

2.4.2.2 MR Pulse Sequences

MR imaging usually involves a compromise between spatial resolution, signal to noise ratio (SNR), contrast to noise ratio (CNR) and acquisition time. There exist many MR pulse sequences that have been designed to optimise image contrast and enhance the visibility of important tissues or pathologies. MR pulse sequences are constituted of a series of wave forms (RF pulse and gradients) that generate different tissue response. In MR imaging of the knee joint, the pulse sequence is usually optimised to improve contrast between the knee bone, cartilage, menisci and ligament tissues and increase the homogeneity of the intensity within the structures. In the presented research, both spin-echo and gradient-echo (GRE) MR sequences were utilised to study the knee joint. The following paragraphs provide a brief overview of the pulse sequences and measurement techniques developed for visualisation, diagnosis and quantification of the knee joint, with a focus on the MR sequences used in this PhD research. A listing of these MR sequences and their major characteristics is provided in Table 2.3.

Spin-echo sequences

These pulse sequences use a 90° B_1 RF pulse to flip the NMV into the transverse plane. As B_1 is turned off, T_1 - and T_2 -relaxations begin. A single or multiple 180° pulses then refocus the transverse magnetisation at a time $\frac{1}{2}T_E$ and generate spin-echoes at $t_k = k \times T_E$, $k \in \mathbb{N}$ [Brown 1999, Bitar 2006]. The parameters of the spin-echo MR sequences used to obtain variable tissue contrast are the number of refocusing pulses and phase-encoding gradients.

Single-echo spin-echo – As illustrated in Fig. 2.10 (top-left) single-echo spin-echo MR sequences utilise an initial 90° RF pulse and a single 180° refocusing pulse per cycle. The RF pulses are generated in the presence of a slice excitation gradient of fixed amplitude throughout cycles, and although the phase-encoding gradient amplitude varies for each cycle, a single amplitude is used per RF excitation pulse. The echo generated by the refocusing pulse is read in the presence of a readout gradient of fixed amplitude throughout the cycles. Single-echo spin-echo MR sequences are commonly used to generate T_1 -weighted MR images using short T_R and T_E .



Figure 2.10: MR pulse sequence diagrams for the *(top-left)* single-echo spin-echo MR sequence, *(top-right)* multi-echo spin-echo MR sequence and *(bottom-right)* Echo-train spin-echo MR sequence (e.g., 3D-Turbo-spin-echo). This Figure is adapted without permission from [Brown 1999].



Figure 2.11: MR pulse sequence diagrams for the *(top-left)* FLASH, *(top-right)* FISP, *(bottom-left)* PSIF and *(bottom-left)* TrueFisp MR sequence. This Figure is adapted without permission from [Chavhan 2008].

Multi-echo spin-echo – Multi-echo spin-echo MR pulse sequences utilise several 180° refocusing pulses applied at time $k \times \frac{1}{2}T_E$, $k \in \mathbb{N}$ to generate an equal number of spin-echoes per cycle at times $k \times T_E$, $k \in \mathbb{N}$ (Fig. 2.10 *(top-right)*). The pulse sequence has to be repeated as many times as the image has lines and each line is characterised by a different phase-encoding gradient amplitude and a fixed T_E . Multi-echo spin-echo MR sequences commonly utilise a long T_R (to allow complete T_1 relaxation) and are used to create T_2 -weighted images (long T_E) or intermediary-weighted MR images (short T_E).

Turbo spin-echo – Turbo spin-echo (TSE), also known as fast spin-echo or echo-train spin-echo is a pulse sequence characterised by an initial B_1 pulse followed by a set of rapidly applied 180° refocusing pulses that create multiple spin-echoes (Fig. 2.10 (*bottom-right*)). The series of echoes is called the echo-train and the number of applied refocusing pulses is the echo-train length (or turbo factor). Multiple spin-echoes are detected per cycle, each with a different phase-encoding gradient amplitude, which allows to fill multiple lines of the k-space per cycle. The time required to acquire an image is therefore reduced by a factor roughly equal to the echo-train length. As the echo-train length increases, the acquisition time decreases but so does the SNR as refocusing RF pulses do not affect T_2 dephasing and the NMV amplitude decreases. The echo-train length is thus limited by T_2 decay and long echo-trains will result in T_2 blurring.

2D-TSE MR imaging with intermediary-, PD- or T_2 -weighting is the most common pulse sequence used in clinics to diagnose pathologies in soft-tissues such as ligaments, menisci or articular cartilages [Cheung 1997, Bredella 1999, Sonin 2002, Kijowski 2009]. Typical images are characterised by a high in-plane resolution and a large slice-thickness which limits accuracy in the detection of small lesions and the achievable accuracy in quantification of small structures. Acquisition of newer isotropic 3D-TSE MR images (SPACE: sampling perfection with application-optimised contrasts using different flip angle evolutions) as a replacement to 2D-TSE is an avenue to solve this limitation [Glaser 2015]. The typical appearance of the knee joint in a 3D-TSE MR image is illustrated in Fig. 2.12.

Gradient-echo sequences

GRE sequences do not use 180° refocusing pulses and instead use gradients of opposite polarity to dephase and rephase transverse net-magnetisation, generating a detectable gradient-echo. The absence of refocusing pulses allows the use of shorter T_R and faster acquisitions. Because shorter T_R will not



Figure 2.12: From *left* to *right* shows a sagittal 3D WE-DESS $(0.4 \times 0.4 \times 0.7\text{mm})$, FS 3D-TSE $(0.5 \times 0.5 \times 0.6\text{mm})$, FS 3D-TrueFisp $(0.4 \times 0.4 \times 1.5\text{mm})$ and FS 3D-FLASH $(0.3 \times 0.3 \times 1.5\text{mm})$ MR image acquired for the same subject. Acquisition time for MR images was 8:51 minutes, 7:56 minutes, 6:25 minutes and 10:16 minutes, respectively.

Table 2.3: Characteristics, advantages and shortcomings of common MR imaging pulse sequences.

	Characteristics	Shortcomings		
	— Spin-echo —			
	Fast acquisition	Image blurring with long echo-train Flow artifacts		
	Versatile contrast (T_1, T_2, PD)			
TSE / FSE	True T_2 weighting			
	Decrease in chemical shift artifacts			
	Decrease in magnetic susceptibility signal loss			
	Sensitive to collagen content/organisation	Long acquisition time		
T_2 mapping	Sensitive to contagen content organisation	Less sensitive to PG content than $T_{1\rho}$		
		Low spatial-resolution		
T. manning	Sensitive to GAG and PG content	Long acquisition time		
$1_{1\rho}$ mapping	More sensitive than T_2 in detection of degeneration	Low spatial-resolution		
	— Gradient-echo —			
	T_1 weighting	Low cartilage/synovial-fluid contrast		
FI ASH / SPGR	Bright & homogeneous cartilage signal	Low meniscus/cartilages contrast		
	Excellent cartilage morphology	Low overall meniscus contrast		
	Excellent bone-cartilage interface	Moderate acquisition-time		
	T_1 and T_2^* weighting			
	Bright synovial fluid signal	Signal inhomogeneity within cartilage Long acquisition time		
DESS	Intermediate cartilage signal			
	Good cartilage/synovial-fluid contrast			
	Moderate overall meniscus contrast			
	Bright cartilage	Increased T^* weighting		
	Good bone/cartilage interface	Magnetic susceptibility artifacts		
FISP / GRASS	Dark menisci with good contrast	Gradient inhomogeneity artifacts Signal inhomogeneity within cartilage		
	Fast acquisition			
	Motion insensitivity (TrueFisp)			

permit complete T_1 recovery, GRE sequences usually utilise smaller flip angles α (< 90°) to partially flip the NMV onto the transverse plane.

The repeated RF pulse will result in a decrease of longitudinal magnetisation until the steady-state magnetisation is reached. In this context, a lower flip angle α guarantees a reasonable longitudinal component of the NMV throughout the cycles. The steady-state magnetisation characterises the strength of the measured signal and is affected by the tissue T_1 , T_R and the flip angle α . Basic GRE sequences are thus T_1 -weighted (when $T_R >> T_2$).

GRE sequences are categorised into coherent and incoherent sequences. Coherent sequences use acquisition in the *steady-state*, meaning that T_R is shorter than both the T_1 and T_2 of the tissues. Transverse magnetisation does not decay and only T_2^* occurs. After several cycles, a steady-state of equilibrium is achieved, with constant magnitudes of longitudinal and transverse magnetisation. Two types of signals are then produced, the first one arising from the free induction decay (FID) of the most recent RF pulse (mixed T_1 and T_2^* weighting) and the second one arising from echo reformation prior to excitation (heavy T_2 weighting).

Fast Low Angle Shot (FLASH) – FLASH (Fig. 2.11(a)) is an incoherent GRE sequence that utilises RF or gradient spoiling to destroy the steady-state and remove any remaining transverse magnetisation by removing phase coherence, thereby producing T_1 or PD weighting. The sequence provides a means to achieve high T_1 contrast with short T_R while maintaining reasonable SNR. T_1 weighting is achieved with a short T_R and T_E and a large flip angle, while *PD*-weighting is achieved using small flip angle. As illustrated in Fig. 2.12, FLASH MR images feature bright and homogeneous intensity within the cartilage, excellent cartilage morphology and good demarcation with the bones. There is however low contrast between the menisci and the cartilage and the acquisition time is long.

FISP, PSIF and True-FISP – Fast Imaging with Steady Precession (FISP) is a coherent GRE sequence that utilises a refocusing gradient along the phase-encoding axis (phase rewinder) to maintain residual transverse magnetisation (Fig. 2.11(b)), increasing T_2^* -weighting. It is a postexcitation refocused steady-state sequence that measures the FID part of the signal produced in the steady state. FISP has an overall good demarcation between the knee bones, cartilages and menisci and a fast acquisition time. FISP has good motion insensitivity but is prone magnetic susceptibility and gradient inhomogeneity artifacts.

PSIF is a time-reversed FISP and a pre-excitation refocused steady-state sequence. It is used to collect the echo-like component of the signal rather than the FID-like signal. As such PSIF measures

 T_2 rather than T_2^* (Fig. 2.11(c)).

True-Fisp is a FISP that uses balanced gradients⁵ along all three axes. The balanced gradients refocus both FID and echo-like signal components at the centre of the T_R interval as a single echo (Fig. 2.11(d)). In the True Fisp MR sequence, both the FID-like and echo-like signal produced are used for image formation. The contrast in the image is dependent of the ratio T_2/T_1 . A TrueFISP MR image is shown in Fig. 2.12.

Dual Echo Steady State (DESS) – DESS is a variation of the True-FISP [Hardy 1996, Eckstein 2006]. It utilises the FID-like signal measured by the FISP and the echo-like signal measured by the PSIF in separate acquisition periods (T_{E1} for FISP, T_{E2} for PSIF) to create the MR image. Both the phase and slice-encoding gradients are balanced to maintain the transverse component of the steady-state and the readout-gradient is extended to allow for echo formation and acquisition of both FISP and PSIF. The heavy T_2 -weighting from the PSIF allows to obtain bright intensity of cartilage and fluid with low SNR, while the signal FISP provides a high SNR. The signal in the DESS MR image is averaged voxel-wise from the two signals. DESS provides bright synovial fluid intensity, moderate cartilage intensity, good contrast between the knee bone and cartilage and moderate contrast between the menisci and surrounding tissues. However, it suffers from long acquisition times and inhomogeneities within the cartilage and menisci.

2.4.2.3 Fat Suppression Techniques

Fat suppression (FS) is a technique that aims at suppressing the signal from fat to enhance the signal from other non fatty tissues [Del Grande 2014]. It is usually used to optimise dynamic range of tissue intensity in the MR image and to limit chemical shift artifacts in GRE sequences. There are three techniques commonly used to suppress fat signal from MR images, fat-saturation, water excitation and inversion recovery. In the images obtained or acquired for this work, fat-saturation and water-excitation were utilised and will be described below.

Fat-saturation involves applying a RF pulse at the beginning of the sequence followed by spoiler gradient that shifts the net magnetisation of fat in order to obtain zero longitudinal magnetisation, allowing for signal suppression. This process is sensitive to magnetic field inhomogeneities and incomplete fat-suppression may result (i.e., no saturation of the resonance frequency of fat creating very bright fat tissue).

⁵Balanced gradient: net dephasing induced by gradients over a T_R interval is zero



Figure 2.13: The top row shows a T_2 -map generated for a healthy individual (left) and an individual at risk of knee OA development (right). The bottom row shows T_2 -maps generated for the meniscus of individuals with increasing grades of degeneration. Adapted without permission from [Baum 2013] (top) and [Zarins 2010] (bottom)

Water-excitation (WE) is another means to achieve FS in MR images. This technique involves flipping the net magnetisation of water nuclei (only) onto the transverse plane. This is achieved using two RF pulses. The first causes both fat and water magnetisation vectors be tipped partially towards the transverse plane. Fat and water protons will then precess at different frequencies and once the fat and water magnetisation are 180° out of phase, a second non-selective RF-pulse will cancel the the signal from fat (i.e., re-alignment of the magnetisation vector of fat with B_0) while rotating the water NMV further towards the transverse plane.

2.4.2.4 Measuring T_2 and $T_{1\rho}$ Relaxation

T_2 mapping

The rate of T_2 relaxation is largely influenced by the amount of free water molecules in the tissues imaged. T_2 relaxation results in an exponential decay of the transverse component of the NMV. In imaging of the knee joint, T_2 mapping is commonly utilised to measure water content (and water mobility, which is suggested to be affected by the organisation of the collagen matrix and proteoglycan [Zarins 2010]) in cartilaginous structures. In healthy structures, water molecules are trapped within the extracellular matrix and signal intensity in T_2 weighted images is low. In degenerative structures, loss of integrity of the extracellular matrix decreases permeability, resulting in an increase in T_2 relaxation time. Illustrations of T_2 -mapping performed for the cartilage and the meniscus are shown in Fig. 2.13. T_2 mapping typically involves acquiring several T_2 weighted multi-echo spin-echo MR images using a different T_{E_i} for each image *i*. The T_2 -map is then generated by fitting the signal intensity function $S_i = S_0 e^{\frac{-T_{E_i}}{T_2}}$ to the imaging data. In $S_i(t)$, $S_0 = \rho(1 - e^{\frac{-T_R}{T_1}})$ (with ρ proton-density) and since T_{E_i} and $S_i(t)$ are known, S_0 and T_2 can be estimated using a linear least squares fit or a non-linear fit.

$T_{1\rho}$ mapping

 $T_{1\rho}$ relaxation refers to the T_1 relaxation in the rotating frame. It reflects the interactions between water molecules and their local macromolecular environment (especially GAG and proteoglycan content). In particular, the water protons situated in the vicinity of GAG or proteoglycan molecules will be characterised by faster spin-lattice relaxation times in the rotating frame than free water. $T_{1\rho}$ quantitative values are therefore believed to be inversely correlated with PG or GAG content. It could be useful to monitor PG loss in fibrocartilages, an early biomarker of degeneration associated with knee OA.

In $T_{1\rho}$ imaging, the net-magnetisation is first flipped onto the transverse plane and a long B_1 RF pulse (spin lock) is applied parallel to the net magnetisation vector. This pulse will cause $T_{1\rho}$ -relaxation for the duration of the spin lock (T_{SL}) . In a similar way to T_2 -mapping, $T_{1\rho}$ -mapping involves acquiring several $T_{1\rho}$ -weighted images with variable T_{SL_i} . Voxel-wise fitting of the monoexponential decay model is then performed using the function $S_i = S_0 e^{\frac{-T_{SL_i}}{T_2}}$.

 T_2 - and $T_{1\rho}$ -mapping are important for quantitative assessment of the biochemical changes occurring within cartilaginous structure in chronic injuries or early OA and to study overall tissue health and integrity [Zarins 2010, Wilson 2016].

2.4.2.5 Benefits and Shortcomings of MR Imaging

Because signal intensity in MR images is related to the water content of the knee structures, MR imaging has the tremendous advantage of naturally achieving high-contrast between internal tissues without use of contrast agents. Specialised MR pulse sequences can be designed and parametrised to naturally enhance or suppress the signal received from an anatomy of interest or a pathologies. The cross-sectional nature of MR imaging is also a significant advantage, as it allows to "slice" through the anatomy using any desired plane (i.e., flexible orientation of the slices), providing a high-resolution 3D representation of the anatomy. This is important for imaging of the knee joint where the soft-tissues are millimetre thin.

Using these properties of MR imaging, it is possible to:

- Qualitatively assess and diagnose all the structures of the knee joint;
- Extract precise quantitative measurements of the morphology of the soft-tissue structures *in-vivo*;
- Assess the structural integrity of the soft-tissues using T_2 and $T_{1\rho}$ -mapping, which reflect the content or organisation of the collagen matrix.

Recent advances in MR imaging technologies and coil designs have allowed to image patients at high- and ultra-high field strengths (>1.5 Tesla (T)). This considerably reduced acquisition time for all MR sequences while providing a significant increase in SNR, CNR and spatial-resolution. MR imaging at high-field strengths allows to non-invasively look "inside" the tissues of the knee joint, thereby providing opportunities for precise diagnosis of pathologies and early detection of disorders such as OA [Roemer 2012].

An additional considerable advantage of MR imaging over conventional radiography relates to the safety of the patient. MR imaging does not expose patients to ionising radiations and there is currently no contraindication to MR imaging. It is thus suitable to image women during pregnancy and children.

Although MR imaging processes major benefits to study the knee joint, there are still limitations that need to be considered. MR imaging remains an expensive procedure (double the price of a CT and ten times the price of an X-ray) and the most optimised MR pulse sequences currently cannot be utilised in clinical settings due to prohibitively long acquisition times. MR imaging is also prone to artifacts (presented below) which may be more or less obvious in the final image depending on the pulse sequence, magnetic field inhomogeneities and the patient. Finally, it is not always suitable to image patients with metal body-implants such as defibrillator, pacemaker or brain clips due to high magnetic field strengths.

2.4.2.6 MR Imaging Artifacts

Several types of artifacts can occur during MR imaging that may affect the overall quality of the image and the accuracy of diagnoses. They can be separated into patient specific artifacts (e.g., motion, metallic implants) and hardware imperfections (e.g., magnetic field inhomogeneity). This section will provide a short overview of the most common artifacts that will be encountered in the MR images processed in the work of this PhD thesis.



Figure 2.14: (a) Shows a TrueFisp MR image of the knee joint with a strong bias field due to RF inhomogeneity (bottom left of the MR image). (b) shows a TrueFisp MR image with motion artifacts (ghosts of femoral cartilage, distortions at the front of the tibia). (c) shows a TrueFisp MR image with strong B_0 inhomogeneity artifacts.

Motion Artifact – Major physiological movements from a patient (lasting from milliseconds to seconds in duration) can cause either ghosts or blurring in the phase-encoding direction. This is illustrated in Fig. 2.14(a,b) where the femoral cartilage of the knee is visible at multiple positions (ghosts) within the image as a result of knee motion during acquisition.

Black Boundary – Black boundary artifacts occur in GRE sequences when the T_E selected causes the spins of water and fat situated in the same voxel to cancel each other (i.e., no transverse component). It is usually characterised by black bands appearing between adjacent structures high on fat and water content, respectively.

Chemical Shift – In MR imaging, association between the signal received and spatial position is performed using frequency-encoding. If both water and fat protons, which have slightly different precessional frequency, belong to the same voxel, mismapping of the position may occur as the system will consider that either the signal from fat or water seem to arise from a slightly shifted location. In the image, it is usually characterised by a structure that appears to be sliding.

RF Inhomogeneity – RF inhomogeneity will result in undesired variations in signal intensity across an image (usually signal drop-off at the edges of the image). It can be caused by either a nonuniform B1 field or a nonuniform sensitivity in a phased array receive-only coil (or can be influenced by the distance of the structures from the coil elements).

B0 Inhomogeneity – The homogeneity of B_0 impacts upon the Larmor frequency at which the protons precess and the linearity of the gradients used for spatial encoding. Large inhomogeneities can usually

be reduced using shimming⁶, however, other inhomogeneities will cause signal loss, banding artifacts, distortions and reduced efficacy of FS.

Partial Volume Effect (PVE) – PVE arises from the size of the voxel over which the signal is averaged. It occurs when two types of tissue with different magnetic susceptibility are contained within the same voxel and both contribute to the signal received by the scanner. This will result in a weaker signal intensity in the final image. It is more pronounced in MR images that feature low spatial resolution.

Wraparound Artifact – This MR artifact is caused by a mismapping of parts of an anatomy imaged that lies outside of the field of view within the slice volume. It usually occurs when the anatomy imaged is not fully contained within the selected field of view and is instead warped on the opposite side of the image.

Magic Angle – The magic angle artifact occurs in soft-tissues such as tendons, ligaments and cartilages when the angle formed by the well-ordered collagen fibres and the magnetic field B_0 is roughly equal to 54.7°. At this angle, the dipolar interactions exerted on the protons of the water molecules bound to the fibres is minimised. This results in increased T_2 and signal intensity within these tissues.

2.4.3 Dynamic Magnetic Resonance Imaging

Dynamic imaging, involving the "real-time" acquisition of images of the knee joint in motion, is challenging to acquire as a result of the trade-offs necessary to obtain sufficiently sampled data in the temporal domain. Recent advances in imaging hardware designs (open bore, open coil) and acquisition modalities, providing considerable speed-ups of structural imaging techniques, allowed to acquire numerous "snap-shots" of the internal body structures at a relatively close time-interval. As a complementary tool to traditional anatomical diagnoses, analyses of knee joint kinematics can be crucial in the assessment of several pathologies not easily observable in static MR images of the patient [Komistek 2005], to characterise pre- and post-operative joint motion [Blemker 2007], in the design of bone prostheses [Carpenter 2009] or in the investigation of knee joint kinematics and loading mechanisms in healthy and pathological individuals.

The acquisition of 2D or 3D images of the knee joint in active motion and in real-time with MR imaging is currently challenging as a result of the trade-offs in SNR, CNR and spatial-resolution required to acquire sevral images within seconds. It also requires special hardware (open or deformable

⁶Shimming: Use of currents directed through coils to correct magnetic field inhomogeneities

knee coils) that do not provide optimal magnetic field homogeneity and increase imaging artifacts. In this section, an overview of the MR imaging techniques used to image the moving knee joint in real-time and to study knee kinematics is provided.

Cine MR imaging

Cine MR imaging utilises periodical motion in order to acquire a sequence of 2D (or 3D) MR images representing the position of the structure of interest at different points in the cycle. The beginning of the cycle is known by the scanner (motion triggered) and one line of the k-space will be repetitively acquired until the next cycle begins, at which point the second line is acquired. Once the k-space is fully sampled, the alignment of all the cycles acquired provides the information necessary to create an image slice at various points in the cycle. The maximum temporal resolution is therefore controlled by the sampling of one line of the k-space (i.e., defined by the T_R) [Glover 1988]. Cine MR imaging is commonly utilised to study cardiac motion [Hernandez 1993].

This technique is advantageous as it can theoretically acquire 3D MR images of joint motion; however, numerous cycles are necessary to obtain the final image. This is not well suited in MSK applications as repeating cycles periodically is difficult and the individual imaged may tire or be in pain while moving.

Cine Phase Contrast MR imaging

Cine phase contrast (CPC) MR imaging is a dynamic technique that allows the acquisition of a series of MR images (2D) combined with 3D velocity fields for each voxel within the image [Sheehan 1998]. It is a combination of Cine MR imaging and phase-contrast imaging, which is flow sensitive. Phase-contrast pulse sequences utilise phase-shift in order to identify moving spins (in terms of spatial location). Two sequential bipolar gradients are used to encode the velocity of the spins, and moving spins will experience a different gradient magnitude between the first and the second gradient (i.e., their position changed). This results in a phase-shift, which can be utilised to determine the velocity of the spins. CPC MR imaging has the advantage of capturing the real 3D velocity of the structures, and as such has the potential for very accurate subsequent analyses [Borotikar 2012]. However, motion cycles are once again required.

Real-time MR imaging

Comparatively more complex and challenging to develop, real-time dynamic MR imaging using ultrafast GRE sequences is another means to study active knee kinematics from MR images. To reduce acquisition time, reduction of the T_R and improved sampling of the k-space (e.g., sparse or using temporal correlations [Tsao 2003]) can be utilised to acquire fast gradient echo sequences with acceptable temporal resolution (e.g., coherent TrueFISP, FLASH).

For dynamic MR imaging of the knee joint, earliest developments include *Muhle et al.*, who reported a multi-slices gradient-echo acquisition sequence requiring 7 seconds (on a 1.5T ACS II, Philips Medical System) per slice, allowing acquisition of 4 slices at 8 time-points in 28 seconds (FOV: $180mm^2$, thickness: 7mm) [Muhle 1995]. Later, *Quick et al.* utilised echo sharing to improve the temporal resolution of real-time TrueFisp MR sequences, allowing the acquisition of 2D MR images of active MSK joints at six frames per second (FPS) $(1.0 \times 2 \times 6mm)$ [Quick 2002]. More recently *Draper et al.* [Draper 2008] published an interesting feasibility study on the use and accuracy of real-time MR imaging at 1.5T on a standard scanner and at 0.5T on an open-bore scanner. They acquired dynamic images of the knee joints at a rate of 12FPS (FOV: $200mm^2$, in-plane resolution: $1.8mm^2$, thickness: 4.7mm) and 6 FPS (FOV: $160mm^2$, in-plane resolution: $1.9mm^2$, thickness: 5.0mm).

Real time dynamic MR imaging has the advantage of not requiring motions cycles.

2.5 Medical Image Segmentation

The segmentation of anatomical structures in medical images is a challenging process that is often influenced by noise in the images and the overall complexity of the textural information. It is an important prerequisite to many applications related to accurate visualisation and quantification of the internal body structures, which may help clinicians, radiologists and research scientists to diagnose or understand common pathologies. The process of segmenting medical images is a labelling process. It involves assigning a similar label value to all the voxels belonging to an anatomy of interest in the image. The final label image is called the segmentation (also referred to as segmentation mask or segmentation label). Multiple structures can be segmented in one image by assigning a unique label to each anatomy. The domain of application of medical image segmentation is vast and ranges from the detection of pathologies, the visualisation of structures and the quantitative analysis of important anatomies.

The aim of this section is to provide general background information on the field of medical image segmentation to the unfamiliar reader, without focusing on a specific anatomy. The literature review related to the segmentation of the meniscus and PCL from MR images is provided in details in Chapter 3. Here, the major techniques, namely manual segmentation, semi-automated segmentation and fully-automated segmentation are presented sequentially, and the "general algorithms" utilised in automated medical image segmentation are briefly introduced and referenced. These techniques are used throughout the thesis and combined into processing pipelines.

2.5.1 Manual Segmentation

The most common image segmentation technique used in clinical research is currently manual segmentation. This typically requires for an expert operator to manually delineate the outline the structure of interest in each slice of the image volume using an interactive pen displays and a contouring software such as *ITK-Snap* [Yushkevich 2006] or *Mimics* (Materialize Inc., Plymouth, MI). In practice, manual segmentation is a very time- and expertise-intensive process, with an effort involved proportional to the resolution of the image. Considering the recent advances in imaging hardware and sequences, which allow acquisition of highly detailed anatomical information, the process can become a major burden. Manual segmentation is also very subjective and prone to misinterpretations by the observer as a result of the noise in the image, the lack of contrast, partial volume effects and imaging artifacts. This limits reproducibility of the segmentation and can lead to low inter- and intra-observer reliability in the resulting segmentation.

2.5.2 Semi-Automated Segmentation

Semi-automated segmentation methods provide means to save time and reduce the bias introduced by the observer in the segmentation process. They involve incorporating a variably heavy amount of expert knowledge into a software solution to guide the segmentation task. The manual interaction usually tackles the most challenging aspects of the segmentation and guide the software in areas of low contrast or pathology, where the anatomy is not well defined. This segmentation approach is frequently used in clinical studies as it allows expert control on the segmentation while reducing the amount of manual work.

A drawback of semi-automated methods is that they usually require training period during which an experienced observer or radiologist needs to provide instructions on the use of the system and
feedback on the resulting segmentation volumes. That has been reported to take up to a week, while mobilising time from several investigators [Rauscher 2008].

2.5.3 Automated Segmentation

The development of image-processing software to perform automated segmentation of medical images has been a topic of significant research. Fully automated segmentation methods provide a means to efficiently analyse the imaging data while removing the need for manual input. They can facilitate medical diagnoses and clinical research into pathologies by providing reproducible *in-vivo* quantitative measurements of the human anatomy. The aim of this section is to provide an overview of the major classes of algorithms utilised to automatically segment medical images.

The major concern with automated segmentation algorithms relates to precision, and achieving a level of accuracy equivalent to that of manual segmentations is very challenging.

In general it is difficult to design an automated method that will provide optimal segmentation accuracy for all cases, especially if a pathology is involved. The major challenges involved in reproducible and accurate segmentations include image imperfections (partial volume effect, spatial resolution, artifacts, overall contrast) and the population variability in shape and appearance of the anatomy of interest in the image. For these reasons, the development of automated segmentation algorithms for medical images is a consistently growing field. The most common algorithms developed utilise various features of the images and the geometry of the anatomy of interest to obtain the segmentation. The methods can be straightforward and directly process the image by considering the voxel intensity only, but advanced method usually rely on atlases or statistical models to perform the segmentation. In most cases, a robust automated segmentation methods combine these different classes of algorithms into a hybrid method that will provide the most optimal result.

Voxel intensity based segmentation

Voxel intensity based segmentation algorithms are classic methods that purely rely on the image features directly characterising or surrounding each voxel. That includes operations such as thresholding, region-growing, edge extraction, morphological operations (e.g., dilation, erosion, hole filling) or voxel classification.

• Global or local thresholding operations, which involve excluding from the segmentation all the voxels outside of a given intensity range, are commonly used to process X-ray or CT images in

which the contrast between the structure of interest and other structures is very obvious. The thresholds are chosen based training and observations or automatically identified using intensity distributions (e.g., fitting a Gaussian to the image histogram) [Sezgin 2004, Zhang 2010a, Petrou 2010].

- Region growing methods typically start from labelled seed points and propagate a segmentation to neighbouring voxels based on a connectivity and intensity criteria [Adams 1994, Bae 2009]. The procedure is terminated when no voxel surrounding the current segmentation satisfies the constraints or when a stopping criterion is met (e.g., maximum number of iterations or size of the current label). These methods are popular for semi-automated procedures where a seed-point can be manually identified, although they can be utilised in automated schemes by automatic labelling of the initial seeds.
- Edge detection algorithms apply a filter such as a gradient or Laplacian filter to the image in order to identify a strong intensity difference between adjacent voxels [Canny 1986]. These areas typically identify the boundary between different structures in the MR image and the voxels enclosed within the same edge can be labelled as belonging to the same region.

The major drawback of these classic algorithms is that they are very sensitive to noise or signal inhomogeneity (e.g., B_0 or B_1 inhomogeneity artifacts or hyper-intense area caused by a pathology), which are very common in MR imaging. By themselves these algorithms are usually not robust enough to accurately segment MR images.

Atlas (or registration) based segmentation

As their name indicates, atlas-based segmentation techniques utilise a single or multiple atlases with manual segmentations as reference knowledge to segment new images more or less similar to that of the atlas [Rohlfing 2004, Wang 2013]. They usually require some form of registration to import the knowledge of the atlas into the image to segment. Image registration is the process of alignment of two images acquired at different time, using different modalities or from different subjects. The registration algorithm tries to find a transform T that maps the points of the moving image I_m into the fixed image I_f in order to obtain a voxel-wise correspondence between the two images. The transformation is optimised using a similarity metric in such a way that the intensity similarity (*resp.* difference) between the transformed image $T(I_m)$ and the fixed image is maximised (*resp.* minimised). Sum of squares difference (SSD) and cross-correlation are the most commonly utilised similarity metrics

to register images with similar contrast and mutual information (MI, that minimises joint entropy) is preferred for multi-modal registration. Depending on the transformation model, more or less deformations of I_m will be allowed (i.e., variable degrees of freedom). The more common deformation models are rigid (translation and rotation), affine (translation, scaling, rotation, shearing) and non-rigid transformations (free deformation). By allowing more deformation, non-rigid registration usually provides the best mapping between the moving and the fixed image.

Single-atlas based segmentation

Single-atlas based segmentation involves the registration of a single atlas image and corresponding expert manual segmentations onto the case to segment. The transform estimated is then propagated onto the atlas segmentation label for alignment with the fixed case image. The accuracy of this type of approach is purely dependent on how well the two images are aligned by the registration. Non-rigid registration will therefore provide more locally accurate final segmentations than affine or rigid registrations, albeit at the cost of efficiency. To improve registration results and obtain a less biased segmentation result, the atlas utilised is usually a population average image and the expert segmentation will be obtained from several experts and averaged using voting (e.g., select only the voxels segmented by 90% of the experts) [Rohlfing 2004].

Multi-atlas based segmentation

Multi-atlas based segmentation involves the registration of several (*N*) atlases incorporating manual segmentations onto the MR image to segment [Rohlfing 2004]. Once all the images are registered, all the corresponding segmentation masks are aligned with the case to segment and the final segmentation is obtained using voting. This approach will often improve on single-atlas based segmentation and non-rigid multi-atlas based segmentations have been found to generate state-of-the-art segmentation results in terms of accuracy [Heckemann 2006a, Shan 2012, Dowling 2012]. The major shortcoming of the approach is the computational burden, with *N* registrations required.

Multi-atlas patch based segmentation

Multi-atlas patch based segmentation works in a similar way as multi-atlas based segmentation, except that the process does not require the stringent non-rigid registration of the atlases onto the case to segment (I_f) and instead rely on simple linear registrations (e.g., rigid, affine). For each voxel of I_f , a patch will be extracted and compared to patches extracted in a cubic neighbourhood in all the

approximately aligned atlases. The similarity between patches is calculated using metrics such as SSD or normalised mutual information (NMI). The similarity between patches is then used to performed robust weighted label fusion, which will ultimately output the label of the current voxel. This method is more efficient than multi-altas based segmentation and has shown to provide equivalent results in terms of accuracy [Coupé 2011, Pant 2015]. The accuracy of the final segmentation is mostly influenced by the atlas size, the patch size and the size of the search space (i.e., cubic neighbourhood).

Model based segmentation

Model-based segmentation methods rely on deformable models to identify the edges of the structure of interest in the image. The deformation is driven by external forces which are typically image features and by internal forces that constrain the deformation and prevent unlikely segmentation shapes (e.g., limit in shape variability provided by statistical shape model). Internal forces are provided by prior knowledge integrated into the model. Once the model is deformed, the voxels contained within the resulting shape are identified as the segmentation label. This segmentation approach is built upon the assumption that the anatomy to segment has a repetitive form and that the variability exhibited can be described statistically. Examples of existing model-based segmentations include active shape and appearance models [Cootes 1995], active contours [Kass 1988] and level-set [Malladi 1995] based methods. An advantage of model based methods over others is the robustness in obtaining coherent segmentation for structure with missing boundaries and the flexibility in choosing the deformation criteria.

Literature Review

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The first part of this chapter presents a literature review on the current methods utilised in clinical studies for quantitative analyses of the knee menisci from magnetic resonance (MR) images. This focuses on the typical quantitative parameters investigated and their measurement accuracy and reliability. A review of the previous methods developed to segment the knee menisci from MR images is then provided. A review is then provided for the posterior cruciate ligament (PCL) of the knee. The final portion of the chapter reviews the previous work on MR based quantification of human knee kinematics. Throughout this literature, the limitations from previous studies are examined and used to motivate the current research. A summary of the key points is provided as the end of each section.

3.1 Analysis of the Knee Menisci from MR Images

In the previous chapter, it was shown that MR imaging was well suited to diagnose and assess the whole knee joint, including the menisci. In this section, the importance of studying the morphology and biochemistry of these fibrocartilages is first introduced. An overview of existing semi- and fully-quantitative MR analysis methods is then provided and the current limitations for efficient and reproducible analyses are examined. A review of several approaches that proposed to solve these limitations via semi- or fully-automated segmentation of the menisci is then provided.

3.1.1 Introduction

The MM and LM in MR images of knee joints with confirmed rOA are often visibly torn, macerated or substantially destructed [Bennett 2002, Chan 1991], suggesting a strong association between disorder and degeneration. Several clinical studies have reported a widespread presence of degenerative tears in the knee menisci of patients with mild rOA (K/L grade II [Kellgren 1957]) and the partial destruction or extrusion of the menisci at more advanced stages of the disorder (K/L grade IV) [Wirth 2010], with a prevalence of symptoms affecting the MM. Meniscectomy, injury or the presence of degenerative tears in the menisci, by altering normal knee function and loading mechanisms, have since been identified as strong determinants within the multifactorial aetiology of knee OA [Englund 2004, Englund 2007, Englund 2012], and overall health and proper function of the menisci are paramount for the long term health of the knee joint. The exact relationship between damaged menisci and knee OA is however not well understood and is still a significant topic of investigation.

The MM and LM of the knee joint can be damaged acutely via trauma or chronically through degenerative processes commonly associated with knee OA, or secondary to ligamentous injuries affecting normal knee biomechanics such as ACL or PCL injury (see ACL and PCL function in Section 2.1.4). Traumatic injuries often result in visible morphological alterations; however macroscopically evident changes may not be observable in the early stages of degenerative processes where biochemical alterations occur first [Zarins 2010, Juras 2014, Rauscher 2008]. In both cases, quantitative MR imaging of the meniscus can be useful for both clinical and research applications for investigation of meniscal pathophysiology.

Specifically, quantitative morphological MR image analyses of the volume, thickness and position of the meniscus can assist with routine surgery planning and follow-up [Bowers 2010, Baum 2013, Jungmann 2014, Mayerhoefer 2010] or in the identification of early morphological changes associated with OA development [Wirth 2010, Blöcker 2014]. Quantitative biochemical MR analyses such as $T_{1\rho}$ -, T_2 - and T_2^* -mapping, on the other hand, may provide clinical information regarding meniscal tissue health that can influence treatment decision and prognosis in injury states (e.g., the meniscus may have an inferior ability to heal when repaired). They may also provide a powerful tool for early detection of matrix reorganisation in early knee OA (i.e., increased water mobility), which precedes radiographic signs of OA[Rauscher 2008, Juras 2014].

The objective of this review is to provide an overview of the current methods for analyses of the meniscus of the knee joint from MR images and to highlight important clinical parameters related to

Cumulative Grade	Condition
0	All regions with grade 0
1	One region or more with grade 1
2	One region or less with grade 2
3	Two regions or more with grade 2
4	One region or more with grade 3
5	One region or less with grade 4
6	Two region or more with grade 4

Table 3.1: Cumulative grading of the meniscus using WORMS. This table is adapted from [Peterfy 2004]

degeneration of these fibrocartilaginous structures.

3.1.2 Quantitative MR Analysis of the Knee Menisci

3.1.2.1 Semi-Quantitative MR Analysis Methods

Several semi-quantitative MR analysis methods have been proposed to reliably study the knee joint and the meniscus in clinical research. These methods provide a means to standardise analyses by providing a scoring system to assess disease state and monitor progression. The grading systems are usually multi-factorial and include markers such as joint space width, bone marrow lesions or deformations, cartilage thickness and scores to measure meniscus morphology and degeneration. In this review, the focus will be on the methods utilised to score the meniscus. An interested reader may refer to *Guermazi et al.* for a recent and extensive review on semi-quantitative scoring methods for the whole knee joint [Guermazi 2013].

A well accepted semi-quantitative method to evaluate the meniscus has been introduced by *Peter-fry et al.* with the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [Peterfy 2004]. They graded separately the anterior, mid and posterior compartment of the meniscus based on the presence and overall shape of tears in FS T_2 -weighted TSE MR images. The regional scoring was as follow: 0 = intact; 1 = minor radial tear or parrot-beak tear; 2 = non displaced tear or prior surgical repair; 3 = displaced tear or partial resection, 4 = complete destruction or resection. The final grade of the meniscus was obtained by summarising the regional scores into a cumulative value as shown in Table 3.1. Intraclass correlation coefficients (ICC) for inter-observer reliability were 0.94 and 0.81 for the MM and LM. However, the method did not characterise the morphology or position of the meniscus.

The knee osteoarthritis scoring system (KOSS) has been utilised to measure meniscus subluxation (medial or lateral extrusion with regard to the tibia), intra-substance degeneration and tears from mul-

tiple MR sequences (FS PD- and T_2 -weighted dual spin echo and T_1 -weighted GRE) [Kornaat 2005]. The subluxation was scored on a [0 - 3] scale and was defined for the full meniscus structure by the amount of protrusion of the meniscus body from the tibial plateau (0 = no extrusion; 1 = <1/3 meniscus width bulging; 2 = 1/3 to 2/3 meniscus width bulging; 3 = over 2/3 meniscus width bulging). Meniscal tears were classified based on their shape such that: 1 = horizontal; 2 = vertical; 3 = radial; 4 = complex and 5 = bucket-handle tear. No distinction for tear location was made. A high-signal intensity not forming a complete tear (i.e., not extending to a margin of the meniscus) was classified as intra-substance degeneration (Boolean value). Weighted-Kappa measurements of (inter, intra) observer reproducibility were reported for meniscus extrusion (0.65, 0.82), intra-substance degeneration (0.70, 0.78) and tear gradient (0.66, 0.56). FS PD-weighted dual spin-echo MR images, showing the best overall contrast for the meniscus, were used for grading.

Berthiaume et al. utilised 3D-FISP MR images with FS to score the degenerative changes and subluxation of the meniscus and compare these measurements with cartilage loss over a 2 year longitudinal study [Berthiaume 2005]. The degeneration grade was based on the number of meniscus regions (anterior, mid and posterior) affected by signal intensity changes such that 0 = no region; 1 = 1 region; 2 = 2 regions and 3 = 3 regions were involved in degenerative changes. The subluxation was scored based on the extent of meniscal displacement such that 0 = no extrusion; 1 = partial meniscal extrusion; and 2 = complete meniscal extrusion and no contact with the joint space. The clinical investigation identified significantly more cartilage loss in patients with meniscus tears and subluxation than in patients without.

More recently, the Boston–Leeds osteoarthritis knee score (BLOKS) was developed by *Hunter* and colleagues [Hunter 2008]. They proposed to grade meniscal subluxation, signal intensity in the MR and tearing. The extrusion was scored in four regions on a [0 - 3] scale based on the amount of subluxation such that 0 = <2mm; 1 = 2-2.9mm; 2 = 3-4.9mm; 3 = >5mm. The four regions scored were the mid-compartment (extrusion calculated relative to the outermost margin of the tibia in a coronal MR image) and the anterior horns of the two menisci (assessed in a sagittal MR image). A tear in the meniscus was scored separately in the anterior, mid and posterior compartments of the MM and LM such that 1 = high signal intensity (not a tear); 2 = high signal intensity extending to an articular surface; 3 = vertical tear (includes radial and longitudinal tears); 4 = horizontal tear; 5 = complex tear; 6 = root tear (posterior horn); 7 = macerated (loss of normal morphology and increased diffuse signal in the meniscus); 8 = meniscal cyst. High intensity within the meniscus not forming a complete tear (usually synonym of a degenerative meniscus) was also scored separately per region using a Boolean

variable (absence/presence). Weighted-Kappa measurements of inter-observer reliability were 0.51, 0.68 and 0.79 for meniscus subluxation, intra-substance signal degeneration and tear scoring.

In an effort to improve all semi-quantitative methods, *Hunter et al.* proposed the *MR imaging Osteoarthritis Knee Score* (MOAKS) in 2011 [Hunter 2011]. The system used to assess the meniscus is effectively a modified BLOKS. The method used to score extrusion is identical, but several modifications were made for identification of tissue lesions and degeneration. The scale remained unchanged from 1 to 6, but the maceration score was separated into three grades, namely partial maceration, progressive partial maceration and complete maceration. A binary variable scoring meniscus volume increase (pseudo-hypertrophy) was also added. The weighted-Kappa reported for (inter, intra) observer reliability were (0.97, 1.0) and (0.66, 0.82) for scoring of the morphology and subluxation of the MM and (0.95, 0.91) and (0.79, 0.89) for the LM.

These semi-quantitative scoring methods have been used by several investigators in order to compare the morphology of the meniscus in patients with variably advanced knee OA [Am Jung 2010, Hwang 2012]. Major findings indicated that in patients with more severe rOA and medial or lateral JSN, the MM had a significantly greater volume and more subluxation [Am Jung 2010, Blöcker 2013]. Several studies have also shown that greater volume and subluxation of the meniscus were associated with regional cartilage loss [Berthiaume 2005, Hunter 2006].

To summarise, semi-quantitative scoring systems of the meniscus usually involve the measurement of signal changes within the structure and the quantification of morphological parameters including subluxation and volume (height in 2D). They have been shown to provide variable inter- and intra-observer reliability (weighted-Kappa ranging from 0.51 to 1.0) and were sufficiently sensitive to distinguish statistically significant differences in morphology across knees with distinctive grades of rOA. These methods represent the current standard in clinical studies for assessment of the meniscus and provide a standardised, well accepted and validated means to study disease biomarkers for the meniscus.

The major concern with scoring methods involves the qualitative and subjective nature of the process. MR scoring usually involves a two-step subjective decision by an experienced observer, namely the selection of a 2D slice within the MR volume and the qualitative assessment of the grade most appropriate for the visualised structure. This limits the reproducibility of measurements cross-sectionally and over-time as slice position during image acquisition is approximate and may influence the resulting visualisation of the meniscus. The process is also very tedious and requires expert knowledge



Figure 3.1: Illustration of the process utilised by *Wirth et al.* to estimate fully-quantitative parameters of the meniscus. (a) shows the manual delineations of the structures. (b) shows the radial separation of the meniscus into three regions of interest (anterior, mid and posterior regions). (c) shows the various parameters estimated by their method. Adapted without permissions from [Wirth 2010]

for reliable assessment. Using discrete scales to categorise morphology has also a limited sensitivity for detection of small changes and analysis of the progression of the disease biomarkers (sometimes, .5 grades are utilised to indicate progression). Finally, while these methods were developed as a means to standardise radiological assessments of the knee joint (and the meniscus), several "stan-dards" now exist, each incrementing on the previous methods to tailor measurements to their needs [Am Jung 2010, Hwang 2012]. This limits the reproducibility of analyses and comparison across studies. A solution to these limitations is the development of fully-quantitative MR analysis methods for the meniscus, which can provide more sensitive and comparable measurements of the morphology and degeneration of the meniscus.

3.1.2.2 Fully-Quantitative MR Analysis Methods

The earliest work on quantitative MR analysis of the meniscus was performed by *Gale et al.* in a large scale study (233 patients and 58 asymptomatic) utilising sagittal T_2 -weighted and coronal FS PD-weighted spin-echo MR images (3.0/1.0mm slice thickness/gap)[Gale 1999]. They measured the subluxation of the meniscus directly from the 2D images using an MR generated scale and by identifying the maximum distance between the periphery of the meniscus and the tibial rim. Inter-observer

ICC for measurement of medial and lateral subluxation were 0.85 and 0.76. The study reported that subluxation of the meniscus was highly associated with knee OA.

Wirth et al. measured the position, shape and signal intensity of the MM from PD-TSE MR images (2.0 mm slice-thickness) [Wirth 2010]. The superior, inferior and medial surface of the meniscus as well as the medial tibial surface were manually segmented as separate surfaces (Fig. 3.1(a)). From these segmented surfaces, multiple morphological parameters were estimated, including maximum thickness, mean/maximum width and volume of the meniscus. Several parameters describing the position of the MM were estimated, including the area of the tibial plateau covered and "uncovered" by the meniscus surface (as calculated by integration of the triangles of the surface belonging to the overlapping or non-overlapping region of the meniscus and tibial surface) and the 3D extrusion of the meniscus from the tibial outer rim (see Fig. 3.1(c) for illustration). Additional measures of signal intensity (min, max, mean and standard deviation) were estimated within meniscal tissue to characterise degeneration. These parameters were evaluated for the full meniscus and for the anterior, mid and posterior sub-regions, as illustrated in Fig. 3.1(b). The test-retest (two segmentations performed six months apart) root mean square standard deviation (RMSD) originating from manual segmentations were [0.07 - 0.34]mm, [1.99 - 2.18]mm and [60.2 - 131] mm^3 for the thickness, width and regional volume and [13.0 - 66.0] mm^2 and 0.38 - 3.1]mm for the coverage/uncoverage area and extrusion.

The method was later evaluated for inter-observer reliability in *Siorpaes et al.* [Siorpaes 2012]. In the study, they compared the reproducibility of analyses in 2D IW-TSE $(0.36 \times 0.36 \times 3.0mm)$ and in WE-DESS $(0.37 \times 0.37 \times 0.7mm)$ MR images by comparing measurements estimated from segmentations performed by three trained observers. They reported an inter-observer RMSD of [0.50-1.30]mm and [0.42 - 1.62]mm for extrusion measurements in WE-DESS and IW-TSE MR images (inclusive of both the MM and LM), respectively. For other measurements, the coefficient of variation (CV) was reported. Values within [4.33 - 9.18]% and [5.4 - 9.9]% were reported for thickness and volume measurements in WE-DESS MR images and values within [4.22 - 8.39]% and [8.39 - 10.0]% were reported for IW-TSE MR images.

Several clinical studies have used this method to compare the morphology of the MM and LM in healthy individuals [Bloecker 2011], or across groups of patients with variably advanced pain or signs of knee rOA, as measured with JSN or K/L grades [Wenger 2012, Blöcker 2013, Wenger 2013]. Results showed significantly lower tibial coverage for the MM in individuals with medial JSN [Blöcker 2013, Wenger 2013]. This was also reported for both the MM and LM in individuals with K/L grades 2 or 3. Pain was more frequent in individuals with a meniscal subluxation over 3mm for

both the MM and LM [Wenger 2012].

Hunter et al. and *Jung et al.* proposed to manually measure the extrusion and height (thickness) of the meniscus directly in multi-planar PD- and T_2 -weighted TSE MR images using an image visualisation software [Hunter 2006, Am Jung 2010]. The ICC reported by *Jung et al.* for measurement of meniscus height performed by 2 observers was 0.77 in the anterior region, 0.78 in the mid compartment and 0.81 in the posterior region. The ICC reported for measurement of the extrusion of the meniscus was 0.75 in the anterior region and 0.79 in the mid compartment.

Recent advances in MR pulse sequence design allowed Zarins et al. to study the biochemical composition of the meniscus *in-vivo* using $T_{1\rho}$ - and T_2 -mapping performed for 19 controls and 44 OA patients. They first assessed the severity of meniscus degeneration from conventional FS 2D-TSE MR images using WORMS [Peterfy 2004] and compared $T_{1\rho}$ - and T_2 -relaxation values across individuals with variably severe degeneration. Results showed that $T_{1\rho}$ and T_2 measurements were higher in the posterior horn of the MM in patients with WORMS grades > 2. $T_{1\rho}$ and T_2 tended to be higher (non-significantly) in grade 1 compared to grade 0. $T_{1\rho}$ and T_2 of the MM and LM demonstrated significant correlations with pain scores, as measured with the Western Ontario and McMaster Universities Arthritis Index (WOMAC). They suggested that elevations in relaxation measures of the MM and LM may identify individuals at increased risk for OA development.

Chu et al. utilised ultra-short TE (UTE)- T_2^* -mapping to assess the overall health of the posterior portion of the MM in ACL-deficient individuals (scheduled for surgery) and healthy controls [Chu 2014, Williams 2012]. Preoperative UTE- T_2^* in the posterior horn of the MM was 52% higher in patients with ACL injury compared to that of healthy controls. The mean UTE- T_2^* value of the intact menisci 2 years after ACL-reconstruction decreased by 17% and did not differ from uninjured controls. This suggested that UTE- T_2^* -mapping may provide useful information regarding meniscus tissue health and healing properties.

Juras and colleagues attempted to differentiate the normal, degenerative and fully torn meniscus using T_2^* -maps calculated from GRE MR images acquired with multiple echo-times using mono- or bi-exponential fit [Juras 2014]. The anterior and posterior horns of the MM and LM were manual segmented by an expert and further split into the red (outer-third) and white zone. A subset of the data was segmented by three experts. The CV for inter-observer reliability was 9.1% for the combined anterior and posterior region. The ICC reported for intra-observer reliability was 0.9. Significant differences in T_2^* -relaxation were found between normal and degenerative menisci and between normal and torn menisci. The authors concluded that changes in T_2^* values resulted from a reorganisation of the extracellular matrix of the meniscus, which involves collagen fibre re-orientation.

In summary, incremental developments of fully-quantitative MR analysis methods involved the measurement of the volume (previously measured as a Boolean grade of hypertrophy) and subluxation in 3D (i.e., independent of the slice direction) and the addition of several important parameters for assessment of normal meniscus function such as tibial coverage. These parameters have been shown to vary in patients with knee OA [Blöcker 2013] and result in pain [Wenger 2012] and cartilage loss [Hunter 2006].

Recent developments in biochemical MR sequences have allowed investigation of the molecular changes occurring within the menisci in injured or OA knees. These measurements reflect the overall collagen content and the organisation of the extra-cellular matrix of the meniscus. Quantitative measurements estimated from these MR sequences can provide information on tissue health in the injured knee [Chu 2014] and help diagnose early changes in degenerative disorders [Juras 2014].

The primary concern with fully-quantitative methods revolves around the efficient, accurate and reproducible analysis of the imaging data. The identification of the meniscus in the MR images is a prerequisite to all advanced quantitative MR methods and currently represents the major source of time loss and inter- and intra-subject variability [Siorpaes 2012]. This has, to date, prevented analysis of large cohorts and integration of quantitative MR analyses in clinics as a support to qualitative assessment of the meniscus.

3.1.3 Segmentation of the Knee Menisci from MR Images

Segmentation of the menisci from MR images is non-trivial and comes with a range of technical challenges. Depending on the MR imaging sequence involved, the segmentation task is more or less difficult and the problems differ. However, below is a list of the more common challenges to be expected in the segmentation of the knee menisci in **asymptomatic** individuals.

- In the *DESS* MR images, there is a moderate signal / tissue contrast between the menisci and the surrounding cartilage and fat tissues (Fig. 3.2);
- In the *FLASH* MR images, there is a low signal / tissue contrast between the menisci and the surrounding cartilage and fat tissues (Fig. 3.2);



Figure 3.2: Illustration of the contrast appearance of the meniscus in three different MR image sequences. From left to right SAG 3D WE-DESS ($0.36 \times 0.36 \times 0.7mm$), COR 3D WE-FLASH ($0.31 \times 1.50 \times 0.31mm$), SAG IW 2D-TSE ($0.36 \times 0.36 \times 3.0mm$) and SAG PD 3D-TSE (injured MM, $0.5 \times 0.5 \times 0.6mm$).

- MR images with a slice spacing over 1.5mm (large relative to the ~ 3 4mm circumferential thickness of the menisci) will have a partial volume effect limiting the accuracy of the segmentation (e.g., a typical clinical 2D-TSE MR image features high in-plane resolution and large slice thickness (> 3.0mm)). This can be seen in the coronal FLASH shown in Fig. 3.2;
- Low tissue contrast between the anterior horn of the LM and the ACL (insertion area with the tibia, Fig. 2.3(a));
- Low tissue contrast between the posterior horn of the MM and the PCL (insertion area with the tibia, Fig. 2.3(a));
- Signal inhomogeneity within the meniscus tissues;
- Difficult differentiation between the horns of the MM and LM and meniscomeniscal ligament (Fig. 2.3(a));

In this thesis, the major interest is the analysis of the pathological meniscus, which comes with several additional challenges. The major problems involved with the segmentation of the **pathological** structures are listed below.

- The molecular changes of the degenerative meniscus will create "inherent" signal inhomogeneity within meniscal tissue;
- Degenerative menisci are expected to suffer from hypertrophy, deformation and displacement (lateral extrusion with respect to the tibia) as a result of the loss of integrity of the extracellular matrix. This increases the shape variability of the structure;
- Tears and lesions within the meniscus will appear with a hyper-intensity similar to that of knee cartilage (Fig. 3.2(right));

- Meniscectomy or tissue loss will result in further thinning of the meniscus;
- Severe degeneration of the meniscus may cause destruction of the tissue.

The process of MR image segmentation for the menisci can be classified into three approaches: (1) manual, (2) semi-automated and (3) fully automated segmentation methods. The following sections will review previous methods for segmentation of the menisci.

3.1.3.1 Manual Segmentation

Conventional quantitative MR imaging in clinical investigations into the menisci involves deriving the morphological and biochemical parameters from manual segmentations of the structures in the MR image. To be worthwhile for quantitative analyses, the segmentation of the menisci needs to be accurate and thus requires expert knowledge from a radiologist or a trained observer. For segmentation of pathological menisci, the task becomes even more expertise dependent. In manual MR segmentation of the knee menisci, low image contrast, partial volume effect and MR artifacts are the principal sources of subjective interpretations and the major causes of segmentation errors. This can lead to high inter-observer variability and low intra-observer reproducibility [Wong 2009]. For these reasons, quantitative MR analysis of the menisci is not currently utilised in routine clinical workflows, and although it was have shown that it has recently been introduced in clinical studies (especially for investigation into knee OA), the scale of analyses was usually limited by the laborious manual segmentation process.

3.1.3.2 Semi-automated Segmentation

Previous semi-automated segmentation methods include the work from *Rauscher et al.*, who utilised Bezier-spline fitting and edge detection techniques to segment the menisci from FS FLASH MR images $(0.293 \times 0.293 \times 1.0mm)$ [Carballido-Gamio 2005, Rauscher 2008]. The method requires the manual identification of landmark points inside the meniscus that approximately followed the contour of the structure. A Bezier-curve was then fitted to the landmark points, and rays were cast in the perpendicular directions of the curve. The interface with the surrounding tissues was detected along the rays by a strong intensity gradient. The points identified along the edge were used to create updated Bezier-splines demarcating the tissue contour. This process was repeated for each slice of the MR image and a software method allowed for correction of the final position of the contour points. The semi-automated solution necessitated a one week training period with an experienced operator

and supervision from a MSK radiologist [Rauscher 2008]. The method required significant human interaction and no quantitative validation of accuracy was provided.

Hata et al. proposed a method to identify a combined MM and LM region from T_1 -FLASH MR images $(0.62 \times 0.62 \times 1.5mm)$ and T_2 -weighted MR images $(0.62 \times 0.62 \times 1.5mm)$ [Hata 2001]. The T_1 - and T_2 -weighted images were manually co-registered and a single landmark was placed within each meniscus (i.e., 1 per structure, 2 per image). An approximate meniscus region was identified as being situated between the hyper-intensive femoral and tibial cartilages. Fuzzy classifiers then identified the potential meniscus in both MR images separately and a weighted sum of the inference results was used to identify the final voxels classified as meniscus tissue. The method has the disadvantage of requiring acquisition of multiple MR sequences to perform the segmentation and no validation of accuracy was performed.

Swanson et al. implemented a semi-automated method to detect the LM in sagittal T_2 -map MR images of the knee joint (0.313 × 0.313 × 3.0mm) from 24 individuals (10 with no confirmed rOA and 14 with K/L rOA grades ≥ 2) [Swanson 2010]. The semi-automated software required for an operator to select 2 landmark points within the LM for the first and last slice to be segmented. The intensity distribution of the region surrounding the landmark points was identified by fitting multiple Gaussian distributions. Using intensity values identified from these distributions, basic thresholding was applied to identify an initial meniscus segmentation and morphological operators were used to fill holes, dilate the segmentation masks and connect small patches. The method relied on overall minimal human input and achieved a reasonable accuracy on images of the healthy and pathological knee joint, as measured with the Dice similarity index (DSI) [Dice 1945]. The mean DSI reported was 80% for the healthy LM and ranged from 75% to 64% for the LM in MR images from patients with rOA. This research focused on the LM, and an accurate segmentation for the comparatively more complex and interesting MM was not guaranteed.

The major shortcoming of semi-automated methods is that variably heavy manual interactions with the software are still required, limiting the possibility to streamline the process in routine clinical examinations or large scale studies. Most systems also require a period to train the operator and validate the accuracy of the segmentations obtained. Training has been reported to take a week and necessitates an observer familiar with the software as well as an expert radiologist for approval of the results [Rauscher 2008].

3.1.3.3 Automated Segmentation

Developing fast, accurate and robust methods to automatically analyse the menisci from MR images of the knee joint is desirable [Englund 2012] and would be a significant advance for integration of quantitative MR imaging into clinical practice. It would also facilitate current research into the meniscus and provide a powerful tool to analyse large scale longitudinal MR datasets such as the OAI or *the multicenter osteoarthritis study* (MOST) projects [Peterfy 2008, Segal 2013]. This section will provide an overview of the published methods on automated segmentation of the menisci from MR images. Considering the challenges involved in the segmentation of the menisci from MR images, completely removing all human inputs from the segmentation task is difficult. Nevertheless, several methods have been proposed and achieved varying degrees of success.

Initial efforts included the work from *Sasaki et al.*, who segmented the menisci from FS SPGR MR images using direct thresholding and fuzzy tissue classification techniques [Sasaki 1999]. They first identified the high-intensity femoral and tibial cartilages using thresholding. Vertical intensity profiles were then extracted between the cartilage plates and a fuzzy classifier utilising image intensity and weighted by the distance to the centre of the profile was used to identify meniscus tissue. Overall, the method is not suited to segment the pathological meniscus as it assumes homogeneous intensity within the structure and that the meniscus is situated between the femoral and tibial cartilage. This may not be true for the degenerative or traumatic menisci that will often feature intensity inhomogeneity (e.g., tear) and be displaced as a result of a loss tissue integrity (meniscus subluxation in knee OA). No quantitative validation was reported.

Tamez et al. segmented the menisci using a statistical region growing and splitting algorithm [Tamez-Pena 1998, Tamez-Pena 1999]. The criterion for region growing from one voxel to another was the *Mahalanobis* distance [De Maesschalck 2000] between the mean intensity (μ) and standard deviation (σ) of their surrounding region. The parameters of the region growing were automatically and adaptively estimated. The regions obtained were then split into smaller regions based on the local similarity in MR intensity. This method is well suited to segment structures with homogeneous tissue signal intensity but is not appropriate for the segmentation of the menisci in WE-DESS images or for the pathological menisci, where signal intensity often varies within the structure. The method was validated by comparing automated segmentation results with the manual segmentations from a radiologist performed in one MR image and a low spatial overlaps ($(A \cap M)/(A \cup M)$) of 59.1% and 53.73% were obtained for the MM and LM.

Ramakrishna et al. utilised a three step method to identify the menisci in sagittal T_1 -weighted images [Ramakrishna 2007]. First an arbitrary rectangular area was selected to identify the meniscus region in the 2D slices of the MR image. Then bone and cartilage tissues were thresholded out using values specifically chosen for use in their image dataset. Basic morphological operators (small object removal, width×length ratio) were used to identify the meniscus region within the thresholded image. No standard measures of segmentation accuracy were provided with the study; however, visual inspections showed that the anterior and posterior horns of the menisci were successfully identified in 39% of the cases. The method was specifically tailored for their imaging and dataset and unlikely to be generalisable.

Later, *Kose et al.* published a method relying on image-histograms and triangle shape fitting to detect the horns of the menisci from 100 sagittal MR image slices from 30 patients [Köse 2009]. They utilised edge detection and the maximum and minimum values of the vertical and horizontal histograms to locate the meniscus region, which was then further refined using coarse bone segmentations identified from the histograms. The horns of the menisci were finally identified using template matching (triangular shape). The method had the advantage of allowing the detection of pathological meniscus tissue, but is tailored to a specific MR image sequence. The method also lacked the segmentation of the meniscus body (or mid-compartment). The accuracy of the method was not validated using standard measures.

Fripp et al. proposed to fit a deformable model of the menisci to a spatially constrained region of 14 knee FS-FLASH MR images from healthy volunteers [Fripp 2009]. The knee bone and cartilage were first segmented using an automated method [Fripp 2007a]. Distance maps were generated from the cartilages and the voxels situated within 7mm of the bones were labelled as potential meniscus tissue. The intensity distribution was then estimated in this region using an expectation maximisation based gaussian mixture model. A deformable model of the knee menisci was then iteratively deformed in the image. The deformation was performed along the surface normals towards the strongest MR image gradient (i.e, edges) and constrained using probability maps. Plausible shapes were maintained by internal forces provided by a statistical shape model. The method was generic with possible application to multiple MR sequences. However, it required the segmentation of the knee cartilage, which is non-trivial for pathological knees. Identifying strong gradients as menisci edges is also unlikely to perform well on the pathological menisci, where strong gradients are introduced by tears. The method was validated on the 14 knees against manual segmentations and mean DSI values of $75\pm10\%$ and $77\pm10\%$ were reported for segmentation of the MM and LM.

Finally, *Zhang et al.* developed a method based on advanced tissue classifiers to segment a combined structure for the MM and LM in FS FLASH and FISP MR images acquired for 11 healthy volunteers [Zhang 2013]. The classifier combined an extreme learning machine and discriminative random fields to identify the menisci in the images. The discriminative random field introduced spatial constraints (distance from bone features automatically extracted) in order to improve the segmentation results and reduce the likelihood of introducing external tissues into the segmentation. The approach, trained on multiple MR sequences, has the advantage of allowing segmentation of the menisci from multiple MR modalities. They obtained robust segmentations with good accuracy (mean DSI of $81.96\pm3.34\%$ reported for the combined MM and LM structures). A shortcoming of the method is that multiple MR modalities are required to train the models.

To summarise, at this stage, only two of the published automated segmentation methods have obtained reasonable segmentation accuracy [Fripp 2007a, Zhang 2013] (as identified by a DSI over 75%). These however, were designed for the segmentation of the menisci from high-resolution FS-FLASH MR images of the healthy knee joint. The performance of these methods for the segmentation of the menisci with pathology or for the segmentation of conventional clinical MR images (multiplanar 2D-TSE MR images with overall lower spatial-resolution, SNR and CNR) is unknown.

3.1.4 Summary

In this section, a review of the current semi-quantitative and fully-quantitative MR analysis methods for the menisci has been provided. Previous studies have used MR imaging to study the morphology of the meniscus in relation with knee OA [Wirth 2010]. The volume, subluxation and tibial-coverage area of the meniscus have been established as important biomarkers of disease progression, with significant differences identified across patients with variably advanced knee OA [Wenger 2013, Blöcker 2013]. The T_2 , T_2^* , and $T_{1\rho}$ properties of the meniscus have been studied using advanced biochemical MR sequences [Zarins 2010, Chu 2012, Juras 2014]. These measurements provide information regarding the organisation and content of the extracellular matrix of the meniscus that can be useful to assess the changes occurring within the degenerative structure in early OA or post-surgery to assess healing.

Currently, there is no efficient way to perform these quantitative measurements in the MR images. The problem of automated, accurate and reproducible segmentation and analysis of the pathological menisci from MR images remains mostly unsolved. The development of an automated method to perform these segmentations is desirable. The algorithm would ideally provide robust segmentation of the menisci in both the MR sequences typically acquired in research into knee OA and routine clinical diagnosis of the menisci. This would offer a significant advance towards clinical integration of quantitative MR imaging into clinics and facilitate analyses of large scale MR cohorts. It is however important to thoroughly validate the accuracy of such an automated system and to compare segmentation and quantitative measurement outcomes to proven results from manual segmentations. This is addressed as part of *Aim 1* of this PhD thesis and presented in Chapter 4 (*aim 1.1*) and Chapter 5 (*aim 1.2*).

3.2 Analysis of the PCL from MR Images

3.2.1 Introduction

Injuries to the PCL are common in sports and car accidents. Considering the important biomechanical function of this ligament (presented in Section 2.1.4), an untreated injury to the PCL can contribute to chronic instability of the knee joint, altered biomechanics and predispose to progressive joint degeneration and knee OA [Hill 2005].

Conventional MR imaging is the current standard to diagnose the PCL clinically as it provides excellent visualisation of the ligament and allows for accurate diagnosis of acute injuries [Servant 2004]. It is however less sensitive in the assessment of chronic injuries, where the ligament may appear healthy in the MR image while it is in fact functionally deficient [Servant 2004, Tewes 1997, Wilson 2016]. *In-vivo* quantitative measurements of PCL tissue health and structural integrity would be useful in research and clinical examinations to support to visual interpretations and help in the detection of chronic degenerations that may disturb the normal function of the PCL. Segmentation of the PCL from MR sequences sensitive to the biochemical composition of the structure offers an avenue for quantitative diagnosis of the ligament both pre- and post-clinical management (e.g., surgical repair).

The use of biochemical MR sequences to study the cruciate ligaments (ACL and PCL) is relatively recent, and only a few studies have investigated the ligament *in-vivo* in preclinical animal studies and clinical research. The objective of this review is to provide a brief account of these publications and the general conclusions regarding the clinical importance and applicability of quantitative measurement of ligament health *in-vivo*.

3.2.2 Quantitative MR Analysis of the PCL

The foundation on knee ligament integrity quantification from MR images has been established by *Biercevicz et al.* in animal studies [Biercevicz 2014a, Biercevicz 2014b]. In the first study, 15 pigs underwent ligament repair (ACL) and eight of the animals received bio-enhanced repair while the others were left to heal normally (to obtain variable subsequent levels of structural integrity). Fifty-two weeks following the surgery, the knees were imaged using T_1 -weighted 3D FLASH imaging $(0.3 \times 0.3 \times 0.9 \text{mm})$ for estimation of T_2^* -maps. Tensile testing was also performed to assess structural properties of stiffness and loads of the ligaments. Statistical analyses showed that T_2^* -relaxation was strongly correlated with linear stiffness and loads of the ligament ($R^2 > 0.82$). This demonstrated the validity of T_2^* -mapping in the assessment of ligament health and function post surgery.

The goal of their second study was to improve the efficiency of T_2^* -mapping (in terms of acquisition and computational time required to generate the T_2^* -maps) for possible use in clinical settings [Biercevicz 2014b]. They generated T_2^* -maps of the PCL using (1) multi-echo voxel-wise least squares fit and (2) an efficient median ligament intensity non linear least-squares fit (single fit for the whole region). Segmentation of the PCL was performed manually in the images to calculate the median intensity of the PCL. Differences in median T_2^* values of the PCL between both methods were non-significant. This demonstrated that it was possible to acquire T_2^* -maps of the PCL in a clinically acceptable time frame (within minutes).

Recently, *Wilson et al.* measured the T_2 and T_2^* relaxation times in clinically relevant regions of the asymptomatic PCL [Wilson 2016]. The objective was to establish baseline T_2 values of the PCL for use of quantitative T_2 relaxation as a biomarker of tissue health in future assessments of acute or chronic injuries. Multi-echo spin-echo T_2 and T_2^* -maps were acquired for twenty-five asymptomatic volunteers. Manual segmentations of the PCL were performed by two orthopaedic surgeons and a MSK radiologist. T_2 and T_2^* values were estimated within the proximal, middle and distal regions the PCL and reported. The inter- and intra-observer reliability for estimation of regional PCL T_2 values was moderate to good, as demonstrated with an ICC ranging from 0.6-0.9, with the lowest value reported as 0.597.

Preliminary studies have shown that biochemical MR imaging was important to study ligament integrity and can be useful to identify the healing properties of a repaired structure. Efficient calculation of these biochemical maps can be performed within a time frame reasonable for clinical applicability.

Segmentation of the PCL from images is a prerequisite for efficient calculation of T_2 - and T_2^* -maps



Figure 3.3: Illustration of the variety of PCL shape characteristics encountered in the T_2 -map MR images. Images are viewed in the sagittal plane.

and estimation of the quantitative measurements. With current methods for segmentation of the PCL from the MR images (i.e., manual), quantitative MR imaging of the biochemical properties of the PCL cannot be utilised in clinical settings due to the prohibitively long and laborious segmentation process. Manual segmentation has been shown to provide moderate inter-observer reliability in estimation of regional quantitative T_2 -values, which may impact on the reproducibility of estimated measurements. A solution is to obtain the required segmentations automatically using efficient and robust image-processing algorithms.

3.2.3 Automated Segmentation of the PCL

To be worthwhile in clinical applications, quantitative MR analyses of the PCL require the precise segmentation of the structure in the images. The task is technically challenging for the following reasons:

- Ligament shape and visualisation in the MR image is highly dependent on joint positioning (i.e., bending of the knee will change the overall shape of the PCL);
- The PCL has similar contrast characteristics as the menisci and the contiguous ACL (bottomright image in Fig. 3.3);

• Biochemical MR sequences typically feature a low-spatial resolution, creating substantial partial volume effects that prevent the use of several segmentation techniques relying on gradient information (e.g., deformable models);

Considering these challenges, manual delineation remains the primary means to obtain reliable segmentations with good accuracy. The development of an automated method for robust segmentation of the PCL in T_2 -maps could facilitate large scale clinical studies into the PCL and provide a significant advance for integration of quantitative MR analyses of the repaired PCL into routine examinations.

The automated segmentation of the PCL in MR images has received scarce attention, and to the author's knowledge, only two methods have been published [Zarychta 2016, Uozumi 2015].

In the first study, the PCL was segmented individually in each 2D slice of T_1 -weighted MR images using a region growing based method [Zarychta 2014, Zarychta 2016]. A region of interest was first identified using fuzzy c-means clustering with median modification and the estimation of axes based upon the clustered regions (e.g., femoral shaft). A region-growing based upon fuzzy connectivity identified the PCL in this region [Eckhardt 2003]. In this method, manual placement of the initial seed point was required. No validation of accuracy was performed, and an overall failure rate of the method was identified as > 20% [Zarychta 2010] and 12% [Zarychta 2016].

In the second study, the PCL was segmented using arbitrary thresholding within a cylindrical region which was identified automatically between the attachment points of the PCL to the knee bones. The segmentation of the knee bones was obtained from a CT image [Uozumi 2013, Uozumi 2015]. No measure of accuracy was reported.

It is unfortunate that no validation of accuracy was reported in these publications. However, we argue that voxel intensity based segmentation techniques will not provide robust identification of the PCL in T_2 -maps, where tissue contrast is not always optimal with the surrounding tissues and inhomogeneity of the signal intensity is expected within the injured PCL. From the literature, it is apparent that there is a lack of well validated automated solution for the segmentation of the PCL from MR images.

3.2.4 Summary

Measurement of the structural integrity of the PCL from biochemical MR images such as T_2 - and T_2^* maps is important for the diagnosis of chronic injuries and assessment of ligament health and function post-surgery [Biercevicz 2014a, Wilson 2016]. There is currently no method to estimate these measurements accurately and efficiently from the MR images and current investigations relied on timeand expertise-intensive manual segmentations. Considering the demonstrated potential of quantitative MR imaging for the assessment of PCL integrity, it is expected that more clinical studies will be dedicated to analyses of these biomechanically important structures. An efficient and cautiously validated automated algorithms for segmentation of the PCL in the MR images would facilitate quantitative MR analyses in clinical trials and provide a significant advance towards applicability in routine examinations. This is addressed as part of *Aim 2* of this PhD thesis and detailed in Chapter 6.

3.3 Analysis of Kinematic Images of the Knee

3.3.1 Introduction

Quantitative kinematic MR imaging of the knee involves the evaluation of the different interactions between the bones and soft-tissue structures that comprise the knee joint, and the assessment of joint alignment across a specific range of motion. This is important clinically for accurate diagnosis of subtle pains occurring only while moving (e.g., PFPS, loose meniscus flap, joint dislocation or grinding), which would help in the identification of the best treatment. Kinematic imaging can also be useful in the identification of abnormal loading mechanisms resulting from a deficient or repaired ACL, PCL or meniscus, to assess subsequent risks of accelerated cartilage wear and development of knee OA. Other applications include the design of prostheses for total knee arthroplasty to study knee function post-surgery and modelling of the normal knee kinematics to evaluate the impact of altered knee kinematics on the loading mechanisms of the cartilage.

While a large body of research has been published in relation to altered knee kinematics in such pathologies [Fukubayashi 1980, Long 1996, Connolly 2009c, Hamai 2009, Wilson 2009a, Pal 2011, von Eisenhart-Rothe 2012, Freedman 2013, Pal 2013], analysing quantitatively bone trajectory and the contact mechanisms of the knee joint in motion remains challenging. The two major technical challenges relate to the data acquisition method and the efficient analysis of the large amount of imaging data generated.

Until recently, analysing knee kinematics involved capturing motion from markers placed on the skin or in-vitro using cadavers [Baratz 1986, Andriacchi 1998, Cohen 1999, Iwaki 2000, Tang 2004]. Skin markers are limited to measuring surface anatomy and lack accuracy as a result of skin mo-

tion, and measurements estimated from cadavers do not replicate the active physiological processed occurring in living subjects (e.g., muscle forces) [Reinschmidt 1997, Blemker 2007]. More recently, advances in imaging technologies offered new opportunities to study these mechanisms *invivo* [Blemker 2007, Shapiro 2012], and two major analysis methods to study knee kinematics have emerged.

The first and comparatively simple approach is to measure passive knee kinematics from volumetric images of the knee joint acquired with variable degrees of knee flexion. This has been mainly utilised to estimate 3D measurements of bone alignment and cartilage contact mechanisms of the knee joint in loaded conditions and at discrete positions. The second type of methods aims at quantifying active knee kinematics from dynamic images acquired in real-time during knee motion (flexion/extension). As we have seen in Section 2.4.3, capturing active motion using MR imaging is complex and requires numerous trade-offs in image quality and spatial-resolution to allow for a sufficient temporal sampling of the image sequence. This typically involves the acquisition of multiple 2D snapshots of the knee joint at very close time-intervals. As a result, the acquisition of complementary high-resolution MR scans is required for precise identification of the knee anatomy, which is then mapped onto the dynamic sequence to obtain function.

The objective of this review is to provide a general overview of the literature published in relation with the two common analysis schemes for *in-vivo* estimation of 3D knee kinematics from quasi-static and dynamic MR imaging technologies. The review will focus on the presentation of the clinical parameters commonly estimated from the kinematic MR images and on the methods developed for estimation. For the sake of brevity, the scope of the review will be restricted to research studies using MR imaging technologies. Major work using other imaging modalities including mono-/bi-plane fluoroscopy or dynamic CT imaging will not be covered as the analysis techniques are not transferable to MR imaging and the details entailed go beyond the scope of this thesis. An interested reader could explore these references for major work [Kubo 2007, Li 2008, Nha 2008, Bingham 2008, Bey 2008, Hamai 2009, Scarvell 2010, Nakajima 2010, Suzuki 2012, Baka 2012, Qi 2013, Muhit 2013].

3.3.2 Quasi-Static Analysis Methods

Patel et al. evaluated the feasibility of utilising MR imaging to study the normal tibiofemoral kinematics in weight bearing conditions [Patel 2004]. They acquired FLASH MR images $(0.23 \times 0.23 \times 2.0\text{mm})$ of the loaded knee joint at 5 different flexion angles for ten volunteers and



Figure 3.4: Illustration of the process utilised by *Eisenhart-Rothe et al.* for estimation of the tibiofemoral and patellofemoral kinematics from GRE MR images of the knee joint. (a) shows the measurement of the patellar tilt, (b) shows the transepicondylar axis of the femur used to calculate the position of the femur relative to the tibia, (c) and (d) show the calculated contact areas for the tibiofemoral and patello femoral articulation. Adapted without permissions from [von Eisenhart-Rothe 2004].

aimed at quantifying normal knee kinematics. For each participant dataset, the MR images were imported into the Analyse Software, co-registered with respect to the tibia and manually segmented. 3D surface models of the knee bones were then reconstructed. The femur models were registered throughout the sequence to obtain the transformation matrices describing the flexion angle, varus, valgus movements, longitudinal rotation, anterior-posterior translation and medial-lateral translation. Intra- and inter-observer CV ranged from [6.2 - 26]% for translation and rotation measurements and [3.8 - 11.4]% for of contact-areas measurements.

The reproducibility (test, re-test) of a quantitative technique for determination of 3D knee kinematics was evaluated by *Eisenhart-Rothe et al.* [von Eisenhart-Rothe 2004]. T_1 weighted 3D GRE images ($0.86 \times 0.86 \times 1.875$ mm) were acquired on an open MR system (0.2T) for ten healthy volunteers. The segmentation of the patella, tibia and femur bone was performed semi-automatically in each MR image. Bone-based coordinate systems were calculated using the principal axes of the reconstructed 3D surfaces of the bones and measurements including patellar tilt, shift contact area between the cartilages were estimated. The study showed good reproducibility, and the CV for estimation of the patellar tilt, shift and the surface area of contact between cartilages were 7.19% and 8.34%, and



Figure 3.5: Illustration of the process utilised by *Yamada et al.* for estimation of the patellofemoral kinematics from FLASH MR images of the knee joint. From left to right, illustration of the registration results, patellofemoral contact areas estimated in a healthy subject, calculation of the patellar tilt and patellar shift. Adapted without permissions from [Yamada 2007a].

8.6% (8.3% patellofemoral, 8.6% tibiofemoral). The method for calculation of the parameters for the patella is illustrated in Fig. 3.4.

In a study by *Johal et al.*, quasi-static FLASH MR images were acquired for 10 male and 2 female participants standing in an open MR scanner while performing a squat [Johal 2005]. The aim of the study was to investigate knee kinematics gender and laterality differences as well as variations in contact mechanisms between the normal and the loaded knee joint. Images were acquired from -5° to 120° of knee flexion (subjects were static during the acquisition of each MR image) and the acquisition was repeated in normal and unloaded conditions. The contact points between the femoral and tibial cartilage were evaluated in the 2D slices by fitting a circle to the femoral condyle and projecting the centre of the circle onto the tibial plateau. No gender or side differences were found in contact kinematics. The knee in weight bearing conditions showed earlier and more substantial femoral rotation over the same arc of flexion than the non-weight bearing knee.

Connolly et al. studied patellofemoral kinematics using TrueFisp MR images acquired for ten healthy and ten PFPS knee joints at 15, 30 and 45° of flexion [Connolly 2009b]. The patella and femur bones and associated cartilages were manually segmented and reconstructed as 3D surfaces. The contact areas were estimated based on the Euclidean distance between femoral and patellar cartilage surfaces and tracked via measurement of the displacement of their centroid through flexion. The study successfully identified significant differences in contact mechanisms (measured as differences in surface area and displacement) between healthy and pathological subjects.

Yamada studied patellar alignment in 12 patients with recurrent patellar dislocation and 15 healthy participants using 3D FLASH MR images ($0.8 \times 0.5 \times 3.2$ mm interpolated to 0.8 mm) acquired on a 0.5T open bore MR scanner [Yamada 2007a]. Patients laid supine in the scanner and images were acquired across a $0 - 50^{\circ}$ range of knee flexion every 10° . Knee bone and cartilage segmentation

was performed semi-automatically using a commercial software and 3D surface models were reconstructed using the marching cube algorithm. Patella, tibia and femur bone motion was estimated by registration of the MR images across the kinematic sequence using the normalised cross correlation metric. Measurements of patellar tilt, shift and patellofemoral contact areas were performed automatically using features from the bone surface (including the transepicondylar axis and mid-sagittal plane of the femur, see Fig. 3.5). Errors in motion estimations were < 0.445mm in translation and < 0.374° in rotation. Inter- and intra-observer CVs were 18.07% and 21.54% in patellar tilt, 5.79% and 6.80% in patellar shift. Relevant clinical results included a larger degree of patellar shift from 0° to 50° and smaller contact areas from 20° to 50° in patients than in healthy subjects.

Another demonstration of a typical clinical application is the work from *Carpenter et al.*, who acquired axial TSE MR images of the extended and flexed (in loading conditions) knee joints from 9 healthy volunteers and 13 patients with total knee arthroplasty in order to study patellar tilt, shift and patellofemoral contact areas and to investigate the performance of two prosthesis design in reproduction of normal knee kinematics [Carpenter 2009]. The femur was automatically identified in the images using a custom MATLAB software (not described) and the MR images were co-registered with respect to the femur using the iterative closest point (ICP) algorithm. From the aligned MR images, patellar tilt and shift were identified in the images based on manually placed bone landmarks. Significant differences were found in the resulting kinematic characteristics from both prosthesis. Although measurements were performed fully manually, this study is important to highlight the value of kinematic MR imaging in a clinical environment.

Yao et al. acquired GRE MR images $(0.27 \times 0.27 \times 1.5 \text{mm})$ of the extended and deeply flexed knee joint in 10 participants laying prone in the MR scanner [Yao 2008a, Yao 2008b]. Their aim was to quantify meniscal deformation and cartilage-meniscus contact mechanisms. The bones were manually identified in the MR images and reconstructed as point clouds. The knee motion was estimated by registering the point clouds using the ICP algorithm. Contact regions between cartilage and meniscus tissues were also manually traced and utilised to calculate surface area measurements. The displacement of these contact areas was estimated as the displacement of the centroids of the traced areas in a bone-based coordinate system. Intra-observer standard deviation for measurements of contact surface areas and displacements were 30mm^2 and 0.2 mm. The *in-vivo* data were later successfully utilised in a finite-element-modelling study that investigated the impact of the variation in knee kinematics on the contact mechanisms of the knee joint [Yao 2008b].

Chen et al. developed a method to study 3D knee kinematics from a combination of high resolution

MR images $(0.31 \times 0.31 \text{ mm}, \text{slice thickness} = 0.7 \text{ mm})$ and quasi-static MR images $(1.1 \times 1.1 \text{ mm}, \text{slice thickness/gap} = 4.5/0.5 \text{mm})$ [Chen 2010]. Manual segmentation of the knee bones was performed in all the MR images. For each volunteer, the three bony structures were aligned separately using image registration of the quasi-static MR images onto the high-resolution MR image to obtain functional knee information. The contact areas were identified in 2D in the MR images and in 3D from the surfaces and tracked throughout knee flexion. No validation of accuracy was reported and the study was purely qualitative; however, authors insisted on the importance of fully-automated analyses for the study of larger cohorts and the significance of validating these approaches in future experiments.

In a recent study, *Noehren et al.* measured the tibiofemoral and patellofemoral alignment of the knee joint during a neutral and valgus squat (30°) using GRE MR imaging (1.5mm slice-thickness) [Noehren 2012]. One aim of the research was to determine the relationship between 2D and 3D measurements of knee kinematics. Images were acquired at 0.6T on a vertical open scanner using orthogonal coils such that one coil was positioned anterior to the patella in the coronal plane and another one surrounded the knee. The patella, tibia and femur bones were manually segmented and reconstructed as 3D surfaces. The models were registered using the ICP algorithm and the external rotation and lateral patellar translation of the tibia were measured and compared to traditional 2D measurements of patellar tilt and bisect-offsets (in the axially reformatted MR images). Moderate correlations were found between 2D and 3D measurements, suggesting that measuring knee kinematics in 3D is important.

There exist other clinical studies that performed kinematic analyses of the knee joint fullymanually (e.g., [Wretenberg 2002, Scarvell 2007]). While clinical outcomes of these articles are interesting, they will not be reviewed as they add little value to this review.

To summarise, quasi-static MR studies utilised the benefits of radiation-free standard MR imaging, which allows the detailed identification of all the important functional structures of the knee, especially the knee bone and cartilage, to precisely quantify knee bone alignment (e.g., patellar tilt and lateral displacement) and cartilage contact areas. They demonstrated the importance of normal knee kinematics and highlighted the value of kinematic MR imaging in clinical assessment of the knee post-surgery or in modelling the impact of altered knee kinematics on contact mechanisms. Several research studies have however demonstrated that considerable differences exist between passive and active knee motion as a result of the missing active muscle forces applied to the joint structures [Shellock 1992, Shellock 1993, Brossmann 1993, Smith 2003, d'Entremont 2013].



Figure 3.6: Kinematic analysis pipeline developed by *Barrance et al.* (a) and *Borotikar et al.* (b). Adapted without permission from [Barrance 2005, Borotikar 2012].

3.3.3 Dynamic Analysis Methods

Analysis of the active knee joint kinematics using MR imaging technologies has been introduced by *Sheehan et al.* [Sheehan 1998]. They evaluated the accuracy of CPC MR imaging for *in-vivo* measurement of 3D bone motion. They first tracked a motion phantom in 2D purely based on velocity data provided by the CPC MR images and compared it to manual tracking of fiducial markers. They identified a mean displacement errors of 0.55 ± 0.38 mm and 0.36 ± 0.27 mm in the x and y axes. They later used the method in a pilot study to track bone motion in 18 healthy volunteers [Sheehan 1999]. Sagittal CPC MR sequences $(1.4\times1.4\times10$ mm, 1 slice, 1 frame per 84ms) were acquired while the participants performed cyclic knee flexion/extension in a prone position (35 cycles/minute). Bone motion was estimated by Fourier integration of the 3D velocity data provided by the CPC MR sequence and then converted into 3D orientation angles. The mean absolute angular errors in tracking of the patella were found to be less than $4.1 \pm 3.1\%$ in all axes.

Barrance et al. presented a method to model knee kinematics via registration of subject-specific bone surfaces and optimisation using data provided by CPC MR images (sagittal, 24×10 mm thick 2D slices) [Barrance 2005]. Bone 3D models were reconstructed from manual segmentations performed in GRE MR images (axial, FOV = 180×180 mm, matrix = 256×256 , slice thickness/grap = 1.0/1.0mm). The trajectory of the bones was then modelled from the pose of the bones estimated using the CPC data (presented in Section 2.4.3). The calculated trajectory was optimised to minimise the error between the modelled trajectory and that obtained from CPC data. The proposed pipeline is

provided in Fig. 3.6(a). Validation using a phantom with a magnetic tracking system showed a root mean squared error of 2.82mm in anterior-posterior translation and 2.63° in axial rotation. Test-retests showed root mean squared errors of 1.44mm and 2.35°. The method was later successfully utilised to investigate abnormal knee kinematics in ACL-deficient knee joints [Barrance 2006]. Significantly more anterior tibial translation and external rotation were found in ACL-injured patients compared to healthy subjects.

Draper et al. studied the feasibility of using real-time MR imaging to quantify knee joint kinematics (in 2D) [Draper 2008], and later investigated the kinematic characteristics of PFPS patients with and without patellar brace or sleeve[Draper 2009a]. In their feasibility study, they tracked a moving phantom using optical motion capture and real-time MR imaging (single slice, $1.8 \times 1.8 \times 4.7$ mm). Tracking of the centroid of the phantom yielded an accuracy within 2mm for motions slower than 217 mm/s (at 1.5T). The clinical study involved acquiring real-time MR images of the knee in active flexion/extension from 0° to 60° for 13 healthy and 23 PFPS females. Manual bony landmarks were then placed in the first frame of the sequence and identified throughout the other images using registration. Patellar tilt and shift were calculated from the bony landmarks. Significantly greater patellar shift was noted in PFPS syndrome females between 0° to 50° and significantly greater patellar tilt between 0° and 20°.

To study PFPS, *Souza et al.* acquired axial dynamic MR images of the knee joint from 15 healthy and 15 PFPS female subjects in weight bearing conditions (squatting exercise) using an open MR system equipped with a flexible transmit-receive surface knee coil [Souza 2010]. The MR sequence utilised was a fast GRE pulse sequence allowing acquisition of one 5mm thickness image slice per second. Patellar tilt, shift and rotation were manually measured at 45°, 30°, 15°, and 0° of knee flexion, and ICCs calculated for intra-observer repeatability were 0.91, 0.95, and 0.99, respectively. PFPS females demonstrated significantly greater lateral patella shift at all angles and significantly greater lateral patella tilt at below 30° of knee flexion.

Borotikar et al. validated a method to quantify the contact kinematics of the patellofemoral joint in twelve healthy subjects [Borotikar 2012]. FS 3D-GRE MR images of the knee joint were acquired for each patient in a static position. Cine-phase-contrast (CPC) (2D+t) and multi-phase-contrast (MPC) (3D+t) dynamic MR sequences were acquired while the patient actively performed knee flexion/extension cycles (30 cycles/min). 3D surface models and point-clouds of the patella and femur bones were reconstructed from the manually segmented static MR scans and in each 3D MPC images. Knee motion was estimated by (1) registering the bone 3D point-clouds from the MPC onto the 3D bone models of the knee in extended position using the ICP algorithm and (2) integrating the 2D velocity fields of the CPC data (pipeline shown in Fig. 3.6(b)). Using the CPC-identified knee kinematics as reference, the average absolute error ranged between [0.60 - 1.36]mm in medial, superior and posterior translation, and between $[0.40 - 2.41]^{\circ}$ for rotation of the patella and femur. Only qualitative analysis results of contact analyses were provided.

D'Entremont et al. compared the kinematic descriptors of the knee joint in active motion and 'passive motion' using three different kinematic MR methods to image ten volunteers, namely standard quasi-static (2D-TSE, 16 slices), fast quasi-static (ultra fast GRE, 8 slices) and dynamic MR imaging (ultrafast gradient echo, 8 slices) [d'Entremont 2013]. An additional high-resolution 2D-TSE MR image was also acquired in unloaded conditions for manual segmentation and accurate 3D modelling of the bone anatomy. Surfaces of the bones were also manually identified in each of the low-resolution sets (standard, fast, dynamic) and the various motions were estimated by registering the high-resolution bone models onto those reconstructed in the kinematic MR sequences. Mixed linear models were used to compare descriptors of knee kinematics estimated from the dynamic and quasi-static MR sequences. These showed significant differences in patellar flexion, tilt, and lateral shift and in tibial abduction, tibial internal rotation and anterior translation (p < 0.5). This indicates active and passive knee kinematics are significantly different.

Finally, *Lin et al.* investigated a slice-to-volume region methods for identification of knee kinematics from a high-resolution MR image $(0.39 \times 0.39 \times 0.8 \text{mm})$, multiple quasi-static MR images, and a real-time dynamic FLASH MR sequences $(1.0 \times 1.0 \times 6 \text{mm}, 3 \text{ FPS})$ [Lin 2013]. Motion was controlled by a tailor built guiding jig. Knee bones and cartilages (tibia and femur) were manually segmented from the high-resolution MR images. The bone volumes obtained were then manually aligned with the first slice of the dynamic sequence. Bone regions were subsequently cropped and registered throughout the sequence in a pairwise fashion such that for each time frame, the position obtained for the previous frame was used as initialisation (i.e., registration throughout the full sequence via small increments). After transformation of the surfaces throughout the dynamic MR sequence, the method was validated by comparison with surfaces reconstructed manual segmentations of the quasi-static MR images. Quantitative results showed an error of 0.6mm in translation and 0.2° degrees in rotation for the femur and 0.5mm and -0.4° for the tibia.

3.3.4 Summary

In this section, a review of the methods developed to analyse the kinematic properties of the knee joint from MR images was provided. Previous studies have used quasi-static and dynamic imaging of the knee joint to evaluate the loading mechanisms of the cartilage [Borotikar 2012] and to track the bones throughout variable knee flexion angles [Yamada 2007b]. Measurements of patellar tilt, shift and contact-areas were the most commonly estimated values due to their implications in PFPS [Yamada 2007a, Souza 2010]. Preliminary assessment of abnormal knee kinematics in relation with ligament deficiency has also been obtained via analyses of tibiofemoral contact kinematics [Barrance 2006]. These measurements can provide useful information on patellar maltracking and abnormal patellofemoral or tibiofemoral contact mechanisms that may improve diagnosis and treatment of PFPS, and can help study the impact of injuries to important functional knee structures on healthy knee kinematics.

Currently, all analysis methods require varying degrees of manual processing of the imaging data (usually manual segmentation of the knee bones and cartilages or the measurement of quantitative values). This can become problematic considering the large amount of imaging data acquired by kinematic MR imaging techniques. No fully-automated analysis pipeline to perform segmentation and quantitative analysis of kinematic MR images of the knee joint has been published. Successful implementation of such a pipeline would facilitate clinical studies into *in-vivo* knee kinematics and provide a significant step towards clinical applicability of kinematic MR imaging for improved diagnoses and prediction of cartilage wear in ligament- or meniscus-deficient patients.

The pipeline would require (1) accurate segmentation of the knee bones and cartilages from the MR images and (2) robust mapping of the segmented anatomy onto the functional kinematic MR images. As a consequence of the custom hardware required for acquisition of kinematic MR images (open coils, open or large bores) which can impact upon the quality of the images acquired, there are significant technical challenges involved in the automation of quantitative analyses.

- MR images typically feature a lower SNR and CNR in comparison with those acquired on a standard MR hardware for the knee joint;
- Trade-offs in spatial resolution will introduce significant partial volume effects (Fig. 3.7(a));
- Due to custom hardware designs, increased field inhomogeneity artifacts will appear in the MR images (Fig. 3.7(b, and d));



Figure 3.7: Common MR artifacts in dynamic MR imaging. (a) shows partial volume effects of the cartilage tissue in a WE-TrueFisp (1.5mm thickness), viewed in the axial plane. (b) shows chemical shift artifact and signal drop of in cartilage tissue, resulting in absence of contrast (WE-TrueFisp). (c) shows a motion artifact in a dynamic TrueFisp and (d) shows a mixture of motion and inhomogeneity artifacts resulting in signal loss and blurring for the tibia bone and cartilage.

• If the imaged individuals move fast during acquisition of dynamic MR images, motion artificats will appear throughout the MR sequence (Fig. 3.7(c)).

The automated quantitative MR analysis of kinematic MR images is addressed as part of *Aim 3* of this PhD thesis and detailed in Chapter 7.
Chapter 4

Segmentation of the Menisci from MR Images of the Knee

4.1	Introduction
4.2	Material and Method
4.3	Results
4.4	Discussion
4.5	Conclusion

This chapter presents and discusses the research performed to attain **Aim 1.1**, related to the automated segmentation of the knee menisci from magnetic resonance (MR) images of the knee joint. The focus will be the presentation and validation of the method for segmentation of the individual medial meniscus (MM) and lateral meniscus (LM) from MR images of healthy and pathological knees. One of the major goals of the research was the investigation of the pathological menisci. The algorithm is therefore tested on MR images typically acquired in clinical research into knee osteoarthritis or routine clinical MR examinations. This includes dual-echo steady-state and turbo-spin-echo fatsuppressed MR sequences, which feature a dark signal intensity in bone and meniscus tissues and bright cartilage tissue and synovial fluid.

This chapter is organised as follows: a short introduction will highlight the research problem and motivation associated with the segmentation of the knee menisci from MR images. The following section will describe the datasets utilised to evaluate the performance of the algorithm. The core of the chapter will then detail the method developed to generate the statistical shape models and tissue models of the individual MM and LM and to segment the MR images. The evaluation of the performance of the method is finally presented and discussed. The core material detailed in this chapter has been published in Osteoarthritis & Cartilages [Paproki 2014].

4.1 Introduction

Meniscal degeneration, by altering normal knee function and loading mechanisms, has been identified as a strong determinant within the multi-factorial aetiology of knee OA [Englund 2004, Hunter 2006, Englund 2007] (For extensive review, see Section 3.1.1). The exact relationship between structure degeneration and development of knee OA, however, remains elusive. Quantitative analysis of the MM and LM from MR imaging technologies offers opportunities to better understand the pathophysiological processes involved in the structural and biochemical degeneration of these fibro-cartilaginous structures in relation to knee OA.

These analysis methods require the segmentation of the individual MM and LM from the MR images. Although automated segmentation algorithms have been a topic of significant research over the past few years, identifying the menisci in MR images of the knee joint remains challenging and a major obstacle to integration of quantitative MR imaging in clinics and large scale research.

Manual or semi-automated segmentation of the menisci are the primary means to analyse the menisci in the MR images, which is time- and expertise-intensive (35 minutes reported for segmentation of a single coronal reformat of WE-DESS MR images [Blöcker 2014]) and associated with variable reliability in subsequent measurements (in terms of intra-observer and inter-observer reliability [Siorpaes 2012]). Specifically, it requires numerous subjective interpretations for separating adjacent structures with comparable signal contrasts (e.g., ligaments near the meniscal horns, fat tissue at the periphery of the mid-compartment) and thus expert knowledge is paramount for correct decision making. To facilitate analyses, automated MR image segmentation algorithms could provide an efficient and unbiased alternative to current manual methods.

Currently, there are a limited number of automated solutions for segmentation of the knee menisci [Ramakrishna 2007, Boniatis 2008, Fripp 2009, Swamy 2012, Zhang 2013] (see Section 3.1.3.3 for a detailed review). Whilst some provided reasonable accuracy for segmentation of both the MM and LM from the MR images [Fripp 2009, Zhang 2013], the methods were developed for analysis of the healthy menisci or were tailored to cartilage specific MR pulse sequences not routinely used in clinical workflows. Developing a method for robust segmentation of the pathological menisci in MR scans

typically acquired in clinical research into knee pathologies or acquired in routine diagnostic MR imaging is desirable.

Combined acquisition of three multi-planar 2D-TSE MR images or (more recently) a single 3D-TSE MR image is the preferred approach for non-invasive morphological diagnosis and clinical decision making for the menisci. These sequences provide good contrast between the MM, LM and the surrounding tissues apart from the ACL and PCL and allow the diagnosis of lesions within the menisci with high sensitivity. In clinical studies, cartilage specific WE-DESS MR imaging is usually preferred due to the high-spatial resolution and good contrast between the cartilages and surrounding tissues, including the menisci. The contrast between the menisci and fatty tissues is however more limited, and the degenerative menisci may feature a similar signal intensity as cartilage tissue in different regions. A complete listing of the challenges associated with the segmentation of the healthy and pathological menisci from MR images is provided in Section 3.1.1. The typical appearance of the menisci in WE-DESS, 2D- and 3D-TSE MR images from pathological knee joints can be seen in Fig. 4.1 and Fig. 4.2.

In this chapter, we explore the use of an active shape model (ASM) method for the segmentation of the individual MM and LM from MR images of the knee joint. The scheme deforms a model of the menisci in the image based on a template matching process. The deformation is constrained to plausible menisci shapes using statistical shape models (SSM(s)) of the MM and LM describing the variability of shapes in a cohort of healthy and pathological knees. The outline of the chapter is as follows: we first describe the scheme developed to create the SSMs and grey level models (GLM(s)) providing priors on meniscal shape and tissue intensity profiles typically surrounding the menisci in the MR images. The process used to deform the models of the menisci in the image is then detailed. The method is finally validated and discussed.

4.2 Material and Method

4.2.1 MR Image Datasets

The MR data utilised for automated analysis of the menisci were obtained from three separate sources. The first source was the *Osteoarthritis initiative* (OAI), from which three separate datasets (A), (B) and (C) of WE-DESS MR images were investigated. Dataset (A) was utilised for quantitative validation, while datasets (B) and (C) allowed for further qualitative validation and quantitative MR analyses. A



Figure 4.1: (a) Manual segmentation of the MM and LM in a 3D WE-DESS MR image acquired in the sagittal plane and viewed in the sagittal *(left)*, coronal *(middle)* and axial *(right)* plane. Coronal view, MM = medial meniscus, LM = lateral meniscus, FM = femur, T = tibia, C = cartilage, F = fat. (Right) Axial view, AH = anterior horn, PH = posterior horn. (b) A 3D sagittal WE-DESS MR image of relatively healthy menisci demonstrating high tissue intensity homogeneity and clear demarcation with the surrounding cartilages and reasonable contrast with fat tissues. (c) Appearance of the MM and LM in a patient with moderate signs of rOA of the knee joint, demonstrating signal changes within the structures and blurred demarcations with surrounding tissues (blue arrows).



Figure 4.2: (a & b) Typical clinical **3D**-TSE and **2D**-TSE MR images from the SPRI dataset for two patients with combined ACL and meniscus injury. The magnified areas illustrate some of the challenges involved in the segmentation task. (c) Example of a 3D WE-DESS MR image from the UQ 7T MR dataset acquired for an asymptomatic volunteer. Green arrows show the good depiction of the roots of the menisci, which cannot be seen at 3T. From left to right, the figure shows the sagittal, coronal and axial plane.

second dataset of 2D-TSE and 3D-TSE MR images was provided by the *Steadman Philippon Research Institute* (SPRI). A subset of the data was utilised for quantitative validation. The final source was the *University of Queensland* (UQ) and involved the acquisition of pilot WE-DESS MR images on a 7 Tesla MR scanner. Details of each dataset are provided in the next few sections.

The OAI study was approved by the institutional review board at the *University of California, San Francisco* and the data provided were anonymised. The SPRI dataset was acquired in the United States as part of a study approved by the institutional review board at the *Steadman Philippon Research In-stitute*, all subjects provided informed written consent and the MR images received were anonymised. The 7T MR imaging study was approved by the medical research ethics committee of the *University of Queensland* and informed written consent was obtained from all participants involved in the research. The 7T data utilised in this research were anonymised.

4.2.1.1 The Osteoarthritis Initiative WE-DESS MR Dataset

The Osteoarthritis Initiative is a large multi-centre, cross-sectional and longitudinal prospective study into knee OA. The OAI is a public–private partnership sponsored by the National Institute of Health and various private organisations that focuses on the identification of promising MR biomarkers to study the onset and development of knee OA [Peterfy 2008]. The initiative involves the annual acquisition of MR images and X-rays of knee from 4796 patients with confirmed or at strong risks of developing knee OA. These acquisitions are paired with clinical assessments and all anonymised data are publicly available upon request to the OAI (http://www.oai.ucsf.edu/datarelease/). For each patient, a total of 8 different MR sequences are acquired: 3D sagittal WE-DESS (left and right knee), 2D coronal IW-TSE (left and right knee), 2D sagittal FS IW-TSE (left and right knee), 3D coronal T_1 -weighted WE-FLASH (right knee) and a 2D sagittal multi-echo spin echo T_2 -map (right knee).

For this study, WE-DESS MR images of the knee acquired for 88 patients (45 males, 43 females) were selected from the OAI baseline (V00) and 12 months (V01) image releases for initial segmentation experiments and validation. This dataset is referred to as dataset (A) in the remainder of this chapter. The knees from the patients of dataset (A) were all pathological and had confirmed radiographic OA (rOA), as graded with a composite OA grade by a certified radiologist (approaching the Kellgren & Lawrence grade presented in the literature [Kellgren 1957]). These images were acquired on a 3T MR imaging scanner using the parameters provided in Table 4.1. The knee menisci were

Scan	3D we-DESS (OAI)	2D TSE (SPRI)	3D TSE (SPRI)	3D we-DESS (UQ)
Field Strength	3T	3T	3T	7T
Plane	Sagittal	3-planes	Sagittal	Sagittal
FS	WE	FS	FS	WE
FOV (mm)	140	120	150	160×130
Matrix	384×384	640×640	256×256	640×520
No of slices	160	30	176	224
Resolution (mm)	0.365	0.188	0.586	0.25
Slice thickness/gap (mm)	0.699/0	3.0/0	0.699/0	0.5/0
<i>Flip angle (</i> $^{\circ}$ <i>)</i>	25	120	120	18
TE/TR (ms)	4.7/16.3	40/5590	45/1200	2.5/8.68

Table 4.1: MR acquisition parameters for the different protocols used for segmentation of the knee menisci. The 3T WE-DESS MR images were acquired by the OAI and the 2D and 3D-TSE FS were acquired at SPRI. The 7T MR images were acquired at the University of Queensland.

manually segmented in all the WE-DESS MR images of dataset (A) and kindly provided by *Imorphics* (Manchester, UK), resulting in individual segmentation labels for the MM and LM. The manual segmentations were performed by a single operator trained by a MSK radiologist (Charles Hutchinson) and an expert observers (Mike Bowes). The operator had passed the *Imorphics* cartilage segmentation training protocol, which requires an intra-observer coefficient of variation lower than 3% on paired test images for the segmentation of cartilages. The segmentations were reviewed by the expert observer. MR images from dataset (A) were used to train our models (for WE-DESS MR image segmentation) and to quantitatively validate the performance of the segmentation algorithm.

In addition, two longitudinal datasets (B) and (C) of sagittal 3D WE-DESS MR images of the knee were selected from the OAI image release 0.E.1, 1.E.1, 3.E.1 and 5.E.1 (baseline, +12, +24 and +36 months release). Datasets (B) and (C) consist of 22 and 129 patients (with left and right knees) randomly selected from the OAI progression (confirmed rOA) and OAI incidence (asymptomatic with high risk factors of developing knee OA) cohorts. MR images from (B) and (C) were utilised to qualitatively evaluate the performance of the method on a larger spectrum of meniscal shapes and pathologies and to perform subsequent clinical quantitative investigations (see Chapter 5). An illustration of the typical appearance of the healthy and pathological knee menisci in the WE-DESS MR images is shown in Fig. 4.1.

As the demographic data were numerous for the patients of this MR dataset, all the information relevant to Chapter 4 and 5 have been summarised in Table 4.2 for the three datasets (A), (B) and (C).

		A)	(B)		(C)	
	Male	Female	Male	Female	Male	Female
Ν	45	43	12	10	43	86
Age (yrs)	62.02±10.89	$60.42 {\pm} 8.982$	$56.58{\pm}9.29$	$60.44 {\pm} 9.68$	$56.47 {\pm} 9.03$	$57.81 {\pm} 8.6$
Height (cm)	176.7±6.39	$163.1 {\pm} 5.80$	$178.3 {\pm} 5.68$	$164.6 {\pm} 7.56$	$176.9 {\pm} 5.85$	$162.2 {\pm} 6.46$
Mass (kg)	96.31±14.76	83.67±14.87	$94.54{\pm}18.04$	$78.14{\pm}16.36$	$86.24{\pm}14.27$	$75.24{\pm}14.46$
BMI (kg/m ²)	30.51±3.87	$31.65 {\pm} 5.26$	$29.64{\pm}4.97$	$28.68{\pm}4.98$	27.55 ± 4.22	$28.59 {\pm} 5.27$
Pain Score [0,20]	5.07±3.85	$5.84{\pm}4.27$	1.75 ± 2.34	2.67 ± 3.12	$3.95{\pm}4.32$	4.57±4.37
Time-points		2	2	4	2	1
Left & right	נ	No	Yes		Yes	
# Baseline Knees	:	88	4	-2	12	27
# Total Knees	1	76	1:	58	75	58
rOA Grades	(0, 0, 1)	5 5 (17)	(0, 0, 1)	7 14 2)	(202.22	10 7 1)
$(0, 1, 2, 3, 4) \tag{0, 0, 15, 56, 17}$		5, 50, 17)	(0, 9, 17, 14, 2)		(203, 33, 10, 7, 1)	
mJSN scores	(16 55 17)		(20, 10, 2)		(240, 12, 2)	
(0, 1, 2)	(10, 55, 17)		(30, 10, 2)		(240, 12, 2)	
lJSN scores	(74	14.0	()(1(0)	(251	2 0)
(0, 1, 2)	(/4,	14,0)	(20,	10, 0)	(251,	5,0)

Table 4.2: Relevant demographics for the patients from Datasets (A), (B) and (C) selected from the OAI cohort.

4.2.1.2 The Steadman Philippon Research Institute TSE MR Dataset

These images were acquired as part of a clinical study performed at the Steadman Philippon Research Institute. Between December 2011 and April 2014, 80 patients (38 females, 42 males) with a mean age of 31 years (18-82 years) scheduled to undergo arthroscopic knee surgery for treatment of an acute ACL injury, acute meniscus injury or an acute combined ACL and meniscus injury received a 3T MR examination. The MR images were acquired up to 90 days prior to arthroscopy (average of 11 days between MR imaging and arthroscopy) on a clinical Siemens Verio 3T MR scanner (Siemens Medical Solutions, Erlangen, Germany) with a gradient field strength of 40mT/m using a 15 channel multi-element phased-array knee coil (Quality Electrodynamics LLC, Ohio, USA). All patients were positioned supine during the acquisition with the knee centred in the coil. For each patient, either (a) sagittal, coronal and axial 2D FS PDw-TSE MR images (n = 37) as commonly used in current standard clinical knee examinations or (b) a single 3D-TSE MR image (isotropic with enhanced multi-planar reformatting, N = 43) were acquired. A detailed listing of the important MR imaging parameters utilised for these MR sequences is provided in Table 4.1. Illustrations showing the typical intensity contrast for the knee menisci in the clinical 3D and 2D-TSE MR imaging sequences are provided in Fig. 4.2(a & b).

For validation, a subset of MR images from 31 patients ($N_{2D-TSE} = 15$, $N_{3D-TSE} = 16$) was

blindly selected for baseline manual segmentation and analysis of the menisci. To obtain manual segmentations representative of both the injured and non-injured menisci (as confirmed by arthroscopy), half of the MR images were randomly selected from the group of patients with ACL only injury and half were randomly selected from the group of patients with combined ACL and meniscus injury. For each selected patient, the MM and LM were manually segmented in the sagittal plane of the 3D-TSE or sagittal 2D-TSE MR images by two experienced musculoskeletal observers using an interactive touch-screen drive with stylus (Katharine J. Wilson using Mimics (Materialize Inc., Plymouth, MI) and Mark Strudwick using ITK-Snap [Yushkevich 2006]). A segmentation of a 3D-TSE MR image was performed by both experts and once consensus was reached regarding the segmentation conventions and resulting menisci volumes, each expert manually segmented half of the selected data. The segmentation of both the MM and LM in a single 3D-TSE and 2D-TSE MR image required 120 minutes and 60 minutes. The expert observers were blind to the automated segmentation method.

The manual segmentations were used to train the models required by the segmentation algorithm (for 2D and 3D-TSE MR images) and to quantitatively validate the performance of the segmentation algorithm for analysis of the pathological menisci in typical routine clinical MR scans.

4.2.1.3 The University of Queensland Ultra-high Field MR Dataset

This dataset of MR images was acquired on a Siemens 7T Magnetom MR scanner as part of a project at the University of Queensland for the development of leading software technologies (ChondralHealth) to monitor the health of the joint cartilages and soft-tissues. This project involves the acquisition of ultra-high field MR images of the asymptomatic knee joint from up-to 30 subjects over a period of 12 months. Besides healthy knee joints (with no reported or known pathology), inclusion criteria included a balanced number of males and females and an age range of 18-45 years. So far, MR data from 10 volunteers have been acquired, including MR images from several subjects which were used for optimisation of the MR pulse sequences.

Three volunteer MR images were manually segmented by an experienced MSK observer (Mark Strudwick) and were used for pilot quantitative validation of the performance of the method on images from novel 7T MR scanners. Other MR data were utilised for further qualitative assessments of segmentation performance. These scanner may offer better opportunities for accurate morphological and biochemical analyses, although current MR image acquisitions may suffer from artifacts as MR pulse sequences are still in a state of optimisation.

4.2.2 MR Image Preprocessing

Prior to any training or segmentation, all the MR images were processed using identical filters. To correct for low frequency signal introduced in the MR image by inhomogeneities in the magnetic fields of the MR scanner, the N4 bias-field correction from the *insight registration toolkit* (ITK) was utilised [Tustison 2010]. A median smoothing algorithm was then used in order to limit the influence of noise on the method and to sharpen the boundaries between different tissues. To avoid training our models twice for the left and right knee anatomy, all the left knee MR images were flipped sagittally to mirror right knee MR images. All subsequent algorithms then treated the MR image to process as a right knee image.

Considering the comparably higher slice thickness of the 2D-TSE MR images in comparison to the 3D-TSE and WE-DESS MR images (0.7 vs 3.0mm), additional processing steps were implemented in order to combined the imaging data provided by the axial, coronal and sagittal 2D-TSE MR images. The scheme, shown at the top of Fig. 4.5, involved fusing the images from the three planes into a composite MR image of higher spatial resolution. Each MR image was first resampled into an image featuring higher out-of-plane resolution using b-spline interpolation ($\approx 0.7mm$, to obtain a slice thickness on par with the 3D imaging modalities). Noise in the images and blur caused by the interpolation were reduced using a gradient anisotropic diffusion smoothing filter (time-step=0.02, iterations=10) [Ibanez 2003] and the axial and coronal scans were co-registered onto the sagittal image using symmetric rigid registration [Rivest-Hénault 2015]. Histogram matching was generated to normalise the signal intensity across the three images, and the final composite image was generated by averaging the signal intensity across the co-registered images. Fig. 4.3 illustrates (a) an initial raw sagittal 2D-TSE MR image visualised in the coronal plane, (b) the up-sampled MR image and (c) the final composite MR image.



Figure 4.3: Representation of the 2D-TSE MR images throughout the fusion scheme. (a) shows the raw sagittal MR image visualised in the coronal plane $(0.19 \times 0.19 \times 3.3 \text{ mm})$. (b) shows the up-sampled version of the MR image (b-spline interpolation: $0.31 \times 0.31 \times 0.69 \text{ mm}$). (c) shows the final composite image resulting from the fusion scheme $(0.31 \times 0.31 \times 0.69 \text{ mm})$.

4.2.3 Atlas Creation, Statistical Shape and Texture Modelling

In this section, the methodology involved in the creation of the mandatory components of the ASMmodel technique is presented, including the steps involved in the creation of a population average knee image and combined menisci surface, SSMs and GLMs of the menisci. The creation of the affine image and surface is straightforward, however the training process involved in the generation of the SSMs and GLMs is more complex and a complete pipeline (shown in Fig. 4.4) was designed for accurate modelling of population variability. Three sets of models were trained separately based on the manual segmentations of the (1) WE-DESS MR images from the OAI dataset, (2) 2D-TSE MR images and (3) 3D-TSE MR images from the SPRI dataset.



Figure 4.4: Training pipeline used to create the SSMs and GLMs of the knee menisci.

4.2.3.1 Affine average atlas image and surface

To initialise the deformable model method, we utilised an affine registration of a population average atlas MR image and surface, which has been shown to improve the generalisability and accuracy of registration based initialisation schemes [Rohlfing 2004]. In this work, affine average atlas image and surface accounting for the population pose variability and morphology were computed and used to



Figure 4.5: Full pipeline implemented for the segmentation of the individual MM and LM.

robustly initialise the ASM-fitting stage. They were obtained by affine registration of all the preprocessed images (with manual segmentations) to a common isotropic image-space and averaging of the resulting images into an affine atlas. The transformations obtained were then propagated onto the respective menisci surfaces with point-wise correspondence (S_i in Section 4.2.3.2) and the mean shape for the combined MM and LM was calculated in the atlas space using Equation 4.2. Illustrations of the 3 patient MR images from the OAI co-registered in the common space and the overall final average atlas image are provided in Fig. 4.6.



Figure 4.6: From left to right, the three first MR images show the co-registration results for three patient MR images of the OAI to the common atlas space. The image on the right shows the resulting average atlas MR image.

4.2.3.2 Statistical Shape Models

In this work SSMs of the individual MM and LM and of the combined MM and LM were built upon the initial datasets of manual segmentations following the method outlined by *Cootes et al.* [Cootes 1995]. Following the pipeline presented in Fig. 4.4, both the MM and LM structures were reconstructed as 3D surfaces using the marching cube algorithm [Lorensen 1987], and a set of N menisci surfaces $M = \{M_0, ..., M_{N-1}\}$ was obtained. In M each M_i is represented by a vector of n_i 3D points such that $M_i = (x_0^i, y_0^i, z_0^i, ..., x_{n_i}^i, y_{n_i}^i, z_{n_i}^i)$.

SSMs require point-wise correspondences to be established across all the surfaces. These were obtained by non-rigid registration of the surfaces of the MM and LM of the first case of the dataset M_0 onto all the other surfaces M_i using the expectation maximisation iterative closest point algorithm (EM-ICP) [Combès 2010, Dore 2011]. The EM-ICP algorithm is not central to this research work, and is presented in Appendix A.1 for the readers' interest. The EM-ICP resulted in a set of N surfaces S_i featuring the same number of vertices ($n = n_0$). To obtain a higher fidelity between the registered surfaces S_i and the initial marching cube surfaces M_i , the surfaces S_i were further relaxed along their surface normals towards the strongest gradient of the initial manual segmentation images. Each $S_i \in S$ was then expressed as a uni-dimensional vector of 3n components as defined in Equation 4.1:

$$S_i = (x_0^i, y_0^i, z_0^i, ..., x_n^i, y_n^i, z_n^i))^T \quad , \quad i = 0, ..., N - 1$$
(4.1)

in which (x_k^i, y_k^i, z_k^i) were the coordinates of the k^{th} point on the surface S_i , and $n = n_0 \in \mathbb{N}^{*+}$ the number of points in all the training surfaces (in this case, the number of points in $M_0 = n_0$). Absolute correspondences across S allowed the optimal shape alignment via Procrustes analysis [Gower 1975],

and the definition of a point distribution model (PDM). The mean shape \overline{S} and the $3n \times 3n$ covariance matrix C of the training set were subsequently computed from the PDM using Equation 4.2 and 4.3.

$$\overline{S} = \frac{1}{N} \sum_{i=0}^{i < N} S_i \tag{4.2}$$

$$C = \frac{1}{N} \sum_{i=0}^{i < N} (S_i - \overline{S}) (S_i - \overline{S})^T$$
(4.3)

The eigenvectors p_k (k = 1, ..., 3n) and eigenvalues $\lambda_k \in \lambda$ were extracted from C and described the direction and the magnitude of the menisci shape variability across the atlas, respectively. Selecting the t largest λ_k allowed to model the most meaningful variations of the menisci while discarding the variability associated to noise. Using standard principal component analysis (PCA) [Jolliffe 2002], each S_i was then described as a weighted sum of the mean \overline{S} and the t major eigenvectors of C, as expressed in Equation 4.4.

$$S_i^* = \overline{S} + Pb \tag{4.4}$$

in which $P = p_1, ..., p_t$ was the matrix of the t major eigenvectors, and $b = b_1 ... b_t$ a vector of weights called shape parameters. Varying the values of the weights b in an acceptable range allows to reconstruct plausible meniscus shapes in a bounded space modelling the variability of the training set. This was the basis of our segmentation method.

In this work, the SSMs were further optimised by repeating the non-rigid EM-ICP surface nonrigid registration process using the calculated mean \overline{S} instead of M_0 as template. This allowed to reduce the registration error introduced by a strong bias when using the shape of a given patient as initial surface to deform. As illustrated by the first mode of variation plotted for each SSM in Fig. 4.7, the SSM of the combined menisci described mostly the positional variability of the MM and LM, and individual MM and LM SSMs characterised the local variability.

4.2.3.3 Grey Level Models

GLMs are bundles of template intensity profiles used to drive the deformation of the ASM. They are constituted of the tissue intensity profiles surrounding the menisci in the training-set and provide *a-priori* information regarding the intensity profiles typically found at each vertex of the meniscus surfaces. They were generated from the preprocessed MR images using the relaxed surfaces S_i obtained



Figure 4.7: Illustration of the first mode of variation of the SSM for the combined MM and LM (*left*), the individual MM (*middle*) and LM (*right*).

in the previous section. For each surface S_i and each vertex $k = (x_k^i, y_k^i, z_k^i) \in S_i$, a one dimensional intensity profile $P_{i,k}$ of length l and spacing s was extracted along the surface normal in the positive and negative direction, and added to the model.

In a similar way to the SSMs, separate GLMs were generated for the combined MM and LM and for the individual MM and LM structures, each containing $n \times N$ likely menisci profiles of length 2l + 1 (corresponding to the PDM). An illustration of grey level profiles extracted for a small area of a menisci surface is provided on Fig. 4.5 (entitled GLM).

To decrease the likelihood of converging towards local minima while deforming the SSMs along the intensity profiles, a 2 level multi-resolution image pyramid scheme was utilised and GLMs were extracted for each level of the image pyramid.

4.2.4 Segmentation Procedure

The ASM-based segmentation method, relying on the trained models presented in the previous section, is illustrated in Fig. 4.5. ASM segmentation methods consist of three components: (1) an initialisation method that is used to bring the deformable model in the image, (2) a deformation criteria that defines how the vertices of the surface move at each iteration and (3) a SSM that constrains the deformation by defining an allowable shape space for the deformation. The next few paragraphs will describe how this was performed in this research.



Figure 4.8: Illustration of the template matching procedure utilised to deform the menisci surfaces in the image.

Following the pipeline, the MR image to segment – denoted I – was first preprocessed as described in Section 4.2.2, and the average atlas image was registered to I using a robust symmetric blockmatching affine registration algorithm [Rivest-Hénault 2015]. The affine transformation obtained was then propagated to the mean atlas surface \overline{S} , resulting in a mean shape S_I aligned with I.

Subsequently, the ASM fitting stage deformed the aligned surface S_I towards the most likely shape and position in the MR image *I*. The deformation is an iterative process based on a template profile matching relying on the normalised cross correlation (NCC) metric. The iterative process, described in Fig. 4.5 and in details in Fig. 4.8 was as follow:

- 1. Grey level intensity profiles $P_{I,k}$ of length $r \times l$ and spacing *s* were extracted along the normal of each vertex of S_I . $r \in [1.5; 2.0]$ is a capture ratio allowing the extraction of intensity profiles longer than that of the GLM;
- Extracted profiles were then compared to that of the GLMs using the process illustrated in Fig.
 Briefly, the GLM profiles P_{i,k}, (i = 0, ..., N 1; k = 0, ..., n 1) of the model were translated along the current profiles P_{I,k}, and for each profile and displacement, the NCC γ between the two profiles was evaluated using Equation 4.5, in which p and q are the two profiles compared. p.q and ||p|| represent the dot product and magnitude operators, respectively;
- 3. For each vertex of S_I , the GLM profile and displacement offset maximising γ characterised the translation of the surface vertex along its normal;
- 4. Depending on parameter sets, shape constraints (i.e., constraints on b in Equation 4.4 when trying to reconstruct a plausible menisci shape from the deformed surface) or smoothing could be applied to the deformed surface to restrain the deformation in a bounded search space representative of typical menisci shapes;

5. The process was then repeated from step 1 until the average deformation obtained was too small or the maximum number of iteration was reached.

$$\gamma = \frac{p \cdot q}{\|p\| \|q\|} \in [0-1]$$
(4.5)

To optimise the accuracy of the segmentation, the ASM-fitting process was broken down into three parts (see dark grey area in Fig. 4.5), such that in the first pass, a combined model of the MM and LM describing 60% of the shape variability (i.e. modelling mainly the pose variability) was fitted to I in order to refine the pose of the menisci obtained by the initialisation. This step was performed using a 2 level Gaussian image-pyramid scheme to avoid converging towards a local minimum. In a second pass, individual models of the MM and LM describing 95% of the shape local variability were separately deformed in I to obtain refined and plausible morphologies for both the structures. In the first and second pass, shape-constraints were applied to the surface after each deformation iteration to ensure that the deformation remained in a shape space consistent with known menisci shapes.

To allow the ASMs to deform towards shapes slightly different than meniscus structures known *a-priori* (i.e., not typical of the training set), the individual MM and LM models were relaxed separately in *I* without shape constraints and for a few iterations. Smoothing was applied at each iteration to remove noise from the deformed surface. The obtained MM and LM surfaces were finally voxelised to obtain the ASM segmentation masks.

To further increase the segmentation accuracy and remove eventual segmentation leaks in the tissues surrounding the menisci, a classification method was used. From the segmentation masks, the tissue intensity properties of the MM and LM were estimated by a Gaussian distribution (σ , μ), and each voxel was affected a probability based upon its distance to μ . In particular, voxels featuring an intensity lower than μ or deviating by less than 1.5σ from it were classified as meniscus tissue. Other pixels were discarded as cartilage tissue or synovial fluid. To account for tears, eventual holes in the segmentation labels were filled using sequential label dilation and erosion. The post-processed masks were the final MM and LM segmentations.

4.2.5 Validation Strategy

The automated segmentation algorithm was applied to all the MR images presented in Section 4.2.1. The method was quantitatively validated using a leave-one-out strategy for the datasets from the OAI (section 4.2.1.1) and SPRI (section 4.2.1.2). The leave-one-out strategy involved omitting the case being currently segmented from the training of all the models incorporating prior knowledge (including the average surface and atlas MR image, SSM(s) and GLM(s)). The automatic and manual segmentations were compared separately for the MM and LM using the sensitivity, specificity, DSI [Dice 1945] and mean absolute surface distance (MASD) [Gerig 2001] values as per Equations 4.6, 4.7, 4.8 and 4.9:

$$Sensitivity = \frac{TP}{TP + FN} * 100 \tag{4.6}$$

$$Specificity = \frac{TN}{TN + FP} * 100$$
(4.7)

$$DSI = 2\frac{A \cap M}{|A \cup M|} * 100 \tag{4.8}$$

$$MASD = \frac{D(A, M) + D(M, A)}{2}$$
 (4.9)

in which TP, TN, FP, FN are the number of true positives, true negatives, false positives and false negatives (in terms of voxels segmented), and A and M are the automatic and manual segmentation masks (or surface), respectively. The sensitivity, specificity, DSI and MASD quantified the percentage of true positives, true negatives, the spatial overlap and the average forward and backward Euclidean distances (D(x,y)) between automatic and manual segmentation volumes [Gerig 2001].

The distribution of segmentation error over the surface was calculated using the Hausdorff distance between the relaxed deformable models of the MM and LM and the reconstructed manual segmentation surfaces [Aspert 2002]. The operation was performed for all the patients with manual segmentations and the median Hausdorff maps were generated for both the MM and LM in order to locate the most problematic areas to segment. Separate maps were generated for the two time-points of dataset (A) from the OAI, and separate maps were generated for the 2D-TSE and 3D-TSE MR images from SPRI. In the dataset (A) from the OAI, for both the MM and LM, differences in DSI values were examined by calculating the Wilcoxon rank-sum tests across rOA grades and the Wilcoxon signed-rank tests between time-points in order to investigate the impact of rOA severity and eventual progression on the segmentation method. Non-parametric tests were used due to a negative skew in the distributions of the DSI obtained (as observed in histograms presenting the spread of the DSI values). A significance level p < 0.05 was assumed.

All quantitative validations were performed using the R statistical framework version 3.0+.

Results obtained for the dataset of ultra-high field 7T MR images were assessed qualitatively and shown as spatial overlays of the segmentation masks onto the initial MR images only.

Automated reports of segmentation results were generated for each dataset and can be publicly accessed online on the milxXplore platform: https://milxview.csiro.au/public/xplorer_studies/Public [Bourgeat 2013]. The websites contain overlays of the automated and manual (when available) segmentation results onto the initial MR images and allow to visualise the good level of agreement obtained for the majority of the subjects.

4.3 Results

4.3.1 The OAI WE-DESS MR Dataset

There was good spatial overlap between the manual and automated segmentations obtained for the (MM, LM) structures, with mean \pm standard-deviation DSI values of (75.2 \pm 10.8%, 82.0 \pm 6.1%) calculated at V00 and (73.7 \pm 10.5%, 81.5 \pm 6.2%) calculated at V01 (Table 4.3). For each meniscus, there were no significant differences in DSI values across the rOA grades (p>0.05 for all Wilcoxon rank-sum tests) or between the time-points V00 and V01 (Wilcoxon signed-rank tests p>0.05) (see Fig. 4.9(a)). Segmentations for the MM and LM in two representative cases are provided in Fig. 4.10 to visualise the typically good agreement between the automatic and manual segmentations. A histogram presenting the spread of the DSI values across a [25–95%] range is presented in Fig. 4.9(b).

The algorithm had difficulties in the segmentation of the severely damaged menisci (e.g., when over 50% of the structure was missing or completely macerated), as shown in Fig. 4.11 for the segmentation of a MM completely missing the anterior horn and a part of the mid-compartment. These cases presented low DSI values, and overall, the selection of a DSI value $\leq 60\%$ as a threshold (fat tail of the DSI distribution in Fig. 4.9(b)) allowed to estimate the failure-rate of the method as $\frac{15}{176} \approx 8.5\%$

for the MM and $\frac{3}{176} \approx 1.7\%$ for the LM in MR images from patients with mild, moderate or severe knee rOA.

The MASD between automated and manual MM and LM surfaces was inferior to 0.78mm for the MM and inferior to 0.52mm for the LM in the WE-DESS MR images. The mapping of the Hausdorff distance onto the menisci surfaces are provided in Fig. 4.15 *(left)* and showed that the tip of the horns and the external portion of the mid-compartment were the regions with the largest segmentation errors. The median Hausdorff distance was inferior to 1.2mm in the mid compartment and 1.5mm for the tip of the horns.

Table 4.3: Quantitative validation of the segmentation results for the OAI dataset.

V00	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)
Medial Meniscus	75.4±9.33	100±0.0205	75.2±10.8	0.655±0.85
OA Grade II	71.1±11.4	$100{\pm}0.0178$	75.6±14	$0.539 {\pm} 0.405$
OA Grade III	76.8±7.95	$100{\pm}0.0193$	75.6±10.1	$0.702{\pm}1.03$
OA Grade IV	74.8±10.9	$100{\pm}0.0241$	73.6±10.5	$0.604{\pm}0.317$
Lateral Meniscus	78.1±7.44	100±0.0087	82±6.12	0.406±0.318
OA Grade II	75.3±6.11	$100{\pm}0.00608$	82.1±4.14	$0.351{\pm}0.0918$
OA Grade III	79±7.44	$100{\pm}0.00828$	$82.4{\pm}6.03$	$0.399{\pm}0.346$
OA Grade IV	77.7±8.25	$100{\pm}0.0107$	$80.9{\pm}7.89$	$0.475 {\pm} 0.351$
V01	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)
Medial Meniscus	75.9±9.36	100±0.0236	73.7±10.5	0.711±0.838
OA Grade II	71.8±13.5	$100{\pm}0.0202$	75.4±15.2	$0.56 {\pm} 0.445$
OA Grade III	77±8.44	$100 {\pm} 0.0239$	73.2±9.62	$0.786{\pm}1.01$
OA Grade IV	76±7.21	$100 {\pm} 0.0223$	$73.6 {\pm} 8.61$	$0.6 {\pm} 0.233$
Lateral Meniscus	77.8±7.24	100±0.01	81.5±6.2	0.424±0.294
OA Grade II	75±7.58	$100{\pm}0.0051$	81.9±4.79	$0.378 {\pm} 0.138$
OA Grade III	$78.9{\pm}6.88$	$100{\pm}0.00938$	$81.8 {\pm} 5.89$	$0.407 {\pm} 0.287$
OA Grade IV	76.7±7.74	$100 {\pm} 0.0135$	80.1±8.21	$0.522 {\pm} 0.395$

 Table 4.4: Quantitative validation of the segmentation results for the SPRI dataset.

	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)
		3D-TSE M	IR images	
Medial Meniscus	83.11±5.615	99.98±0.0301	84.29±9.019	0.355±0.279
Lateral Meniscus	$87.39{\pm}5.208$	$99.98 {\pm} 0.03704$	85.12±10.45	$0.333 {\pm} 0.328$
		2D-TSE M	IR images	
Medial Meniscus	73.39±9.455	99.97±0.03142	76.37±7.874	0.456±0.306
Lateral Meniscus	78.11±5.691	99.96±0.04131	76.45±11.9	$0.485 {\pm} 0.51$

	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)
		Medial Mer	niscus	
Mean	85.7±6.5	99.97±0.02	79.3±2.7	0.483±0.019
Case 1	92.3	99.95	80.6	0.499
Case 2	85.6	99.98	81.1	0.462
Case 3	79.2	99.98	76.2	0.488
		Lateral Mer	niscus	
Mean	83.4±9.1	99.98±0.02	80.5±4.1	0.419±0.122
Case 1	86.7	99.98	85.2	0.308
Case 2	73.1	99.98	78.1	0.549
Case 3	90.5	99.98	78.1	0.401

Table 4.5: Quantitative validation of the segmentation results for the UQ dataset.



Figure 4.9: (a) DSI of the OAI dataset vs rOA grades. (b) & (c) Histograms showing the repartition of the DSI for the OAI and the SPRI datasets.

4.3.2 The SPRI 2D & 3D TSE MR Dataset

The mean DSI values calculated for the menisci in the subset of patients randomly selected for manual segmentations are provided in Table 4.4. The mean DSI values obtained for the MM and LM volumes were $84.29 \pm 9.019\%$, $85.12 \pm 10.45\%$ for the 3D-TSE MR images and $76.37 \pm 7.87\%$, $76.45 \pm 11.9\%$ for the 2D-TSE MR images, respectively. Manual and automated segmentations of the MM and LM overlaid in two illustrative patients 3D-TSE MR images (Fig. 4.12) and 2D-TSE MR images (Fig. 4.13) visually demonstrate this agreement. The failure rate of the automated segmentation method, as identified by a DSI value lower than 65% for either the MM or LM (threshold selected based on the tail visible in the DSI spread histogram provided in Fig. 4.9 (c)) was $\frac{1}{16} \approx 6.2\%$ for the 3D-TSE MR images and $\frac{1}{15} \approx 6.6\%$ for the 2D-TSE MR images for the complete population of 80 patients identified

that $\frac{76}{80} \approx 95\%$ of the patient MR images were successfully segmented using the automated method.

The MASD between automated and manual meniscal surfaces was inferior to 0.36mm for the 3D-TSE MR images and inferior to 0.5mm for the 2D-TSE MR images. The median Hausdorff distance maps of the menisci surface are provided in Fig. 4.15 *(right)* and show that once again, the tip of the horns and the external portion of the mid-compartment of the menisci were the regions with the largest segmentation errors. The error was inferior to 1mm for the 3D-TSE MR images and 2mm for the 2D-TSE MR images.

4.3.3 The University of Queensland Ultra-high Field MR Dataset

The automated method performed well on the pilot segmentations of the WE-DESS MR images from the UQ 7T MR scanner. Utilising the models trained from the WE-DESS MR images of the OAI dataset, the mean DSI values obtained for the three MR images with manual segmentations were $79.3 \pm 2.7\%$ for the MM and $80.5 \pm 4.1\%$ for the LM. The DSI values obtained for all three cases are provided in Table 4.5. Further visual inspections of the overlay of the automated segmentation results onto the original MR images (as illustrated in Fig. 4.14) showed good segmentation accuracy.

4.3.4 Computational Time

The computational time was investigated to quantify the efficiency of the algorithms. For all cases, the pipeline was run on a laboratory computer equipped with a 24 cores Intel(R) Xeon(R) CPU E5-2630 2.60GHz. All individual elements of the pipeline were implemented in C++ and linked using python. All experiments were performed under Linux Ubuntu 14.04.

For the OAI dataset, the average time required to segment a case was 27.7 ± 1.2 minutes. This included 0.8 ± 0.1 minutes of image preprocessing, 3.1 ± 0.5 minutes of initialisation (affine registration) and 23.9 ± 1.0 minutes of ASM fitting. In these stages, the preprocessing and the affine initialisation were multi-threaded, and the ASM was single threaded.

For the SPRI dataset, on average, the time required to run the pipeline was 23.6 ± 1.5 minutes, including 0.4 ± 0.1 minutes for the preprocessing stage, 3.8 ± 1.3 minutes to run the block matching affine initialisation and 19.4 ± 0.9 minutes to perform the meniscus ASM fitting.

4.4 Discussion

The approach obtained robust segmentation results with good accuracy on several different datasets of MR images of the knee from pathological patients. The method was tested and validated on MR protocols utilised to diagnose the menisci in routine clinical examinations, including standard multi-planar 2D-TSE and newer 3D-TSE MR images, and on cartilage-specific MR pulse sequences optimised for research into the knee degenerative disorders such as WE-DESS MR images. In addition, pilot experiments were performed on WE-DESS MR images acquired on a 7T MR scanner.

The primary advances provided by the automated method were that: (1) no manual input was required to process the MR images, (2) the method provides segmentation of the MM and LM as separate labels, (3) the performance of the method was shown to be robust to the severity of knee OA (to the extent of the limitations presented below), (4) it readily segmented the menisci in knees with acute injury (ACL or meniscal tear), (5) it did not utilise segmentations of the bones or articular-cartilages as priors and finally (6) is allowed the robust identification of the knee menisci in MR images typically acquired for clinical diagnosis of the menisci. This is will discussed in the following paragraphs and the limitations of the method will be acknowledged and reviewed.

Regarding the performance of the method on WE-DESS MR images from the OAI, a small decrease in DSI values was noted across groups with increasingly severe signs of rOA (for the MM) and between time-points (Table 4.4, Fig. 4.9). The primary reason for the differences relates to the increased inhomogeneity in the knee menisci from patients with more severe rOA and a complexification of the shape associated with disease progression (e.g., volume increase, tearing or deformations from compression loads). These factors tended to blur the boundary with articular-cartilage tissue and weakened the effectiveness of the templates profiles driving the ASM. However, statistical comparisons performed across groups of patients with mild, moderate and severe rOA did not show significant differences, suggesting that the method was robust to the severity of knee rOA. The rOA grade being a composite measure taking into account multiple factors including JSN (reflecting alterations such as cartilage loss, meniscus subluxation), subchondral sclerosis and osteophytes, it should be acknowledged that in rare cases, the severity of meniscal pathology may differ between individuals within the same rOA grade (hence the presence of outliers at all grades in Fig. 4.9(a)).

Severe destruction or maceration of a meniscus structure caused the segmentation algorithm to fail, as shown for the MM in Fig. 4.11. The reason behind this issue is simply that the model had

no structure to deform into in the MR image. Our experience showed that such cases could be easily and efficiently identified by visual inspections as the knee will always be in a very advanced stage of knee OA. The visual inspections can be easily performed using an automated clinical reporting system [Bourgeat 2013]. With a failure rate of 8.5% for the MM and 1.7% for the LM for the segmentation of the menisci in a population of patients with mild, moderate or several rOA, we consider the method suitable for analysis of the menisci in a framework of early OA assessment where there is a limited interest in the analysis of severely damaged structures.

To investigate the possibility of a bias introduced in the segmentation pipeline as a result of the training stage being performed with manual segmentations from the first time-point, all experiments were repeated using the second time-point as training dataset. Results showed an analogous non-significant decrease in the DSI values between the first and second time-point (Wilcoxon signed-rank test MM: p=0.11, r=0.12; LM: 0.53, r=0.05), which reduced the likelihood that this difference was induced by a training bias.

On the clinical dataset of 2D and 3D-TSE MR images from patients with acute knee injury (SPRI dataset), the mean DSI calculated for the 16 3D-TSE MR images was superior to that calculated for the 2D-TSE MR images ($\approx 8\%$ spatial overlap difference). This difference was expected and can be readily attributed to the lower spatial-resolution of the raw 2D-TSE images (0.7mm verse 3.0mm slice thickness), which led to a low voxel count of meniscal tissue (impacting directly on the DSI formula), greater partial volume averaging and resampling errors at the edge of these thin curved structures. Nevertheless the pre-processing scheme implemented to combine the multi-planar 2D-TSE MR scans allowed to reliably segment the menisci in these clinical images and an accuracy comparable to that of the WE-DESS MR images from the OAI was obtained.

The segmentation accuracy was overall higher in the SPRI dataset compared to the OAI dataset. This is mainly explained by the better contrast of the menisci with the surrounding tissues (especially articular cartilage) in the 2D- and 3D-TSE MR images compared to the typical contrast visualised in WE-DESS MR images (natural to the MR image characteristics). Secondly, it is also explained by overall healthier menisci in this cohort, with no OA-related degenerations impacting on the meniscus (e.g., increase in signal intensity which are not tears), as well as no severely damaged structure (e.g., complete maceration, hypertrophied structures).

The mean DSI values obtained for the segmentation of the menisci in 3D-TSE MR images (0.7mm) from pathological knees were superior to previously reported results ($\approx 81\%$ [Zhang 2013] and

 $\approx 75\%$ [Fripp 2009] for the segmentation of healthy menisci in FS SPRG MR images with a 1.5mm slice thickness), while the performance for segmentation for the 2D-TSE MR images (3.0mm slice thickness) was slightly worse or equivalent. Segmentation of the LM in MR images from patients with knee OA was investigated by *Swanson et al.* and their semi-automated method provided reasonable DSI values ranging from [64 – 75%] for the segmentation of the LM in T_2 -map images (3.0mm thickness). The method developed in this research work has the advantage of being fully-automated and to segment both the MM and LM with better accuracy. It should be acknowledged that when comparing the performance of the method with previous studies, part of the difference in DSI may be caused by the different MR image characteristics (notably MR image slice thickness, which is specified for each comparison). To facilitate the comparison of automated meniscus segmentation algorithms in future experiments, utilising public datasets with expert manual segmentations such as Dataset (A) from the OAI is desirable. These can be obtained freely from the OAI website.

For both the MM and LM, the most problematic areas to segment were the external surface of the mid-compartment and the tip of the horns of the menisci. For the mid-compartment area, this was mostly influenced by a low signal contrast with the surrounding fat tissues in this region (especially for the WE-DESS images) and the slice-thickness (for the 2D-TSE images), since the curve of the external surface of the menisci is tangential to the slice direction in sagittal images, limiting the available information in demarcation area (e.g., axial view in Fig. 4.2 (b)). For the horns of the menisci, this can be partially explained by an arbitrary decision required during the manual segmentation process to stop the segmentation at a different slice (e.g., this can be visualised in the axial view on the WE-DESS MR image in Fig. 4.1), partially explained by the natural absence of demarcation between the meniscus and menisco-meniscal ligament (connecting the posterior horns of the MM and LM), by the lack of spatial details in the region where the meniscal roots are attached to the tibia bone and by magic angle artifacts in this specific area (causing an increase in signal intensity). Of the three imaging protocols investigated, the 3D-TSE MR images were the least problematic to segment due to their high-spatial resolution and good contrast with all surrounding tissues including fat. The 2D-TSE MR images presented the largest segmentation error as a result of the low resolution, while the WE-DESS MR images showed moderate segmentation error.

Regarding the pilot experiments on 3D WE-DESS MR images acquired at 7T, the results obtained were promising with reasonable accuracy reported from quantitative and visual evaluations while using models trained on a different sequence (in this case the WE-DESS MR images acquired at 3T). These MR images provided better spatial resolution, allowing to discern the attachments of the

meniscal roots into the bones, which may prove useful in clinical decision making as repairing the roots in meniscal injury is paramount for normal meniscal function. However, this area could not be precisely segmented by the current models trained from lower resolution images. Training better models from MR data acquired at 7T is an avenue for future work.

The computational time required to segment the data from the OAI dataset was slightly greater than that of the SPRI dataset. This can be explained by the difference in the number of surfaces and images used to create the models (SSMs/GLMs) and the number of vertices of the surface models (OAI: 85 surfaces, 8000 vertices; SPRI: 75 surfaces, 5124 vertices). In the OAI dataset, the algorithm had more surface vertices and candidate GLMs to go through in the ASM-fitting step. An immediate consequence is that the efficiency of the algorithm can be improved upon using either simpler models, a GLM pre-selection scheme or by multi-threading the grey level profile search. This has not been investigated in this thesis and provides another possibility for future improvements. The image size also impacted upon the time required to preprocess the images and initialise the method using the affine registration [Rivest-Hénault 2015].

4.5 Conclusion

In this chapter, a deformable-model based segmentation of the menisci from MR images of the healthy and pathological knee joint was presented (Aim 1.1). Robust segmentations and good accuracy were obtained for the segmentation of the individual (MM and LM) in MR protocols used for clinical studies $(75.2 \pm 10.8\% \text{ and } 82.0 \pm 6.1\%$ in WE-DESS MR images acquired at 3T) and in routine clinical MR examinations ($84.3 \pm 9.0\%$ and $85.1 \pm 10.5\%$ in 3D-TSE MR images, $76.4 \pm 7.9\%$ and $76.5 \pm 11.9\%$ in 2D-TSE MR images). The method was robust to the severity of the knee OA (with good segmentations obtained in patients mild, moderate and severe rOA) and to common knee pathologies including ACL and meniscus injury. In this chapter, the segmentation algorithm was also shown to be applicable MR images acquired on novel 7T MR scanners (mean DSI of $79.3 \pm 2.7\%$ and $80.5 \pm 4.1\%$ obtained for 3 participants).

The method provides a robust and efficient basis for the subsequent quantitative analysis of the morphological (e.g., volume, position) and biochemical (e.g., T_2) properties of the menisci, which will be investigated in Chapter 5. This will provide a significant advance for translation of quantitative MR analyses into routine clinical MR examinations and enhance investigation into knee OA from large scale MR studies such as the OAI or the MOST studies.



Figure 4.10: Illustration of the automated segmentation results obtained for 2 representative patients of the OAI dataset. The segmentation is viewed in the sagittal plane and the segmentation of the MM and LM are shown in blue and purple, respectively.



Figure 4.11: Example of segmentation of the MM that could not be performed accurately. In this case, the meniscus is missing over 50% of its tissue and the deformable model has no structure to deform into.



Figure 4.12: Example of segmentation results obtain for the 3D-TSE MR images of the SPRI dataset for 2 patients. The segmentation is viewed in the sagittal plane and the segmentation of the MM and LM are shown in blue and purple, respectively.



Figure 4.13: Example of segmentation results obtain for the 2D-TSE MR images of the SPRI dataset for 2 patients. The segmentation is viewed in the sagittal plane and the segmentation of the MM and LM are shown in blue and purple, respectively.



Figure 4.14: Example of automated and manual segmentation results obtained for 2 volunteers in WE-DESS MR images from the UQ 7T MR study.



Figure 4.15: Median Hausdorff distance map (maximum forward/backward distance between automatic and manual surface) overlaid on the mean surface of the OAI (*left*) and SPRI (*right*) datasets [Aspert 2002]. For the data from the OAI,(*top*) and (*bottom*) show the surface map for the baseline and 12 months time-points, respectively. For the data from the SPRI dataset, (*top*) and (*bottom*) show the surface map for 3D-TSE and 2D-TSE MR images, respectively. The blue and red areas represent the areas with the smallest and largest median segmentation error. The tip of the horns and the external surface of the mid-compartment of both menisci were the areas most problematic to segment.

Chapter 5

Quantitative MR Analysis of the Menisci

Contents

5.1	Introduction
5.2	Material and Method
5.3	Results
5.4	Discussion
5.5	Conclusion

In this chapter, the research related to Aim 1.2 is presented. It involves the automated estimation of important quantitative measurements of the menisci from magnetic resonance (MR) images and the validation of the accuracy of the resulting measurements. To achieve this, the automated segmentations of the medial meniscus and lateral meniscus obtained in Chapter 4 are used as basis for the automated quantitative analysis of the morphology (dataset from the Osteoarthritis Initiative (OAI)) and biochemistry (dataset from the Steadman Philippon Research Institute (SPRI)) of the knee menisci from MR images. The focus of the chapter will be the presentation of the algorithms used to estimate the quantitative values and their validation. Validation was achieved by comparing the values derived from the automated segmentations to those obtained from the manual segmentations.

The chapter is structured as follows: The research problem and motivation are first briefly introduced. The algorithms used to estimate the morphological and biochemical parameters of the menisci from the OAI and the SPRI datasets are then presented. The accuracy of the resulting measurements is then assessed and proof of concept experiments are subsequently reported that compare estimated measurements of the menisci across clinically relevant groups in both the OAI and SPRI datasets. The method is discussed in the final section.

The core material related to analyses of the morphology of the menisci has been published in Osteoarthritis & Cartilages [Paproki 2014]. The content related to analyses of the biochemistry of

the menisci is under review in Academic Radiology

5.1 Introduction

In recent years, several fully-quantitative MR analysis methods have been proposed to study the burden of knee OA and monitor progression [Wirth 2010], allowing the identification of a number of important morphological factors of the knee menisci (mainly volume, subluxation and tibial-coverage) associated with knee rOA [Blöcker 2013, Hwang 2012, Wenger 2013] (for extensive review, see Section 3.1.1). Besides quantifying the morphology of the MM and LM, several studies have suggested that $T_{1\rho}$ -, T_2 - and T_2^* -mapping of the menisci were sensitive to the increased water content and mobility within the tissues which may result from the deterioration of the collagen network or proteoglycan loss. These methods enable quantitative evaluation of meniscal integrity, which is important for assessment of early degenerative changes associated with knee OA and to study the healing properties of the menisci post-surgery [Hutchinson 2013, Juras 2014, Chu 2014].

Previous clinical studies relied on the manual or semi-automated segmentation of the menisci in the MR images to extract these important quantitative measurements (e.g., [Wirth 2010, Chu 2014]). Manual segmentation is prohibitively time-intensive and subjective by nature for potential integration of quantitative MR imaging in clinical evaluation of the menisci. Manual interactions also limit the scale of clinical studies into meniscal degeneration, as large amounts of cross-sectional and longitudinal data cannot be analysed efficiently. Estimating the measurements from automated segmentations of the menisci in the MR images is an alternative that does not suffer from these drawbacks. However, a primary concern of quantitative MR analyses lies in the accuracy of the measurements. It is therefore necessary to first validate the accuracy of measurements estimated from automated segmentations.

In this chapter, we evaluate the performance of several automated image- and surface-processing algorithms for estimation of important morphological (volume, subluxation and tibial coverage) and biochemical (T_2 -relaxation) properties of the MM and LM from automatically segmented MR images of the knee joint. In particular, we aim at evaluating the accuracy of the measurements by comparing parameters estimated from automated and manual segmentations and by comparing statistical outcomes of both methods in proof of concept group comparisons.

5.2 Material and Method

5.2.1 MR Image Datasets

The automated segmentations obtained in the WE-DESS MR images from the OAI were used to calculate morphological parameters of the meniscus which have been shown to vary with the severity of knee rOA. This included parameters characterising the shape (e.g., volume) or position of the meniscus (e.g., subluxation or the area of the meniscus covering the tibial plateau). Quantitative measurements estimated from the automated segmentations were validated against quantitative measurements estimated from the manual segmentations performed in dataset (A) (88 patients at baseline (V00) and 12 months (V01), presented in Section 4.2.1.1). Datasets (B) and (C) were used to estimate quantitative values for a larger cohort of patients and to compare quantitative values across clinically relevant groups of patients.

The 80 clinical MR images from the SPRI dataset (2D- or 3D-TSE, presented in Section 4.2.1.2) were used in combination with sagittal multi-echo spin-echo T_2 -maps acquired for each patient in order to study the regional T_2 -relaxation properties of the menisci in the injured knee joint. This is important in this population in order to study secondary degeneration of the menisci as a result of ACL injury and to study the overall tissue health pre- and post-surgery. Validation involved comparing the T_2 -values estimated from automated segmentations against T_2 -values calculated from manual segmentations performed in the second echo of the T_2 -maps of 31 patients by the two expert raters (see Section 4.2.1.2). The T_2 -map MR parameters were as follow, $T_R/(T_Es)$: 2570/(13.8, 27.6, 41.4, 55.2, 69, 82.8, 96.6) ms, flip angle: 180°, resolution: $0.546 \times 0.546mm$, slice thickness/gap: 2.0/2.0mm, FOV: 140mm, number of images: 7. The T_2 -maps were calculated from the multiple spin-echoes using a voxel-wise, mono-exponential least-squares-fit (syngo MapIt; Siemens Healthcare, Erlangen, Germany) (See Section 2.4.2.4 for generation information regarding T_2 -maps.

5.2.2 Morphological Analyses from the OAI dataset

Based upon the segmentations of the individual MM and LM obtained from the WE-DESS MR images from the OAI, 3D triangulated surfaces of the menisci were reconstructed using the marching cubes algorithm [Lorensen 1987] and smoothed [Gelas 2009]. Several morphological parameters of interest were subsequently calculated based upon the geometrical features of the resulting surfaces.



Figure 5.1: Illustration of a segmented tibia bone in a WE-DESS MR image from the OAI and surface reconstruction used to calculate the meniscus tibial-coverage and subluxation parameters.

Abbreviation	Description
$MM.Vol (mm^3)$	Volume of the medial meniscus
$LM.Vol~(mm^3)$	Volume of the lateral meniscus
MM.Cov (%)	Percentage of the medial tibial plateau covered by the MM
LM.Cov (%)	Percentage of the lateral tibial plateau covered by the LM
MM.Sub (mm)	Subluxation of the MM
LM.Sub (mm)	Subluxation of the LM
MM.TA	Medial tibial plateau area
LM.TA	Lateral tibial plateau area

 Table 5.1: Nomenclature for the morphological parameters estimated in the OAI dataset.



Figure 5.2: Schematic representation of the computation of the meniscus tibial-coverage and subluxation parameters. (a) shows the segmented MM and LM as transparent surfaces, the medial and lateral tibial plateau surfaces in yellow (MM.TA and LM.TA) and the area of the tibia covered by the menisci in orange (MM.Cov and LM.Cov). (b) shows the MM as a dotted/transparent surface and the two points used to calculate the amount of extrusion of the meniscus (in this case MM). The red and green dashed lines represent the external margin of the tibial plateau and MM, respectively.
In particular, both the MM and LM were automatically analysed for volume, tibial coverage area and medial (for the MM) or lateral (for the LM) subluxation. These parameters are important considering their demonstrated strong associations with the severity of rOA [Blöcker 2013].

In order to estimate the subluxation and the tibial-coverage parameters, the segmentation of the tibia bone in the WE-DESS MR images from the OAI was required. These segmentations were obtained automatically using an in-house implementation of the ASM-method proposed by *Fripp et al.* for accurate segmentation of the knee bones and the estimation of the bone-cartilage interface (BCI) from MR images [Fripp 2007b]. After processing, the success and quality of all the tibia bone segmentations were visually assessed. The evaluated medial and lateral BCI regions were utilised as medial and lateral tibial plateau areas. An example of a typical tibia segmentation and surface reconstruction obtained in a WE-DESS MR image from the OAI is provided in Fig. 5.1.

Meniscus Volume

The volume of a segmented structure in an MR image is commonly calculated by direct numerical integration of the voxels belonging to the segmented region. In this work, the volume was obtained by summing the volume of all the voxels belonging to the segmented regions for the individual MM and LM.

Tibial Coverage

An important function of the MM an LM is to protect the articular cartilages of the knee from highfocal stress by spreading compression loads on larger surface areas (see Section 2.1.3). This is directly dependent on the surface area of the tibial plateau covered by the menisci. To obtain this measure, the surfaces of the MM and LM were projected onto the medial and lateral tibial plateaus and marked as separate areas. This is illustrated in Fig. 5.2(a), where medial and lateral tibial plateau areas (MM.TA and LM.TA, obtained from the BCI probability [Fripp 2007b]) are shown in yellow and the projections of the MM and LM are shown as orange areas and labelled as MM.Cov and LM.Cov. The coverage area parameters were then obtained by integration of the triangles belonging to the projection regions of the MM and LM (orange) and normalisation of the estimated surface area by the total surface area of the medial and lateral tibial plateaus, respectively (yellow \cup orange region in Fig. 5.2(a)).



Figure 5.3: Meniscus partitioning. (a) Schematic of the regional partitioning of the MM and LM with (1) the anterior, (2) the mid-compartment and (3) the posterior region of the menisci. (b) Surface reconstruction of a partitioned MM and LM segmentation (from a T_2 -map MR image).

Medial and Lateral Subluxation

Meniscus subluxation is a displacement of the structure from the normal position which occurs when the meniscus loses integrity (e.g., tear, degeneration) and cannot resist compression loads applied by the femur. This results in medial (for the MM) or lateral (for the LM) extrusion of the structure from the joint line. In this work, the subluxation was calculated in the mid-compartment region of the MM and LM (which was shown to provide better reliability for this measurement than the full structure [Siorpaes 2012]) as the maximum distance between the external surface of the meniscus and the external margin of the tibial plateau. This is demonstrated in Fig. 5.2 (b) for the MM, where the external margin of the tibial plateau (t_{ext}) and meniscus (m_{ext}) are shown with dashed red and green lines and the effective subluxation is shown with as a blue arrow drawn between the two points maximising the distance between t_{ext} and m_{ext} .

5.2.3 Biochemical Analyses from the SPRI dataset

Based upon the segmentations of the menisci in the 2D/3D-TSE MR images, the regional evaluation of the T_2 properties (reflecting water mobility) of the MM and LM was performed by transferring partitioned segmentation masks onto the multi-echo spin-echo T_2 -maps.

Partitioning of the Knee Menisci

Prior to biochemical analysis, each meniscus label was further partitioned into three regions of clinical interest, namely the anterior, mid-compartment and posterior regions. The partitioning was performed purely based on the geometrical features of the meniscus, such that the segmentation masks of the MM

and LM were split into three regions of equal arc length, as measured from the centroid of the MM and LM respectively. A schematic illustration of the meniscus partitioning process is displayed in Fig. 5.3(a). An example of partitioned meniscal surfaces is shown in Fig. 5.3(b).

Co-registration of the 2D/3D-TSE and *T*₂**-map images**

The partitioned segmentation masks of the MM and LM were transferred onto the T_2 -map MR images using co-registration. To achieve this, an approximate region of interest for the combined MM and LM volumes was first estimated within a 25 voxel range of the segmentation of the menisci in both the 2D/3D-TSE MR images and the T_2 -maps. The extraction of the approximate meniscal region in the T_2 -maps relied on the assumption that the TSE and T_2 -map images obtained from the scanner were coarsely aligned for a given patient (i.e., motion between MR scans within a 25 voxel size at maximum). Although not required for this study, a global rigid pre-registration could be used to coarsely realign the images prior to identification of the region of interest. The cropped areas of the combined MM and LM were finally registered using rigid registration. The registration algorithm employed is based on a robust block-matching optimisation strategy that generates inverse-consistent registrations of images [Rivest-Hénault 2015]. This registration method was utilised as it had been shown to provide robust alignments for MR images featuring different signal intensity contrasts. This stage resulted in partitioned segmentation masks of the MM and LM in the T_2 -map images.

Estimation of the T₂-properties of the MM and LM

Descriptive statistics of the T_2 relaxation properties of the individual MM and LM were estimated within the complete meniscal region and within the sub-regions of the structures in the T_2 -maps thresholded between 1 - 50ms at the peripheries and 1 - 150ms within the body of the meniscus. These thresholds were selected subjectively based on testing and evaluation of the results. The thresholding operations were performed in an effort to exclude any surrounding cartilage tissue from the meniscal region and for the removal of mono-exponential fit errors in the image (very high intensity pixels).

5.2.4 Statistical Analyses

The statistical analyses performed can be separated into two categories: the validation of the accuracy of the method, and proof of concept experiments. The proof of concept experiments aimed at comparing clinical outcomes to findings previously published and at comparing outcomes obtained with the automated and manual methods.

5.2.4.1 Validation Strategy

Associations between meniscal parameters estimated from the automated and manual segmentations of the MM and LM were evaluated using the Pearson product-moment correlation coefficient (r) [Lee Rodgers 1988], the intraclass correlation coefficient (ICC - two-way random single measure)[Koch 1982] and Bland-Altman analyses [Bland 1986]. In this research work, correlations were considered to be strong when the ICC and r coefficients were above or equal to 0.75, moderate to strong if the coefficients were situated between 0.5 and <0.75 and weak otherwise. Bland-Altman analyses were used to identify any strong bias in the automated estimation of the measurements and to quantify the mean bias. These statistics were generated for the meniscal volume, subluxation and tibial coverage estimated in the OAI dataset, as well as for the mean T_2 -values estimated in the SPRI dataset.

To account for the negative skew of the DSI distributions and outliers in the segmentation results (plotted in Fig. 4.9 for both the OAI and SPRI datasets and acknowledged in Chapter 4 Section 4.4), the correlation analyses were performed on the datasets trimmed by 5% of the cases with the minimum and maximum DSI.

To validate the accuracy of the co-registrations of the MM and LM segmentations onto the T_2 maps, the DSI and the MASD were calculated between the co-registered segmentation masks and the manual segmentations of the T_2 -maps in 31 patients, as described in Equations 4.8 and 4.9 in Section 4.

5.2.4.2 **Proof of Concept Experiments**

Morphological Analyses

Using the baseline imaging data pooled over all datasets (A), (B) and (C) from the OAI, the volume, subluxation and tibial coverage of the MM and LM estimated using the automated method were compared for differences: (1) across groups of individual with no-rOA (rOA grade 0 or I), mild-rOA (rOA grade II) and advanced rOA (rOA grade III-IV), and (2) between individuals with variably severe medial and lateral JSN (grades 0, I and II). All the important demographic and clinical data for the OAI datasets are provided in Table 4.2. The comparisons were performed using the Wilcoxon rank-sum tests adjusted for false discovery rate in case of multiple comparisons [Benjamini 1995].

Biochemical Analyses

Estimated global and regional T_2 values for the MM and LM were compared for statistical differences across the injury groups (i.e. isolated ACL (ACL_i) or meniscus (MEN_i) injury or combined ACL/meniscus injury (COM_i)) and meniscus pathology (tear / no-tear classification) using the Wilcoxon rank-sum test adjusted for false discovery rate [Benjamini 1995]. These statistics were computed for the complete dataset of patients successfully segmented, and for the subset of patients with manual segmentations to compare outcomes from manual and automated methods. A significance level of p<0.05 was assumed for all tests.

All statistical analyses were performed using the "R statistical framework" version 3.0+.

5.3 Results

5.3.1 Morphological Analyses of the OAI dataset

As demonstrated in Fig. 5.4, there were strong or moderate correlations between the morphological parameters estimated from the automated and manual segmentations of the menisci at both V00 and V01. In particular, correlations were strong for the volume of the MM ($r_{V00} = 0.80$, $ICC_{V00} = 0.80$; $r_{V01} = 0.78$, $ICC_{V01} = 0.78$), and the volume of the LM ($r_{V00} = 0.91$, $ICC_{V00} = 0.90$; $r_{V01} = 0.89$, $ICC_{V01} = 0.78$), and the volume of the subluxation of the MM ($r_{V00} = 0.83$, $ICC_{V00} = 0.83$; $r_{V01} = 0.70$, $ICC_{V01} = 0.69$); and strong for the subluxation of the LM ($r_{V00} = 0.92$, $ICC_{V00} = 0.83$; $r_{V01} = 0.70$, $ICC_{V01} = 0.89$). Correlations estimated for the tibial-coverage of the MM were strong ($r_{V00} = 0.82$, $ICC_{V00} = 0.81$; $r_{V01} = 0.81$, $ICC_{V01} = 0.79$) and correlations estimated for the tibial coverage of the LM were strong or moderate ($r_{V00} = 0.83$, $ICC_{V00} = 0.82$; $r_{V01} = 0.71$, $ICC_{V01} = 0.70$). Bland-Altman analyses for comparison of the volume, subluxation and tibial-coverage between the manual and automated segmentation volumes showed an even distribution of the differences between methods for both the MM and LM (no apparent funnelling effects) with a bias of (-4.45\%, 6.46\%), (-0.525mm, -0.266mm) and (-1.98\%, -1.64\%) for the (MM, LM) volume, subluxation and tibial coverage, respectively (Fig. 5.4). The agreement between tibial-coverage and subluxation estimated from the automated and manual segmentations can be seen in Fig. 5.5.

As reported in Table 5.2 and Table 5.3, the MM in the knee of individuals with rOA and mJSN had significantly more subluxation and less tibial-coverage than the MM in knees without rOA or mJSN

(p<0.05). Similar differences were noted for the MM of knees with advanced-rOA compared to knees with mild-rOA. The volume of the MM in knees with mJSN and advanced-rOA knees was significantly greater than in knees with no-mJSN and no-rOA. The subluxation of the MM was significantly greater in knees with advanced-rOA compared to mild-rOA knees. For the LM, significantly greater meniscal volume and tibial-coverage were found in knees with rOA and IJSN compared to knees without rOA or no-IJSN (Table 5.2 and 5.3, p<0.05). The volume of the LM was also greater in knees with IJSN. The subluxation of the LM did not vary significantly across groups with variable rOA or IJSN (p>0.05).

Automated segmentations of the MM and LM were also performed to obtain volume, subluxation and tibial-coverage measurements at baseline, 12, 24 and 36 months follow-up for the OAI Progression (B) and Incidence (C) datasets (described in Section 4.2.1.1). At this stage, clinical data related to the progression of the disease in patients were not available and results are simply reported in Table 5.4, with additional data such as rOA grade and compartmental JSN progression required for downstream analyses and validation.

The computational time required to calculate the morphological parameters (bone segmentation included), was 5.1 ± 0.5 minutes (with a majority of the time required to segment the bones).



Figure 5.4: Scatter plots and Bland-Altman plots comparing the volume (**a**), subluxation (**b**), and tibial-coverage (**c**) parameters estimated from the automated and manual segmentations of the MM (green) and the LM (blue). The scatter plots present the automated segmentation parameters plotted against the manual segmentation parameters. The Bland-Altman analyses present the relative (for volume and tibial coverage) or absolute (for the subluxation) difference between automated and the manual segmentation parameters, plotted against the mean of the two values. The absolute error (expressed in mm) is used for the subluxation due to the presence of zero valued parameters.



Figure 5.5: Visual comparison of the tibial coverage obtained from the automated and manual segmentations of the menisci. The tibial coverage areas obtained from the automated and manual segmentations are displayed in red and yellow respectively. The overlap between the two areas appears in orange.

	no-rOA		m	ild-rOA	a	dv-rOA	p-value, effect-size		
	MD	IQR	MD	IQR	MD	IQR	no- vs mid-rOA	no- vs adv-rOA	mild- vs adv-rOA
MM.Vol (mm ³)	1949	1465-2406	2100	1484-2678	2350	1873-2857	0.126;0.09	<0.001;0.27	0.091,0.16
LM.Vol (mm ³)	1631	1386-2016	2331	1599-2854	2243	1730-2746	<0.001;0.28	<0.001;0.40	0.814,0.02
MM.Sub (mm)	2.31	1.31-3.38	2.74	2.10-3.94	4.59	3.56-5.50	0.013;0.15	<0.001;0.54	<0.001;0.47
LM.Sub (mm)	0.17	-0.14-0.94	0.57	0.00-1.58	0.60	0.00-1.31	0.097;0.11	0.078,0.12	0.902,0.01
MM.Cov (%)	45.2	42.0-48.7	42.8	39.2-46.3	38.1	35.0-43.5	0.016;0.14	<0.001;0.43	0.001,0.29
LM.Cov (%)	42.9	39.5-45.7	44.8	42.1-48.1	44.9	42.2-48.2	0.014;0.15	<0.001;0.20	0.865,0.015

Table 5.2: Median values (MD), interquartile range (IQR), significance values (p) and effect-sizes (r) calculated for the MM and LM volume, subluxation, and tibial-coverage for comparisons between knees with no-rOA, mild-rOA, and advanced-rOA.

]	no-JSN	m	ild-JSN	a	dv-JSN	р-у	value, effect-siz	e
	MD	IOR	MD	IOR	MD	IOR	no- vs	no- vs	mild- vs
							mid-JSN	adv-JSN	adv-JSN
MM.Vol	1058	1472 2410	2205	1873 2825	2675	103/ 2002	~0 001.0 22	0.001.0.10	0 200 0 11
(mm ³)	1938	14/2-2419	2293	1875-2825	2075	1954-5095	~0.001,0.22	0.001,0.19	0.290,0.11
LM.Vol	1751	1440 2242	2620	1772 2007			~0.001.0.22		
(mm ³)	1/31	1449-2243	2029	1/23-288/	-	-	\0.001;0.22	-	-
MM.Sub	2 25	1 46 2 42		2 21 5 51		1 25 5 42	~0 001.0 11	<0.001.0.37	0.008.0.17
(mm)	2.33	1.40-3.42	4.41	5.51-5.51	4.07	4.25-5.45	~0.001;0.44	\0.001;0.5 7	0.098,0.17
LM.Sub	0.25	0 11 1 02	0.86	0.00.1.44			0.052.0.10		
(mm)	0.23	-0.11-1.02	0.80	0.00-1.44	-	-	0.033,0.10	-	-
MM.Cov		<i>41 2 49 2</i>	20.2	265 11 9		20.8.41.1		<0.001.0.20	0.013.0.25
(%)	44.3	41.3-48.3	39.3	30.3-44.8	33.5	29.8-41.1	~0.001;0.31	<0.001;0.29	0.015,0.25
LM.Cov	12.6	40 1 46 4	15 5	10 2 19 9			0.078.0.00		
(%)	43.0	40.1-40.4	43.3	40.3-40.8	-	-	0.078,0.09	-	-

Table 5.3: Median values (MD), interquartile range (IQR), significance values (p) and effect-sizes (r) calculated for the MM and LM volume, subluxation, and tibial-coverage for comparisons between knees with no-JSN, mild-JSN, and advanced-JSN.

			Medi	al Meniscus				
		Baseline	12	Months	24	Months	36	Months
	MD	IQR	MD	IQR	MD	IQR	MD	IQR
				Volum	$me (mm^3)$			
OAI Progression (B)	2291	1870-2629	2551	2012-3244	2379	2053-2906	2405	2065-2899
OAI Incidence (C)	1884	1477-2346	1832	1395-2258	1804	1432-2279	1837	1496-2313
				Subluxa	tion (mn	<i>ı</i>)		
OAI Progression (B)	3.26	2.40-4.13	3.51	2.37-4.61	3.77	2.29-4.59	3.94	2.62-4.77
OAI Incidence (C)	1.96	1.17-3.10	2.04	1.24-2.88	2.19	1.22-3.07	2.12	1.15-2.98
				Tibial Co	overage (%)		
OAI Progression (B)	39.6	37.1-46.0	43	37.9-46.1	42.8	35.0-46.5	38.2	36.9-45.2
OAI Incidence (C)	45.5	41.9-49.5	45.4	42.1-48.8	45.6	41.2-48.5	45.8	41.7-48.4
			Later	al Meniscus				
		Baseline	12	Months	24	Months	36	Months
	MD	IQR	MD	IQR	MD	IQR	MD	IQR
				Volum	$me (mm^3)$			
OAI Progression (B)	3054	2707-3542	3093	2865-3456	3139	2888-3536	3095	2846-3463
OAI Incidence (C)	1524	1347-1918	1534	1334-1974	1542	1319-1944	1609	1353-2002
	Subluxation (mm)							
OAI Progression (B)	0.82	0.094-1.48	0.86	0.29-1.73	0.91	0.22-1.37	0.76	0.00-1.67
OAI Incidence (C)	0.25	-0.097-0.92	0.19	-0.17-1.22	0.36	-0.029-1.15	0.2	-0.043-1.18

Table 5.4: Median values (MD) and interquartile range (IQR) calculated for the MM and LM volume, subluxation, and tibial-coverage calculated at baseline, 12, 24 and 36 months.

5.3.2 Biochemical Analyses of the SPRI dataset

42.2-48.6

40.0-45.5

46.3

43.2

45.7

43

OAI Progression (B)

OAI Incidence (C)

All co-registrations of the 2D/3D-TSE MR images onto the T_2 -maps were successful and resulted in accurate segmentations of the MM and LM in the T_2 -maps. This is illustrated in Fig. 5.6 with

41.8-48.3

40.2-46.5

Tibial Coverage (%)

46

42.9

43.6-49.7

40.2-46.8

44.4

43.7

41.7-47.9

39.9-46.2

checkerboard overlays of the co-registered 2D/3D TSE MR images and T_2 -maps. The mean DSI values calculated between the co-registered segmentation masks and manual T_2 -map segmentations were 75.2% for the MM and 76.1% for the LM (Table 5.5). The correlations between the mean T_2 -values estimated from the manual and automated segmentations were strong for both the values derived from the segmentations of the 3D-TSE and 2D-TSE MR images (0.89 < r, ICC <0.99) (illustrated in Fig. 5.7(a) and Table 5.5). Bland-Altman analyses showed no funnelling effects and the mean biases calculated were 2.2% for the MM and 0.1% for the LM (Fig. 5.7(b)).

For the 76 patients with successful automated segmentations, the T_2 -values of the MM were significantly higher in the tear group than in the non-tear group (p<0.05, Table 5.6); a finding consistent across each sub-region of the MM (p<0.05 for the anterior, mid and posterior region). Numerically, T_2 -values of the MM were higher in the COM_i and MEN_i groups than in the ACL_i group but none of these values were significantly different (p>0.05 for all regions, Table 5.8). No significant differences were found in the LM T_2 -values when comparing injury groups (COM_i , MEN_i or ACL_i) or meniscus pathology groups (tear, no-tear). In the current cohort of patients, the non-torn LM had significantly higher T_2 -values than the non-torn MM (p<0.05 for the full meniscus and all sub-regions, Table 5.7). The T_2 -mapping obtained in three patients from different injury groups is provided in Fig. 5.8, which demonstrates the higher T_2 -values obtained for the LM and the injured MM (bottom row).

These results obtained from the complete patient cohort are in agreement with the statistics generated for the subset of 31 patients for whom manual segmentations were performed (Fig. 5.10). For both the T_2 -statistics estimated from the automated and manual methods, the non-torn LM had significantly higher T_2 -values than the non-torn MM (p<0.05, Fig. 5.10(a)). The MM had significantly higher T_2 -values in patients with MM tears (p<0.05 for both the automated and manual analyses, Fig 5.10(d)). Comparison across injury groups did not yield significant differences (p>0.05). The T_2 values estimated regionally for the MM and LM did not differ significantly for either the automated or manual analyses (Fig. 5.10(b) and (c)).

The time required to perform the co-registration of the data for a case was 1.9 ± 0.6 minutes on average. The T2-analysis took less than 3 seconds.



3D-TSE onto T2-maps

2D-TSE onto T2-maps

Figure 5.6: Checkerboard overlay of the co-registrations of the 3D (*left*) and 2D (*right*) TSE images onto the T₂-maps.



Figure 5.7: Correlation (left) and Bland-Altman (right) analyses comparing the T_2 -values estimated from the automated (T_2 .A) and manual (T_2 .M) segmentations.



Figure 5.8: Visualisation of the automated T_2 -mapping performed for three patients from the ACL_i , COM_i and MEN_i groups of the SPRI dataset. Bottom shows an obvious bucket-handle tear appearing in the mid-compartment of the MM.



Figure 5.9: Reconstruction of the partitioned segmentation masks obtained for three 2D-TSE *(bottom)* and three 3D-TSE *(top)* MR images.



Figure 5.10: T_2 analyses performed for the subset of MR images that were manually segmented. In the plots, values suffixed with *.M and *.A are the values estimated from the automated segmentations (orange) and the manual segmentations (blue), respectively. (a) Comparison of the T_2 values of the non-torn MM and the non-torn LM for both the automated and manual methods. (b & c) Regional analysis of the MM and LM T_2 -values. Ant.*, Mid.* and Post.* describe the T_2 statistics estimated for the anterior, mid and posterior regions, respectively. (d & e) Comparison of the MM and LM T_2 -values between the tear and no-tear group.

Table 5.5: Validation of the accuracy of the segmentation of the MM and LM in the T_2 -maps, as measured with the DSI and the MASD. Validation of the T_2 -measurements using the Pearson (r_{T_2}) and intraclass (ICC_{T_2}) correlation coefficients calculated between the T_2 means estimated from the automated $(T_2.A)$ and manual segmentations $(T_2.M)$. The correlation coefficients were calculated for the combined dataset of 2D/3D-TSE MR images and separately for the segmentations derived from the 2D and 3D-TSE MR images.

	DSI	MASD	T_2 .M	$T_2.A$	r_{T_2} ; ICC_{T_2}	r_{T_2} ; ICC_{T_2}	r_{T_2} ; ICC_{T_2}
	(%)	(mm)	(ms)	(ms)	(overall)	(from 2D-TSE)	(from 3D-TSE)
MM	75.2±7.8	0.50±0.34	28±3.82	27.4±4.31	0.95;0.94	0.95;0.93	0.95;0.95
LM	76.1±10.6	$0.45 {\pm} 0.45$	31.2±3.05	31.1±3.18	0.97;0.97	0.89;0.89	0.99;0.99

Table 5.6: Comparison of the T_2 values estimated for the torn and the non-torn MM and LM. Significant differences are shown in bold font.

	No-'	Tear (n=51)	Te	ar (n=25)	No-tear vs Tear
MM Region	MD	IQR	MD	IQR	P-value;Effect-size
Full	26.76	24.85-29.02	28.96	27.1-29.91	0.004;0.32
Anterior	26.54	24.63-29.26	28.63	26.77-30.24	0.01;0.28
Mid	28.22	24.25-31.06	31.12	27.99-32.13	0.02;0.27
Posterior	26.43	24.37-28.84	28.26	26.31-29.28	0.041;0.23
	No-	tear (n=38)	Te	ar (n=38)	No-tear vs Tear
LM Region	MD	IQR	MD	IQR	P-value;Effect-size
Full	30.36	29.55-31.75	30.59	29.39-32.88	0.51;0.08
Anterior	30.43	29.27-32.08	30.26	28.78-33.98	0.96;0.01
Mid	30.89	28.51-33.39	32.46	28.7-34.93	0.38;0.10
Posterior	30.15	29.06-31.87	30.8	27.98-32.55	0.78;0.032

Table 5.7: Comparison between the T_2 values estimated for the non-torn MM and the non-torn LM.

	MM (n=51)		L	M (n=38)	MM vs LM
Region	MD	IQR	MD	IQR	P-value;Effect-size
Full	26.76	24.85-29.02	30.36	29.55-31.75	<0.001;0.59
Anterior	26.54	24.63-29.26	30.43	29.27-32.08	<0.001;0.55
Mid	28.22	24.25-31.06	30.89	28.51-33.39	<0.001;0.36
Posterior	26.43	24.37-28.84	30.15	29.06-31.87	<0.001;0.57

	AC	ACL _i (n=21)		MEN _i (n=11)		<i>COM</i> _i (n=44)		p-value, effect-size		
LM	MD	IOR	MD	IOR	MD	IOR	ACL_i vs	ACL_i vs	MEN_i vs	
		iųn	MD	iųn	MD	iųn	MEN_i	COM_i	COM_i	
Full	30.35	29.88-32.16	30.33	28.13-31.16	30.6	29.44-32.38	0.41;0.20	0.86,0.023	0.41,0.18	
Anterior	29.64	29.04-32.48	29.88	27.59-30.18	30.81	29.14-33.14	0.29;0.23	0.63,0.061	0.08,0.30	
Mid	31.84	29.11-33.71	30.47	27.89-33.07	31.38	28.73-34.66	0.49;0.18	0.87,0.021	0.49,0.16	
Posterior	30.18	28.16-32.6	30.13	28.99-31.48	30.59	28.3-32.27	0.72;0.13	0.83,0.03	0.72,0.10	
MM	MD	IOP	MD	IOP	MD	IOP	ACL_i vs	ACL_i vs	MEN_i vs	
IVIIVI		IQK	MD	IQK	MD	IQK	MEN_i	COM_i	COM_i	
Full	26.76	24.83-29.17	28.48	26.26-29.45	27.57	25.76-29.62	0.60;0.16	0.60,0.11	0.80,0.04	
Anterior	26.84	25.12-30.04	27.28	26.81-30.48	27.43	24.93-29.22	0.47;0.20	0.97,0.01	0.47,0.14	
Mid	28.29	23.97-30.24	29.11	25.67-31.89	29.22	26.66-31.85	0.69;0.14	0.69,0.13	1.00,0.00	
Posterior	26.36	24.33-29.69	27.08	25.68-29.02	26.85	24.87-29.09	0.93;0.09	0.93,0.10	0.93,0.01	

Table 5.8: Comparison of the T_2 values (ms) estimated for the MM and LM between knee pathology groups.

5.4 Discussion

Assessment of the menisci using quantitative MR imaging currently requires considerable time and expertise, with limited numbers of studies having directly evaluated the knee menisci with biochemical MR imaging [Zarins 2010, Juras 2014, Chu 2014, Baum 2013, Subburaj 2015]. The primary objective of this chapter was to demonstrate that quantitative MR analysis of the morphological and T_2 properties of the knee menisci can be performed efficiently and reliably using the automated algorithms developed in this PhD work. This was demonstrated by cautious comparison of the estimated automated measurements against measurements calculated from expert manual segmentations of the menisci. The method was validated for suitability in analyses of the knee joint with common pathologies (OA, meniscus or ACL tear) from MR protocols typically acquired in research studies (WE-DESS MR images), current routine clinical examinations (2D-TSE MR images) and a promising MR sequence for clinical diagnosis the menisci (3D-TSE MR images). To the best of the author's knowledge, this constitutes a first attempt at evaluating the accuracy of a fully-automated quantitative MR analysis method for the individual MM and LM, and no standards for precision have been set.

The parameters estimated from the automated segmentations of the menisci in the WE-DESS MR images showed overall good correlations with those estimated from expert segmentations (r and *ICC* > 0.7 for all measurements), suggesting that the automated method may provide a suitable alternative to manual methods in clinical studies into the menisci. The method was sufficiently sensitive to discern meaningful differences in the morphology of the MM and LM across groups of individuals demonstrating variable rOA and JSN characteristics which are in agreement with the literature.

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In particular, the MM showed an overall greater volume, subluxation and a smaller tibial-coverage area in individuals with more advanced rOA and mJSN, concurrent with recent findings of semiand fully-quantitative clinical studies [Blöcker 2013, Hwang 2012, Am Jung 2010], despite the differences in initial study design, MR sequences, population size and demographics. The LM showed a greater median volume in knees with rOA and mJSN but no significant differences in subluxation, although numerical values were slightly greater in pathological individuals. Interestingly, as a result of significantly greater volumes and only minor positional differences, the tibial-coverage of the LM was found significantly greater in knees with rOA. This has been previously reported in *Wenger et al.*, where a 4.4% relative difference was found (although this difference was not reported significantly with a calculated p = 0.051 [Wenger 2013]). This difference was not found significantly different between knees with and without IJSN.

With respect to the analysis of the T2 relaxation of the menisci from T_2 -maps, the co-registration algorithm was robust and allowed transfer of the segmentation information obtained in the TSE MR images into all the T_2 -maps. The resulting segmentation accuracy was found to be superior to that obtained by *Swanson et al.* in the segmentation of T_2 -maps (mean DSI 76% vs 69%), although it should be acknowledge that the initial populations were different.

There were strong positive correlations between the T_2 values estimated from the automated and manual methods, for both T_2 -map segmentations derived from routine 2D-TSE and newer 3D-TSE MR images. Both the automated and manual methods distinguished similar patterns of differences in the prototype group comparisons. Namely, T_2 -mapping of the MM showed significantly higher T_2 -values in patients with meniscal tears, a pattern of difference which has been previously reported [Liu 2015]. The non-torn LM was characterised by a significantly higher T_2 -relaxation than the nontorn MM, which may be related to secondary early degeneration of the LM as a result altered loading mechanisms in ACL deficient knee joints [Feucht 2015]. Outcomes from the subset of patients with manual segmentations were further confirmed using the 76 patient MR images successfully segmented with the automated method (Table 5.5, 5.6 and 5.8). A limitation of these T_2 measurements is that part of the variations observed in this study may be caused by changes in the orientation of the fibres of the knee menisci (magic angle artifacts, see Section 2.4.2.6), although the relatively long echo times likely limited this effect. This has not been investigated in this study as a complete dataset of confirmed healthy individuals would be required. This provides an avenue for future research.

Despite the demonstrated good performance of the automated quantitative MR analysis method for investigation of the pathological knee joint from MR images, there are several limitations that need to be acknowledged.

We have seen in Chapter 4 that the external margin of the mid-compartment of the menisci was a problematic area to segment with the algorithm (usually over-segmentation occurs). This has a direct impact on the accuracy of the estimated subluxation parameter and explains the moderate correlation with manual segmentation measurements for the MM, with a calculated mean bias of 0.52mm. Nevertheless a calculated correlation with manual measurements over 0.7 was found sufficiently accurate to replicate current clinical findings of the literature. Extending the training dataset of tissue profiles is an avenue to improve segmentations in this area.

A second limitation relates to the tibia bone segmentation, which was obtained automatically in this study and was not quantitatively validated. The published method has however demonstrated strong segmentation performance in the segmentation of the tibia (mean DSC 96%) and in the identification of the BCI region (0.16mm MASD) in FS SPGR MR images with lower spatial resolution (1.5mm slice thickness). Based on visual inspections, we assume the obtained segmentations to be accurate representation of the true anatomy of the tibia for this PhD work. Future work should involve quantifying the bias introduced by the automated bone segmentation.

Regarding the T_2 -mapping experiments, it is unfortunate that the spatial-resolution of the T_2 -map MR images did not allow for analysis of the T_2 properties separately for the three important circumferential zones of the meniscus (white, red-white and red zone, see Section 2.1.3 for details). This would provide opportunities to investigate healing and repair capabilities of each zone and could influence current treatment of common injuries (described in Section 2.3.1). Estimating the T_2 -maps from WE-DESS MR images or utilising biochemical MR sequences from newer 7T MR scanners would provide opportunities to further split each meniscus into three circumferential areas and is an avenue for straightforward extension of the analysis method (illustrations are provided in Fig. 5.11).

While magic angle artifacts were a potential cause of segmentation error near the horns of the knee menisci, greater T_2 relaxation values were expected in these areas [Du 2011], where the orientation of the fibres is roughly 55° with the head to foot B_0 magnetic field. In our study, the reported increase in T_2 -relaxation was not observed, but should be investigated in more details in future work.

5.5 Conclusion

This chapter demonstrated that the automated segmentation and quantitative MR analysis method provides a promising alternative to manual analyses method for investigating the morphology and biochemistry of the meniscus (Aim 1.2). Following accurate segmentation of the MM and LM, quantitative analyses obtained Pearson correlations ranging from 0.70 to 0.92 between manual and automated estimation of meniscal volume, subluxation and tibial-coverage of the meniscus and over 0.9 for estimation of T_2 -relaxation values. Proof of concept experiments obtained patterns of differences corroborating recent clinical findings for both morphological and T_2 analyses. The scheme is well suited to efficiently process and analyse large-scale MR cohorts such as the OAI, thereby facilitating investigations into early degeneration of the menisci associated with knee OA. The method also represents a significant advance towards clinical applicability of T_2 -mapping, requiring minimal visual inspections of the results to account for the failure rate of the automated segmentation method.



Figure 5.11: Illustration of the pilot results on circumferential partitioning of the meniscus and T_2 -mapping at 7T.

Segmentation and Analysis of the PCL from T_2 -Map MR Images of the Knee

Co	nter	nts

6.1	Introduction
6.2	Material and Method
6.3	Results
6.4	Discussion
6.5	Conclusion

This chapter presents the research related to Aim 2 of this PhD project. It involves the automated segmentation and quantitative analysis of the knee posterior cruciate ligament (PCL) from T_2 -map magnetic resonance (MR) images. The central goal is to evaluate the performance of a multi-atlas patch-based method for segmentation of the PCL from routine clinical multi-echo spin-echo T_2 -map MR images of the knee joint. The validation is performed against manual segmentations of the PCL carried out by an expert for 26 T_2 -maps of the asymptomatic knee joint. Quantitative values (PCL volume, length and T_2 -relaxation) are derived from the automated and manual segmentations and compared. In the framework of knee OA, the method is applied on a cohort of 88 pathological knee T_2 -map MR images from the osteoarthritis initiative and the resulting T_2 measurements are compared across knees with variably advanced radiographic osteoarthritis.

The chapter is organised as follows: A short introduction will highlight the research problem, motivation and challenges associated with the segmentation of the PCL from T_2 -maps. In the following section the MR datasets are presented and the patch-based multi-atlas segmentation framework is described. The segmentation and quantitative analysis results are finally presented and discussed. The core material detailed in this chapter has been published and presented at the ITEE International Symposium In Biomedical Imaging (ISBI 2016) [Paproki 2016b].

6.1 Introduction

The clinical potential of biochemical MR imaging techniques such as T_2 -mapping for assessment of the PCL has been recently demonstrated [Biercevicz 2014a, Wilson 2016] (for detailed review, see Section 3.2). These MR sequences allow for quantitative evaluation of the structural integrity of the PCL *in-vivo*. This, in turn, can be critical for accurate diagnosis of chronic injuries that may not show apparent signal changes in conventional MR images [Servant 2004] and in the assessment of ligament health and function post-surgery [Biercevicz 2014a].

Accurate segmentation of the PCL in the biochemical MR images is a prerequisite for analyses. Manual segmentation remains the standard for quantitative assessment of the PCL in clinical MR studies. This process is expertise- and time-intensive. It also involves considerable subjective interpretations by the observer as a result of a ligament visualisation highly dependent on joint positioning and the similar contrast characteristics of the PCL with the knee menisci and ACL in biochemical MR sequences such as T_2 -maps (A listing of all the challenges is provided Section 3.2.3). The shape and contrast characteristics of the PCL in a T_2 -map MR image are illustrated in Fig. 6.1.

Automated segmentation of the PCL from MR images remains mostly unexplored, with only two methods published that did not perform thorough validation of accuracy [Zarychta 2016, Uozumi 2015]. The development and cautious validation of an automated method to segment the PCL from the MR images is therefore desirable. It would facilitate clinical studies into the PCL and provide a significant advance for integration of quantitative MR analyses of the PCL in routine examinations.

Model-based techniques (described in Section 2.5) are usually inadequate for segmentation of MR sequences where limited spatial information is available at the edge of the segmented structures (large slice thickness/gap). Alternatively, multi-atlas analysis methods have become popular tools for precise automated segmentation of MR images and have been successfully applied in various fields including brain, prostate or MSK imaging [Heckemann 2006b, Dowling 2011, Xia 2013]. They utilise the non-rigid registration of multiple atlases incorporating reliable expert priors and label fusion to identify the segmentation, although computational complexity becomes a major limitation. Patch-based multi-atlas segmentation solutions have been developed to relieve the computational bottleneck



Figure 6.1: (*left*) The top row shows the typical PCL characteristics in a T_2 -map MR image, visualised in the sagittal, coronal and axial planes. The bottom row shows an overlay of the segmentation of the PCL onto the T_2 -map. (*right*) shows the surface rendering of the PCL segmentation. This illustrates the lack on contrast between the PCL and surrounding tissues, especially in the coronal and axial planes, which display strong partial volume effects. The T_2 -map MR image was selected from the OAI MR dataset.

[Coupé 2011, Wu 2015, Pant 2015]. These methods do not require stringent pair-wise non-rigid registration with atlases and instead determine a label for each voxel of the MR image using patches extracted from its neighbourhood and matched with patches of the coarsely aligned atlases (e.g., rigid or affine registration). Implementation of this method using sparse optimisation provided more efficient analyses and results reported for segmentation of the hippocampus showed high accuracy [Coupé 2011, Pant 2015].

In this chapter, the performance of a sparse patch-based method for automated segmentation and quantitative analysis of the PCL in T_2 -map MR images of the knee is investigated. The method is evaluated quantitatively for accuracy using manual segmentations of the PCL in T_2 -maps acquired for 26 asymptomatic subjects. Further qualitative validation is performed using 88 T_2 -map MR images from the OAI. Pilot experiments are used to investigate the differences in PCL T_2 -relaxation values across patients with differing levels of knee rOA.

6.2 Material and Method

6.2.1 MR Image Datasets

6.2.1.1 The Steadman Philippon Research Institute T₂-Maps

This study was approved by the institutional review board of the Vail Valley Medical Center. Informed consent was obtained from all participants included in the study. Twenty-six asymptomatic volunteers (11 males, 15 females, 14 right and 12 left knees, aged between 18-62 years) were enrolled as part of a study external to this research that aimed at quantifying the biochemistry and morphology of the PCL (natural variability found in the asymptomatic population) [Wilson 2016]. Standard, unilateral multi-echo spin-echo T_2 -map MR images were acquired for the knee joint of each volunteer. The subjects had no prior history of knee surgery and standard objective clinical and MR examinations deemed them asymptomatic. Images were obtained on a 3T Magnetom Verio MR scanner (Siemens Healthcare, Erlangen, Germany) with a gradient strength of 40mT/m using a 15-channel multi-element knee coil (Quality Electrodynamics, LLC, OH, USA) with the subjects' knee extended and carefully placed at the centre of the coil. A detail listing of the MR parameters is provided in Table 6.1. The PCL was manually segmented in the T_2 -maps of each participant by a MSK radiologist using Mimics (Materialise, Plymouth, MI, USA).

Illustrations of the T_2 -map MR images acquired by SPRI for three participants are provided in Chapter 3, Fig. 3.3 (top row). This dataset was utilised as atlas for the training and validation of the method.

6.2.1.2 The Osteoarthritis Initiative T₂-Maps

An additional dataset of 88 T_2 -map MR images was selected from the OAI database (45 males, 43 females), which is available for public access at http://www.oai.ucsf.edu for further processing and analysis. A detailed description of the OAI has been provided in Section 4.2.1.1 and the reader should refer to this section for more information. The general demographic data for these patients have also been provided in Section 4.2.1.1 and Table 4.2 (dataset (A)). Clinical assessments related to the knee joints imaged are however different for part of the data (standard MR imaging protocol by the OAI involves acquisition of T_2 -maps for the right knee only [Peterfy 2008]) and this particular dataset covered the full spectrum of grades of knee rOA. In particular, the dataset was constituted of T_2 -maps

Scan	SPRI T ₂ -maps	OAI T_2 -maps
Plane	Sagittal	Sagittal
FOV (mm)	80	120
Matrix	128×128	384×384
No of slices	11	27
Resolution (mm)	0.625×0.625	0.313×0.313
Slice thickness/gap (mm)	2.0/2.0	3.0/0.5
TE/TR (ms)	2000/10.7-74.9	2700/10-70
Number of echoes	7	7
Acquisition Time (min:sec)	4:44	10:36

Table 6.1: MR parameters used by SPRI and the OAI to acquire the T_2 -maps.

of the right knee joint with no-rOA (N=3, near K/L grade 0), possible rOA (N=10, near K/L grade I), mild-rOA (N=18, near K/L grade II), moderate rOA (N=45, near K/L grade III) and severe-rOA (N=12, near K/L grade IV).

Illustrations of the T_2 -map MR images acquired by the OAI for three patients are provided in the bottom row of Fig. 3.3.

6.2.2 Segmentation Method

As illustrated in Fig. 6.2, the automated segmentation pipeline consists of 4 main stages (1) preprocessing of the T_2 -map MR image, (2) affine alignment of the MR image with the co-registered atlases, (3) multi-scale patch-based PCL segmentation and (4) post-processing. In this research, the T_2 -map MR images and associated expert manual segmentations from the SPRI dataset were used as atlases. Automated segmentation was performed directly onto the T_2 -maps (as opposed to segmenting a specific echo image), which provided comparable and homogeneous quantitative measurements across subjects for the PCL and surrounding tissues (i.e., independent of the T_E).

6.2.2.1 T_2 -map Pre-processing

Atlas pre-processing – In order to remove the hyper-intense voxels introduced in the T_2 -maps by exponential fit errors, to reduce the noise in the MR images and to improve the interface between tissues with different signal intensity, the images were thresholded between [0 - 400]ms and a gradient anisotropic smoothing filter with modified curvature diffusion equation was used (time-step=0.02,



Figure 6.2: Processing pipeline for the segmentation of the PCL in the individual T_2 -maps.

conductance=0.8, iterations=20) [Whitaker 2001, Ibanez 2003]. The signal intensity was then normalised across all the images of the atlas using intensity rescaling and all left knees were flipped in the sagittal plane to mirror the right knee anatomy.

All the images of the atlas were then affine co-registered to a common space (that of a case of the dataset) using a robust inverse-consistent block-matching affine registration algorithm (MIRORR [Rivest-Hénault 2015]). The transformations obtained were used to import the manual segmentations from the expert into the atlas space.

Target image pre-processing – In the first step of the segmentation pipeline, the target MR image to segment – denoted I_t – was pre-processed using similar thresholding, smoothing and intensity rescaling operations that were used for the atlases. The left knee images were flipped sagittally into right knees. This processing was specific to the segmentation stage and was not utilised for the subsequent T_2 analysis stage.

6.2.2.2 Affine initialisation

The target image I_t was then coarsely aligned with the canonical space of the atlases. The alignment was performed using symmetric affine registration (i.e., result independent of the direction of the registration), once again estimated using the MIRORR algorithm [Rivest-Hénault 2015].

6.2.2.3 Patch-based segmentation

Patch-based methods segment each individual voxel in an MR image by comparison of their surrounding patch with patches estimated in the training atlases, and in which the segmentation label of the central voxels are known. If the patch under consideration resembles a patch in an atlas image, the central voxels of these two patches are considered to belong to the same anatomy. This particular patch from this atlas will then weigh on the final segmentation label of the voxel based upon its degree of similarity to the target patch considered.

The patch-based segmentation utilised in this study has been proposed by *Pant et al.* [Pant 2015]. For each voxel $x \in I_t$, a patch is extracted and expressed as a linear combination of the patches estimated in the N atlases in a cubic neighbourhood $y \in n(x)$ of the voxel x of interest. Specifically, if we express the target patch as a feature vector A and the patches of the atlases as a matrix V of feature vectors v_b (b = 1, ..., Q)_{$Q=N \times |n(x)|$} arranged column-wise, then the problem to solve can be expressed as $A = V \times W$ subject to the sparse constraint min $||W||_1$, where W is a concatenation of weights $w_b(b = 1, ..., N)$ that are mostly zero. The weights w_b can be obtained by solving the L_1 minimisation problem proposed in equation 6.1 using the *sparse learning with efficient projections* (SLEP) library [Liu 2009] and a group Lasso method [Meier 2008].

$$\hat{W} = \arg\min_{W} \frac{1}{2} \|A - V \times W\|_{2} + \lambda \|W\|_{1}$$
(6.1)

In equation (6.1), λ is a scalar that controlled the strength of the sparsity. The binary label of each voxel x in the image I_t was then determined from the non-zero weights of W using weighted voting, as expressed in equation 6.2.

$$L_{x} = \arg\min_{m=1...M} \sum_{b=1}^{Q} (w_{b} \cdot \delta(L_{b}, L_{m}))$$
(6.2)

In this equation, δ is a Dirac function equal to one only when the labels L_b and L_m are similar, zero otherwise. In the case of the PCL segmentation, only one label exists (M = 1) and the function will be equal to one only when the patch considered has the segmentation label corresponding to the PCL.

To precisely characterise the local anatomical information of the PCL, different image scales were used to create multi-scale patches, such that each patch was constituted of three patches describing the local information of the PCL with variable levels of fine detail. The image pyramid was created by convolution of the image I_t with discrete Gaussian kernels and down-sampling by a factor of four (coarser scale), two and one (original fine scale). Such multi-scale feature patches have been shown to provide better similarity response when comparing patches and increased precision in segmentation schemes [Wu 2015, Pant 2015].

6.2.2.4 Post-processing

Eventual gaps in the segmentation masks of the PCL were filled using the hole-filling filter available in ITK [Ibanez 2003]. The segmented voxels separated from the largest PCL region were removed.



Figure 6.3: Illustration of the process used to calculate the length of the PCL. (a) shows the overlay of the reconstructed surface of the segmented PCL (transparent blue) in the T_2 -map. The red line drawn between the two red points illustrates the effective PCL length measurement. (b) provides a closer look at the projection of the PCL into sagittal plane in orange.

Finally, the segmentation mask was transformed back into the original T_2 -map space using the inverse of the transform obtained in Section 6.2.2.2 for use in T_2 analyses.

6.2.3 Quantitative Analyses

From the segmentation masks of the PCL in the original T_2 -map space, descriptive statistics of the T_2 -relaxation properties of the PCL were estimated from the T_2 -maps thresholded between [0 - 150]ms in both the OAI and the SPRI dataset. These thresholds were selected in an effort to removed hyperintense voxels introduced in the images during the mono-exponential least-squares-fit used to obtain the T_2 -maps from the multi-echo images. The images were further processed using median smoothing $(1 \times 1 \text{ region size in the in-plane direction})$.

In addition, morphological parameters including length and volume of the PCL were estimated. The volume was calculated by integration of the voxels belonging to the PCL segmentation mask. The length of the PCL was calculated as the maximum distance between the two extremities of the PCL (i.e., corresponding to the attachment points with the bones). As illustrated in Fig. 6.3, this measurement was evaluated in a plane parallel to the slice of the T_2 -maps and passing through the centroid of the PCL volume for increased consistency in the measurements and to minimise the contribution of the 'cross-sectional' component of the PCL length to the variability. These morphological measurements may be useful in characterising the laxity of the ligament post-surgery. The PCL length relied on bone segmentations to identify the extremities of the PCL (which was obtained from 2D-TSE MR images for the SPRI dataset and WE-DESS MR images for the OAI dataset).

6.2.4 Statistical analyses

Using the SPRI dataset of 26 asymptomatic volunteers, the automated segmentation results were compared to the manual segmentations from the expert using the sensitivity, specificity, DSI and MASD, as previously defined in equations 4.6, 4.7, 4.8 and 4.9. Experiments were performed using a *leaveone-out* strategy such that the case being segmented I_t was removed from the atlases used in the patch-base segmentation.

To investigate the performance of the automated method in quantitative MR analyses of the PCL, correlations between volume, length and T_2 parameters estimated from the automated and manual segmentations were calculated using Pearson (r) and intra-class correlation coefficients (ICC two-ways random single measures) [Koch 1982]. To account for outliers and the negative skew of the DSI distributions, correlations were calculated on the dataset trimmed by 5% of maximum and minimum DSI. Correlations between parameters were strong when the ICC and r coefficients were above or equal to 0.75, moderate to strong if the coefficients were situated between 0.5 and <0.75 and weak otherwise.

PCL T_2 -values estimated for the OAI dataset were compared across groups of patients with norOA (K/L grade 0 or I), mild-rOA (K/L grade II or III) and severe-rOA (K/L grade IV) of the knee using Wilcoxon rank-sum tests corrected for false discovery rate [Benjamini 1995].

6.3 Results

6.3.1 The SPRI T₂-Map MR Images

In this section, the segmentation results obtained on the SPRI dataset are quantitatively evaluated. The patch-based method performed well for the automated segmentation of the PCL in the T_2 -maps, obtaining a mean spatial overlap with the manual segmentations of $74.5 \pm 3.7\%$ using the leaveone-out strategy. This is illustrated in Fig. 6.5 where automated and manual segmentations of the PCL are shown for two participants and demonstrate good visual agreement. From the distribution of the DSI obtained for the 26 subjects (Fig. 6.4), we identified that no segmentation failed in this particular dataset (DSI > 65% for all subjects), although the DSI of several cases skewed negatively the distribution of the DSI. The MASD calculated between surfaces of the PCL reconstructed from the automated and manual segmentations was inferior to the in-plane resolution (0.51mm < 0.63mm) and slice-thickness $(0.51mm \ll 2.0mm)$ of the T_2 -maps. From the high specificity and comparatively low sensitivity reported in Table 6.2, we concluded that under-segmentation was the most common segmentation error obtained.

The correlations calculated between the parameters estimated from the automated and manual segmentations were moderate for the volume ($r_V = 0.67$, $ICC_V = 0.67$), strong for the PCL length ($r_L = 0.88$, $ICC_L = 0.85$) and moderate to strong for the T_2 relaxation ($r_{T_2} = 0.79$, $ICC_{T_2} = 0.74$) (table 6.3, Fig. 6.7). Bland-Altman analyses performed for the volume, length and T_2 properties of the PCL showed no apparent funnelling effect or strong bias (Fig. 6.7), with a mean bias of 1.5%, 3.0% and -5.2% calculated between the manual and automated measurements, respectively. The typical good agreement obtained between the automated and manual methods for T_2 -mapping of the asymptomatic PCL is shown for two participants in Fig. 6.6.

Table 6.2: Quantitative validation of the automated segmentation of the PCL in the SPRI dataset by comparison to the expert manual segmentations.

	Sensitivity (%)	Specificity (%)	Mean DSI (%)	MASD (mm)	
PCL	74.0±8.10	99.76±0.09	74.5±3.7	0.51±0.08	

Table 6.3: Comparison of the parameters estimated from the automated and manual segmentations of the PCL in the T_2 -maps (SPRI dataset).

Correlations							
Auto Manual r ICC							
Volume (mm ³)	1691±349	1755±416	0.67	0.66			
T_2 (ms)	29.4±5.4	27.9±3.7	0.79	0.74			
Length (mm) 37.9±3.2 39.2±4.1 0.88 0.							



Figure 6.4: Spread of the DSI values obtained for the 26 asymptomatic knee T_2 -maps with manual segmentations.



Figure 6.5: Visual comparison of the automated and manual segmentation of the PCL in two T_2 -maps from the SPRI dataset. Both cases are representative of the average accuracy, with a DSI of 75.8% and 73.6% obtained for participant (a) and (b), respectively.



Figure 6.6: Illustration of the T_2 -mapping of the PCL performed in two healthy participants from the SPRI dataset using the automated and manual methods.



Figure 6.7: Correlation and Bland-Altman plots for the volume, length and T_2 -relaxation parameters of the PCL. In these graphs, M and A represent the measurements estimated from the *Manual* and *Automated* segmentations of the PCL, respectively.

6.3.2 The OAI T_2 -Map MR Images

In this section, the segmentation results obtained on the OAI dataset are qualitatively evaluated. The automated method was successfully applied on the 88 T_2 -maps from the OAI. The typical quality of the automated segmentations obtained can be visualised in Fig. 6.8, showing the segmentation of the PCL in two T_2 -maps from patient with mild and severe knee rOA. Visual inspections of each PCL segmentation showed that the method performed well for the majority of the patients ($80/88 \approx 91\%$), which highlights the generalisability of the method to T_2 -maps different from that of the initial training set.

Several cases (n=8) from the OAI dataset could not be segmented accurately, as identified by erroneous overlays of the segmentation results onto the T_2 -maps (Fig 6.9). This was primarily caused by motion artifacts in the T_2 -maps (i.e., patient movement during or between acquisition of the multiple echoes of the T_2 -maps) or severe damage to the knee as a result of knee OA, which led to further blurring of the boundary of the PCL with adjacent structures. This is illustrated in Fig. 6.9 where
the meniscus, ACL and PCL were poorly delineated, which caused segmentation difficulties. Among these patients, four were from the group of patients with severe rOA, three from the group of patients with moderate knee OA and one from the group of patients with mild rOA.

Initial quantitative experiments comparing the T_2 -relaxation values of the PCL in the 80 patients with successful segmentations showed no numerical differences in the T_2 relaxation values of the PCL across groups of individuals with variably advanced radiographic OA (P > 0.05 for all tests, Fig. 6.11). Specifically, the median (interquartile range) T_2 values calculated were 41.67(40.51 - 42.98)ms for the group of patients with no confirmed rOA, 41.67(39.78 - 42.54)msfor the group of patients with mild to moderate rOA and 41.38(40.21 - 42.91)ms for the group of patients with severe rOA. An illustration of the automated T_2 -mapping obtained for three patients with mild or moderate knee rOA is shown in Fig. 6.10.



Figure 6.8: Visual overlay of the automated segmentation of the PCL in the T_2 -weighted MR images (second echo) of two patients from the OAI dataset with mild (left, K/L grade II) and severe (right, K/L grade IV) knee rOA.



Figure 6.9: Illustration of two patients for which the segmentation of the PCL was made difficult by motion artifacts (visible in (b)) in the MR images or severe damage to the knee. (a) notably shows an osteophyte near the insertion point of the PCL into the tibia and (b) shows severe JSN, which increased the bending the PCL. Overlay is shown in T_2 -weighted MR images (second echo).



Figure 6.10: Illustration of the T_2 -mapping of the PCL performed in three patients from the OAI dataset using the automated methods. From top to bottom, the figure shows the knee of a patient with (a) moderate knee rOA (K/L grade III) and (b,c) two patients with mild rOA (K/L grade II).



Figure 6.11: Comparison of the median T_2 -relaxation values estimated automatically in patients with no rOA (K/L grade 0 or I), mild-rOA (K/L grade II or III) and severe rOA (K/L grade IV).

6.3.3 Computational Time

All experiments were performed on a laboratory computer previously described in Section 4.3.4.

For the SPRI dataset, on average, the time required to run the segmentation pipeline was 17.7 ± 1.0 seconds, which included 8.3 ± 1.2 seconds to perform the preprocessing and affine initialisation with the atlas of images and 9.4 ± 0.6 seconds to run the patch based segmentation. The T2 analysis of the segmented PCL took less than 3 seconds, while the morphological analysis required 3.2 ± 0.5 minutes (including the time required to extract several bone features used to calculate the PCL length).

For the OAI dataset, the average time required to run the segmentation was 1.5 ± 0.0 minutes, including 1.2 ± 0.0 minutes of preprocessing and affine initialisation and 16.1 ± 0.5 seconds of patch based segmentation. The T2 analysis required 6.4 ± 0.2 seconds on average and the morphological analysis required 5.7 ± 0.7 minutes (including the bone segmentation).

6.4 Discussion

In this chapter, a fully automated approach for the successful segmentation of the PCL from T_2 -map MR images was presented. The method relied on a multi-scaled patch-based segmentation strategy that obtained robust segmentation results with good accuracy when utilising a baseline dataset of 26 T_2 -maps with manual segmentations as training atlas. This was demonstrated quantitatively using a leave-one-out strategy to process the training dataset, with a mean DSI calculated as 74.4±4.2%. Further results obtained for the segmentation of the PCL on a cohort of 88 pathological knee T_2 -maps were promising, although the evaluation of the performance relied on visual inspection only.

Unfortunately, published methods for the segmentation of the PCL from MR images did not provide quantitative validation of the results obtained and thus no baseline values of accuracy exist [Zarychta 2010, Zarychta 2014, Uozumi 2015]. Nevertheless, the segmentations obtained in this research compare well with existing work on the automated segmentation of the ACL, where a mean DSI of 66.5% has been reported for analysis of T_2 -maps with similar characteristics [Lee 2014]. However, it should be acknowledged that direct comparison is not straightforward given the anatomical differences between the ACL and the PCL, which may impact upon the initial challenges involved in the segmentation task.

Quantitative validation and visual inspections showed that under-segmentation was the most likely error in the current datasets. This can be readily attributed to unclear demarcation of the PCL with the surrounding tissues in areas of partial volume effect as a result of the low spatial resolution of the T_2 -maps, which caused segmentation difficulties. Such voxels were characterised by a signal intensity averaged from different types of tissues and thus did not have the normal tissue intensity of the PCL volume. The classification of these voxels depended on the number and similarity of matched patches from the atlas that also included partial volume voxels and their categorisation by the rater. The scheme is therefore dependent on the interpretation from the expert rater which may vary from one atlas to another. Increasing the size of the atlas is an avenue to reduce discrepancy in segmentation accuracy by increasing prior knowledge on PCL shape characteristics and on the correct classification of the voxels with partial volume effect.

Overall, a mean DSI of 74.4% for segmentation of the PCL in anisotropic and low resolution T_2 -maps obtained moderate to strong correlations between the morphological and biochemical parameters estimated from the automated and manual segmentations. These results, in addition to the promising segmentations of the PCL obtained in T_2 -maps from pathological knee joints suggest that the method may develop into a robust and accurate tool well suited to analyse the morphological and T_2 relaxation properties of healthy and pathological PCL. This could facilitate the assessment of the integrity and healing properties of the PCL in clinical studies and provide opportunities for integration of quantitative assessment of the PCL as a support to routine qualitative MR assessment of the ligament.

There are some limitations that should be acknowledged, including the relatively small sample (N=26) of T_2 -maps used to quantitatively validate the method. Increasing the size of the atlas of T_2 -maps with manual segmentations would provide opportunities to further validate the segmentation algorithm while at the same time improve segmentation accuracy by increasing the amount of expert

knowledge available for the patch-based method.

In addition, several T_2 -maps from the OAI could not be segmented accurately as a result of motion artifacts or severe degeneration of the knee investigated (Fig. 6.9). While the lack of contrast between ACL, PCL and knee menisci played a role in the segmentation errors encountered, several other factors such as the severity of JSN or bone deformations (e.g., osteophytes near insertion area of the PCL into the tibia) were believed to also contribute to inaccuracies as they indirectly impacted upon the shape characteristics of the PCL in the images (e.g., JSN increased bending of the PCL). Incorporating T_2 maps of the pathological knee with expert PCL segmentations to the baseline atlas is desired and could improve the segmentation results and success rate of the method (currently estimated as 80/88 for the pathological knee). In future work, it will also be important to extend the quantitative validation of the automated method to the analysis of the pathological knee joint.

As per Chapter 4, experiments performed as part of this PhD thesis showed that cases for which the segmentation failed could be easily identified by visualising overlays of the automated segmentation results onto the original MR images. These can be efficiently generated using a web-based automated clinical reporting tool [Bourgeat 2013]. As with any automated system, such quality check procedure should be incorporated in the study design of any clinical study to avoid the introduction of a strong bias in analyses. In this study, quality checks were performed for each MR image from the OAI dataset, and the proof of concept experiments excluded 8 cases which were identified as inaccurate.

It should be noted that the T_2 -relaxation values estimated from the OAI dataset were 10 ms higher on average than that of the SPRI dataset. This can be explained by the fact that spin-echo MR images were acquired using different MR parameters (T_E/T_R , FOV), on separate MR scanners and from different individuals (healthy vs pathological). Magic angle effect may also be partly responsible as knee positioning relative to the orientation of B_0 was likely different. Considering the high curvature of PCL, this ligament is particularly prone to the artifact, with a fibre orientation with B_0 likely to reach 55° somewhere along the PCL. To evaluate this, regional partitioning and T2-evaluation of the PCL is required (as per [Wilson 2016]) and should be considered in future work.

While the T_2 properties of the PCL were compared between groups in a pilot experiment, analyses were not extended to the morphological parameters of volume and length of the PCL. Because positioning of the knee joint during acquisition of this dataset was not optimised for consistency in the measurement of PCL morphology, discerning meaningful differences between grades of knee rOA is difficult as most of the variability would be explained by differences in the degree of knee flexion across patients (appreciable in Fig. 3.3). Further, while the method performed well for segmentation of multi-echo spin-echo T_2 -maps, these images are typically characterised by low spatial resolution and not optimal for morphological analyses. Newer 3D MR images with near isotropic resolution are usually preferred.

Finally another limitation relates to the restriction of the automated segmentation and analysis study to the PCL. Indeed, crossways from the PCL runs the ACL, which is another crucial stabiliser of the knee joint. In this thesis, the automated segmentation and analysis method was developed as part of a clinical study aiming to quantify the T_2 and T_2^* properties of the normal PCL in a rigorously prescreened cohort [Wilson 2016]. As a consequence, the data collected and expert image assessments for this aim focused on the PCL. It is desirable to extend the evaluation of the patch-based method to the ACL in future work.

6.5 Conclusion

In this chapter, we evaluated a fully automated method for the segmentation and quantitative analysis of the PCL from T_2 -map MR images of the knee joint (Aim 2). Using a baseline dataset of 26 T_2 -map MR images incorporating expert PCL segmentations as atlas, the multi-scale patch-based method provided robust segmentation of the PCL with acceptable accuracy (mean DSI=74.4±4.2%). Moderate to strong correlations were obtained when comparing PCL volume, length and T_2 -relaxation measurements estimated from the automated and the manual segmentations. Results of the segmentation method on a cohort of pathological knee joints were promising. We believe that increasing the size of the baseline atlas used for segmentation will improve accuracy. This may, in turn, develop the current pipeline into a robust and accurate tool well suited to analyse the morphological and T_2 relaxation of the healthy and pathological PCL. This will facilitate the assessment of the integrity and healing properties of the PCL in clinical research. Further validation is required to evaluate the suitability of the method for use in routine MR examinations of the PCL.

Chapter 7

Automated Analysis of *in-vivo* Knee Motion from Kinematic MR Images

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Contonto

This chapter presents and discusses the research performed to attain Aim 3. It involves the fullyautomated segmentation and analysis of kinematic magnetic resonance (MR) images of the knee joint. The method extends the approach developed in Aim 1 for the segmentation of the knee menisci to the segmentation of the articulating knee bones from MR images of the joint at full extension. A preexisting hybrid method is used for accurate segmentation of the cartilage plates. These segmentations are registered across multiple MR images acquired for the knee joint with increasing degrees of knee flexion (3D quasi-static) and in active motion (real-time dynamic 2D+t). Selected kinematic parameters are then automatically estimated from the bone and cartilage surfaces, including measurements of patellar tilt and shift as well as the contact areas between the articulating cartilage plates of the knee joint.

The method is applied on a pilot MR dataset acquired from 12 healthy volunteers. For each participant, six quasi-static 3D MR images and a real-time dynamic MR sequence were acquired. Results of knee kinematics obtained for the quasi-static MR images are validated quantitatively using manual segmentations, and qualitative validation is performed for the analysis of the dynamic MR images.

The structure of the chapter is as follow. First, an overview of the research motivation is presented before the study design and acquisition of the data are explored. The developed algorithms are then detailed and the results obtained are presented and discussed.

The material in this chapter forms the basis of a journal paper in preparation for Magnetic Resonance In Medicine.

7.1 Introduction

Accurate and efficient estimation of bone motion and cartilage contact mechanisms from kinematic MR images of the knee joint is essential for studying pre-osteoarthritic knee joints to identify changes in loading mechanisms as a result of a damaged meniscus or ligament [Barrance 2006]. It is also important for biomechanical modelling, to generate realistic *in vivo* models of knee kinematics [Yao 2008b], and in diagnostic imaging of the knee joint, to detect abnormal kinematic character-istics in pathological joints (e.g., patellar tracking in PFPS patients [Draper 2009a, Souza 2010] or improvement of prosthesis design [Carpenter 2009]) (For a detailed review, see Section 3.3).

In clinical research, the standard method to evaluate 3D patellofemoral and tibiofemoral kinematics from MR images involves the segmentation of the knee bones and cartilages from a high-resolution MR scan, followed by the identification of the trajectory of the bones throughout quasi-static or dynamic MR sequences using various means (e.g., CPC-data [Borotikar 2012], ICP registration of manually segmented bones [d'Entremont 2013]). Currently, all published methods required varying degrees of manual processing to analyse the imaging data. Usually, it involves the manual segmentation of the MR image of the knee joint at full extension for precise identification of the bone and cartilage structures, or the direct manual measurement of parameters in the MR images (e.g., patellar tilt and shift [Draper 2009b]).

With the large amount of data generated in kinematic MR imaging, manual processing can become very time-consuming. Furthermore, the task is very subjective and dependent on the expert observer, with measurements demonstrating variable reliability between observers (e.g., coefficient of variation of 21.54% reported between observers for the measurement of patellar tilt [Yamada 2007b]). It is desirable to investigate the use of automated image-processing algorithms for analysis of the data, which would provide a more efficient and objective means to estimate biomechanical and clinically-relevant measurements from the images.



Figure 7.1: Illustration of (a) the 1.5T Siemens Magnetom Espree MR scanner which features a large bore (70cm) allowing for an increased range of motion of the knee joint and (b) the open knee coil and mounting setup used for the acquisition of the structural MR images of the knee joint with different flexion configuration. The schematic of the knee coil is adapted without permission from [Li 2012].

This chapter describes an automated method for segmentation of the articulating bones and cartilage plates of the knee from MR images acquired with variable degrees of joint flexion and in active motion. Specifically, the anatomy of the bones and cartilages of the knee joint is first obtained from static MR scans of the knee joint at full extension using pre-existing automated image-processing algorithms. Bone and cartilage 3D models are subsequently reconstructed and mapped onto the kinematic MR images using two registration-based automated methods tailored for analysis of quasi-static MR images and dynamic MR sequences. The methods incorporate artifact reduction strategies to improve robustness. Surface processing algorithms then estimate clinically relevant parameters of knee kinematics, including the contact areas between the cartilages and the shift and tilt angle of the patellar. The final sections present and discuss the results obtained for quasi-static and dynamic MR sequences acquired from 12 healthy volunteers.

7.2 Material and Method

7.2.1 Acquisition Setup and MR Dataset

7.2.1.1 Clinical MR Scanner and Open Knee Coil Setup

Twelve volunteers were recruited for acquisition of structural MR images and dynamic MR sequences of the knee joint. This study was approved by the medical research ethics committee of the University

of Queensland. All volunteers provided informed consent and the data were anonymised prior to processing. The volunteers were aged between 18-50 years with no reported knee pain or pathology, and with no biomechanical problems impeding normal knee motion. All the MR images were acquired at a private clinic (XRadiology, Toowong, Australia) on a 1.5T Siemens Magnetom Espree MR scanner. The scanner was equipped with a custom receive-only 3-element open phased-array knee coil [Li 2012]. The MR scanner had a large bore (70 cm) allowing for a wide range of knee motion (Fig. 7.1 (a)). The open knee coil was mounted on a tailor built foot-rest setup allowing the acquisition of structural MR images of the knee joint with variable degrees of knee flexion while maintaining comfort for the subjects imaged. Participants adopted a prone position throughout the acquisition. As illustrated by the notches carved in the foot mounting system in Fig. 7.1, the device allowed imaging of the knee joint with six different flexion angles (approximately corresponding to a $[0 - 40]^{\circ}$ range) including the knee joint in the extended position.

7.2.1.2 MR Dataset

The time for acquisition of six quasi-static structural MR images and one dynamic MR sequence was thirty minutes per volunteer. This included the time required for the radiographer to provide instructions to the volunteer and to update the coil setup between MR scans (i.e., change 'flexion notch'). WE-TrueFisp MR imaging provided the best overall balance in acquisition duration, spatial-resolution and contrast between knee bones, cartilages and surrounding tissues. FLASH and DESS MR imaging (presented in Section 2.4.2), providing the best SNR, CNR and contrast characteristics for MR imaging of the knee bone and cartilage, were not used due to long acquisition durations, especially with the fat-suppression necessary for enhanced bone-cartilage interface. Acquisition of 2D-TSE MR images was an alternative to TrueFisp, but was not used due to the large slice-thickness of the resulting MR images.

Two sets of MR images were acquired for each participant: (1) six conventional sagittal WE-TrueFisp MR images were acquired for the knee joint with variable degrees of flexion and (2) real-time dynamic 2D TrueFisp or Half-Fourier Acquisition Single-shot TSE (Haste) dynamic MR sequences of the joint in active motion. The quasi-static MR images were acquired as per traditional MR imaging, with the volunteer laying immobile while the sequence was being acquired. For acquisition of the dynamic MR sequence, the participant was asked to freely (but slowly) perform knee flexion/extension motion upon hearing a sound cue synchronised with the beginning of the sequence acquisition. The range of knee motion varied across participants of different height and was limited to the size of the

Scan	3D TrueFisp	2D+t TrueFisp	2D+t HASTE
Field Strength	1.5T	1.5T	1.5T
Plane	SAG	SAG	SAG
FS	WE	No	No
FOV (mm)	140	140	160
Matrix	320×320	384×384	384×384
No of slices	80	1	1
No of images	6	40	50
Resolution (mm)	0.438	0.360	0.420
Slice thickness/gap (mm)	1.5/0	6.0/0	6.0/0
Flip angle ($^{\circ}$)	30	68	150
TE/TR (ms)	6.24/14.21	2.73/5.46	30/800
Acquisition Time	2:20min	0.52s	0.43s

Table 7.1: MR parameters utilised for the acquisition of the static 3D WE-TrueFisp, dynamic 2D+t TrueFisp and dynamic HASTE MR sequences.

bore. While the dynamic MR sequences were constituted of 2D slices, their representation in 3D space was used for analyses (i.e., single-slice 3D MR image, with orientation and position obtained from the MR scanner).

A detailed listing of the MR parameters utilised for acquisition are provided in Table 7.1. An illustration of three frames of the quasi-static and dynamic MR sequences acquired for the knee joint of one participant is provided in Fig. 7.2. This illustrates the typical characteristics of the MR images analysed in this study. The use of the custom open knee coil introduced several imaging artifacts into the MR images, including magnetic field inhomogeneity artifacts that tended to get worse with increasing degrees of knee flexion (with standard manual shimming insufficient to improve magnetic field homogeneity). The most commonly affect areas of the image were the near the tibia bone and the tibiofemoral area, although it extended to the whole volume for several volunteers. In the quasi-static MR images, the artifact resulted in bright signal within the bones and suppressed cartilage signal in some areas. In the dynamic MR slices, it was manifested by a signal drop-off sliding in and out of the tibia and tibiofemoral regions as the knee was flexed and extended.

7.2.1.3 Manual Segmentations

For this study, the patella, tibia and femur bones of the knee joint as well as the associated patellar, medial/lateral tibial, and femoral cartilages were manually segmented by the author under expert guidance in the six quasi-static TrueFisp MR images of 10 participants (with the exception of one participant dataset, which was segmented by Dr. Mark Strudwick). A total of sixty WE-TrueFisp MR images were thus available for quantitative validation of accuracy. The manual delineations were per-



Figure 7.2: Example of kinematic MR images acquired in this study. The top row shows quasi-static TrueFisp MR images of the knee joint with three different degrees of knee flexion. The bottom row shows three 2D TrueFisp slices out of the 40 slices constituting the real-time dynamic MR sequence acquired in active motion. This illustrates the impact of the MR imaging artifacts with increased knee flexion.

formed in the MR images using an interactive WACOM DTZ-2100 touch screen with stylus and the ITK-Snap software [Yushkevich 2006]. The segmentations were performed every second slice in the images and a shape-based interpolation algorithm was utilised to obtain a full segmentation volume from the segmented slices [Raya 1990, Herman 1992].

The time required for the segmentation of a single TrueFisp MR image ranged between 4 and 5 hours depending on the difficulty of interpretations, resulting in an approximate total processing time of 250–300 hours to process the six MR images from the ten participants.

7.2.2 Automated MR Segmentation of the Bones and Cartilages of the Knee

The first step in the assessment of 3D knee kinematics from quasi-static and dynamic MR images is the segmentation of the articulating knee bones and cartilages from MR images. For each volunteer, these baseline segmentations were obtained automatically from the first quasi-static MR image of the knee joint at full extension using a hybrid approach. Specifically, the method extends on the algorithm presented in Chapter 4 for the segmentation of the menisci, to the segmentation of knee bones from the MR images. Methods from the literature are then used to extract the bone-cartilage interface and



Figure 7.3: Pipeline utilised to train the models used for bone and cartilage segmentation. In this pipeline, the stars (*) are used to show the stages that are illustrated only using the tibia bone for ease or demonstration.

segment the cartilage plates of the knee joint [Fripp 2007b, Fripp 2007a].

The following two sections detail the process used to train the models and the algorithms used for segmentation of the bones and cartilages.

7.2.2.1 Statistical Shape and Texture Modelling

The mandatory components of the bone ASM-fitting method (average atlas image and surface, SSMs and GLMs of the knee bones) were obtained using the method previously described in Section 4.2.3.2 and illustrated in Fig. 7.3. The only difference was how the point-wise correspondence was obtained across the surfaces of the training set. Although the EMICP method was initially utilised and performed reliably, the comparatively simple shape of the bones in comparison to the menisci allowed to use a more flexible method to obtain anatomical correspondence, which is the deformation of an icosahedron (sphere) within the surfaces. The advantage of this method is that it allows for the subsequent re-sampling of the surface tessellation while maintaining the point-wise correspondence across the surfaces. Increased mesh resolution becomes advantageous to model precise local variability in bone shape.



Figure 7.4: Three stage pipeline used to segment the knee bones and cartilages from the WE-TrueFisp MR images.

As shown in Fig. 7.3, bone surfaces were first obtained using the marching cube algorithm and a window sync surface smoothing algorithm (relaxation factor: 0.1, iterations: 10) [Lorensen 1987, Gelas 2009]. The patella, tibia and femur surfaces were then co-registered individually across the training set using the ICP algorithm [Besl 1992] and an icosahedron template was deformed to match the outline of each co-registered surface using *Deformetrica v2.1* (INRIA) [Durrleman 2014]. The software provides a framework for template shape creation by deformation of the ambient space. In this case, it was used to generate a mapping of the sphere within all the training surfaces. The surfaces were then transformed back into the original image space using the inverse of the ICP transformation. Relaxation of the surfaces along their vertex normals in the label image was then used to increase fidelity to the manual segmentations. SSMs and GLMs were finally generated separately for the combined and individual knee bones as described in Section 4.2.3.2.

As per [Fripp 2005], the probability of having cartilage tissue in the vicinity of each vertex of the bone model was mapped onto the surface. The mean cartilage thickness and population variability associated to each non-zero probability was also incorporated into the model. These were calculated using the overall presence/absence and thickness of manual cartilage segmentation label along the normals of the bone models. These information were required by the cartilage segmentation method [Fripp 2010].

The models were trained on MR datasets with manual segmentations external to this study and described elsewhere [Fripp 2007a].

7.2.2.2 Segmentation Procedure

The procedure for segmentation of the bones and cartilages of the knee joint was constituted of three main stages (Fig. 7.4): (1) MR image preprocessing, (2) ASM-based bone segmentation and (3) hybrid knee model based cartilage segmentation.

MR Image Pre-processing

For segmentation of the knee bones and cartilages, the TrueFisp MR image of the extended knee was processed using N4 bias field correction to remove global intensity inhomogeneities and processed using intensity rescaling. In order to minimise the influence of noise on the performance of the automated segmentation algorithm and homogenise the signal intensity within cartilage, a median smoothing filter was used (radius $1 \times 1 \times 1$).

Bone Segmentation

The ASM-based bone segmentation method was initialised by registration of the average knee image onto the MR image to segment using an inverse consistent affine registration [Rivest-Hénault 2015]. The affine transformation was applied to the average knee surface, resulting in an approximate alignment of the bone models with the bones of the MR image to segment.

Following initialisation, the segmentation of the patella, tibia and femur bones was obtained using a hierarchical ASM-fitting scheme. The deformation of the models involved an iterative translation of the vertices of the surfaces towards template features known *a priori* to surround the knee bones in MR images (bundled into the trained GLMs). The deformation was constrained by application of internal forces provided by the SSMs (the deformation process of the ASM has been described in details in Section 4.2.4).

The hierarchical ASM-fitting scheme for the bone models was separated into three stages. A combined model of the bones describing (mainly) the variability in knee flexion across the population was first deformed in the image to identify a refined pose for each bone. This step was performed using a 2 level Gaussian image-pyramid scheme to avoid converging towards a local minimum. Individual models of the patella, tibia and femur bones describing the shape local variability were then separately fitted to obtain the local anatomy of each bone. Shape-constraints provided by the SSM were applied to the surface after each iterative deformation to maintain plausible bone shapes (i.e., within the local variability described by the SSMs). Finally, for better definition of the bone surface around the BCI region, the patella, tibia and femur models were deformed individually for a few iterations without shape constraints. To avoid irregularity of the deformed surface, window sync smoothing was applied after each iteration.

The final bone segmentation was obtained by voxelisation of the resulting surfaces into a label image matching the original image in size, spacing and orientation.

Cartilage Segmentation

From the deformed surfaces, the cartilage segmentation was obtained using a cartilage thickness model based algorithm [Fripp 2007a]. Briefly, the method relies on the statistical information embedded into the bone models regarding the cartilage tissue probability and population mean thickness and variability (illustrated in Fig. 7.3 under 'Hybrid Knee Model'). For each deformed bone surface, a potential cartilage region was identified within an 8mm vicinity of the BCI. A probability map was generated within this region using the properties of the tissues (expectation maximisation Gaussian mixture models) and a distance map calculated from the BCI. Intensity profiles were extracted along the normals of the BCI vertices and the likely edge of the cartilage was identified as the position along the profile that maximised the image gradient and the probability map value. Thickness constraints were then applied using the population variability embedded into the models. This process was iterated several times using the newly identified cartilage regions to generate the probability maps. For details, see [Fripp 2007a].

After this stage, automated MR segmentations of the individual bones and cartilages were available for each volunteer. These were reconstructed as 3D surface models using the marching cubes algorithm [Lorensen 1987] and smoothed.

7.2.3 Estimation of Bone Motion

Following the segmentation of the MR image of the knee joint at full extension, the trajectory of each bone (and associated cartilage) was identified separately in the quasi-static (six "time-points") and dynamic (40 "time-points") MR sequences using two registration-based schemes. The registration schemes are illustrated in Fig. 7.5(A & B) and will be described in the next two sections.

7.2.3.1 Registration of Quasi-static MR Images

Inhomogeneity Correction

To improve the signal homogeneity within the knee bones throughout the quasi-static MR sequence, an artifact reduction strategy was implemented. For a given image, a strong median smoothing filter (radius $8 \times 8 \times 4$, sufficiently large to remove cartilage tissue from the smoothed image) was utilised to extract an inhomogeneity map of the image (shown in Fig. 7.6). The original image was then divided by the inhomogeneity map, resulting in reduction of the inhomogeneity artifacts. This allowed for

A. Quasi-static Knee Kinematics





Figure 7.5: Bone-wise/Pairwise registration schemes developed to obtain knee motion from the quasi-static (A) and dynamic (B) MR sequences. In this figure, the registration schemes are demonstrated for the tibia bone for ease of interpretation.



Figure 7.6: Illustration of the scheme utilised to normalise the intensity across the WE-TrueFisp MR images. This scheme was developed to reduce the impact of MR artifacts on the bone-specific pairwise registration algorithm.

normalisation of the overall intensity across the quasi-static MR sequence. A side effect of this method was an overall reduction of the dynamic range of the MR image. It was found that the corrected MR images were more suitable for registration, where the similarity between MR images represents more useful information than the dynamic intensity range.

Pair-wise/Bone-wise Registration

To obtain the bone motion from the quasi-static MR images, each bone of the knee joint was registered individually throughout the six MR images of the sequence. For ease of interpretation, the MR images acquired with increasing degrees of knee flexion will be referred to as "time-points". The proposed registration pipeline is shown in Fig. 7.5(A). From the corrected MR images, the bones (and bone segmentations) were cropped in the first two time-points of the sequence and co-registered rigidly. A symmetric block matching rigid registration method optimising the normalised mutual information was used [Rivest-Hénault 2015]. A padding of 25 voxels around the bone mask was used to allow cropping of the bone in the target MR image (i.e., second time-point). The transformation obtained was used to align the bone segmentation with the target MR image. The process was repeated in a *bone-specific pairwise* fashion throughout all the pairs of images, resulting in bone segmentations identified throughout the quasi-static MR sequence.

To limit the influence of the propagated registration error, the bone regions identified in the MR sequence were individually registered onto the bone region of the first time-point. This registration was initialised using the inverse of the transformation obtained by composition of the transformations calculated between all the previous time-points (e.g., for T_3 the transform was $(T_2 \circ T_3)^{-1}$, assuming $T_1 = Id$). For this registration, the metric was optimised within a dilated region of the cartilage structure(s), which was found to improve the accuracy of the registration.

The resulting transformations were then inverted and applied onto the baseline segmentations and associated 3D surface models of the knee bones and cartilages to obtain accurate motion trajectories throughout the quasi-static MR sequence.

7.2.3.2 Registration of Dynamic MR Images

To obtain the 3D trajectory of the bones and cartilages from the dynamic 2D+t MR sequences (represented as single-slice images in 3D space), the scheme shown in Fig. 7.5(B) was implemented. The scheme was initialised by averaging a thick slice from the first quasi-static MR volume and rigidly registering the resulting image onto the first 2D slice of the dynamic MR sequence (represented in 3D space as a single-slice 3D image). The registration transform obtained was used to align the baseline segmentation of the knee bones and cartilages with the dynamic MR sequence. Following this, all the MR slices of the sequence were co-registered with regard to the femur, which is generally the least mobile bone. The aligned MR images were then utilised to identify the redundancies in knee positions (in terms of degrees of knee flexion) throughout the flexion and extension cycles. For a given MR slice, these were obtained by comparison with all the other slices of the sequence using normalised mutual information. This step was required for the artifact reduction scheme incorporated into the registration pipeline.

Utilising a scheme similar to that described in the previous section, the patella and tibia bones were registered individually throughout the sequence using cropping and pairwise rigid registrations. Whilst the MR images of the sequence were 2D slices, the registration were performed in 3D space using the slice position and orientation obtained from the scanner. To improve the robustness of the registrations against signal drop-off, an artifact reduction strategy was incorporated into the scheme. Specifically, for a given time-point, cropping of the bone region was also performed in the slices previously identified as redundancies of the current knee position and all the cropped regions were rigidly co-registered and averaged (iterative process). This resulted in attenuation of the artifacts as the position of the signal drop-off was slightly different in all MR slices. This is illustrated in Fig . 7.5(B) for the tibia bone of time-point 10.

The final transformations were obtained by composition of the pairwise transforms identified throughout the sequence, which were then applied onto the baseline 3D surface models to estimate 3D motion.

7.2.4 Estimation of Kinematic Descriptors

In this section, the algorithms developed to estimate quantitative measurements describing 3D knee kinematics from the surfaces are presented. As part of this research, the contact areas between the knee cartilages and measurements of patellar tilt and shift were estimated automatically. These quantitative values were among the most commonly studied in clinical studies (overview presented in Section 3.3) and were selected for their potential utility in clinical or research applications (e.g., PFPS detection, contact mechanisms in meniscus- or PCL- deficient knees).



Figure 7.7: Schematic illustration of the process used to calculate the contact areas between the cartilages, and the patellar shift and tilt. (a) shows the distance map built from the femoral cartilage segmentations to calculate the contact areas between femoral and patellar cartilages, (b) shows the distance mapped onto the patellar cartilage surface. (c) shows the effective contact area obtained by thresholding of the distance. (d) shows the spheres fit to the medial and lateral epicondyles of the femur, which are used to calculate the transepicondylar axis. (e) shows the mid-sagittal plane of the femur utilised to calculate the patellar shift (red) and (f) shows the medial-lateral patellar and transepicondylar vectors used to calculate the patellar tilt.

7.2.4.1 Cartilage Contact-Areas

The contact-areas between the cartilages of the patellofemoral, medial tibiofemoral and lateral tibiofemoral articulations were estimated using a proximity algorithm. Specifically, the contact-area between two cartilages was identified by the vertices of the first cartilage plate situated within 2.5mm of the other cartilage surface. This is illustrated in Fig. 7.7 (top row), where a distance map was generated from the femoral cartilage (a) and utilised to map the distance onto the patellar cartilage surface (b). The thresholded contact-region is shown on the right (c).

A total of six cartilage contact-areas were estimated per knee joint surface, two per articulation. These were mapped onto the surface reconstructions of the patellar cartilage, the medial and lateral tibial cartilages and the femoral cartilage.

7.2.4.2 Patellar Tilt and Shift

The patellar tilt and shift characterise the external rotation and lateral translation of the patella that occur during knee flexion. Prior to calculating these measurements, the transepicondylar axis and mid sagittal plane of the femur were identified using surface feature extraction algorithms.

The transepicondylar axis of the knee joint was first obtained by fitting a sphere onto the medial and the lateral condyles of the femur using the ICP algorithm [Besl 1992] and calculating the normalised vector between their centres (denoted as C_1 and C_2). An illustration of the sphere fitting process is shown in Fig. 7.7(d). The transepicondylar axis obtained from these spheres is shown in Fig. 7.7(e & f). The normal of the mid sagittal plane of the femur was then defined as the normalised transepicondylar vector and the origin as the average position of C_1 and C_2 . The mid-sagittal plane is shown in Fig. 7.7(e).

The medial-lateral axis of the patella was subsequently calculated using two feature points maximising the distance between the medial and lateral extremities of the patella. To reduce the impact of the surface topology on the orientation of this axis (e.g., flat edge for surfaces reconstructed from manual segmentations), the two extremities were calculated as the centroids of the most medial and lateral regions rather than two select points. The lateral shift of the patella was calculated as the distance between lateral extremity of the patella and the mid-sagittal plane.

There is currently no standardised method to calculate the patellar tilt. Several investigators utilised a reference axis passing through the most posterior [Draper 2009b] or anterior [Nha 2008] aspects of the medial and lateral femoral condyles, as well as an axis passing through the centre of the

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two femoral condyles [Yamada 2007a, Suzuki 2012]. In this study, the transepicondylar axis was used as reference as it was the feature that could be identified most reliably. The measurement of patellar tilt was then calculated as the angle formed by the transepicondylar axis and the medial-lateral patellar axis.

7.2.5 Validation Strategy

The accuracy of the automated method for segmentation of the knee bones and cartilages in the quasistatic MR images was evaluated quantitatively against the manual segmentations of the MR images. The comparison was performed individually for the patella, tibia and femur bones and for the patellar, medial tibial, lateral tibial and femoral cartilages using the sensitivity, specificity, DSI [Dice 1945] and MASD [Gerig 2001] values, calculated as per Chapter 4 equations 4.6, 4.7, 4.8 and 4.9. Differences in accuracy across the different degrees of knee flexion were examined using paired t-tests calculated between the DSI obtained for the MR images acquired with increasing degrees of knee joint flexion and the DSI obtained for the the baseline segmentations (knee at full extension).

To evaluate the accuracy of the cartilage contact areas identified using the automated method, the spatial overlap between the regions obtained from the automated and manual segmentations were calculated using the DSI. The formula used for calculation is equivalent to that utilised to compare segmentation volumes (equation 4.8), except that the triangles of the surface mesh were used instead of image voxels. Associations between quantitative values (patellar shift, tilt and surface area of contact between the cartilages) estimated from the automated and manual segmentation volumes were evaluated using the Pearson correlation coefficient (r) [Lee Rodgers 1988], the ICC [Koch 1982] and Bland-Altman analyses [Bland 1986].

At this stage, 3D knee kinematics estimated from the dynamic MR images was evaluated qualitatively by the author. This study did not control for the speed or the trajectory of movement during the acquisition. This prevented the use of the manual segmentations performed in the quasi-static MR images as reference to validate the motion estimated from the dynamic sequence (as performed in a previous study that controlled knee flexion using a testing jig [Lin 2013]).

7.3 Results

The ASM-fitting method performed well for the baseline automated segmentation of the bones from the WE-TrueFisp MR images of the knee joint at full extension, obtaining mean DSIs with the manual segmentations of $89.8\pm3.2\%$, $95.0\pm1.5\%$ and $96.2\pm0.3\%$ for the patella, tibia and femur bones (Table 7.2, flexion 1). Subsequent cartilage segmentations allowed the identification of the patellar, medial tibial, lateral tibial and femoral cartilages with good accuracy, achieving mean DSIs of $76.6\pm6.0\%$, $78.4\pm3.2\%$, $71.0\pm4.8\%$ and $76.6\pm2.0\%$ (Table 7.3 flexion 1).

The registration-based scheme developed for the quasi-static MR images successfully tracked the bones and cartilages throughout the different degrees of knee flexion for all the participants. Quantitative validation of the results showed mean DSIs ranging from [88.6-88.9]%, [91.8-94.1]% and [95.0-95.8]% for the segmentation of the patella, tibia and femur bones from flexion II to VI (Table 7.2). The range of mean DSIs were [67.3-75.7]%, [71.8-76.3]%, [66.0-69.1]% and [67.6-74.5]% for the patellar, lateral tibial, medial tibial and femoral cartilages (Table 7.3). A decrease in mean DSI was noted with increased degrees of knee flexion (p<0.05 in most cases, Table 7.2 and 7.3). A visual demonstration of the typical level of agreement between automated and manual segmentations is provided for one participant in Fig. 7.8 (shown for flexion I, III and VI).

The automated segmentation of the individual knee cartilages combined with the proximity-based approach allowed to identify the contact areas between the cartilages with good accuracy. The mean DSIs calculated between automated and manual contact areas were $83.97\pm8.25\%$, $86.97\pm3.98\%$, $89.96\pm4.63\%$ for the patellar, medial tibial and lateral tibial cartilages and $86.73\pm8.38\%$, $90.53\pm2.53\%$ and $90.17\pm3.69\%$ for the femoral patellofemoral, femoral medial tibiofemoral and femoral lateral tibiofemoral cartilages (Table 7.4). The level of agreement (r;ICC) between the surface-areas estimated from the automated and manual segmentations was moderate or strong for the patellar (0.74;0.74), medial tibial (0.66;0.66) and lateral tibiofemoral (0.69;0.69) regions. The correlation for the femoral lateral tibiofemoral region was weaker (0.46;0.46). Bland-Atlman analyses showed that the automated method tended to under-estimate contact-areas, with mean biases calculated from the Bland-Altman analyses of 6.2%, 1.9% and 9.3% for the patellar, medial tibial and lateral tibiofemoral, respectively. The mean biases are provided in more details in Table 7.4 and Fig.

7.10. To visually demonstrate the level of agreement between methods, the contact areas estimated for one participant using the automated and manual segmentations are displayed in Fig. 7.9 (flexion I, IV and VI).

Measurements of patellar shift estimated from the surface reconstruction of the automated segmentations showed strong correlations with those derived from the manual segmentations (r = 0.93; ICC = 0.92). Correlations were weaker for the patellar tilt (r = 0.43; ICC = 0.43) (Fig. 7.11). Mean biases of 0.4% and 1.3° were found for the identification of the patellar shift and tilt, respectively.

Qualitative inspections of the results obtained by the registration-scheme developed for the dynamic MR sequence showed that the bone structures could be tracked reliably in the MR sequence of all participants. This is demonstrated in Fig. 7.12, which shows the intersection of the bone surfaces with different slices of the dynamic MR sequence (top row), and the obtained 3D trajectory (bottom row). Close inspections showed that the scheme could not accurately capture out-of-plane motion (caused by a knee flexion extension not following the orientation of the MR slices, and by the natural external rotation of the femur and tibia as well as the lateral shift of the patella occurring naturally during normal knee motion). This is illustrated in Fig. 7.13, which compares the pose of the knee bones obtained by mapping of the knee anatomy onto the quasi-static and dynamic MR sequences. This is shown for two positions within the flexion/extension cycle that coarsely corresponded between the quasi-static and dynamic frames (no exact match was available).

On a laboratory computer system (described in Section 4.3.4), the time required to perform the bone and cartilage segmentation was 459.6 ± 76.6 minutes. This included 17.1 ± 1.2 seconds of preprocessing, 6.3 ± 1.1 minutes of affine initialisation, 452.3 ± 76.6 minutes of bone ASM-fitting and 41.5 ± 5.3 seconds of cartilage segmentation. The computational time necessary to complete the quasistatic MR sequence registration scheme was 40.7 ± 2.9 minutes on average (six 3D MR images per case), while the time required by the real-time dynamic MR image sequence registration scheme was 103.6 ± 13.0 minutes (40 or 50 MR images). The CPU time required to extract the patellar tilt and shift for one surface was 54.8 ± 6.9 seconds on average, and the time required to calculate the contact areas was 1.3 ± 0.1 minutes.

— Bone Segmentation —					
Patella	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	89.77±3.345	99.88±0.08018	88.46±4.007	0.879±0.338	
– Flexion I	90.61±1.959	$99.89 {\pm} 0.08282$	89.83±3.243	$0.78 {\pm} 0.266$	-
– Flexion II	90.45±2.112	99.88±0.08291	88.92±3.319	$0.848 {\pm} 0.263$	< 0.01
– Flexion III	90.02±1.793	99.88±0.07469	88.65±3.171	$0.855 {\pm} 0.261$	0.02
– Flexion IV	89.39±2.745	99.88±0.07462	88.64±2.854	$0.858 {\pm} 0.243$	0.09
– Flexion V	90.36±2.016	99.88±0.07616	89.07±2.536	$0.82{\pm}0.209$	0.15
– Flexion VI	87.76±6.621	99.84±0.09843	85.65±6.89	1.11±0.599	0.04
Tibia	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	91.64±3.131	99.74±0.08563	93.21±1.779	0.968±0.203	-
– Flexion I	93.97±2.811	99.79±0.07392	94.95±1.449	0.746±0.186	-
– Flexion II	93.27±2.658	99.75±0.07927	94.11±1.442	0.866±0.161	< 0.01
– Flexion III	91.5±2.529	99.72±0.09444	93.03±1.414	1.01 ± 0.158	< 0.01
– Flexion IV	90.97±2.743	99.74±0.09752	92.86±1.401	1.01 ± 0.146	< 0.01
– Flexion V	90.65±3.256	99.72±0.08487	92.5±1.607	$1.05 {\pm} 0.144$	< 0.01
– Flexion VI	89.5±3.021	99.71±0.07412	91.83±1.709	1.13±0.188	< 0.01
Femur	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	94.92±1.193	99.69±0.06655	95.57±0.6499	0.692±0.124	-
– Flexion I	95.83±0.6111	99.71±0.07053	96.18±0.3036	$0.574{\pm}0.0632$	-
– Flexion II	95.33±1.039	99.69±0.07922	95.81±0.3458	$0.634{\pm}0.0585$	0.01
– Flexion III	94.79±1.245	99.68±0.06497	95.43±0.5826	$0.713 {\pm} 0.0861$	< 0.01
– Flexion IV	94.17±1.571	99.67±0.07717	95.07±0.9784	0.787±0.192	< 0.01
– Flexion V	95.01±0.8365	99.69±0.05643	95.64±0.3994	$0.688 {\pm} 0.096$	< 0.01
– Flexion VI	94.39±1.046	99.69±0.05541	95.3±0.4778	$0.755 {\pm} 0.077$	< 0.01

Table 7.2: Quantitative validation of the automated segmentation of the knee bones from quasi-static MR images of the knee joint with different degrees of knee flexion.

— Articular Cartilage Segmentation —					
Pat. Cart.	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	71.92±10.12	99.96±0.01554	73.32±10.06	0.546±0.15	-
– Flexion I	$75.66{\pm}7.852$	99.97±0.01672	$76.62{\pm}5.958$	$0.508{\pm}0.0797$	-
– Flexion II	$73.22{\pm}8.036$	99.97±0.01343	$75.75{\pm}6.907$	$0.523{\pm}0.112$	0.33
– Flexion III	$70.86{\pm}8.329$	99.96±0.01645	73.01±9.493	$0.557{\pm}0.141$	0.08
– Flexion IV	70.32±11.94	99.96±0.01668	72.41±12.8	$0.534{\pm}0.177$	0.14
– Flexion V	74.64±6.813	99.96±0.01069	$74.83{\pm}6.436$	$0.502{\pm}0.11$	0.12
– Flexion VI	66.82±15.1	99.95±0.01853	67.31±14.91	$0.651 {\pm} 0.22$	0.03
L.Tib Cart.	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	70.21±6.76	99.98±0.01131	74.44±5.454	0.481±0.127	
– Flexion I	72.96±4.715	$99.98{\pm}0.007633$	$78.43 {\pm} 3.195$	$0.409{\pm}0.0775$	-
– Flexion II	$70.37{\pm}4.044$	$99.98{\pm}0.00553$	$76.34{\pm}2.514$	$0.452{\pm}0.084$	0.01
– Flexion III	70.12±7.12	99.97±0.009658	73.91±6.2	$0.479 {\pm} 0.133$	0.06
– Flexion IV	69.14±8.126	$99.98{\pm}0.009525$	$73.74{\pm}4.936$	$0.496{\pm}0.101$	< 0.01
– Flexion V	$70.32{\pm}7.833$	99.97±0.01917	$72.38{\pm}7.288$	$0.5 {\pm} 0.147$	0.01
– Flexion VI	68.34±8.324	99.97±0.008334	71.82±5.248	0.548±0.174	< 0.01
M.Tib Cart.	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	61.6±8.971	99.98±0.006868	68.11±5.356	0.55±0.156	-
– Flexion I	63.75±10.92	99.99±0.006761	$70.98{\pm}4.752$	$0.543{\pm}0.173$	-
– Flexion II	$60.36 {\pm} 6.391$	99.98±0.007304	$68.88 {\pm} 4.682$	$0.579 {\pm} 0.165$	0.18
– Flexion III	$62.68 {\pm} 8.393$	$99.98{\pm}0.005486$	69.12±3.695	$0.541 {\pm} 0.143$	0.23
– Flexion IV	61.56±9.539	99.98±0.005515	$67.2 {\pm} 5.418$	$0.537 {\pm} 0.127$	0.02
– Flexion V	61.77±10.2	$99.98{\pm}0.008787$	$66.44{\pm}5.897$	$0.556{\pm}0.189$	0.03
– Flexion VI	59.48±9.423	99.98±0.005341	66.03±6.782	0.541±0.166	0.02
Fem. Cart.	Sensitivity (%)	Specificity (%)	DSI (%)	MASD (mm)	p-value
Overall	70.14±5.983	99.87±0.03435	72.53±4.603	0.438±0.0793	-
– Flexion I	$74.72{\pm}2.834$	$99.88 {\pm} 0.0319$	$76.59{\pm}1.95$	$0.377 {\pm} 0.0493$	-
– Flexion II	71.84±4.416	$99.88{\pm}0.03952$	$74.48 {\pm} 3.169$	$0.411 {\pm} 0.0647$	0.01
– Flexion III	69.43±7.017	99.87±0.03794	$72.08 {\pm} 4.726$	$0.455 {\pm} 0.09$	0.01
– Flexion IV	68.57±6.997	99.87±0.02039	71.7±4.695	$0.451{\pm}0.0857$	0.01
– Flexion V	$70.53 {\pm} 5.551$	99.87±0.03716	72.69 ± 3.308	$0.423{\pm}0.063$	< 0.01
– Flexion VI	65.74±5.166	$99.84{\pm}0.02672$	67.67±4.45	$0.51 {\pm} 0.0616$	< 0.01

Table 7.3: Quantitative validation of the automated segmentation of the knee cartilages from quasi-static MR images of the knee joint with different degrees of knee flexion.

— Articular Cartilage Contact Areas —					
Cartilage	DSI (%)	Auto Area (mm^2)	Manual Area (mm ²)	r;ICC	
Patellar	83.84±8.23	565.7±166.2	613.1±166.6	0.74;0.74	
MedialTibial	86.97±3.98	603.6±70.97	618.9±77.6	0.66;0.66	
LateralTibial	89.96±4.63	472.7±65.01	527.4±83.3	0.63;0.61	
Femoral.PF	86.73±8.38	535.1±194.9	548.7±160.5	0.83;0.82	
Femoral.MTF	90.53±2.53	541.8±75.13	551.2±75.6	0.69;0.69	
Femoral.LTF	90.17±3.69	455.5±63.95	497.1±71.7	0.46;0.46	

Table 7.4: Quantitative validation of the contact-areas estimated from the automated and manual segmentations of the cartilage.



Figure 7.8: Illustrative comparison of the automated and manual segmentation results obtained for three quasi-static MR images from one participant.



Figure 7.9: Contact areas estimated at three time-points in the quasi-static images using the manual and automated segmentations. The view is normalise column-wise.



Figure 7.10: Correlation analyses for the contact-areas estimated from the automated and manual segmentations. In the plots, Femoral.PF, Femoral.MTF and Femoral.LTF correspond to the patellofemoral, medial tibiofemoral and lateral tibiofemoral contact-areas mapped on the femur.



Figure 7.11: Correlation analyses for the patellar tilt and shift estimated from the surfaces reconstructed using the automated and manual segmentations.



Figure 7.12: Visualisation of the results of the registration-based identification of the bone trajectory throughout the dynamic MR sequence of one participant. For each frame, the top row shows the overlay of the bone segmentation onto the original MR slice (intersection of the volume with the single 3D slice) and the bottom row shows the original segmentation surface transformed throughout the MR sequence.



Figure 7.13: Comparison of the bone trajectory obtained using the quasi-static and dynamic MR sequences. The figure does not represent an exact match of the knee pose within the flexion/extension cycle (as it was not available) but a close match. Discrepancies may thus also relate to the different degree of knee flexion between the two knee poses and a different motion trajectory performed during acquisition

7.4 Discussion

In this chapter, a method for the automated segmentation and analysis of kinematic MR images of the knee joint has been presented and evaluated (Aim 3). The method accurately identified the knee anatomy (cartilages, bones) from 3D MR images of the joint at full extension using a hybrid method combining ASM-based bone segmentation and thickness-based cartilage segmentation. Bone-specific registration schemes successfully estimated the trajectory of the knee bones (and associated cartilages) throughout quasi-static MR images of the joint acquired for different degrees of knee flexion and throughout dynamic MR images of the joint in active motion. Important kinematic descriptors

including cartilage contact areas and patellar tilt and shift were automatically identified from the resulting segmentations. This represents a first attempt to completely remove human interaction from a pipeline utilised to evaluate *in-vivo* 3D knee kinematics from MR images.

With the current method, the accuracy of the baseline bone and cartilage segmentations is paramount. The method for segmentation of the knee bones obtained a competitive accuracy for the 3D WE-TrueFisp MR dataset in comparison with the methods of the literature [Fripp 2007b, Dodin 2011]. The primary area of concern was the segmentation of the patella, where the delineation with the patellar tendon was not clear (shown in Fig. 7.2) and for which the position in the MR image varied considerably. The ASM-fitting scheme recovered well from coarse affine initialisations for identification of the patella position, but a systematic over-segmentation occurred over the patellar tendon. An avenue for improvements would involve training new models (GLMs) using WE-TrueFisp MR scans (current models were generated from WE-DESS and FS-FLASH external to this study). This may provide opportunities for a better template matching accuracy in the ASM-fitting. Nevertheless, current bone segmentations were always accurate around the BCI region and provide a robust basis for segmentation of the knee cartilages.

The method used for segmentation of the cartilages obtained good accuracy. The segmentation errors were mainly due to a frequent intensity inhomogeneity within cartilage tissues (e.g., magic-angle artifacts causing a hyper-intensity similar to that of synovial fluid, especially frequent in the highly curved cartilage of the femoral condyles, see Section 2.4.2.6 for details). These created strong gradients that were identified as cartilage boundary (Fig. 7.14(a)). Adjusting the tissue classier to handle these cases is an avenue to improve cartilage segmentation for this specific dataset (e.g., using an advanced classifier such as Markov Random Fields [Zhang 2013]). However, it can be argued that adapting the study design to incorporate the acquisition of a high-resolution FS FLASH MR image of the extended knee joint (with excellent BCI demarcation and cartilage morphology) would provide better opportunities for increased accuracy in the segmentation of both the bones and cartilages. Over-all the cartilage segmentation algorithm performed well for the current dataset and the accuracy was sufficient to identify the cartilage contact areas with good accuracy.

Susceptibility and chemical shift artifacts, which introduced a dark area between the knee bones and cartilages, were another source of inaccuracy for the segmentation of these two structures. For manual segmentations, it usually requires subjective decisions from observers to identify the BCI. For the proposed automated method, relying on GLMs trained using these manual segmentations, an equivalent error was introduced. To evaluate this error, comparison of the MR bone segmentations 188

against segmentations obtained from CT images (gold standard) is required. This was not performed as part of this thesis, however, a recent study comparing manual segmentations of the knee bones in CT and MR images suggested that MR imaging was a suitable alternative to CT for bone segmentation and obtained comparable accuracy, although slightly inferior [Neubert 2016c] (abstract) [Neubert 2016b] (under review). Overall, this segmentation error did not directly affect the accuracy of the kinematic parameters estimated, which mainly relied on the contact surfaces of the cartilage plates and gross bone features.

The major challenges and concerns with the two registration-schemes for identification of the bone trajectories were related to the quality of the MR images and the strong MR artifacts affecting all the MR sequences. These artifacts (detailed in Section 7.2.1.2 and shown in Fig. 7.2) reduced the amount of useful information for the registration schemes to accurately track the bones throughout the sequences, while adding features likely to drive the registrations towards an erroneous position.

Nevertheless, for the quasi-static MR images, the artifact reduction scheme that normalised the signal intensity across the sequence (while preserving edge information) allowed for robust bone-specific registration of the images throughout the sequence for all the cases. Good cartilage segmentation accuracy was maintained at all flexion angles, although an expected decrease in mean DSI was noted (p<0.05). This can be explained by an inferior registration precision for MR images with lower quality (greater degrees of joint flexion involved more severe MR artifacts), but may also result from the subjective nature of the manual cartilage segmentations in several areas where cartilage morphology had to be interpreted for the most part (example shown in Fig. 7.14 (b)). Notwithstanding this, the results of cartilage segmentation throughout the quasi-static MR sequence were promising (mean DSI > 66%) and laid foundation for robust analyses of cartilage contact mechanisms.

The proximity algorithms extracted the contact areas between the cartilages with good accuracy (mean DSI > 83%), and moderate to good correlations were identified between measurements derived from the automated and manual segmentations. Automated measurement of the patellar shift was found to be highly reliable, with strong correlations and a negligible bias (0.4%) identified between automated and manual values. The patellar tilt was more problematic to estimate and resulted in weaker correlations. Measurement of this small angle in 3D is challenging as small variations in the features extracted for calculation can cause several degrees of difference in the measured angle. The major cause of variation between automated and manual measurements of patellar tilt was the difference in the shape of the patella derived from the automated and manual segmentations (e.g., flat border in manual segmentations, over-segmentation of the patella). Improvement of this measurement
involves more accurate segmentation of the patella bone. Patellar tilt, however, has been shown to be equally complicated to reliably measure using manual segmentations, with inter-observer coefficients of variation ranging from 10-20% reported [Yamada 2007b] (representing over 1.3° of variation), or a root mean square error of 3° reported for semi-automated tracking of manual bony landmarks used for 2D measurements [Draper 2009b]. In this study, a mean bias of 1.3° was identified, which may be sufficiently small to discern meaningful differences in PFPS patients, where relatively large variations in tilt angle have been reported (15° verse 8° reported for controls [Pal 2012]).

These results are promising and suggest that the method could be developed into a tool well suited to streamline quantitative analyses of knee kinematics from quasi-static MR images in research studies. This could save considerable time that would otherwise be dedicated to manual segmentation of the imaging data (which required several hundred hours in this study), while providing objective measurements with increased reproducibility. It is important however, to qualitatively evaluate the success of the automated segmentation of the knee bones and cartilages throughout the MR sequence. This can be performed efficiently by generating automated segmentation overlays onto the original MR images and surface rendering of the bones and cartilages displaying important features extracted (e.g., Fig. 7.7) as well as the cartilage contact areas (e.g., 7.9).

For the dynamic MR sequences, the MR artifacts were reduced using the redundancy of information available throughout the cycles of the knee flexion/extension. Registration of the resulting MR slices in 3D allowed to track the bones throughout the MR sequence with good accuracy and to obtain plausible bone trajectories (Fig. 7.12). The lack of 3D information in the 2D slices, however, did not allow to capture out-of-plane motion such as external rotation of the femur or tibia bones or the lateral shift of the patella. As knee motion was not controlled in this study, the simple discrepancy between the freely performed knee motion and the orientation of the slices of the MR sequence led to inaccuracies in bone tracking. For several cases, this resulted in overlapping cartilage plates that prevented accurate identification of cartilage contact areas (assessed visually as illustrated in Fig. 7.13).

An avenue for improvement would require the use of a specific jig to guide and maintain knee flexion within a defined acquisition plane. In combination with a slice-to-volume method to reduce translational error [Lin 2013], this could result in a more accurate bone tracking, but would still not allow modelling of the longitudinal rotations of the femur and tibia bones or the tilt of the patella. With the recent advances in MR hardware (high-field strength) and pulse sequences (k-space sampling [Tsao 2003, Pedersen 2009]), acquisition of multiple slices in real-time can potentially provide a more accurate means to track active knee motion [d'Entremont 2013], in which case the scheme developed

for quasi-static MR images could be adapted for analyses.

While there exist a plethora of methods to calculate kinematic parameters of the knee joint (a subset of the most important MR based work is provided in Section 3.3), several methods have been widely accepted by the biomechanics community. These include the six-degree-of-freedom instrumented spatial linkage method proposed by Grood et al. [Grood 1983] or Fujie et al. [Fujie 1996] for the tibiofemoral joint, extended to the patellofemoral joint by several investigators [Lin 2003, Rainbow 2013]. These methods are advantageous as they provide moderately standardised measurements which can be compared between clinical studies and have been extensively used in in-vitro studies. In this thesis, which focused on evaluating the achievable accuracy of a fully automated method, axes calculated from bone features were utilised to calculate the patellar tilt and shift, as per several previous clinical 'imaging-based' studies [Yamada 2007a, Suzuki 2012]. This may limit the clinical applicability of the present method. In addition, in order to compensate for under-segmentations of the cartilages, the threshold distance utilised to calculate the contact-areas between articulating cartilage plates was also greater than that of previous studies [Anderst 2003, Connolly 2009b, Connolly 2009a]. At this stage, the methods allowing the extraction of kinematic parameters with the highest accuracy and reproducibility were utilised, with further research required for standardisation of the parameter extraction algorithms.

Other limitations of the study include to the relatively small sample of images acquired (12 subjects) and the quality of the manual segmentations of the MR images. With the ambiguous demarcation of the bones, cartilages and surrounding tissues in the MR images affected by MR artifacts, it is desirable to evaluate the manual segmentations of inter- and intra-observer reliability in future work. Increased sample size and quantitative evaluation of the differences in measurements derived from manual segmentations from multiple observers would provide information regarding the performance of the automated method by quantitative evaluation of the typical human error obtained in manual analyses.

With regards to future directions for the research, an area for possible improvements is the acquisition protocol utilised for automated analyses. In future experiments, an additional high-resolution MR scan providing optimal contrast between the bones, cartilages and surrounding tissues can be acquired for improved baseline segmentation accuracy. WE-DESS or WE-FLASH are candidate MR pulse sequences for improved bone-cartilage interface and better definition of cartilage morphology. For acquisition of dynamic 2D+t MR images, motion should be controlled to ensure that knee motion occurs mainly in the imaging plane. Alternatively, multi-slice dynamic MR images can be acquired, which can provide opportunities for increased accuracy in estimation of active 3D knee kinematics.

Currently the computational time required to segment the knee bones and cartilages is prohibitively long (several hours). This is mainly caused by the lengthy process of segmenting the bones with the ASM-fitting scheme using high-resolution models (30726 vertices, and 81 surfaces in the models (GLMs/SSMs)). This was required as the common bone segmentation method proposed by *Fripp et al.* [Fripp 2007b] was not robust to the various MR artifacts, with the bone segmentation failing for several cases (this scheme requires less than 5 minutes to obtain the bone segmentation regardless of the MR image). While current scheme allowed to obtain accurate bone segmentation regardless of the MR imaging artifacts, experimenting with different model resolutions and multi-threading the GLM profile search is an avenue for improvements of the computational time (e.g., dividing the number of vertices by two and performing the GLM search for 4 vertices at the same time (4 threads) would allow to execute the bone segmentation scheme within an hour). The impact of reducing the number of vertices of the models on the segmentation accuracy should however be investigated as resulting segmentation labels would be smoother, with a decreased accuracy (sharpness) in highly curved areas.

7.5 Conclusion

In this chapter, an automated registration-based method for segmentation and quantitative analysis of quasi-static and dynamic MR images of the knee joint was presented (Aim 3). The method for analysis of the quasi-static MR images showed promising segmentation accuracy, with mean DSI calculated for the knee joint with different degrees of knee flexion of (88.4, 93.2, 95.6)% for the (patella, tibia, femur) bones and (73.3, 74.4, 68.1, 72.5)% for the (patellar, medial tibial, lateral tibial, femoral) cartilages. Feasibility of extracting accurate contact areas between the articulating cartilages was demonstrated (mean DSI > 83%). Subsequent comparison of cartilage contact surface areas, patellar shift and tilt derived from the automated and manual segmentations showed correlations ranging from 0.43 to 0.93, with most correlations being moderate to strong. Bone tracking in the dynamic MR sequence could be performed reliably (qualitative evaluation only); however, the resulting 3D transformations were inadequate to model the rotational and translational components associated with the motion occurring outside of the imaging plane. This resulted in overlapping cartilages in several cases.

The results indicate that the automated method developed to estimate 3D knee kinematics from quasi-static MR images could facilitate clinical studies into passive knee kinematics.



Figure 7.14: Visualisation of several issues involved in the analysis of the kinematic MR images.

Chapter 8

Summary, General Discussion and Conclusion

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8.3	General Conclusion

This chapter summarises and discusses the main findings of this thesis, with a particular focus on the major contributions to the field of quantitative magnetic resonance imaging of the knee joint. In the discussion, current limitations and the future directions for this research are highlighted.

8.1 Summary of the Findings and Key Contributions

In this thesis, several automated image analysis algorithms have been developed to facilitate quantitative MR analyses of the knee joint. The major contributions within each aim are outlined below.

(Aim 1) Automated segmentation and quantitative analysis of the menisci from MR images of healthy and pathological knee joints

Key findings of the research:

The automated method developed to segment the knee menisci can obtain reliable and accurate segmentations from MR images of the healthy and pathological knee joints acquired using pulse sequences typically used in routine clinical MR examinations (2D/3D-TSE) and clinical research (WE-DESS);

- 2. The automated segmentations can be used to reliably and accurately estimate morphological (volume, subluxation and tibial coverage) and T2 measurements of the knee menisci;
- 3. The method can be used to identify significant differences in the morphology and T2 relaxation properties of the menisci between clinically relevant groups.

This was demonstrated in Chapters 4 and 5 with the careful validation of a set of image analysis algorithms for the segmentation (Aim 1.1) and quantitative analysis (Aim 1.2) of the morphology and T_2 relaxation properties of the knee menisci from MR images. The ASM-based method for automated segmentation of the individual knee MM and LM was successfully validated using multiple MR datasets (mean DSI between [74.5 – 84.3]% for the MM and [76.5 – 85.1]% for the LM), which included diverse MR sequences (clinical 2D/3D-TSE, 3D WE-DESS) acquired from patients with variably severe knee pathologies (OA, ACL and/or meniscus injury, healthy). The automated segmentation results were of equivalent or superior accuracy to previous automated methods developed for segmentation of the menisci in healthy knees [Fripp 2009, Zhang 2013]. Initial results for segmentation of the menisci in pilot scans (WE-DESS) from new 7T MR scanners showed promising accuracy (mean DSI of 79.3% and 80.5% for the MM and LM).

Subsequent quantitative measurements of the morphology (volume, subluxation and tibial coverage) and T_2 relaxation properties of the menisci derived from the automated segmentations were well correlated with those obtained from manual segmentations (r > 0.7). Proof of concept experiments investigating for differences in meniscal morphology and biochemistry (water mobility) across clinically relevant groups of patients (rOA/JSN severity, meniscal tear) showed patterns of significant differences in agreement with the literature [Blöcker 2013, Wenger 2013, Liu 2015].

(Aim 2) Automated segmentation and quantitative analysis of the PCL from MR images of the knee joint

Key findings of the research:

- 1. The automated method developed to segment the knee PCL can obtain reliable and accurate segmentations from T_2 -map MR images of the knee joint;
- 2. The resulting segmentations can be used to reliably and accurately estimate T_2 -properties of the knee PCL.

This was demonstrated in Chapter 6 with the validation of image-processing algorithms for automated segmentation and T_2 -mapping of the knee PCL from MR images. The multi-scale patch-based segmentation method was successfully validated on a dataset of T_2 -map MR images acquired from 26 asymptomatic volunteers (mean DSI of $74.5 \pm 3.7\%$). The dataset was balanced in gender, laterality and was representative of a wide age range. The minimum DSI obtained for this dataset was 65%, showing that the method obtained reliable segmentations for all cases. To the author's knowledge, no other quantitative validation of automated segmentation results for the PCL has been reported, with only two semi-/fully-automated methods published that did not report measurements of accuracy [Uozumi 2015, Zarychta 2016]. The segmentation algorithm seems to outperform results reported for the contiguous ACL structure in T_2 -maps with similar characteristics [Lee 2014], although comparison is not straightforward given the anatomical differences between the ACL and the PCL.

Moreover, the suitability of the method for segmentation of T_2 -maps from pathological knee joints was investigated using images from 88 patients of the OAI. Qualitative inspections of the resulting segmentation volumes by overlaying onto the original T_2 -maps showed good accuracy for a great majority of the dataset, which included patients characterising the full spectrum of rOA (K/L grades 0-IV).

From the automated segmentation volumes, the T_2 -relaxation properties of the PCL were estimated accurately, with moderate to strong correlations calculated between measurements derived from automated and manual segmentations (r > 0.74). Pilot evaluation of the T_2 -values of the PCL across patients with variably advanced knee OA showed no numerical differences in T_2 -values.

(Aim 3) Automated segmentation and quantitative analysis of kinematic MR images of the knee joint

Key findings of the research:

- 1. The automated pipeline developed for analysis of quasi-static MR images can successfully segment and track the bones and cartilages throughout the varying degrees of knee flexion;
- 2. Automated segmentations obtained for the knee joint with variable degrees of knee flexion can be used to quantitatively evaluate 3D knee kinematics with variable degrees of reliability:
 - Cartilage contact kinematics can be estimated reliably and accurately;
 - Patellar shift can be estimated reliably and accurately;

- Patellar tilt is difficult to measure reliably and weaker correlations were obtained by comparison with measurements derived from manual segmentations.
- The method developed for the dynamic MR sequences can reliably track the bones (obtained from the baseline WE-TrueFisp segmentations) throughout the 2D+t sequence (qualitative evaluation);
- 4. With the current method, estimation of 3D motion by registration of 2D-slices in 3D space (with the position of the slice in 3D space obtained from the MR scanner) is inadequate to reliably evaluate 3D knee kinematics.

This was demonstrated in Chapter 7 with the development and evaluation of automated image analysis algorithms for segmentation and tracking of the knee bones and cartilages in: (1) quasi-static (3D+t WE-TrueFisp) MR images acquired for the knee joint with six different degrees of flexion; and (2) real-time dynamic (2D+t TrueFisp or HASTE) MR sequences of the knee joint in active motion.

A hybrid method combined with bone-specific pairwise registration and an artifact reduction strategy obtained good segmentations of the knee bones and cartilages throughout the quasi-static MR sequences (mean DSI above 88.4% for the bones and above 68.1% for the cartilages). Contact regions between the cartilages as well as measurements of patellar tilt and shift were estimated using proximity and surface feature extraction algorithms. Contact regions derived from the automated and manual segmentations showed good spatial agreement, with mean DSI above 83.97% calculated for the patellofemoral and medial/lateral tibiofemoral articulations. The comparison of the quantitative measurements (surface area of the contact regions, patellar tilt and shift) derived from the automated and manual segmentations showed correlation ranging from 0.43 to 0.93, with most correlations being moderate to strong.

For the dynamic (2D+t) MR sequences, an analogous registration-based method was used to track the bones throughout the 2D+t MR sequence (registration performed between single slices represented in 3D space). Visual inspections of overlays of the automated bone segmentations onto the 2D slices of the MR sequence showed that tracking was performed accurately within the space of the 2D slices. However, the pipeline was inadequate to accurately identify 3D bone trajectories due to missing 3D information necessary to model external rotation of the femur and tibia bones as well as the tilt and lateral shift of the patella.

8.2 Implications of the Findings, Limitations and Future Directions for Research

(Aim 1) Automated segmentation and quantitative analysis of the menisci from MR images of healthy and pathological knee joints

The automated segmentation approach was successfully validated on clinical and research MR scans of the pathological knee joint, representing a significant advance towards clinical applicability of quantitative MR analyses of the knee menisci. This could allow for accurate pre- and post-surgery assessment of functional loss using conventional MR imaging (e.g., quantification of the volume removed in partial meniscectomy [Bowers 2007, Bowers 2010]); or assessment of repair status using biochemical MR sequences [Chu 2014].

Moreover, the automated method provides opportunities to more efficiently study these biomechanically important fibro-cartilaginous structures in large-scale longitudinal MR studies into knee OA such as the OAI [Peterfy 2008]. This can help improve current understandings regarding the relationship between degeneration of the menisci and knee OA development. The method is readily suitable to automatically analyse large amounts of imaging data and investigate early changes in meniscal morphology and T_2 properties in pre-osteoarthritic knee joints.

As any automated system, the method requires minimal visual inspection of the resulting segmentation volume to account for the low failure rate and the limitations of the method, discussed in details in Chapters 4 and 5 and summarised below.

A limitation of the automated menisci segmentation method relates to the systematic segmentation error identified in the mid-compartment and the tip of the horns of the menisci. These can be attributed to the poor delineation of the menisci with the surrounding fatty tissues (especially in the mid compartment) or the lack of detailed anatomical information in these areas (e.g., significant partial volume effects near the roots and mild compartment). To improve accuracy, incorporating the latest developments in robust or focused shape modelling [Schmid 2011, Chandra 2014] into the method is an avenue for future developments. Replacing the current unconstrained surface relaxation stage by a weighted deformation may help maintain more regular meniscus shapes and minimise errors in these areas. In addition, increasing the size of the training set (i.e., number of tissue profiles used as templates in the deformation of the models) is another possible solution for improvement. Another limitation of the method is the low accuracy (DSI<65% for either the MM or LM in roughly 7% of the patients) obtained for segmentation of severely damaged menisci (e.g., destruction or maceration of most of the meniscal tissue). The reason behind this issue is simply that for these cases, the model-based segmentation scheme has close to no meniscal tissue to deform into. Further work will be required to handle these cases and creating models incorporating patient specific information is an avenue for improvement of the method. The occurrence of these inaccuracies was low considering the current dataset of knees with a wide spectrum of pathologies (mild to severe knee OA and acute meniscal tears) and the method is sufficiently accurate to study the menisci in a framework of early knee OA assessment.

In future research, quantitative validation (larger dataset) of the automated method for segmentation of the knee menisci in 7T MR scans will be performed. These images provide opportunities for increased segmentation accuracy and precise regional analyses of the morphology and T_2 relaxation values of the menisci (i.e., red, red-white and white zone, See Section 2.1.3 and Fig. 5.11).

(Aim 2) Automated segmentation and quantitative analysis of the PCL from MR images of the knee joint

This study is the first to quantitatively validate an automated method for segmentation for the PCL in MR images. The quantitative results of accuracy reported may serve as a baseline for future studies seeking to automate the segmentation of the PCL from MR images of the knee joint. This is important considering the recent clinical interest for the development of quantitative methods to evaluate the T_2 - and T_2^* -properties of the PCL for pre- and post-surgery assessment of the repair status and function of the ligament [Biercevicz 2014a, Wilson 2016]. The method is readily applicable to clinical studies into the PCL, under the same caveat conditions as for meniscus analyses (i.e., visual inspections to confirm segmentation success).

Although the results are promising, the obvious limitation of the study is the relatively small sample size (N=26) of manual segmentations used to quantitatively validate the method.

Future work would require the use of an increased number of atlases and associated expert manual segmentations. The benefits of this would be twofold. First, it would allow for a more thorough validation of the method, for assessment of the robustness against a larger range of PCL morphology and shape characteristics in the MR images (highly dependent on knee positioning during acquisition); and to precisely identify the problematic areas to segment. Second, it would provide opportunities to

difficult voxels (e.g., partial volume voxels). Incorporating advanced image preprocessing techniques such as super-resolution methods [Van Reeth 2012] into the pipeline to reduce partial volume effects can also be explored in future research.

In future work, it is also desirable to quantitatively validate the performance of the automated method on: (1) MR images of the pathological knee joint and (2) multiple MR sequences commonly used to study and diagnose the knee joint. This would provide further information regarding the reliability of the segmentation method and its potential clinical applicability.

(Aim 3) Automated segmentation and quantitative analysis of kinematic MR images of the knee joint

The automated segmentation and quantitative analysis method developed to assess passive knee kinematics from quasi-static MR images can save considerable amounts of time in comparison to manual analysis of the data, which required several hundred hours of tedious manual labour in this study. The method provides a means to facilitate clinical studies evaluating *in-vivo* passive knee kinematics from series of static MR images of the knee joint with increasing degrees of knee flexion. Examples of possible applications for the automated method include the analysis of passive patellofemoral kinematics in patients with patellar pathologies [Yamada 2007b] or tibiofemoral kinematics in weightbearing conditions [Patel 2004]. The results obtained for the automated estimation of *in-vivo* active knee kinematics from dynamic (2D+t) MR sequences suggest that accurate modelling of 3D bone trajectory from 2D slices requires control of the knee motion trajectory (e.g., guided by a jig [Lin 2013]) to minimise displacement outside of the imaging plane.

There are several technological areas related to image acquisition and analysis that can be improved.

The patella bone and articular cartilages were the major areas of concern in the baseline segmentations, which impacted upon the accuracy of quantitative measurements of knee kinematics. Due to the lack of contrast with the patellar tendon, over-segmentation of the patella usually occurred. A solution for improvement would involve training new models using a sufficiently large WE-TrueFisp MR dataset (current models were generated from external WE-DESS and FS-FLASH). This can improve the template matching process used in the ASM fitting. Cartilage segmentation errors were mainly caused by intensity variations within the tissues that were falsely identified as cartilage boundary. Although sophisticated classifiers could potentially improve modelling of tissue properties [Zhang 2013], an alternative solution that would benefit both the knee bone and cartilage segmentations involves the inclusion of a high-resolution WE-DESS or WE-FLASH MR image with fat suppression (which provide excellent bone contrast and cartilage morphology) in the acquisition protocol.

The method developed to track the bones and cartilages throughout the quasi-static MR images obtained promising accuracy. However, due to inhomogeneity MR artifacts, a significant decrease in DSI was identified for the resulting segmentations in comparison to baseline segmentation results. Although the method developed incorporated an artifact reduction strategy, there is currently no method that allows to entirely correct this type of artifacts. The feasibility of using MR sequences less sensitive to magnetic field inhomogeneity (e.g., TSE) for acquisitions is a worthwhile direction for future investigations. Nevertheless, the registration scheme maintained sufficient bone and cartilage segmentation accuracy to allow the reliable quantitative measurement of 3D knee kinematics for all cases (cartilage contact areas and patellar shift).

The method developed for registration of the 2D slices of the dynamic MR sequence (represented as single-slice 3D images) could reliably track the bones (and associated cartilages) throughout the sequence. However, to subsequently achieve accurate quantification of 3D knee kinematics remains challenging due to the lack of information characterising the motion occurring outside of the imaging plane. Recent studies suggested that using a guiding jig to constrain knee motion within the imaging plane during acquisition and correcting knee pose using a slice-to-volume registration algorithm (which would correct for medial-lateral translations only) could obtain reliable 3D knee kinematics [Lin 2013]. However, with the recent advances in MR imaging hardware (stretchable or open coils, high-field strength) and pulse sequence design (e.g., optimised filling of the k-space [Tsao 2003, Pedersen 2009]), acquisition of multiple slices in real-time may be a better alternative [d'Entremont 2013]. In this case, analyses could be performed using the automated method developed for quasi-static MR images with some adaptation.

8.3 General Conclusion

This thesis presents a set of innovative image-processing algorithms for the automated segmentation and quantitative analysis of the morphology and biochemical composition of the knee MM, LM and PCL as well as the automated *in-vivo* quantification of the kinematic characteristics of the knee joint from MR images.

The methods developed for automated segmentation of the menisci and PCL obtained good accuracy and provided a robust basis for automated and accurate estimation of clinically relevant measurements describing the morphology (meniscus volume, subluxation and tibial coverage) and T_2 relaxation properties (water mobility) of these structures from MR images of the knee joint. This represents a significant step towards clinical applicability of quantitative MR imaging of the menisci and PCL and provides a means to facilitate clinical studies focusing on *in-vivo* quantitative evaluation of these important knee structures.

The automated analysis of kinematic MR images enabled the segmentation and tracking of the knee bones and cartilages of the joint with different degrees of knee flexion (3D+t) and in active motion (2D+t). The automated analysis developed in this thesis show the promise of these techniques. However, further technical improvements in image acquisition and analysis are currently required before possible clinical applicability.

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Appendix A Technical Background

A.1 EM-ICP Surface Registration

In the work of this thesis, the point-wise correspondence between the MM and LM surfaces necessary for the calculation of the SSMs was generated using the EM-ICP algorithm [Combès 2010, Dore 2011]. The method allows the non-linear registration of point sets (in our case surface meshes) based on a symmetric cost function ensuring smooth and consistent registration results. In our case, the registration was performed between a template surface M_0 and all the other surfaces M_i of the dataset.

The EM algorithm takes into account both the forward deformation field T_f from M_0 onto M_i and the backward deformation field T_b from M_i onto M_0 . The matrix describing the matches between the vertices of $T_F(M_0)$ and M_i (resp. $T_b(M_i)$ and M_0), denoted A_f (resp. A_b) is constituted of probability values ($A_{f_{i,j}} \in [0, 1]$) that two vertices are matched.

Taking into account T_f , T_b , A_f and A_b as well as two weighting scalars α and β , the symmetric cost-function defined by *Combes et al.* [Combès 2010] is as follow:

$$\varepsilon(T_f, T_b, A_f, A_b) = \varepsilon_d(M_0, T_b(M_i), A_b) + \varepsilon_d(M_i, T_f(M_0), A_f) + \alpha \varepsilon_c(T_b \circ T_f, I) + \alpha \varepsilon_c(T_f \circ T_b, I) + \beta \varepsilon_r(T_f) + \beta \varepsilon_r(T_b)$$
(A.1)

In this equation A.1, ε_d is a term quantifying how different the two surfaces are and the regularity of the matching matrix. It is calculated using equation A.2. ε_c and ε_r measure the discrepancy between backward and forward deformation fields (i.e., how different their composition is to the identity transform (equation A.3)) and the regularity of the transformations. ε_c and ε_r are weighted using the α and β scalars.

$$\varepsilon_d(M_0, T_b(M_i), A_b) = \frac{1}{N} \left[\sum_{i,j} (A_{b_{i,j}} \| y_i - T_b(x_j) \|^2) + \sigma^2 \sum_{i,j} (A_{b_{i,j}} \log(A_{b_{i,j}})) \right]$$
(A.2)

$$\varepsilon_c(T_b \circ T_f, I) = \frac{1}{N} \sum_{x_j \in M_i} (\|T_b \circ T_f(x_j) - x_j\|^2)$$
(A.3)

The proposed cost-function is then minimised in a two steps iterative process. In the first step, the transformations T_f and T_b are initialised as identity transforms and set fixed while the optimizer updates the correspondence matrices A_f and A_b to minimise ε . In the second step, the correspondences A_f and A_b are fixed and the optimizer minimises ε by updating the parameters of the transformations T_f and T_b . Utilising both the forward and backward transforms prevents the optimizer from converging towards a local minima.