

Numerical Characterization of Ultrasound Elastography for the Early
Detection of Deep Tissue Injuries

by

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Abstract

Deep tissue injuries—casually termed “bedsores”—are a type of wound often suffered as secondary injuries in persons with reduced mobility such as those with spinal cord injuries, the elderly, and people with multiple sclerosis. Deep tissue injuries form when excess pressure is applied to tissue for extended periods of time without relief and begin as the necrotic breakdown of deep tissues at the bone-muscle interface. As these wounds progress, they “tunnel” up toward the surface of the skin where they break open into late-stage pressure ulcers and are completely unnoticeable if the patient lacks sensation. There is currently no clinical tool for detecting these injuries as they form and progress and as such these wounds represent a severe burden on both patients and the health care system alike.

The goal of this work was to numerically characterize the use of three modalities of ultrasound elastography—quasi-static ultrasound elastography, acoustic radiation force impulse imaging, and shear wave speed quantification—for the early detection of deep tissue injuries. Ultrasound elastography is an imaging modality capable of imaging the mechanical stiffness of soft tissue which is a key measure of tissue health. Through combinations of k-space pseudo-spectral techniques, finite-element modelling, and image processing methods, the ability of ultrasound elastography to detect and accurately diag-

nose deep tissue injuries was explored. Parametric studies were undertaken to investigate the effect of a wide range of parameters relevant to the detection sensitivity of ultrasound elastography including both device-design parameters and deep tissue injury lesion properties.

Through the numerical characterizations performed in this work, an understanding of the benefits and limitations of using ultrasound elastography to detect deep tissue injuries was achieved. Shear wave speed quantification was found to provide the most accurate measures of tissue health, however its effectiveness may be limited in very deep tissues. The understanding gained from this work may lead to investigating ultrasound elastography as a viable detection modality for early deep tissue injuries in both animal models and human subjects—these real world tests are the next step on the way to clinical adoption of ultrasound elastography for the early detection of deep tissue injuries.

Preface

Chapter 3 of this thesis has been published as K. Hamaluik, W. Moussa, M. Ferguson-Pell, “Numerical Characterization of Quasi-Static Ultrasound Elastography,” *IEEE Transactions on Medical Imaging*. I was responsible for the study design, data collection, and manuscript composition. W. Moussa and M. Ferguson-Pell were the supervisory authors and assisted with manuscript composition.

Dedication

This work was written for all those who have lovingly supported me throughout it's creation.

To my mother Meridel, who instilled in me the desire to always better myself and persist through the greatest of difficulties. Even when things got difficult, you gently pushed me to continue on.

To my late father David, who taught me about the world and inspired my combination of creativity, critical analysis, and work ethic. I wasn't able to finish before he left us, but I know he would be proud of what I accomplished in the end.

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I truly stand as a dwarf upon the shoulders of giants.

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Nomenclature

Mathematical Symbols

Symbol	Meaning
α	Acoustic absorption coefficient
α_0	Power law prefactor
B/A	Acoustic nonlinearity parameter
b_i	Body force
b_r	Blurred lesion blur radius
b_ρ	Clustered lesion density
C	Elasticity tensor
c_0	Speed of sound
c_T	Shear wave speed
d	Lesion depth
d_f	Focal depth
δ_{sep}	Co-located lesion separation distance
E	Young's modulus
E_{lesion}	Young's modulus of lesion
$E_{rel,meas}$	Lesion stiffness ratio
$E_{rel,nom}$	Nominal lesion stiffness ratio
E_{tissue}	Young's modulus of tissue
ε	Strain
ε_{app}	Transducer-applied strain
ε_{lesion}	Measured lesion strain
ε_p	Percent error
$\varepsilon_{rel,meas}$	Measured lesion strain ratio

Symbol	Meaning
$\varepsilon_{rel,true}$	True lesion strain ratio
ε_{tissue}	Measured tissue strain
F	Applied body forces
f	Ultrasound frequency
f_i	Applied load
G_m	Shear modulus of the m^{th} branch of a Maxwell model
Γ	Boundary domain
h	Lesion altitude
I	Acoustic intensity
I_{SPPA}	Spatial peak pulse average intensity
I_{SPTA}	Spatial peak time average intensity
K	Bulk modulus
k	Wave number
λ_{tissue}	Lamé constant
λ_{wave}	Ultrasound wavelength
MI	Mechanical index
MSE	Mean squared error
μ_{tissue}	Lamé constant (shear modulus)
n_c	Number of acoustic periods
∇	Del operator
P_r	Refractory pressure
P_{source}	Ultrasound transducer source pressure
p	Acoustic pressure
r_{lesion}	Lesion radius
r_{bl}	Clustered lesion radius
ρ	Acoustic density
ρ_0	Equilibrium density
S_M	Acoustic pressure source term
$\varnothing S$	Lesion diameter
$\varnothing L$	Visible Human lesion width
σ	Stress tensor
σ_0	Initial stress distribution
$\sigma_{applied}$	Stress applied to tissue

Symbol	Meaning
t_{inson}	Insonification time
τ_m	Relaxation time of the m^{th} branch of a Maxwell model
\vec{u}	Particle displacement
\vec{v}	Particle velocity
u_0	Initial displacement
v_{max}	Maximum tissue displacement in the axial direction
w_{active}	Total width of active transducer elements
y	Power law exponent

Abbreviations

Abbreviation	Meaning
ARFI	Acoustic radiation force impulse
DTI	Deep tissue injury
IES	Intermittent electrical stimulation
MRI	Magnetic resonance imaging
NPUAP	National Pressure Ulcer Advisory Panel
PU	Pressure ulcer
SCI	Spinal cord injury
USE	Ultrasound elastography

Chapter 1

Introduction

1.1 Motivation

Pressure ulcers are debilitating wounds often suffered by people with limited mobility such as those undergoing lengthy surgical procedures, the elderly, and those with spinal cord injuries (SCI) [1]—up to 80 percent of people with SCI will develop a pressure ulcer in their lifetime [2]. Pressure ulcers are generally characterized by a deterioration of the skin leading to painful open wounds and while many pressure ulcers may be blamed on excess friction and moisture at the skin surface, many start as “deep tissue injuries” (DTI) which start deep below the skin surface—most often at the bone-muscle interface [3]. DTI are generally thought to be formed due to some combination of excessive deformation and ischemia resulting from sustained loading on localized tissue [4]–[6]. As of the time of writing, there is no clinically feasible method of detecting deep tissue injuries until they begin to damage superficial skin—even the National Pressure Ulcer Advisory Panel’s description of them is largely based on their appearance after the fact [7]. With our inability to detect these

forming injuries and subsequently implement deep tissue injury prevention and mitigation protocols, the injuries may eventually progress to form large subcutaneous cavities which eventually break through the surface of the skin and reveal themselves as stage III or IV pressure ulcers [8], [9].

Currently, the only tool capable of readily detecting early deep tissue injuries is T_2^* -weighted MRI [6], [10]. Unfortunately, MRI is not cost-effective for detecting the onset of DTI in a clinical population. Alternately, ultrasound is a much more cost-effective, if less sensitive imaging modality. While it has been shown that some DTI may be discerned using classical b-mode ultrasound imaging [3], [11], the sonographic features of DTI are difficult to separate from regular tissue inhomogeneities. To overcome this, ultrasound elastography may provide more reliable results by imaging the mechanical tissue stiffness rather than its acoustic properties. Ultrasound elastography is an imaging modality which utilizes sonographic techniques to determine the localized mechanical stiffness of tissue and is currently used clinically to detect breast and prostate cancer lesions [12], [13] as well as liver fibrosis [14]. It is known that as DTI form, they undergo mechanical stiffness changes throughout their progression [9], [15], [16], with tissue undergoing significant 1.8 – 3.3-fold mechanical stiffening during injury formation [5]. Initially damaged tissues show signs of increased relative stiffness due to edema-related swelling while eventually showing signs of decreased relative stiffness due to decomposition and necrosis [17]. Since ultrasound elastography is capable of imaging these stiffness changes, it follows that the formation and progression of DTI may be imaged using ultrasound elastography. In fact, ultrasound elastography has shown to be a valid technique for imaging the formation of a DTI in a rat model [18]. Before this technique can be fully understood and used

in human patients, the various parameters involved in performing ultrasound elastography must be characterized with respect to detecting DTI in humans.

1.2 Objective

The broad objective of this work was to numerically characterize the use of ultrasound elastography to detect and monitor formative and progressive deep tissue injuries. Although it has been shown that ultrasound elastography is capable of imaging DTI [18], the degree of suitability of this technique with regard to DTI is not yet understood. When the effects of numerous interrogation parameters on detection sensitivity and ability are known, the technology may be evaluated on its feasibility and usefulness to detect deep tissue injuries. The ultimate goal of this characterization is to be the first stage in the process of allowing ultrasound elastography to be implemented clinically for detecting DTI. It is reasoned that if early detection modalities are implemented clinically, both patients and the health care system may benefit by lowering the incidence and outright cost of treating fully-formed deep tissue injuries.

1.3 Methodology

In order to investigate the use of ultrasound elastography for the detection of deep tissue injuries, the technology must first be characterized and fully understood. While traditional experimentation provides an opportunity to work with physical subjects it can be severely limiting as absolute control over all investigated parameters is relinquished. Further, subject recruitment may present an insurmountable barrier to the execution of such a study. As

such, in this exploratory work, various numerical models of the technology have been utilized to investigate the controlled effect of a broad number of parameters relating to each technology. Specifically, k-space models of ultrasonic wave propagation and finite-element models of tissue deformation have been developed. These models were coupled with tissue strain estimation algorithms to fully simulate ultrasound elastography procedures. Parametric studies on the detection sensitivity and ability of the various ultrasound elastography modalities were carried out with respect to various lesion and technological parameters. Chief parameters of interest included those related to the physical realities of deep tissue injuries such as lesion depth, size, and relative mechanical stiffness as well as parameters related to the design and development of appropriate ultrasonic transducers such as probing frequency, transducer dimensions, etc.

1.4 Thesis Outline

In this work, three methods of ultrasonic elastogram image formation have been investigated: quasi-static ultrasound elastography, acoustic radiation force impulse imaging, and shear wave speed quantification. While all three methods may be used to interrogate tissue stiffness, each does so in a distinctively unique way. The academic background leading to the motivation for this work and the development of the numerical models is presented in Chapter 2.

Quasi-static ultrasound elastography estimates tissue strain by tracking inhomogeneities across pre- and post- compression b-mode scans where the compression is generated by manual indentation of the transducer against the surface of the skin. Naturally, mechanically stiffer regions of tissue will strain

significantly less than the relatively unstiff surrounding tissue. To investigate this technique, two-dimensional b-mode ultrasound scans of simulated pre- and post-compressed tissue were generated. A finite-element model of tissue deformation was utilized to generate the post-compression simulated scans. A published tissue strain estimation algorithm was utilized to then generate elastograms for the parametric study. The models and results pertaining to this technique are presented in Chapter 3.

After performing experiments using quasi-static ultrasound elastography on a phantom model, it became clear that quasi-static methods present significant challenges that acoustic radiation force impulse imaging may overcome. Chief amongst these challenges is the repeatability and inter-operator reliability of the technique as quasi-static elastography is heavily reliant upon manual force generation. Acoustic radiation force impulse imaging estimates tissue strain by applying an acoustic radiation force body load to deep tissue, causing the interrogated tissue region to deform which is then tracked using conventional ultrasound beams fired at a high frame rate. The magnitude of deformation and tissue relaxation time may then be correlated to tissue stiffness. This technique presents an advantage over quasi-static elastography in that the interrogation process is entirely automated, hence more repeatable and reliable. To simulate acoustic radiation force impulse imaging, a k-space pseudo-spectral method was used to generate simulated acoustic body loads which were then combined with a finite-element model of tissue deformation to analyze the sensitivity of ARFI imaging to investigate formative DTI. The models and results for this technique are presented in Chapter 4.

Although acoustic radiation force impulse imaging has some advantages over quasi-static elastography, it only provides qualitative measures of relative

tissue stiffness which is limited utility. To provide a quantitative measure of tissue stiffness and subsequently, tissue health, shear wave speed quantification may be used. Shear wave speed quantification quantifies tissue stiffness by tracking shear waves generated by an acoustic radiation force impulse and correlating the speed of the relatively slow-moving generated shear waves to the mechanical stiffness of the tissue. To simulate shear wave speed quantification, the k-space pseudo-spectral method of simulating acoustic body loads adopted in Chapter 4 was used in combination with a finite-element model of tissue deformation to investigate the interaction between lesions and shear wave speed. The models and results for this technique are presented in Chapter 5.

Finally, the conclusions derived from this work and their implications along with suggestions for future studies are discussed in Chapter 6. Data tables for all the characterization plots that are presented in this work are given in Appendix A, while the MATLAB[®] source code for performing the simulations are given in Appendix B. Lastly, experimental protocols used in the acquisition of experimental validation data are given in Appendix C.

Chapter 2

Literature Review

In order to understand the need for a clinical method of detecting deep tissue injuries, the full scope of the issue must be explored. To this end, the current state of the literature regarding deep tissue injuries, how they form, what factors characterize them, and how they are currently treated is explored here. In order to relate this disease to the detection modalities proposed in this work, the mechanics and history of ultrasound elastography are also explored and related back to the problem at hand. The major gaps in the current literature regarding the use of ultrasound elastography for detecting and monitoring deep tissue injuries are presented as this work attempts to partially fill those gaps and bring the technology one step closer to clinical implementation.

2.1 Deep Tissue Injuries

Pressure ulcers, commonly referred to as “bedsores”, are an extraordinarily large problem facing the health care system today. At least \$11 billion is spent in the United States of America alone treating approximately 500,000 injuries

annually [19], [20] while only a minute fraction of that is spent toward pressure ulcer research [21]. Compared to hospital stays for all other conditions, patients with at least a secondary diagnosis of a pressure ulcer were more often discharged to a long-term care facility and more likely resulted in death [20]. These injuries place an extremely significant burden on the people who suffer from them—pressure ulcers were found to have a profound impact on people’s lives including: altering their physical, social, and financial status; changing their body image; losing independence and control; and subjecting them to the grieving process [22], [23]. These debilitating wounds are often suffered by people with limited mobility such as those undergoing lengthy surgical procedures, the elderly, and those with spinal cord injuries (SCI) [1]—approximately 80 percent of people with spinal cord injuries (SCI) will develop at least one pressure ulcer during their lifetime [2] and approximately 19 percent of elderly patients in long-term care facilities will develop one [24]. Pressure ulcers exist throughout the entire health-care system and are often formed when undergoing hospitalization [25]. These injuries have a tendency to become chronic, non-healing wounds and many patients die from complications related to them [26]. Furthermore, patients who have developed at least one pressure ulcer in their life are at a significantly greater risk of developing a second one [27].

Pressure ulcers generally form over bony prominences with approximately 64% occurring over the ischial tuberosities, trochanter, or sacrum [28] and typically start at the surface of the skin and progress deep in the tissue. Deep tissue injuries—currently defined as a type of pressure ulcer—form in the same regions as pressure ulcers but generally form at the bone-muscle interface deep in the tissue [3]. In general, these injuries are characterized by a some manner of tissue loss through necrosis of the tissue, though there is currently

some debate on the exact nature of these wounds as well as the accuracy of the clinical descriptions attributed to them by the National Pressure Ulcer Advisory Panel (NPUAP).

The NPUAP defines pressure ulcers as a “localized injury to the skin and / or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and / or friction” and are generally staged according to a tiered system of increasing damage [7]. The various stages of pressure ulcer classifications are depicted in Fig. 2.1 and described as follows [7]:

Suspected Deep Tissue Injury

Purple or maroon localized area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and / or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue.

Stage I

Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area.

Stage II

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open / ruptured serum-filled blister.

Stage III

Full thickness tissue loss. Subcutaneous fat may be visible but bone,

undermining and tunnelling.

Unstageable

Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, grey, green, or brown) and / or eschar (tan, brown or black) in the wound bed.

The NPUAP’s definitions of pressure ulcers arise from clinical experiences with them and are largely based on the ulcer’s appearance after they have formed and do not necessarily reflect the true aetiological factors that lead to these conditions. For example, a significant body of literature scientifically describes deep tissue injuries as being much more insidious than a “localized area of discoloured intact skin” and suggests that many Stage III and IV pressure ulcers are actually advanced deep tissue injuries rather than advanced Stage I or II ulcers [17]. This chasm between the clinically accepted and scientifically observed definitions of deep tissue injuries is likely due to the lack of any clinical detection ability [29]. What is agreed upon is that deep tissue injuries are a major problem and more needs to be done to facilitate preventing and treating them [30], [31]. One of the largest hurdles to preventing and treating DTI is the lack of any substantial early detection ability [32], [33].

2.1.1 Aetiology and Histology

Deep tissue injuries are thought to occur through the combinatory effects of three distinct but related mechanisms: ischemia, insufficient lymph drainage, and cell deformation. Ischemia is a condition where the blood supply to tissue has been cut off, rendering the tissue unable to function appropriately. Insufficient lymph drainage refers to how waste products may accumulate in

tissue when the lymph vessels that normally carry them away become occluded. Cell deformation occurs when mechanical strains are imparted upon the tissue, causing excessive deformation in not only the extracellular matrix, but in the cells as well. Taken together, the presence of these factors has been shown to greatly increase the risk of developing a deep tissue injury [4].

For quite some time, ischemia was regarded as the chief acute risk factor for developing late-stage pressure ulcers [34]–[36]. Although studies have shown that healthy tissue is able to survive complete ischemia for approximately 4 hours before severe necrosis sets in [37], [38], deep tissue injuries are clinically found when loading times are substantially less than this [25], [39]. The model of ischemic damage alone could not account for the rate of late-stage pressure ulcers that we were witnessed.

Once it was realized that ischemia alone could not be the culprit behind deep tissue injury formation, ischemia-induced reperfusion injury became implicated in the formation of DTI [40]–[42]. An ischemia-induced reperfusion injury is caused when blood is allowed to flow back into a region of tissue that was previously ischemic. While seeming somewhat contrary to its expected effect, the restoration of circulation results in a swelling and inflammatory effect which causes extensive microvascular damage [41]. The effect of reperfusion was confirmed when comparing pure ischemic conditions in tissue to a cycle of ischemic-reperfused conditions over the same period of time, where it was found that significantly greater damage was caused by repeated loading and unloading rather than simple constant loading [42], [43]. While ischemia-reperfusion injuries provide a more complete explanation about the formation of deep tissue injuries, they still do not account for those injuries acquired under constant pressure over short time periods.

In order for cells to function in a healthy manner, the waste they produce must be constantly carried off and processed via the lymphatic system and its series of lymph vessels that perfuse tissue. If the magnitude of pressure applied to tissue reaches a threshold level, the pressure occludes the lymph vessels and lymphatic drainage ceases [44]. Once lymphatic drainage ceases, cell waste accumulates in the tissue and is thought to initiate necrosis in the cells [45]–[47].

In order to account for deep tissue injuries that form over short time periods, a model of cell deformation leading to necrosis has more recently been proposed [48]–[50]. It has constantly been observed that tissue regions which eventually form deep tissue injuries exhibit signs of locally increased strains [10], [16], [51]–[53], with greater degrees of deformation correlating to greater degrees of damage. To account for these results, it has been proposed that excessively deforming strains applied to cells over extended periods of time can alter the permeability of the cell’s plasma membranes, leading to an overall reduced cell viability [54]. Further, it has been shown both in finite-element models and experimentally that the stiffness of soft tissue and the corresponding strains that are developed within them are closely related [5], [55]–[57]. Not only does the amount of deformation depend on the stiffness of tissue, but the stiffness of tissue was found to correlate to the level of deep tissue injury damage seen in the resulting histology [58] with immediate 1.6-fold to 3.3-fold stiffening of the tissue occurring immediately after injury [5], [15]. Further, the stiffness of tissue severely drops below that of healthy tissue when it begins to decompose [5], [59], leading to a relationship between injury progression and stiffness as shown in Fig. 2.2 (adapted from [17]).

There have been many models of deep tissue injury formation throughout

2.1.2 Prevention and Treatment

The current state of deep tissue injury treatment and prevention largely reflects the lack of a quantifiable detection modality. One of the most commonly used preventions is called “turning” whereby patients are repositioned in their beds or wheelchairs such that individual regions of tissue are intermittently relieved of pressure. Although commonly implemented in health care settings, turning has repeatedly been found to be inadequate at reducing the incidence of pressure ulcers [61], [62]. A more technological means of reducing the mechanical loads on tissue lies in support surface design [63]. Unlike turning, pressure-redistribution foam mattresses have repeatedly shown their ability to reduce the incidence of pressure ulcers in a cost-effective manner [64], [65]. Despite the effectiveness of these surfaces, the overall prevalence of pressure ulcers has not changed significantly—suggesting that appropriate preventions are not being utilized in health-care settings [31].

An emerging technology in the realm of pressure ulcer prevention is intermittent electrical stimulation (IES). IES is the process by which electrical impulses are utilized to activate muscle fibres and contract the muscle. IES has been found to not only increase the oxygenation in deep tissue [66], but also significantly reduce the damage caused from excessive loading [67]. IES prevention paradigms are still being developed but the technology may prove to be an extremely effective preventative therapy for DTI.

While various technologies exist or are in development for preventing pressure ulcers, little is available to treat them when they occur. Generally, pressure ulcer treatment involves optimizing regional blood flow, managing underlying illnesses, and providing adequate nutrition [26]. If a pressure ulcer

has become chronic, treatment switches to controlling the symptoms and preventing complications [26]. Negative pressure wound therapy is a process by which a slight vacuum is applied to the open wound for several weeks and has shown some success in reducing the severity of late-stage pressure ulcers [68]. Surgical techniques such as debriding may also be used in an attempt to remove necrotic tissue from the wound and prevent it from growing any larger [69], [70]. Skin-flap surgery is often used on chronic ulcers in an attempt to protect the wound bed [71].

When various prevention and treatment paradigms are implemented, the incidence of hospital-acquired pressure ulcers may decrease dramatically [72]–[74]. However, one of the key required areas of improvement is in the detection and monitoring of pressure ulcers [33]—without the ability to continually monitor a wound, the true effectiveness of any given therapy is ultimately indeterminate.

2.1.3 Detection

As previously mentioned, there is a lack of means for detecting the early onset of deep tissue injuries in a clinical setting [32], [33]. Currently, when attempting to detect and diagnose a deep tissue injury or pressure ulcer, clinicians generally rely upon a risk-factor scale for patients rather than actually detecting a lesion. Popular risk assessment tools include the Norton, Braden, and Risk Assessment Pressure Sore scales which each attempt to predict the formation of a pressure ulcer in a patient given their scores in a series of relatively subjective variables such as “general physical condition” and “mental state” [75]–[77]. Aside from these main risk-assessment scales, multiple other scales

have been proposed for specific populations such as SCI patients [2] and oncology patients [78]. While these tools assist health-care practitioners to manage their limited resources with regards to patient care, at best they only provide guesses as to who will develop pressure ulcers or not. The sensitivity—the ability to correctly diagnose an existing condition—of these techniques ranges from approximately 42 % – 87 % while the specificity—the ability to correctly determine that no condition is present—ranges from 57 % – 88 % [79]. Other studies have shown that nurses have great difficulty detecting and diagnosing suspected deep tissue injuries given the current frameworks they are provided [80], while physicians may be even worse [81]. While these scales are “better than nothing” at diagnosing patients with pressure ulcers, they are far from ideal and are simply not capable of actually diagnosing this disease—for that, a quantifiable detection technology is required.

In pressure ulcer research it is common to evaluate the extent of deep tissue injury formation through the use of T_2^* -weighted MRI [6], [10], [16]. T_2^* -weighted MRI is able to detect deep tissue injury by investigating tissue oxygenation as a proxy for detecting the lack of cellular activity due to necrosis. Although this technique is well suited for research purposes, it is simply not viable for detecting and monitoring the progression of DTI in the large population of at-risk patients. At the time of writing, MRI scans can easily cost thousands of dollars and take over an hour to complete [82]–[84]. Further, a large proportion of the at-risk population cannot undergo MRI scans for various reasons such as having medical implants or being unable to relocate from their hospital beds to a stationary MRI machine. Of the alternative diagnostic imaging modalities that currently exist, ultrasound provides the most promise due to its ability to noninvasively interrogate tissues in a mobile and

cost-effective manner.

B-mode ultrasound scans involve the sonographic interrogation of a tissue’s acoustic properties by transmitting sound waves on the order of multiple MHz and “listening” to the waves as they are reflected in tissue. B-mode ultrasound imaging has been used to identify hypo-echoic regions in sub-epidermal tissue related to DTI [3], [11], [85], however the results from these studies are somewhat unclear and require a degree of interpretation of the results. After combining thermographic techniques with b-mode imaging, it may be possible to increase the accuracy of early deep tissue injury detection [86]. As a more reliable alternative, ultrasound elastography—a sonographic technique for interrogating tissue strains rather than acoustic properties—has been proposed as a possible tool for clinical diagnosis of DTI [17], [87], [88]. Some exploratory studies have successfully used this technique to quantify deep tissue injury formation not only numerically, but in PVA-cryogel phantoms as well as in a rat model [18], [89]. While these studies show promise, they are only the beginning for the adoption of ultrasound elastography as a viable clinical detection modality for deep tissue injuries.

Recently, another possible avenue for DTI detection has arisen which lies in the biochemical markers present in a patient’s blood or urine. Rhabdomyolysis refers to the process when myoglobin proteins from damaged skeletal muscle enter the bloodstream due to a breakdown of muscle fibres in the body. Although this condition may be caused by numerous factors such as hyperthermia, ingestion of various drugs, alcohol abuse, toxins, autoimmune disease, or physical damage [90], [91], it may also be an indicator of formative DTI in at-risk patients who do not present with any of the aforementioned risk factors. Myoglobin proteins present in the blood get filtered in the kidneys

and as such can present in the urine, turning it tea-brown [92].

With the many avenues of DTI detection currently being explored and utilized, it is most likely that a combination of all the techniques will provide the most utility. For example, upon hospital admission or with a reasonably high risk assessment score, a patient may be given a blood test which confirms the presence of a forming injury or not. Patients with forming injuries may then be scanned using ultrasound technology to locate and quantify the injury. That patient may then receive more targeted care, of which the effectiveness may be continually monitored using both blood and ultrasound tests. It is expected that the targeted care that this approach would provide would increase patient health and well-being while at the same time decreasing the overall load on the health-care system.

2.2 Ultrasound Elastography

Ultrasound elastography is a relatively new imaging modality which is capable of imaging the stiffness of soft tissue using ultrasound waves [93] and has its roots in the millennia-old clinical practise of manually palpating tissues to detect localized changes in the mechanical properties of the tissue [94]. In general, the principle of ultrasound elastography is to visualize the deformation of soft tissue in response to an externally applied force [95]. This is in contrast to traditional ultrasound images which are created by interrogating tissue with high-frequency acoustic waves and “listening” to their echoes as they reflect off of tissue boundaries and small tissue irregularities (scattering centres) [96]. The externally applied force in ultrasound elastography may come from manual indentation of the ultrasound probe, a secondary external

vibrator, or as an acoustic radiation force impulse (ARFI) generated by the ultrasound transducer itself [93]. Ultrasound elastography is a proven technology when it comes to detecting very stiff lesions against relatively unstiff backgrounds—it has successfully been used to detect breast and prostate cancer lesions [12], [13], liver fibrosis [14], [97], and atherosclerosis [98]. There are generally three distinct methodologies or algorithms for generating soft tissue elastograms: quasi-static methods which rely upon the manual indentation of the transducer probe; ARFI imaging which measures the dynamic response of tissue due to ARFI excitation; and shear wave speed quantification which measures shear wave speeds developed in tissue due to ARFI excitation.

2.2.1 Quasi-Static Ultrasound Elastography

Quasi-static ultrasound elastography was the earliest and most simple form of ultrasound elastography [99], [100] and generally operates by cross-correlating axial scan lines of tissue in pre- and post- deformed states. The term “quasi-static” is used in this method as the deformation applied to the tissue is very slow compared to the measurement time. Quasi-static ultrasound elastography provides a qualitative measure of stiffness as the mechanical conditions involved during quasi-static interrogation cannot be fully known. Despite this, it is possible to obtain relative stiffness estimates by comparing lesionous regions against background tissue with a high spatial resolution and without modification to conventional ultrasound hardware [101], [102]. While quasi-static elastography originally relied upon one-dimensional ultrasound A-lines, the technique has since advanced to two-dimensional B-mode images [103] and even three-dimensional B-mode images [89], [104].

The cross-correlation foundation of quasi-static ultrasound elastography works by tracking the displacement of scattering centres which are inherently anchored to the tissue they are embedded within [105], [106] in much the same manner as contact free strain measurements may be obtained using optic means [107]. There have been numerous different quasi-static strain estimation algorithms developed, each with various advantages and disadvantages [102]. The most common algorithm involves simple cross-correlation maximization and was among the first algorithms to be proposed [103]. One of the most promising algorithms models compressed regions of interest as both scaled and translated versions of their uncompressed counterparts [95], [108] which can overcome poor correlations in simpler algorithms due to warping of the tissue under compression. This technique has successfully been used to investigate a deep tissue injury in: a finite-element model; a tissue phantom; and a rat model [18].

2.2.2 Acoustic Radiation Force Impulse Imaging

Acoustic radiation force impulse imaging is a more recent alternative to quasi-static ultrasound elastography which may greatly increase the inter-operator reliability of the technique by precisely controlling the externally applied mechanical interrogation force [109], [110]. While quasi-static ultrasound elastography relies upon the ultrasound operator to manually indent the tissue, ARFI imaging generates spatially focused ultrasound waves for relatively long periods of time (10s to 100s of μ s) compared to typical diagnostic procedures in order to generate an acoustic radiation force at the focal region [111]–[113]. Once the acoustic radiation force is generated within the tissue, the proce-

dure is extremely similar to the technique used in quasi-static ultrasound elastography—the deformation in the tissue caused by the externally applied force is tracked using classical ultrasound beams at high sampling frequencies. Although the magnitude of the resulting deformation is generally less than $20\text{ }\mu\text{m}$ [111], ultrasound beams are still able to detect deformations of less than $2\text{ }\mu\text{m}$ [114], [115]. By comparing the level of deformation throughout the tissue to a homogeneous interrogation force, the relative stiffness of individual regions of tissue may be ascertained—relatively stiff regions of tissue will deform less than relatively unstiff regions of tissue.

Since the development of acoustic radiation force within deep tissue requires greater amounts of applied pressure for longer durations than classical ultrasound b-mode imaging, the safety of the technique becomes an important consideration. Health Canada guidelines assert that ultrasound technologies be applied to patients only when medically necessary and exposures should be kept as low as reasonably achievable in any imaging mode [116]. Health Canada also places a limit on the derated spatial-peak time-average intensity, I_{SPTA} of 720 mW cm^{-2} which is derived from FDA regulations [117]. Since I_{SPTA} is a temporal average, the compliance of this value can be easily controlled by controlling the repetition time of scans—simply disabling ultrasonic push beams for long enough that the tissue has a chance to recover from the initial burst of pressure will allow the device to operate with safety in regards to this parameter. A much more critical parameter is the derated spatial-peak pulse-average intensity, I_{SPPA} , which is not considered by Health Canada but limited to 190 W cm^{-2} by the FDA [117] for classical diagnostic imaging. This measure is important as it relates to the peak intensity developed in the tissue during an interrogation pulse and is a limit that may need to be pushed in

order to develop adequate deformation in deep tissues. Later revisions to FDA guidelines have allowed greater values of I_{SPPA} for alternate imaging modes, with values up to 933 W cm^{-2} being allowed for combined B and M-mode imaging [96].

2.2.3 Shear Wave Speed Quantification

Shear wave speed quantification represents the most complicated method of interrogating tissue stiffness using ultrasound technology, however these added complications come with the ability to obtain quantitative measures of tissue stiffness instead of the qualitative measures presented by quasi-static elastography and ARFI imaging. Unlike the longitudinal waves that are used in classical ultrasound imaging, shear waves travel perpendicular to the direction of particle motion and travel at relatively low speeds of $1 \text{ m s}^{-1} - 10 \text{ m s}^{-1}$. The speed of travel of shear waves is highly dependent on the density and stiffness of tissue as per equation 2.1 where μ_{tissue} is the shear modulus of the tissue and ρ is the density. Since density cannot be measured *in vivo*, the measurement of shear speed and an assumption of tissue density can be used to calculate the shear modulus [96].

$$c_T = \sqrt{\frac{\mu_{tissue}}{\rho}} \quad (2.1)$$

In order to generate shear waves in tissue, a focused acoustic radiation impulse force must be applied to the tissue to generate shear waves which radiate from the focal point, much like creating ripples in a pond or ringing a bell [118]. As these shear waves travel outwards from the ARFI focal point, the deformation they create in the tissue can be tracked using classical ultrasound

beams sampled at extremely high frequencies. In order to image a large region of tissue at once using generated shear waves, a series of progressively deepening acoustic radiation impulses may be applied in an axial line to generate a “mach cone” of shear waves throughout an entire region of tissue [119].

Shear wave speed quantification has been successfully used to noninvasively determine the mechanical properties of not only tissue mimicking materials [120] but numerous human soft tissues *in vivo* [121]. Further work has been done to construct various viscoelastic models of soft tissue behaviour based on shear wave speed elastography including Kelvin-Voigt, Maxwell, and Zener models [122], [123]. Even more complete models have been constructed by combining shear wave speed quantification with ultrasonic computed tomography to calculate not only the shear modulus of tissue but the bulk modulus as well [124]. Finally, shear wave speed elastography has successfully been used to investigate crush injuries in rabbits which are aetiologically similar to deep tissue injuries [125].

2.3 Conclusion

Pressure ulcers and deep tissue injuries are severe wounds that place a tremendous burden not only on those who suffer from them, but on the health care system as well. These injuries are generally caused by some combination of ischemia and reperfusion injury as well as excessive cell deformation. Deep tissue injuries are substantially more difficult to detect than pressure ulcers due to where they form—DTI generally form deep in tissue immediately superior to bony prominences and follow a “bottom-to-top” tunnelling pattern that is hardly detectable until it is “too late” and the wound has broken open

as a late-stage pressure ulcer. Deep tissue injury prevention generally relies upon mechanically offloading at-risk tissue areas by “turning” the patient or by utilizing special pressure-redistribution support surfaces, while deep tissue injury treatment is somewhat limited and relies upon increasing a patient’s overall health or resorting to surgical techniques. Recent research suggests that intermittent electrical stimulation may provide substantial benefits for preventing deep tissue injuries, however without a feasible means of reliably detecting them, the effectiveness of these treatments cannot be adequately gauged.

While detection of deep tissue injuries may be done in a research setting by using T_2^* -weighted MRI, this is not a cost-effective approach and is generally not used clinically. Instead, health-care practitioners rely upon risk-assessment scales which provide a somewhat subjective and qualitative measure of a patient’s chance of forming a pressure ulcer or DTI instead of actually detecting the disease. Relatively recent advances in ultrasound technology may be able to bridge this gap by imaging the relative stiffness of tissue since it is known that deep tissue injuries undergo significant stiffness changes through their lifetime. The technique of using ultrasound to image tissue stiffness is called “ultrasound elastography” and it works through the estimation of relative local tissue deformations under a commonly applied load. Ultrasound elastography generally encompasses three main techniques of interrogating tissue: manually by indenting the transducer head and tracking displacement of scattering centres before and after the deformation; utilizing an acoustic radiation force to specifically displace a region of tissue and measuring its dynamic response; and utilizing an acoustic radiation force to generate shear waves in the tissue and measuring the shear wave speeds as they travel through the tissue.

While preliminary work has shown that quasi-static ultrasound elastography has the potential to be used for the early detection of deep tissue injuries [18], the technique is not yet fully understood in this regard. Further, the use of ARFI imaging and shear wave speed quantification have not yet been explored as a means of detecting DTI. In order to advance the science and move closer to a clinical implementation of this technology, all modes of ultrasound elastography must be characterized with regards to their use in detecting deep tissue injuries.

Chapter 3

Numerical Characterization of Quasi-Static Ultrasound Elastography

3.1 Introduction

The goal of this study was to numerically characterize various important parameters related to detecting DTI using quasi-static ultrasound elastography (such as lesion geometry, material properties, and transducer characteristics) in order to examine the feasibility of using the technique to detect early DTI in humans. Quasi-static ultrasound elastography involves displacing the surface of the skin such that internal tissues are placed under a strain field. Ultrasound signals are used to track internal strains which then relate to the localized mechanical stiffness of the tissue—local regions that are significantly more or less stiff than surrounding tissue may be classified as either undergoing rigor mortis or necrosis and may present cause for concern.

3.2 Method

In order to evaluate the sensitivity of using quasi-static ultrasound elastography to detect deep tissue injuries, a numerical model of these injuries was created such that a subset of the investigated cases mimicked a physical phantom model which was used for validation. This numerical model allowed the rapid modification of numerous parameters related to DTI to examine their effect on the method’s detection sensitivity where detection sensitivity is defined as the slope of the given characterization plot. An ideal detection sensitivity would resemble a unary mapping between the measured lesion stiffness ratio and the true lesion stiffness ratio. Lesions are considered to be “detectable” when the measured strain ratio of the lesion is significantly greater than or less than 1. Lesions with measured strain ratios of 1 would appear the same as healthy tissue and would most likely not be detected in the elastogram. To fully understand the problem, 5 general model cases were studied with each case generating numerous sub-studies on the effect of various parameters relating to that case. These parameters included: lesion depth; lesion altitude (distance of the lesion above deep bone); lesion diameter; ratio of the stiffness between the lesion and the surrounding tissue; ultrasound probing frequency; strain level applied by the transducer; the separation distance between two co-located lesions; radius of a circular averaging filter applied to the lesion boundaries; the number of smaller clustered lesions per unit area—noting that the small lesions in this model may overlap each other; the radius of each individual clustered lesion; the width of the lesion in a Visible Human [126] model and the depth of the lesion in a Visible Human model. The range of values for the tested parameters are given in Table 3.1 which resulted in a total

of 144 model cases that were analyzed. The geometry of the models shown in Fig. 3.1 include: a cross-section of a simple spherical lesion embedded within a 2-dimensional rectangular zone of soft tissue; two lesions located at the same depth separated laterally by a finite dimension, δ_{sep} ; a cross-section of a spherical lesion without hard boundaries; a cluster of small lesions which together form a larger lesion area; and a lesion with MRI-acquired geometry [67] embedded in geometry obtained from a Visible Human slice [126].

In Fig. 3.1e, the lesion is located superficial to the left ischial tuberosity in the transverse plane. The lesion geometry was obtained from an MRI scan of a real deep tissue injury induced in a porcine model [67]. The generic soft tissue in this model is modelled after muscle, with a layer of adipose tissue residing at the surface of the model.

Note that the axial direction referred to henceforth as the “axial” direction of an ultrasound transducer placed along the top (superficial) surface of the domain such that it becomes the “vertical” direction.

Table 3.1: Range of values of investigated parameters

Parameter	Symbol	Values	Units
Lesion depth	d	3.5, 6.5, 8.5, 10.0	cm
Lesion altitude	h	1.25, 2.50, 3.75	cm
Lesion diameter	$\varnothing S$	0.5, 1.0, 2.0, 2.5	cm
Lesion stiffness ratio	E_{rel}	0.32, 0.56, 1.80, 3.20	—
Ultrasound frequency	f	2, 4, 8	MHz
Transducer-applied strain	ε_{app}	2.5, 5.0, 10.0	%
Co-located separation distance	δ_{sep}	1.25, 1.50, 1.75, 2.00	cm
Blurred lesion blur radius	b_r	1.0, 2.5, 5.0, 7.5	mm
Clustered lesion density	b_ρ	10, 20, 30, 40	cm ⁻²
Clustered lesion radius	r_{bl}	0.5, 1.0, 1.5	mm
Visible human lesion width	$\varnothing L$	0.5, 1.0, 2.0, 2.5	cm
Visible human lesion depth	d	6.25, 6.75, 7.25	cm

3.2.1 Formation of B-Mode Ultrasound Images

Through the convolution of a point spread function and a normal random distribution of scattering centres, simulated ultrasound images were generated. The point spread function was defined axially as a cosine function operating at the ultrasound probing frequency modulated by a Gaussian distribution defined by $\mu = 2\lambda_{wave}$ and $\sigma = 2\lambda_{wave}$ where λ_{wave} is the wavelength of the ultrasonic probing waves. Laterally, the point spread function was modelled as a Gaussian distribution defined with a mean of 0 and a standard deviation of $0.25w_{active}$ where w_{active} is the total width of the active transducer elements during scan-line acquisition. This resulted in the point spread function given in Fig. 3.2. Resulting images were composed of 192 scan lines each sampled at 50 MHz.

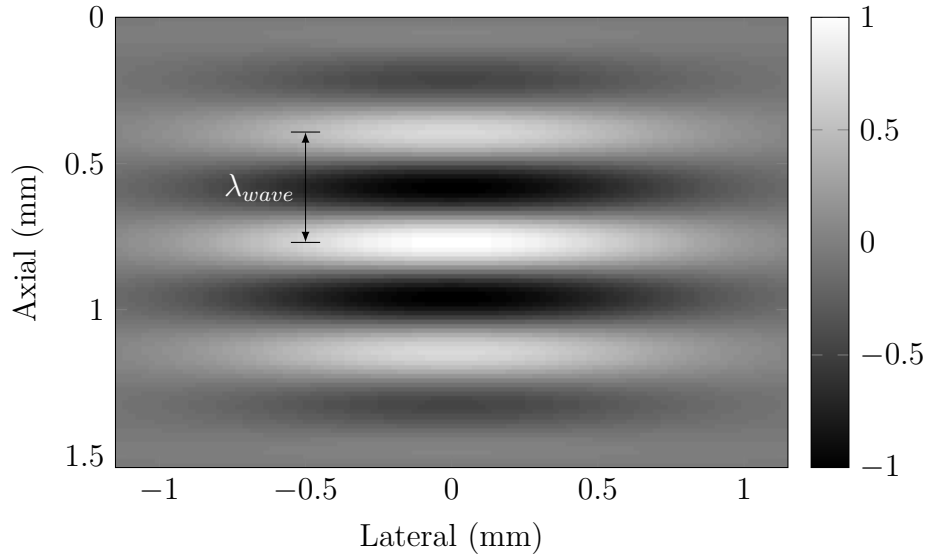


Fig. 3.2: Point spread function used for simulating b-mode ultrasound scans. The function is defined axially by a cosine function at the probing frequency and modulated by a Gaussian function both axially and laterally.

3.2.2 Finite-Element Model of Tissue Deformation Under Surface Distortion

As a response to an external load being applied to the boundary of a domain, internal structures deform. In the case of a relatively stiff deep tissue injury embedded within surrounding soft tissues, this implies that when the surface of the skin is depressed, the relatively stiff lesion will not strain to the same magnitude that the surrounding soft tissue does. In order to simulate the deformation of interrogated tissue, the displacement field for the simulated models was calculated according to equation 3.1 where σ is the Cauchy stress tensor and F are the applied body forces. Simulations were performed assuming a 2-dimensional linearly elastic material deformation model under plane strain conditions.

$$-\nabla \cdot \sigma = F \quad (3.1)$$

A 3-dimensional model was also considered, however the deformations differed from the 2-dimensional simulation by less than 1% so a 2-dimensional model was deemed adequate. Soft tissue was modelled using a Young's modulus of elasticity of 25 kPa, Poisson's ratio of 0.499, and density of 998 kg m^{-3} [128]–[130]. Bone was modelled in the Visible Human model with a Young's modulus of elasticity of 18.6 GPa, Poisson's ratio of 0.15 and density of 297 kg m^{-3} [131]–[133]. The only difference in lesion mechanical properties from the surrounding soft tissue was the modulus of elasticity which varied according to the simulation parameters. The bottom of the domain was held fixed such that equation 3.2 held true.

$$\vec{u} = 0, \quad \Gamma = \Gamma_{bottom} \quad (3.2)$$

While this boundary condition represents an idealized scenario, it may be likened to that of tissue located superficial to a relatively stiff anchoring bone below since the stiffness of bone is several orders of magnitude greater than soft tissue and will not significantly deform under the loads explored in this model. This lower region is where deep tissue injuries generally form and is therefore of special importance. Compressive strains were applied to the top of the domain so as to induce strain along the top boundary as per equation 3.3. A visual representation of these boundary conditions is given in Fig. 3.3.

$$\vec{u} = (0, -u_0), \quad \Gamma = \Gamma_{top} \quad (3.3)$$

From these simulations, displacement fields throughout the domain were calculated which were then used to displace tissue (including scattering centres) in the simulated ultrasound images in both the axial and lateral directions. This process resulted in pairs of pre- and post- compression simulated b-mode images of lesions of varying parameters which could then be analyzed and characterized. Sample source code for calculating these finite-element models using COMSOL Multiphysics[®] is given in listing B.2 in Appendix B.

3.2.3 Characterizing Quasi-Static Ultrasound Elastography

Utilizing a 2-D locally regularized tissue strain estimation algorithm [108], pairs of pre- and post- compression images were used to calculate elastogram

ROI overlaps of 80 %.

3.2.4 Model Validation Using a Commercially Available Phantom

Utilizing a CIRS Elasticity QA Phantom model 049, a subset of the results obtained from the finite-element simulations and numerical characterizations were compared against their physical phantom equivalents. The phantom mimics acoustically homogeneous soft tissue with embedded lesions which vary in depth, size, and mechanical stiffness. Nominal mechanical properties of the phantom as given by manufacturer specifications are summarized in Table 3.2. Pre- and post- compression b-mode ultrasound images were obtained of lesions in the phantom and the resulting strain ratios for each lesion were compared to the simulated strain ratios for the specific combination of parameters. Specifically, lesions at a depth of 3.5 cm, a diameter of 2.0 cm, and with true stiffness ratios of 0.56, 1.80, and 3.20 were examined. Surface indentation was performed manually with the transducer indenting approximately 0.5 cm (6.25 %) at the surface. The detailed experimental protocol that was followed for these validations is given in Section C.1 in Appendix C.

Table 3.2: CIRS phantom model mechanical properties

Property	Symbol	Value	Units
Nominal basal elastic modulus	E_{tissue}	25	kPa
Lesion elastic modulus	E_{lesion}	8, 14, 45, 80	kPa
Speed of sound	c_0	1540	m s^{-1}
Acoustic attenuation	α	0.5	$\text{dB cm}^{-1} \text{ MHz}^{-1}$
Lesion diameter	$\varnothing S$	10 and 20	mm
Lesion depth	d	15 and 35	mm

3.3 Results and Discussion

Following the procedure outlined in Section 3.2, finite-element models of ultrasonic b-mode image formation and tissue deformation were synthesized. The results of these models were then fed into the local strain estimation algorithm described in Section 3.2.3. The resulting numerical characterizations of the relationship between measured and true strain ratios in the simulated tissue and their dependence on the various lesion parameters given in Table 3.1 were examined. Finally, the local strain estimation algorithm was carried out on a physical phantom and compared against a subset of the simulated cases.

3.3.1 Finite Element Models of Ultrasound and Deformation

Sample images generated using both the acoustic and deformation finite-element models are given in Figs. 3.4c – 3.4d. In Fig. 3.4c, a sample generated b-mode ultrasound scan is given. Fig. 3.4a shows the lateral displacement field generated by the deformation finite-element model while Fig. 3.4b shows the axial displacement field. The entire top surface of the model has been displaced axially by 6.25 mm (5%), which caused deformation of both the soft tissue and embedded lesion within. Since the lesion was modelled as being 3.2 times stiffer than the surrounding tissue, the lesion underwent less strain which consequently resulted in the lesser displacement depicted. Fig. 3.4d shows the resultant b-mode image generated by applying the displacement field given in Figs. 3.4a and 3.4b to the tissue and embedded scattering centres used to create Fig. 3.4c. What results is a locally scaled and translated version of

Fig. 3.4c that corresponds to indenting the surface of the skin above a stiff lesion. The large anechoic region located at the bottom of the domain is tissue that was not modelled in the pre-compression image as it was outside of the original domain. This area represents the region of tissue that is undetectable with the strain-estimation algorithm given in Section 3.2.3 as the information contained there is only available in one of the two input images and so is considered incomplete data. Sample source code for generating the b-mode images seen in Fig. 3.4 is given in listing B.1 in Appendix B.

3.3.2 Resulting Elastograms

The 2-D locally regularized tissue strain estimation algorithm described in Section 3.2.3 was used in combination with the simulated resultant b-mode ultrasound images (Figs. 3.4c and 3.4d) in order to generate elastogram images which were used in the subsequent analysis. Sample source code for generating these elastograms is given in listing B.3 in Appendix B. An example elastogram resulting from the simulation presented in Fig. 3.4 is shown in Fig. 3.5. Throughout the entire domain on this sample elastogram, regions outside of the stiff lesions showed compressive strains of approximately 5 % as expected due to the compression applied to the upper boundary of the model. The entire lesion region showed relatively consistent low strain amounts of approximately 2.5 %, which is consistent with the lesion being stiffer (and so straining less) than the surrounding tissue. Of note is the increased strain pattern which appeared both axially and laterally around the lesion. While generally symmetric about the axial direction, this stress field was largely concentrated above the lesion when the lesion was deep (close to the bone). This may be explained as a stress concentration brought about by the sudden change in mechanical material properties of the tissue and may serve to fuel the conditions of excessive cell deformation and ischemia which initiated the formation of a deep tissue injury in the first place, exacerbating the wound and assisting its expansion toward the surface. Further, a largely variable strain field artifact is seen along the superior surface of the elastogram shown in Fig. 3.5. While this field does not appear to affect the remainder of the generated elastogram, it will serve to mask any extremely shallow lesions in the tissue, though given as deep tissue injuries generally form immediately superior to

given in Table 3.1. “Measured” strain ratios for each elastogram were obtained by comparing the mean strain within each lesion with the mean engineering strain of the surrounding tissue such that:

$$\varepsilon_{rel,meas} = \frac{\varepsilon_{tissue}}{\varepsilon_{lesion}} \quad (3.4)$$

ε_{tissue} was sampled as the mean strain in the region of tissue with the same geometry as the lesion located immediately superficial to the lesion in all cases.

In order to characterize how each parameter of interest affects the detection sensitivity of quasi-static ultrasound elastography, measured strain ratios for various lesions were calculated and compared against $\varepsilon_{rel,true}$. $\varepsilon_{rel,true}$ is derived from the relative Young’s modulus of elasticity of the lesion such that:

$$\varepsilon_{rel,true} = \frac{\varepsilon_{tissue}}{\varepsilon_{lesion}} = \frac{\left(\frac{\sigma_{applied}}{E_{tissue}}\right)}{\left(\frac{\sigma_{applied}}{E_{lesion}}\right)} = \frac{E_{lesion}}{E_{tissue}} \quad (3.5)$$

Fig. 3.6 portrays the severe error involved with using the methods described in Section 3.2 to investigate extremely low stiffness lesions where the percent error was calculated as per equation 3.6 where Y_i are the measured values for the true / nominal values \hat{Y}_i . In nearly all investigated cases where the true lesion stiffness ratio was 0.32, the algorithms described severely misrepresented the measured strain ratio of the lesion, often portraying these extremely low stiffness regions as being more stiff than they truly were. It is hypothesized that the excessively large localized deformations in these lesions interrupted the algorithm’s ability to sufficiently track the displacement of scattering centres within the tissue, lowering the magnitude of displacement within the lesion and subsequently increasing it’s “measured” strain ratio.

ultrasonic gel). This difficulty suggests that acoustic radiation force impulse (ARFI) elastography would be a more appropriate method to acquire DTI elastograms. ARFI elastography works on the same principles as quasi-static elastography with the exception that tissue deformation is caused by localized large-amplitude acoustic waves generated by the transducer such that human factors play a far less substantial role in image acquisition.

3.4 Conclusion

This work represents a numerical characterization of the use of quasi-static ultrasound elastography for the early detection of deep tissue injuries (DTI). There is a real clinical need for an objective tool that is capable of detecting the formation and progression of DTI in human subjects as these wounds are generally not visible from the surface of the skin until they have broken through and already caused substantial damage.

Through this numerical characterization, quasi-static ultrasound elastography was found to be an effective tool for detecting and monitoring DTI in theoretical simulations. Overall, detection sensitivity was less than expected. Small lesions (with diameters ≤ 1.0 cm) were more difficult to differentiate due to the low lesion detection sensitivity. While lesion depth, altitude above the underlying bone, and probing frequency did not have significant effect on the lesion detection sensitivity, it was found that applying high levels of compressive strain (10 %) introduced severe error for both very unstiff and very stiff lesions, thus it is recommended that diagnosticians only apply moderate (≤ 5 %) compressive strain when interrogating potential lesions. Larger strains may alternately be induced by slowly palpating the tissue with very

minor strains frame-by-frame and cumulating the displacement fields across these smaller palpations. Care must be used when palpating the tissue, lest “vigorous” palpations cause harm to the already sensitive injury. In the more complicated model of co-located lesions, while the separation distance between adjacent lesions did not affect the detection sensitivity, the placing of adjacent lesions generated “phantom” lesion regions with altered strain that may appear to be diseased tissue when they are in fact healthy. In a model lesion with gradual blurred boundaries, the effect of blur radius only affected the detection sensitivity and ability to differentiate unstiff lesions. Specifically, unstiff lesions with large blur radii became nearly impossible to differentiate as these lesions all showed a measured lesion stiffness ratio of approximately 1 which would show up as regular, healthy tissue. In the case of numerous clustered small lesions, both decreased lesion density and decreased individual lesion size caused a decrease in lesion detection sensitivity, likely due to the averaging effect of healthy tissue and diseased tissue in near proximity. Finally, in the Visible Human-MRI acquired lesion model, lesions with widths ≤ 1.0 cm are nearly impossible to differentiate as they are hidden by the strain field generated by the bony prominence. Lesion depth did not have an effect on the detection sensitivity, though deeper lesions (lesions which were closer to the bony prominence) had overestimated stiffnesses with respect to their more superficial counterparts.

Although the studies presented here resulted in less-than-ideal detection sensitivities, the technique was still able to pick out lesions from the surrounding unstiff (and hard) tissue. Work done by Solis et al. [67] has shown that untreated DTI are multiple centimetres in size, while work done by Gefen et al. [5] has shown that deep tissue injuries exhibit 1.8-fold to 3.3-fold mechanical

stiffening. The work presented here has shown that quasi-static ultrasound elastography is adequate at detecting deep tissue injury lesions in these ranges of parameters and will thus be adequate to detect and monitor progress DTI. However, without further real-world experimentation on the exact nature of newly-forming DTI, the detection sensitivity required to detect newly-forming DTI is indeterminate.

A subset of the results found through simulation were compared with similar experiments done using a tissue mimicking phantom model. The experimental results using the phantom model generally agreed with those found from simulation cases. It was also noted that the manual skin indentation technique involved with quasi-static ultrasound elastography proved to be difficult to produce reliable images. This difficulty suggests that an alternate method of performing ultrasound elastography may be preferable to quasi-static ultrasound elastography with manual indentation. Acoustic radiation force impulse (ARFI) elastography may be a more appropriate method to acquire DTI elastograms as although ARFI elastography works on the same principles as quasi-static elastography, the difference lays in the fact that tissue deformation is caused by localized large-amplitude acoustic waves generated by the transducer. This means that human factors play a far less substantial role in image acquisition and would likely improve repeatability and inter-operator reliability. Nevertheless, the work done here to characterize the use of quasi-static ultrasound elastography is an important step along the path of generating a useful clinical tool for detecting formative and monitoring progressive deep tissue injuries.

Chapter 4

Numerical Characterization of Acoustic Radiation Force Impulse Imaging

4.1 Introduction

Acoustic radiation force impulse imaging presents a chief benefit over quasi-static ultrasound elastography in that since the external deformation force is applied by the transducer itself rather than through manual indentation of the transducer by the diagnostician, the inter-operator reliability may be greatly increased. The net effect of this is an expected decrease in the required amount of training of diagnosticians as well as an expected increase in the sensitivity and specificity of early deep tissue injury detection.

4.2 Method

In order to numerically characterize acoustic radiation force impulse imaging for the early detection of deep tissue injuries, a combinatory model of acoustic radiation force simulations and time-domain finite-element models of tissue deformation were used. Acoustic radiation force distributions were calculated using a k-space pseudo-spectral model of ultrasonic acoustics which simulated the acoustic intensities and subsequent radiation force developed by an ultrasonic transducer applying deep body loads to soft tissue. These forces were then combined with a temporal finite-element model of tissue deformation to model the response of the tissue to the body force impulses generated by the transducer. The use of these models allowed extensive simulation and parameter sensitivity analysis in order to numerically characterize the use of acoustic radiation force impulse imaging for detecting deep tissue injuries.

4.2.1 K-Space Pseudo-spectral Model of Acoustic Fields

In order to simulate the body loads generated within deep tissue by a continuous ultrasound beam, a k-space pseudo-spectral model of acoustic field intensities was generated. The body load fields that were generated as a result of this model were fed into a temporal soft tissue deformation model to investigate the dynamic response of tissue to ARFI loads.

The governing equations used for the k-space pseudo-spectral model were the set of coupled first-order partial differential equations 4.1a – 4.1c. These equations are the first-order equivalents of the wave equation given in equation 4.2 taking into account acoustic absorption, tissue heterogeneities, and acoustic wave non-linearities [134]. Equations 4.1a, 4.1b, and 4.1c represent

the momentum conservation, mass conservation, and pressure-density relation terms respectively.

$$\frac{\partial \vec{v}}{\partial t} = -\frac{1}{\rho_0} \nabla p \quad (4.1a)$$

$$\frac{\partial p}{\partial t} = -(2\rho + \rho_0) \nabla \cdot \vec{v} - \vec{v} \cdot \nabla \rho_0 \quad (4.1b)$$

$$p = c_0^2 \left(\rho + \vec{u} \cdot \nabla \rho_0 + \frac{B}{2A} \frac{\rho^2}{\rho_0} - \mathbf{L}\rho \right) \quad (4.1c)$$

In equations 4.1, \vec{v} is the acoustic particle velocity, p is the acoustic pressure, ρ is the acoustic density, ρ_0 is the equilibrium density, c_0 is the acoustic sound speed, \vec{u} is the acoustic particle displacement, and B/A is a nonlinearity parameter which models alterations to the sound speed [135].

$$\nabla^2 p - \frac{1}{c_0^2} \frac{\partial^2 p}{\partial t^2} = 0 \quad (4.2)$$

The \mathbf{L} operator used in equation 4.1c accounts for acoustic absorption and dispersion which follows a frequency power law and is defined as per equations 4.3a – 4.3c where α_0 is the power law prefactor and y is the power law exponent of the tissue. τ and η represent absorption and dispersion proportionality coefficients respectively.

$$\mathbf{L} = \tau \frac{\partial}{\partial t} \left(-\nabla^2 \right)^{\frac{y}{2}-1} + \eta \left(-\nabla^2 \right)^{\frac{y+1}{2}-1} \quad (4.3a)$$

$$\tau = -2\alpha_0 c_0^{y-1} \quad (4.3b)$$

$$\eta = 2\alpha_0 c_0^y \tan \left(\frac{\pi y}{2} \right) \quad (4.3c)$$

In order to integrate pressure sources in equations 4.1a – 4.1c, equation 4.1b is modified to include a mass source term, S_M which counts as a pressure source term through changing density to form equation 4.4.

$$\frac{\partial p}{\partial t} = -(2\rho + \rho_0) \nabla \cdot \vec{v} - \vec{v} \cdot \nabla \rho_0 + S_M \quad (4.4)$$

The k-Wave MATLAB[®] toolbox version 1.0 was used to solve for the time-variant intensities resulting from simulated acoustic radiation force impulses applied to heterogeneous soft tissue using equations 4.1a, 4.4, and 4.1c with the acoustic properties listed in Table 4.1. Sample source code for performing these simulations using the k-Wave toolbox is given in listing B.4 in Appendix B.

Table 4.1: K-Space pseudo-spectral model parameters

Property	Symbol	Value	Units
Nonlinearity parameter	B/A	8	—
Power law prefactor	α_0	0.7	Np (rad/s) ^{−y} m ^{−1}
Power law exponent	y	0.95	—
Density	ρ_0	1,060	kg m ^{−3}

4.2.2 Derivation of Acoustic Radiation Force

Acoustic radiation force arises as the result of absorption of linear momentum within tissue as acoustic waves travel through it with the requirement that the tissue is a viscoelastic medium—no energy would be absorbed in a purely linear elastic model. Further, at the super-MHz frequencies involved in ultrasound interrogation, tissue may be considered a viscous fluid [113].

Using a perturbative expansion of the general equation of linear momentum given in equation 4.5, acoustic radiation force can be expressed as per equations

4.6 [136]. In equations 4.6, $\langle \rangle$ represents the time-average operator, \vec{v}_1 and \vec{v}_2 are the first and second order terms in the perturbative expansion of particle velocity, p_2 is the second order pressure term in the perturbative expansion, while \vec{F} represents the acoustic radiation force developed in the tissue.

$$\sigma_{ij,j} + \rho b_i = \rho f_i \quad (4.5)$$

$$\vec{F} = \nabla p_2 - \mu_{tissue} \nabla^2 \vec{v}_2 \quad (4.6a)$$

$$\vec{F} = \rho \langle \vec{v}_1 \nabla \cdot \vec{v}_1 + \vec{v}_1 \nabla v_1 \rangle \quad (4.6b)$$

For a plane wave, equation 4.6b can be reduced to equation 4.7. Further, substituting the generalized wave particle velocity solution given in equation 4.8 in equation 4.7, the magnitude of acoustic radiation force may be calculated as per equation 4.9.

$$\vec{F} = 2\rho \langle \vec{v} \vec{v}_{,x} \rangle \quad (4.7)$$

$$\vec{v} = i\omega A e^{-\alpha x + i(\omega t - kx)} \hat{x} \quad (4.8)$$

$$|\vec{F}| = A^2 e^{-2\alpha x} \rho \alpha \quad (4.9)$$

Further using the acoustic field intensity, the acoustic radiation force may be calculated as per equation 4.10 where α is the absorption coefficient of the tissue in Np m^{-1} , I is the temporal average acoustic intensity in W m^{-2} , and

c is the longitudinal speed of sound in the tissue in m s^{-1} [113].

$$|\vec{F}| = \frac{2\alpha I}{c} \quad (4.10)$$

Once acoustic radiation force body loads were calculated as per equation 4.10, they were used as initial conditions to the temporal finite-element model of soft tissue deformation described in Section 4.2.3.

4.2.3 Temporal Finite-Element Model of Soft Tissue Deformation

In response to the relatively short duration (“impulse”) acoustic radiation force body load applied to tissue in ARFI imaging, the interrogated tissue will exhibit a dynamic response—namely that tissue deformation will propagate outwards as the absorbed acoustic energy diffuses through the soft tissue.

In order to simulate the dynamic tissue deformation generated by the acoustic impulse force, a generalized Maxwell viscoelastic model of tissue deformation was used [137]. The simulated tissue properties are summarized in Tables 4.2 and 4.3.

Table 4.2: ARFI model tissue properties

Property	Symbol	Value	Units
Bulk Modulus	K	515.7	kPa
Shear Modulus	μ_{tissue}	1.0	kPa
Density	ρ	1,060	kg m^{-3}

The time-dependent displacement fields were calculated according to equation 4.11 where σ is the Cauchy stress tensor, \vec{F} are the applied body forces, and \vec{u} is the particle displacement, and ρ is the density.

Table 4.3: ARFI Maxwell model tissue properties

Branch	Shear Modulus (Pa)	Relaxation Time (s)
1	791.0	2
2	66.5	40
3	0.6	80

$$\rho \frac{\partial^2 \vec{u}}{\partial t^2} - \nabla \cdot \sigma = \vec{F} \quad (4.11)$$

In order to include viscoelastic effects through a generalized Maxwell model of soft tissue, equation 4.12 was used where σ_0 is the initial stress distribution in the tissue, C is the 4th order elasticity tensor, ε is the strain, G_m and τ_m are the shear modulus and relaxation time of the m^{th} branch of the Maxwell model respectively, and γ_m is an additional auxiliary degree of freedom used to represent the extension of the abstract springs in the Maxwell model.

$$\sigma - \sigma_0 = C : \varepsilon + \sum_m 2G_m \tau_m \dot{\gamma}_m \quad (4.12)$$

In the simulations, the boundary equations 4.13 were used to apply a fixed boundary condition to the both the bottom (deep) and top (superficial) boundaries of the model in the axial direction at both boundaries and in the lateral direction at the deep boundary. All other boundaries of the model were free to translate in all dimensions. A visual representation of these boundary conditions is given in Fig. 4.1. The acoustic radiation force was applied as a body load to the tissue in the model with the distribution calculated by the k-space pseudo-spectral model and resultant body forces described in Sections 4.2.1 and 4.2.2. In order to prevent reflections from the model boundaries that

4.2.4 Characterizing Acoustic Radiation Force Impulse Imaging

In order to fully understand the suitability of using ARFI imaging to detect and monitor deep tissue injuries, 1 model of unlesioned tissue and 4 general models of deep tissue injury lesions were modelled. Each model was investigated over a range of parameters in order to determine the relationship between the detection sensitivity and the various parameters that were studied. The unlesioned model was used to investigate the general effects of acoustic radiation force impulse forces in soft tissue. The investigated lesionous models included a hard-boundaried spherical lesion embedded in a homogeneous soft tissue domain, a lesion with blurred boundaries that “fades” into the homogeneous soft tissue background, a cluster of small lesions which together comprise a greater lesionous region, and a lesion with MRI-acquired geometry [67] embedded in geometry obtained from a Visible Human slice [126]. Schematics of the four investigated models are given in 4.2.

In order to characterize ARFI imaging, ranges of parameters pertinent to each investigated model were studied. The parameters relating to general soft tissue response to acoustic body loads included: the ARFI interrogation frequency used to excite the tissue with acoustic radiation force; the transducer width which applies the acoustic radiation force to the tissue; the number of pulse cycles (loading time) applied by the transducer; and the pressure applied by the transducer. The lesionous models investigated yet more parameters including: lesion depth; lesion diameter; lesion relative stiffness ratio; lesion blur radius; the number of tightly-packed lesions in a clustered lesion model; the radii of the individual tightly-packed lesions in a clustered lesion model;

Table 4.4: Range of values of investigated parameters in the various ARFI models that were studied.

Parameter	Symbol	Values	Units
ARFI interrogation frequency	f	1, 2, 4, 6	MHz
Transducer width	w_{trans}	4, 8, 10	cm
ARFI pulse cycles	n_c	3, 100, 300, 500, 700	—
ARFI source pressure	P_{source}	4, 5, 6, 7, 8	MPa
Lesion depth	d	1, 2, 3, 4, 5, 6, 7, 8, 9	cm
Lesion diameter	$\varnothing S$	0.5, 1.0, 2.0, 2.5	cm
Lesion stiffness ratio	E_{rel}	0.32, 0.56, 1.80, 3.20	—
Blurred lesion blur radius	b_r	1.0, 2.5, 5.0, 7.5	mm
Clustered lesion density	b_ρ	10, 20, 30, 40	cm ⁻²
Clustered lesion radius	r_{bl}	0.5, 1.0, 1.5	mm
Visible human lesion width	$\varnothing L$	0.5, 1.0, 2.0, 2.5	cm

In order to calculate the measured lesion stiffness ratios that are presented in Section 4.3.3, equations 4.14 may be applied. Assuming a constant force applied to the both the lesionous region and the soft tissue reference point, the stiffness ratio of the lesion may be calculated as the ratio between the measured tissue deformation and the measured lesion deformation. As the acoustic radiation force impulse interrogation process is highly dynamic, the maximum induced deformation in the region of interest after application of the acoustic radiation force ceased was used in all characterizations.

$$\sigma = E\varepsilon \quad (4.14a)$$

$$\sigma_{lesion} = \sigma_{tissue} \quad (4.14b)$$

$$E_{lesion}\varepsilon_{lesion} = E_{tissue}\varepsilon_{tissue} \quad (4.14c)$$

$$E_{rel} = \frac{E_{lesion}}{E_{tissue}} = \frac{\varepsilon_{tissue}}{\varepsilon_{lesion}} = \frac{\Delta L_{tissue}}{\Delta L_{lesion}} \quad (4.14d)$$

4.2.5 Physical Phantom Validation

The same CIRS Elasticity QA Phantom model 049 that was used in the quasi-static studies described in Chapter 3 was used to experimentally validate a subset of the ARFI simulations described here. Using a Siemens ACUSON S2000TM portable ultrasound machine with a Siemens 9L4 transducer, ARFI images were acquired of lesions within the phantom. The 9L4 transducer is a compounding transducer which operates from 4 MHz – 9 MHz and with the ACUSON S2000TM is capable of performing quasi-static elastography, ARFI imaging, and shear wave speed quantification. The stiffness ratios of these lesions according to the acquired ARFI telemetry across 10 trials for each nominal lesion stiffness were then compared with their simulated counterparts in an effort to validate the work completed. The results of this characterization are presented in Section 4.3.4. The detailed experimental protocol that was followed for these validations is given in Section C.2 in Appendix C.

4.3 Results

Using the k-space pseudo-spectral model of ultrasound acoustics described in Section 4.2.1, acoustic radiation force distributions were acquired and analysed for the range of input parameters give in Table 4.4. These force distributions were then fed into the time-domain finite-element model of soft tissue deformation described in Section 4.2.3 to examine the difference in relationships between the true and measured tissue stiffness ratios due to the various lesion and transducer parameters that were investigated. The result of these characterizations are presented here.

4.3.1 K-Space Pseudospectral Models of Acoustic Radiation Force

In order to adequately simulate complete ARFI imaging sequences, the magnitude and distribution of acoustic radiation force impulses was simulated according to the procedure outlined in Sections 4.2.1 and 4.2.2. By calculating the temporal average of the intensity distributions, the spatially-varying acoustic body load was obtained. A sample generated force distribution is depicted in Fig. 4.3 for the case when a 2 MHz beam focused at a depth of 4 cm was applied to the tissue for 300 pulse cycles, or 150 μ s.

As expected, the force distribution is strongly concentrated around the focal point, extending axially below the focal point as per typical b-mode ultrasound acoustic beams. The net effect of the force distribution depicted in Figs. 4.3a and 4.3b is to push the tissue deeper axially and toward the focal point laterally. This resulted in a peak acoustic radiation force of approximately 175 kN m^{-3} located at the focal point.

Since the k-space pseudo-spectral models employed to simulate acoustic radiation force impulse distributions included absorption and attenuation of the ultrasound waves according to the effects seen in real soft tissues, the depth at which the probe is focused at becomes a critical parameter—the greater the focal depth, the more tissue that the ultrasound must pass through and therefore the more attenuated the signal becomes. This effect is less noticeable with lower frequency ultrasound waves as less energy is absorbed when the particle motion is limited. The resulting acoustic body force generated in the tissue at the focal point for a range of depths of interrogation frequencies is presented in Fig. 4.4.

tissue and f is the ultrasound frequency. While an MI less than 0.7 generally means that no cavitation may occur, cavitation is largely only a concern in tissues where cavitation is real possibility—only tissues with embedded gas bodies may cavitate. Since deep tissue injuries are largely focused around the sacrum and heels of tissue, the effects of cavitation in ARFI imaging are not largely relevant.

$$MI = \frac{P_r}{\sqrt{f}} \quad (4.16)$$

Maximizing the forces developed in the tissue can be detrimental to that tissue's health and well-being. To investigate this, the spatial peak pulse average intensity (I_{SPPA}) of the acoustic body load simulations was calculated for the range of depths and frequencies investigated in Fig. 4.4 and is shown in Fig. 4.8. Based on a maximum I_{SPPA} exposure of 933 W cm^{-2} [96], the use of ultrasound probes operating at or above 1 MHz and focused at depths greater than 3 cm should be safe for use in examining deep tissue injuries which are generally well separated from the much more sensitive cardiovascular and fetal imaging.

tissue injuries including: the distribution of acoustic radiation force generated by transducers; the generalized tissue response to these acoustic radiation forces; and the use of ARFI imaging to distinguish both early and formative deep tissue injuries from surrounding healthy tissue. Although the principles of operation for ARFI imaging and quasi-static ultrasound elastography are the same—detecting the relative magnitude of deformation in regions of tissue in response to externally applied forces—ARFI imaging presents a key advantage over quasi-static ultrasound elastography in that it allows much greater inter-operator reliability and repeatability. ARFI imaging generates deformation within tissue automatically and without dependence on the operator which is key to developing a successful diagnostic modality.

A key parameter relating to the ability of acoustic radiation force impulses to generate adequate body loads in tissue is the depth at which the radiation force is focused at—increasing depth was found to induce the greatest reduction in the magnitude of the radiation forces and the subsequent magnitude of tissue deformation. This is of concern, as once the magnitude of tissue deformation becomes small enough these deformations will no longer be able to be tracked using conventional ultrasound beams. In order to counteract this, lower frequencies and greater transmit pressures may be used, however care must be taken to ensure the safety of patients undergoing such techniques as the energy resulting from acoustic radiation has the potential to result in tissue damage.

The results shown in Section 4.3.3 show that ARFI imaging is a suitable technique for differentiating both stiff and unstiff lesions from surrounding healthy tissue which may be indicative of deep tissue injury formation and progression. Overall, the detection sensitivity of ARFI imaging is less than

ideal with the stiffness of stiff lesions consistently underestimated and the stiffness of unstiff lesions consistently overestimated. ARFI imaging was found to not be dependent on lesion radius above radii of approximately 2.5 mm and aside from issues with deformation magnitude, the depth of the lesions has no appreciable effect on their detection ability. The amount of lesion blur also did not affect the detection sensitivity, which is advantageous for detecting lesions without clearly defined boundaries. Regions of clustered deep tissue injury lesions were detectable however decreasing the ratio of diseased to healthy tissue area in the lesion resulted in lower detection sensitivities. Lesions were still detectable in the complicated model of MRI-acquired geometry embedded within soft tissue layout extracted from the Visible Human project, although to a slightly lesser extent than uncomplicated hard-boundaried spherical lesions. The overall technique was experimentally validated, however it was found that the simulated lesions underestimated the lesion stiffness compared to their parametrically-identical experimental counterparts.

Future work involving ARFI imaging should investigate the disparity between the experimentally-acquired lesion stiffness ratios and the simulated lesion stiffness ratios in order to increase the validity of the models. In order to truly advance the technology toward its clinical adoption, experimental studies in animals and humans with known deep tissue injuries must be carried out to determine the applicability of ARFI imaging in a real-world setting.

Chapter 5

Numerical Characterization of Shear Wave Speed Quantification

5.1 Introduction

Shear wave speed quantification offers the most desirable method of detecting early deep tissues injuries as it takes the transducer-generated external deformation force that is the chief benefit of ARFI imaging and combines it with a quantitative measure of tissue elasticity rather than the qualitative measures used in both quasi-static elastography and ARFI imaging. Specifically, monitoring the speed of shear waves that are generated in the tissue as a response to a localized acoustic radiation force allows the calculation of tissue stiffness which may again be used as an analogue of tissue health. Further, since the technique is quantitative in nature, tissue stiffness may be accurately tracked over time, enabling physicians to appropriately monitor the progression and

treatment of a given deep tissue injury on a per-patient basis.

5.2 Method

In order to investigate the sensitivity and applicability of shear wave speed quantification for the early detection of deep tissue injuries, a combination of k-space pseudo-spectral models of acoustic wave propagation and time-domain finite-element models of tissue deformation were employed. The theory and procedure behind both the generalized acoustic simulations using k-space pseudo-spectral models and time-dependent solid mechanics finite-element models used here were presented in Chapter 4. As an alternative to monitoring the dynamic response of tissue at the focal point as in ARFI imaging, shear wave speed quantification tracks the velocity of shear waves which radiate laterally outward from the focal point of an ARFI load. If the focal point is positioned such that the generated shear waves propagate through a lesionous region and the speed of the generated shear wave is monitored, the stiffness of that region may be calculated.

5.2.1 Shear Wave Speed

The foundation of shear wave speed quantification with regards to detecting lesionous regions lies in the quantifiable relationship between shear wave speed and tissue stiffness. This relationship is derived here, assuming a linear elastic, isotropic material. Soft tissue is generally considered a viscoelastic material and as such modifications to the linear elastic wave speed are taken into account.

Equation 5.1 represents the constitutive equation of a linear elastic material

where the strain tensor is defined as per equation 5.2 such that equation 5.3 holds true.

$$\sigma_{ij} = \lambda_{tissue} \delta_{ij} \varepsilon_{kk} + 2\mu \varepsilon_{ij} \quad (5.1)$$

$$\varepsilon_{ij} = \frac{1}{2} (u_{i,j} + u_{j,i}) \quad (5.2)$$

$$\sigma_{ij} = \lambda_{tissue} \varepsilon_{ii} \delta_{ij} + \mu (u_{i,j} + u_{j,i}) \quad (5.3)$$

Neglecting time-invariant body loads, the balance of linear momentum is given for a linear elastic continuum is given in equation 5.4.

$$\sigma_{ij,j} = \rho \ddot{u}_i \quad (5.4)$$

Substituting equation 5.3 into equation 5.4 yields equation 5.5 which may be rearranged into equation 5.6 by noting that $\varepsilon_{ii,j} = u_{j,ij}$.

$$\lambda_{tissue} \varepsilon_{ii,j} + \mu (u_{i,jj} + u_{j,ij}) = \rho \ddot{u}_i \quad (5.5)$$

$$\rho \ddot{u}_i = (\lambda_{tissue} + \mu) u_{j,ji} + \mu u_{i,jj} \quad (5.6)$$

Utilizing the Helmholtz decomposition of the particle displacement given in equation 5.7, equation 5.6 becomes equation 5.8.

$$u_i = \partial_i \phi + \varepsilon_{ijk} \partial_j \psi_k \quad (5.7)$$

$$\nabla \left[(\lambda_{tissue} + 2\mu) \nabla^2 \phi - \rho \ddot{\phi} \right] + \nabla \times \left[\mu \nabla^2 \vec{\psi} - \rho \ddot{\vec{\psi}} \right] = 0 \quad (5.8)$$

Examining the transverse propagation component of equation 5.8 in one direction yields the familiar shear wave equation given in equation 5.9 such that the shear wave speed is given by equation 5.10.

$$0 = \frac{\partial^2 \vec{\psi}}{\partial x^2} - \frac{\rho}{\mu} \frac{\partial^2 \vec{\psi}}{dt^2} \quad (5.9)$$

$$c_T = \sqrt{\frac{\mu}{\rho}} \quad (5.10)$$

While the above equation holds for linear elastic materials, soft tissues in the human body are generally considered viscoelastic [138], [139]. In the case of viscoelastic tissues, complex Lamé parameters must be used, such that the shear wave speed is represented by equation 5.11 [123]. Note that viscoelastic shear wave speeds of viscoelastic tissues are generally acquired through empirical measurements rather than any sort of mathematical derivation [140], [141].

$$c_T = \sqrt{\frac{\mu^*}{\rho}} \quad (5.11)$$

5.2.2 Model Set Up

In order to study the feasibility of using shear wave speed quantification to detect and monitor deep tissue injuries, a collection of deep tissue injury models were investigated including: spherical lesions with hard and unstiff boundaries, clusters of small lesions that make up a larger lesionous region, and a

lesion with MRI-acquired geometry [67] embedded in geometry obtained from a Visible Human slice [126]. Each model investigated numerous parameters relating to the detection of lesions including ARFI focal depth, ARFI interrogation frequency, lesion size, distance of the focal point from the lesion (lesion offset), lesion blur radius, clustered lesion density, the size of individual lesions in the clustered lesion model, and the size and altitude of the lesion in the Visible Human model. The range of parameters investigated for each model are summarized in Table 5.1.

Figs. 5.1 portray the schematics of the lesion models investigated. Note that shear wave speed quantification typically applies the acoustic radiation force impulse to a location of tissue adjacent to the desired region such that the shear waves are fully developed by the time they reach the investigated region.

Table 5.1: Range of values of investigated parameters

Parameter	Symbol	Values	Units
Lesion depth	d	1, 2, 3, 4, 5, 6, 7, 8, 9	cm
Lesion diameter	$\varnothing S$	0.5, 1.0, 2.0, 2.5	cm
Lesion offset	d_{off}	0.00, 1.25, 2.50, 3.75	cm
Lesion stiffness ratio	E_{rel}	0.32, 0.56, 1.80, 3.20	
Blurred lesion blur radius	b_r	1.0, 2.5, 5.0, 7.5	mm
Clustered lesion density	b_ρ	10, 20, 30, 40	cm^{-2}
Clustered lesion radius	r_{bl}	0.5, 1.0, 1.5	mm
Visible human lesion width	$\varnothing L$	0.5, 1.0, 2.0, 2.5	cm

In all the shear wave speed quantification models, the acoustic radiation force and time-domain finite-element models of tissue deformation were the same as were used in the ARFI imaging simulations in Chapter 4 and described in Sections 4.2.1 – 4.2.3. The difference with the shear wave speed quantification presented here and the ARFI imaging presented in Chapter 4

in Section 5.3.2 by working through a sample dataset result.

5.2.3 Model Validation

In order to validate the results presented in Section 5.3, a subset of the results were compared with experimental results obtained with a physical tissue mimicking phantom. The phantom used was the same CIRS Elasticity QA Phantom model 049 that was used in Chapter 3. The phantom models both stiff and unstiff lesions at two different depths and lesion sizes. The material properties of the phantom are listed in Table 3.2. Both tissue and lesion shear wave speeds were acquired using a Siemens AG ACUSON S2000TM ultrasound system running the Virtual TouchTM Quantification unistiffware suite with a Siemens 9L4 transducer. Measures of relative lesion stiffness were calculated as per equations 5.12 in an identical fashion to the simulated lesion cases and experiments were carried out over 10 trials for each investigated nominal lesion stiffness ratio. The detailed experimental protocol that was followed for these validations is given in Section C.3 in Appendix C.

5.3 Results and Discussion

Following the procedure outlined in Section 5.2, k-space models of ultrasound acoustics and finite-element models of temporal soft tissue deformation were synthesized and the resulting shear wave speeds developed in the tissue were analyzed according to the method laid out in Section 5.3.2. These shear wave speeds were used to calculate the relative stiffnesses of a variety of lesions with varying parameters as described in Section 5.2.2 which were then used to numerically characterize the use of shear wave speed quantification for the

detection of early deep tissue injuries. The results of this characterization are presented here.

5.3.1 Acoustic Radiation Force Impulse Simulations

Since the acoustic radiation force impulse simulations were run in exactly the same manner for shear wave speed quantification as in the ARFI imaging presented in Chapter 4, the results are identical—see Section 4.3.1 for the results. For completeness, the force distribution which generated the shear waves studied in Section 5.3.2 is plotted in Fig. 5.2. against a schematic of the lesion in order to better visualize the shear wave speed quantification process. Fig. 5.2 shows the focal line of the shear wave speed quantification technique, along which the axial displacement of the tissue is continuously monitored in order to calculate the localized shear wave speed of the tissue. This focal line extends laterally from the focal point of the acoustic radiation force impulse through the lesion to the edge of the tissue domain.

5.3.2 Sample Shear Wave Speed Measurement

Although measuring the shear wave speed of tissue may quantify the tissue stiffness through equation 5.11, the results presented here represent the measured stiffness ratio of lesions in order to present continuity with Chapters 3 and 4. In all cases where relative lesion stiffness is presented, it was calculated through comparison of the mean shear wave speed in the defined lesion region with the mean shear wave speed outside of the lesion region along the path of the lateral shear wave radiation direction. Specific ratios may be calculated using equation 5.12 where E_{rel} is the relative stiffness ratio, μ_l and μ_t are

readily accounted for. Another key observation is that the underestimated lesion stiffness ratio for stiff lesions that was seen in Fig. 5.22 correlates well with the results obtained experimentally.

5.4 Conclusions

The results given in Section 5.3 represent a numerical characterization of the use of the ultrasound elastography technique of shear wave speed quantification toward the detection and monitoring of early and progressive deep tissue injuries. This work presents arguably the most useful technology for monitoring deep tissue injury progression as it provides quantitative measures of lesion stiffnesses as opposed to the qualitative measures provided by quasi-static elastography and acoustic radiation force impulse imaging.

The results presented here show that shear wave speed quantification is a viable tool for both detecting and monitoring deep tissue injuries, provided the injuries are in general greater than 1 cm in diameter and are closer to the surface of the skin than 8 cm. In order to provide the most accurate results, ARFI focal points should be located approximately 1.25 cm – 2.50 cm away from the desired region of interest, allowing the shear waves to fully develop before they pass through the lesion for measurement. Blurring the lesions had no appreciable effect on the detection sensitivity whatsoever, however clusters of small lesions comprising a larger lesionous region did—reducing the area ratio of lesionous tissue to that of healthy tissue consistently resulted in lower detection sensitivities. To relate the findings from the simpler model geometries, a simulated lesion with MRI-acquired geometry was placed in a cross-sectional slice of human tissue with geometry obtained from the Visible Human project.

The results of the numerical characterizations were consistent with those found using a simpler, spherical model. Finally, the entire simulation pipeline was validated using a tissue mimicking phantom and an ultrasound machine capable of performing shear wave speed quantification where physical lesions presented similar results to their simulated counterparts.

With a firm understanding of the parameters that affect deep tissue injury detection using shear wave speed quantification, future work may entail investigating the use of shear wave speed quantification in both animal and human subjects who are either at an elevated risk of developing deep tissue injuries or are known to be suffering from such injuries. These steps will be necessary before the technique may be used in a clinical setting—an eventuality that will hopefully result from this work.

Chapter 6

Conclusion

Pressure ulcers and deep tissue injuries are an incredible problem facing the health of society today. They arise most often as complications in the elderly and those with spinal cord injuries and present an extremely significant burden on both the health care system and individual patients alike. Deep tissue injuries are somewhat more insidious than pressure ulcers due to how they form—deep tissue injuries begin at the bone-muscle interface deep within tissue and aren't readily noticeable on the surface of the skin until they have broken through as late-stage pressure ulcers. Although DTI prevention and mitigation strategies do exist, their efficacy is highly variable and the treatments are largely untargeted blanket programs which may not adequately treat the needs of patients with formative DTI and may waste money on those without issue. Without a proper clinical diagnostic capability, the incidence of pressure ulcers and DTI has remained largely unchanged for decades. Currently, the only tool capable of detecting formative deep tissue injuries in their early stages—before they tunnel to the surface—is T_2^* -weighted MRI which images oxygen content (or lack thereof) as a proxy for tissue health. While

MRI may be effective in research settings, it is hardly suitable for large-scale clinical adoption due to the excessive monetary and temporal costs as well as its lack of mobility and lack of ability to image people with critical medical implants such as pacemakers.

Ultrasound elastography is a relatively new imaging modality that has shown some promise toward the detection of early deep tissue injuries by imaging the stiffness changes that tissue undergoes beginning immediately after an injury has occurred—injured tissue shows 1.6-fold to 3.3-fold stiffening after the initial injury and after becoming necrotic shows stiffness below that of healthy tissue. There are three main technologies relating to ultrasound elastography: quasi-static elastography, acoustic radiation force impulse imaging, and shear wave speed quantification. Quasi-static ultrasound elastography is a technique whereby the deflection and deformation of acoustic scatterers embedded throughout soft tissue are tracked between externally-applied pre- and post- compression states. Regions of tissue which deform less than their surroundings are mechanically stiffer than their surroundings and may represent a formative deep tissue injury. Acoustic radiation force impulse imaging operates on much the same principle as this, however the externally-induced tissue deformation is generated through the application of acoustic radiation forces stemming from specialized pulses emitted from the ultrasound transducer itself. By generating tissue deformation in this manner, the repeatability and inter-operator reliability of diagnostic scans may be improved due to the automatic and computer-controlled nature of the acoustic radiation forces. While quasi-static ultrasound elastography and acoustic radiation force impulse imaging provide only qualitative measures of tissue stiffness relative to its surroundings, shear-wave speed quantification can pro-

vide quantitative measures of tissue elasticity through the direct computation of a region of tissue's shear modulus by its measured velocity and an assumed tissue density. Shear-wave speed quantification tracks the velocity of shear waves generated using an acoustic radiation force as they pass through both diseased and healthy tissue using regular ultrasound tracking beams sampled at extremely high frequencies. Through these methods, it is expected that a clinical tool may be developed for not only detecting the early onset of deep tissue injuries but also for tracking their progress over time. The work completed here represents the first step in that goal and numerically characterized the use of all three techniques toward the detection of both early and late-stage deep tissue injuries.

6.1 Comparisons Between Methods

In the quest to understand the use of the various ultrasound elastography imaging modalities toward early detection of deep tissue injuries, the sensitivity of numerous parameters relating to each modality were studied. Amongst the studied parameters, a subset of studies are directly comparable between modalities—parameters such as lesion size, depth, blur radius, cluster density, and the use of “real-world” geometry were all examined at parametrically identical values. This allows the direct comparison between modalities and may lead to recommendations for future clinical use of ultrasound elastography.

Simulated Lesions

Across the range of simulated lesions using the quasi-static elastography, ARFI imaging, and shear wave speed quantification modalities, hard boundaried le-

spherical, hard-boundaried lesions, different lesion geometries were studied. One such case is where a lesion will not have rigidly defined boundaries and may “fade” into the background healthy tissue. To investigate this, lesions with blurred boundaries that fade into the background were studied using all three elastography modalities. The characterization curves of a lesion with a radius of 10 mm which was blurred using a kernel blur radius of 7.5 mm across the three modalities are given in Fig. 6.3. As expected, shear wave speed quantification again revealed itself to produce the most accurate results with a nearly one-to-one mapping between true and measured lesion stiffness. Quasi-static elastography and ARFI imaging paralleled each other however quasi-static elastography was generally unable to distinguish unstiff blurred lesions against the background, making ARFI imaging much more preferable than quasi-static elastography when examining late-stage DTI.

Again as expected, shear wave speed quantification resulted in substantially less error for characterizing all stages of deep tissue injuries than both quasi-static elastography and ARFI imaging as Fig. 6.4 shows. Once again, the least stiff lesions that were investigated—those with a relative stiffness ratio of 0.32—were the most difficult to detect accurately and presented with the greatest amount of error. Of further note is that although quasi-static elastography was worse at accurately detecting unstiff deep tissue injury lesions than ARFI imaging, quasi-static elastography portrayed less error when detecting stiff (early) deep tissue injury lesions. This suggests that quasi-static elastography is not well suited for detecting unstiff lesions and that the more reliable ARFI imaging should be used where possible if shear wave speed quantification cannot be used.

Since lesionous regions may not be completely homogeneous regions of

The lesser detection sensitivity with all investigated imaging modalities that was portrayed in Fig. 6.5 results in a greater amount of error across all imaging modalities and lesion stiffness ratios as seen in Fig. 6.6. For all but the least stiff of lesions, ARFI imaging had the greatest amount of error when attempting to detect these lesionous clusters, while shear wave speed quantification continued to generally produce the least amount of error. The overall increased error in this model is somewhat expected however, due to the nature of how the models were constructed and evaluated. In the clustered lesion models, only a portion of the lesionous region actually contains “injured” tissue—averaging out the true stiffness over the entire lesionous area would result in a less pronounced stiffness for that region, rather than the “spikes” that are seen in the clustered model. This means that if such a lesionous region were to exist, the severity of the injury may not be adequately represented by *any* of the three imaging modalities. Further work should be done to examine this problem further and investigate any alternative technologies which may be able to adequately granularize clusters of small lesions.

The final major model to be evaluated across quasi-static elastography, ARFI imaging, and shear wave speed quantification was the use of geometry obtained from MRI scans of real deep tissue injuries in pigs which were then placed in a background of tissue with geometry obtained from the Visible Human project. The purpose of these models was to place the various simulation techniques in the context of detecting “real-world” deep tissue injury lesions. The characterization curves of the three investigated modalities for a lesion with a width of 20 mm located at a depth of 6 cm are given in Fig. 6.7. A lesion depth of 6 cm was chosen in these models as in the Visible Human tissue domain this depth placed the lesion to sit immediately

sure; transducer size; etc, as well as physical lesion-specific parameters such as: depth; size; geometry; etc. Through the comparisons made in Section 6.1, it is clear that shear wave speed quantification is the ideal ultrasound elastography modality with regards to detecting deep tissue injuries. Not only is shear wave speed quantification a quantifiable technology which would allow clinicians to directly track the progression of an injury over time, but it was found to consistently provide the most accurate results compared to both quasi-static elastography and ARFI imaging. Shear wave speed quantification is not without its limits however, as the acoustic radiation force impulses which give rise to deformation deep within tissue may not be large enough to be readily detected by the ultrasound machine. To overcome these limitations, the ultrasonic transmission power may be increased and the interrogation frequency may be decreased, but such measures may only go so far and have profound tissue health implications. Further, since only specific, localized regions of tissue may be interrogated using shear wave speed quantification, quasi-static ultrasound elastography or ARFI imaging may be used to image much larger regions of tissue in order to search for specific regions of interest. Although such “fishing” expeditions may not provide truly accurate and quantifiable data, they may guide the use of shear wave speed quantification to provide a more complete picture of tissue health.

From the work presented here, it is fully expected that ultrasound elastography is capable of becoming a clinical tool to be used in the early detection and monitoring of deep tissue injuries. The adoption of this technology for such a venture would have wide-ranging consequences from potentially increasing quality of life of at-risk patients, to decreasing the financial burden on the health care system, to even providing future avenues for deep tissue

injury research—without a quality early deep tissue injury detection method, the bulk of deep tissue injury research focuses on late-stage ulcers for which treatments are often applied “too late”. With a firm understanding of the mechanics and principles involved with ultrasound elastography, the next stage in this technology’s development is to investigate its use in animal models where deep tissue injury lesions may be tightly controlled and the lesions can be co-investigated using MRI techniques. Once early deep tissue injury detection is well understood in living tissue, trials should move to at-risk human patients. Since ultrasound and subsequently ultrasound elastography are non-invasive tools with relatively inexpensive equipment, it is expected that clinical adoption will be swift once the technology is proven in human tissue. Although as of the time of writing there are commercially available ultrasound elastography systems, future work may also involve developing application-specific probes or even entire devices devoted to applying ultrasound elastography toward deep tissue injuries which can provide the necessary parameters to optimize detection and ease of use.

Ultrasound elastography is a powerful tool which through the numerical simulations performed in this work was found to be able to distinguish both early and late stage deep tissue injuries and may provide for the first ever clinical tool to reliably detect DTI with a thought toward improving patient care and quality of life.

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Appendix A

Data Tables

A.1 Quasi-Static Ultrasound Elastography

Table A.1: Data for Fig. 3.9

r_{lesion}	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
2.5	0.84	0.92	1.09	1.20
5.0	0.77	0.83	1.22	1.48
10.0	0.92	0.73	1.41	1.93
12.5	0.92	0.70	1.47	2.10

Table A.3: Data for Fig. 3.11

h	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
1.25	0.70	0.72	1.53	2.11
2.50	0.92	0.70	1.47	2.10
3.75	0.81	0.69	1.49	2.13

Table A.2: Data for Fig. 3.10

d	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
3.5	0.91	0.74	1.42	2.00
6.5	0.80	0.71	1.51	2.19
8.5	0.87	0.70	1.49	2.14
10.0	0.92	0.70	1.47	2.10

Table A.4: Data for Fig. 3.12

f	$E_{rel,nom}$			
(MHz)	0.32	0.56	1.80	3.20
2	0.67	0.72	1.47	2.06
4	0.92	0.70	1.47	2.10
8	0.71	0.69	1.47	2.09

Table A.5: Data for Fig. 3.13

ε_{app}	$E_{rel,nom}$			
(%)	0.32	0.56	1.80	3.20
2.5	0.85	0.77	1.40	1.98
5.0	0.92	0.70	1.47	2.10
10.0	1.34	0.93	1.35	1.20

Table A.6: Data for Fig. 3.14

δ_{sep}	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
1.25	0.78	0.86	1.18	1.40
1.50	0.77	0.86	1.19	1.39
1.75	0.76	0.85	1.19	1.41
2.00	0.75	0.84	1.20	1.42

Table A.7: Data for Fig. 3.16

b_r	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
1.0	0.93	0.69	1.49	2.17
2.5	0.93	0.87	1.51	2.24
5.0	0.91	1.00	1.52	2.30
7.5	0.91	1.00	1.50	2.28

Table A.8: Data for Fig. 3.17

b_ρ	$E_{rel,nom}$			
(cm ⁻²)	0.32	0.56	1.80	3.20
10	0.78	0.79	1.29	1.66
20	0.85	0.73	1.38	1.87
30	0.86	0.71	1.42	1.96
40	0.76	0.71	1.43	1.99

Table A.9: Data for Fig. 3.19

r_{bl}	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
0.5	0.72	0.82	1.25	1.58
1.0	0.86	0.71	1.42	1.96
1.5	0.90	0.72	1.44	2.01

Table A.10: Data for Fig. 3.20

$\varnothing L$	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
0.5	1.15	1.17	1.17	1.26
1.0	1.01	1.09	1.21	1.28
2.0	0.83	0.93	1.21	1.49
2.5	0.76	0.88	1.25	1.59

Table A.11: Data for Fig. 3.22

d	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
6.5	0.68	0.75	1.13	1.46
6.75	0.77	0.81	1.18	1.51
7.25	0.76	0.88	1.25	1.59

A.2 Acoustic Radiation Force Impulse Imaging

Table A.12: Data for Fig. 4.4

Depth, d_f (cm)	Body Force at Focal Point, $F_{b,f}$ (kN m ⁻³)			
	f = 1 MHz	f = 2 MHz	f = 4 MHz	f = 6 MHz
1	151.5	194.0	122.1	128.5
2	113.0	97.9	83.1	29.2
3	81.7	46.9	33.2	13.3
4	57.3	24.2	12.2	2.2
5	40.7	12.8	4.0	0.2
6	29.6	7.2	0.8	0.0
7	21.8	4.2	0.1	0.0
8	16.3	2.5	0.0	0.0
9	12.4	1.5	0.0	0.0

Table A.13: Data for Fig. 4.5

Frequency, f (MHz)	Body Force at Focal Point, $F_{b,f}$ (kN m ⁻³)		
	$w_{active} = 4$ cm	$w_{active} = 8$ cm	$w_{active} = 10$ cm
1.0	55.3	85.0	96.6
1.5	19.1	25.9	24.7
2.0	15.3	18.0	12.5
3.0	16.4	10.2	5.6
4.0	1.0	0.3	0.1

Table A.14: Data for Fig. 4.6

n_c	$F_{b,f}$ (kN m ⁻³)
3	0.2
100	2.6
300	7.2
500	7.3
700	7.3

Table A.15: Data for Fig. 4.5

Depth,	Body Force at Focal Point, $F_{b,f}$ (kN m ⁻³)				
d_f (cm)	$P = 4$ MPa	$P = 5$ MPa	$P = 6$ MPa	$P = 7$ MPa	$P = 8$ MPa
3	66.7	103.5	147.8	199.3	257.5
4	34.4	53.5	76.6	103.4	133.9
5	18.1	28.2	40.4	54.5	70.6
6	10.3	16.0	22.9	30.9	40.0
9	2.1	3.3	4.7	6.4	8.3

Table A.16: Data for Fig. 4.8

Depth,	Spatial-Peak Pulse-Average Intensity, I_{SPPA} (W cm ⁻²)			
d_f (cm)	$f = 1$ MHz	$f = 2$ MHz	$f = 4$ MHz	$f = 6$ MHz
1	1,992	1,705	1,399	1,465
2	1,400	749	388	347
3	982	321	182	140
4	673	154	151	137
5	478	117	146	110
6	352	95	142	118
7	265	103	128	120
8	206	79	126	106
9	165	64	159	100

Table A.17: Data for Fig. 4.9

Depth,	Maximum Induced Tissue Displacement, $ v _{max}$ (μm)			
d_f (cm)	$f = 1$ MHz	$f = 2$ MHz	$f = 4$ MHz	$f = 6$ MHz
1	3.10	3.29	3.87	3.77
2	2.90	1.93	1.70	1.52
3	2.47	1.13	0.76	0.52
4	1.83	0.63	0.30	0.18
5	1.40	0.37	0.15	0.10
6	1.15	0.22	0.09	0.08
7	1.07	0.13	0.05	0.07
8	0.85	0.08	0.00	0.00
9	0.58	0.05	0.00	0.00

Table A.18: Data for Fig. 4.10

Depth, d_f (cm)	Maximum Induced Tissue Displacement, $ v _{max}$ (μm)				
	$P = 4$ MPa	$P = 5$ MPa	$P = 6$ MPa	$P = 7$ MPa	$P = 8$ MPa
3	1.61	2.52	3.62	4.93	6.44
4	0.90	1.40	2.02	2.75	3.59
5	0.52	0.81	1.17	1.60	2.09
6	0.31	0.49	0.70	0.95	1.24
9	0.07	0.10	0.15	0.20	0.26

Table A.19: Data for Fig. 4.11

Frequency, f (MHz)	Maximum Induced Tissue Displacement, $ v _{max}$ (μm)		
	$P = 4$ MPa	$P = 6$ MPa	$P = 8$ MPa
1	1.83	4.10	7.28
2	0.31	0.70	1.24
4	0.14	0.36	0.79
6	0.12	0.33	0.73

Table A.20: Data for Fig. 4.12

r_{lesion} (mm)	$E_{rel,nom}$			
	0.32	0.56	1.80	3.20
2.5	0.80	0.87	1.21	1.50
5.0	0.60	0.76	1.34	1.78
10.0	0.58	0.74	1.35	1.81
12.5	0.57	0.74	1.37	1.84

Table A.22: Data for Fig. 4.16

b_r (mm)	$E_{rel,nom}$			
	0.32	0.56	1.80	3.20
2.5	0.58	0.74	1.36	1.81
5.0	0.58	0.74	1.36	1.82
7.5	0.58	0.74	1.36	1.81

Table A.21: Data for Fig. 4.14

d (cm)	$E_{rel,nom}$			
	0.32	0.56	1.80	3.20
2	0.57	0.76	1.32	1.74
4	0.58	0.74	1.35	1.81
6	0.53	0.71	1.35	1.81
8	0.57	0.75	1.35	1.79

Table A.23: Data for Fig. 4.18

b_ρ (cm^{-2})	$E_{rel,nom}$			
	0.32	0.56	1.80	3.20
10	0.77	0.85	1.22	1.52
20	0.71	0.82	1.27	1.62
30	0.66	0.79	1.30	1.69
40	0.63	0.77	1.32	1.74

Table A.24: Data for Fig. 4.20

r_{bl}	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
0.5	0.85	0.91	1.15	1.37
1.0	0.66	0.79	1.30	1.69
1.5	0.60	0.75	1.34	1.78

Table A.25: Data for Fig. 4.22

$\varnothing L$	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
0.5	0.91	0.95	1.09	1.24
1.0	0.75	0.87	1.21	1.47
2.0	0.56	0.75	1.30	1.67
2.5	0.56	0.75	1.31	1.69

A.3 Shear Wave Speed Quantification

Table A.26: Data for Fig. 5.8

r_{lesion}	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
2.5	0.75	0.81	1.07	1.21
5.0	0.47	0.68	1.26	1.48
10.0	0.20	0.58	1.57	3.35
12.5	0.06	0.53	1.65	4.18

Table A.27: Data for Fig. 5.10

Δ_{off}	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
0.00	0.28	0.57	1.76	3.73
1.25	0.14	0.53	1.77	2.94
2.50	0.20	0.58	1.57	3.35
3.75	0.45	0.67	1.81	2.05

Table A.28: Data for Fig. 5.12

d	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
2	0.49	0.68	1.63	3.97
4	0.20	0.58	1.57	3.35
6	0.36	0.56	1.90	3.47
8	0.87	0.28	1.25	1.74

Table A.29: Data for Fig. 5.14

b_r	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
2.5	0.16	0.53	1.85	3.02
5.0	0.16	0.53	1.82	3.08
7.5	0.19	0.54	1.79	3.01

Table A.30: Data for Fig. 5.16

b_ρ	$E_{rel,nom}$			
(cm ⁻²)	0.32	0.56	1.80	3.20
10	0.73	0.82	1.32	1.70
20	0.59	0.73	1.48	2.17
30	0.49	0.68	1.58	2.34
40	0.44	0.63	1.62	2.42

Table A.31: Data for Fig. 5.18

r_{bl}	$E_{rel,nom}$			
(mm)	0.32	0.56	1.80	3.20
0.5	0.73	0.82	1.32	1.70
1.0	0.59	0.73	1.48	2.17
1.5	0.49	0.68	1.58	2.34

Table A.32: Data for Fig. 5.20

$\varnothing L$	$E_{rel,nom}$			
(cm)	0.32	0.56	1.80	3.20
0.5	0.98	1.03	1.26	1.47
1.0	0.84	0.95	1.44	1.74
2.0	0.05	0.64	1.86	2.57
2.5	0.03	0.52	2.13	3.19

C.1 Quasi-Static Ultrasound Elastography

1. Apply a layer of ultrasound gel to the active transducer area
2. Begin a new “2D” imaging sequence on the machine using the “Breast” preset
3. Position the transducer for the desired lesion
 - (a) Note the planar location of the lesion denoted on the sides of the phantom model
 - (b) Place the active component on the surface of the phantom model
 - (c) Align the transducer so as to intersect the lesion’s planar location in a perpendicular manner
4. Adjust the depth of the image to reach the full domain depth of the phantom model (approximately 7.5 cm)
5. Save the current screen
6. Manually indent the transducer into the tissue by approximately 0.5 cm
7. Save the current screen
8. Repeat steps 3 – 7 until all desired images have been acquired
9. Export the images to “USB in PC format”
10. Import the images into MATLAB®
 - (a) Crop the images so only the imaged domain is visible
11. Process the cropped images using a strain estimation algorithm

C.2 Acoustic Radiation Force Impulse Imaging

1. Apply a layer of ultrasound gel to the active transducer area
2. Begin a new “2D” imaging sequence on the machine using the “Breast” preset
3. Position the transducer for the desired lesion
 - (a) Note the planar location of the lesion denoted on the sides of the phantom model

- (b) Place the active component on the surface of the phantom model
 - (c) Align the transducer so as to intersect the lesion’s planar location in a perpendicular manner
- 4. Adjust the depth of the image to reach the full domain depth of the phantom model (approximately 7.5 cm)
- 5. Using the ultrasound machine’s trackball, select the “Virtual Touch imaging” button
- 6. Ensure the elastogram colour map is a gradient from black to white
- 7. Using the trackball and the “Next” button, adjust the position and size of the region of interest in order to fully capture the lesion and surrounding tissue
- 8. Press the “Update” button and hold the transducer as motionless as possible while the scan completes
- 9. Save the current screen
- 10. Wait for the cooling process to complete then press the “Freeze” button to unfreeze the image
- 11. Repeat steps 3 – 10 until all desired images have been acquired
- 12. Export the images to “USB in PC format”
- 13. Import the images into MATLAB®
- 14. Calculate the stiffness ratios by comparing the mean brightness of the elastograms inside the lesion to the mean brightness of the elastograms in an identical area located superior to the lesion

C.3 Shear Wave Speed Quantification

- 1. Apply a layer of ultrasound gel to the active transducer area
- 2. Begin a new “2D” imaging sequence on the machine using the “Breast” preset
- 3. Position the transducer for the desired lesion
 - (a) Note the planar location of the lesion denoted on the sides of the phantom model
 - (b) Place the active component on the surface of the phantom model

- (c) Align the transducer so as to intersect the lesion's planar location in a perpendicular manner
- 4. Adjust the depth of the image to reach the full domain depth of the phantom model (approximately 7.5 cm)
- 5. Using the ultrasound machine's trackball, select the "Virtual Touch Quantification imaging" button
- 6. Using the trackball, position the region of interest within the lesionous region
- 7. Press the "Update" button and hold the transducer as motionless as possible while the scan completes
- 8. Record the shear wave speed (V_s) of the interrogated region
- 9. Wait for the cooling process to complete then press the "Freeze" button to unfreeze the image
- 10. Using the trackball, position the region of interest outside the lesionous region
- 11. Press the "Update" button and hold the transducer as motionless as possible while the scan completes
- 12. Record the shear wave speed (V_s) of the interrogated region
- 13. Wait for the cooling process to complete then press the "Freeze" button to unfreeze the image
- 14. Repeat steps 3 – 13 until all desired lesions have been investigated