# KNEE CARTILAGE SEGMENTATION USING MULTI PURPOSE INTERACTIVE APPRAOCH

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# KNEE CARTILAGE SEGMENTATION USING MULTI PURPOSE INTERACTIVE APPRAOCH

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requirements for the award of the degree of
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Dedicated to my beloved family and friends

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# ABSTRACT

Interactive model incorporates expert interpretation and automated segmentation. However, cartilage has complicated structure, indistinctive tissue contrast in magnetic resonance image of knee hardens image review and existing interactive methods are sensitive to various technical problems such as bi-label segmentation problem, shortcut problem and sensitive to image noise. Moreover, redundancy issue caused by non-cartilage labelling has never been tackled. Therefore, Bi-Bezier Curve Contrast Enhancement is developed to improve visual quality of magnetic resonance image by considering brightness preservation and contrast enhancement control. Then, Multipurpose Interactive Tool is developed to handle users' interaction through Label Insertion Point approach. Approximate Non-Cartilage Labelling system is developed to generate computerized non-cartilage label, while preserves cartilage for expert labelling. Both computerized and interactive labels initialize Random Walks based segmentation model. To evaluate contrast enhancement techniques, Measure of Enhancement (EME), Absolute Mean Brightness Error (AMBE) and Feature Similarity Index (FSIM) are used. The results suggest that Bi-Bezier Curve Contrast Enhancement outperforms existing methods in terms of contrast enhancement control (EME = $41.44 \pm 1.06$), brightness distortion (AMBE = $14.02 \pm 1.29$) and image quality (FSIM = $0.92 \pm 0.02$). Besides, implementation of Approximate Non-Cartilage Labelling model has demonstrated significant efficiency improvement in segmenting normal cartilage ($61\text{s} \pm 8\text{s}$, $P = 3.52 \times 10^{-5}$) and diseased cartilage ($56\text{s} \pm 16\text{s}$, $P = 1.4 \times 10^{-4}$). Finally, the proposed labelling model has high Dice values (Normal: $0.94 \pm 0.022$, $P = 1.03 \times 10^{-9}$; Abnormal: $0.92 \pm 0.051$, $P = 4.94 \times 10^{-6}$) and is found to be beneficial to interactive model ($+0.12$).

# ABSTRAK

Model interaktif menggabungkan tafsiran pakar dan segmentasi automatik. Namun, struktur tulang rawan manusia yang rumit, perbezaan ketara tisu imej magnetik resonan yang tidak jelas menjejas tafsiran pakar dan teknik interaktif sedia ada menghadapi isu-isu teknikal seperti masalah segmentasi dua label, masalah jalan pintas dan sensitif terhadap hingar imej. Selain itu, isu-isu bertindih disebabkan oleh pelabelan tisu bukan tulang rawan masih belum ditangani. Maka, teknik Peningkatan Ketaraan Lengkung "*Bi-Bezier*" dibangunkan untuk meningkatkan kualiti penglihatan imej magnetik resonan dengan mengambilkira pemeliharaan kecerahan dan mengawal kadar peningkatan kontras ketaraan. Kemudian, Alat Interaktif Serbaguna dibangunkan untuk mengendalikan interaksi pengguna melalui teknik sisipan titik label. Sistem pelabelan anggaran "*Non-Cartilage*" dibangunkan bagi menjana label pengkomputeran untuk tisu bukan rawan tulang, sementara meninggalkan tisu tulang rawan untuk dilabel oleh pakar. Input daripada kedua-dua label interaktif dan pengkomputeran akan memulakan model segmentasi berasaskan "*Random Walks"*. Untuk menilai teknik peningkatan ketaraan, Ukuran Peningkatan (EME), Ralat Kecerahan Purata Mutlak (AMBE) dan Indeks Kesamaan Ciri (FSIM) telah digunakan. Keputusan analisis menunjukkan bahawa teknik Peningkatan Ketaraan Lengkung "*Bi-Bezier*" mempunyai kelebihan dari segi kawalan peningkatan ketaraan (EME = $41.44 \pm 1.06$), herotan kecerahan (AMBE = $14.02 \pm 1.29$) dan kualiti imej (FSIM = $0.92 \pm 0.02$). Selain itu, model Pelabelan anggaran "*Non-Cartilage*" menunjukkan kelebihan dari segi kecekapan segmentasi tulang rawan normal (61s$\pm$8s, $P = 3.52 \times 10^{-5}$) and tidak normal (56s$\pm$16s, $P = 1.4 \times 10^{-4}$). Akhirnya, model pelabelan yang dicadangkan mempunyai nilai "*Dice*" yang tinggi (Normal: $0.94 \pm 0.022$, $P = 1.03 \times 10^{-9}$; Tidak normal: $0.92 \pm 0.051$, $P = 4.94 \times 10^{-6}$) dan ia didapati akan memanfaatkan model interaktif ($+0.12$).

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## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| 2D | - | Two dimensional |
| 3D | - | Three dimensional |
| 3T | - | Three tesla |
| ALI | - | Additional label insertion |
| ANCAL | - | Approximate non-cartilage labelling |
| ANN | - | Approximate nearest neighbour |
| ACL | - | Anterior cruciate ligament |
| ACM | - | Active contour model |
| AID | - | Absolute intensity difference |
| AMBE | - | Absolute mean brightness error |
| ASM | - | Active shape model |
| BBCCE | - | Bi-Bezier curve contrast enhancement |
| BBD | - | Balanced box-decomposition |
| BBHE | - | Bi-histogram equalization |
| BCI | - | Bone-cartilage interface |
| CEDHE | - | Contrast enhancement dynamic histogram equalization |
| CRW | - | Conventional random walks |
| DESS | - | Dual echo steady state |
| DICOM | - | Digital imaging and communications in medicine |
| DMOAD | - | Disease modifying osteoarthritis drug |
| DOF | - | Degree of freedom |
| DSIHE | - | Dualistic sub-image histogram equalization |
| EME | - | Contrast enhancement degree |
| FCM | - | Fuzzy c means |
| FFD | - | Free form deformation |

| | | |
|---|---|---|
| fMRI | - | Functional magnetic resonance |
| FN | - | False negative |
| FP | - | False positive |
| FSIM | - | Feature similarity index model |
| HE | - | Histogram equalization |
| IDV | - | Intensity discrepancy value |
| JSW | - | Joint space width |
| KL | - | Kellgren-Lawrance |
| $k$NN | - | k nearest neighbour |
| MBOBHE | - | Multipurpose beta optimized bi-histogram equalization |
| MIT | - | Multipurpose interactive tool |
| MMBEBHE | - | Minimum mean brightness error bi-histogram equalization |
| MMP | - | Matrix metalloproteinase |
| MR | - | Magnetic resonance |
| MS | - | Manual segmentation |
| NIH | - | National Institute of Health |
| NMI | - | Normalized mutual information |
| NNS | - | Nearest neighbour searching |
| OA | - | Osteoarthritis |
| OAI | - | Osteoarthritis initiative |
| O1 | - | Observer 1 |
| O2 | - | Observer 2 |
| PDF | - | Probability density function |
| PCL | - | Posterior cruciate ligament |
| RMSHE | - | Recursive mean separate histogram equalization |
| RSIHE | - | Recursive sub-image histogram equalization |
| THE | - | Traditional histogram equalization |
| TKA | - | Total knee replacement |
| TN | - | True negative |
| TP | - | True positive |

# LIST OF SYMBOLS

| | | |
|---|---|---|
| $A$ | - | Adjacency matrix |
| $D$ | - | Degree matrix |
| $h$ | - | Parametric domain |
| $G$ | - | Graph representation |
| $\mathcal{V}$ | - | Node |
| $\mathcal{E}$ | - | Edge |
| $\mathcal{F}$ | - | Foreground |
| $\mathcal{B}$ | - | Background |
| $I$ | - | General Image |
| $L$ | - | Laplacian matrix |
| $\mathcal{P}$ | - | Image pixels |
| $C$ | - | Graph partition using “cut” |
| $S$ | - | Source |
| $T$ | - | Sink |
| $X$ | - | MR image of knee |
| $w$ | - | Weight of edge |
| $f$ | - | Pixel label |
| $U$ | - | Unallocated pixels |
| $b$ | - | Label index |
| $pl$ | - | Plateau/ platform |
| $cf$ | - | ANCAL classification function |
| $cc$ | - | Cluster centre |
| $cl$ | - | Cluster of image |
| $\vec{v}(.)$ | - | General contour function |
| $E_{int}(.)$ | - | Internal energy of contour |

| | | |
|---|---|---|
| $E_{ext}(.)$ | - | External energy of contour |
| $\mathrm{argmin}(.)$ | - | Argument of the minimum |
| $l(.)$ | - | Length of walk between two nodes |
| $pdf(.)$ | - | General probability density function |
| $cdf(.)$ | - | General cumulative density function |
| $cdf_{lower}(.)$ | - | Cumulative density function of lower sub-image |
| $cdf_{upper}(.)$ | - | Cumulative density function of upper sub-image |
| $f_{lower}(.)$ | - | Transform function for lower sub-image |
| $f_{upper}(.)$ | - | Transform function for upper sub-image |
| $B_{n,i}(.)$ | - | Bernstein polynomial with binomial coefficients $i$ and $n$ |
| $CP(.)$ | - | Critical point |
| $Q(.)$ | - | Bezier curve |
| $Q(.)$ | - | ANCAL cost function |
| $D\|.\|$ | - | Dirichlet integral |
| $\chi(.)$ | - | Sign function |
| $N(.)$ | - | Second order neighbour of pixel |
| $\vartheta$ | - | ANCAL cost function constant |
| $\Phi$ | - | Orthogonal transforms |
| $\Omega$ | - | Image spatial domain |

# LIST OF APPENDIX

# CHAPTER 1

# INTRODUCTION

## 1.1 Introduction

Osteoarthritis (OA) is the most prevalent joint disease (Brooks, 2006) and the second most debilitating global disease after cardiovascular disease in western society (McCauley and Disler, 1998; Haq *et al.*, 2003). Aged population, especially women aged 65 years old and above, is typically prone to be affected by OA (Lawrence *et al.*, 2008). Since human knee cartilage is innervated, affected patients at early stage will endure gradual loss of cartilage without any apparent symptoms (Bijlsma *et al.*, 2011). As OA worsens, knee cartilage has been exhausted and the bone surface is exposed. Some patients will rush to seek medical treatments after realizing the disease, but it is already too late (Bijlsma *et al.*, 2011). Given that OA is a biomechanical related disease (Englund, 2010), joint pain is the most common and predominant characteristic (Bauer *et al.*, 2006). Unbearable pain forces patients to favour normal side of their knee over the abnormal side as well as addicted to pain relieving drugs. Eventually, chronic OA patients will experience loss of function which severely degrades their qualities of life (Brooks, 2002; Losina *et al.*, 2011).

Patients can fall easily into depression and sleep disorder on the ground that no existing OA drugs or treatment can provide effective solution to implications associated with the disease (Breedveld, 2004). Patients with sleep disturbance due to agonizing joint pain cannot depend on pain relieving drugs because the drugs will only bring short term relief to them. Besides, human's level of self-efficacy is gauged by their capabilities to carry out a task independently but chronic OA patients are hindered by physical limitation. As a result, these patients will incline to develop low self-esteem and pessimistic personalities that encourage them to isolate themselves from the society. Negative social effects, in turn, contribute to massive and direct economic downturn in multiple ways (Reginster, 2002).

Besides, economic losses are caused by huge medical expenditures spend on total knee replacement (TKA) surgeries and other pain relieving treatments. TKA is the last and few option recommended for chronic OA patients who cannot bear with excruciating joint pain. According to compiled statistics, more than 615,000 TKA surgeries have been performed annually in the United States (Eckstein *et al.*, 2013). Hence, medical insurers worldwide need to spend approximately $3,108.698 on women and $3,040.444 on men annually, which translate into $149.4 billion each year. In addition, evidence shows that men have to spend $612.120 while women have to spend $770.077 each year on OA associated medical costs (Kotlarz *et al.*, 2009). Furthermore, productivity of affected people are expected to reduce dramatically due to physical movement constraint. In some cases, affected patients are forced out of their jobs because their employers do not want to cover their medical fees. Given that the dreadful economic implications associated with OA, understanding the progression of OA will promote future development of preventive measures.

## 1.2 Pathophysiology of Osteoarthritis

OA is also known as degenerative arthritis or hypertrophic arthritis. Anatomically, the disease is characterized by inevitable structural change of diarthrosis joint (Loeser *et al.*, 2012) resulted from continual loss of articular cartilage when attempted repair of articular cartilage is constantly outpaced by degradation of cartilage tissue. At the onset of OA progression, cartilage irregularities evolves into fissure and roughens the articular surface. The fissure will slowly extend toward the subchondral bone and expose knee bone to erosion. Figure 1.1 explains the fissure extending through different cartilage layers (wear and tear).

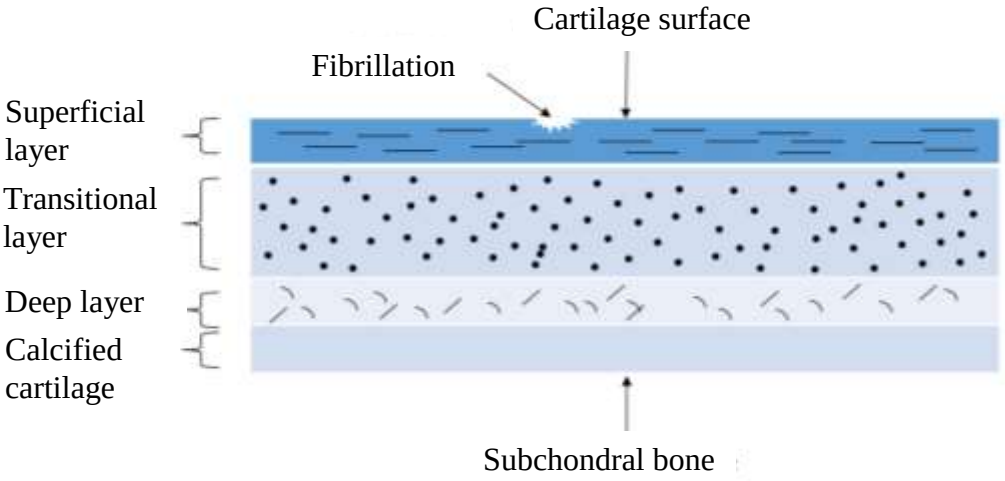


**Figure 1.1** Degradation of cartilage (Pearle *et al.*, 2005)

OA are characterized by clinical symptoms like appearing sclerosis of subchondral bone, formation of subchondral bone cysts and marginal osteophytes. Palpable signs such as joint pain, restriction of motion, knee crepitus, joint effusion or swelling and deformity reaffirm one is being affected by OA.

OA can be classified into primary OA and secondary OA. Primary osteoarthritis is alternatively referred as idiopathic OA because its cause remains unidentified. Recently, substantial amount of researches have related the pathogenesis of primary OA to mechanical stress (Brandt *et al.*, 2009), aging (Shane

Anderson and Loeser, 2010), genetic predisposition (Valdes and Spector, 2009), influence of sex hormones (Linn *et al.*, 2012) and inflammatory . Secondary OA is mainly attributed to joint injury, infection, or one of a variety of hereditary, developmental, metabolic and neurologic disorder (Creamer and Hochberg, 1997). One recent finding indicates that the degradation of knee cartilage is also driven by multiple synovial tissues inside knee joint (Scanzello and Goldring, 2012). The synovial tissues include articular cartilage, subchondral and metaphyseal bone, synovium, ligaments, joint capsule and various muscles that act across the joint. Involvement of these tissues, combined with complex sequence of factors mentioned above, degrades the integrity of human knee joint. Hence, it is appropriate to call OA as a "whole joint disease" (Lories and Luyten, 2011).

There are two groups of natural enzymes responsible for the construction of cartilage matrix such as collagens, proteoglycans non-collagenous proteins and membrane protein and degradation of cartilage matrix such as metalloproteinases, aggrecanase and other proteinases (Goldring, 2000). Under normal consequence, both types of enzymes will balance each other. However, external disruption to this metabolism such as mechanical stress and insult will cause degradation mechanism to outpace cartilage synthesis. Chronology of the irreversible damage to knee cartilage is generally presumed to occur in three distinct stages i.e. disruption to cartilage matrix structure, imbalance chondrocyte-MMP response which contributes to tissue damage and decline of chondrocyte synthetic response that eventually leads to progressive loss of tissue. Nevertheless, current research on the intriguing cartilage degradation remains far from full-fledging.

Due to limited understanding, effective medical options remain available (Wang *et al.*, 2012). Existing pain relieving therapeutic treatments can only provide short term solution but fail to check on the progression of OA. Intuitively, one possible long term solution is to predict disease progression using biomarker, identify patient most likely to progress and then develop efficacious disease modifying osteoarthritis drug (DMOAD) (Eckstein *et al.*, 2012). In next section, identification of potential imaging is presented.

## 1.3 Imaging Biomarker

Traditional studies using clinical end points of morbidity and mortality are standard to study a disease's progression. Traditional clinical studies follow strict reference standard, so their findings are very reliable. Nonetheless, traditional approach inherits serious drawbacks. First, continual monitoring on the disease's development will consume long span of years and large amount of resources. Besides, subjective issue is often associated with the traditional endpoint because this approach obtains data by using scaling measure, questionnaire and observation (Kraus *et al.*, 2011). For example, morbidity is derived from measuring the degree of severity of a disease but the measurement of disease severity's level may vary according to different definitions. So the measure itself may not reflect the whole situation appropriately (Smith *et al.*, 2003). In addition, maintaining a clinical study requires great financial support over number of years so most pharmaceutical companies often shun such high risk investment.

Biomarker is presumably a very good replacement to traditional end points studies. It can be anything that can indicate a particular disease state, a healthy biologic process or pharmacologic responses to a therapeutic intervention (Atkinson *et al.*, 2001; Kraus *et al.*, 2011). General biomarkers can use molecules, gene, body temperature, blood pressure or image to quantify the development of a specified disease. Biomarkers can be categorized into "wet" biomarker and "dry" biomarker (Kraus *et al.*, 2011). Wet biomarker refers to fluid such as serum, urine or blood that can indicate the change of response while dry biomarker usually refers to imaging modalities, questionnaires and other visual analog scales. Imaging biomarker, defined as "any anatomic, physiologic, or molecular parameter detachable with one or more imaging methods used to help establish the presence and/or severity of disease (Smith *et al.*, 2003), offers great potential to osteoarthritis research.

Information from medical image allows us to test on numerous quantitative metrics that best descripts progression of OA. Initial attempt includes joint space width (JSW) using X-ray image of knee to diagnose OA (Roemer *et al.*, 2011).

Measurement of JSW is performed by using ruler, callipers or computer software to where measurement less than the minimal JSW indicates joint space loss (Wright, 1994). The joint space loss signals loss of knee cartilage. However, reliability of radiography technology is confined by numerous constraints. In terms of safety, radiography technology exposes subjects to radiation and present long term health hazard to subjects. In terms of flexibility, radiography is a 2D imaging technology, which hinders an overall assessment of the cartilage loss.

More important, reliability of JSW as indicator for cartilage loss has raised intense concern after evidences from other studies have pointed out that JSW may not solely reflect cartilage loss. Intriguingly, meniscal extrusion has been reported to contribute significantly to the narrowing of knee joint in the absence of cartilage thinning (Adams *et al.*, 1999; Sharma *et al.*, 2008). Alas, the degree of medial meniscal subluxation has direct influence on the amount of medial JSW in both genders (Gale *et al.*, 1999) and technical error during image acquisition will alters the measurement of JSW based on the fact that this biomarker is sensitive to malpositioning (Segerink *et al.*, 2006). Consequently, credibility of JSW as imaging biomarker for OA has been discounted.

Unlike 2D radiography, magnetic resonance (MR) imaging delineates knee cartilage in 3D view; allowing direct monitor of OA progression (Augat and Eckstein, 2008). Besides, MR imaging is non-invasive and non-radiation; thus presents no safety hazard to patients. Quantification of MR image of knee through morphometric analysis in MRI (Eckstein *et al.*, 2006) and T2 measurement in functional MRI (fMRI) (Carballido-Gamio *et al.*, 2008) are potential biomarkers to examine the progression of OA based on clinical variables like cartilage thickness, volume, surface area and curvature (Hayashi *et al.*, 2012; Eckstein *et al.*, 2013).

## 1.4 Problem Statements

Development of an intuitive segmentation model is challenging. Major problems associated with cartilage segmentation have been identified as follows:

1) Inferior visual appearance of the MR image of knee. MR image of knee has low intensity value and indistinctive tissue contrast; thus contribute to high degree of ambiguity during image review (Fripp *et al.*, 2007)
2) Existing interactive methods fail to provide convenient segmentation. As such, current interactive algorithms have reported various types of implementation problems. For example, popular graph cuts are typically sensitive to smallcut problem while livewire depends heavily on excessive human guidance to achieve desirable results (Couprie *et al.*, 2011).
3) Redundancy in traditional interactive model. Redundancy issue in knee cartilage segmentation model is caused by tedious non-cartilage labelling, but the problem has never being tackled (Wenxian *et al.*, 2010).
4) Cartilage has exhibited great anatomical variation. Thin, irregular cartilage structure and pathological characteristic demands expert supervision (Tamez-Pena *et al.*, 2012; Dodin *et al.*, 2010; Fripp *et al.*, 2010).

## 1.5 Research Objective

In order to address aforementioned problems, several objectives have been identified as follows:

1) To propose a **spline derived tissue contrast improvement method**. The proposed method utilizes Bezier curve to curb degree of contrast improvement ignored by most contrast improvement methods.
2) To develop an **adaptive and convenient multilabel random walks segmentation method**. The versatility of random walks method is further strengthened with interactive features so it can be used dynamically by clinicians for cartilage segmentation.
3) To propose an **efficient approximate label generation method based on fuzzy cluster centroid**. The concept of computer-aided labelling is introduced by learning from human feature integration theory in order to replace manual labelling to maximum degree.
4) To develop a **highly reproducible expert-guided cartilage segmentation model** and **study the effect of factors in the model on reproducibility**. Although the proposed segmentation model highlights on shift from traditional paradigm, high reproducible property remains essential and should co-exist with expert control property. Then, interactive factors of this model is further studied in order to better understand the interactive model.

## 1.6 Research Scope

OA researches can be further divided into cartilage analysis, bone analysis (Karsdal *et al.*, 2008; Dodin *et al.*, 2011; Li *et al.*, 2013), muscles analysis (Frobell *et al.*, 2009; Prescott *et al.*, 2011), clinical morphologic analysis (Schneider *et al.*, 2012; Joseph *et al.*, 2012) and other types of OA researches (Wildi *et al.*, 2011). This study focuses on cartilage analysis. Intuitively, the MR image of knee was first enhanced with tissue contrast improvement method, then cartilage was segmented interactively with the support of computerized non-cartilage label and adaptive segmentation algorithm. Lastly, evaluation on the proposed model was performed by experts. Details of research scope of this study are given below:

1) Use of dual echo steady state (DESS) with water excitation (we) MR image of knee from medical ethical compliant Osteoarthritis Initiative (OAI) dataset. All OAI DESSwe MR Images were acquired in sagittal view and has magnetic strength of 3 Tesla (T).
2) Classification of MR image into normal and diseased classes based on Kellgren-Lawrence grades.
3) Division of cartilage computation into global cartilage and individual cartilage.
4) Exclusion of advanced clinical considerations such as weight bearing regions.
5) Algorithms are developed using MATLAB 2014a (Mathworks, Natick, MA).
6) Segmentation is performed in 2-dimensions (2D).
7) Exclusion of advanced clinical evaluation metrics such as change of cartilage volume and cartilage thickness.

## 1.7 Research Contributions

Most existing interactive methods adhere strictly to traditional ideology. Hence, conventional model is not comprehensive enough to address various problems reported during interactive segmentation. By analysing the problems from different perspective, a new type of segmentation model can potentially serve as stimulus for future interactive segmentation model. For instance, development of tissue contrast enhancement that emphasizes on curbing the degree of contrast elevation using Bezier transform curve has proven to produce resultant image with natural appearance and excellent image quality, which is essential for clinicians to review the image. Besides, generation of approximate label using cluster centroid represents another significant paradigm shift from traditional interactive cartilage segmentation model. The model effectively reduce the degree of human interaction while preserve the desirable expert control over final cartilage segmentation result.

Development of an expert based-interactive cartilage segmentation model that supports the insertion of several types of interactive label and pre-generated label with swift computation present a straightforward approach for clinicians to insert their intentions easily. Although it is not emphasized in current segmentation model, this is utter important given that expert role remains indispensable in medical research, where there are many ambiguities and uncertainties that demand expert interpretation. Moreover, the proposed model is robust to image noise; thus allows direct implementation of MR image. Lastly, the study on numerous factors of interactive model is performed in order to acquire comprehensive understanding of interactive segmentation. The findings unveil important clues that can help improve future interactive procedures and method development.

## 1.8 Thesis Organization

This thesis describes the development of an improved interactive knee cartilage segmentation model. Chapter 1 provides general overview of the study. Problem statements establishes research objectives of this study and research scope defines the study's boundary. Finally, contributions of study are elaborated.

Chapter 2 reviews different types of method implemented in tissue contrast enhancement as well as manual, interactive and automated cartilage segmentation models. Through the review, conceptual development, advantage and disadvantage of relevant methods are discussed.

Chapter 3 describes the study's methodology in three sections. The first section focuses on development of pre-segmentation methods i.e. label pre-generation model and tissue contrast improvement. The second section focuses on development of interaction tool and implementation of graph based segmentation method. The last part focuses on refinement procedures.

Chapter 4 presents the results and discussion about the performance of the proposed model. In first part, properties of tissue contrast enhancement techniques are evaluated and compared. In second part, efficiency of the proposed interactive tool and human interactive behaviour are studied. In third part, performance of the proposed segmentation model and its implications are evaluated.

Chapter 5 concludes the significance of study and gives meaningful recommendations in future work.

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# APPENDIX

## LIST OF PUBLICATIONS

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