Development of Polymer-based Gels for Multimodal Medical Imaging Phantoms

by

Eunji In

A thesis submitted in conformity with requirements for the degree of Doctor of Philosophy
Department of Mechanical and Industrial Engineering
University of Toronto

© Copyright by Eunji In 2016
Abstract

In the field of medical imaging, there have been numerous efforts to combine multiple imaging modalities such as ultrasound (US), Magnetic Resonance Imaging (MRI), x-rays and Computed Tomography (CT), positron emission tomography (PET), ultrasound (US), and single photon emission CT. Multimodal imaging allows the fusion and analysis of various image data to provide morphological and functional information. With the progress in medical imaging technology and increased importance of quality assurance, the research in medical imaging phantom is necessary. Phantom is an anthropomorphic object that mimics the properties of human tissue for calibration, training and surgical planning purposes. This research thesis examines four different types of polymer-based materials for constructing medical phantoms: carrageenan-based polymer gel, polymer cross-linked aerogels, UV-curable silicone and self-healing polymer materials.

In the first study, water-based carrageenan gel found to have a good correlation with the imaging properties of human tissue, but its long-term stability issue restricts its applicability as commercial phantoms. Since samples contained high water content, mechanical and
imaging properties of carrageenan-based gel fluctuated due to water expulsion and absorption cycles over six-week period.

In the second study, silica and cellulose aerogel cross-linked with polymer was also investigated as a phantom material. Contrast agents are cross-linked to fabricate an MRI/CT-compatible material. Results demonstrate that the imaging properties of these aerogels met the values of some human tissue values but due to volume shrinkage and complex fabrication process restricts its production in large scale.

Furthermore, in the third study UV-curable silicone material was considered as a 3D printable phantom material. The addition of hydrophilic silicone and water is shown to improve the curing time and imaging properties of silicone. With suitable properties of UV-curable silicone, it will assist to produce real-size liver phantom using 3D printing technique for a patient-specific phantoms.

There is an increased demand for phantom application in clinician training and surgical planning with needle-insertion or dissection is necessary. In the final chapter, self-healing silicone with microcapsule healing mechanism was investigated as proof-of-concept for surgical planning tool. Throughout four different studies, different polymer-based materials are examined subsequently with novelty in each study.
Acknowledgment

I would like to thank Professor Hani Naguib for his patience, support and guidance throughout Ph.D research. During Ph.D years, there were many times that I wanted to give up, was in doubt of myself and required motivation and encouragements on different level from MASc research. Without Professor Naguib’s support in many ways, I wouldn’t have been able to complete my studies. I was very fortunate to have him as my supervisor for 10 years.

I would also like to thank all of my fellow lab mates and colleagues in SAPL; Reza Rizvi, Shahrza Ghaffari, Harvey Shi, Gary Sun, Nazanin Khalili, Carlton Hoy, Sherif Ramadan, Farooq Al Jahwari, Muhammad Anwer, Sharon Li, and Kyle Eastwood for aiding me through their technical and spiritual support. With countless memories with them, I was able to overcome the times when I am discouraged, stressed or confused. I would like to acknowledge my undergraduate and M.Eng students Rohit Rathi, Marina Noguchi, William Sun, Xiaoji Zhang, Hwi Jang and Elisabeth Walker for their dedication, creativity and enthusiasm.

I would like to acknowledge Aaron Boyes at Sunnybrook Hospital, Dr. Karim Danaei and Dr. Bahman Lashkari for their assistance and knowledge on MRI, XRD and US experiments.

I would like to dedicate this thesis to my family and friends, Deokyoung, Jeeyoung, Eric, Yongsuk, Juhee, and Norman for their encouragement, belief and endless love. Without their support and prayers, I would not be where I am now.

I learned a lot during my years at University of Toronto and ready to take next step to a new chapter of my life.
# Table of Contents

Abstract ........................................................................................................................... ii

Acknowledgment ........................................................................................................ iv

Table of Contents .......................................................................................................... v

List of Tables ................................................................................................................. x

List of Figures ................................................................................................................ xi

List of Abbreviations ..................................................................................................... xv

1 Introduction .................................................................................................................. 1

1.1 Preamble ....................................................................................................................... 1

1.2 Medical Imaging Phantom ........................................................................................ 1

1.3 Problem Statement and Objectives .......................................................................... 3

1.3.1 Problem Statement ............................................................................................... 3

1.3.2 Objectives ............................................................................................................. 3

1.4 Thesis Organization .................................................................................................. 4

2 Background and Literature Review ............................................................................ 6

2.1 Ultrasound ................................................................................................................. 7

2.1.1 Ultrasound imaging technique ............................................................................ 7

2.1.2 US Imaging Techniques ....................................................................................... 9

2.1.2.1 Contrast-specific Techniques ......................................................................... 9

2.1.3 Ultrasound Phantoms ........................................................................................ 11

2.1.3.1 Ultrasound Phantom Applications ................................................................. 12

2.1.4 Phantom Materials .............................................................................................. 12

2.1.4.1 Agar ................................................................................................................ 12

2.1.4.2 Polyvinyl Alcohol Cryogel (PVA) ................................................................. 13

2.1.4.3 Polyacrylamide Hydrogel ............................................................................. 14

2.2 Computed Tomography ............................................................................................ 14

2.2.1 Image construction .............................................................................................. 15

2.2.2 Computed Tomography Scanning Procedure ..................................................... 15

2.2.3 Computed Tomography Sequences ..................................................................... 17

2.2.4 Image Quality ...................................................................................................... 18

2.2.5 Computed Tomography Phantoms ...................................................................... 18

2.2.6 Phantom Materials .............................................................................................. 19

2.2.6.1 Polyethylene ................................................................................................. 19

2.2.6.2 Epoxy ............................................................................................................ 20
2.3 Magnetic Resonance Imaging ................................................................. 21
  2.3.1 Signal Generation .................................................................................. 22
  2.3.2 Signal Detection: Relaxation ................................................................. 23
    2.3.2.1 Longitudinal Relaxation .................................................................. 23
    2.3.2.2 Transverse Relaxation ..................................................................... 24
  2.3.3 Image Reconstruction ............................................................................ 24
  2.3.4 Magnetic Resonance Imaging Phantoms ................................................. 25
  2.3.5 Phantom Materials .............................................................................. 26
    2.3.5.1 Carrageenan ..................................................................................... 27
    2.3.5.2 TX-150 and TX-151 ......................................................................... 27
    2.3.5.3 Polyvinyl Alcohol Cryogel .............................................................. 28

2.4 Multimodal imaging .................................................................................. 28
  2.4.1 Positron emission tomography (PET)/Computed Tomography (CT) ........ 30
    2.4.1.1 Potential and Limitations of Combined PET/CT ................................. 32
    2.4.1.2 Co-registration Errors ...................................................................... 32
    2.4.1.3 Breathing Artifacts .......................................................................... 32
    2.4.1.4 Contrast Agents .............................................................................. 32
  2.4.2 Positron Emission Tomography (PET)/ Magnetic Resonance Imaging (MRI) 33
    2.4.2.1 Technical Challenges ....................................................................... 33
    2.4.2.2 PET/MR Development ................................................................. 34
    2.4.2.3 PET Attenuation Correction based on MRI Data ............................... 35
  2.4.3 Phantom Materials .............................................................................. 35
    2.4.3.1 Agarose ......................................................................................... 35
    2.4.3.2 Polyvinyl Chloride .......................................................................... 36
    2.4.3.3 Polyvinyl Alcohol Cryogel ............................................................. 36
    2.4.3.4 Silicone ....................................................................................... 37

2.5 Radiation Therapy Phantoms .................................................................... 37
  2.5.1 Radiation Therapy Planning ................................................................. 38
    2.5.1.1 External-beam Radiation Therapy ................................................. 38
    2.5.1.2 Internal Radiation Therapy ........................................................... 38
    2.5.1.3 Systemic Radiation Therapy ......................................................... 39
  2.5.2 Radiation Phantoms ............................................................................... 39

2.6 Summary .................................................................................................... 40

3 Mechanical Stability Analysis of Carrageenan-Based Polymer Gel for MRI Liver Phantom with Lesion Particles ................................................................. 41
  3.1 Introduction ............................................................................................... 41
3.2 Motivation and Objectives ......................................................................................... 41
3.3 Experimental Setup ................................................................................................. 43
   3.3.1 Experimental Materials .................................................................................. 43
   3.3.2 Fabrication of Carrageenan-based Polymer Gel .............................................. 43
   3.3.3 Characterization ............................................................................................. 44
      3.3.3.1 Chemical Properties of carrageenan-based polymer gel ............................. 44
      3.3.3.2 Mechanical Properties of carrageenan-based polymer gel ..................... 44
      3.3.3.3 Dielectric Properties of carrageenan-based polymer gel ....................... 45
      3.3.3.4 Imaging Properties of carrageenan-based polymer gel ......................... 46
      3.3.3.5 Polymer Gel Liver Phantom with Lesion Particles .................................... 47
3.4 Results and Discussion ......................................................................................... 48
   3.4.1 Chemical Properties of carrageenan-based polymer gel ............................... 48
   3.4.2 Mechanical Properties of carrageenan-based polymer gel ............................ 49
   3.4.3 Dielectric Properties of carrageenan-based polymer gel ............................... 52
   3.4.4 Imaging Properties of carrageenan-based polymer gel ............................... 54
   3.4.5 Polymer Gel Liver Phantom with Lesion Particles ........................................ 57
3.5 Summary ................................................................................................................. 58

4 Novel Development of Organic and Inorganic Aerogels for Medical Imaging
Phantom Application .................................................................................................. 60
   4.1 Introduction ......................................................................................................... 60
   4.2 Motivation and Objectives .................................................................................. 60
   4.3 Experimental Setup ............................................................................................. 61
      4.3.1 Experimental Materials ............................................................................. 61
      4.3.2 Fabrication Procedure ............................................................................... 62
         4.3.2.1 Fabrication of Silica Aerogel ................................................................. 62
         4.3.2.2 Fabrication and Cross-linking of Cellulose Aerogel ............................... 62
      4.3.3 Characterization .......................................................................................... 63
   4.4 Results and Discussion ....................................................................................... 64
      4.4.1 Structural and Morphological Properties of Aerogels .................................. 66
      4.4.2 Chemical Properties of Silica and Cellulose Aerogels ................................. 68
      4.4.3 Imaging Properties of Silica and Cellulose Aerogels ................................. 69
   4.5 Summary ............................................................................................................. 75

5 Novel Development of 3D-Printable UV-Curable Silicone for Multimodal Imaging
Phantom ..................................................................................................................... 76
   5.1 Introduction ......................................................................................................... 76
   5.2 Motivations and Objectives ................................................................................ 76
5.3 Experiments ........................................................................................................... 77
  5.3.1 Experimental Materials .................................................................................. 77
  5.3.2 Preparation of Silicone Gel Samples ............................................................. 77
  5.3.3 Characterization ............................................................................................. 78
    5.3.3.1 Experimental Setup: Silicone Curing ...................................................... 78
    5.3.3.2 Experimental Setup for Ultrasound ......................................................... 79
    5.3.3.3 Experimental Setup for MRI and CT ......................................................... 80
5.4 Results and discussions ......................................................................................... 80
  5.4.1 Polymer Conversion: Curing Time ................................................................. 81
  5.4.2 Chemical Properties of Silicone Gel ............................................................. 83
  5.4.3 Hardness of Silicone Gel ............................................................................... 84
  5.4.4 Ultrasound Properties of Silicone Gel .......................................................... 85
  5.4.5 MRI Properties of Silicone Gel .................................................................... 86
  5.4.6 CT scan of Silicone Gel ............................................................................... 88
5.5 Summary ............................................................................................................... 89

6 Self-Healing Silicone for Future Phantom as training and surgical planning tool .... 91
  6.1 Introduction ....................................................................................................... 91
  6.2 Motivation and Objective .................................................................................. 91
  6.3 Experimental Setup .......................................................................................... 93
    6.3.1 Experimental material ............................................................................... 93
    6.3.2 Fabrication Methods .................................................................................... 93
      6.3.2.1 Microcapsule Fabrication .................................................................... 93
      6.3.2.2 Self-healing Sample Fabrication .......................................................... 94
    6.3.3 Characterization of self-healing silicone ..................................................... 95
      6.3.3.1 Microscope Characterization of self-healing silicone ......................... 95
      6.3.3.2 Mechanical Characterization of self-healing silicone ......................... 95
      6.3.3.3 Ultrasonic Characterization of self-healing silicone ......................... 95
  6.4 Results and Discussions ..................................................................................... 96
    6.4.1 Physical Properties of self-healing silicone ............................................... 96
    6.4.2 Structural and Morphological Properties of Self-healing Silicone .......... 97
    6.4.3 Self-healing properties of silicone .............................................................. 99
    6.4.4 Ultrasound Measurement of Self-healing silicone ..................................... 101
  6.5 Summary .......................................................................................................... 101

7 Conclusions and Recommendations ...................................................................... 103
  7.1 Concluding Remarks ......................................................................................... 103
  7.2 Contributions .................................................................................................... 108
  7.3 Recommendations ............................................................................................. 108
List of Tables

Table 1.1 Normal Liver Tissue Properties.................................................................4
Table 2.1. Propagation speed of US in various media [2].................................................8
Table 2.2. Acoustic parameters for various tissues [23, 24].............................................11
Table 2.3. Typical T₁ and T₂ values for various tissues measured at 1.5T and 3T [68].........26
Table 3.1 Contents of carrageenan, agar, GdCl₃, and water in the polymer gel samples........44
Table 3.2. Dielectric properties of human organs [117]..................................................45
Table 3.3 T₁ and T₂ relaxation times of human tissues at 3T [68, 119-121]..........................55
Table 5.1. Human liver tissue values [135, 143, 144]....................................................78
Table 7.1. Summary table of property values of each phantom materials........................107
List of Figures

Figure 1.1. Thesis organization chart..................................................................................................................5

Figure 2.1. Positions of various imaging methods in the electromagnetic spectrum [1]..................6

Figure 2.2. Principle of propagation of US..............................................................................................................8

Figure 2.4. Ranges of CT values of the most important organs .................................................................16

Figure 2.5. MRI of the skull metastasis from hepatocellular carcinoma. (A) T1-weighted MRI and (B) T2-weighted MRI demonstrating a homogeneous, well-defined, and iso-signal intensity mass in the occipital midline. (C) Gadolinium-enhanced T1-weighted MRI showing a strong enhancement of the tumor [65]...........................................................................................................25

Figure 2.6. Schematic workflow of the PET/CT examination. (a) A fast scout scan to determine examination regions for PET and diagnostic CT. (b) The acquisition of either a low-dose or diagnostic CT scan. (c) PET data acquired at multiple bed positions, reconstructed and corrected for attenuation. (d) PET and CT images are registered and displayed as fused images. [78]..................................................................................................................31

Figure 2.7. Potential realizations of PET/MRI scanners. (a) PET/MRI side by side. Two individual devices are mounted back-to-back and have a common control unit. (b) PET inserted within an MRI; the bore size is drastically reduced and the PET detectors have to be compact. (c) PET detector embedded into an MRI system. Both devices are merged together into one multimodality scanner. [78]..................................................................................................................34

Figure 3.1. Schematic diagram of polymer gel lesion and phantom fabrication.................................47

Figure 3.2. (a) Spherical lesion particle placement and (b) a fabricated phantom with embedded lesion particles..................................................................................................................48

Figure 3.3. FTIR graph of carrageenan-based polymer gel.................................................................48

Figure 3.4 Density changes in the carrageenan-based gel samples .................................................49

Figure 3.5 Changes in elastic modulus of eight polymer gel samples over six weeks: (a) Samples with various agar concentrations (0.0–1.5 wt%); (b) Samples with various carrageenan concentrations (1.0–3.0 wt%).................................................................................................51

Figure 3.6 Compressive strength of eight polymer gel samples over six weeks .........................52
Figure 3.7 (a) Permittivity and (b) conductivity of sample 4 over six weeks..................53
Figure 3.8 $T_1$ and $T_2$ maps of polymer gel samples at week 3, generated by a MATLAB algorithm........................................................................................................54
Figure 3.9 $T_1$ and $T_2$ relaxation times of polymer gel samples after five weeks...........55
Figure 3.10 $T_1$ and $T_2$ relaxation times of sample 2 over six weeks...........................56
Figure 3.11 CT numbers obtained from Aquilion ......................................................................57
Figure 3.12 $T_1$ and $T_2$ maps of the phantom layer with lesion particles .........................58
Figure 4.1 Silica aerogels with increasing concentrations of di-isocyanate ..................65
Figure 4.2 Cellulose aerogels with increasing in CoFe$_2$O$_4$ concentrations ..................65
Figure 4.3 SEM images of non-cross-linked and cross-linked silica aerogels (SA, surface area; wt% indicates cross-linking polymer [di-isocyanate] concentration)........................66
Figure 4.4 (a)-(c) SEM images of non-cross-linked cellulose aerogel with increasing cellulose content; (d)-(f) cross-linked cellulose aerogel with higher content of superparamagnetic nanoparticles........................................................................67
Figure 4.5 FTIR spectroscopy of silica aerogels cross-linked with varying concentrations of di-isocyanate ........................................................................................................68
Figure 4.6 XRD pattern of non cross-linked cellulose Aerogel and cross-linked with CoFe$_2$O$_4$ ................................................................................................................................69
Figure 4.7 (a) The effect of di-isocyanate cross-linker and (b) Gd concentrations on MRI $T_1$ and $T_2$ relaxation times (ms) ........................................................................................................71
Figure 4.8 (a) The effect of di-isocyanate and (b) Gd concentrations on CT number (HU) ..72
Figure 4.9 MRI (left) and CT (right) images with Hounsfield units for silica aerogels...........72
Figure 4.10 MRI (a) and CT (b) of cross-linked cellulose aerogel with 0.24 mol/L CoFe$_2$O$_4$ complex with increase in cellulose content ........................................................................74
Figure 5.1. Experimental setup of ultrasonic measurement system of the samples .............80
Figure 5.2. Fabricated Silicone samples with different concentrations of deionized water and hydrophilic silicone..................................................................................................81
Figure 5.3. FTIR of liquid and solid states of silicone samples (liquid with 10 vol% HS and 20 vol% water; solid with 10 vol% and 20 vol% HS and 20 vol% water).............................84

Figure 5.4. Hardness of silicone samples with increase in water content.................................85

Figure 5.5. US measurements performed on silicone samples a) SOS (m/s) and b) attenuation coefficient (dB/cm-MHz)..........................................................................................86

Figure 5.6. Effect of water content (vol %) on the $T_1$ relaxation times for 10, 20 and 30 vol% HS content......................................................................................................................87

Figure 5.7. Effect of water content (vol %) on the $T_2$ relaxation times for 10, 20, and 30 vol% HS content..........................................................................................................................88

Figure 5.8. Effect of HS content (vol%) and $T_1$ and $T_2$ Relaxation times .................................88

Figure 5.9. CT Hounsfield Unit values of silicone over 80, 100, 120 and 135 kVp (a) 10 vol% HS and (b) 20 vol% HS ..................................................................................................................89

Figure 6.1. Vinyl-terminated polydimethylsiloxane (PDMS) resin and platinum catalyst encapsulated together in poly(urea-formaldehyde) (UF) shell. Poly(methylhydrosiloxane) copolymer is encapsulated separate in the same shell. Both capsules are embedded in vinyl-terminated PDMS base matrix. ........................................94

Figure 6.2. At room temperature or higher, liquid polymethylhydrosiloxane copolymer and liquid vinyl-terminated polydimethylsiloxane (PDMS) resin react to form solid, inert vinyl-terminated PDMS. ........................................................................................................96

Figure 6.3. Ruptured self-healing silicone samples with 0, 10, 15, and 20 wt% of microcapsule A and fixed 5 wt% of microcapsule B.................................................................97

Figure 6.4. Optical Microscope image of rupture region of samples with different microcapsule A concentrations. a) 10 wt%, b) 15 wt% and c) 20 wt%..............................98

Figure 6.5. SEM image of cross-section region of ruptured silicone with self-healing microcapsules at different magnifications ...............................................................................99

Figure 6.6. Young's modulus of undamaged self-healing silicone with 0, 10, 15 and 20 wt% microcapsule part A .................................................................................................................99

Figure 6.7. Load-displacement graph of undamaged samples with different concentrations of microcapsule A content.................................................................................................100
Figure 6.8. Load-displacement graph of damaged samples with different concentrations of microcapsule A content.

Figure 6.9. Attenuation Coefficient of self-healing samples with different concentrations.
List of Abbreviations

Chapter 1

CT – Computed Tomography
US – Ultrasound
MRI – Magnetic Resonance Imaging
HU – Hounsfield Unit
UV – Ultraviolet

Chapter 2

RF – Radio frequency
SPECT – Single photon emission tomography
PET – Positron emission tomography
USCAs – Target specific ultrasound contrast agents
CFM – Color-flow mapping
MB – Microbubbles
SAE – Stimulated acoustic emission
TM – Tissue mimicking
SOS – Speed of Sound
QA – Quality assurance
PVA – Polyvinyl alcohol cryogel
PAA – Polyacrylamide gel
HIFU – High-intensity focused ultrasound
BSA – Bovine-serum albumin
PAG – Polyacrylamide hydrogel
WL – Window level
WW – Window width
TF – Table feed
SC – Slice thickness
MSCT – Multi-slice CT
SSCT – Single-slice CT
CTDI – CT dose index
PMMA – Polymethyl methacrylate
AAPM – The American Association of Physicists in Medicine
PE – Polyethylene
EMF – Electromotive force
SNR – Signal-to-noise ratio
CNR – Contrast-to-noise ratio
NIST – National Institute of Standards and Technology
NIRS – Near-field infrared spectroscopy
EEG – Electroencephalography
MEG – Magnetoencephalography
PMT – Photomultiplier tubes
APD – Avalanche photodiode
TRUS – Transrectal ultrasound
PVC – Polyvinyl chloride
CRT – Conformal radiation therapy
IGRT – Image-guided radiation therapy
IMRT – Intensity-modulated radiation therapy
IGRT – Image-guided radiation therapy

Chapter 3

Gd-DTPA – Gadopentetic acid
FTIR – Fourier transform infrared spectroscopy
DI – De-ionized water

Chapter 4

TEOS – Tetraethyl orthosilicate
SPIIONs – Superparamagnetic iron oxide nanoparticles
TMOS – Tetramethyloxysilicate
APTES – 3-aminopropyl triethoxysilane
HDI – Hexamethylene di-isocyanate
XRD – X-ray diffraction
SSA – Specific surface area
BET – Braunauer-Emmet-Teller
SEM – Scanning electron microscopy

Chapter 5

PDMS – Polydimethylsiloxane
DLP – Digital Light Processing
HS – Hydrophilic Silicone
SLA – Stereolithography
PMMA – Poly(methyl methacrylate)
ATR – Attenuated Total Reflectance

Chapter 6

DCPD – Dicyclopentadiene
ROMP – Ring-opening metathesis polymerization
EMA – Poly(ethylene-alt-maleic anhydride)
NaOH – Sodium hydroxide
HCl – Hydrochloric acid
UF – Poly(urea-formaldehyde)
RF – Radio frequency
Chapter 1
Introduction to the Dissertation

1 Introduction

1.1 Preamble

This thesis examines various polymer-based materials for the construction of medical imaging phantoms. A medical imaging phantom is an anthropomorphic object that mimics the properties of human tissue. It is used for calibration, training, and surgical planning purposes. Different imaging modalities are based on different physics theory and measurement parameters, their requirements also vary. Novel polymer-based materials were developed and their physical, mechanical, and imaging properties were examined. Each study addresses new findings and problems with existing phantom materials. First, long-term stability of water-based polymer gel was investigated and the problem with consistency and clinical accuracy of the phantom was addressed. This suggests that although most of the water-based materials provide good tissue-mimicking properties, the values may not be consistent. Based on the first study, novel development of organic and inorganic aerogel was suggested as a solid phantom material. Aerogels were found to have similar imaging properties to human tissue upon incorporation of contrast agents. Their potential application is perfusion flow phantoms to simulate in-vitro blood flow. Another type of solid material, UV-curable silicone was investigated for 3D printable phantom material. Incorporation of hydrophilic silicone and water changed the imaging properties to mimic human liver tissue. With fine-tuned properties, UV-curable silicone can be used as 3D printing resin to allow doctors and health technicians to easily print the phantom of target area based on US, CT, and/or MRI images. Lastly, growing need for training and surgical planning phantoms motivated the study of self-healing polymer material. Training and surgical planning often requires multiple needle-insertion or dissection of the phantom under different modalities such as MRI and US. In order to endure multiple needle insertion without leaving behind a visible scar is desired. The proof-of-concept self-healing silicone material was fabricated and its self-healing efficiency and ultrasound property was examined.

1.2 Medical Imaging Phantom

In healthcare, medical imaging is a vital tool for the prevention and early detection of diseases, helping to identify the optimal treatment and need for surgical intervention, and monitoring the response to treatment. Since the first discovery of x-rays, the medical uses of
radiation quickly spread and evolved. However, the harmful effects of high radiation doses became apparent with the occurrence of side effects such as erythema and cell squamation. This restricted further developments, as people were reluctant to volunteer for radiation experiments. As the harmful effects of radiation were realized, physicists developed tissue substitutes, known as phantoms, to simulate the response of real patients, thus allowing dosimetric measurements and identifying the limitations of their systems. These medical imaging phantoms are anthropomorphic objects that is scanned or imaged by imaging technicians to evaluate, analyze, and tune the performance of various medical devices for optimal results. The phantom is used instead of a living subject or a cadaver because it gives more consistent results and avoids unnecessarily exposing patients to excess radiation. This process should be done regularly to tune the devices to ensure accurate, clear results and avoid misdiagnoses and oversights.

Other uses of medical imaging phantoms include simulating the conditions of a procedure to measure the radiation within the phantom, simulating patient’s motion that occur during radiotherapy treatments, testing new medicine or protocols or practicing surgical procedure. The purpose of the phantom will dictate the physical design of the phantom, such as the size, shape, composition, and other details of the phantom such as composition.

The earliest phantoms took the form of water tanks or wax blocks for the measurement of radioactive sources or x-ray beams. Water is a very good approximation of the human tissue, but it is difficult to simulate tissues with different properties, both physical and radiological. Ideally, a phantom should reflect these physical and radiological properties as accurately as possible. The variety of wax types, however, led to inconsistent measurements and a lack of tissue equivalency at low energies, and so wax was not a particularly good material for phantom applications. Wood was proposed as a potential tissue substitute, and became fairly popular in this role during the 1930s, but, like wax, suffers from problems regarding the degree of variability among each wood sample.

In the 1970s, the applicability of phantoms expanded from dosimetry in radiotherapy treatments to various imaging systems such as mammography, computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI). Phantoms are mainly designed to test the image quality of such systems. They have become increasingly complex and reliable in this role as the materials used in their construction became more reproducible and able to accurately mimic tissues over a wider range of energies. In recent years, with the rise in popularity of computer simulations in the field of medical physics, the detail and complexity
of computational phantoms have increased significantly, with advanced imaging modalities such as CT and MRI aiding the creation of these complex computational phantoms.

1.3 Problem Statement and Objectives

1.3.1 Problem Statement

Multimodal imaging allows the fusion and analysis of image data, which provides morphological and functional information that can be used towards the ultimate goal of the early detection of disease at the vascular, cellular, or genomic level. With rapid technological developments and attempts to fuse two or more modalities together, there is a significant need for the development of phantoms that can evaluate quality of number of imaging modalities. Phantom studies have been conducted for individual imaging modalities, but there is a lack of development in the area of multimodal imaging. Furthermore, the future of phantoms lies in their application to surgical planning and patient customization. Thus, such phantom material development is necessary.

1.3.2 Objectives

The goal of this research is to fabricate and characterize several phantom materials to mimic the characteristics of human tissue and enhance the performance of different medical imaging modalities, specifically for multimodal applications. The scope of this project is the fabrication and characterization of polymer gel materials to satisfy the calibration requirements of several modalities including MRI, CT, and US. To ensure accurate performance under multiple imaging modalities, evaluation of standard values should be performed regularly to control the quality and reliability of images. Therefore, a phantom that behaves similarly to human soft tissue is developed to replace the need for a real human volunteer. In consideration of these goals, the objectives of this dissertation are as follows:

1. To fabricate and characterize phantom materials to mimic the properties of human tissue, specifically human liver tissue;
2. To study the chemical and mechanical properties of these materials and their stability over an extended period of time;
3. To investigate the imaging properties of each material, including the $T_1$ and $T_2$ relaxation times for MRI, the Hounsfield units for CT, and the speed of sound and
attenuation coefficient for US. These imaging properties will be compared with those of normal liver tissue values.

Table 1.1 Normal Liver Tissue Properties

<table>
<thead>
<tr>
<th>Modality</th>
<th>Property</th>
<th>Liver Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>(T_1)</td>
<td>812 (\pm) 64 (ms)</td>
</tr>
<tr>
<td></td>
<td>(T_2)</td>
<td>42 (\pm) 3 (ms)</td>
</tr>
<tr>
<td>CT</td>
<td>HU</td>
<td>+40 to +60 (HU)</td>
</tr>
<tr>
<td>US</td>
<td>Speed of Sound</td>
<td>1549 (m/s)</td>
</tr>
<tr>
<td></td>
<td>Attenuation Coefficient</td>
<td>0.9 dB/(cm-MHz)</td>
</tr>
<tr>
<td></td>
<td>Elasticity</td>
<td>6.4-60 kPa</td>
</tr>
</tbody>
</table>

\(T_1\) and \(T_2\) relaxation times are measure of how quickly magnetized vectors return to its equilibrium state at either longitudinal or transverse direction. CT housfield unit (HU) is a scale measurement of linear attenuation coefficient with respect to distilled water at standard pressure and temperature. Speed of sound is speed of ultrasound waves travel through different tissues and attenuation coefficient is a measure of energy loss as sound propagates in a media.

The materials investigated in this study are carrageenan, silica aerogel and cellulose aerogel, silicone, and self-healing polymer.

1.4 Thesis Organization
The body of this thesis is organized into seven chapters, as illustrated in Fig. 1.1. Chapter 1 gives a statement of the problem and outlines the objectives of the dissertation. Chapter 2 provides a brief but relevant literature review on the current state of research into medical imaging modalities and their phantoms. Chapter 3 describes an investigation of the mechanical stability of carrageenan-based polymer gel for an MRI liver phantom with lesion particles. The development of organic and inorganic aerogels for medical imaging phantoms is discussed in Chapter 4. Chapter 5 then examines 3D printable UV-curable silicone for multimodal imaging phantoms. Chapter 6 investigates a self-healing polymer that can be used to create training phantoms for radiation therapy or surgical planning. Finally, a summary of this research and its key contributions are provided in Chapter 7, along with recommendations for future work on medical imaging phantoms. Each chapter describes the
motivation and objectives behind the study, and details the experimental procedure and materials. Results for the physical, mechanical, and imaging properties of each material are also presented.

Figure 1.1. Thesis organization chart
Chapter 2

2 Background and Literature Review

In diagnostic imaging, various medical imaging modalities are used to generate an image of the body, either through the detection of photons or the use of electromagnetic waves. Each imaging modality is distributed in different regions of the electromagnetic spectrum, as shown in Fig. 2.1. For example, MRI employs radio frequency (RF) or short waves to produce images of the body. The x-ray spectrum can be divided into two regions: soft (low-energy) and hard (high-energy). To image soft tissue, low-energy x-ray photons are used, because high-energy x-ray photons would probably penetrate the tissue without sufficient attenuation. For example, mammographic imaging uses low-energy x-rays, whereas CT uses high-energy x-ray photons. Gamma cameras, single photon emission tomography (SPECT), and positron emission tomography (PET) all produce images through the detection of gamma rays. The difference between x-rays and gamma rays is in the source of the radiation. X-rays are produced as a result of the movement or acceleration/deceleration of electrons, whereas gamma rays are produced as a result of a nuclear decay process. This literature survey discusses the three imaging modalities of MRI, CT, and US, and looks at their combinations and phantom materials.

Figure 2.1. Positions of various imaging methods in the electromagnetic spectrum [1]
2.1 Ultrasound

Ultrasound is one of the most common techniques used in diagnostic investigations. Compared with some other diagnostic modalities, it is safe, noninvasive, and inexpensive, making it relatively convenient and stress-free for patients. With advances in sonographic equipment and techniques and the introduction of commercially produced echo-enhancing agents, there have been substantial improvements in US image quality, and this has widened the scope of sonography. Furthermore, new US technologies such as μ-ultrasound and the feasibility of creating target-specific US contrast agents (USCAs) for molecular imaging have opened up new possibilities in the field of experimental pharmacology. These have allowed the noninvasive visualization of biological processes in living animals, the real-time tracking of the spread of diseases, and the observation of the effects of a drug throughout the system.

2.1.1 Ultrasound imaging technique

The US waves are generated by piezoelectric elements such as tiny chips of vibrating quartz. These produce elastic vibrations that are transmitted to the target material. When sound waves are transmitted from the transducer, the elastic vibrations emanate from the transducer in the direction of propagation of the waves. A sound wave consists of a series of compressions and rarefactions. The distance between the start of a wave and the next is denoted as one wavelength (λ). The number of vibrations per second at one point is the frequency (f). The relationship between the wavelength, frequency, and velocity of propagation (v) is as follows (see Fig. 2.2):

$$\lambda = \frac{v}{f}$$
The speed of sound is material-specific, depending on the density and the amount of mass particles (see Table 2.1).

<table>
<thead>
<tr>
<th>Media</th>
<th>Density (g/cm$^3$)</th>
<th>Propagation Speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>$1.2 \times 10^{-3}$</td>
<td>330</td>
</tr>
<tr>
<td>Water (37°C)</td>
<td>1.0</td>
<td>1,520</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>1.026</td>
<td>1,540 (mean)</td>
</tr>
<tr>
<td>Bone</td>
<td>1.9</td>
<td>3,800</td>
</tr>
</tbody>
</table>

The phenomena of reflection and refraction, which take place at the transition between materials with different propagation velocities, also occur with sound waves. The reflected portion of the ultrasonic energy depends on both the difference between the velocity of sound in the two media and on the angle of the incident beam with respect to the interface. When light moves through tissue, the energy of the wave weakens continuously due to internal friction, also known as absorption. The specific absorption rate is not the same for all frequencies: low frequencies have a relatively low absorption rate compared with high frequencies. Low frequencies also have the disadvantage of having a low spatial resolution, which increases with frequency. Depending on the diagnostic targets and the penetration depths needed, different types of transducers with different frequencies are used.
2.1.2 US Imaging Techniques

The basis for the medical use of US began with the discovery of the piezoelectric effect. This effect is a characteristic of crystals or ceramic materials, which become electrically polarized under physical pressure. Such materials begin to vibrate and emit high-frequency acoustic waves when charged with an alternating electrical voltage. The ultrasonic waves reflected by the body are collected by the transducer and converted by piezo elements into electrical signals, which are then processed by the US machine and represented as pixels. Since the discovery of the piezoelectric effect, several researchers have developed US machines. The “A mode” technique uses the amplitude over a period of time to obtain the backscattered signal intensities. The amplitude reflects the intensity of the backscattered ultrasonic signals, and the distance between peak amplitudes gives the running time. This A mode enabled the differentiation of healthy and tumorous intestine and breast tissue. The “B mode” approach was developed to provide real-time images for clinical use. The B mode is a modified representation of the A mode, where the amplitudes of the A-mode lines are translated into gray tones. The highest amplitude is assigned the brightness value white, whereas the zero line of the amplitude scale is assigned the brightness value black. Intermediate amplitudes are assigned gray tones on an appropriate scale (maximum 256). The next qualitative leap in medical US was the use of the Doppler effect to measure blood flow. Doppler’s acoustic law states that frequency changes occur in the sound field if the transmitter and receivers move in relation to one another. To determine the blood flow, the transducer emits ultrasonic waves of a known frequency that are reflected by the blood cells and received again by the transducer. The received frequencies will differ depending on the direction in which the blood cells are flowing. For example, blood cells moving towards the transducer will emit higher frequencies, whereas those moving away will produce lower frequencies. This discovery led to the development of the continuous Doppler (CW-Doppler), pulse Doppler (PW-Doppler), color-flow mapping (CFM), and intensity-Doppler modes. [3-10]

2.1.2.1 Contrast-specific Techniques

The beginnings of diagnostic US were characterized by USCA-free examinations for the morphological characterization of tissue, followed soon after by functional examinations through the introduction of Doppler technologies. Gas-filled microbubbles (MBs) were then used to enhance the contrast due to their special physical and acoustic characteristics. The contrast characteristics of MBs can be induced and employed as a function of the frequency
and sound intensity of the irradiated ultrasonic wave. Some techniques involve the destruction of these MBs, whereas they are preserved in others. Ultrasonic waves of very low sound intensity lead to a resonant oscillation of the MBs. Acoustic waves of the same frequency to which these MBs have been exposed are reflected and converted into an image by the US device [11, 12].

An increase in sound intensity causes asymmetrical oscillations in the MBs, since the encapsulated gas bubbles oppose compression with a greater resistance than they do expansion. During this process, other frequencies besides the output frequency are also emitted in the signal response. These other frequencies are known as harmonic frequencies, or overtones and undertones. The second harmonic overtone frequency is particularly important because of its high amplitude. The basic frequency received from tissue and the contrast-agent bubbles is suppressed by special filtering techniques during signal processing. This procedure results in a clear reduction of the tissue signal portion, resulting in a more intensive representation of the contrast signal in relation to the tissue and an improved signal-to-noise ratio (SNR). As opposed to second-harmonic imaging, the technology of wideband harmonic imaging uses the entire frequency spectrum to represent the contrast-agent-specific signals. This method achieves higher signal intensity from the contrast-agent bubbles, and the use of a wideband transducer results in better spatial resolution than with second-harmonic imaging. [11, 13-16]

Although most procedures do not destroy the contrast-agent bubbles, other technologies utilize their destructibility. At very high sound intensities, the MBs are destroyed by mechanical force. Sound pressure can vary in intensity because of the different morphologies presented by various USCAs. Three mechanical destroying phenomena have been identified: the fragmentation of gas bubbles, the destruction of the bubble shell, and the radiation effect. It is known that the wall thickness and elasticity of the material encapsulating the gas MBs are crucial in triggering the destruction of the encapsulation. Fragmentation causes one gas MB to create many smaller bubbles. The destruction of the encapsulation causes the gas to escape through a tear in the encapsulating material and dissolve in the blood. [17] Using this observation, the color pixels on the monitor of the US device during the destruction of polymer-coated air MBs can provide an indicative medium. During the destruction process, a short-lived wideband, nonlinear frequency signal is emitted, which is called the stimulated acoustic emission (SAE). The discovery of the SAE signal provided a crucial basis for the new field of diagnostic molecular imaging with US. [18]
2.1.3 Ultrasound Phantoms

Ultrasound phantoms have been constructed to model the human anatomy and tissue characterization. Early phantoms were essentially water-filled containers, with metal rods at specific locations to provide some distance calibration. As US equipment became more advanced, new phantom materials (known as “tissue mimicking”) were developed to ensure the transmission of sound at the correct speed, incorporate reflectors that caused an echo to be returned to the transducer, and provide sound attenuation similar to that experienced in tissues. The physical basis for US imaging is rather complex, which raises the necessity of accurate physical parameters in US phantoms used for image quality measurements. The three key parameters are (1) the speed of sound (SOS), (2) attenuation and its frequency dependence, and (3) scattering. Other physical parameters include the density, which is a nonlinear parameter (B/A). [19] These physical properties should be applicable over the frequency range of most clinical diagnostic US systems (2–15 MHz). In response to the development of higher-frequency probes for higher resolution imaging (preclinical at 20 MHz and above), characterizations at higher frequencies are also desirable [20-22]. Typical ranges of these parameters for a set of tissues are listed in Table 2.2.

Table 2.2. Acoustic parameters for various tissues [23, 24]

<table>
<thead>
<tr>
<th>Tissue/Material</th>
<th>Velocity (m/s)</th>
<th>Attenuation (dB/(cm-MHz))</th>
<th>Density (kg/m³)</th>
<th>Acoustic impedance (MRayl)</th>
<th>Backscatter coefficient (10⁻⁴/(cm-sr))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>330</td>
<td></td>
<td>1.2</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>Water</td>
<td>1480</td>
<td>0.0022</td>
<td>1000</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>1540</td>
<td>0.3-0.8</td>
<td>1043</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>Muscle (average)</td>
<td>1547 – 1600</td>
<td>0.2-0.6</td>
<td>1050</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>1560 – 1584</td>
<td>0.2</td>
<td>1060</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1510</td>
<td>0.75</td>
<td>1020</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1555–1595</td>
<td>0.4 – 0.7</td>
<td>1060</td>
<td>1.69</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>1576</td>
<td>0.52</td>
<td>1060</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>1450–1480</td>
<td>0.5–1.8</td>
<td>950</td>
<td>1.40</td>
<td></td>
</tr>
</tbody>
</table>

More recently, mechanical (viscoelastic) properties have been characterized to enable the analysis of US echo signals under varying degrees of compression or through the use of acoustic radiation. [23, 25, 26] It is desirable to mimic the properties of tissue in which the Young’s modulus is from 6–12 kPa (or stiffer with inclusions or lesions).
2.1.3.1 Ultrasound Phantom Applications

There are three major applications for ultrasound phantoms. First, they are used as test tools for SOS, attenuation, and backscatter measurements. Typically, the phantom is immersed in water to control the temperature and provide a coupling medium for the acoustic transducers. The second application is for teaching and training. Ultrasound technicians must understand the underlying anatomy and its appearance as they perform studies. Anthropomorphic phantoms are intended to provide a reusable, repeatable, and realistic representation, or to allow the trainee the experience of placing the US probe on the correct part of the body. Phantoms used for training purposes can have a mannequin-like appearance. Small portions of the phantom may be enclosed within a box, with an opening for the insertion of the transducer [27]; or include target cysts and lesions for practicing needle-based biopsy procedures or performing peripheral nerve blocks under US guidance. The third, most common application is for the verification of imaging system performance, such as with Doppler phantoms.

2.1.4 Phantom Materials

2.1.4.1 Agar

Cannon et al. [28] developed a novel agar-based tissue-mimicking material for use in clinically relevant, quality assurance (QA), and anthropomorphic breast phantoms. The motivation for their work was to simulate the properties of the tissue types in the breast, primarily glandular tissue, subcutaneous fat, pectoral muscle, areola, and malignant and benign lesions. The samples were fabricated with a mixture of agar, silicon carbide, and aluminum oxide in deionized water, and their acoustic characteristics were obtained. The SOS of the samples ranged from 1490–1570 m/s, their attenuation coefficients ranged from 0.1–0.9 dB/(cm MHz), and the relative backscatter ranged from -20–0 dB. The acoustic properties of the materials were independent of frequency in the wide diagnostic ranges, demonstrating their suitability for high-frequency applications. Agar is relatively easy to manufacture and its acoustic properties are easily controlled. By tailoring the acoustic properties, agar can mimic the values of human tissue. Thus, it is suitable for use in clinically relevant, QA, and anthropomorphic phantoms.

Foroozandehasl et al. [29] fabricated agar-based tissue-mimicking material for US breast phantoms. They chose agar because it is inexpensive, reproducible, and nontoxic. The phantom was fabricated with agar, 2-isopropyl alcohol, anise oil, tartrazine, and distilled
water. The effect of physical properties such as temperature and the percentage composition on the SOS was evaluated. The SOS increased from 1400 m/s to 1600 m/s over the temperature range 15–35°C. The SOS was also found to be inversely proportional to the concentration of anise oil.

2.1.4.2 Polyvinyl Alcohol Cryogel (PVA)

Price et al. [30] studied the optical and x-ray properties of a compressible polyvinyl alcohol cryogel (PVA-C) breast phantom for dual-modality imaging. A solution of PVA in ethanol creates a solid yet elastically compressible gel whose x-ray attenuation coefficients are equivalent to breast tissue. Titanium dioxide can be added to obtain the desired transport scattering coefficient. The phantom contains a compressible inclusion made of an inflatable latex tube, and different volumes of dye were injected to simulate the blood flow into a lesion. Gels with 5–20% w/v concentrations demonstrated linear x-ray attenuation within the range 0.76–0.86 cm⁻¹, which is equivalent to that of healthy breast, adipose, and glandular tissue.

Zell et al. [31] compared the acoustic properties of agar, silicone, PVA, and polyacrylamide gel (PAA) for breast phantoms. Two US sources of 5 MHz and 20 MHz core frequencies were used to compare the acoustic attenuation in each gel. The results showed that PVA exhibits the best acoustical properties up to 10 MHz, although it has the disadvantage of a time-consuming preparation procedure. Agar, on the other hand, is quick and easy to prepare, and offers satisfactory acoustic properties, but its long-term stability is not good. The acoustical properties of silicone do not fit perfectly with the required values, but it is a good material for a stable phantom. PAA is not a good candidate due to its potential toxicity during preparation.

Surry et al. [32] created PVA-C phantoms for use in US and MR imaging. The properties of the PVA-C samples varied depending on the number of freeze–thaw cycles (FTCs) and the rate of temperature change. The velocity of sound was found to be 1520–1540 m/s, which is well within the typical range for tissue. However, the attenuation coefficients were just 0.075–0.28 dB/(cm MHz), compared to the value of 1 dB/(cm MHz) for tissue. The obtained $T_1$ values of 680–980 ms were similar to those for gray and white matter and muscle, whereas the $T_2$ values varied from 100–150 ms. Fabricated brain, vessel, and breast biopsy phantoms demonstrated that small, regularly, or irregularly shaped volumes could be made to mimic human tissue values by varying the number of FTCs.
2.1.4.3 Polyacrylamide Hydrogel

Choi et al. [33] studied phantoms with similar acoustic properties to human tissue to visualize the therapeutic effects of high-intensity focused ultrasound (HIFU). The minimally invasive nature of HIFU surgery offers an advantage over other therapeutic means of tumor treatment. The conventional bovine-serum albumin (BSA)-polyacrylamide hydrogel (PAG) reported by Lafon et al. [34] does not recreate the scattering and attenuation of biological tissue. Therefore, Choi et al. modified the standard BSA-PAG by increasing the concentration of acrylamide to adjust the attenuation coefficient and suspending glass beads to tune the backscatter coefficient. The constructed BSA-PAG exhibited acoustic properties close to those of liver tissue, and had thermal and optical characteristics comparable to the standard BSA-PAG.

2.2 Computed Tomography

The penetrating characteristics of x-ray photons are used in medicine to generate patient images. X-ray photons are usually produced by x-ray tubes, whereby focused emitted electrons generated from a cathode filament are accelerated at high potential difference toward a rotating anode. These electrons are stopped as they interact with atoms of the anode at the focal spot region. Since these emitted x-ray photons undergo x-ray absorption and scattering interaction processes in tissue, not all of the incident x-ray photons get penetrated. The degree of photon attenuation depends on the incident x-ray photon energy and the atomic number, thickness, and physical and electronic densities of the interacting material. The gradient of the x-ray linear attenuation coefficient varies with the tissue type, and is thus imaged with a different gray scale. For example, air is imaged as black because of its low x-ray linear attenuation coefficient, whereas bone is imaged as white due to its much higher x-ray linear attenuation coefficient. Soft tissue is often represented between these extremes as some shade of gray. The resulting image is a 2D representation of the total x-ray beam interacting with the various material atoms in the exposed patient volume. Since its first clinical application in 1972, developments in x-ray CT have given it several advantages over conventional or digital radiography. [35] These advantages can be summarized as follows.
1. A sequential CT comprises a set of 2D cross-sectional images instead of a single 2D image obtained by compressing a 3D body structure volume onto a 2D image plane. Therefore, it gives a clear image containing the location and contrast of the subject tissue. [36]

2. The volume of data can be reformatted in various planes (sagittal, coronal, and axial) or even as a volumetric (3D) representation (e.g., multiplanar reformation, maximum intensity projection, and virtual colonoscopy) of the structure.

3. The sensitivity of CT to subtle differences in x-ray attenuation is increased by a factor of 16 compared with normal film/screen radiography systems. This can be achieved using a much narrower, finely collimated CT x-ray beam profile that reduces the scatter photon contribution and the use of detectors with higher x-ray absorption efficiencies.

2.2.1 Image construction

In sequential CT, 2D images (or slices) are typically acquired in a $512 \times 512$ image matrix with 16-bit resolution. The picture element (or pixel) after digitization is given in Hounsfield units (HU) (or simply the CT number), which are defined as:

$$\text{CT Number (HU)} = C \cdot \frac{\mu_p - \mu_w}{\mu_w}$$

where $C$ is an integer constant called the contrast scale (typically set to 1000); $\mu_p$ is the calculated pixel mean x-ray attenuation coefficient; and $\mu_w$ is the mean x-ray attenuation coefficient of water or water-equivalent phantoms. Because x-ray attenuation coefficients are affected by the x-ray beam energy, it is important to properly evaluate the CT scanner x-ray tube generator to ensure accurate and reproducible CT numbers. The calibration is energy-dependent, and must be carried out for the complete range of available tube voltages, proliferations, filtration shapes, and so on. When quantitative analysis is required, it is recommended that a calibration phantom is scanned prior to the actual scans. [37, 38]

2.2.2 Computed Tomography Scanning Procedure

In third-generation CT scanner geometry, the patient lies on an examination table that can be moved through the scanner gantry, and the x-ray tube and detector array, which are mechanically fixed directly opposite the x-ray tube, rotate around the patient at some fixed
radius from the gantry center of rotation. Sequential 2D images can then be reconstructed from multiple x-ray projections acquired by rapidly rotating the x-ray tube 360° around the patient while exposing a detector subsystem to the transmitted x-radiation. At specific x-ray tube angles, the intensity of the transmitted x-ray photons is measured and the collected data are combined to form a single view or projection. The image is reconstructed from approximately 1000 views, which are used to compute the mean x-ray attenuation coefficient of the tissue at each voxel (the position on the image) and the CT number.

Because the human body comprises fluids and tissue that can vary in their x-ray attenuation properties, a single CT image can have voxels with CT numbers ranging from −1000 (air) to 2000 HU (dense cortical bone). This would require 3000 or more gray levels to differentiate different types of tissue/fluids in one image, as demonstrated in Fig. 2.4. Therefore, windowing is required to assign the total monitor display intensity to the CT number range of interest. For example, voxels with CT values below the lower window (L) will be displayed as black, whereas voxels with CT values above the upper window (U) setting will be displayed as white. The windowing procedure is performed by the CT operator according to two parameters: the window level (WL) and the window width (WW). The WL is chosen to correspond to the mean CT number of the tissue structure of interest, and the WW is chosen to determine the display contrast of the image. As the WW decreases, the range of CT numbers represented by each gray level becomes smaller, which improves the display contrast visibility. A narrow WW can display very small x-ray attenuation differences, whereas a wider WW can display larger differences in x-ray attenuation.

Figure 2.3. Ranges of CT values of the most important organs
2.2.3 Computed Tomography Sequences

To optimize image quality while minimizing x-ray radiation exposure to the patient, image artifacts, and study acquisition times, CT manufacturers and the medical community have implemented various improvements in modern CT scanners, such as third-generation geometry, $\frac{1}{4}$ detector width offset relative to the gantry center of rotation, low-voltage slip rings, and multiple ceramic detector arrays. These major technological improvements allow CT scanners to be operated in numerous acquisition modes.

First, a scout image is acquired to assist the CT operator in planning the patient protocol and to establish the target organ location. Scout images are generated by selecting an x-ray tube orientation with respect to the patient or table, then moving the table at constant speed through the gantry. Since the x-ray tube and detector array do not rotate around the patient during the acquisition, the resulting image looks similar to a regular x-ray radiograph.

In axial (or step-and-shoot) acquisition, the x-ray tube continuously rotates around the patient while the table travel is adjusted and moved in predefined increments on the z-axis. Since the table is fixed during the image acquisition process, axial scanning is preferred for high-quality CT imaging.

In spiral (helical) acquisition, the x-ray tube rotates around the patient and the table moves continuously through the gantry at a predefined speed throughout the scan. This approach has no interscan delays and can scan a large target volume very quickly. The volume coverage obtained during a helical scan acquisition is determined by a scan parameter called the helical pitch, which is defined as:

$$\text{Helical Pitch} = \frac{TF}{SC}$$

where TF is the table feed per rotation (mm/rotation) and SC is the slice thickness. The helical pitch value depends on the examination, as the tradeoff between coverage and effective slice thickness accuracy must be considered. Despite the advantages of helical scan acquisition, there is not enough projection data collected on any one helical loop to reconstruct a 2D axial slice, since the table is in constant motion. This problem can be overcome by using multi-slice CT (MSCT) scanners. MSCT scanners are similar to single-slice CT (SSCT) scanners, but the detector array consists of more than one row of detectors. The major benefits of MSCT are their shorter acquisition times, retrospective creation of thinner or thicker sections from the same raw data, increased speed of volume coverage, and
the ability to achieve isotropic voxel resolution to reduce the helical artifacts. The added image slice data allow larger and more accurate volume datasets to be obtained, resulting in improved 3D reconstruction and rendering techniques.

Real-time CT fluoroscopy acquisition generates continuous images from a fixed z-axis position, which is updated several times per second. CT fluoroscopy is often used to guide biopsy and aspiration procedures, but risks unnecessary x-ray radiation exposure to the patient. To minimize this exposure, the recent trend is toward a series of discrete rapid acquisitions. [39, 40]

2.2.4 Image Quality

Manufacturers are continuing to optimize the image quality of CT by examining aspects of noise, resolution, and helical pitch. Noise in CT images is measured by calculating the standard deviation of a region of interest in a homogeneous water phantom. The noise level depends on the object of the scan, the tube current, and the size of the detector. The standard deviation of the CT value in an image is calculated as [39]:

\[
\sigma = C_R \sqrt{\frac{I_0}{I}} \varepsilon QS
\]

where the factor \(C_R\) varies with the reconstruction algorithm, \(\varepsilon\) is the efficiency of the overall system, \(Q\) is the current-scan time product (mAs), and \(S\) is the slice thickness. A higher ratio of \(I_0/I\) denotes higher attenuation, which results in more noise. As the volume of the patient increases, the noise level also increases.

The in-plane spatial resolution in CT is a function of focus size, detector size, and the movement of the focus, as the x-ray source continuously moves during the scanning. This resolution can be measured using wire phantoms that provide a line-spread function.

The image quality of SSCT decreases with increasing helical pitch. There are two reasons for this. First, nominal slice thickness broadening occurs with increasing table speed, and second, the z-interpolation errors increase during image reconstruction as the helical data loops become stretched.

2.2.5 Computed Tomography Phantoms

Various new CT technologies have emerged, such as multi-slice, current-modulated, half-second rotation, dual-energy, dedicated breast, and 4D cone beam CT. As a result, the
development of suitable and effective phantoms is important in verifying that these CT scanners balance patient safety and diagnostic capabilities.

There are three types of phantoms for CT: 1) those for determining dosimetry; 2) those for examining image quality; and 3) anthropomorphic phantoms. Dosimetry can be characterized using the CT dose index (CTDI). The CTDI considers the dose profile to be a superposition of a primary dose distribution, related to the portion of the x-ray beam modulated by the pre-patient collimator, which is used to produce the image, and a scatter profile given by the interaction of the primary beam with the phantom material. Typically, the standardized phantom material used in CDTI measurements is polymethyl methacrylate (PMMA). [41]

CT phantoms for assessing image quality aim to quantify the main properties of the CT images, such as their spatial resolution under low- and high-contrast background, image noise, slice thickness, and certain artifacts (motion, beam hardening, uniformity). [42-44] E. McCullough et al. developed a guide for quality control and dosimetry known as The American Association of Physicists in Medicine (AAPM) CT test phantom, which includes inserts for of the dose profile measurements and alignment. [45-47] However, this phantom is inconvenient, as it must be filled with water. Thus, QA CT phantoms were improved using tissue-equivalent epoxy resin [48] or with holes for inserting small disks that provide specific information about image quality parameters. [49]

Anthropomorphic phantoms were introduced to mimic human tissue radiation absorption properties and average anatomical characteristics such as electron density and effective atomic number variations. Alderson et al. [50] introduced the concept of tissue-equivalent material associated with a human-shaped phantom for applications in radiation therapy treatment plans. These phantoms are usually associated with the insertion of film or thermoluminescent dosimeters, which assist dose investigations. [53, 54]

2.2.6 Phantom Materials

2.2.6.1 Polyethylene

Kalender et al. [55] have fabricated a calibration phantom for quantitative CT. They used different concentrations of polyethylene (PE) and calcium hydroxyapatite \([\text{Ca}_3(\text{PO}_4)_2\text{OH}]\) to fabricate water-equivalent and bone-equivalent phantoms. The CT numbers (HU) for the water-equivalent plastic and bone-equivalent plastic were -6.0 and 291.8, respectively, at 96
kVp. These phantoms were placed in a cutout of the table map to compare the uncalibrated and calibrated HU values of a reference phantom. The results show that the HU values changed from 399 to 322 HU following calibration. Although two reference materials cannot ensure the accuracy of the calibration, the small phantom cross-section is very lightweight, making for easy handling and improved patient comfort, since the patient is essentially supported by the table mat.

2.2.6.2 Epoxy

Iodinated phantoms have been studied for quality control measurements and system calibration. However, liquid phantoms suffer from variability between repeated dilutions, inhomogeneities from air bubbles or precipitates, and long set-up times. Therefore, Hill et al. [56] investigated a durable and reproducible iodinated phantom material that remains stable over time. Two different sets of calibration materials were fabricated with epoxy as the matrix and iodine concentrations of 0.0–3.0 mg/ml. They found a good agreement between the molded and experimentally determined $\mu_{\text{eff}}$, although some small systematic difference appeared. In addition, both demonstrated a linear relationship between $\mu_{\text{eff}}$ and iodine concentrations. The relationship between the linear attenuation coefficient and the iodine concentration is shown in Fig. 2.5. The material uniformity can be improved by using a shorter cure time at an elevated temperature. The manufacturing reproducibility of the iodine concentration was 0.03 mg/ml between each manufacturing run. Over the first six months, and then for another 1.5-year period, there was no statistically significant change in the $\mu_{\text{eff}}$ value of the calibration phantoms.

2.2.6.3 Polymethyl methacrylate (PMMA)

Dynamic contrast-enhanced imaging allows the assessment of functional information in addition to morphology using various modalities. Brauweiler et al. [57] developed a phantom for generating reproducible contrast-enhancement curves and providing a standard for the comparison of different protocols and modalities in dynamic imaging. Polymethyl methacrylate was used as the base material of the phantom, and the water flow was generated by a peristaltic pump with injected contrast agents. The phantom was used to assess the perfusion, SNR, spatiotemporal resolution, and reproducibility. The phantom showed good reproducibility in repeated measurements, with maximal deviations of 4% for time to peak,
9% for mean transit time, and 8% for peak enhancement. The area under the curve was constant to within 3.5% for different injection protocols. For the static case, highly constrained back projection (HYPR) LR maintained its spatial resolution, whereas for the dynamic case, it reduced the spatial resolution by up to 19% for the highest dynamics. The proposed phantom demonstrated good reproducibility, enabling it to act as a reference standard for comparing sampling strategies, injection protocols, and post-processing methods for QA.

2.2.6.4 Various Polymer Materials

Homolka et al. [58] compared different polymer materials for water equivalent phantom materials to study the temperature dependence on HU values. They examined epoxy resin, polyethylene, polystyrene–polypropylene mixture, and commercially available phantom materials (Solid Water™ and Plastic Water™). Cylindrical samples of each material were scanned using a Tomoscan SR-6000 (Philips) at 120 kV and temperatures of 15–40°C. Their results demonstrate that, at a reference temperature of 20°C, materials gave HU values close to zero, while the commercial materials exhibited an offset of 119.77 HU (Plastic Water) and 27.69 HU (Solid Water). The temperature dependence was lowest for epoxy-based materials and highest for a polyethylene-based material, as demonstrated in Fig. 2.6. Polystyrene or mixtures with polypropylene are appropriate phantom materials, because they have lower thermal expansion and lower sensitivity to temperature changes.

2.3 Magnetic Resonance Imaging

Magnetic resonance imaging uses the macrolevel behavior of atomic nuclei that possess magnetic properties under a strong magnetic field. Hydrogen (H) atoms are the most abundant element in the human body, and these are used in MRI. There are several advantages of MRI over other imaging modalities. Unlike CT, SPECT, and PET, MRI operates in RF range; thus, there is no ionizing radiation involved. Furthermore, MRI can generate excellent soft tissue contrast, and is capable of producing 3D volumetric images. MRI can produce images at any orientation, whereas CT is limited to axial slices and other orientations are reconstructed through post-processing interpolation. For each tissue, the
image pixel values vary according to their intrinsic properties. Thus, we can obtain exquisite images by enhancing or suppressing the effects of the desired parameters in terms of anatomical, functional, and molecular imaging. The MRI process can be divided into three steps: signal generation, detection, and reconstruction. [59]

2.3.1 Signal Generation

A fundamental property of nuclei is that those with odd atomic weights or atomic numbers possess angular momentum, often referred to as spin. A nucleus with nonzero spin rotates around its own axis. If there is a net electrical charge associated with that nucleus, a magnetic field is created. For example, H atoms are used in MRI because of their abundance in the human body in the form of water (H₂O). Since H atoms have one proton, they have a net angular momentum. Under normal conditions, the magnetic fields are oriented in random directions, canceling each other out and resulting in zero net magnetization. During the imaging, a strong magnetic field B₀ is applied to create coherent magnetization M, which restricts the probability of the spin canceling itself out. This coherence alone is not sufficient to generate a detectable signal, as static magnetic fields do not generate any signal. Once coherence has been achieved, an input signal (RF excitation), denoted by B₁(t), is applied to the system to change the direction of M. This induces a change in the magnetic field, which generates a response that is recorded as the output signal. B₁(t) is applied perpendicular to B₀ for a short duration, and falls into RF range in the following form:

\[ B₁(t) = Bₑ₁(t)e^{-i(ω₀t + Φ)} \]

where Bₑ₁(t) is the envelope of the pulse, ω₀ is the excitation carrier frequency, and Φ is the initial phase, generally assumed to be zero. The spin causes the nucleus to rotate around its own axis at a frequency of ω. To provide coherent spin transitions from the equilibrium state to another, we use the Larmor frequency ω₀, which lies within the RF range and is given by:

\[ ω₀ = γB₀ \]

where γ is the gyromagnetic ratio constant and is characteristic of a particular nuclide. [60]
2.3.2 Signal Detection: Relaxation

After the magnetized spin has been disturbed from its equilibrium state by an RF pulse, it will return to the equilibrium state once the RF pulse is removed. This process is known as free induction decay or relaxation. The recovery of the longitudinal component $M_z$ is called longitudinal or $T_1$ relaxation, whereas the decay of the transverse magnetization $M_{xy}$ is called transverse or $T_2$ relaxation. The underlying mechanism is complicated; however, we can account for the $T_1$ and $T_2$ relaxation in the Bloch equation:

$$\frac{dM}{dt} = M \times \gamma B = \frac{M_z i + M_y j}{T_2} = \frac{(M_z i + M_0)k}{T_1}$$

where $M$ and $B$ are vector forms of the magnetization and magnetic field, respectively, and $i, j,$ and $k$ are unit vectors along the $x, y,$ and $z$ directions, respectively. In the Bloch equation, the first term on the right-hand side describes the rotational behavior, whereas the relaxation terms describe the exponential behavior of the transverse and longitudinal magnetization components. The rotational term does not change the magnitude of the magnetization vector, whereas the relaxation processes do.

2.3.2.1 Longitudinal Relaxation

The longitudinal relaxation process is governed by

$$\frac{dM_z}{dt} = \frac{(M_z - M_0)}{T_1}$$

where $T_1$ is the spin-lattice relaxation time constant, which determines the time taken to return to equilibrium along the direction of the $B_0$ field. [60] We can solve this equation for $M_z$:

$$M_z = M_0 + \left(M_z(0) - M_0\right)e^{-t/T_1}$$

At 90° excitation, $M_z(0)=0$, which can further simplify the equation as:

$$M_z = M_0 \left(1 - e^{-t/T_1}\right)$$
where $T_1$ is a field-strength-dependent parameter that measures the amount of energy exchanged between the nuclei and the surrounding lattice. At higher frequencies, a greater energy exchange is required to switch between equilibrium and non-equilibrium states. Thus, $T_1$ increases with $B_0$.

### 2.3.2.2 Transverse Relaxation

The transverse component of magnetization behaves according to [60]

$$\frac{dM_{xy}}{dt} = \frac{M_{xy}}{T_2}$$

where $T_2$ is the spin–spin relaxation time constant, which describes the decay of the transverse magnetization. Under longitudinal relaxation, the xy-components of the fluctuating magnetic dipoles at the spin resonant frequency are responsible for $T_1$ relaxation. Under transverse relaxation, the $z$-component fluctuation and xy-component fluctuations account for $T_2$ relaxation, which makes $T_2$ greater than $T_1$. Since $z$-component fluctuation often dominates $T_2$ relaxation, it is largely independent of the field strength. [60]

### 2.3.3 Image Reconstruction

According to Faraday’s law of induction, the changing magnetic field induces an electromotive force (EMF) in the receiver coil through precession. The RF coil that generates the RF excitation field can be used to detect this signal, commonly known as free induction decay (FID). Once the signal has been recorded, the inverse Fourier transform can be used to reconstruct the image or spin distribution $m(x, y)$. There are several acquisition techniques, such as parallel imaging. An example of a skull in a $T_1$-, $T_2$-weighted MRI is shown in Fig. 2.7.
2.3.4 Magnetic Resonance Imaging Phantoms

MRI phantoms are fluid-filled objects that mimic body shapes and dimensions. Phantoms can be constructed to evaluate image contrast, SNR, image uniformity, spatial resolution, slice thickness, and geometric accuracy. Examples of MRI phantoms include the Magphan® qualitative imaging phantom to measure SNR, contrast-to-noise ratio, or image contrast and spatial distortion [66] or and the phantom created by the National Institute of Standards and Technology (NIST) that upholds national standards [67].

Although widely appreciated for its high-resolution, soft tissue imaging, MRI is also a quantitative technique that can measure several tissue-specific characteristics such as proton density and relaxation time. The tissue-specific longitudinal relaxation time ($T_1$) and transverse relaxation time ($T_2$) depend on molecular motion and the local microenvironment. Therefore, tissue relaxation times that differ from normal indicate inflammation, edema, microhemorrhage, or biological dysfunction. For accurate and precise measurements of human $T_1$ and $T_2$ values, standardized pulse sequences are essential. Furthermore, $T_1$ and $T_2$ are also strongly influenced by the viscosity of rigidity of a tissue. If a tissue or a phantom has the greater viscosity and rigidity, the value for $T_1$ and $T_2$ are smaller. For most soft tissues in the body, the proton density is homogeneous and it does not contribute significantly to the strength of the MRI signal. Table 2.3 presents typical $T_1$ and $T_2$ values for common tissues imaged at 1.5 and 3.0T and measured in vitro immediately after excision. [68] Phantoms have been constructed using aqueous solutions doped with paramagnetic ions such as GdCl$_3$, MnCl$_2$, CuSO$_4$, and NiCl$_2$. These phantoms provide a homogeneous solution in a rigid container, but generally suffer from flow or motion artifacts. Thus, gelatin phantoms doped with paramagnetic ions are developed with polyacrylamide, polyvinyl alcohol, gelatin,
carrageenan, agarose, or agar. NaCl can be used to modify conductivity, GdCl₃ to modify $T₁$, and agarose to modify $T₂$.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$T₁$ values (ms)</th>
<th>$T₂$ values (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3T</td>
<td>1.5T</td>
</tr>
<tr>
<td>Blood</td>
<td>1932 ± 85</td>
<td>1441 ± 120</td>
</tr>
<tr>
<td>White matter</td>
<td>1084 ± 45</td>
<td>884 ± 50</td>
</tr>
<tr>
<td>Gray matter</td>
<td>1820 ± 114</td>
<td>1124 ± 50</td>
</tr>
<tr>
<td>Muscle</td>
<td>1412 ± 13</td>
<td>1008 ± 20</td>
</tr>
<tr>
<td>Liver</td>
<td>812 ± 64</td>
<td>576 ± 30</td>
</tr>
</tbody>
</table>

Diffusion-weighted MRI is a quantitative method that measures tissue-specific diffusion characteristics, such as the apparent diffusion coefficient, mean diffusivity, and fractional anisotropy. These help clinicians to better understand the brain architecture and microscopic characteristics. Diffusion techniques can be extensively used for imaging neurological dysfunction and disease such as inflammation, multiple sclerosis, traumatic axonal injury, cellular infiltration/activation, and connectivity studies [69, 70].

### 2.3.5 Phantom Materials

MRI phantoms can be used for the development, adjustment, or maintenance of a system, as well as for evaluating MR image performance, determining the application range for new systems and pulse sequences, training MRI operators, and establishing standardization. Phantoms are used to study MRI systems without the need for human subjects. For such purposes, MRI phantoms must have the following characteristics: (1) relaxation times equivalent to human tissues; (2) dielectric properties equivalent to human tissues; (3) homogenous relaxation times and dielectric properties throughout the phantom; (4) sufficient strength to fabricate a torso without the use of physical reinforcements; (5) possible to fabricate in the shape of human organs; (6) ease of handling; and (7) chemical and physical stability over an extended time. [71]. In recent years, there have been many studies on tissue-mimicking polymers for calibration phantoms of medical imaging modalities. In the following section, the properties of various polymer gel materials are described in detail.
2.3.5.1 Carrageenan

carrageenan is a polysaccharide that can be extracted with hot water from Chondrus, Gigartina, Eucheuma, Furcellaria, and Phylllophora. There are three main carrageenans: κ-carrageenan, ι-carrageenan, and λ-carrageenan. All three types can be prepared in a solution with concentrations of up to 10% in water above 70°C. Similar to agar, carrageenan gels are thermally reversible, so they melt when heated above 55–85°C. The gel strength and viscosity of the carrageenan solution increase non-linearly with the concentrations of carrageenan [72]. Kato et al. [73] found that carrageenan is ideal for providing gel phantoms with sufficient mechanical strength, and has little impact on the $T_1$ and $T_2$ relaxation times. In addition, Yoshimura et al. [74] asserted that carrageenan has a higher elasticity and is less brittle than agar gel. These mechanical properties enable the gels to be molded into a range of different shapes. This particular study uses 3% carrageenan and 1% agarose to make a body phantom for a shape-retaining capability test. The gel was found to suffer minimal sagging under its own weight, and was thus deemed appropriate for creating a phantom that is capable of retaining its shape. Similar to agar, carrageenan phantoms are prone to water loss, which leads to changes in the $T_1$ and $T_2$ relaxation times. The above study mentioned that a good seal around the container can minimize water loss, but the long-term stability of the phantoms is yet to be explored. Despite the common water evaporation problem, carrageenans are among the most suitable materials for creating a phantom, since they are easy to handle, transparent, have a minimal effect on $T_1$ and $T_2$ relaxation times, and offer reliable mechanical strength [74].

2.3.5.2 TX-150 and TX-151

One of the earliest variations of polymer gel phantoms was created by using a polysaccharide material. A study conducted by Groch et al. [75] described the development of a novel phantom material named polysaccharide, which is a natural structural element of tissue cell walls and connective tissues. The study claimed that polysaccharides have an advantage over animal gelatin or agar in that they can be cast at relatively low temperatures (5–10°C) and produce phantoms with contiguous regions of differing relaxation properties. A modified polysaccharide, TX-151, is more realistic, inexpensive, and easy to mold compared to TX-150. Mazzara et al. [76] demonstrated that TX-151 can be used to fabricate tissue-equivalent material to mimic the human breast. Furthermore, the study revealed that this novel polysaccharide material experiences temporal changes in $T_1$ and $T_2$ relaxation times.
Refrigerated samples exhibit smaller changes in $T_1$ and $T_2$ values than room temperature samples, and sealed samples perform better in maintaining their $T_1$ and $T_2$ values. [76]

2.3.5.3 Polyvinyl Alcohol Cryogel

Polyvinyl alcohol cryogel is considered to be one of the most promising water-based polymers, as it exhibits a similar texture and has the mechanical and imaging properties of soft tissues. It is a nontoxic, water-soluble polymer that is synthesized from polyvinyl acetate through hydrolysis to remove the acetate groups. The liquid PVA solution undergoes an FTC in which it freezes to a set temperature at a specific rate and is then thawed to room temperature. The number of FTCs transforms the liquid PVA solution into an elastic, semi-opaque gel known as PVA-C. The mechanical and imaging properties of PVA-C vary with the number of FTCs.

In recent years, several research groups have focused on fabricating PVA-C phantoms for different modalities. For instance, PVA-C was adapted by Mano et al. [77] into gels of 70, 75, 80, and 85% water content, and the resulting $^1$H density, $T_1$ and $T_2$ values were measured. They also studied the effect of adding Ni$^{2+}$ and graphite at different concentrations. It was found to be difficult to obtain a combination of $T_1$ and $T_2$ values that correspond to living tissue over a wide range. The long-term stability of the PVA gels was also examined, with 1% weight reduction and $T_1$ and $T_2$ value reductions of 4–12% after six months.

2.4 Multimodal imaging

Medical imaging plays an important role in the field of healthcare, both in clinical settings and for research and development. It is used in the prevention and early detection of disease, in choosing the optimal treatment, during surgical interventions, and for monitoring the treatment effects. In recent years, noninvasive multimodal imaging has become standard clinical practice, and is rapidly changing the evolving field of molecular imaging. As a result, researchers and engineers from fields such as molecular pharmacology and nanotechnology have worked together to enhance the state-of-the-art. Multimodality imaging involves the incorporation of two or more modalities within the setting of a single examination. For example, US or optical studies can be performed within MRI, SPECT, or x-ray CT environments. Clinically, the best examples of rapidly evolving multimodality imaging are the PET-SPECT and PET-CT scanner hybrids. The use of PET in single, hybrid, and
multimodal imaging methods is a result of the functional and anatomic information it provides.

The role of multimodal imaging is to identify the exact localization, extent, and metabolic activity of the target tissue, yield the tissue flow and function or functional changes within the surrounding tissues, and highlight any pathognomonic changes leading to eventual disease. Newer tools that possess the potential to be integrated in multimodal utilities include near-infrared spectroscopy or optical imaging for real-time assessment of wavelength specific absorption of photons by oxygenated and deoxygenated tissues. Two-dimensional electroencephalography and magnetoencephalography techniques, as well as functional MRI, also exhibit potential for multimodal imaging. [78]

Despite considerable advances over the past few decades, rapid changes in technology and the variety of imaging parameters that differ between manufacturers have restricted further development. Furthermore, to allow the development of image-guided therapeutic interventions and diagnostic imaging techniques and systems, phantoms that simulate human or animal tissue are required.

As mentioned above, there has been intensive research on combining several imaging modalities to provide morphological and functional image data that can be divided in several ways to provide the necessary data. For visual fusion, images obtained from two independent acquisitions are displayed and analyzed side by side by an observer. This method is time-consuming, and the success of revealing additional information from two independently acquired images depends on the experience and skill of the observer. However, this method is widely used, since it requires no technical infrastructure and is cost-effective. The use of software fusion techniques is increasingly attractive, as these use fully automated algorithms and computing power, which provide a time-effective workflow. [79] Software-based fusion typically employs fiducial markers or contour-finding algorithms to determine landmarks within both images and find the “best fit” with the fewest discrepancies. Since this is a rigid fusion, any distortion caused by patient repositioning or the movement of internal organs makes it difficult to accurately fuse the images [80]. More advanced non-rigid transformation techniques often require manual user assistance, and are therefore more time-consuming. To reduce the probability of patient or organ movement during scans, multimodality imaging can be used. In this case, both modalities are physically mounted next to each other, and they are fully integrated into one device with a fixed and known transformation matrix. Since the patient bed is transferred from one to the other modality, the movement of the patient is minimized. However, to minimize the movement of internal organs over longer scan times,
advanced non-rigid image fusion algorithms should be adopted to ensure higher accuracy. In
the following section, the theory, potential, and limitations of PET/CT and PET/MRI are
discussed.

2.4.1 Positron emission tomography (PET)/Computed Tomography (CT)

Positron emission tomography is one of the most meaningful functional imaging technologies
because of its high sensitivity in the picomolar range, as well as its ability to observe
metabolic processes over time and track radiolabeled bio-markers. Although PET data are
very quantitative, they lack spatial resolution and do not provide sufficient anatomical
information. This limitation often requires additional morphological data to provide more
accurate oncological diagnosis, tumor staging, or radiation therapy planning. [82, 83] Thus,
x-ray CT is used to provide anatomical information to the PET data, since this technique is
well established in the field of clinical oncological imaging and provides very good spatial
resolution. In general, hybrid PET/CT devices are basically the two individual devices
mounted next to each other, with a patient bed to transfer the patient from one device to the
other controlled by one computer console (see Fig. 2.8). A very fast CT projection scan is
used for anatomical orientation and to plan the examination regions for the PET and CT
scans. After planning, low-dose or diagnostic CT scans are performed. Following the CT
scans, PET images are acquired in a multi-bed position mode to cover the whole body of the
patient. Special fusion software is then implemented to overlay the acquired image datasets.
Usually, when gamma rays penetrate through tissue, there is a known probability that they
will be absorbed. This is called attenuation, and leads to a subsequent quantification error. In
PET/CT systems, the CT scan can be used for attenuation correction. These data are acquired
at a lower energy, typically 80–120 keV, and up-scaled to the tissue absorption factors at 511
keV. The CT can be performed much faster than conventional transmission scans, resulting in
a drastic reduction of the overall examination time. Thus, PET/CT systems provide
anatomical information within a shorter examination time than conventional PET. [84, 85]

The use of a combined PET/CT system enables tumor detection and staging as well as
therapy monitoring and planning in a single device. Several studies have shown the clear
advantage of combined PET/CT over PET or CT alone or when carried out side by side. A
study by Antoch et al. [86] that considered 260 patients with different tumor diseases
revealed that the staging accuracy was 84% when combined PET/CT was used, compared
with an accuracy of only 76% when images were evaluated side by side. The staging
accuracy was only 63% (64%) when CT (PET) information was used alone. In addition,
PET/CT exhibits great potential for the planning of radiation therapy, especially when tumor regions are difficult to define. With both PET and CT information, a more accurate definition of irradiation regions is possible. Areas showing high tumor activity in PET images may not necessarily be detected by CT, and might thus be overseen by conventional therapy planning based on CT alone. Furthermore, tissue appearing as lesion expansion in CT may be indicated as benign in a PET scan, and thus not irradiated. [87]

Figure 2.5. Schematic workflow of the PET/CT examination. (a) A fast scout scan to determine examination regions for PET and diagnostic CT. (b) The acquisition of either a low-dose or diagnostic CT scan. (c) PET data acquired at multiple bed positions, reconstructed and corrected for attenuation. (d) PET and CT images are registered and displayed as fused images. [78]
2.4.1.1 Potential and Limitations of Combined PET/CT

Besides the shorter scan times available with PET/CT systems, the CT-based attenuation map also produces better statistics. Therefore, a lower noise contribution than conventional attenuation is measured with 511 keV gamma sources. Despite these advantages, in regions with high-density materials, such as inlays or obese patients, CT causes beam-hardening artifacts whereby the lower x-ray energy attenuates more than the high energies, resulting in a shift of the polychromatic x-ray spectra to higher energies. This effect can cause significant artifacts in the CT images, and lead to false attenuation values for the PET images.

2.4.1.2 Co-registration Errors

Shorter scan times result in increased patient comfort and a reduced probability of misalignment of the PET and CT data caused by patient-induced motion artifacts. However, a significant time-window remains between the CT scan and the last PET bed position. To avoid patient motion during the acquisition, comfortable and secured patient bedding is mandatory.

2.4.1.3 Breathing Artifacts

Breathing artifacts represent another source of misaligned PET and CT data. Computed tomography scans are usually very fast and can be acquired during inspiration according to standard diagnostic CT scan protocols. However, PET scans are acquired over several minutes while the patient breathes normally. This can lead to a mismatch between the PET and CT data, especially around the diaphragm, thorax, and abdomen. To avoid such artifacts, examination protocols use instructed respiration cycles (mid-expiration, breath-hold) or CT scans during normal respiration. [89, 90]

2.4.1.4 Contrast Agents

Diagnostic CT usually requires the intake of contrast agents either intravenously or orally. Contrast agents help to distinguish the vascular system and digestive tract from other soft tissue. However, the effects of CT contrast agents are not included in the linear scaling model for calculating PET attenuation correction data from x-ray absorption factors. These contrast agents contain iodine and range from 100–1000 HU. [85] The contrast-enhanced structures are considered as bone in the attenuation map, which might lead to a false PET attenuation correction if the PET/CT examination protocols are not adjusted accordingly.
2.4.2 Positron Emission Tomography (PET)/ Magnetic Resonance Imaging (MRI)

As mentioned in the previous section, the use of PET/CT systems introduces advantages such as more accurate diagnosis and shorter scan times. However, CT cannot achieve adequate soft-tissue contrast. If the contrast agents or CT radiation dose is not applied, the morphology and image quality is insufficient for clinical purposes. On the other hand, MRI provides excellent soft-tissue contrast in regions such as the brain or abdomen. In addition, MRI examinations do not require the use of ionizing radiation, thus minimizing the radiation dose to the patient. [91, 92]

2.4.2.1 Technical Challenges

However, it is a challenge to combine two modalities without compromising their performance or causing mutual interference. One of the main challenges in merging the hardware of PET and MRI into a single device is that conventional PET detector designs use photomultiplier tubes to detect light. The functional principles of accelerating electrons in a strong electric field inside a vacuum tube mean that these photomultiplier tubes are very sensitive to magnetic fields. If PET and MRI are combined for simultaneous use, both fields of view have to be physically aligned. This means that the PET detectors need to be built within the MRI bore, resulting in very limited space for the PET detectors. To combine PET and MRI, alternative PET detectors have been studied.

The avalanche photodiode (APD), which was developed as an alternative light detector, which is capable of detecting very small amounts of scintillation light. [93-95] Although the internal gain of an APD is only of order 100–1000 and a charge-sensitive preamplifier is needed to obtain a readout, APDs provide sufficiently fast and low-noise electrical signals. APDs are known to be insensitive to magnetic fields and have a very small size. However, for combined PET/MRI, the charge-sensitive preamplifiers require very careful design to avoid potential interference with the MRI radiofrequencies or gradients.

Furthermore, MRI requires a homogeneous static magnetic field; materials inside the detector interacting with the magnetic field may cause distortions, which will show up as artifacts. Using a PET detector inside a magnet requires the insertion of different materials, such as scintillator crystals, a light detector, electronics, and electronic shielding materials. These different components must be magnetically compatible with susceptibilities close to that of human tissue to maintain acceptable MRI performance. Most of the material-related
MRI artifacts can be avoided if the PET detector is located outside the RF probe and preserves a certain distance to the object. Additionally, electronic components such as capacitors, amplifiers, and resistors must be nonmagnetic, and large solid areas of metal should be avoided.

2.4.2.2 PET/MR Development

Unlike the simple combination of PET/CT, PET/MRI involves major modifications, especially to the PET detector technology. The three basic concepts of combined PET and MRI are shown in Fig. 2.9. First, the simplest approach is to mount the PET and MRI side by side. This design results in limited latitude for the data acquisition. The major drawback is that the scans cannot be performed simultaneously. Since MRI is much slower than CT imaging, this increases the examination time. This issue also rules out the possibility of acquiring two different sets of information simultaneously from PET and MRI. To achieve simultaneous PET/MRI data acquisition, the PET detector must be fully integrated inside the MRI scanner. In general, there are two different ways to construct an integrated PET/MRI scanner: the first method of inserting a PET detector in a standard MRI (Fig. 2.9(b)) will drastically reduce the bore size, but does allow the MRI scanner to be used without PET; the second technique of fully embedding the PET detector into the MRI scanner hardware maintains a larger clear MRI bore (Fig. 2.9(c)), but this preferable solution represents the most expensive and challenging PET/MRI system.

![Figure 2.6. Potential realizations of PET/MRI scanners. (a) PET/MRI side by side. Two individual devices are mounted back-to-back and have a common control unit. (b) PET inserted within an MRI; the bore size is drastically reduced and the PET detectors have to be compact. (c) PET detector embedded into an MRI system. Both devices are merged together into one multimodality scanner. [78]](image)
2.4.2.3 PET Attenuation Correction based on MRI Data

As discussed for PET/CT systems, accurate PET quantification requires mandatory correction of the 511-keV photon attenuation caused by the tissue. In contrast to PET/CT, where the CT image data provide an attenuation map for the PET images, MRI image data contain information about the tissue proton density. The proton density does not necessarily reflect the photon attenuation probability; thus, a simple re-mapping of the MR signal intensities would not provide accurate PET attenuation correction. There are several approaches for deriving PET attenuation data for a combined PET/MRI scanner from the MRI data. These include regional segmentation of the images into body regions and organs, [96] and support vector machines [97]. However, it is still unclear which attenuation correction approach is better for PET/MRI data.

The original aim of combining PET and MRI as a dual-mode imaging system was to overcome the weaknesses of existing PET/CT systems, namely the lack of soft-tissue contrast and relatively high radiation dose from CT. However, not only does MRI offer high-quality anatomical images with high soft-tissue contrast, but also functional information such as fMRI and proton spectroscopy. Therefore, the potential for PET/MRI extends beyond tracer uptake and morphology towards multifunctional imaging.

2.4.3 Phantom Materials

2.4.3.1 Agarose

Huber et al. [98] fabricated a phantom for transrectal ultrasound (TRUS) combined with PET, CT, and MRI. This TRUS was found to provide good anatomical detail of the prostate region and accurate measurements of the prostate volume. Two basic tissue-mimicking materials were fabricated for high- and low-scatter US with different concentrations of agarose, gelatin, and deionized water, with the addition of GeCl\textsubscript{4} radioactivity in a 0.5 molar hydrochloric acide (HCl) solution for repeated PET imaging. The PET-TRUS prostate phantom did not exactly mimic the PET and TRUS properties of the prostate region, but as this phantom was only used to validate image co-registration, it was sufficient for interventional procedures such as brachytherapy. The diffusion of the \textsuperscript{68}GeCl\textsubscript{4} molecules rendered this phantom unsuitable for long-term use. The mechanical properties appeared stable, and there was no sign of bacterial or fungal invasion in the phantom when stored at room temperature for ten months.
2.4.3.2 Polyvinyl Chloride

Hungr et al. [99] attempted to fabricate a deformable phantom for prostate cancer to help robot-assisted image-guided needle insertion. The imaging modalities of US, CT, and MRI are most commonly used for prostate techniques. The objective of this study was to improve the anatomical realism, adapt the phantom for transrectal US applications, and ensure its multimodality applicability while satisfying the required mechanical and imaging characteristics. Six common base materials were considered for phantom construction, including agarose, gelatin, PVA-C, polyvinyl chloride (PVC), silicone, and the proprietary commercialized material of Zerdine (CIRS). However, agarose and gelatin were found to be too fragile, the CIRS phantoms exhibited no evident deformation during needle insertion and are expensive, PVA-C has a long, complex preparation procedure, and silicone has inappropriate acoustic properties. Thus, PVC was used for phantom fabrication, and the SOS, stress–strain relationship, storage methods, imaging, needle-insertion force, and deformability characteristics were evaluated. The average SOS in the phantom was 1380±20 m/s, and the stress–strain relationship was found to be viscoelastic, which is within the range of typical prostatic tissues. The phantom had a clearly distinguishable morphology in all three imaging modalities, with embedded targets that could be precisely segmented, resulting in an average US-CT rigid registration error of 0.66 mm, as illustrated in Fig. 2.10. The mobility of the phantom prostate upon needle insertion was 2–4 mm, with 0–2 rotations. These mechanical and imaging characteristics remained stable at cooler storage temperatures.

2.4.3.3 Polyvinyl Alcohol Cryogel

Chen et al. [100] fabricated a PVA-C brain phantom for multimodal imaging using the Colin27 brain dataset. The objective of this study was to simulate anatomically accurate cortical structures using a mold fabricated by stereolithographic printing, recreate the texture of live human cerebral tissues, and obtain CT, US, and MR images. To increase the backscattering of sound waves in US imaging, commercial-grade talcum powder was added to the phantom. Powdered barium sulfate (BaSO₄) was used as a contrast agent in CT imaging, and CuSO₄ was used to increase the contrast in T₁ and T₂ weighted images. A PVA-C “tumor” was created using 4% PVA solutions with one FTC to test the guidance accuracy in surgical procedures. It was found that 5% BaSO₄, 0.2% CuSO₄, and 5% talcum as contrast agents in 8% PVA with two FTCs provided adequate contrast for CT, MR, and US, respectively. However, the rheological and mechanical properties of these phantoms require
further investigation. Moreover, the MR contrast agent, CuSO₄, diffuses from the spherical tumor phantom into the surrounding tissue.

2.4.3.4 Silicone

Goldstein et al. [101] studied silicone gel for MRI, PET, and CT imaging phantoms. Silicone gel has $T_1$ and $T_2$ values that are similar to the human tissue range and can easily be molded into any shape. It is also easy to inject solutions into pre-molded cavities within the phantom to produce regions with different contrast. The $T_1$ and $T_2$ relaxation time values were obtained with different resin-to-catalyst ratios and different mixing times. The $T_1$ values ranged from 430–500 ms and the $T_2$ ranged from 50–130 ms. The corresponding CT number was 160 HU. The gel sealed itself immediately after needle puncture, preventing any leakage back into the puncture canal.

Chmarra et al. [102] also studied silicone as a potential multimodal phantom material. The goal of their work was to develop a protocol and manufacture a multimodal liver phantom. The main requirements for the phantom were its suitability for US, CT, and MR imaging modalities; ease of production; standardized fabrication; low cost; and life-cycle friendliness, i.e., re-usability of phantom parts and materials and avoidance of using toxic resources. The phantom was fabricated with a silicone container, tumor tissue using agarose gel, and liver parenchyma using candle gel and silicone string to mimic portal veins. The researchers obtained US, CT, and MRI images, but could not produce an exact representation of the portal and hepatic veins or various lesions.

2.5 Radiation Therapy Phantoms

Radiation therapy uses high-energy radiation to shrink tumors and kill cancer cells. X-rays, gamma rays, and charged particles are all used for the treatment of cancer. The radiation may be delivered externally by a machine (external-beam radiation therapy) or from a radioactive substance placed internally near to the cancer cells (internal radiation therapy, or brachytherapy). Systematic radiation therapy uses radioactive substances, such as radioactive iodine, that travel in the blood to kill cancer cells. Radiation therapy kills cancer cells by damaging their DNA directly or creating free radicals within the cells that can in turn damage the DNA. [103]
2.5.1 Radiation Therapy Planning

When a patient is diagnosed with cancer, a radiation oncologist develops a treatment plan through a process called treatment planning. This process begins with a simulation, during which medical imaging such as CT, MRI, PET, or US is performed to locate the patient’s tumor and the surrounding normal tissue. CT is most commonly used in treatment planning. During the simulation, the patient must repeatedly take exactly the same position relative to the machine delivering the treatment. Body molds, head masks, or other devices may be constructed to make it easier to position the patient. Radiation doses for cancer treatment are measured in grays (Gy), which are defined as the number of joules of radiation energy absorbed by one kilogram of human tissue. Different doses of radiation are needed to kill different types of cancer cells.

2.5.1.1 External-beam Radiation Therapy

External-beam radiation therapy is usually delivered in the form of photon beams (i.e., x-rays or gamma rays). Many types of external-beam radiation therapy are delivered using a machine called a linear accelerator, which uses electricity to form a stream of fast-moving subatomic particles. This high-energy radiation may be used to treat cancer over the course of several weeks. Common types of external-beam radiation therapy are 3D conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) [104], image-guided radiation therapy (IGRT) [105], tomotherapy [106], stereotactic radiosurgery, stereotactic body radiation therapy [107], and proton therapy [108]. During IGRT treatment, repeated imaging scans (CT, MRI, or PET) are performed to identify the change in tumor size and location from the planned radiation dose, enabling a future treatment plan to be formulated.

2.5.1.2 Internal Radiation Therapy

Internal radiation therapy (brachytherapy) is radiation delivered by radioactive substances that are placed within or on the body. [109] Radioactive isotopes may be sealed in pellets that are placed inside the patient using delivery devices such as needles, catheters, or other types of carrier. As the isotopes decay, they give off radiation that damages nearby cancer cells. There are three types brachytherapy. Interstitial brachytherapy uses a radiation source placed within tumor tissue. Intercavity brachytherapy uses a source placed within a surgical cavity near a tumor. Episceral brachytherapy uses a source that is attached to the eye to treat melanoma inside the eye.
2.5.1.3 *Systemic Radiation Therapy*

In systemic radiation therapy, a patient swallows or is injected with radioactive material, such as radioactive iodine or a radioactive substance bound to a monoclonal antibody that helps to accurately locate and kill the tumor cells.

2.5.2 Radiation Phantoms

The successful use of high-energy external beam radiation for therapeutic purposes depends on the spatial distribution of the absolute dose within the patient. Since the therapy is three-dimensional in nature, particles not only affect the immediate interaction site but also the surrounding, healthy tissues. Thus, precise knowledge and control of the dose distribution is critical to maximize the therapeutic effect of the radiation. To ensure the accuracy of the imaging data and dose deposition, phantoms are used to investigate the effects of radiation beams. Phantom materials range from water to complex chemical mixtures that mimic how the human body interacts with radiation.

There are two primary uses of therapeutic dosimetry phantoms: (1) characterization and calibration of delivered external radiation beams, and (2) validation of numerical dose modeling and design through treatment planning. Ideally, the dose distribution could be measured within a patient in real time during beam delivery, enabling the dose to be adjusted as necessary. The advantages of using a phantom are that the object can receive repeated doses and can be created in various geometries and densities to allow for the interpretation of measurements for comparison with calculations.

There are several design goals for therapeutic dose measurements from both a material and geometry perspective:

1. Similarity to tissue so that the dose to tissue can be estimated from the measurements
2. Ease of traceability to reference standards
3. Composition that can be well characterized by radiation type and energy and is reproducible
4. Robustness to radiation damage
5. Ability to accommodate various beam field sizes and shapes in an accurate and efficient manner

Dosimetry phantoms can be divided into water and non-water categories. Water is commonly used because it is contained in major tissue components and is suitable for calibration standards. The non-water materials are used for setup efficiency, compatibility with film, and as a component for integrated phantoms.
Furthermore, with surgical placement and practices, phantoms specific to brachytherapy are needed for image evaluations. Many of the imaging modalities used within radiation therapy clinics for external-beam radiography, such as x-ray, CT, and MRI, are also available for brachytherapy.

2.6 Summary
In this chapter, several modalities and their phantoms have been discussed. As each modality functions with different background physics and imaging parameters, the functions of the phantoms vary. In the following chapters, we will discuss several materials that can be used to construct multimodal imaging phantoms for use in MRI, CT, and US.
Chapter 3

3 Mechanical Stability Analysis of Carrageenan-Based Polymer Gel for MRI Liver Phantom with Lesion Particles

3.1 Introduction
In this study, soft-tissue-equivalent carrageenan-based polymer gel is fabricated and its mechanical and imaging properties are determined. These properties include the density, dielectric constant, and modulus values, as well as MRI relaxation times and CT numbers. These properties are observed over a prolonged period to analyze the stability of the materials. Since carrageenan gels consist of almost 97% water, certain properties are susceptible to fluctuation over time, possibly because of water evaporation during storage. Finally, an MRI phantom is fabricated from carrageenan gel with small particles to represent liver lesions.

3.2 Motivation and Objectives
Among medical imaging modalities, MRI is recognized as the most advanced for detailed 3D visualizations of the internal structures and soft tissues of the body. Unlike imaging methods such as x-rays and CT, MRI does not utilize ionizing radiation, and therefore the harmful side effects associated with prolonged exposure to radiation are eliminated. Physicians can use MRI to detect and evaluate lesions, multiple sclerosis, tumors, and strokes within soft tissues. The technology involved in MRI has improved over recent decades, leading to enhanced image quality and various diagnostic techniques and image-guided therapy. To ensure an accurate diagnosis, MRI requires regular systematic calibration of the equipment using a phantom that mimics human tissue. An imaging phantom is a calibration medium that is scanned or imaged to evaluate, analyze, and tune the performance of various imaging devices. A phantom used to evaluate an imaging device should respond in a manner similar to that of human soft tissue in the specific imaging mode. Currently, a normal human patient is used for imaging calibration, but this process is time-consuming, costly, and does not
provide consistent values suitable for calibration. Therefore, a phantom that behaves similarly to human soft tissue functions as a replacement.

The optimal characteristics of MRI phantoms used for such purposes are as follows: (1) relaxation times equivalent to those of human tissues, (2) dielectric properties equivalent to those of human tissues, (3) relaxation times and dielectric properties that are homogeneous throughout the phantom, (4) mechanical properties suitable for fabricating a human torso without the need for reinforcement, (5) able to form shapes of human organs, (6) easy to handle, and (7) stable physical and imaging properties over an extended period. [73]

Over the past few decades, several studies have been conducted on water-based polymer gels with paramagnetic ions as potential materials for MRI phantom materials. Paramagnetic ions (i.e., CuSO₄, NiCl₂, MnCl₂, and GdCl₃) are known to improve the visibility of internal body structures in MRI by altering the $T_1$ and $T_2$ relaxation times. The $T_1$ and $T_2$ relaxation times represent the rate at which the longitudinal and transverse components of the magnetization vector of human tissue return to their thermodynamic equilibrium. Some polymer gels that have been investigated include agarose, [72, 110, 111] agar, [112, 113], PVA, [114] gelatin, [77] and polysaccharide gels TX-150 [75] and TX-151 [76]. These materials have the potential to be used in phantoms, but are limited by their fragility and storage issues.

Similar to the materials stated above, the viability of carrageenan-based gel as an MRI phantom material has been studied. [73] The results demonstrated that, by varying the concentrations of carrageenan and a modifier, the $T_1$ and $T_2$ values could be modified to match those of human tissues. However, no studies have investigated the mechanical stability of carrageenan-based materials, except for a brief report on fungal growth over time. Because carrageenan gels have a high water content, their properties may fluctuate with time due to the continuous cycles of water expulsion and absorption. For the purpose of commercialization, it is essential that the material properties of a phantom, such as the density, elastic modulus, and $T_1$ and $T_2$ relaxation times, remain stable owing to the required long shelf life. If the properties of a phantom varied with time, false results would be obtained when used to evaluate the performance of an MRI system.

Therefore, the objective of this study is to identify changes in the properties of a carrageenan-based gel phantom by investigating its stability over a six-week period. A carrageenan-based liver phantom was fabricated by the copolymerization of carrageenan, and
agar and gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA) were used as $T_1$ and $T_2$ modifiers. To investigate the effects of the polymer and modifier on the structural integrity and relaxation times of the phantom, eight material samples with different concentrations of the polymer and modifier were fabricated and characterized. The sample densities and chemical, dielectric, mechanical, and imaging properties (relaxation times and CT number) were determined and compared with those of human tissue. The properties of each sample were measured and analyzed to assess their stability for MRI phantom application. Furthermore, a polymer-based liver phantom was fabricated with embedded lesion particles (i.e., cyst, hemangiomas, and tumors). The lesions are spherical particles of 1–10 mm diameter that are randomly distributed between layers of phantom material.

3.3 Experimental Setup

3.3.1 Experimental Materials

Polymers with two gelling agents, namely carrageenan and agar, were used for the study. Commercial-grade type-I carrageenan (Sigma Life Science) was used as a gelling agent, and agar (BioShop) was used as both a gelling agent and $T_2$ modifier. Gd-DTPA Omniscan gadodiamide injection ISP 287 mg/ml (0.5 mmol ml) (GE Healthcare) was used as the $T_1$ modifier. Table salt was used to enhance the conductivity, and NaN$_3$ was employed as an antiseptic to prevent the polymer gel from deteriorating over a prolonged period.

3.3.2 Fabrication of Carrageenan-based Polymer Gel

The polymer gel samples were fabricated in test tubes prior to the phantom study for characterization. Different degrees of cross-linking were achieved using various amounts of the gelling agents. One-hundred mL of deionized water (DI) was heated to 70–85°C in a 150 ml beaker. A parabolic-shaped glass lid was placed on top of the beaker to minimize evaporation during heating. Eight different samples with various concentrations of carrageenan (1–3 wt%) and agar (0–1.5 wt%) were fabricated by pouring a powder mixture of carrageenan and agar into the heated water. The solution was stirred to obtain a homogeneous solution of the powder, and 1.7 µL of Gd-DTPA was dropped into the solution via a micropipette (Finnepipette). The sample compositions are listed in Table 3.1. After mixing for approximately 30 min to ensure homogeneity, the gel mixture was poured into a
15 mL glass test tube and set at room temperature for 30 min for cooling and to remove air bubbles. Parafilm was used to seal the open end of the glass test tube to minimize water evaporation during storage. The samples were then stored in a refrigerator at 4°C, and changes in their properties were observed.

Table 3.1 Contents of carrageenan, agar, GdCl$_3$, and water in the polymer gel samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Carrageenan (g)</th>
<th>Agar (g)</th>
<th>GdCl$_3$ (µL)</th>
<th>H$_2$O (mL)</th>
<th>Sample</th>
<th>Carrageenan (g)</th>
<th>Agar (g)</th>
<th>GdCl$_3$ (µL)</th>
<th>H$_2$O (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>0.0</td>
<td>1.7</td>
<td>97</td>
<td>5</td>
<td>2.5</td>
<td>1.5</td>
<td>1.7</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>0.5</td>
<td>1.7</td>
<td>96.5</td>
<td>6</td>
<td>2.0</td>
<td>1.5</td>
<td>1.7</td>
<td>96.5</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>1.0</td>
<td>1.7</td>
<td>96</td>
<td>7</td>
<td>1.5</td>
<td>1.5</td>
<td>1.7</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>1.5</td>
<td>1.7</td>
<td>95.5</td>
<td>8</td>
<td>1.0</td>
<td>1.5</td>
<td>1.7</td>
<td>97.5</td>
</tr>
</tbody>
</table>

3.3.3 Characterization

The polymer gel samples were categorized according to their chemical properties, mechanical properties (density and compressive modulus), dielectric properties (conductivity and permittivity), and imaging properties ($T_1$ and $T_2$ relaxation times and HUs). Three samples of each were tested to examine the repeatability.

3.3.3.1 Chemical Properties of carrageenan-based polymer gel

Fourier Transform Infrared Spectroscopy (FTIR) was performed with a Bruker Alpha FT-IR spectroscope to analyze the spectrum of the polymer gel.

3.3.3.2 Mechanical Properties of carrageenan-based polymer gel

The density of the polymer gels was compared to that of real human tissue, known to be 1.03 g/cm$^3$. [115] The relationship between the material composition and density of the polymer gel can be established to match the real human tissue density. The density of each gel sample was determined by dividing its mass by its volume. This procedure was carried out over the testing period to monitor any density change in the polymer gels stored in the refrigerator.

The compressive modulus was measured using an Instron compression-testing machine with a 500 N load cell in accordance with ASTM standards. [116] With regards to the polymer gel, a significant correlation can be found between the compressive modulus and the
ability for the polymer gel to retain its shape. A cylindrical disk was cut from the mold in size of 16mm diameter and 10mm height. A 2cm × 2cm piece of Kimwipe was placed on the test plate to prevent the sample from slipping away during the experiment. The cylindrical disk samples were placed on the compression testing plate and a 500 N load cell was slowly lowered until it made contact with the sample. The contact between sample and the plate was ensured by slowly moving the plate down until the Instron detects the load. The compression test, which was conducted after calibration, was conducted with a 500N load cell at a rate of 1 mm/min. A significant correlation was observed between the compressive modulus of the polymer gel and its ability to maintain its shape without sagging or distortion.

3.3.3.3 Dielectric Properties of carrageenan-based polymer gel

The dielectric properties of a material, such as its conductivity (σ) and permittivity (ε), vary with the test frequency range. Gabriel et al. [117] studied the dielectric properties of biological tissue in a frequency range of 10Hz–20 Hz (see Table 3.2). As listed in the table, muscles and high-density tissues have relatively high conductivity and permittivity. On the other hand, low-water-content tissue, such as adipose or fat, has comparatively low permittivity and conductivity values. As the frequency increases, it was found that the permittivity decreases and the conductivity increases.

<table>
<thead>
<tr>
<th>Organs</th>
<th>Conductivity Range (S/m)</th>
<th>Permittivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain (Grey Matter)</td>
<td>1.0e-1 – 1.0e+1</td>
<td>1.0e+2 – 1.0e+6</td>
</tr>
<tr>
<td>Heart Muscle</td>
<td>1.0e-1 – 1.0e+2</td>
<td>1.0e+2 – 1.0e+7</td>
</tr>
<tr>
<td>Kidney (Cortex)</td>
<td>1.0e-1 – 1.0e+2</td>
<td>1.0e+2 – 1.0e+8</td>
</tr>
<tr>
<td>Liver</td>
<td>1.0e-2 – 1.0e+1</td>
<td>1.0e+1 – 1.0e+7</td>
</tr>
<tr>
<td>Lung</td>
<td>1.0e-2 – 1.0e+1</td>
<td>1.0e+1 – 1.2e+7</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.0e-1 – 1.2e+1</td>
<td>1.2e+1 – 1.5e+7</td>
</tr>
<tr>
<td>Muscle (along)</td>
<td>1.0e-1 – 1.0e+1</td>
<td>1.0e+1 – 1.0e+8</td>
</tr>
<tr>
<td>Uterus</td>
<td>1.0e-1 – 1.2e+1</td>
<td>1.2e+2 – 1.2e+9</td>
</tr>
<tr>
<td>Skin</td>
<td>1.2e-4 – 1.0e+1</td>
<td>1.0e+1 – 1.0e+5</td>
</tr>
<tr>
<td>Adipose</td>
<td>1.0e-2 – 2.0e+1</td>
<td>2.0e+1 – 1.0e+7</td>
</tr>
<tr>
<td>Cartilage</td>
<td>2.0e-1 – 2.0e+0</td>
<td>1.0e+1 – 1.1e+3</td>
</tr>
</tbody>
</table>

The dielectric properties of the polymer gel samples were measured using a dielectric Win DETA 5.64 (Novocontrol Technologies, Germany). The samples were cut to have flat surfaces and placed between two gold plates to obtain accurate results. The gold plates were placed in the dielectric equipment between two electrodes and secured by tightening the
sample mounting screw. The dielectric properties were measured over a frequency range of $1.0 \times 10^{-1} – 3.0 \times 10^5$ Hz. [117]

### 3.3.3.4 Imaging Properties of carrageenan-based polymer gel

An MRI technician at Sunnybrook Hospital (Toronto, Canada) assisted the acquisition of the imaging properties of the polymer gel samples. We examined the stability of the properties over six weeks and assessed the viability of the polymer gels as MRI phantom materials. The prepared samples in glass test tubes were arranged on a Styrofoam tube rack. The $T_1$ and $T_2$ relaxation times of the samples were obtained using a GE 3 Tesla MRI system with a 32-channel head coil. The sample was placed inside the head coil of the MRI and aligned with the guideline. Inversion recovery was applied to measure the $T_1$ value, and spin echo was used to determine the $T_2$ sequence. To measure the $T_1$ relaxation time, repetition time ($T_R$) values of 2400, 1700, 1000, 500, 300, 150, 90, and 50 ms were used. The $T_2$ relaxation time was measured using echo time ($T_E$) values of 10, 20, 30, 50, 75, 100, 150, 200, and 300 ms and $T_R$ of 2500 ms. The image resolution was 256×256 over a 16 cm field of view with a pixel size of 0.625 mm and 5 mm slice thickness. After the MRI images of the polymer samples had been obtained, a MATLAB algorithm was used to analyze the $T_1$ and $T_2$ values for every pixel of an image and store them in a large matrix form. For this particular experiment, a nonlinear least-squares fit equation was used to fit the test data to a high-order polynomial. The following equations were used to obtain the $T_1$ and $T_2$ signal values for the calculation:

\[
S = M_0 \left(1 - \exp \left(-\frac{T_R}{T_1}\right)\right) \tag{1}
\]

\[
S = M_0 \exp \left(-\frac{T_E}{T_2}\right) \tag{2}
\]

where $S$ is the signal intensity and $M_0$ is the initial magnetization. [30] A set of eight different samples was stored in a low-temperature refrigerator for six weeks and then tested under MRI to examine the stability of the $T_1$ and $T_2$ values of the polymer gels over time. SNRs of 435–850 were calculated.

Computed tomography measurements were performed using wide-volume CT (Toshiba 320 MDCT Aquilion ONE, Toshiba Medical Systems, Japan). The samples were aligned and
attached to a template and placed perpendicular on the CT scanning platform. The scanning conditions were set to use 0.5 mm detector collimation, 0.5 s gantry rotation time, 50 mA nominal tube current, and tube potentials of 80, 100, 120, and 135 kVp. The images were reconstructed using a single filter kernel with 1 mm sections at 0.5 mm intervals.

3.3.3.5 Polymer Gel Liver Phantom with Lesion Particles

Following the fabrication of the polymer gels, a liver phantom of 1 L volume was constructed with embedded lesions, as illustrated in Fig. 3.1. First, spherical lesion particles with diameters of 1–10 mm were pre-fabricated with different agar and carrageenan concentrations. The molten polymer gel solution was extracted with a 10 mL syringe and dropped into chilled oil. The chilled oil was composed of olive and castor oils to obtain high viscosity, thus allowing the polymer gel particles to slowly sink to the bottom. As the particles sink to the bottom of the oil beaker, they retain their spherical shape. The size of the lesion particles can be varied according to the force exerted on the syringe. The size of the spherical inclusions was measured after fabrication.

![Figure 3.1. Schematic diagram of polymer gel lesion and phantom fabrication](image)

To mimic the liver tissue, 1 L of polymer gel solution was prepared. A small amount of NaN₃ was added as antiseptic material to enhance the quality of the phantom and prevent fungus forming over time. A layer of polymer gel was poured into a plastic container of size 10 cm × 10 cm × 10 cm, and this was placed in a vacuum chamber to remove air bubbles and then into the freezer to quickly solidify. When the solution had solidified, pre-fabricated lesions of different sizes were spread on top of the polymer gel layer. Another layer of molten gel was
slowly poured to avoid melting or disrupting the location of the lesions. Once four layers of polymer gel had been stacked with lesion particles, a final layer was poured on top to cover the phantom. The lesion placement and final phantom is illustrated in Fig. 3.2. The phantom was stored in the refrigerator until it was ready to be imaged under MRI.

Figure 3.2. (a) Spherical lesion particle placement and (b) a fabricated phantom with embedded lesion particles

3.4 Results and Discussion

3.4.1 Chemical Properties of carrageenan-based polymer gel

The compositions of the carrageenan gel samples were examined by FTIR, as shown in Fig. 3.3. The samples exhibited similar IR peaks, such as the strong broad band at 3150–3350 cm\(^{-1}\), which corresponds to the O-H stretch, and a peak at 1640 cm\(^{-1}\), which indicated the C=O stretch bond. The broad peaks reflect the high water content of the samples. The height of the peak increased with increasing water content.

Figure 3.3. FTIR graph of carrageenan-based polymer gel
3.4.2 Mechanical Properties of carrageenan-based polymer gel

Changes in the density of the gel samples with different agar and carrageenan concentrations were observed over six weeks to establish the density–time relationship. Samples subjected to density measurements were cut into cylindrical disk shapes and brought to room temperature for 30 min. The volume and mass of each sample were then measured to calculate the density. As shown in Fig. 3.4, there was no distinct pattern in the density changes. However, the density fluctuation was more pronounced in samples with higher water content and lower gelling agent concentrations. Density changes occur when water vapor is saturated and expelled to the wall of the glass container, or when the water droplets accumulate on the wall of the glass container and condense back into the gel mass. The air temperature and humidity of the refrigerator were kept constant to minimize the water-release cycle. Thus, samples with higher water content will be subject to more dynamic density changes. The densities of samples 7 and 8, which respectively contained 1.5 and 1.0 g of carrageenan together with 1.5 g of agar, exhibited greater fluctuations. The average fluctuation of sample 7 was 17.7%, whereas that of sample 8 was 10.3%. To make the densities of the samples similar to that of human tissue (1.03 g/cm³), the agar and carrageenan concentrations can be varied as shown in Fig. 3.4, where the densities of the different samples can be observed to match that of human tissue at different times.

![Figure. 3.4 Density changes in the carrageenan-based gel samples](image-url)
The mechanical properties of the elastic modulus and compressive strength were measured to determine the compressive force that the gel samples could withstand while retaining their shape. A cylindrical disk was cut from the sample in similar fashion to the density measurements, and the elastic modulus was measured once per week over a six-week period. Changes were observed in all samples, although the magnitude of this change varied. As shown in Fig. 3.5, the modulus of samples with different agar concentrations fluctuated more dramatically than that of samples with different carrageenan concentrations. For example, the modulus of sample 4 initially increased by 25% from 0.51 to 0.64 MPa, but dropped back to 0.45 MPa after three weeks. The modulus changes continuously with time, and the fluctuation of the modulus values may be due to inconsistencies in the water content. Although the samples were completely sealed with Parafilm and the container cap, they continually release and absorb water vapor within the glass container. Thus, the rigidity of each sample could change. Similar trends in the modulus were observed in samples with different concentrations. It can be seen from Fig. 3.5 that samples with lower concentrations of carrageenan, which acts as a gelling agent, had lower modulus values of about 0.1–0.4 MPa. The elastic modulus of normal liver tissue reported in the literature ranges from 6.4–60 kPa. [118]. Comparing the modulus values of liver tissue, the elastic modulus obtained from carrageenan samples ranged from 0.13–0.66 MPa. The results are two orders of magnitude higher than that of normal human liver tissue. Considering the wide range of modulus values that can be achieved by varying the carrageenan and agar content, polymer gel can be tailored to match the modulus of human liver tissue.
Figure 3.5 Changes in elastic modulus of eight polymer gel samples over six weeks: (a) Samples with various agar concentrations (0.0–1.5 wt%); (b) Samples with various carrageenan concentrations (1.0–3.0 wt%)

Similarly, the compressive stress at maximum load of the samples, as determined by the Instron compression test machine, exhibits some variations. As can be seen from Fig. 3.6, the compressive stresses were highest for sample 1 (0.181 MPa) and lowest for sample 8 (151 kPa). This is understandable, as sample 1 had the highest carrageenan concentration, whereas sample 8 had the lowest. Furthermore, the compressive strength fluctuated over time. In the case of sample 1, the strength initially increased by 42% from 0.128 to 0.181 MPa, and then
decreased back to 0.171 MPa after six weeks. The percentage change in the compressive strength was greatest for samples 1 and 8 (42% and 53%, respectively), which had the highest water content.

![Figure 3.6 Compressive strength of eight polymer gel samples over six weeks](image)

3.4.3 Dielectric Properties of carrageenan-based polymer gel

The conductivity (σ) and permittivity (ε) of soft human tissue can take a wide range of values and vary with the test frequency. The dielectric properties of phantom materials need to be similar to those of human tissue, because the homogeneity of the magnetic field depends on the wavelengths of the tissue and air. The wavelength of an RF field in air is about 468 cm⁻¹, but is much higher in human tissue. If the wavelength of the RF field were different from that in human tissue, it would create constructive or destructive interference with the transmitted field, resulting in regional brightening or signal loss. [71] Thus, to achieve optimal calibration, the dielectric properties of polymer gels should mimic those of human tissue. The dielectric properties of the polymer gel samples were measured using a dielectric Win DETA 5.64 (Novocontrol Technologies) over a frequency range of 1.0×10²–3.0×10⁵ Hz. Normally, the dielectric test of human tissue is conducted using frequencies between 915 MHz and 2.45 GHz,[71] which is beyond the range of the machine. However, the results of the present test show that the conductivity increased and the permittivity decreased with increasing frequency. As shown in Fig. 3.7, the conductivity and permittivity of sample 4 exhibited no significant
changes over six weeks.

Figure 3.7 (a) Permittivity and (b) conductivity of sample 4 over six weeks
3.4.4 Imaging Properties of carrageenan-based polymer gel

The $T_1$ and $T_2$ relaxation times of the samples were determined using a GE 3.0 Tesla head MRI system, and their variation with time was investigated. The $T_1$ and $T_2$ maps of the samples are shown in Fig. 3.8.

![T1 map](image1) ![T2 map](image2)

Figure 3.8 $T_1$ and $T_2$ maps of polymer gel samples at week 3, generated by a MATLAB algorithm

Figure 3.9 compares the effects of the agar, carrageenan, and Gd-DTPA concentrations on the relaxation times. Theoretically, carrageenan should not have any effect on the relaxation times, because it was only used as a gelling agent. Higher concentrations of agar, which was used as a $T_2$ modifier, should give lower $T_2$ values. Similarly, Gd-DTPA, which was used as a $T_1$ modifier, was expected to suppress the $T_1$ values of the samples. The $T_1$ and $T_2$ values varied among the samples according to the different carrageenan and agar concentrations. For sample 5, the $T_1$ values ranged from 186.56–232.41 ms, and the $T_2$ values were 72.43–88.77 ms. As expected, the $T_2$ values for samples 1 and 4 were different. The $T_2$ values for samples 6, 7, and 8 were similar, whereas that for sample 5 was much lower at 78 ms. As each sample had the same GdCl$_3$ concentration, the $T_1$ value was expected to remain constant; however, it varied among the samples. These results indicate that the agar and carrageenan concentrations can be used to further modify the $T_1$ and $T_2$ values. Therefore, further study on the effect of the constituent concentrations on the $T_1$ and $T_2$ values should be pursued to achieve polymer gels that mimic the $T_1$ and $T_2$ values of human tissue and lesion particles given in Table 3.3. [68, 119-121]
Figure. 3.9 T₁ and T₂ relaxation times of polymer gel samples after five weeks.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>T₁ (ms)</th>
<th>T₂ (ms)</th>
<th>Tissue</th>
<th>T₁ (ms)</th>
<th>T₂ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>812±64</td>
<td>42±3</td>
<td>White matter</td>
<td>1084±45</td>
<td>69±3</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>1412±13</td>
<td>50±4</td>
<td>Gray matter</td>
<td>1820±114</td>
<td>99±7</td>
</tr>
<tr>
<td>Heart</td>
<td>1471±31</td>
<td>47±11</td>
<td>Optic nerve</td>
<td>1083±39</td>
<td>78±5</td>
</tr>
<tr>
<td>Kidney</td>
<td>1194±27</td>
<td>56±4</td>
<td>Spinal cord</td>
<td>993±47</td>
<td>78±2</td>
</tr>
<tr>
<td>Cartilage 0°</td>
<td>1168±18</td>
<td>27±3</td>
<td>Blood</td>
<td>1932±85</td>
<td>275±50</td>
</tr>
<tr>
<td>Cartilage 55°</td>
<td>1156±10</td>
<td>43±2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Several studies conducted on other polymer gel phantoms have not revealed significant changes in the T₁ and T₂ relaxation times when the phantoms were stored in tightly sealed containers. [122] Thus, further time-sensitivity studies of T₁ and T₂ should be conducted using more reliable storage systems.

The T₁ and T₂ relaxation times of sample 2 over six weeks are shown in Fig. 3.10. T₁ changed by 29% (from 204.27 to 286.8 ms) over three weeks. However, T₂ changed by 23% (from 91.09 to 119.04 ms) in the first two weeks. These changes are notable because any inconsistency in the relaxation times over a phantom’s lifetime could result in inaccurate MRI calibration.
A CT scan was also performed using a clinical Toshiba One Aquilion CT scanner to confirm the HU values of the carrageenan gel samples. The CT numbers of gel samples 3–6 at 120 kVp are illustrated in Fig. 3.11. The values varied from 24.6–57.5 HU. There is no correlation between the carrageenan and agar content and the HU values. These values correspond to the value of kidney, muscle, blood, and liver. Tailoring the concentrations of carrageenan, agar, and GdCl₃ would enable samples to be produced for specific parts of organs.

Figure. 3.10 $T_1$ and $T_2$ relaxation times of sample 2 over six weeks
3.4.5 Polymer Gel Liver Phantom with Lesion Particles

A 1-L volume phantom was constructed layer by layer as described in Sec. 3.2.3.5. Magnetic resonance images were taken, and the $T_1$ and $T_2$ values were measured for both the phantom and lesions, as shown in Fig. 3.12. We have successfully fabricated a phantom with embedded lesion particles located randomly between the layers. The $T_1$ and $T_2$ values of the lesions were obtained using a MATLAB program. The $T_1$ values ranged from 411–766 ms and the $T_2$ values were 102–209 ms. Compared with the relaxation values in Table 3.3, these results are closer to normal liver tissue. The relaxation times of liver cyst and hemangioma can be obtained by changing the concentrations of carrageenan, agar, and Gd-DTPA in the lesion solution. Despite the success of our liver phantom with lesion particles, several
obstacles were encountered during the imaging. For example, the stacked layers of polymer gel for lesion placement caused bubbles to form around the lesion particles. After the lesion particles were placed on the first layer, a heated gel solution was poured on top of a solidified layer to create a second layer. During this process, the heated solution that is poured on the first layer could melt and shift the location of the lesion particles, resulting in air pockets that appear as artifacts on the images. On the $T_1$ map, the edges of the lesions are blurry, which is possibly due to the diffusion of paramagnetic ions or poor SNR related to problems encountered during imaging.

![T2 T1 19° flip,T1](image)

Figure. 3.12 $T_1$ and $T_2$ maps of the phantom layer with lesion particles

### 3.5 Summary

With improvements in medical imaging technology, there is an increasing need for new phantoms to be developed for calibration and training purposes. Although studies have been conducted on polymer-based phantom materials, the viability and durability of these phantoms are yet to be investigated. In this study, carrageenan-based polymer gel samples were fabricated and their chemical, mechanical, dielectric, and imaging properties were examined to assess their similarity to human tissue. A six-week stability test was also conducted on each property. Mechanical properties such as the density and elastic modulus fluctuated over time with no specific pattern, which is potentially due to the expulsion and absorption of water by the samples. The dielectric properties of the samples, namely the conductivity and permittivity, did not change with time. The imaging properties of the samples were also examined, and the $T_1$ and $T_2$ relaxation times were observed over six weeks, and changes of 23–29% were observed. For accurate calibration over the shelf life of a phantom, the fluctuation in these properties should be minimized. Although these changes
in properties have no direct effects in terms of calibration accuracy and clinical relevance, they do have an indirect impact on the performance of a phantom. The shelf life of a phantom should be at least six months, and ideally up to three years. If the physical, mechanical, and imaging properties change significantly over a six-week period, they can be projected to change even more over the longer period of the phantom’s shelf life. Each property is of different importance, with the mechanical and physical properties being more important as they may change the shape or rigidity of the phantom over time. The most significant factor is the imaging performance, since this is related to the phantom’s calibration accuracy and clinical relevance. Since our aim in this study is to mimic the parameters of liver and lesion particles to provide a standard value for comparison to human tissue, it is important to retain stability. There is no standard guideline that defines an acceptable degree of variation. However, since the $T_1$ and $T_2$ relaxation times found in the literature [33, 34] have standard deviations of 45 ms for $T_1$ and 4.4 ms for $T_2$, the degree of variation in our measurements should be within this range. The difference in relaxation times in sample 2 demonstrates a variation of 84 ms for $T_1$ and 28 ms for $T_2$. These are much larger fluctuations over time than the measurement range of human tissue at 3 T. Therefore, we can conclude that the change in relaxation values is not within an acceptable range, and thus, the carrageenan or agar gel does not perform as a stable material for the construction of phantoms. CT numbers were also obtained at 120 kVp, and the values were consistent with those of human tissue. However, the long-term stability of the CT numbers was not validated.

A carrageenan gel phantom with embedded lesion particles was fabricated to simulate human liver tissue and imaged under MRI. The $T_1$ and $T_2$ maps demonstrate the potential of carrageenan gel as an MRI phantom material, and the ability of lesion particles to represent various $T_1$ and $T_2$ relaxation times. However, several challenges remain in the production procedure to reduce the generation of air bubbles and diffusion of paramagnetic ions.
Chapter 4

4 Novel Development of Organic and Inorganic Aerogels for Medical Imaging Phantom Application

4.1 Introduction
This chapter studies a polymer-reinforced silica aerogel and a cross-linked cellulose aerogel. The unique properties of aerogels, such as low density, small pore size, mesoporosity, large surface area, and excellent thermal insulation, are suited to many applications. However, aerogels have not been investigated for medical phantom applications. This chapter emphasizes the applicability of organic and inorganic aerogels to medical imaging phantoms by examining their mechanical and imaging properties.

4.2 Motivation and Objectives
The study described in Chapter 3 found that agar or carrageenan water-based gels have long-term stability issues. These issues are mainly due to a high water content—water-based gels are susceptible to changes over time because of the continuous water expulsion and absorption cycles. As medical imaging phantoms serve as a calibration medium to provide standard testing, the stability of the phantoms is crucial. Therefore, there is a need to develop a solid material that can be imaged under MRI with $T_1$ and $T_2$ values and CT numbers that are similar to those of human tissue. In this study, we investigate the potential of aerogels to be used as a non-water-based MR/CT-compatible phantom material.

Aerogels are known for their high specific surface area (500–1200 m$^2$/g), small pore size, ultralow density (0.003–0.5 g/cm$^3$), low dielectric permittivity (1.0–2.0), and low thermal conductivity (0.005–0.1 W/(m K)). These unique properties suggest promising applications in catalysts, photography, electronics, antibacterial, and optical applications. [123] Aerogels can be synthesized from a number of different precursors including tetraethyl orthosilicate (TEOS), certain metal oxides such as Gd$_2$O$_3$, cellulose, and various polymers, which result in aerogels with very different properties. [124-127] In this study, silica and cellulose aerogels were examined. Aerogels are non-water-based materials that can serve as water reservoirs...
similar to conventional aqueous phantoms. The advantage of an aerogel is its long shelf-life and its ability to be stored in a dried state. Moreover, as the water content in aerogels is low, they do not experience property fluctuations caused by water. In addition, since aerogels use different contrast agent solutions, their imaging properties can be tailored easily. However, the fabrication of aerogels is costly and time-consuming.

In this study, the objective is to fabricate a silica aerogel and cellulose aerogel and verify whether these non-water-based materials have the potential to be used to construct phantoms. Silica aerogels were cross-linked with di-isocyanate, a polyurethane group that bonds covalently to the surface of the aerogel, to enhance their mechanical stability by widening the neck regions with the minimum loss of porosity. A cellulose aerogel was chosen because it has a low density and relatively high strength and ductility compared to inorganic or polymeric aerogels. To obtain MRI/CT-compatible material, each aerogel was incorporated with different modifiers. Dry silica aerogel was fabricated and immersed in a Gd-DTPA doped solution of different concentrations before imaging. Cellulose aerogel was immersed in a solution of superparamagnetic iron oxide nanoparticles (SPIONs) before subject to supercritical drying. These SPIONs have been successfully used as contrast agents for clinical applications. [128-130]

4.3 Experimental Setup

4.3.1 Experimental Materials

For preparing the silica aerogel, tetramethyl orthosilicate (TMOS) and 3-aminopropyl triethoxysilane (APTES) were used as the silica precursor and base catalyst, respectively. Both the materials were purchased from Sigma Aldrich. Acetonitrile (CH$_3$CN) was used as a solvent and was obtained from EMD Chemical Inc. The polymer cross-linker, Desmodur N-3200, which is composed of 1,6-hexamethylene di-isocyanate (HDI)-based oligomers, was donated by Bayer Corporation. The Gd-DTPA Omniscan gadodiamide injection ISP 287 mg.ml (0.5 mmol/ml) from GE Healthcare was used as a contrast agent.

The cellulose aerogel was prepared with Sigmacell cellulose, urea, and sodium hydroxide solution, which were purchased from Sigma Aldrich. Cobalt (II) nitrate hexahydrate (Co(NO$_3$)$_2$·6H$_2$O) and iron (II) nitrate nonahydrate (Fe(NO$_3$)$_3$·9H$_2$O) for the superparamagnetic ions were also purchased from Sigma Aldrich.
4.3.2 Fabrication Procedure

4.3.2.1 Fabrication of Silica Aerogel

The native silica aerogel was prepared via a sol-gel process by mixing two separate solutions, A and B. In solution A, both TMOS and APTES (Sigma Aldrich) were mixed together with CH$_3$CN to obtain a 2.0 mol/L total silane. Solution B was prepared by mixing equal amounts of CH$_3$CN and water to achieve an H$_2$O content of 10.0 mol/L. Two different H$_2$O concentrations (10.0 and 15.0 mol/L) were used to investigate the effect of water on the properties of silica aerogels. Prior to mixing, the solutions A and B were cooled in a dry ice/acetone bath at −78 °C to avoid premature gelation. After cooling, the solutions were mixed and stirred vigorously in a parafilm-capped beaker. Immediately after mixing, the mixture was poured into cylindrical molds (14 mL centrifuge test tubes, Falcon). The molds were sealed with parafilm. Gelation occurred within 1–2 min while the solution was still cold. The gels were allowed to age for 24 h. The wet gels were carefully removed from the molds and washed with CH$_3$CN three times every 24 h. Owing to their internal structure, silica aerogels are susceptible to damage even by small external forces. To strengthen the silica aerogel framework, the wet gels were cross-linked with di-isocyanate by immersion in baths of di-isocyanate in acetonitrile (0, 20, 40, and 50 wt%) and were oven cured at 71 °C for 72 h.

4.3.2.2 Fabrication and Cross-linking of Cellulose Aerogel

The cellulose hydrogel was synthesized by dissolving cellulose powder (Sigmacell cellulose) and urea in a sodium hydroxide solution. Various concentrations of cellulose (5 wt%, 7.5 wt%, 10 wt%) were dispersed in an aqueous solution of sodium hydroxide at room temperature. The solution was then frozen for 30 min and thawed at room temperature. The resultant cellulose solution was centrifuged for 10 min to prevent bubble formation in the viscous solution and cast in the mold. The sample solution was then immersed in ethanol to coagulate and regenerated for 4 h. The hydrogel was then thoroughly washed in deionized water to remove any residual chemicals.

To cross-link the cellulose hydrogel with superparamagnetic ions, the hydrogel samples were immersed in a freshly prepared aqueous solution containing cobalt (II) nitrate hexahydrate (Co(NO$_3$)$_2$•6H$_2$O) and iron (II) nitrate nonahydrate (Fe(NO$_3$)$_3$•9H$_2$O) for 24 h. The cellulose aerogel was cross-linked with SPIONs rather than with Gd-DTPA because SPIONs can adhere better to the nanofibril structure of cellulose aerogels. The molar ratio of
the cobalt and iron ions remained constant at [Fe]/[Co] = 2. Three concentrations of superparamagnetic ions (0.06, 0.12, and 0.24 mol/L) were used. The cellulose hydrogel was immersed and stirred in metal precursor solution for three days to ensure a homogeneous distribution throughout the cellulose network. The hydrogel was transferred into an aqueous NaOH solution (2 mol/L). The color of the sample changed immediately once it was immersed in NaOH solution. After the cellulose hydrogel had been cross-linked with CoFe$_2$O$_4$ complex, it was transferred to an oven at 90°C for 4 h to promote further transformation of soluble iron/cobalt hydroxides to insoluble oxyhydroxide complexes. The hydrogel was then washed in NaOH solution at 90°C for 16 h to remove any unreacted residue.

After the fabrication of both the silica and cellulose hydrogels, they were subjected to supercritical drying in a temperature-controlled pressure chamber for conversion to aerogels. The pressure was set at approximately 1480 psi for 10 h. During this interval, the pressure was released and reapplied every 2 h (total 5 cycles). After 10 h of pressurizing with CO$_2$ gas, the temperature was increased from 25 to 45 °C, which caused the pressure to increase to approximately 3200 psi. At this point, the CO$_2$ gas reached its supercritical state. The gas was slowly vented and the dry aerogels (silica and cellulose) were formed. In order to confirm the reproducibility of the synthesis procedure reported here, each sample was fabricated three times.

### 4.3.3 Characterization

Several characteristics tests were performed to evaluate the structural, chemical, and imaging properties of the silica and cellulose aerogels. Microstructural analysis was performed using two scanning electron microscopes (SEM): (Hitachi S-5200; Hitachi Ltd., Tokyo, Japan) and (FEI QUANTA FEG 250 ESEM; FEI, Hillsboro, OR, USA). The sample surfaces were carbon coated to provide electrical conductivity. The chemical properties were analyzed by Fourier transform infrared (FTIR) spectrometry (PerkinElmer; PerkinElmer Inc., Walthan, MA, USA) for the silica aerogel and wide-angle X-ray diffraction (XRD; Rigaku MiniFlex 600; Rigaku Corp, Tokyo, Japan) for the cellulose aerogel. The surface area ($S_{BET}$) was calculated from the N$_2$ adsorption isotherms by Brunauer-Emmett-Teller (BET) analysis of the amount of gas adsorbed at P/P$_0$ in the range of 0.05–0.3. For FTIR, the samples were powdered and mixed with spectral-grade potassium bromide (KBr) for forming translucent
pelletized discs. The discs were then placed into the FTIR machine and the IR spectra were recorded in the 4000–400 cm\(^{-1}\) region at room temperature. For XRD, Cu K\(\alpha\) radiation at 40 kV and 15 mA was used and the diffraction patterns were recorded for 20 values ranging from 5 to 80°. The specific surface area (SSA) was determined using the BET method from the N\(_2\) adsorption isotherm. Magnetic resonance imaging was performed at Sunnybrook Hospital to acquire the \(T_1\) and \(T_2\) relaxation times using a GE Discover MR750 3.0T MRI system (GE Healthcare) with a 32-channel head coil. After obtaining MRI images, a MATLAB algorithm was used to analyze the \(T_1\) and \(T_2\) values. Computed tomography measurements were also performed at Sunnybrook Hospital using a Philips CT system (Philips Healthcare, USA).

4.4 Results and Discussion
The silica aerogels with varying di-isocyanate concentrations are shown in Fig. 4.1. Despite their unique properties, fragility and environmental sensitivity restrict the use of monolithic silica aerogels. Fracture of silica aerogels occurs mainly because of their ball-like particles that are accumulated in the neck regions and create a "pearl necklace-like" structure with large voids\(^{17-19}\). Fracture may also occur at the interface of these particles when an external load is applied. Since the structural stability of imaging phantoms is important, we investigated cross-linking of silica aerogels with di-isocyanate. Polyurethane group of di-isocyanate bonds covalently to the surface of the silica aerogel and enhances its mechanical stability by widening the neck regions with a minimum loss of porosity\(^{21,22}\).

As described above, non-cross-linked silica aerogels have a translucent glassy appearance with small cracks inside the structure. They are susceptible to damage by small external forces and can be crumbled into pieces with a force exerted by hands. It is hypothesized that when liquid in a porous material is removed by evaporation, the capillary stress in the pores causes the structure of the pore network to collapse and shrink. Since the pore network in a native silica aerogel is not reinforced, the pore walls are easily broken and lose their integrity. Compression from a tightly sealed pressure chamber cap and highly pressurized gas can also cause cracks. On the other hand, the di-isocyanate cross-linked aerogels were opaque and became dull with the increasing polymer concentrations. In comparison with the cross-linked aerogels, the native aerogels showed a considerable shrinkage. Similar phenomena were observed for the cellulose aerogels as shown in Fig. 4.2. Unlike the wet aerogels, the dried
cellulose aerogels shrank and sometimes fractured upon drying. The color of the cellulose aerogel became darker as the concentration of superparamagnetic ions increased.

We faced a few challenges during the fabrication of the silica and cellulose aerogels. First, the fabrication of an aerogel sample was a lengthy procedure, which required approximately 2 weeks, and the final sample was sensitive to changes in various parameters such as temperature, time, and concentrations of contrast agents. Also, the aerogels were susceptible to volume shrinkage after the supercritical drying procedure, which made it difficult to control the shape and size of the final aerogel sample.

Figure 4.1 Silica aerogels with increasing concentrations of di-isocyanate

Figure 4.2 Cellulose aerogels with increasing in CoFe$_2$O$_4$ concentrations
4.4.1 Structural and Morphological Properties of Aerogels

High-resolution scanning electron microscopy (SEM) was used to observe the microstructural morphology of the non-cross-linked and cross-linked aerogels. Figure 4.3(a) shows the non-cross-linked aerogel, in which primary particles are clustered together to form secondary particles arranged in a string-of-pearls structure. The bonding between these secondary particles is weak, and the structure is easily broken when force is applied. Di-isocyanate cross-linking reinforces the bonding between the secondary particles. The di-isocyanate polymer accumulates within the neck regions of the secondary particles, which become wider, while the primary particles remain in a mesoporous structure. The SEM image of the 20 wt% cross-linked aerogel in Fig. 4.3(b) shows the secondary particles connected by bridges that improve the structure of the aerogel and allow it to withstand greater forces. The neck region between the secondary particles of a 40 wt% cross-linked silica aerogel is shown in Fig. 4.3(c). At this concentration, the region became wider and fused. This strengthened the structure, but significantly decreased the amount of void space, while simultaneously increasing the bulk density. The BET surface area analysis to examine the effects of cross-linking on the total surface area (SA) showed that SA decreased from 417.6 m²/g to 104.0 m²/g when the aerogel was cross-linked with 20 wt% di-isocyanate. This is thought to be due to the decrease in the amount of void space as the polymer accumulated in the neck regions of the secondary particles during cross-linking.

![SEM images of non-cross-linked and cross-linked silica aerogels](image)

Figure 4.3 SEM images of non-cross-linked and cross-linked silica aerogels (SA, surface area; wt% indicates cross-linking polymer [di-isocyanate] concentration)
Figure 4.4 shows SEM images of non-cross-linked and cross-linked cellulose aerogels prepared by the in situ synthesis of CoFe$_2$O$_4$ nanoparticles in the cellulose matrix. The non-cross-linked cellulose aerogels formed a long and entangled nanofibril network of cellulose. As the cellulose content increased, it was found that branching occurred in the cellulose nanofibril network, which resulted in a dendritic structure (Fig. 4.4(a)–(c)). It can also be observed that the CoFe$_2$O$_4$ nanoparticles are located on the nanofibril surfaces. As the cellulose aerogel was cross-linked with higher concentrations of CoFe$_2$O$_4$ complex, more superparamagnetic nanoparticles were attached to the cellulose nanofibril network (Fig. 4.4(d)–(f)). The surface area, $S_{\text{BET}}$, was inferred from the N$_2$ adsorption isotherms via the BET analysis of the amount of gas adsorbed at P/P$_0$ values of 0.05–0.3. The surface area of pristine cellulose aerogel was 180 m$^2$/g, and this increased slightly to 214, 137, and 243 m$^2$/g with an increase in the nanoparticle content. Nanoparticles bind to the cellulose matrix and by incorporating a higher nanoparticle content, the total surface area of the nanoparticles increases. However, the pore volume and porosity decrease with increasing CoFe$_2$O$_4$ content. [129].

Figure 4.4 (a)-(c) SEM images of non-cross-linked cellulose aerogel with increasing cellulose content; (d)-(f) cross-linked cellulose aerogel with higher content of superparamagnetic nanoparticles
4.4.2 Chemical Properties of Silica and Cellulose Aerogels

The FTIR spectra for non-cross-linked and cross-linked aerogels (20, 40, and 50 wt% polymer concentrations) are shown in Fig. 4.5. The 1,6-hexamethylene di-isocyanate known as HDI is a major chemical component of Bayer’s Desmodur N3200. In the present study, we found that adding this polymer rendered a slight change in the infrared absorption performance. The spectra of non-cross-linked and cross-linked aerogels had similar IR peaks. The absorption band around 3500–3300 cm\(^{-1}\) is consistent with the presence of a hydroxyl group with hydrogen bonding between water molecules. A broad absorption band around 1065–1105 cm\(^{-1}\) is due to the asymmetric stretching vibration of the Si-O-Si bonds. The absorption band at 692 cm\(^{-1}\) represents the Si-O functional groups, and the additional peaks on the cross-linked aerogel spectrum, including the broad band near 1740 cm\(^{-1}\) and another band around 1690 cm\(^{-1}\), correspond to a carbonyl stretch in the diazetidinedione group of the N3200 and the carbonyl stretch of the silica-isocyanate composite. The polyurethane is incorporated into the silica network via a hydrogen-bonding interaction between polyurethane and siloxane groups. [131, 132]

![Figure 4.5 FTIR spectroscopy of silica aerogels cross-linked with varying concentrations of di-isocyanate](image)

Figure 4.6 shows the XRD pattern of the non-cross-linked and cross-linked aerogels. The diffraction peaks at \(\theta = 20.1^\circ\) and \(21.9^\circ\) are believed to represent the (1 0 \(\overline{1}\)), and (0 2 1)
planes of cellulose II crystalline, respectively. [92] In addition to the cellulose II peaks, there are diffraction peaks that confirm the presence of CoFe$_2$O$_4$, especially at $2\theta = 35^\circ$ (powder diffraction file, JCPDS card no. 79-1744). The diffraction peaks are considerably broad, which indicates the low crystallinity or very small crystalline size of the cellulose matrix. The electron-rich oxygen atoms in the cellulose matrix attract electropositive metal cations. The Co$^{2+}$ and Fe$^{3+}$ ions present at the surface of the cellulose nanofibrils ultimately led to the nucleation of CoFe$_2$O$_4$ and prevented the growth of these nanoparticles. [134]

![Figure 4.6 XRD pattern of non cross-linked cellulose Aerogel and cross-linked with CoFe$_2$O$_4$](image)

4.4.3 Imaging Properties of Silica and Cellulose Aerogels

The potential usefulness of the silica aerogels as a material for multimodal imaging phantoms was examined by determining the $T_1$ and $T_2$ relaxation times in MR imaging and the CT numbers. First, silica aerogels cross-linked with different di-isocyanate concentrations were immersed in Gd-DTPA solution to enhance the MR imaging. The 20 wt% di-isocyanate cross-linked aerogel was then immersed in solutions containing 0.085, 0.17, and 0.34 µL/mL Gd-DTPA to study the effects of varying concentrations of contrast material. The non-cross-linked silica aerogel was not used because of its extensive shrinkage upon supercritical drying. Although it was difficult to visualize the nanoporous structure of the aerogels, we were able to obtain values of 614–2983.8 ms for $T_1$ and 9.2–690.6 ms for $T_2$, as illustrated in
Fig. 4.7. The $T_1$ values decreased slightly as the di-isocyanate concentration increased from 20–50 wt%, whereas the $T_2$ values increased markedly, from 334–690 ms. The effect of polymer density on $T_2$ values has not previously been studied, but $T_2$ values in human tissues under 3T imaging are known to increase with density or viscosity (Table 4.1). [135] To study the effect of Gd-DTPA, the silica aerogel sample with 20 wt% di-isocayante was chosen since it provided the lowest $T_2$ value. As shown in Fig. 4.7(b), at a known and constant value of $T_2$, the Gd-DTPA concentration increased with a decrease in the $T_1$ value. These values mimicked those of liver tissue, breast fibroadenoma, and bone marrow (see Table 4.1). Although cross-linking with di-isocyanate enhanced the mechanical stability of the silica aerogel, it caused some deviation in the $T_1$ and $T_2$ relaxation times from those of human tissue. For instance, the values for human lung are reported to be $T_1 = 1013 \pm 150$ ms and $T_2^* = 1498 \pm 393$. [136] By adjusting the concentrations of di-isocyanate and Gd-DTPA, we should be able to match the specific human tissue values, including in lung tissue. It is known that MRI is sensitive to hydrogen atoms, and if there is insufficient hydrogen within the material, it is difficult to acquire useful images, as for the dry aerogel sample. Further investigation is needed to establish sample preparation and enhancement methods and MR imaging protocols for silica aerogels without the need for immersion in a contrast solution.
Figure 4.7 (a) The effect of di-isocyanate cross-linker and (b) Gd concentrations on MRI $T_1$ and $T_2$ relaxation times (ms)
Figures 4.8 and 4.9 show the CT imaging results of the silica aerogels. The aerogel samples had HU values of 142–227 (Fig. 4.8). The HU values increased with increasing di-isocyanate concentration. It is known that, as the density of human tissue increases, the HU value increases (i.e., bone = 3000 HU). Thus, while an increase in the HU values with increased density due to the increased di-isocyanate concentrations was anticipated, we noted that the changes were not significant. Furthermore, when the aerogels were immersed in a doped solution of Gd-DTPA (0.24 mol/L), the HU value was decreased by 37 units. These values are consistent with the values for human soft tissues, which are in the range of +100–+300 HU.

Figure 4.8 (a) The effect of di-isocyanate and (b) Gd concentrations on CT number (HU)

Figure 4.9 MRI (left) and CT (right) images with Hounsfield units for silica aerogels
Three cellulose aerogels at each superparamagnetic concentration were fabricated and imaged under MRI and CT to validate their feasibility as phantom materials, as demonstrated in Fig. 4.10. The MRI results demonstrate that the cross-linked cellulose aerogel only gave a signal when immersed in water. Furthermore, only samples cross-linked with 0.24 mol/L CoFe$_2$O$_4$ were visible under these modalities. The $T_1$ value ranged from 172–536 ms and the $T_2$ value ranged from 52–77 ms. As shown in Figure 10(a), as the cellulose concentration increased from 5–10 wt%, the $T_1$ value decreased and $T_2$ increased. On comparison these values for human tissue, as given in Table 4.1, $T_1$ value was found to be close to that of bone marrow, and the $T_2$ value matched those for various tissues. By altering the concentrations of CoFe$_2$O$_4$, the resulting $T_1$ and $T_2$ values could mimic those of human tissues, as indicated in Table 4.1. The HU values for the non-cross-linked and cross-linked cellulose aerogels were also measured. The HU value decreased from 250 HU to a value in the range of 167–395 HU upon cross-linking. A further decrease in the HU value was observed with the increasing cellulose concentration. Despite the success in imaging these samples, the samples shrank during the drying process, thus making it difficult to control the final volume of the samples.
Each aerogel has its advantages and disadvantages as an MR/CT-compatible phantom material. Although the silica aerogel showed good mechanical stability with di-isocyanate cross-linking, the values obtained from the MRI and the CT measurements did not resemble specific human tissue values, especially the $T_2$ values. However, by using different contrast agent solutions, different imaging properties of the silica aerogel could be obtained. On the other hand, the cellulose aerogel with 0.24 mol/L CoFe$_2$O$_4$ demonstrated good MRI and CT measurements. Nevertheless, during the supercritical drying process of the cellulose aerogel, it was difficult to control the changes in the shape and the size, as the hydrogel was too soft.
4.5 Summary

In this study, the feasibility of silica and cellulose aerogel as a material for medical imaging phantoms was examined. As silica aerogel was cross-linked with di-isocyanate, it widened the neck regions of the microstructure. This helps the material to withstand applied force, as confirmed by SEM images. The diagnostic imaging properties of silica aerogels, including $T_1$ and $T_2$ relaxation times for MRI and CT numbers, indicated some correlation between the aerogels and human tissues. Cellulose aerogel cross-linked with a superparamagnetic complex was also examined as a potential medical imaging phantom material. X-ray diffraction was performed to confirm the presence of $\text{CoFe}_2\text{O}_4$ using powder diffraction file, JCPDS card no. 79-1744. With the uptake of water, the cellulose aerogel demonstrated MRI/CT compatibility. The $T_1$ value ranged from 172–626 ms and the $T_2$ value varied from 36–129 ms. The CT number ranged from 167–395 HU. However, at $\text{CoFe}_2\text{O}_4$ concentrations of 0.06 mol/L and 0.12 mol/L, MRI and CT results could not be obtained. Thus, a higher concentration should be examined to verify the effect of superparamagnetic concentrations on the MRI results. The $T_1$ and $T_2$ values varied according to the modifier concentrations (Gd-DTPA and $\text{CoFe}_2\text{O}_4$).

To mimic a specific human tissue, we can tailor the aerogel concentrations to reach the desired values. Since aerogels have a dried form, they can be reused with different concentrations after the subsequent drying process. Their structural stability and ability to be imaged under MRI and CT give silica and cellulose aerogels the potential to be used as a perfusion phantom to mimic the porous structure of the lungs.

The significant shrinkage in aerogel volume during the supercritical drying process restricts the fabrication of aerogel phantoms at human tissue sizes. Thus, various drying procedure conditions should be examined in an attempt to minimize this change in volume.
Chapter 5

5 Novel Development of 3D-Printable UV-Curable Silicone for Multimodal Imaging Phantom

5.1 Introduction
This chapter examines the fabrication of silicone, known as polydimethylsiloxane (PDMS), as a multimodal phantom material. Several studies have examined the suitability of silicone in the construction of phantoms. Silicone is robust, easily molded into different shapes, and applicable under different modalities. In this study, hydrophilic silicone and deionized water are added to study their effects on the properties of silicone, particularly on the imaging properties. Furthermore, because of its fast UV-curing rate, we propose that silicone be used in a Digital Light Processing (DLP) 3D printer. With the development of 3D printable silicone, doctors could easily create customized phantoms using to assist with radiation therapy, surgical planning, or training purposes.

5.2 Motivations and Objectives
As mentioned in previous chapters, water-based gels, which are the conventional phantom material, have limited long-term stability and repeatability of measurements. Recently, a number of papers have addressed the use of silicone in the development of phantoms. The advantages of silicone are that it can be molded into different shapes, achieve various viscosities, and be imaged under different modalities.

High-temperature vulcanization is the most common silicone curing method, whereby the homolytic cleavage of organic peroxides generates free radicals that attack the vinyl C=C double bond with the formation of chemical crosslinks between the polymeric chains. During this curing reaction, known as hydrosilation, one hydrogen atom and one silicon atom are added to form a new silicon–carbon bond, which gives rise to a crosslink between silicone polymer chains. [137-139]

Despite the advantages of silicone, its slow curing time can be problematic. With advances in medical technology and the customization of medical devices for improved
patient care, faster silicone curing is desirable. This could allow doctors to obtain computer-aided design models from MRI or CT images and customize patient’s organ phantoms for surgery planning or training. Thus, we propose the use of photo-polymerization.

Photo-polymerization uses light irradiation to initiate chemical reactions, leading to the formation of new polymers. The resulting rapid cure times, low energy requirements, room temperature treatment, and lower material costs make photo-polymerization preferable to the thermal cure process. [99] Photo-polymerization reactions require a photoinitiator, which generates a photoactive species when exposed to light irradiation, and a reactive multifunctional monomer or oligomer that gives rise to cross-linking. Many researches have studied the effective curing of different UV-curable silicone with various platinum-based catalysts such as platinum (II) acetylacetonate (Pt(acac), diphenyl iodonium hexafluorophosphate salt, and N-alkyl morpholino acetophenone. [137, 141, 142]

The objective of this study is to develop a human liver tissue-mimicking UV-curable silicone phantom that can be used to accurately assure the quality of the multimodal medical imaging devices. In this study, we use commercially available silicone with a fast curing speed that can be applied to 3D printing techniques.

5.3 Experiments
5.3.1 Experimental Materials
UV-curable silicone and its catalysts, UV Electro 225 and UV LSR catalyst, were kindly provided by Momentive Performance Materials. Silicone thinner and hydrophilic silicone were purchased from Smooth-On Inc. and United Chemical Technologies, respectively.

5.3.2 Preparation of Silicone Gel Samples
Silicone gel samples were fabricated from Momentive Silopren UV Electro 225 and UV LSR catalyst. Momentive is a photo-polymer composed of a catalyst (part A) and resin (part B). A mixture was prepared by adding a 2:1 ratio of Momentive UV Electro 225 with Smooth-On Silicone thinner. The silicone thinner decreases the viscosity and stiffness of the silicone. Momentive UV LSR catalyst was added to the mixture to initiate the photo-polymerization reaction. Hydrophilic silicone (HS) and deionized water was also added at different
concentrations to study the effects on the mechanical and imaging properties of the silicone samples. Hydrophilic silicone assists the addition of water to silicone. The mixture was stirred until a homogeneous solution was achieved and poured into an aluminum mold. The solution was then exposed to UV light (Swordfish UV lamp at 36 W) until a completely cured sample was obtained.

5.3.3 Characterization

Several characterization tests were performed to determine the mechanical, and imaging properties of the silicone gel. Because deionized water had been incorporated into each sample, thorough mixing of the contents was essential to obtain homogeneous samples. The properties of the silicone samples were compared with reference human liver values found in the literature as indicated in Table 5.1. [135, 143, 144]

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>812 ± 64 (ms)</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>42 ± 3 (ms)</td>
</tr>
<tr>
<td>HU</td>
<td>40–60 (HU)</td>
</tr>
<tr>
<td>Refractive Index</td>
<td>1.37</td>
</tr>
<tr>
<td>Speed of Sound</td>
<td>1575 ± 10(m/s)</td>
</tr>
<tr>
<td>Elasticity</td>
<td>6.4–60 kPa</td>
</tr>
</tbody>
</table>

5.3.3.1 Experimental Setup: Silicone Curing

The key to this study is to develop a solid silicone material that can be fabricated using a 3D rapid prototyping to print any organ shape. Some studies have examined phantoms have used negative molds that were produced with fused deposition 3D printing and the material is poured into the mold in order to obtain its shape. However, theses approaches lack of accuracy, have a slow build speed, and involve a complicated processing for the phantom. In this study, we propose a UV curable silicone solution that can be used as a resin for the stereolithography (SLA) additive technique termed DLP. Using DLP, UV-curable resin material is positioned in a tank under the UV light source, and the UV light is projected in a graphic pattern, which forms and hardens in a thin solid layer of material. A thin layer is cured within a few seconds, and the platform is lowered to obtain another cross-sectional layer of the desired part. DLP is preferred to SLA techniques used in most other studies [145, 146] because of its bottom-up approach, the absence of a molding procedure, fast curing, and
easy to change UV-curable resin. Since the platform of DLP 3D printer moves, viscosity of the resin should be low enough to avoid any shifts in position. In this study, we applied a 0.5 mm-thick layer of homogeneous solution on an aluminum foil and irradiated it with UV light to promote curing. The produced parts have high resolutions under 30 microns and smooth surfaces.

To ensure the complete conversion of the polymer, an FTIR measurements were taken to compare the peaks of the silicone in the liquid and cured solid states. Attenuated Total Reflectance (ATR) measurements were performed using an Bruker ALPHA FTIR (Massachusetts, USA). The sample in the liquid state was carried in a dark container to minimize its exposure to UV light. Cured samples with hydrophilic silicone concentrations of 10 and 20 vol% were compared to observe the differences in their IR peaks.

### 5.3.3.2 Experimental Setup for Ultrasound

We performed US experiments as illustrated in Fig. 5.1. Two ceramic transducers were placed facing each other and immersed in water with the sample located between them. The transmitter was a focused 3.5 MHz transducer with a focal distance of 5 inches (~127 mm) and the receiver was a flat 3.5 MHz transducer. The transmitted signal was amplified using a computer-controlled pulser/receiver (NDT Model 5800, Olympus Panametrics, Japan). Data acquisition and signal processing were performed on a PC using the LabView software. The US samples were disk-shaped with a diameter of 8 mm and thickness of 3–6 mm to allow the signal to pass through without any turbulence. To transmit the detected signals to the software, an analog-to-digital converter (ADC, PXIe-1082) and NI-SCOPE software (National Instruments, Austin, TX) were used. A total of ten measurements were taken from each sample. The acquired data were used to calculate the average SOS and attenuation coefficients of each sample. [147, 148] The water used as the ultrasonic coupling fluid had a temperature of 23 ± 2°C.
5.3.3.3 Experimental Setup for MRI and CT

Magnetic resonance images to acquire the $T_1$ and $T_2$ relaxation times were taken at Sunnybrook Hospital using a GE Discover MR750 3.0T MRI system (GE Healthcare) with a 32-channel head coil. For the $T_1$ relaxation time measurements, $T_R$ times of 2400, 1700, 1000, 500, 300, 150, 90, and 50 ms were used. The $T_2$ relaxation time was measured using $T_E$ values of 10, 20, 30, 50, 75, 100, 150, 200, and 300 ms and a $T_R$ value of 2500 ms. After obtaining the MR images, a MATLAB algorithm was used to analyze the $T_1$ and $T_2$ values.

Computed tomography measurements were performed using a wide-volume CT system (320 MDCT Aquilion ONE, Toshiba Medical Systems, Japan). The samples were aligned and attached to a template, and placed perpendicularly on the CT scanning platform. The scanning conditions were set up to have 0.5 mm detector collimation, 0.5 s gantry rotation time, 50 mA nominal tube current, and tube potentials of 80, 100, 120, and 135 kVp. The images were reconstructed using a single filter kernel with 1 mm sections at 0.5 mm intervals.

5.4 Results and discussions

As shown in Fig. 5.2, the UV-cured silicone samples were prepared with four concentrations of deionized water (0, 5, 10, 20 vol%) and two concentrations of hydrophilic silicone (HS, 10, 20 vol%). Samples with 0 vol% water have a gooey texture with a soft structure. As the water and hydrophilic silicone concentration increases, the silicone becomes more rigid and whiter in appearance.
Figure 5.2. Fabricated Silicone samples with different concentrations of deionized water and hydrophilic silicone

5.4.1 Polymer Conversion: Curing Time

The imaging properties of samples with various concentrations of HS and deionized water were examined. A thin layer of silicone sample solution was cured under UV light to observe the effect of the water and HS content on curing time. To apply the silicone as DLP resin, it is important to decrease the curing time to 3–10 s. Although silicone is a good material for phantom applications, high-temperature vulcanized silicone has a curing time of 16–24 h, which makes it unsuitable as a 3D printing resin. In this experiment, we examined the change in curing time with respect to different concentrations of deionized water and HS.

Photo-polymerization is initiated by a photoinitiator or catalyst, which generates a photoactive species when exposed to light irradiation, and a reactive multifunctional monomer or oligomer promotes cross-link polymerization. During this process, the physical energy of light is transformed into suitable chemical energy in the form of reactive intermediates. The local temperature increase initiates the monomer polymerization, and the heat released during the curing process helps to continue the polymerization throughout the sample, a process known as thermal frontal polymerization. As illustrated in Fig. 5.3(a), at 10 vol% HS, the UV-curing time was observed to decrease from 55 to 20 s as the water content increased from 0 to 30 vol%. As the water content increased from 0–5 vol%, the curing time decreased by 20 s, which indicates that the addition of water enhances the curing of the silicone. Typically, during hydrosilation, the cleavage of organic peroxides generates free radicals that attack the vinyl C=C double bond with the formation of chemical cross-links between polymeric chains, as shown in the following scheme:
In this process, one hydrogen atom and one silicon atom are added across a multiple bond. [137-139, 149] The hypothesis is that water exhibits a fast curing rate, whereby the addition of water to a UV-curable monomer results in a net decrease in the curing time. As water reacts with silicone, more carbon double bonds are broken down, enhancing the formation of cross-linked silicone polymer chains.

On the other hand, as Fig 5.3(b) indicates, the curing time increased considerably as the HS content increased from 20–30 vol%, regardless of water content. This indicates that increasing the HS content increases the curing time. The addition of HS increases the [SiR₂-O-] backbone structure, adding functional groups to which the photo-catalysts can adhere and polymerize. Thus, the catalyst effect on the silicone curing process decreases as the HS content increases.
5.4.2 Chemical Properties of Silicone Gel

To identify the chemical change during the UV-curing process, FTIR was performed on samples in the liquid and solid states after polymerization. First, it was found that the spectrum of the solid samples does not change, as shown in Fig. 5.4. The other FTIR results confirmed that the infrared spectra of silicone samples do not alter with the HS and water concentrations.

The liquid and solid states of silicone generally demonstrate similar absorption peaks. The liquid state exhibits two peaks at 1600–1680 cm\(^{-1}\) for the C=C stretching of alkene and a broad band at 3200–3500 cm\(^{-1}\) representing the O-H stretch of H-bonds. This proves that the mixture contains HS, which contains alkene oxides as well as water. When the sample is cross-linked, an absorption peak appears at around 2800–2950 cm\(^{-1}\) because of the C-H stretch. As the UV-curing finishes, the carbon double bonds are broken down into single bonds and cross-links in the silicone polymer chains. This verifies that UV-curing was successful.
Figure 5.3. FTIR of liquid and solid states of silicone samples (liquid with 10 vol% HS and 20 vol% water; solid with 10 vol% and 20 vol% HS and 20 vol% water)

5.4.3 Hardness of Silicone Gel

The hardness of the silicone samples was compared using an Instron Shore Hardness Tester with a OOO-type load. Three samples of each concentration were measured and compared. As Fig. 5.5 demonstrates, there were no drastic differences in the hardness of the samples with different water and HS concentrations. However, it is interesting to note that the 0 vol% water sample remains soft and gooey after complete curing. As the water content increases, the sample becomes more rigid and the hardness increases. This is contrary to the silicone solution prior to curing, where the viscosity was lowered by the addition of water. As hypothesized earlier, water enhances the cross-linking polymerization of the silicone, which could increase its rigidity.
Figure 5.4. Hardness of silicone samples with increase in water content

5.4.4 Ultrasound Properties of Silicone Gel

Figure 5.6 shows the measured SOS and attenuation coefficients for disk-shaped silicone samples. These measurements were performed at a frequency of 3.5 MHz and repeated ten times for different samples.

The measured SOS was between 1275 ± 40 m/s and 1237 ± 47 m/s for each HS content at 5 vol% water. This is much lower than the SOS of normal human liver tissue (1575±11 m/s [144]). The SOS value decreased to 906 and 1094 m/s at a water content of 20 vol%. Lower SOS values could be due to the inhomogeneity in the solution and uneven sample surfaces. Previously reported values for different types of silicone were in the range 969–1250 m/s. [109] The attenuation coefficients were 0.40 ± 0.183 and 0.35 ± 0.056 dB/(cm MHz) at a frequency of 3.5 MHz for 10 and 20 vol% HS content at 5 vol% water. The attenuation also decreased at higher water contents. Normal human liver tissue has an attenuation coefficient of 0.52 ± 0.03 at 1 MHz. [144] Considering that the attenuation coefficient increases linearly with the frequency, the extrapolated normal liver attenuation coefficient at 3.5 MHz would be approximately 2.4 [151] The values for the silicone samples are significantly lower than those of liver tissue, and thus it may not be give a good representation of human tissue. Further studies should be performed to improve the acoustic properties of the silicone phantom by adding metal particles or other polymer materials such as graphite powder [152], evaporated milk [153, 154], Al₂O₃ [155] and/or poly(methyl methacrylate) PMMA microsphere [156].
5.4.5 MRI Properties of Silicone Gel

The $T_1$ and $T_2$ relaxation times were obtained using a GE Discover MR750 3.0T MRI system and compared with the values of human liver tissue. The $T_1$ and $T_2$ values represent the rates at which the longitudinal and transverse components of the magnetization vectors of human tissues return to their thermodynamic equilibrium. Theoretically, since MRI detects the presence of hydrogen protons, water content plays an important role in the signal detection. Thus, it is hypothesized that higher water contents will decrease $T_1$ and increase $T_2$. Since HS is a non-reactive silicone fluid with alkene oxides that has been modified to enhance the solubility in water, altering the amounts of alkene oxide (hydrophile) and dimethylsiloxane (lipophile), the desired hydrophilicity can also be achieved. As shown in Figs. 5.7 and 5.8, $T_1$ increases and $T_2$ decreases as the water content increases to 10 vol%. Up to 10 vol%, the water content enhances both $T_1$ and $T_2$ relaxation values at 448 ms and 40 ms, respectively, which are close to the values in human liver tissue of $T_1 = 812 \pm 64$ ms and $T_2 = 42 \pm 3$ ms. [135]
However, with a further increase in water content to 20 vol%, the $T_1$ value decreases and $T_2$ increases for each concentration of HS. In free water, the water molecules are moving fast because of their small size, which reduces the match between the proton frequencies and the molecular environment. This causes freely bound water to have a relatively large $T_1$ value. Hydrophilic silicone chemically enables water to mix homogeneously into the hydrophobic silicone mixture. Thus, increasing the water content changes the overall $T_1$ value of the silicone.

A similar trend was established for the $T_2$ relaxation times. The addition of water to the silicone solution created inhomogeneities in the sample, whereby the proton spins could experience different magnetic fields and rotate faster or slower, resulting in smaller $T_2$ values.

Figures 5.7 and 5.8 demonstrate that the $T_1$ increases and $T_2$ relaxation time decreases with the HS content. A further study was performed to examine the effect of HS content on the relaxation times with a water content of 0 vol% (see Fig. 5.9). The results indicate that an increase in HS content causes $T_1$ to increase and $T_2$ to decrease. The $T_1$ value increases from 306 ms at HS 10 vol% to 620 ms at HS 50 vol%, whereas the $T_2$ value decreases from 110 ms to 54 ms over the same range of HS content.

Based on the MRI data, we can extrapolate that the $T_1$ and $T_2$ values would match those of human liver tissue with a water content of 10 vol% and HS content of 50 vol%. However, one drawback to this concentration would be the long curing time.
5.4.6 CT scan of Silicone Gel

CT scan was also performed on samples at four different peak kilovoltages (80, 100, 120 and 135kVps). Fig. 5.10 demonstrates that the HU decreases linearly with increasing the kVp. As the water concentration increases from 0 to 20 vol% the HU values decreases. For CT number accuracy, the American College of Radiology (ACR) recommends that the scans were performed between 120 and 130kVp. [115] At 120kVp, the HU value of sample with 0 vol% water and 10 vol% HS is 142, whereas the HU value of sample with 20 vol% water and 10 vol% HS is 77. Also, at higher HS content, the HU values tend to be higher. At 120kVp,
the HU value of samples with 10 vol% water varied between 100 and 125 at 10 and 20 vol% HS content. The higher HU value may be due to higher density of the sample with higher HS content. In comparison to human soft tissue values, the HU values are slightly higher. However, this can be adjusted with higher water content or higher silicone thinner content to decrease the density of the samples.

![CT Hounsfield Unit values of silicone over 80, 100, 120 and 135 kVp](image)

**Figure 5.9.** CT Hounsfield Unit values of silicone over 80, 100, 120 and 135 kVp (a) 10 vol% HS and (b) 20 vol% HS

### 5.5 Summary

In this study, the potential for UV-curable silicone to mimic human liver tissue as a 3D printable multimodal imaging phantom material was investigated. The results demonstrate that increasing the water content decreases the UV curing time, with just 20 s curing time.
required at 20 vol% water content. Ideally, a curing time of less than 10 s is needed for 3D printing application. An FTIR study confirmed the occurrence of silicone polymerization by breaking down the double carbon bonds. Hardness does not vary significantly but, as the water content increases, cured silicone samples become more rigid and less gooey. The US results indicate a lower SOS than that of human liver tissue value at 1575 m/s. The MRI results suggest that a water content of 10 vol% gives $T_1$ and $T_2$ relaxation times that are close to those of human liver tissue. As the HS content increases, the $T_1$ value increases and $T_2$ decreases toward the values of human liver tissue. In future, higher HS contents at 10 vol% water should be investigated to acquire relaxation values close to the target.

This study has demonstrated that silicone is a suitable material for the construction of a liver phantom. The addition of water and HS improved the mechanical and imaging properties. To enhance the imaging properties of silicone further, it may be possible to add subsequent contrast agents. With suitable properties of UV-curable silicone, we intend to fabricate a real-size liver phantom using DLP 3D printing for the customization of patient-specific phantoms.
6 Self-Healing Silicone for Future Phantom as training and surgical planning tool

6.1 Introduction
Several phantom materials have been investigated in previous chapters for applications in multi-modal imaging. Clinical simulators or phantoms provide similar properties or requirements as that of real medical procedures, and therefore, they are commonly used for clinicians’ training and the calibration or testing of medical devices [158]. The advancement of technology and the increasing concern for quality assurance and patient-specific activities has resulted in phantoms playing an important role in the medical industry. Recently, phantoms are gaining importance as tools for training in needle-based procedures that use needles, catheters, guidewires, and other small-bore instruments. Currently, it is mandatory for nurses and clinicians to be trained using medical phantoms for all needle-based procedures [159]. To employ phantoms for training, it is essential to develop tissue-mimicking phantoms with self-healing properties for recovery from needle insertions. In this chapter, self-healing silicone with microcapsules was investigated as a proof-of-concept for this purpose. Based on the results obtained from previous chapter, silicone provided imaging properties similar to human liver tissue values for multiple imaging devices. Self-healing was studied as an additional property to enhance the function of silicone as phantom material. The morphological, mechanical, and ultrasound properties of self-healing silicone were investigated.

6.2 Motivation and Objective
There is an increased need for phantoms in radiation therapy and surgical planning. Phantoms are primarily used in training clinicians and surgeons to locate tumors and targeted areas accurately. When performing real-life surgical simulation training, needle insertion or dissection of the phantom structure is inevitable. However, it would defeat the purpose of the training if a trainee can observe the cut made by a previous trainee. Further, these phantom structures are not easy to fabricate and commercial phantoms are expensive; therefore, the
phantom material should also be reusable. Thus, the development of a phantom material with self-healing property is required. A phantom with self-healing properties is particularly useful for training ultrasonography (US) -guided needle interventions; the needle tracks should be invisible on the US image for repeated training. [160]

Over the past decades, materials that display self-healing properties either with or without the presence of external stimulants such as UV light and heat have attracted considerable research interest. The first self-healing system was developed by White et al. [119] and it contained a microencapsulated dicyclopentadiene (DCPD) monomer and a solid phase Grubbs’ catalyst embedded in an epoxy matrix. Damage served as the trigger mechanism when an approaching crack ruptured the embedded microcapsules releasing DCPD into the crack plane through capillary action. Ring-opening metathesis polymerization (ROMP) of the liberated DCPD was initiated by contact with the embedded catalyst, bonding the two crack faces together. Self-healing polymers can be categorized into three classes: (1) capsule-based, (2) vascular-based, and (3) intrinsic. The first mechanism to achieve self-healing is embedding microcapsules containing healing agents in the base material. On damage, the microcapsules rupture and release the healing agents, which fill the damage area by polymerizing new material [161–167]. Most techniques involve the combination of two types of microcapsules or one type of capsule with a catalyst. Examples of healing agents include a metal catalyst (Grubb’s catalyst) and DCPD or any form of polymer with its catalyst. Capsule-based polymers are designed for one-time healing response, and they are limited by the number of microcapsules present in the epoxy matrix.

A vascular-based self-healing polymer stores healing agents either in the embedded vascular microchannel or in the external reservoir [168–171]. For the latter ones, the microvascular serves as a channel for directing the flow of healing agents. When the composite is damaged, the healing agent is charged into the composite through these microchannels. The system of vascular-based composites can be categorized into 1D, 2D, and 3D designs. Although the depletion of the healing agent is not problematic, the viscosity of healing agents and the complexity of the fabrication method and limited size restrict the use of this type of polymer. Vascular-based polymers can be designed for both single- and multiple-time healing responses.

Intrinsic polymers contain reversible bonds that are activated after being subjected to damage and these are generally designed to face repetitive damages. The intrinsic healing can be achieved through thermally reversible reactions, hydrogen bonding, and macromolecular
diffusion. According to the literature, intrinsic polymers can withstand a considerable amount of repetitive damage [172–174]. However, the disadvantage of these polymers is that the process for preparing a sample is more complex compared with microcapsule-based and vascular-based techniques, and the reaction kinetic can be very slow or difficult to achieve successful self-healing.

Cheung et al. [175] created pediatric-sized abdominal organs to investigate silicone rubber for magnetic resonance (MR) imaging and surgical robot validation. Keller et al. proposed a microcapsule-based healing system, which consist of two parts of microcapsules, one with vinyl-functionalized polydimethylsiloxane (PDMS) resin and platinum catalyst, and the other containing poly(methylhydrosiloxane) copolymer. [162]

In this study, we investigate PDMS using the microcapsule self-healing system. The advantages of PDMS are its inertness, ease of fabrication, and high deformability. The objective of this project is to develop a self-healing polymer that can heal intrinsically while simulating the properties of human liver tissue. The phantom should be able to self-heal after multiple cuts without retaining an obvious mark. Further, it should mimic the imaging properties of human tissue under ultrasound.

6.3 Experimental Setup

6.3.1 Experimental material

All materials for the experiment—urea, resorcinol, 1-octanol, 37 wt% formaldehyde solution, poly(ethylene-alt-maleic anhydride) (EMA), ammonium chloride, hydrochloric acid, and heptane—were purchased from Sigma Aldrich. The microcapsule content, Sylgard® 184 Silicone Elastomer, was purchased from Dow Corning.

6.3.2 Fabrication Methods

6.3.2.1 Microcapsule Fabrication

A two-part Sylgard® 184 Silicone Elastomer was used as the healing agent and base matrix. Microcapsules were prepared by in situ polymerization in an oil-in-water emulsion. At room temperature, 50 mL of 2.5 wt% aqueous solution of EMA copolymer was mixed with 200 mL deionized water in a 500 mL beaker. 5 g of urea, 0.5 g of ammonium chloride, and 0.5 g
of resorcinol was added to the solution, and then, it was sonicated using the ultrasonic liquid processor (Misonix, USA) until it was well-mixed. Then, the beaker was transferred to the magnetic stirring plate for constant mixing at a stir rate of 7.5. The stir rate determines the size of the microcapsules. The pH was adjusted to 3.5 by adding either sodium hydroxide (NaOH) or hydrochloric acid (HCl). One to two drops of 1-octanol were added to eliminate surface bubbles. A slow stream of 60 mL microcapsule content, two-part Sylgard® 184 silicone, was added to form an emulsion and was allowed to stabilize for 10 min. After stabilization, 11.18 mL of 37 wt% aqueous solution of formaldehyde was added to obtain a 1:1.9 molar ratio. The emulsion was placed in a water bath and heated at a rate of 1°C/min to achieve the target temperature of 55°C. After 4 h of continuous agitation, the mixture was cooled to room temperature. The microcapsule was suspended under vacuum with a coarse filter. The microcapsules were rinsed with deionized water and air dried for 24–48 h. Microcapsule fabrication was performed for each part of the silicone elastomer separately.

6.3.2.2 Self-healing Sample Fabrication

Once two-part healing agents were encapsulated in poly(urea-formaldehyde) (UF) shells and dried microcapsules were obtained, self-healing samples were fabricated. The two-part Sylgard® 184 Silicone Elastomer was used as the base matrix. As mentioned earlier, microcapsule part A contains PDMS resin and microcapsule part B contains the Pt catalyst. Samples with various concentrations of microcapsule part A (0, 10, 15, and 20 wt%) and part B (fixed at 5 wt%) were fabricated as demonstrated in Fig. 6.1. Three samples of each concentration were fabricated to verify reproducibility.

![Figure 6.1. Vinyl-terminated polydimethylsiloxane (PDMS) resin and platinum catalyst encapsulated together in poly(urea-formaldehyde) (UF) shell. Poly(methylhydrosiloxane) copolymer is encapsulated separate in the same shell. Both capsules are embedded in vinyl-terminated PDMS base matrix.](image-url)
6.3.3 Characterization of self-healing silicone

6.3.3.1 Microscope Characterization of self-healing silicone

An optical microscope (Micromaster, Fisher Scientific, USA) was used to capture images of the surface and microcapsules of the silicone samples. The area of rupture after healing was observed by ultra-compact 14-bit CCD camera (pco.pixelfly, PCO, Kelheim, Germany) equipped in the microscope and image analysis software. A scanning emission microscope (SEM) (JEOL JSM6060, USA) was used to examine the morphology of the microcapsules. Samples were sputter coated with a thin layer of platinum to reduce charging.

6.3.3.2 Mechanical Characterization of self-healing silicone

In order to test the self-healing properties, dogbone-shaped samples were fabricated using a metal mold according to ASTM D638. Tensile tests were performed using Instron 5848 Dual Column Tabletop Testing Systems with a 500 N load cell at a strain rate of 0.1 mm/s until the samples ruptured. Both ends of the sample were gripped tightly with the tensile testing grips. Damaged samples were manually pressed on together to gain instant attachment and cured for 24 h at room temperature. The tensile properties of undamaged and damaged samples were compared.

6.3.3.3 Ultrasonic Characterization of self-healing silicone

Ultrasonic measurements were conducted using a through-transmission normal incidence setup as demonstrated in Fig. 5.2. A 3.5-MHz focused immersion transducer with a focal distance of 17 cm (V381-SU, Olympus Panametrics NDT) was used to transmit a signal, which was received by a 3.5-MHz flat immersion transducer (A381S-SU, Olympus Panametrics NDT). A radio frequency (RF) power amplifier was used to amplify the signal (411LA, ENI Co., 10 W and 40 dB) before transmitting it through a sample. The detected signal was transmitted by an analog-to-digital converter (ADC, PXIe-5122) and NI-SCOPE software (National Instruments) to the LabView software for signal processing. The temperature of the water was 23 ± 2°C. Rectangular samples (180 × 65 × 5 mm³) were fabricated, and an ultrasonic signal was transmitted through five different points across the length of the samples. Speed of sound (SOS) and frequency-dependent attenuation coefficient α(f) were calculated using MATLAB. Note that the arrival time difference dt was taken as the
time difference between the maximum signal of the water and that of the sample as the two waveforms exhibit only a very slight difference. [147, 148]

6.4 Results and Discussions

6.4.1 Physical Properties of self-healing silicone

The monomers of vinyl-terminated PDMS resin (A) and poly(methylhydrosiloxane) copolymer initiator (B) are microencapsulated in UF shells and embedded in the PDMS base matrix. The concentrations of microcapsule part A were varied at 10, 15, and 20 wt%, while that for microcapsule part B was fixed at 5 wt%. The encapsulated monomers were released on damage, and they started crosslinking to form new PDMS in the damaged area. The room temperature curable silicone elastomer used in this study utilized a platinum catalyzed hydrosilylation reaction to crosslink the vinyl-terminated resin as illustrated in Fig. 6.2. When a rupture occurs, crosslinking is initiated between the PDMS resin microcapsule (A) with a functional copolymer and the initiator microcapsule (B) through the action of the platinum catalyst to produce a new PDMS network to heal the system.

![Figure 6.2](image)

Figure 6.2. At room temperature or higher, liquid polymethylhydrosiloxane copolymer and liquid vinyl-terminated polydimethylsiloxane (PDMS) resin react to form solid, inert vinyl-terminated PDMS.

The damaged samples with different microcapsule concentrations are shown in Fig. 6.3. The silicone sample with no self-healing microcapsule is completely transparent. As the microcapsule concentration is increased, the PDMS sample loses its transparency. The size of microcapsules varies throughout the samples.
Figure 6.3. Ruptured self-healing silicone samples with 0, 10, 15, and 20 wt% of microcapsule A and fixed 5 wt% of microcapsule B

6.4.2 Structural and Morphological Properties of Self-healing Silicone

The morphological properties of the self-healed samples are examined at the location of the rupture. Fig. 6.4 shows the rupture area of the damaged sample after it was manually pressed and healed for 24 h. For effective self-healing, the healing agent needs to be released from the ruptured microcapsules, and it has to fill the damaged region. Optical microscope images confirmed that areas of damage were filled with the self-healing PDMS resin. White particles exist in parts of the filled resin (Fig. 6.4 (a) and (b)); these particles are small microcapsules that have not been activated.
Figure 6.4. Optical Microscope image of rupture region of samples with different microcapsule A concentrations. a) 10 wt%, b) 15 wt% and c) 20 wt%

The microstructure of the rupture region of the self-healing silicone was also captured as demonstrated by the SEM image. The SEM images of the cross-section of the rupture region demonstrate microcapsules of different sizes distributed throughout the sample. (Fig. 6.5 (a)–(d)) Three major structures appear in the SEM images of the cross-section of a failure plane: an empty hole, an agglomerate region of multiple small microcapsules, and a filled hole. An empty hole could be air pockets created during the fabrication process or microcapsules from where the healing agent flows out. The next two structures are interesting to consider as clearly illustrated in Fig. 6.5 (c) and (d). As mentioned earlier, microcapsules were fabricated with different sizes. Smaller microcapsules tend to agglomerate in certain areas or pockets. This restricts the microcapsules to activate properly when rupture occurs to polymerize the new form of the PDMS resin. The last region is where holes are present with a thin layer of coating. These holes are considered to be microcapsules that activate upon rupture and release self-healing agents. Although it is difficult to identify which microcapsule healing content was contained, when microcapsule A or B contents are in contact, they start the polymerization to initiate self-healing.
6.4.3 Self-healing properties of silicone

The self-healing property of silicone was examined by tensile tests using an Instron machine. First, the samples were subjected to tensile load at a rate of 0.1 mm/s until the samples were ruptured and its Young’s modulus was obtained. Fig. 6.6 demonstrates that the modulus reduces as the microcapsules are incorporated and it increases as the microcapsule concentration increases. Typically, the Young’s modulus of a human liver tissue ranges between 6.4-60 Pa. [118] The modulus of silicone with microcapsules is much higher than those reported liver values.

Figure 6.5. SEM image of cross-section region of ruptured silicone with self-healing microcapsules at different magnifications

Figure 6.6. Young's modulus of undamaged self-healing silicone with 0, 10, 15 and 20 wt% microcapsule part A
The load-displacement graph was also compared for the control (no microcapsule) and self-healing samples prior to damage and after, as illustrated in Figs. 6.7 and 6.8. It is shown that the samples withstand lower load for longer displacement with an increase in microcapsule concentration. After the sample was ruptured, tensile testing was performed to compare the behavior of the samples with respect to microcapsule concentrations. As demonstrated in Fig. 6.8, the displacement decreased by 20% with 20 wt% microcapsule A content. The self-healing property decreases further when microcapsule A content increases. This may be because the ratio or size of microcapsules A and B is not precise. The microcapsule-based self-healing occurs when parts A and B react and polymerize.

Figure 6.7. Load-displacement graph of undamaged samples with different concentrations of microcapsule A content

Figure 6.8. Load-displacement graph of damaged samples with different concentrations of microcapsule A content
6.4.4 Ultrasound Measurement of Self-healing silicone

Rectangular samples were fabricated with concentration of microcapsule A varied between 5 wt% and 15 wt%, while that of microcapsule B fixed at 5 wt%. The values of SOS and attenuation coefficient ($\alpha$) were measured by the transducer setup described above and calculated. The SOS does not vary with increasing microcapsule concentration (1487 m/s). This value is smaller than the SOS of human liver tissue at 1595 m/s. The attenuation increases with the incorporation of microcapsules as shown in Fig. 6.9; however, this change is not significant. The $\alpha$ value is smaller for self-healing silicone compared with that for the human liver tissue (0.9 dB·cm$^{-1}$·MHz$^{-1}$) [176].

![Figure 6.9. Attenuation Coefficient of self-healing samples with different concentrations](image)

6.5 Summary

With results from previous studies, self-healing silicone was investigated as proof-of-concept of phantoms for surgical simulation training, needle insertion or dissection. In this study, a self-healing silicone was developed through the incorporation of a microcapsule-based self-healing mechanism. Two microcapsules systems are utilized, one containing vinyl terminated PDMS resin and Pt catalyst complexes and the other containing a PDMS copolymer that crosslinks. The presence of microcapsules was confirmed by optical microscope and SEM images. These images demonstrate how the healing agents were released from the microcapsules upon rupture. However, it was not confirmed that the polymerization between the part A resin and the part B catalyst occurred. Although the tensile test demonstrated the capability of the self-healing silicone to recover 30% of the original properties, the self-healing efficiency is not significant. The ultrasound properties were also investigated using a 3.5-MHz transducer setup. The SOS was approximately 1487 m/s and $\alpha$ was in the range of
2.0–4.0 ×10^{-10} \text{ dB/cm-MHz.} These values are lower than those reported for human liver tissue. In the future, the effect of the microcapsule, the ratio of parts A and B, and detailed self-healing testing needs to be performed to confirm the applicability of self-healing silicone as a phantom.
Chapter 7

7 Conclusions and Recommendations

7.1 Concluding Remarks

With the advancement of medical imaging technology and increasing concern for quality assurance, the need for the development of a phantom for calibration and training purposes has risen. The objective of this research was to examine various polymer-based materials for multimodal medical imaging phantoms and to study their physical, mechanical and imaging properties to mimic the human tissue values, mainly human liver tissue. The focus of the project has advanced based on the findings of each study.

First, we started with water-based carrageenan gel for fabrication of phantom with lesion particles. The objective of this study is to validate the viability and durability of the water-based gels since few papers have dealt with its long-term stability and only reported on fungal growth. Carrageenan-based polymer gel samples were fabricated and their chemical, mechanical, dielectric, and imaging properties were examined to assess their similarity to those of human tissue. With variation in the concentrations of constituents, the carrageenan-based gel samples were in good agreement with human liver tissue values. A six-week stability test was also conducted on each property. The mechanical properties such as the density and elastic modulus fluctuated with time with no specific pattern, which was hypothesized to be due to the expulsion and absorption of water by the samples. The dielectric properties of the samples, namely the conductivity and permittivity, did not change with time. The imaging properties, $T_1$ and $T_2$ relaxation times, of the samples were also observed over six weeks. Changes of about 23-29 % were observed in $T_1$ and $T_2$. The CT Hounsfield units were also obtained at 120kVp and the values simulate those of human tissue values. However, the long-term stability of CT numbers is not validated. Although each property does not serve the equal importance, mechanical, physical and imaging properties should be maintained small deviation to maintain its shape, rigidity and calibration accuracy over time. For accurate calibration over the shelf life of a phantom, the fluctuation of its properties should be minimized. The recommended shelf life of a phantom is more than 6 months up to 3 years. If the physical, mechanical and imaging properties change significantly over 6 week period, it can be projected to change with wider range over longer period during the shelf life of the phantom. However, there is no standard guideline to define an acceptable
degree of variation. Based on the reported measurements in the literature, the fluctuation of the measured values on carrageenan-based gels was much bigger than the mean standard deviation on human tissue measurements. Therefore, we conclude that the change in the relaxation values is not within the acceptable range and thus, the carrageenan or agar gel does not perform as stable material for phantom.

Based on the long-term stability validation from the first study, there was an urge to fabricate a solid phantom that is not made of a water-based material. It led us to the second study where the feasibility of silica and cellulose aerogel as a material for medical imaging phantoms was examined. Aerogel has unique properties such as mesoporosity, high surface area, and lightweight. If the aerogel can be immersed in water during calibration procedure and provide tailored imaging properties of human tissue, it can be adequate as phantom application. First, silica aerogel was cross-linked with di-isocyanate to widen the neck regions of the microstructure to help withstand applied force as it was confirmed by SEM images. Diagnostic imaging properties of silica aerogels, including $T_1$ and $T_2$ relaxation times on MRI and CT HU values indicated some correlation between the aerogels and human tissues. Next, cellulose a aerogel cross-linked with superparamagnetic complex was also examined as a potential medical imaging phantom material. XRD was performed to confirm the presence of CoFe$_2$O$_4$ with JCPDS card no.79-1744. With the uptake of water, the cellulose aerogel demonstrated MRI/CT-compatibility. The $T_1$ value ranged from 172 to 626 ms and the $T_2$ value ranges between 36 and 129 ms, while CT number ranged between 167 to 395HU. However, at CoFe$_2$O$_4$ concentrations of 0.06 mol/L and 0.12 mol/L, the MRI and CT result could not be obtained. Thus, a higher concentration should be examined to verify the effect of superparamagnetic concentrations on the MR results. In order to mimic a specific human tissue, we can tailor the concentrations of modifiers (Gd-DTPA and CoFe$_2$O$_4$) to mimic its values. Since aerogel is in dried form, it can be reused with different concentrations after subsequent drying process. Due to its structural stability and ability to be imaged under MRI and CT, silica and cellulose aerogel has potential as perfusion phantom or phantom that mimics the porous structure of human organs. However, due to significant volume shrinkage during the supercritical drying process and complex fabrication setup restricts the mass-production at larger scale phantoms. Thus, various drying procedure conditions should be examined to minimize the volume change.

Aerogels have shown its potential as medical phantom; however, its complicated fabrication process could pose restriction on its use. In this study, UV-curable silicone,
another type of solid polymer, was investigated as potential liver tissue mimicking phantom. With various concentrations of silicone constituents, we proposed 3D printable silicone using DLP technique. Several studies introduced the concept of 3D printing for phantom application but these techniques required fabrication of mold using 3D printing and filling the mold with phantom material. This study suggests a novel material that can be employed as resin for bottom up UV-curing system. Commercially available UV-curable silicone was mixed with hydrophilic silicone and water to alter the properties. Results demonstrate that increasing water content enhances the UV-curing time. The curing time lowered to 20 seconds with 20 vol% water content. It is desirable to achieve less than 10 seconds of curing time to achieve fast curing for 3D printing application. The ultrasound results were lower than the human liver tissue value at SOS of 1575 m/s. MRI results demonstrate that at water content of 10 vol%, $T_1$ and $T_2$ relaxation times were closest to the human liver tissue. As increase in HS content, the $T_1$ increases and $T_2$ decreases, reaching the values of human liver tissue. In the future, higher HS content at 10 vol% water should be investigated to acquire relaxation values close to the target. CT results show that as the water content increases, the HU values lowered as well, reaching the value of human soft tissue values. In this study, silicone has been proven to be good material to be suitable for liver phantom. By addition of water and HS, we improved the mechanical and imaging properties. In order to enhance the imaging properties of silicone further, addition of subsequent contrast agents is suggested. With suitable properties of UV-curable silicone, we will fabricate real-size liver phantom by using Digital Light Processing (DLP) 3D printing technique for customization of phantom specific to a patient.

From the third study, the silicone has proven to be a suitable as tissue-mimicking material. With increase demand for phantom application in clinician training, surgical planning with needle-insertion or dissection, self-healing material is suggested as proof-of-concept in this study. In this study, a self-healing silicone has been developed through incorporation of a microcapsule-based self-healing mechanism. Two microcapsules system is utilized, one containing vinyl terminated poly(dimethyl siloxane) (PDMS) resin and platinum catalyst complexes and the other containing a PDMS copolymer that crosslinks. The presence of microcapsules was confirmed by optical microscope and SEM images. These images demonstrate that the healing agents were released from the burst microcapsules upon rupture. However, it was not confirmed that the polymerization between part A resin and part B initiator has happened. Although the tensile test demonstrated the capability of the self-
healing silicone to recover 30% of the original properties, the self-healing efficiency is not great. The ultrasound properties were also investigated using 3.5MHz transducer setup. The speed of sound was approximately 1487m/s and the attenuation coefficient in the range of 2.0 to $4.0 \times 10^{-10}$ dB/cm-MHz. These values are lower than reported human liver tissue. In the future, the effect of microcapsule, ratio of part A and B, and detailed self-healing testing needs to be performed to confirm the self-healing silicone for its phantom application.

Overall, imaging properties of each material has been summarized in Table 7.1. Concentrations of each material can be selected to simulate different human tissues, organs or abnormalities. Among materials examined in this thesis, silicone is the most suitable candidate for phantom since it can be manufactured with simplicity and well maintains stability of its properties.

There are a number of properties that can be used as measure of tissue equivalence of a phantom. The physical density and effective atomic number ($Z_{eff}$) can be used to provide insight into the physical properties of properties. The electron density ($\rho_e$) and the mass energy-absorption coefficient ($\mu_{en}/\rho$) can be used to find the energy deposited locally in the targeted tissue. If these properties can be controlled, imaging properties will be better controlled.
Table 7.1. Summary table of property values of each phantom materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Modality</th>
<th>Property</th>
<th>Concentration</th>
<th>Values</th>
<th>Liver Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenan Gel</td>
<td>MRI</td>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Carrageenan 3g, Agar 0-1.5g</td>
<td>Values vary between 248 to 364 ms</td>
<td>812±64</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Carrageenan 1-2.5g, Agar 1.5g</td>
<td>Values vary between 230 to 646 ms</td>
<td>42±3</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Carrageenan 3g, Agar 0-1.5g</td>
<td>Values vary between 99 to 169 ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Carrageenan 1-2.5g, Agar 1.5g</td>
<td>Values vary between 78 to 137ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>HU</td>
<td>Carrageenan 3g, Agar 0-1.5g</td>
<td>Values vary between 24 to 48 HU</td>
<td>+40 to +60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carrageenan 1-2.5g, Agar 1.5g</td>
<td>Values vary between 36 to 59 HU</td>
<td></td>
</tr>
<tr>
<td>Silica Aerogel (0.24 mol/L CoFe₂O₄)</td>
<td>MRI</td>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Gd-DTPA, 0.085 – 0.34 µL/mL</td>
<td>Decreases from 1415 to 541 ms</td>
<td>812±64</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Gd-DTPA, 0.085 – 0.34 µL/mL</td>
<td>Increases from 230 to 295 ms</td>
<td>42±3</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>HU</td>
<td>Gd-DTPA, 0.085 – 0.34 µL/mL</td>
<td>Decreases 227 to 190 HU</td>
<td>+40 to +60</td>
</tr>
<tr>
<td>Cellulose Aerogel</td>
<td>MRI</td>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Cellulose 5-10 wt%</td>
<td>Decreases from 536 to 172 ms</td>
<td>812±64</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cellulose 5-10 wt%</td>
<td>Increases 52 to 77 ms</td>
<td>42±3</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>HU</td>
<td>Cellulose 5-10 wt%</td>
<td>Decreases from 395 to 167 HU</td>
<td>+40 to +60</td>
</tr>
<tr>
<td>Silicone</td>
<td>MRI</td>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>HS 30 vol%, Water 0-10 vol%</td>
<td>Increases from 333 to 430 ms</td>
<td>812±64</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>HS 10 – 50 vol% Water 0-10 vol%</td>
<td>Increases from 306 to 620 ms</td>
<td>42±3</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>HU</td>
<td>HS 10 vol%, Water 0-20 vol%</td>
<td>Decreases from 333 to 110 – 54 ms</td>
<td>+40 to +60</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>SOS</td>
<td>HS 20 vol%, 0-20 vol% Water</td>
<td>Decreases from 156 to 123 HU</td>
<td>1549 (m/s)</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>α</td>
<td>HS 10 vol%, 0-20 vol% Water</td>
<td>Decreases from 0.4 to 0.17 dB/(cm-MHz)</td>
<td>0.9 dB/(cm-MHz)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS 20 vol%, 0-20 vol% Water</td>
<td>Decreases from 0.35 to 0.32 dB/(cm-MHz)</td>
<td></td>
</tr>
<tr>
<td>Self-healing</td>
<td>US</td>
<td>SOS</td>
<td>Microcapsule A Content 5-15 wt%</td>
<td>1487 m/s</td>
<td>1549 (m/s)</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>α</td>
<td>Microcapsule A Content 5-15 wt%</td>
<td>2.0-4.0 × 10⁻⁶ dB/cm-MHz</td>
<td>0.9 dB/(cm-MHz)</td>
</tr>
</tbody>
</table>
7.2 Contributions
The key contributions of this research are as follows:

1. Novel polymer-based materials were developed and their physical, mechanical and imaging properties were investigated for multimodality imaging phantom.

2. Long-term stability of water-based polymer gel was investigated and addressed the problem with consistency and clinical accuracy of the phantom. This suggests that although most of the water-based materials provide good tissue-mimicking properties, the values may not be consistent.

3. Novel approach of organic and inorganic aerogels was suggested as a solid phantom material. It was found that aerogels could be used as reservoir of water to function to provide similar imaging properties to human tissue. Prior to the calibration, aerogels with optimal concentrations of contrast agents (Gd-DTPA or CoFe$_2$O$_4$) can be soaked in water to serve as phantom. After the use, the aerogels can be dried again for storage. These materials can be used as perfusion phantoms where water uptake is necessary.

4. UV-curable silicone can open an opportunity for patient-specific customized phantom production. Commercially available phantoms are costly and difficult to fabricate. However, if UV-curable silicone material is fine-tuned to provide optimal concentrations correlated with each human tissue properties, doctors and health technicians can easily print the phantom of target area based on US, CT and/or MRI images.

5. The concept of applying self-healing material for training and surgical planning tool is introduced and proof-of-concept silicone material was fabricated and examined. This new concept will increase the shelf life of the phantom and repeatability of needle-insertion operation.

7.3 Recommendations
Throughout the studies in this research, we have demonstrated fabrication of several polymer-based materials and its properties. With increase need for phantom in different applications, we believe that each studied material has potential as phantom material. In the
following section, few recommendations are provided to improve its feasibility and future research and development.

1. Although results show that properties fluctuate due water expulsion and absorption, the water-based gels still exhibit good tissue-mimicking properties. If an efficient storage system is developed to minimize the fluctuation of water, the change in properties can be minimized, hence the accuracy of the calibration phantom can be consistent.

2. Other drying techniques (freeze drying or ambient drying) should be investigated to improve the aerogel fabrication method. Volume shrinkage and difficult drying process limits the use of aerogel. Furthermore, other contrast agents should be examined to identify the optimal properties and to minimize any artifacts.

3. The curing time plays an important role in 3D printing technique. As results demonstrated, the curing time decreases as the water content increases. Also, the imaging properties were closest to the human liver tissue values when water content is at 10 vol%. Thus, further investigation is recommended to study the effect of HS content or other contents at 10 vol% H2O on imaging properties. To improve US, CT and MRI measurements, addition of iodine, graphite powder or PMMA is suggested.

4. Self-healing silicone was investigated as proof-of-concept. Further investigation on ratio of microcapsule part A and B, other type of self-healing mechanisms and their self-healing efficiency needs to be done. For the purpose of the training and needle-insertion, multiple repetition of the self-healing efficiency is highly recommended. Thus, intense study on the efficiency and repetition of the self-healing ability needs to be carried out.

5. It is highly recommended to investigate a silicone material that have ability to be 3D printed and serve multiple self-healing at the same time to meet the material properties to mimic human tissue values. If such material can be achieved, customization of the phantom can be generalized to promote new surgical procedures or assist training of clinicians.
References


