

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

by

Kenton David Hamaluik

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Mechanical Engineering
University of Alberta

© Kenton Hamaluik, 2014

Abstract

Abstract goes here...

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 even to your own detriment.

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 have be proud of what I accomplished in the end.

To my beautiful wife Dennie, who has stood by me and loved me without condition in the face of adversity and struggle. Without you, I would have given up long ago. You supported me above all others and this work exists as much because of you as it does because of me.

Acknowledgements

This work reflects the endless days I have spent learning, researching, and growing throughout the past several years and would not have been possible without the gracious assistance of the considerable number of people supporting me.

My supervisor, Dr. Waled Moussa has been a constant source of inspiration and learning for me. His enthusiasm and tenacity for research became a model for this work early on in the process. I would like to thank him for providing me with this alongside all the resources and support I needed to complete this work.

I would also like to thank my co-supervisor, Dr. Martin Ferguson-Pell for believing in me since I was an undergrad and continually providing me with opportunities to advance my learning. Despite his tremendous responsibilities, he always made time for me when I needed it and has always provided valuable input and guidance.

I am incredibly grateful for the wonderful guidance, support, and supervision of the entire Project SMART Pressure Ulcer group along with the rest of the PIs and trainees of the Project SMART team. Their gentle leadership, kind friendship, and impressive ability continually inspired me to pursue my best and live up to their remarkable example.

Lastly, I would like to thank my family and friends who have kept faith with me and my work since its inception while only marginally mocking me about my career choices.

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

Table of Contents

1	Introduction	1
1.1	Motivation	1
1.2	Objective	3
1.3	Methodology	3
1.4	Thesis Outline	4
2	Literature Review	6
2.1	Deep Tissue Injuries	6
2.1.1	Aetiology and Histology	10
2.1.2	Prevention and Treatment	13
2.1.3	Detection	15
2.2	Ultrasound Elastography	17
2.2.1	Quasi-Static Ultrasound Elastography	18
2.2.2	Acoustic Radiation Force Impulse Imaging	19
2.2.3	Shear Wave Speed Quantification	20
2.3	Conclusion	20
3	Numerical Characterization of Quasi-Static Ultrasound Elastography	22
3.1	Introduction	22
3.2	Method	23
3.2.1	Formation of B-Mode Ultrasound Images	25
3.2.2	Finite-Element Model of Tissue Deformation Under Surface Distortion	26
3.2.3	Characterizing Quasi-Static Ultrasound Elastography	28
3.2.4	Model Validation Using a Commercially Available Phantom	29
3.3	Results and Discussion	29

3.3.1	Finite Element Models of Ultrasound and Deformation	30
3.3.2	Resulting Elastograms	32
3.3.3	Numerical Characterizations	33
3.3.4	Physical Phantom Validation	48
3.4	Conclusion	51
4	Numerical Characterization of Acoustic Radiation Force Impulse Imaging	55
4.1	Introduction	55
4.2	Method	55
4.2.1	K-Space Pseudospectral Model of Acoustic Fields . . .	56
4.2.2	Derivation of Acoustic Radiation Force	58
4.2.3	Temporal Finite-Element Model of Soft Tissue Deformation	59
4.2.4	Characterizing Acoustic Radiation Force Impulse Imaging	61
4.2.5	Physical Phantom Validation	64
4.3	Results	65
4.3.1	K-Space Pseudospectral Models of Acoustic Radiation Force	65
4.3.2	Temporal Finite-Element Model of Soft Tissue Deformation	72
4.3.3	Numerical Characterization of Acoustic Radiation Force Impulse Imaging	75
4.3.4	Physical Phantom Validation	85
4.4	Conclusion	86
5	Numerical Characterization of Shear Wave Speed Quantification	89
5.1	Introduction	89
5.2	Method	90
5.2.1	Shear Wave Speed	90
5.2.2	Model Set Up	92
5.2.3	Model Validation	94
5.3	Results and Discussion	95
5.3.1	Acoustic Radiation Force Impulse Simulations	95
5.3.2	Sample Shear Wave Speed Measurement	96
5.3.3	Lesion Detection Characterization	101

5.3.4	Physical Phantom Validation	113
5.4	Conclusions	115
6	Conclusion	117
6.1	Comparisons Between Methods	117
6.2	Future Work	119
References		120
Appendix A	Source Code	140

List of Tables

3.1	Quasi-static model investigated parameters	24
3.2	CIRS Phantom Model Mechanical Properties	29
4.1	ARFI Model Viscoelastic Tissue Properties	60
4.2	ARFI Maxwell Model Tissue Properties	60
4.3	ARFI model investigated parameters	63
5.1	Shear wave speed quantification model investigated parameters	93

List of Figures

2.1	NPUAP pressure ulcer staging guidelines	8
2.2	Schematic representation of the time course of tissue stiffness changes in a deep tissue injury site.	12
3.1	Quasi-static model geometries	25
3.2	Point spread function used for simulating b-mode ultrasound scans	26
3.3	Sample deformation finite-element model results for a hard spherical lesion	31
3.4	Sample strain elastogram for a hard spherical lesion	33
3.5	Detection ability as it is related to true lesion stiffness ratio . .	34
3.6	Error characterization for a hard spherical lesion	35
3.7	Error characterization for: co-located, blurred boundary, clustered, and visible human lesion models	36
3.8	Quasi-static lesion size characterization	37
3.9	Quasi-static lesion depth characterization	38
3.10	Quasi-static lesion altitude characterization	39
3.11	Quasi-static ultrasound probing frequency characterization .	40
3.12	Quasi-static applied strain characterization	41
3.13	Quasi-static lesion separation distance characterization	42
3.14	Sample elastogram for two co-located lesions	43
3.15	Quasi-static lesion blur radius characterization	44
3.16	Quasi-static lesion density characterization	45
3.17	Sample elastogram for a set of clustered lesions	46
3.18	Quasi-static clustered lesion radius characterization	47
3.19	Quasi-static Visible Human model lesion width characterization	48
3.20	Sample elastogram of a Visible Human model lesion	49

3.21	Quasi-static characterization of lesion depth in a Visible Human model	50
3.22	Experimental validation of quasi-static model results	51
4.1	ARFI model schematics	62
4.2	Sample acoustic radiation force distribution	66
4.3	Effect of depth and interrogation frequency on magnitude of acoustic body forces	67
4.4	Effect of transducer aperture on the magnitude of acoustic radiation force	68
4.5	Magnitude of developed acoustic radiation force in relation to the number of applied pulse cycles	69
4.6	Strong dependence on source pressure of focal point force	70
4.7	I_{SPPA} safety measures of ARFI pulses	72
4.8	ARFI-induced deformation at various depths and interrogation frequencies	73
4.9	ARFI-induced deformation at various depths and source pressures	74
4.10	ARFI-induced deformation across various interrogation frequencies and source pressures	75
4.11	Numerical characterization of ARFI imaging-acquired stiffness ratio with changing lesion radius	76
4.12	ARFI imaging-acquired lesion stiffness mean squared error related to lesion radius	77
4.13	Numerical characterization of ARFI imaging-acquired stiffness ratio with changing lesion depth	78
4.14	ARFI imaging-acquired lesion stiffness mean squared error related to lesion depth	79
4.15	Numerical characterization of ARFI imaging-acquired stiffness ratio with blurred lesions	79
4.16	ARFI imaging-acquired lesion stiffness mean squared error related to lesion blurring	80
4.17	Numerical characterization of ARFI imaging-acquired stiffness ratio with clustered lesions	81
4.18	ARFI imaging-acquired lesion stiffness mean squared error related to small lesion cluster density	81

4.19	Numerical characterization of ARFI imaging-acquired stiffness ratio with clustered lesions	82
4.20	ARFI imaging-acquired lesion stiffness mean squared error related to small lesion cluster density	83
4.21	Numerical characterization of ARFI imaging-acquired stiffness ratio with changing lesion radii in a visible human model	84
4.22	ARFI imaging-acquired lesion stiffness mean squared error related to MRI-acquired lesion size in a Visible Human model	84
4.23	Experimental ARFI model results	85
4.24	Experimental validation of ARFI imaging model results	86
5.1	Schematic of shear wave speed quantification-investigated lesions	94
5.2	Sample radiation force distribution in relation to lesion location	96
5.3	Sample shear wave motion through time	98
5.4	Sample continuous surface plot of shear wave induced displacement	98
5.5	Sample continuous surface plot of shear wave induced axial displacement highlighting the shear wave location in time	99
5.6	Sample extracted shear wave position-time trace	100
5.7	Sample trace of shear wave speed through the focal line	100
5.8	Numerical characterization of shear wave speed measured stiffness ratio with changing lesion radius	101
5.9	Shear-wave speed quantified squared error related to lesion radius	102
5.10	Numerical characterization of shear wave speed measured stiffness ratio with changing lesion offsets	104
5.11	Shear-wave speed quantified mean squared error related to lesion offset	104
5.12	Numerical characterization of shear wave speed measured stiffness ratio with changing lesion depth	105
5.13	Shear-wave speed quantified mean squared error related to lesion depth	106
5.14	Numerical characterization of shear wave speed measured stiffness ratio with blurred lesions	107
5.15	Shear-wave speed quantified mean squared error related to lesion blurring	108

5.16 Numerical characterization of shear wave speed measured stiffness ratio with clustered lesions	109
5.17 Shear-wave speed quantified mean squared error related to small lesion cluster density	110
5.18 Numerical characterization of shear wave speed measured stiffness ratio with clustered lesions	111
5.19 Shear-wave speed quantified mean squared error related to small lesion cluster density	111
5.20 Numerical characterization of shear wave speed measured stiffness ratio with changing lesion radii in a visible human model	112
5.21 Shear-wave speed quantified mean squared error related to MRI-acquired lesion size in a Visible Human model	113
5.22 Experimental shear wave speed quantification results	114
5.23 Experimental validation of shear wave speed quantification model results	115
6.1 Experimental results of the three methodologies investigated .	118
6.2 Experimental validation of the simulation results across all three methodologies investigated	118

Nomenclature

Mathematical Symbols^{c1}

Symbol	Meaning
b_r	Blurred lesion blur radius
b_ρ	Clustered lesion density
d	Lesion depth
d	Visible Human lesion depth
δ_{sep}	Co-located lesion separation distance
E_{rel}	Lesion stiffness ratio
E_{lesion}	Young's modulus of lesion
E_{tissue}	Young's modulus of tissue
ε_{app}	Transducer-applied strain
ε_{lesion}	Measured lesion strain
$\varepsilon_{rel,measured}$	Measured lesion strain ratio
$\varepsilon_{rel,true}$	True lesion strain ratio
ε_{tissue}	Measured tissue strain
F	Applied body forces
f	Ultrasound frequency
Γ	Boundary domain
h	Lesion altitude
λ	Ultrasound wavelength
μ	Mean value
∇	Del operator
r_{bl}	Clustered lesion radius
$\emptyset S$	Lesion diameter
$\emptyset S$	Visible Human lesion width

^{c1} KH: I'm going to have to clean up these symbols.. a lot get re-used for different purposes

Symbol	Meaning
σ	Stress tensor
σ	Standard deviation
$\sigma_{applied}$	Stress applied to tissue
u	Displacement
u_0	Initial displacement
w_{active}	Total width of active transducer elements

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 % 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 can 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 the 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 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 effect of numerous interrogation parameters on detection sensitivity and ability is 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 the ultrasound ultrasound elastography procedures. Parametric studies on the detection sensitivity and ability of the various ultrasound elastography procedures 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 f-number, 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-compression 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.

Acoustic radiation force impulse imaging estimates tissue strain by applying an acoustic radiation 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. To simulate this procedure, a k-space pseudospectral 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.

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 pseudospectral 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.

Chapter 2

Literature Review

In order to understand the need for a clinical method of detecting deep tissue injuries, the full scope and current state 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 modality 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 these gaps are what this work attempts to begin to fill. ^{c1}

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

^{c1} KH: This sounds super awkward

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 % of people with spinal cord injuries (SCI) will develop at least one pressure ulcer during their lifetime [2] and approximately 19 % of elderly patients in long-term care facilities will develop one [24]^{c2}. 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]. Further, 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 and deep tissue injuries generally form at the bone-muscle interface deep in the tissue [3] with approximately 64 % occurring over the ischial tuberosities, trochanter, or sacrum [28]. 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 /

^{c2} KH: I already mentioned this in the introduction, verbatim. Where should it go?

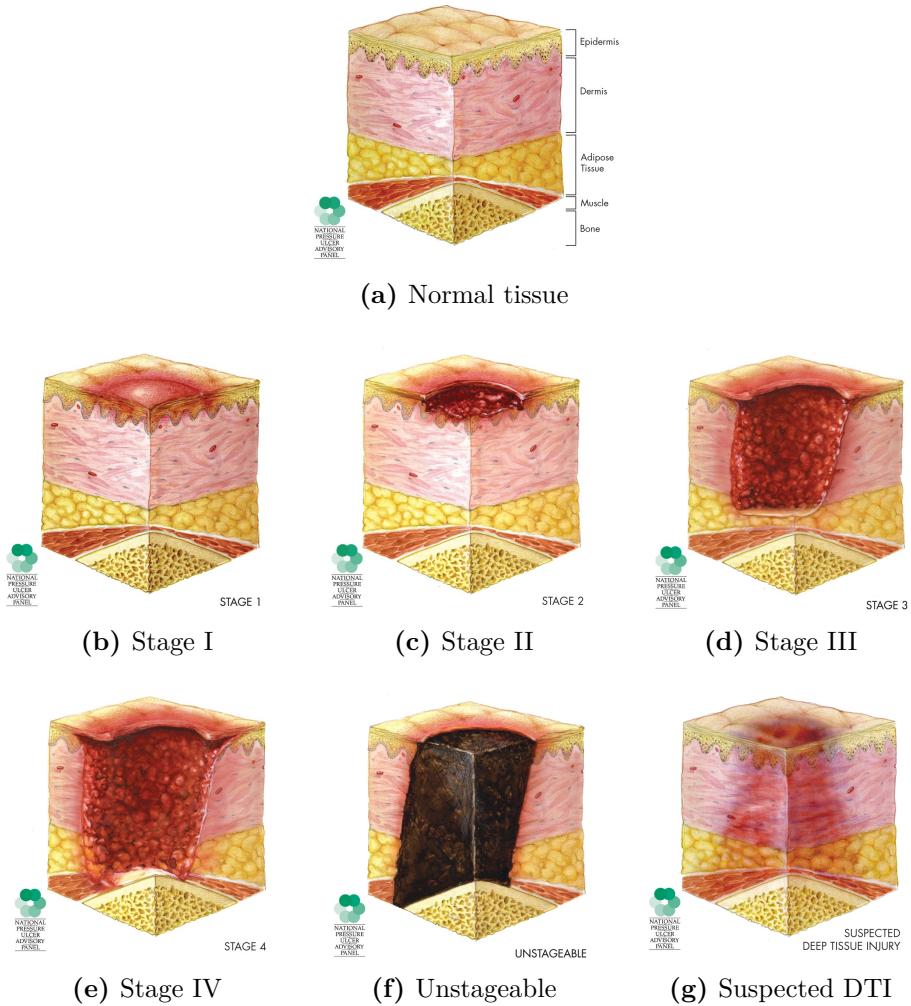


Fig. 2.1: The NPUAP staging guideline illustrations of the various stages / severities of pressure ulcers.

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 are depicted in Fig. 2.1 and described as follows:

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, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. *May* include undermining and tunnelling.

Stage IV

Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include 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 come 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 set 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-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]. Since this model of damage relates to occlusion of vessels, inhibited lymphatic drainage may be categorized as an ischemic risk factor.

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

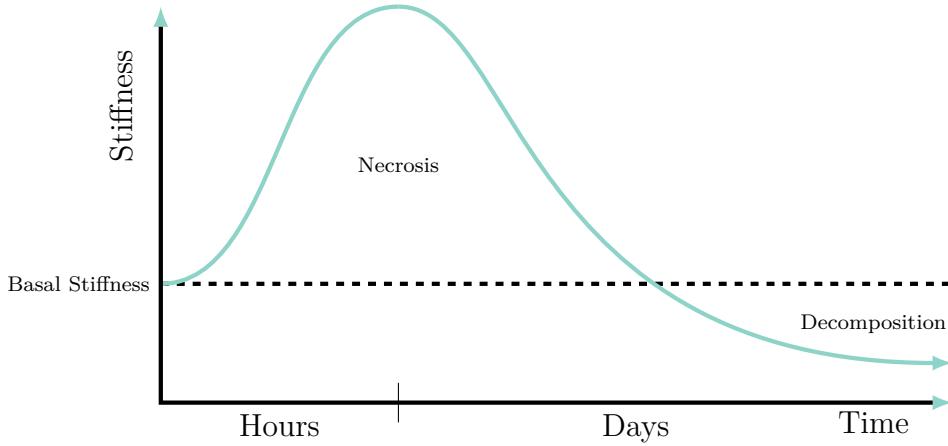


Fig. 2.2: Schematic representation of the time course of tissue stiffness changes in a deep tissue injury site. The estimate for the time-course for local rigor mortis was obtained from animal model studies [60] and the estimate for the time-course for tissue decomposition was obtained from the forensic literature [59]. (Adapted from Gefen 2009 [17])

[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 the years, each relating to different mechanisms, though all relating to me-

chanical stress of the tissue, either through vessel occlusion or direct cellular strain. The truth is most likely a combination of these effects, with cell deformation dominating the damage on shorter time scales with increased applied pressure and vessel occlusion type injuries dominating on longer time scales [4]. In order to further investigate the etiology of PU and DTI, a combination of experimental and numerical studies has been suggested to provide better fundamental knowledge besides existing clinical experience [8]. There is also significant evidence in the literature that suggests that the current NPUAP definitions of PU and DTI are insufficient and not based on scientific evidence and that updating the clinical definitions to better reflect what exists in the literature is crucial to increasing the success of diagnosis and treatment of PU and DTI [17], [29].

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 therapies 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 are 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 necro-

sis. 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 upwards of \$1,000 and take over an hour to complete ^{c1}. 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 non-invasively 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], [82], 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 results, it may be possible to increase the accuracy of early deep tissue injury detection [83]. 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], [84], [85]. 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], [86]. 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.

^{c1} KH: Citation needed!

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 [87], [88], 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 [89].

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 [90] 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 [91]. In general, the principle of ultrasound elastography is to visualize the deformation of soft tissue in response to an externally applied force [92]. 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) [93]. 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 [90]. Ultrasound elastography is a proven technology when it comes to detecting very stiff lesions against relatively soft backgrounds—it has successfully been used to detect breast and prostate cancer lesions [12], [13], liver fibrosis [14], [94], and atherosclerosis [95]. 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 [96], [97] 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 [98], [99]. While quasi-static elastography originally relied upon one-dimensional ultrasound A-lines, the technique has since advanced to two-dimensional B-mode images [100] and even three-dimensional B-mode images [86], [101].

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 [102], [103] in much the same way as contact free strain measurements may be obtained using optic means [104]. There have been numerous different quasi-static strain estimation algorithms developed, each with various advantages and disadvantages [99]. The most common algorithm involves simple cross-correlation maximization and was among the first algorithms to be proposed [100]. One of the most promising algorithms models compressed regions of interest as both scaled and translated versions of their uncompressed counterparts [92], [105] 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 [106], [107]. 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 (10's to 100's of μs) compared to typical diagnostic procedures in order to generate an acoustic radiation force at the focal region [108], [109].

^{c1}

2.2.3 Shear Wave Speed Quantification

^{c2}

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.

^{c1} KH: Need more..

^{c2} KH: Just do it!

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 ARFI to specifically displace a region of tissue and measuring its dynamic response; and utilizing an ARFI 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 [110] 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 [110].

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
Lesion depth	d	[3.5, 6.5, 8.5, 10.0] cm
Lesion altitude	h	[1.25, 2.50, 3.75] cm
Lesion diameter	ϕS	[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	ϕS	[0.5, 1.0, 2.0, 2.5] cm
Visible human lesion depth	d	[6.25, 6.75, 7.25] cm

Simulated ultrasound images were acquired through the convolution of a point spread function with a normally distributed background map of scattering centres [111]. These images were then combined with a finite-element deformation model of the strained tissue to generate both pre- and post- com-

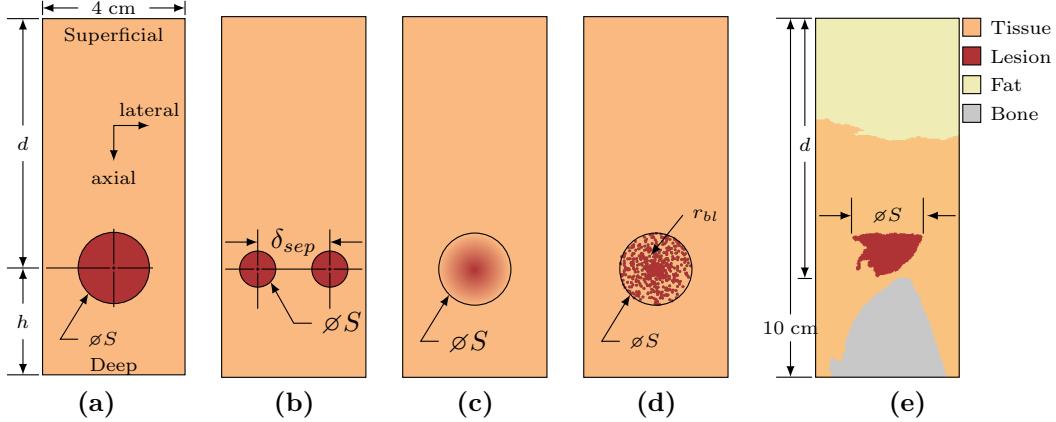


Fig. 3.1: Model geometry showing the investigated lesions embedded in a 4 cm wide soft tissue domain. Axial and lateral directions mimic that of a typical ultrasound transducer placed along the top boundary of the domain. The simplest case of a circular lesion embedded in a soft tissue domain located superior to hard underlying bone is shown in (a). In order to investigate the interference caused by closely-located lesions, the case shown in (b) was investigated. Because of the relatively unknown and variable geometric properties of deep tissue injury lesions, cases (c) and (d) were investigated where the lesion edges were blurred and the lesion was actually a large collection of small lesions, respectively. Finally, to investigate detection sensitivity in a realistic setting, case (e) was investigated where an mri-acquired deep tissue injury was overlaid on a slice from the Visible Human Project such that the injury lesion was located immediately superior to an ischial tuberosity.

pression images of the lesions and surrounding tissue. These images were fed into a tissue strain estimation algorithm to determine the detection sensitivity of the technique. Finally, the technique was validated against a physical phantom model using a subset of the simulated cases.

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 $\mu = 2\lambda$ and $\sigma = 2\lambda$ where λ is the wavelength of the ultrasonic probing waves. Laterally, the point spread function was modelled as a Gaus-

sian distribution defined by $\mu = 0$ and $\sigma = 0.25w_{active}$ 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.

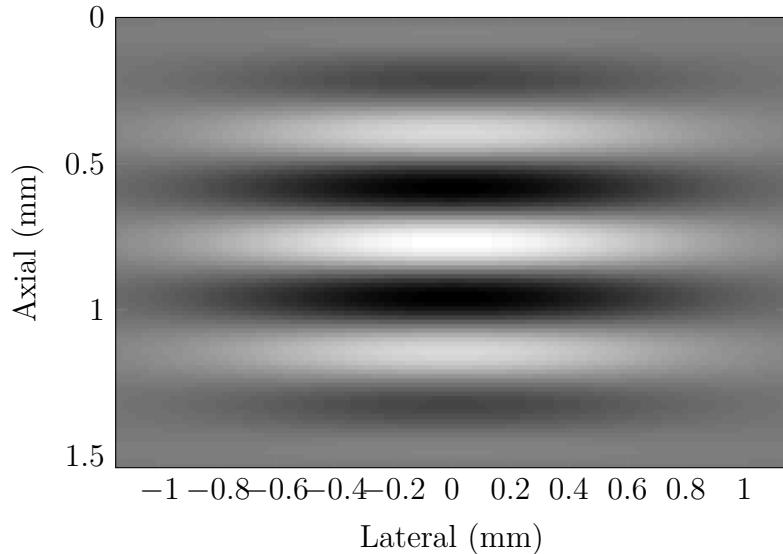


Fig. 3.2: Point spread function used for simulating b-mode ultrasound scans. The function is defined axially by a cosine function at the probing frequency and modulated by a Gaussian function both axially and laterally.

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:

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

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. 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} [112]–[114]. 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} [115]–[117]. 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:

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

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:

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

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.

3.2.3 Characterizing Quasi-Static Ultrasound Elastography

Utilizing a 2-D locally regularized tissue strain estimation algorithm [105], pairs of pre- and post- compression images were used to calculate elastogram estimations for the full range of parameter values of the simulated lesions. The algorithm consists of sweeping the image domain with a series of overlapping regions of interest (ROI). ROI are compared between pre- and post-compression images, with ROI in the post- compression images being axially scaled and translated and laterally translated versions of the same ROI in the pre-compression images.

Qualitatively, the noise and computation time of the resulting elastograms were found to be minimum when using an axial ROI size of approximately 10 times the ultrasound wavelength. Axial ROI overlap was held at 99 % to produce elastograms with minimal noise, even though this introduced significant increases in computation time. Due to the extreme anisotropic nature of ultrasound signals, lateral ROI size was kept to 5 signal widths with lateral 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. 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 each lesion in the phantom and the resulting strain ratio for that lesion was compared to the simulated strain ratio for that 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.

Table 3.2: CIRS Phantom Model Mechanical Properties

Property	Value
Nominal basal stiffness	25 kPa
Lesion stiffness	[8, 14, 45, 80] kPa
Speed of sound	1,540 m s ⁻¹
Acoustic attenuation	0.5 dB cm ⁻¹ MHz ⁻¹
Lesion diameter	[10, 20] mm
Lesion depth	[15, 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 algo-

rithm 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. 3.3c – 3.3d. In Fig. 3.3c, a sample generated b-mode ultrasound scan is given. Fig. 3.3a shows the lateral displacement field generated by the deformation finite-element model while Fig. 3.3b 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. 3.3d shows the resultant b-mode image generated by applying the displacement field given in Figs. 3.3a and 3.3b to the tissue and embedded scattering centres used to create Fig. 3.3c. What results is a locally scaled and translated version of Fig. 3.3c 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.

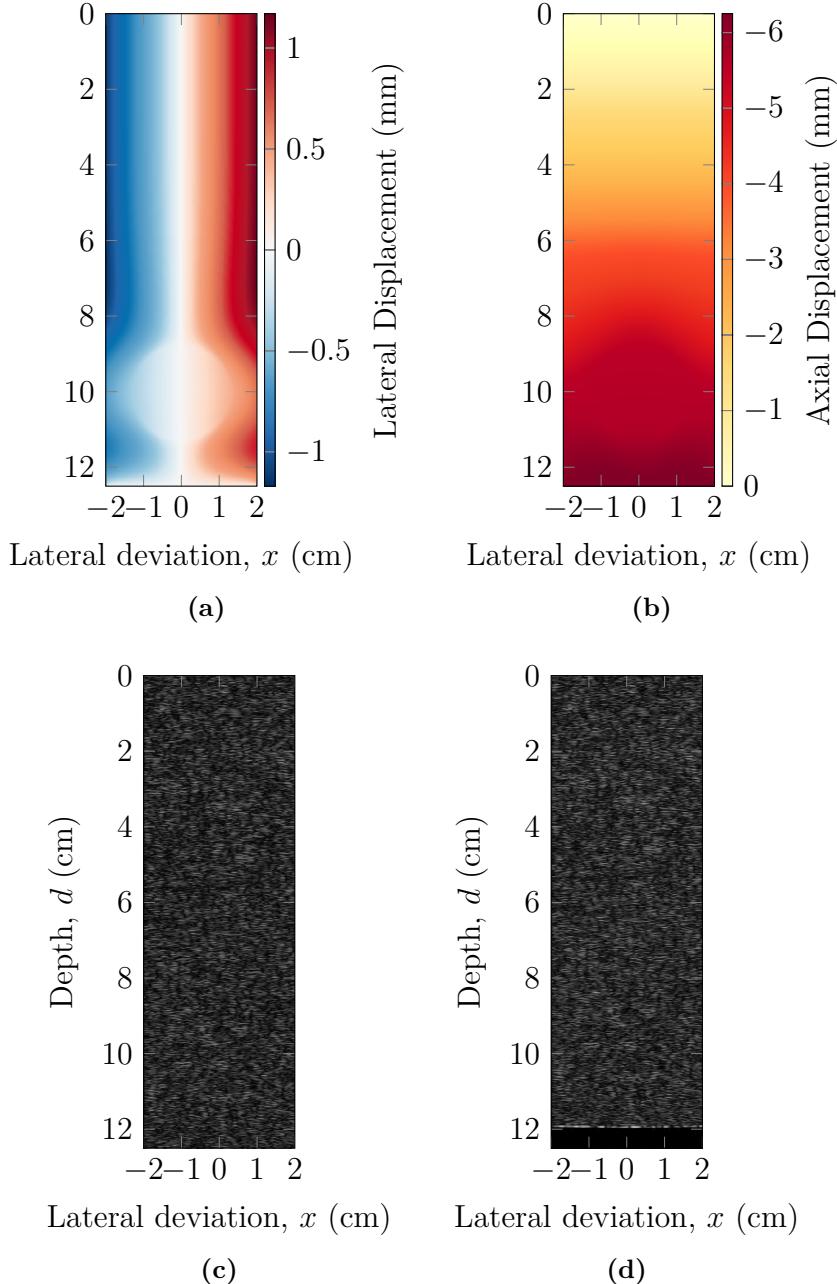


Fig. 3.3: Finite-element model results for the case when $d = 10\text{ cm}$, $\phi S = 2.5\text{ cm}$, $\varepsilon_{rel} = 3.20$, and $f = 4\text{ MHz}$ showing (a) the lateral displacement field and (b) the axial displacement field induced by compressive strain applied to the top of the boundary, (c) a generated b-mode image of the pre-compressed tissue domain, and (d) a generated b-mode image of the post-compressed tissue domain. The included lesion is not visible in (c) and (d) as its acoustic properties were no different than surrounding tissues. An anechoic region is visible along the bottom of the domain in (d) which represents tissue outside of the domain visible in (c).

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. 3.3c and 3.3d) in order to generate elastogram images which were used in the subsequent analysis. An example elastogram resulting from the simulation presented in Fig. 3.3 is shown in Fig. 3.4. 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. 3.4. While this field does not appear to affect the remainder of the generated elastogram, it will serve to mask any extremely shallow legions in the tissue, though given as deep tissue injuries generally form immediately superior to boney prominences, this is unlikely to be the case. It is hypothesized that this variable strain field may be due to the large deformations present along the superior surface of the domain.

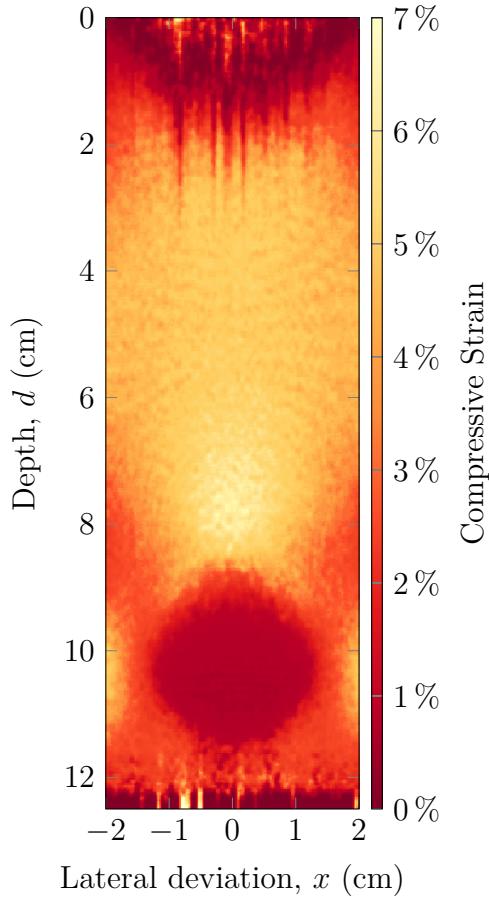


Fig. 3.4: Sample strain elastogram showing estimated strain values for $d = 10$ cm, $\phi S = 2.5$ cm, $\varepsilon_{rel} = 3.20$, $f = 4$ MHz. While undetectable on a single b-mode image, the elastogram clearly shows a low-strain (stiff) lesion located approximately 10 cm from the surface.

3.3.3 Numerical Characterizations

In order to determine the sensitivity of using quasi-static ultrasound elastography to detect deep tissue injuries, elastograms such as the example that was calculated in Section 3.3.2 were calculated for the full range of parameters 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:

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

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:

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

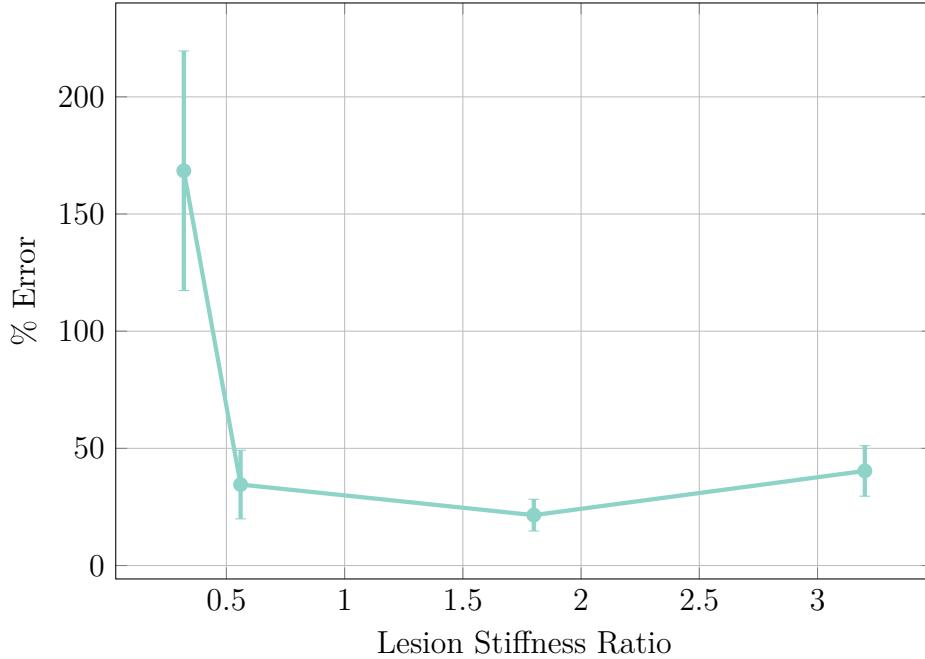


Fig. 3.5: Detection ability as it is related to true lesion stiffness ratio. For all but small lesion stiffness ratios (very soft “lesions”), results are linear and predictable. For small lesion stiffness ratios (0.32), the lesion becomes severely misrepresented. This is likely due to the algorithm “losing track” of scattering centres for the relatively large displacements induced in the significantly less stiff tissue.

Fig. 3.5 portrays the severe error involved with using the methods described in Section 3.2 to investigate extremely low stiffness lesions. 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 its "measured" strain ratio.

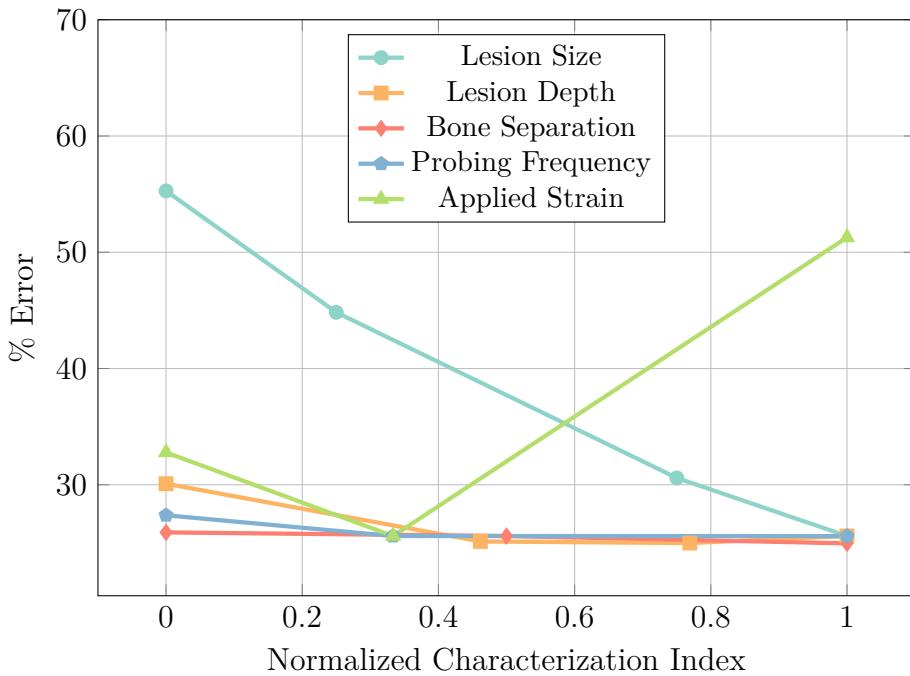


Fig. 3.6: Error characterization for range of studied parameters for the simple model of a spherical lesion embedded within soft tissue as seen in Fig. 3.1a. Each parameter has been normalized to the range studied so overly-sensitive regions may be readily distinguished.

In order to broadly investigate the critical parameter-values of the investigated models, each parameter was normalized to its investigated range and the error resulting over these ranges is given in Figs. 3.6 and 3.7.

In Fig. 3.6, it is clear to see that the most sensitive error-inducing situations occur when either the lesion is very small or if large strains are used to deform the tissue. Similarly, it is expected that if the lesion depth were increased much further, significant errors would arise with increasing depth.

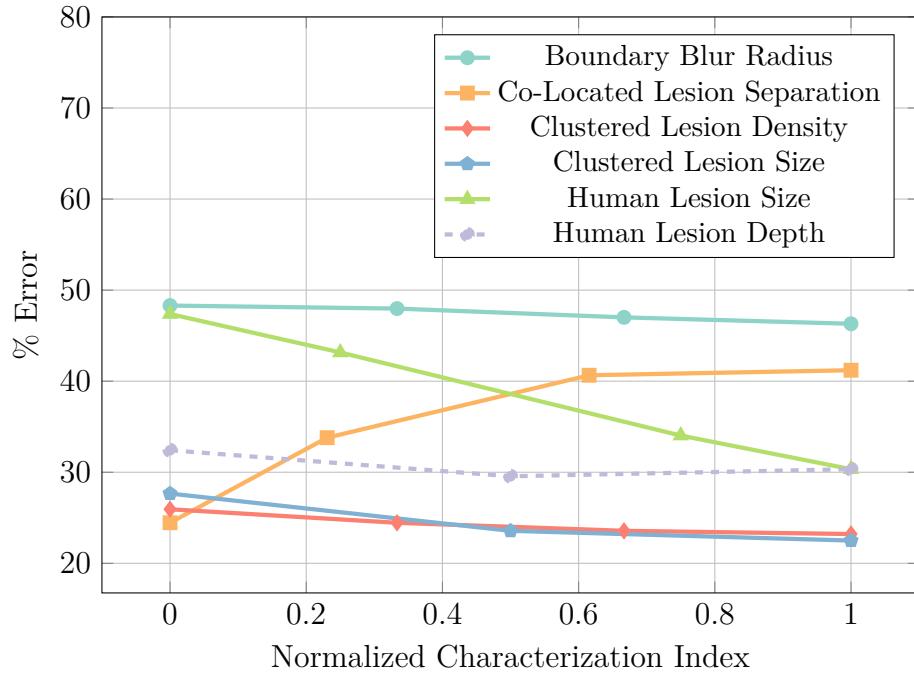


Fig. 3.7: Error characterization for range of studied parameters for the co-located lesions, blurred boundary lesions, clustered lesions, and visible human lesion models as seen in Figs. 3.1b – 3.1e. Each parameter has been normalized to the range studied so overly-sensitive regions may be readily distinguished.

Logically, this may be explained due to the decreasing magnitude of displacement with increasing depth—at a certain point, the magnitude of displacement of scattering centres will be on par with the measurement noise, and the lesion will cease to be detectable.

From Fig. 3.7 it can be seen that small lesions in the Visible Human-MRI model as well as co-located lesions with large separation distances produce greater measurement errors. Conversely, lesion depth in the Visible Human-MRI model; lesion density and individual lesion size in the clustered lesion model; and boundary blur radius in the blurred-edges model do not seem to affect the measurement error significantly. Of note is the relative large amount of static error present in the boundary blur radius model which is hypothesized to be due to lesser mean tissue stiffness in the investigated region than expected.

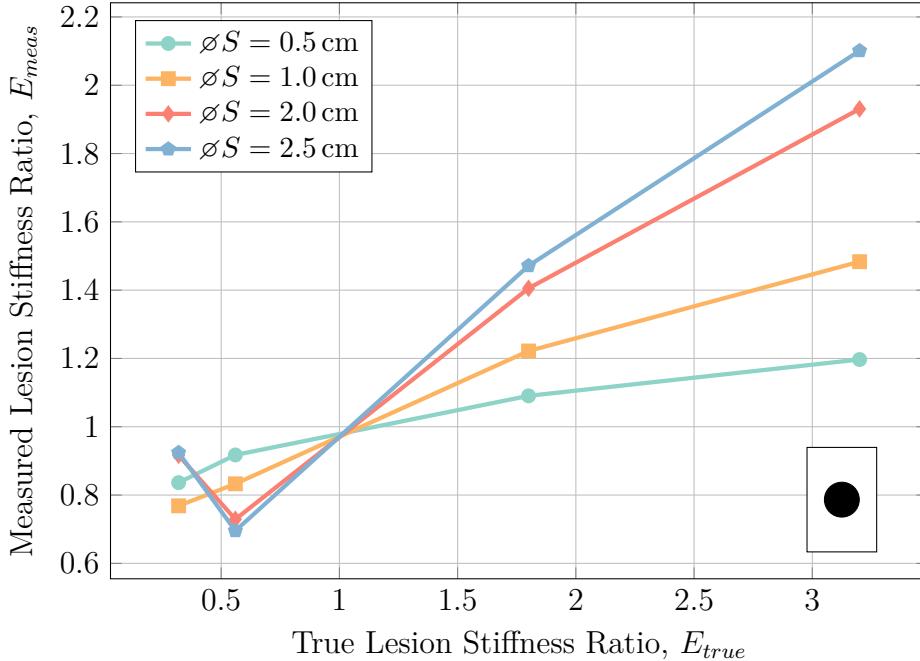


Fig. 3.8: Lesion size characterization at a depth of 10 cm with a 4 MHz ultrasound probing frequency showing increasing detection sensitivity of the lesion with increasing lesion size. Detection sensitivity is less than ideal for all cases, with the best case being for lesions approximately 2.5 cm in diameter.

Fig. 3.8 shows the relationship between lesion size and detection sensitivity for lesions at a depth of 10 cm in a model depth of 12.5 cm interrogated at 4 MHz with 5 % applied strain. Specifically, Fig. 3.8 shows the decreasing detection sensitivity with decreasing lesion size with the best detection sensitivity being with the largest investigated lesions with a diameter of 2.5 cm. On the opposite end, the detection sensitivity of lesions at or below 0.5 cm in diameter is questionable. Although data is lacking on the true size of formative DTI, MRI results indicate that untreated DTI are on the scale of multiple centimetres [67]. Thus, the ability to detect lesions of at least 1 cm in diameter should prove to be adequate to both detect and monitor DTI.

In order to investigate the effect of lesion depth on the detection sensitivity, measured strain ratios for circular lesions with a diameter of 2.5 cm located at various depths were interrogated with a 4 MHz probing frequency, and strained

by 5 %. The results of this investigation are seen in Fig. 3.9.

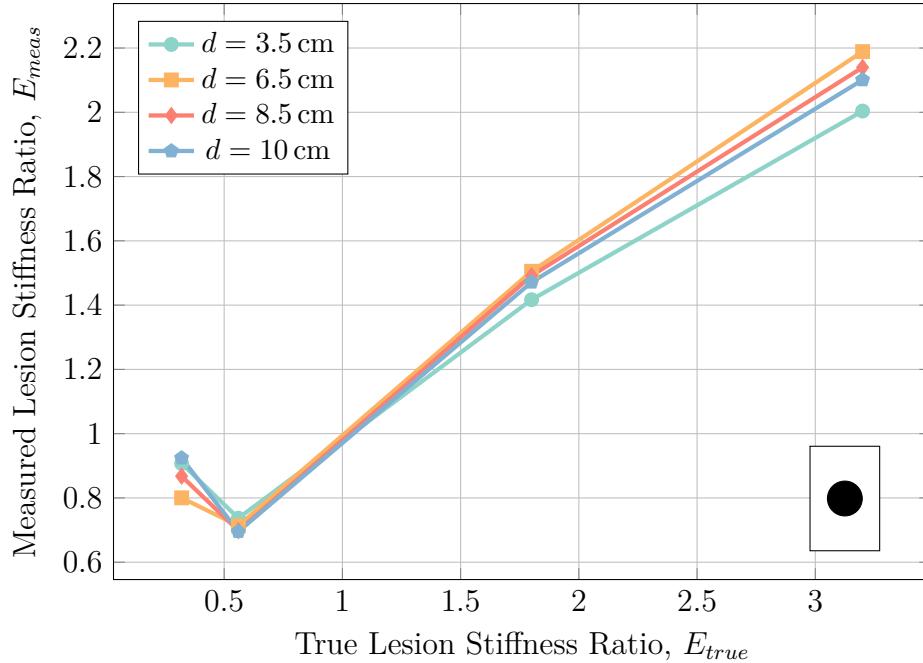


Fig. 3.9: Lesion depth characterization at a lesion diameter of 2.5 cm with a 4 MHz ultrasound probing frequency generally showing general independence of detection sensitivity on lesion depth in the tissue.

In Fig. 3.9, it can be seen that there was little interplay between detection sensitivity and measured strain ratios at the various depths examined for all but the case for very soft (mushy) lesions (with a stiffness ratio of 0.32). At such low stiffness ratios, the excessive tissue deformation interrupts the tissue strain estimation algorithm's ability to adequately track the induced displacements in the lesion.

Since the strain field caused by compressive forces near an extremely rigid structure embedded within a relatively soft domain will be significantly heterogeneous, the effect of lesion altitude above the underlying stiff bone was examined with the hypothesis that if the lesion were too close to the hard bone, it would be masked by the strain field caused by the bone's existence. A 2.5 cm diameter lesion was interrogated with a 4 MHz probing frequency and 5 % applied strain. The results of this characterization are given in Fig. 3.10.

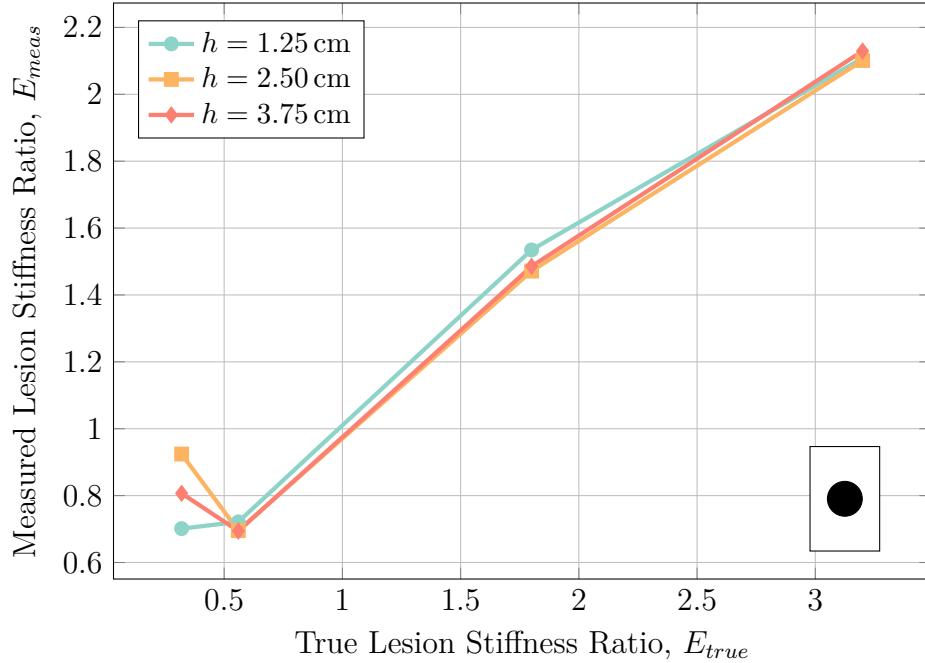


Fig. 3.10: Effect of lesion altitude above the underlying bone. Aside from erroneous results at very low lesion stiffness ratios, the effect is negligible.

In Fig. 3.10, it can be seen that the lesion altitude above the underlying bone had very little effect on the detection sensitivity. Although larger strain fields may be generated near the bone, it is hypothesized that the larger fields also extend larger and so affect healthy tissue to more or less the same degree as the forming lesion.

In order to characterize the effect of using alternate ultrasound probing frequencies, simulations were carried out on lesions using probing frequencies of 2 MHz, 4 MHz, and 8 MHz. The simulated lesions had a diameter of 2.5 cm, were located at a depth of 10 cm and we strain at 5 %. The results of this study are given in Fig. 3.11.

As can be seen from Fig. 3.11, there is very little effect on the detection sensitivity from the ultrasound probing frequency that was used, therefore an appropriate frequency should be chosen so as to reach the full depth of the bone-muscle interface at suspected DTI locations while retaining the best

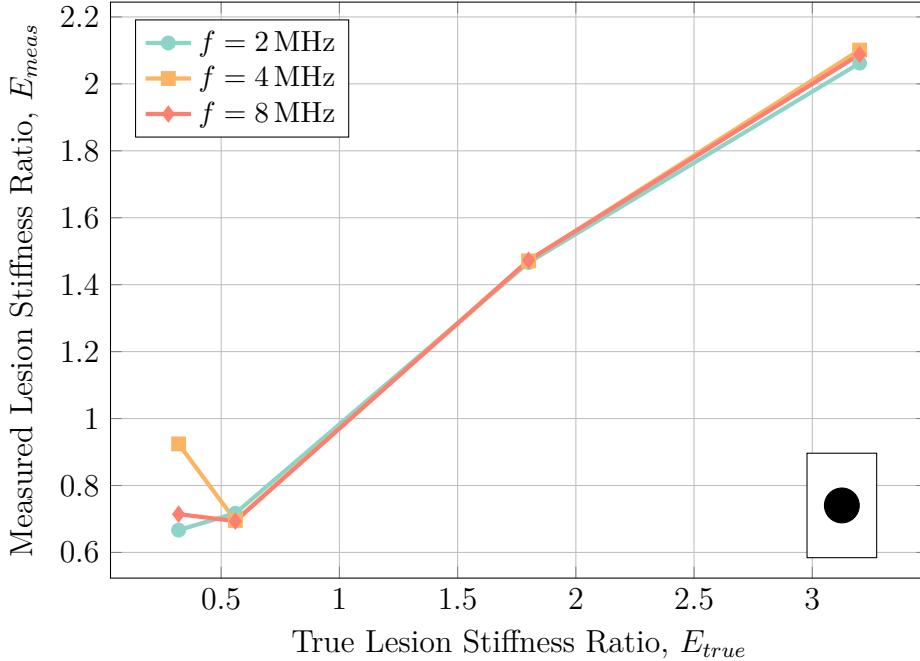


Fig. 3.11: Characterization of ultrasonic probing frequency on detection sensitivity. Apart from the requirement of using an ultrasonic frequency low enough to interrogate the desired tissue, probing frequency has negligible effect on the detection sensitivity.

image resolution.

As quasi-static ultrasound elastography is most likely to be performed via manual indentation where the exact magnitude of applied deformation is unknown, it is important to study the effect of applied strain magnitude on the detection sensitivity. Applied strains of 2.5 %, 5.0 %, and 10 % were investigated on a 2.5 cm diameter lesion at a depth of 10 cm using a probing frequency of 4 MHz; the results are given in Fig. 3.12.

While Fig. 3.12 shows a relatively constant detection sensitivity for compressive strains of 2.5 % and 5 %, compressive strains of 10 % generate significant measurement error for both very soft and very stiff lesions. Under large compressive strains, the tissue (either in the lesion as in the soft lesion case, or the surrounding tissue as in the stiff lesion case) deforms considerably which again interferes with the algorithm's ability to properly track the displacement

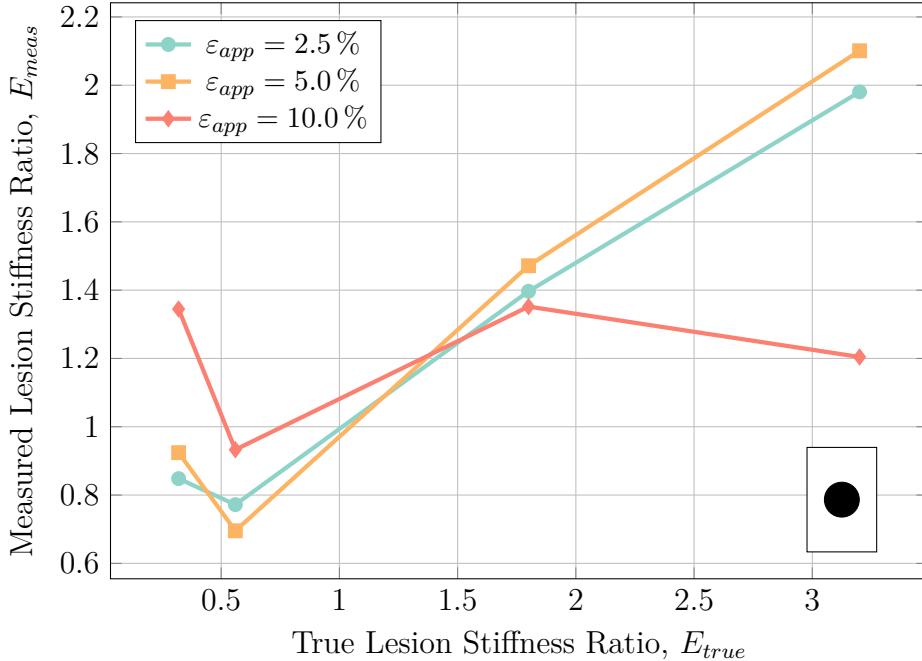


Fig. 3.12: Applied strain characterization plot for lesions with a diameter of 2.5 cm located at a depth of 10 cm interrogated at 4 MHz. There is little difference between 2.5 % and 5.0 % applied strain, while large-magnitude strains of 10 % generate significant error for both very soft and very stiff lesions.

of tissue. It should also be noted that applying overly large strains to an already forming deep tissue injury may cause additional unwarranted damage. Thus it is imperative that applied surface indentation be kept to reasonable bounds (2.5 % – 5 %, or 0.25 cm – 0.50 cm in 10 cm deep domains), not only for safety of the tissue but also for clarity of the diagnostic test.

To study the effect that closely spaced lesions will have on the detection sensitivity as well as how discernible the lesions will be from each other, the separation distance between two 1.0 cm diameter co-located lesions at a depth of 10 cm was examined using a 4 MHz probing frequency with 5 % applied strain magnitude. The results of this study are shown in 3.13.

While Fig. 3.13 shows that the separation distance between co-located lesions causes a negligible effect on the detection sensitivity, Fig. 3.14 shows regions of decreased strain above and below the centreline of the lesions. While

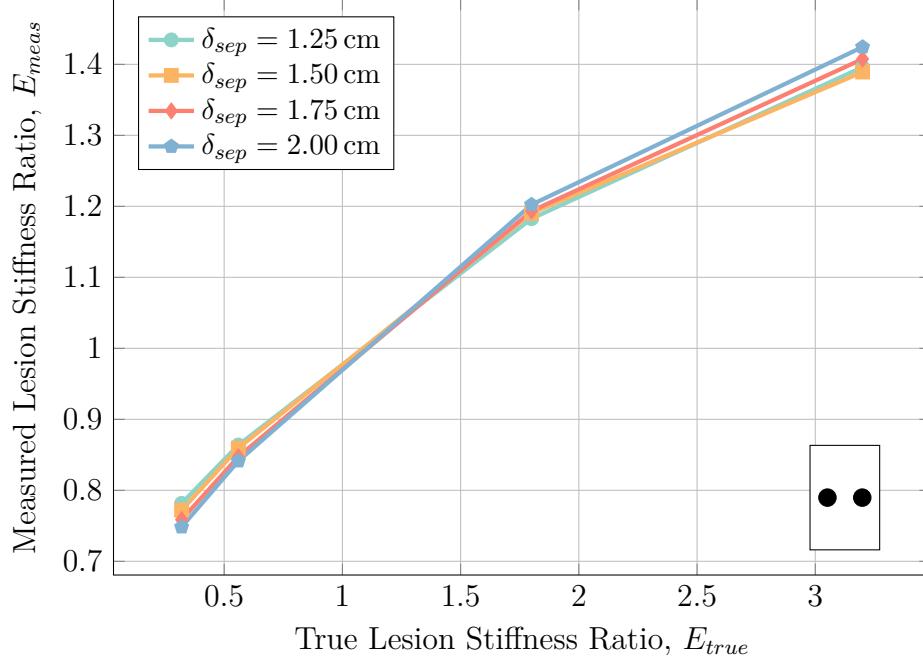


Fig. 3.13: Effect of lesion separation distance on two 1.0 cm diameter lesions co-located at a depth of 10 cm interrogated with a 4 MHz probe with 5 % applied strain. There is no negligible difference between separation distances on the detection sensitivity.

these regions had the same basal stiffness as the bulk tissue, the decreased strain pattern may obfuscate the true results by introducing “phantom lesions” which are not actually present but merely the result of the existing lesions.

While the simulations performed thus far assumed that lesions were perfect spheres with hard boundaries in order to isolate specific parameters of interest, this assumption may not always be accurate. Rather, due to the nature of injury formation, lesions may form gradual boundaries that “fade” from stiff or necrotic tissue to healthy tissue. To investigate the effect of this phenomenon on the detection sensitivity, lesions with “blurred boundaries” were investigated. Hard spherical lesions were blurred by convolving the lesion domain with a disc blurring kernel of varying radius. The results for this investigation on lesions with a diameter of 2.5 cm, at a depth of 10 cm and interrogated with a 4 MHz probing frequency with 5 % applied strain are given in Fig. 3.15.

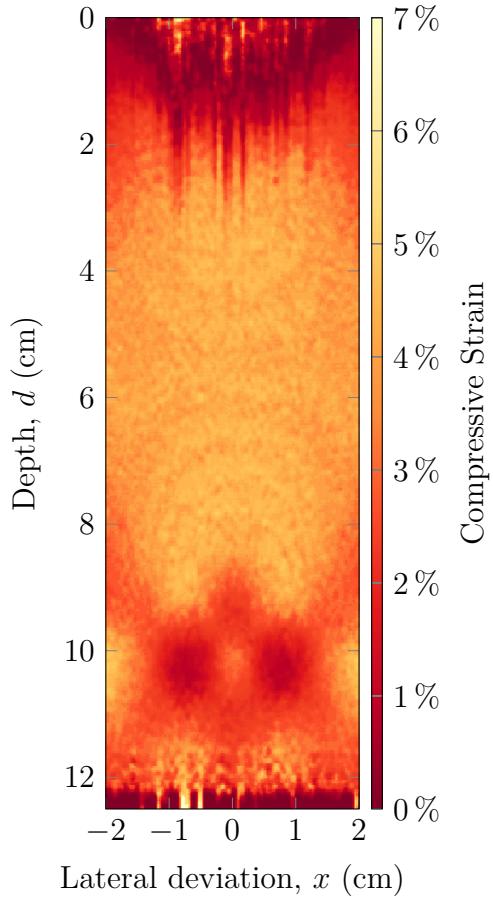


Fig. 3.14: Elastogram for two co-located lesions of 1.0 cm diameter at a depth of 10 cm interrogated using a 4 MHz probing frequency with 5 % applied strain. A pattern of decreased strain is present above and below the centerline between the two lesions while the lesions themselves are not affected by each other.

Fig. 3.15 shows that there is very little dependence on the lesion detection sensitivity for stiff lesions (lesions with a stiffness ratio ≥ 1.0). However, for soft lesions, the tissue strain estimation algorithm seems to over-estimate the stiffness of the lesions.

Similar to how lesions may have “blurred boundaries” rather than hard ones, so too may lesion composition not be homogeneous. In order to study the effect of heterogeneous regions of injured tissue, the detection sensitivity of a set of numerous small lesions located within close proximity to each other so as to form a large, heterogeneous area of diseased tissue was examined. Fig.

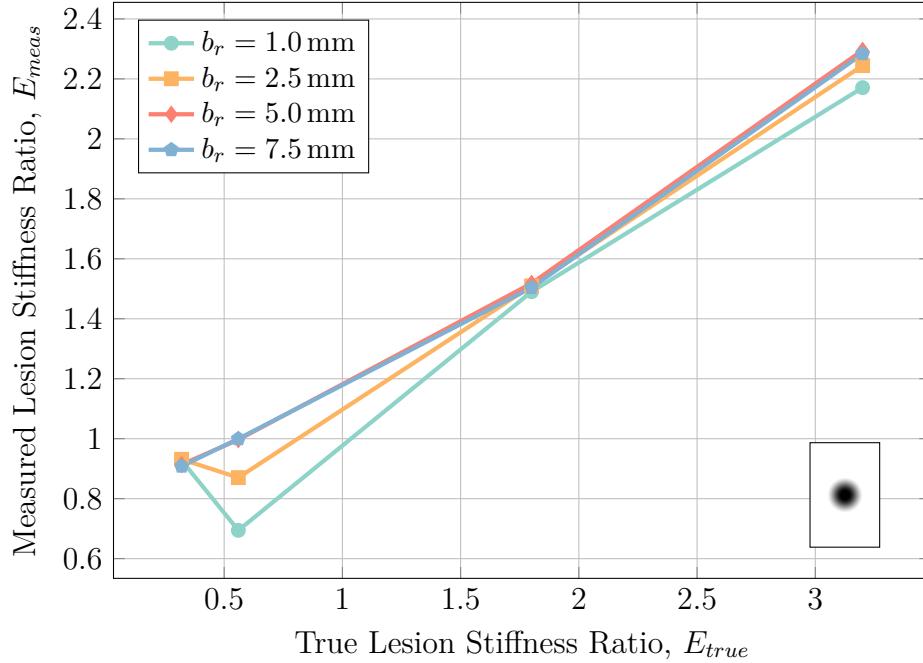


Fig. 3.15: Characterization of the effect of lesion blur radius on lesion detection sensitivity for a 2.5 cm diameter lesion at a depth of 10 cm using a probing frequency of 4 MHz and applied strain of 5 %. While there is negligible effect of the blur radius on stiff lesions, the strain ratio for soft lesions is considerably over-estimated.

3.16 shows the results for this model for varying numbers of 2 mm diameter lesions in a 2.5 cm diameter circle located at a depth of 10 cm with a probing frequency of 4 MHz and 5 % applied strain. Fig. 3.18 further explores this model by investigating the case where there are 30 small lesions per square cm with individual lesions ranging in diameter from 0.5 mm to 1.5 mm.

The characterization plot in Fig. 3.16 for small lesion density is less linear than other characterization plots, with lesion density having a significant effect on the detection sensitivity. Specifically, for low lesion densities, the detection sensitivity is much lower than for high lesion densities. However, this observation is warranted after examination of the elastogram produced from these results, given in Fig. 3.17, which shows how the small lesions are not individually detected but rather the entire region is detected as one large lesion. Since the average stiffness ratio over this region is lesser than the stiffness ratio of

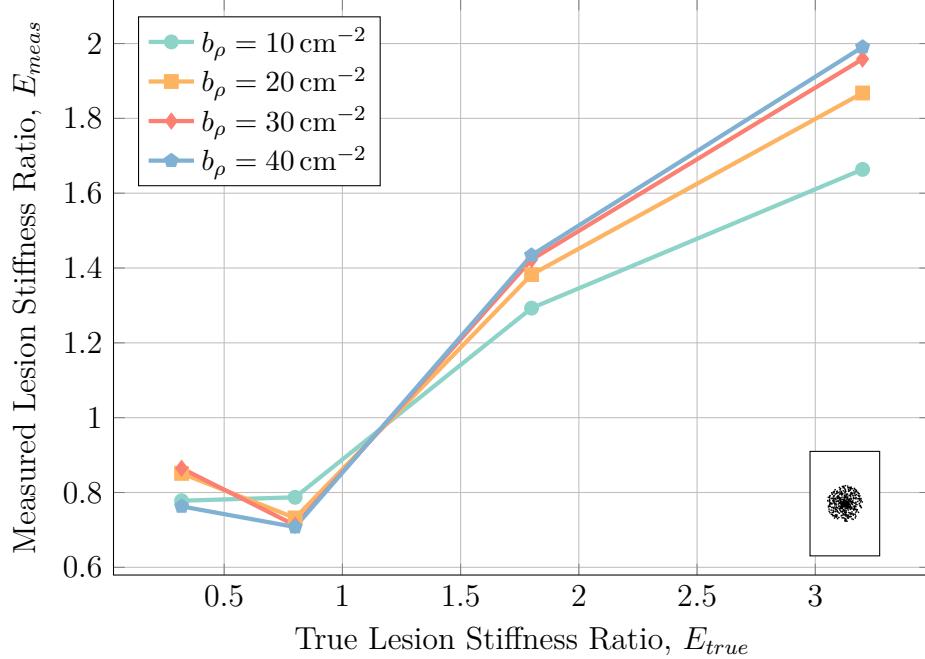


Fig. 3.16: Characterization of lesion density for a group of numerous smaller 2 mm diameter lesions comprising a large area with a diameter of 2.5 cm at a depth of 10 cm interrogated with a 4 MHz probing frequency and 5 % applied strain. Detection sensitivity decreases with decreasing lesion density, as expected.

individual lesions, it makes sense that the “measured” strain ratio will be less than expected.

Similar to the results shown in Fig. 3.16, changing the size of the individual small lesions does have an effect on the measured strain. In this case, when individual lesions are small, the total area occupied by lesions is lesser which results in a lesser average tissue stiffness over the grouped lesion region.

Note that although the elastography algorithm was able to detect the larger lesion-filled regions in these simulations, it was completely unable to discern the individual lesions comprising those regions. This is not surprising due to both the generated strain fields in the healthy tissue throughout the larger lesion area as well as the results presented in Fig. 3.8 showing poor detection sensitivity for lesions with diameters $\leq 1 \text{ cm}$ while the individual lesions in this simulation had diameters of the scale of 0.5 mm – 1.5 mm.

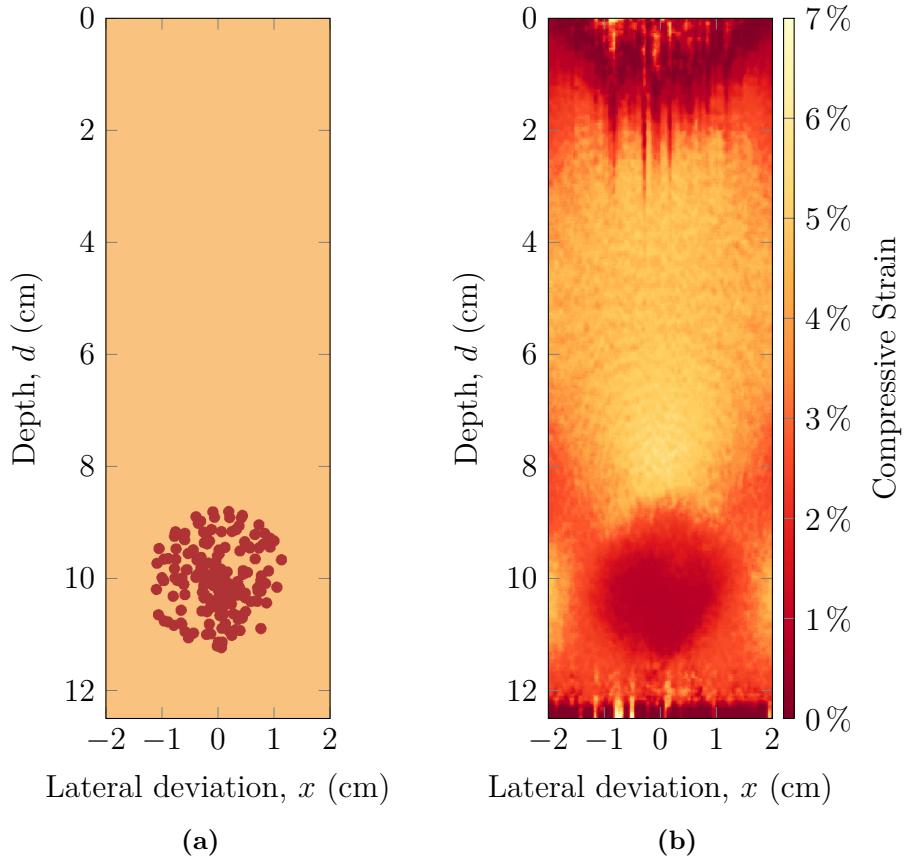


Fig. 3.17: Stiffness map (a) and corresponding elastogram (b) for a group of small lesions with a density of 10 lesions per cm^2 grouped in a 2.5 cm diameter circle at a depth of 10 cm interrogated with a 4 MHz probing frequency and 5 % applied strain. In (a), white regions are regular tissue while black regions are the small lesions. In the elastogram, individual lesions do not stand out, rather the entire region of lesions appears as one large region of unhealthy tissue.

Finally, in order to place these results within the context of a likely real scenario in humans, a more complicated model utilizing an MRI-acquired lesion and slides from the Visible Human Project [110] was developed. Specifically, lesion geometry was taken from a real deep tissue injury in a pig model imaged using T_2^* -weighted MRI. The human geometry was taken from a transverse plane slice across the left ischial tuberosity such that the lesion was placed immediately superficial to the boney prominence. For this model, the overall lesion width and lesion depth were examined with results shown in Figs. 3.19

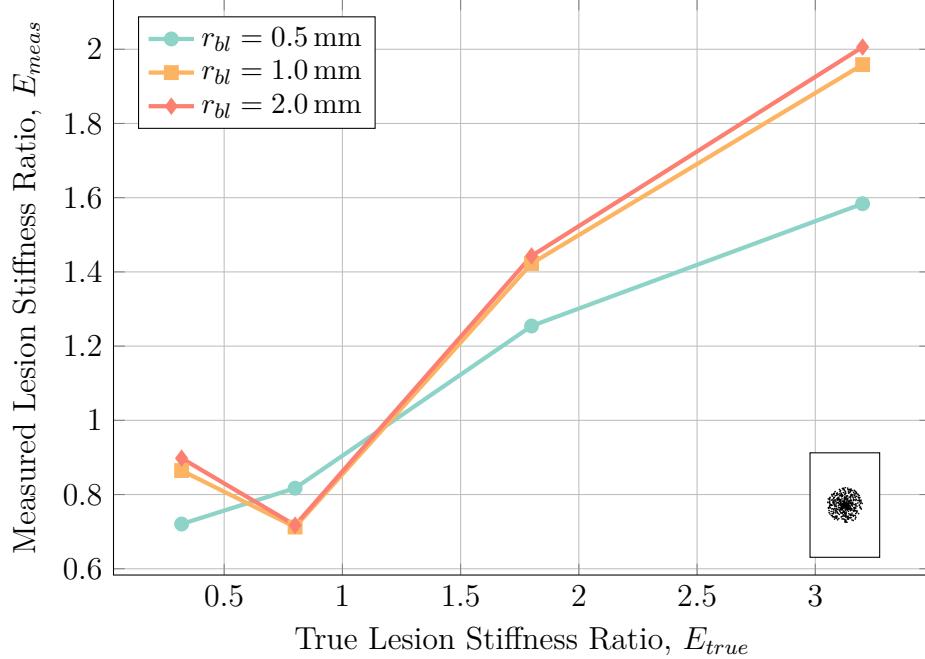


Fig. 3.18: Characterization of lesion radius for a group of numerous smaller lesions with a density of 30 lesions per cm^2 comprising a large area with a diameter of 2.5 cm at a depth of 10 cm interrogated with a 4 MHz probing frequency and 5% applied strain. Detection sensitivity decreases with decreasing individual lesion size, as expected.

and 3.21 respectively.

In Fig. 3.19, it is clear to see than small lesions (with a diameter $\leq 1.0\text{ cm}$) are almost impossible to adequately detect (although larger lesions will be adequately detectable). It is hypothesized that this phenomenon is due to the excessive strain apparent above the boney prominence that is seen in the resultant elastogram given in Fig. 3.20 such that the lesion is “washed out” by the strain field developed by the relatively stiff bone nearby.

In Fig. 3.21, there is little to no dependence of the detection sensitivity on the lesion depth in the Visible Human-MRI model with all depth curves displaying the same profile. However, deeper lesions (lesions closer to the bony prominence) have stiffnesses that are over-estimated with respect to their superficial counterparts. This is hypothesized to be due to the increased strain field present in all of the soft tissue located immediately superior to the bony

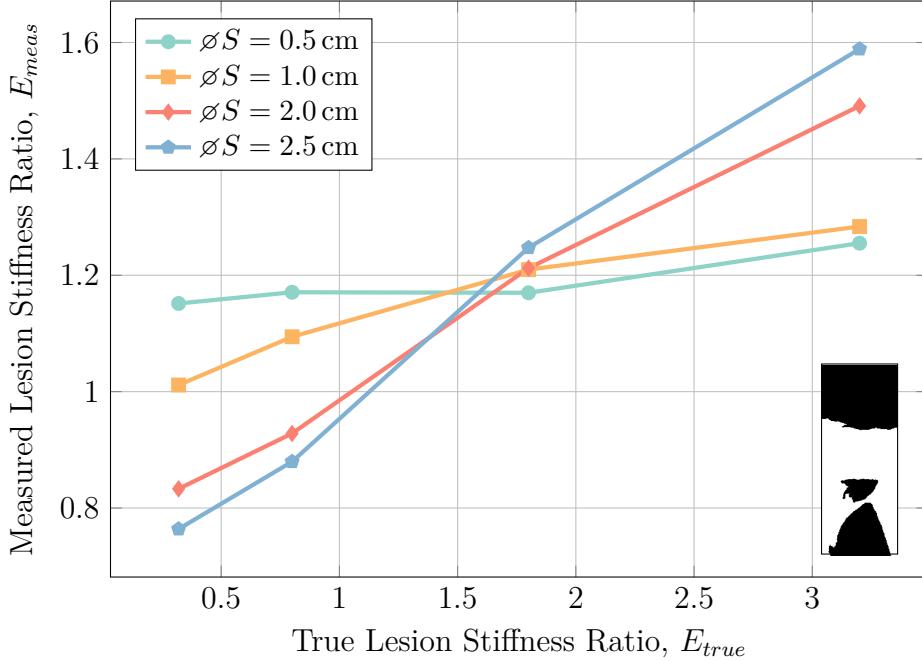


Fig. 3.19: Characterization of lesion width in a Visible Human-MRI model for lesions at a depth of 7.25 cm interrogated with a 4 MHz probing frequency with 5% applied strain. Small lesions (with a width $\leq 1.0 \text{ cm}$) are severely misrepresented and portray general over-estimation of lesion stiffness larger lesions.

prominence, but should not pose a serious problem for imaging lesions of this nature.

3.3.4 Physical Phantom Validation

In order to ensure that the models presented here represented physical realities, a small subset of the cases studied were modelled in a physical phantom, specifically for three lesions with stiffness ratios of 0.56, 1.80, and 3.20 with a diameter of 2.0 cm and at a depth of 3.5 cm, interrogated at 8 MHz with approximately 5% applied strain. The results of this study are summarized in Fig. 3.22.

As can be seen in Fig. 3.22, a relatively simple (although inexact) relationship between simulated and experimental measured strain ratios exists. It must be noted that the finite-element simulations of b-mode image formation

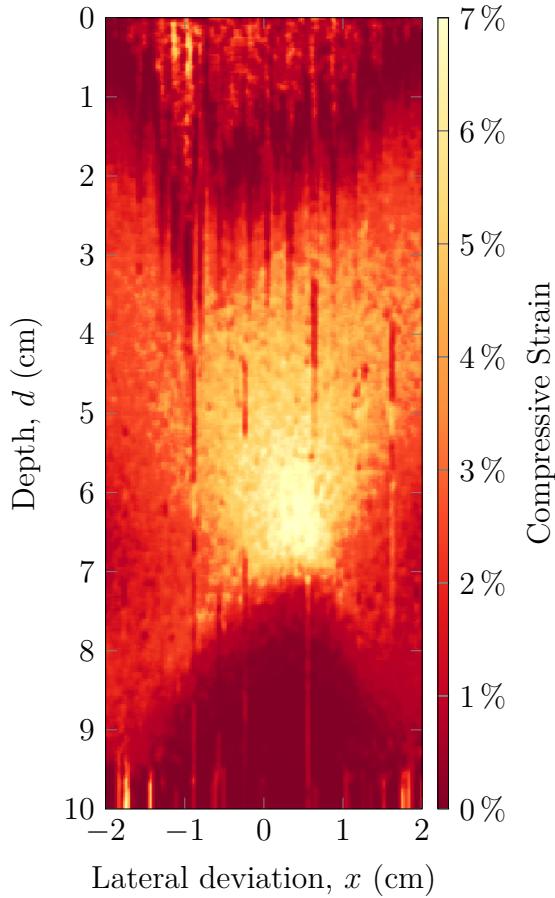


Fig. 3.20: Elastogram for a 0.5 cm wide lesion embedded in the Visible Human-MRI model domain at a depth of 7.25 cm interrogated at 4 MHz with an applied strain of 2.5 %. The lesion is not visible in the resultant elastogram.

and tissue deformation presented here are idealizations of reality and idealization errors such as the ultrasound pulse profile and plane-strain assumption no doubt contributed to the difference seen in Fig. 3.22.

It must be noted that in order to acquire quasi-static elastography results in the physical phantom, the ultrasound transducer was required to be manually manipulated to cause indentation in the phantom, as the technique would most likely be performed in a clinical setting. This was found to be problematic as the ultrasound transducer was difficult to maintain perfectly perpendicular and in-plane during the compression (largely due to the necessity of using coupling ultrasonic gel). This difficulty suggests that acoustic radiation force impulse

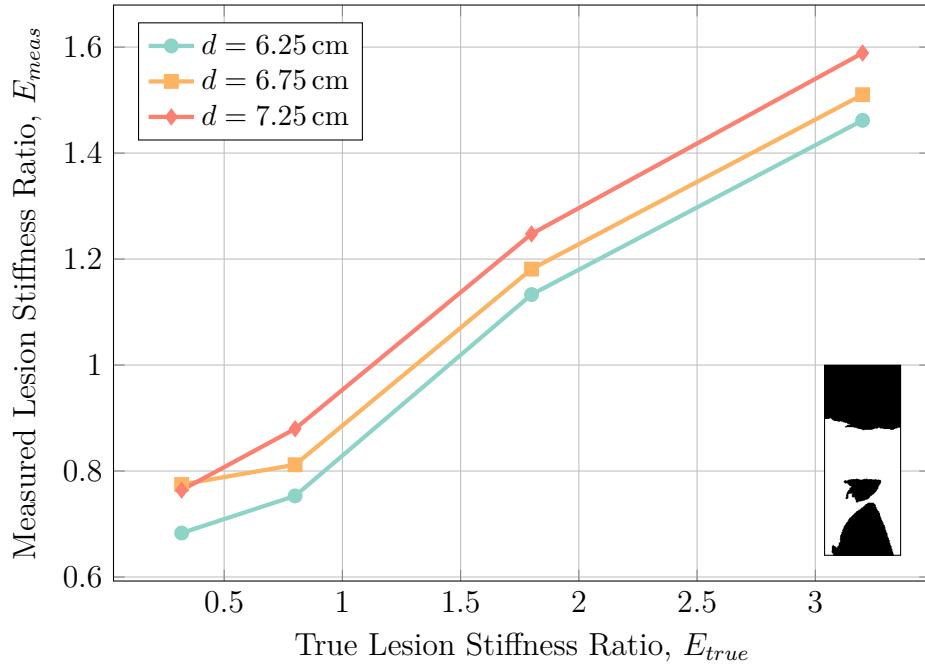


Fig. 3.21: Characterization of lesion depth in a Visible Human-MRI model for lesions with a width of 2.5 cm interrogated with a 4 MHz probing frequency and 5 % applied strain. Deeper lesions (closer to the bony prominence) are have slightly over-estimated lesion stiffness ratios as opposed to more superficial lesions while detection sensitivity is not affected by lesion depth.

(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.

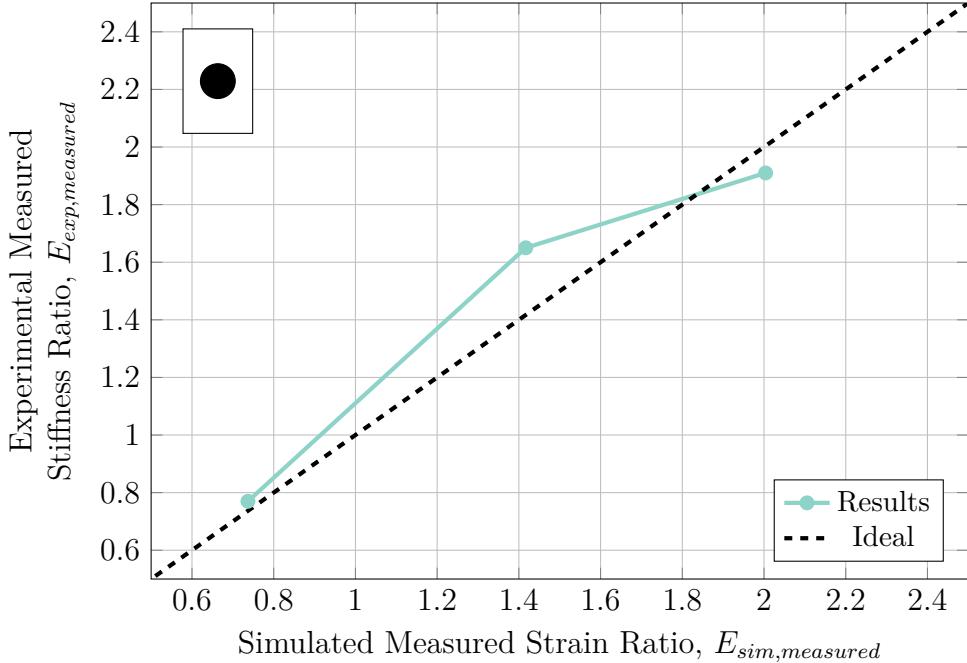


Fig. 3.22: Relation between simulated measured strain ratios and experimental measured strain ratios for a lesion at a depth of 3.5 cm and diameter of 2.0 cm showing general agreement between simulated and experimental cases. Idealization errors are the most likely the cause of the differences seen between simulated and experimental cases.

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 the 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 soft and very stiff lesions, thus it is recommended that diagnosticians only apply moderate ($\leq 5\%$) 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 soft lesions. Specifically, soft 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 soft (and hard) tissue. Work done by Solis et al. [67] has shown that untreated DTI are multiple centimeters 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 pseudospectral 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

4.2.1 K-Space Pseudospectral Model of Acoustic Fields

In order to simulate the body loads generated within deep tissue by a continuous ultrasound beam, a k-space pseudospectral 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 pseudospectral 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 [118]. Equations 4.1a, 4.1b, and 4.1c represent the momentum conservation, mass conservation, and pressure-density relation terms respectively.

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

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

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

^{c1}

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

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.

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

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

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

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.

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

The k-Wave MATLAB® toolbox version 1.0 was used to solve for the time-variant intensities resulting from simulated acoustic radiation force impulses

^{c1} KH: Talk about all the parameters in these equations

applied to heterogeneous soft tissue using equations 4.1a, 4.4, and 4.1c. Sample source code for performing these simulations using the k-Wave toolbox is given in listing A.3 in Appendix A.

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 ^{c1}.

Using a perturbative expansion of equation 4.5, acoustic radiation force can be expressed as per equations 4.6 [119]. 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.

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

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

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

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

^{c1} KH: Add citation!

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} [109].

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

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 de-

formation was used [120]. The simulated tissue properties are summarized in Tables 4.1 and 4.2.

Table 4.1: ARFI Model Viscoelastic Tissue Properties

Property	Value	Units
Bulk Modulus	515.7	kPa
Shear Modulus	1.0	kPa
Density	1060	kg m ⁻³

Table 4.2: ARFI Maxwell Model Tissue Properties

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

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.

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

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 auxillary 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. The acoustic radiation force was applied as a body load to the tissue in the model with the distribution calculated by the k-space pseudospectral 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 might affect the simulation results, the model geometry extended laterally by 5 cm in either direction from the centerline. Simulations were run until the axial displacement at the focal point returned to 1% of its maximal value during the entire simulation—at this point, the tissue was considered to be “relaxed” after being disturbed by the acoustic radiation force.

$$\vec{u} = 0, \quad \Gamma = \Gamma_{bottom} \quad (4.13a)$$

$$u_y = 0, \quad \Gamma = \Gamma_{top} \quad (4.13b)$$

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 modeled. 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 do-

main, 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 [110]. Schematics of the four investigated models are given in 4.1.

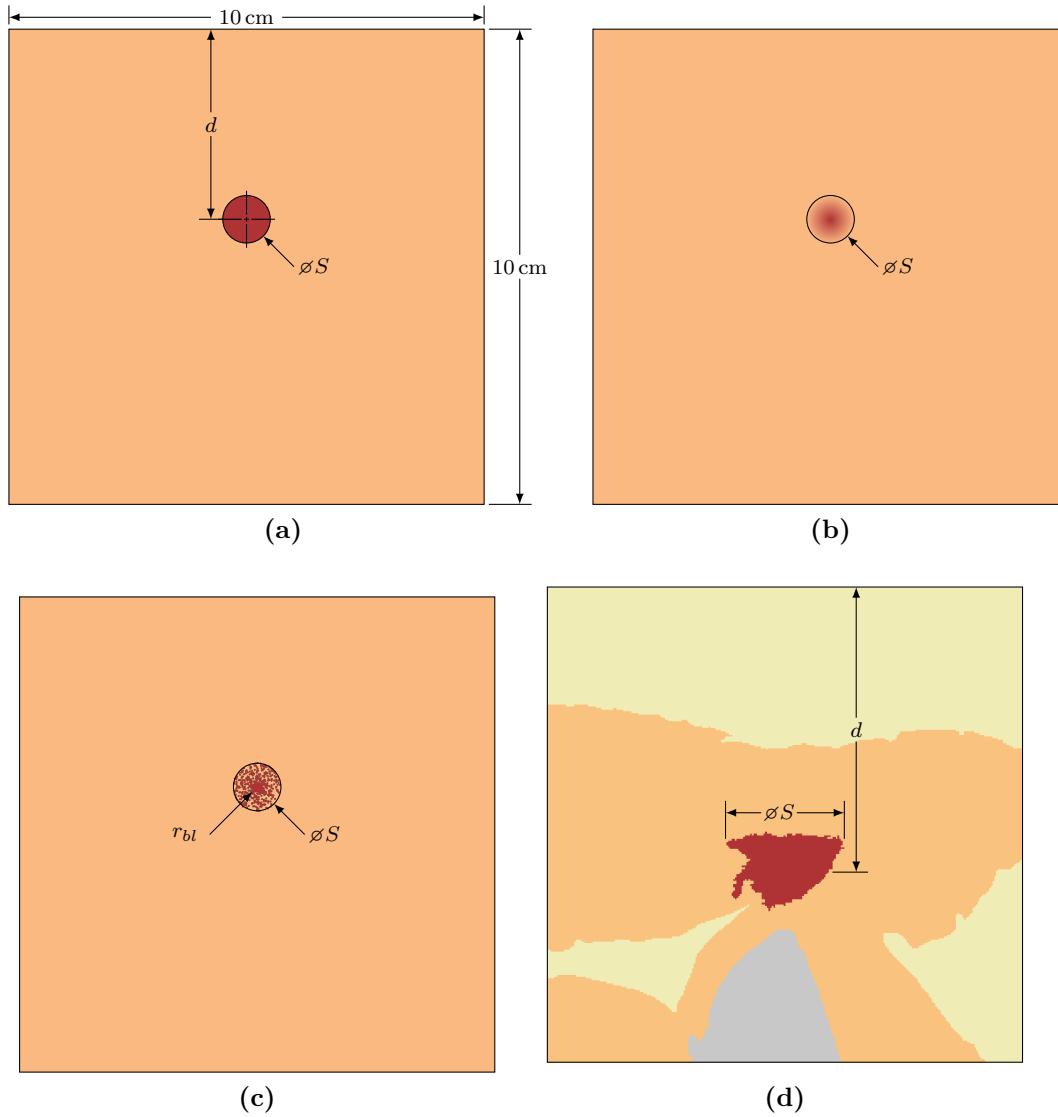


Fig. 4.1: Schematics of the lesion models that were investigated using acoustic radiation force impulse imaging showing (a) a spherical hard-boundaried lesion, (b) a spherical blurred-boundary lesion, (c) a cluster of numerous small lesions composing a larger lesionous region, and (d) the geometry from an MRI-acquired deep tissue injury overlaid on a slice from the Visible Human Project such that the injury lesion was located immediately superior to an ischial tuberosity.

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; and the width (and overall size) of the MRI-acquired lesion in the Visible Human model. The range of values of these investigated parameters are listed in Table 4.3 ^{c1}.

Table 4.3: Range of values of investigated parameters in the various ARFI models that were studied.

Parameter	Symbol	Values
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	ϕS	[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	ϕS	[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, equation 4.14 may be applied. Assuming a constant force applied to the both the lesionous region and the soft tissue reference point,

^{c1} KH: Mention parameters like B/A, density, etc

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 S2000™ ^{c1} portable ultrasound machine with a Siemens 9L4 ^{c2} transducer, ARFI images were acquired of lesions within the phantom. The stiffness ratios of these lesions according the acquired ARFI telemetry 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. ^{c3}

^{c1} KH: Correct naming / registered marks / etc?

^{c2} KH: Describe probe better

^{c3} KH: Mention number of trials (10)

4.3 Results

Using the k-space pseudospectral 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 4.3. 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. 4.2 for the case when a 2 MHz beam focussed 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. 4.2a and 4.2b is to push the tissue deeper axially and towards 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 pseudospectral models employed to simulate acoustic

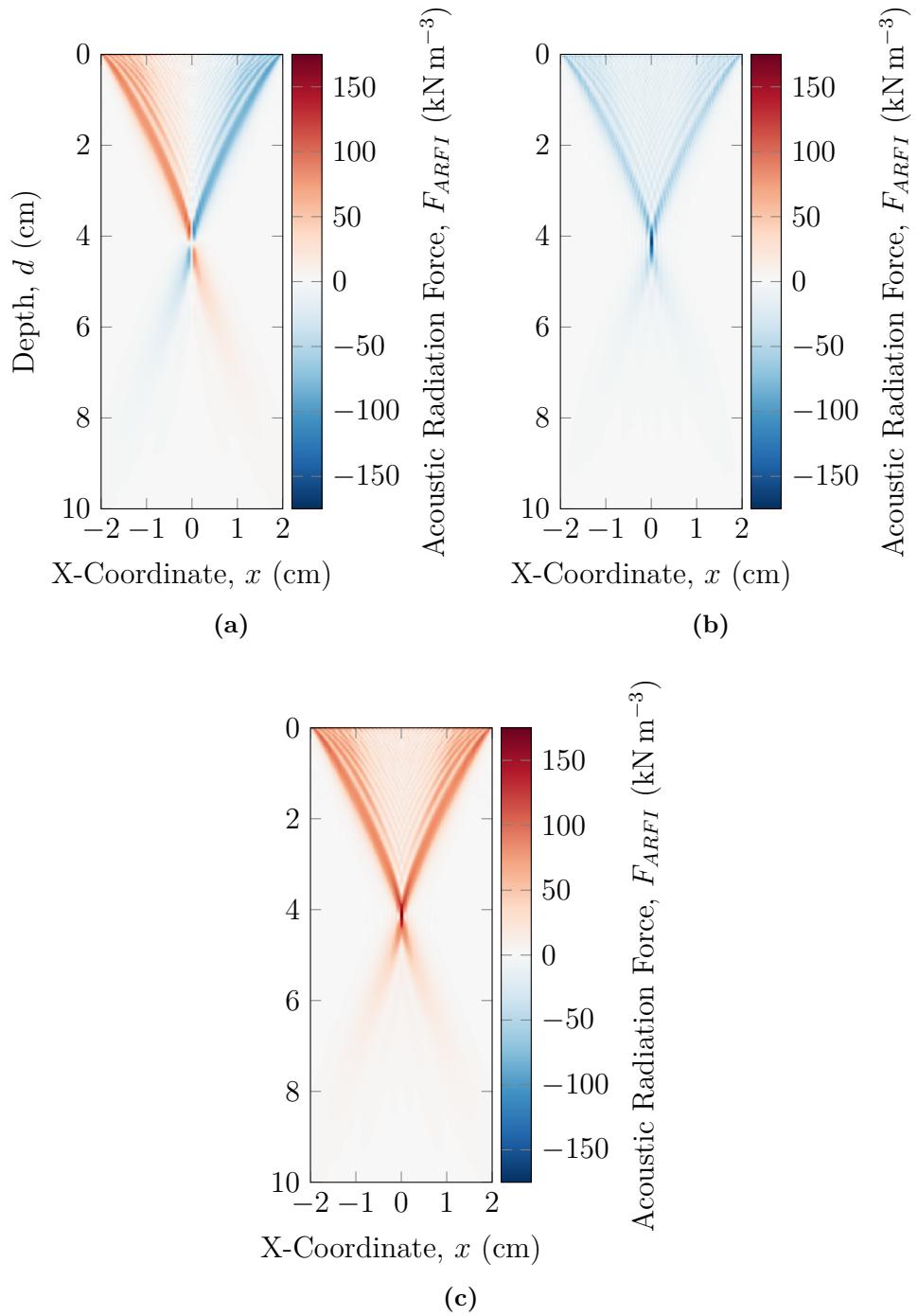


Fig. 4.2: Sample acoustic radiation force distribution in the (a) lateral and (b) axial directions, and (c) the resultant L^2 -norm generated by a 2 MHz transducer operating with an aperture of 4 cm focusing an acoustic beam at a depth of 4 cm continuously for 150 μs applying a pressure of 3.35 MPa.

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 focussed 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 with decreases 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. 4.3.

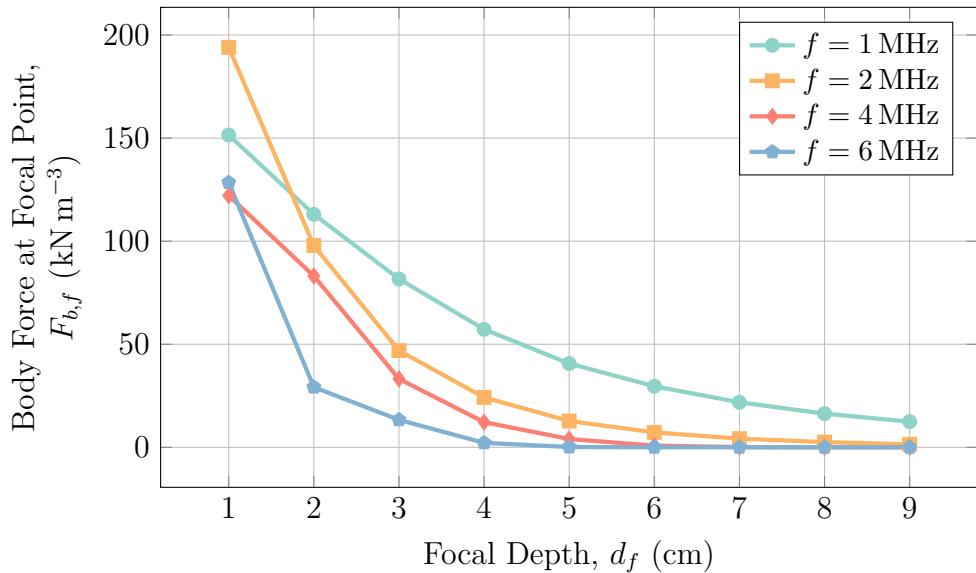


Fig. 4.3: Effect of depth and interrogation frequency on the magnitude of acoustic body forces developed in tissue. Increasing the interrogation frequency or the focal depth results in lesser body loads experienced by the tissue at the focal point, with the greatest loss of magnitude resulting from focal depth.

As Fig. 4.3 shows, increasing focal depth and probing frequency drastically decreases the magnitude of the force at the focal point of the tissue. In general, forces that are greater in magnitude are ideal as the deflection in the tissue that they cause must be detectable by the same transducer that is applying the forces—if the resulting deflections are too low, the tracking waves sent by the transducer will not be able to distinguish the motion. For the Siemens

ACUSON S2000TM machine used in the validation of these studies, this lower limit is quoted as being $1/100$ of the applied wavelength, or approximately $1.7\text{ }\mu\text{m}$ for a 9 MHz probing frequency ^{c1}.

Since the forces developed in the tissue represent a transfer of energy, theoretically increasing the amount of energy input into the system should increase, or at least assist in greater amount of energy being transferred to the tissue. One way of increasing the amount of energy applied to the tissue by the transducer is to increase the size, or the “aperture” of the transducer—an aperture of 8 cm will use twice as many physical pulsing elements than an aperture of 4 cm . To study this, the magnitude of the body force at the focal point was studied in simulation as the aperture changed. The results of this study are shown in Fig. 4.4.

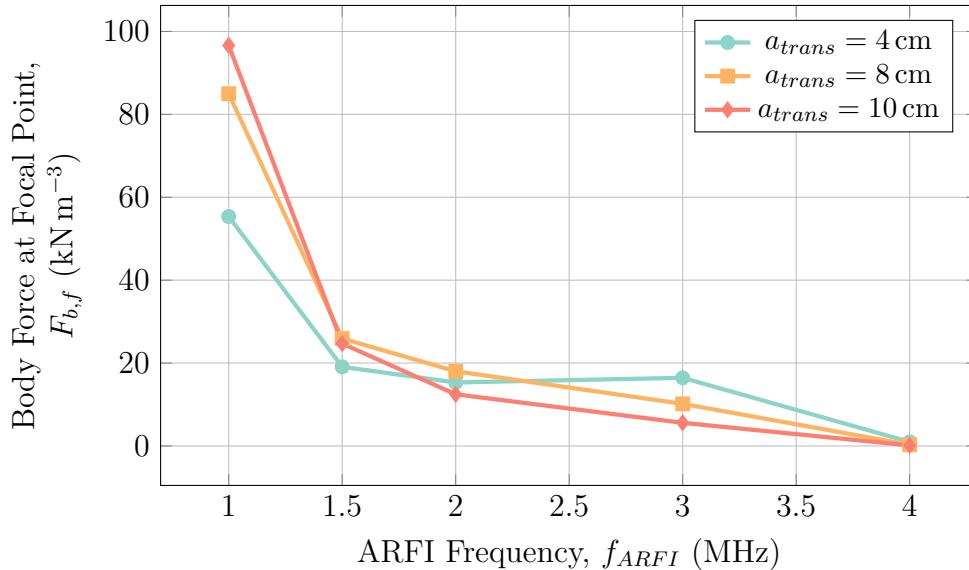


Fig. 4.4: Effect of transducer aperture on the magnitude of developed acoustic radiation force at the focal depth of 6 cm for a range of ultrasound interrogation frequencies.

Surprisingly, there was little consistent effect of the transducer aperture size on the magnitude of the acoustic radiation force that was seen at the focal

^{c1} KH: Need citation for this (in the manual)

point. As expected, the greatest and least forces were developed with the lowest and highest frequencies studied, respectively, as per the results found in Fig. 4.3. The greatest effect of the transducer aperture size occurred at a frequency of 1 MHz, where it is hypothesized that ^{c1}.

Another method of increasing the amount of energy transferred into the system is to increase the duration of time that the system is applying pressure to the tissue. In other words, increasing the number of pulse cycles (insonification time) should generate more energy until tissue is under quasi-steady-state insonification. To investigate this, the effect of the number of acoustic pulse cycles—related to the insonification time by equation 4.15—was investigated, with the results shown in Fig. 4.5.

$$t_{\text{inson}} = \frac{n_c}{f_{\text{applied}}} \quad (4.15)$$

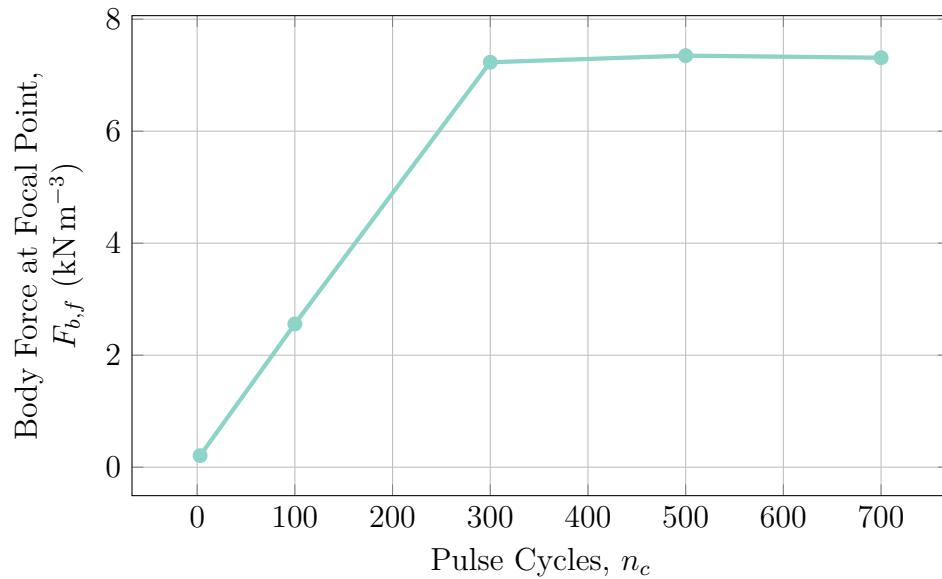


Fig. 4.5: Magnitude of the developed acoustic radiation force in relation to the number of applied pulse cycles in tissue at a focal depth of 6 cm using a transducer aperture of 4 cm and source pressure of 3.35 MPa.

As expected, increasing the number of pulse cycles increased the magnitude

^{c1} KH: hypothesize!

of the acoustic radiation force seen at the focal point until the domain reached quasi-steady-state at approximately 300 pulses, or 150 μ s of insonification. At this point, since the calculation of the acoustic radiation force given in equation 4.10 relies on the *average* intensity during the insonification time, increasing the number of pulse cycles has little to no effect on the resulting acoustic radiation force.

One further way of increasing the energy in the system and thereby increasing the magnitude of the acoustic radiation force at the focal point is to increase the amount of pressure applied by the individual transducer elements. To investigate this technique, a range of acoustic pulsing element pressures were applied across a range of focal depths and the resulting acoustic radiation force at the focal point was monitored. The results of this study are shown in Fig. 4.6.

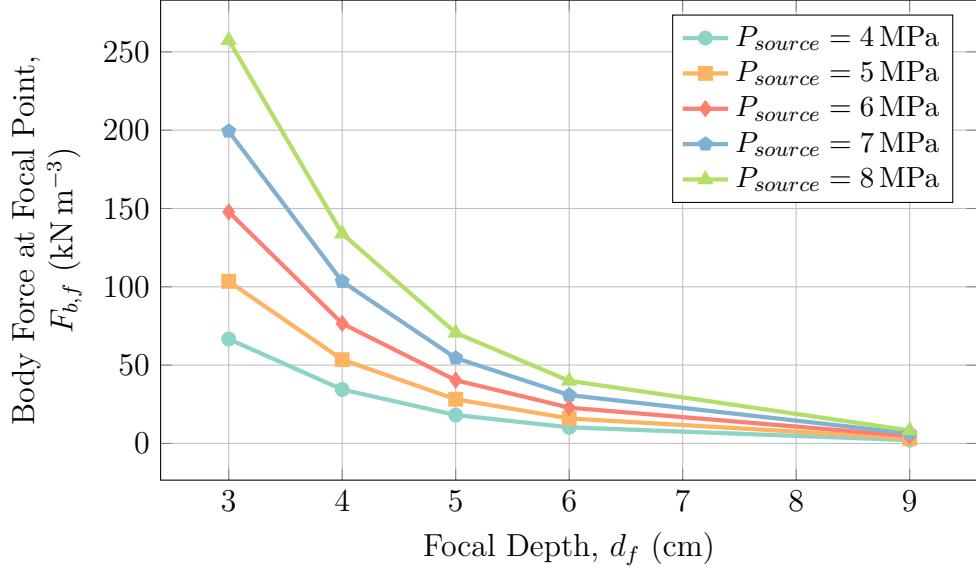


Fig. 4.6: Strong dependence on source pressure of focal point force

As Fig. 4.6 shows and as was expected, increasing the applied pressure results in greatly increasing the magnitude of the resultant acoustic radiation force developed in the tissue—doubling the applied pressure results in nearly

quadrupling the magnitude of the acoustic radiation force at all depths. Note however that a critical measure of the safety of ultrasound is the cavitation pressure of the ultrasonic wave as it travels through the tissue. The safety of cavitation is described by the “mechanical index”, MI , which is calculated according to equation 4.16 [93] where P_r is the peak rarefaction pressure in the 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 focussed 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. 4.3 and is shown in Fig. 4.7. Based on a maximum I_{SPPA} exposure of 933 W cm^{-2} [93], the use of ultrasound probes operating at or above 1 MHz and focussed 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.

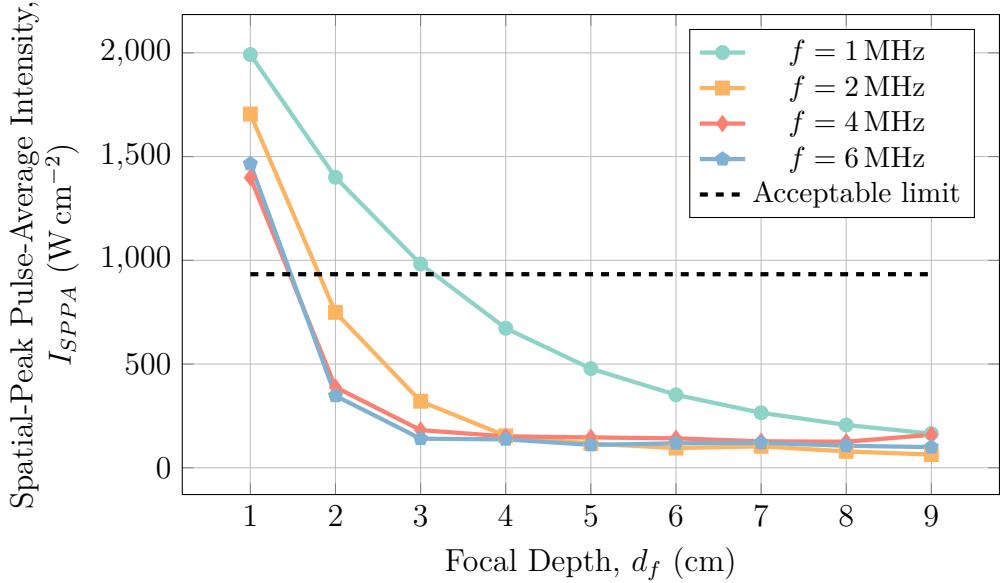


Fig. 4.7: The effect of depth and interrogation frequency on the spatial peak pulse average intensity, I_{SPPA} . I_{SPPA} is a measure of the safety of high-intensity ultrasound applications, with I_{SPPA} values below 933 W cm^{-2} considered acceptable for non-cardiovascular and non-fetal imaging.

4.3.2 Temporal Finite-Element Model of Soft Tissue Deformation

As ARFI imaging relies upon the detection of soft tissue deformation in response to the transducer-applied acoustic radiation force, a key parameter of interest is the magnitude of the deformation generated in the tissue in response to the applied loads. To this end, the temporal finite-element model of soft tissue deformation described in Section 4.2.3 was used to determine the magnitude of the deformation caused by varying acoustic radiation force parameters.

Fig. 4.8 show the relationship between the maximum induced tissue displacement, $|v|_m \text{ ax}$, generated by acoustic radiation forces in soft tissue for a range of focal depths and interrogation frequencies. As expected, significantly greater deformation is generated with shallower focal depths. Further, increases in the interrogation frequency generally resulted in lesser displace-

ment induced in the tissue. The results obtained using a 1 MHz interrogation frequency stood apart from the higher frequencies investigated. This is likely due to the excess acoustic radiation force produced at such low frequencies shown in Figs. 4.3 and 4.7.

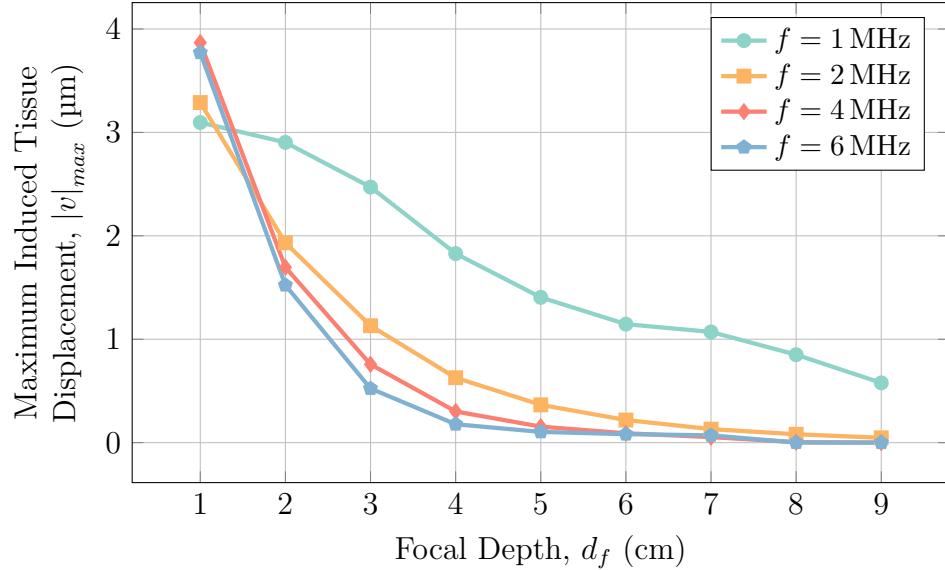


Fig. 4.8: Magnitude of deformation resulting from ARFI interrogation at various focal depths and interrogation frequencies with a transducer aperture of 4 cm and source pressure of 3.35 MPa.

To reiterate the results seen in Fig. 4.6, the maximum induced tissue displacement generated by the applied acoustic radiation force at various focal depths for various source pressures was investigated, the results of which are given in Fig. 4.9. These results echo the results seen in Fig. 4.6, where doubling the applied pressure resulted in approximately quadrupling the maximum displacement seen in the tissue across all focal depths as was expected.

The results given in Fig. 4.9 were further investigated by examining the effect of the interrogation frequency on the maximum induced tissue displacement. As expected, increasing the interrogation frequency resulted in decreases in the magnitude of deformation experienced by the tissue across all source pressures investigated. Further, increasing the amount of source pressure ap-

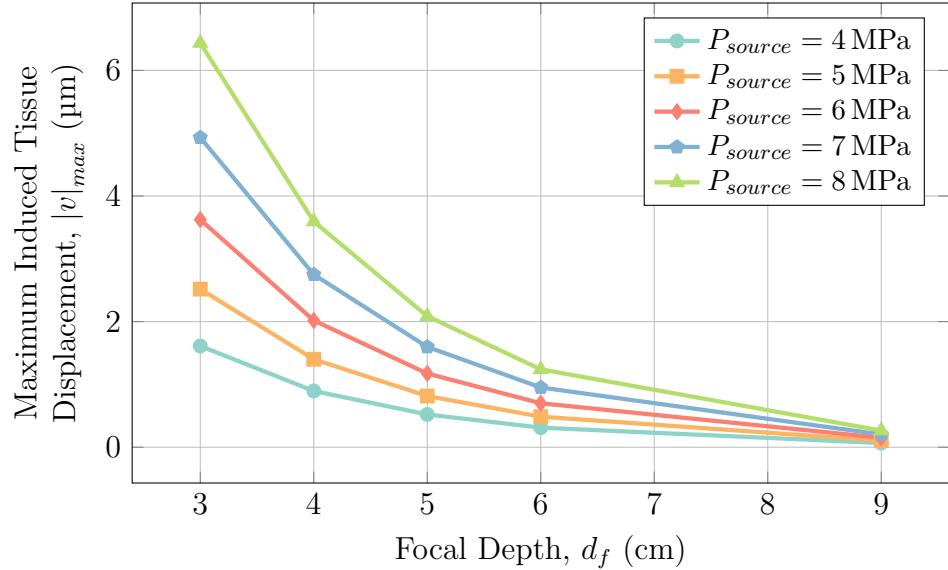


Fig. 4.9: Magnitude of deformation resulting from ARFI interrogation at various focal depths and source pressures at an interrogation frequency of 2 MHz with a transducer aperture of 4 cm and source pressure of 3.35 MPa.

plied by the transducer into the tissue resulted in greater levels of tissue deformation. Of note is that the use of a 1 MHz interrogation frequency affected the magnitude of tissue deformation across the different source pressures much more than any of the higher interrogation frequencies studied, further echoing the results seen in Fig. 4.8.

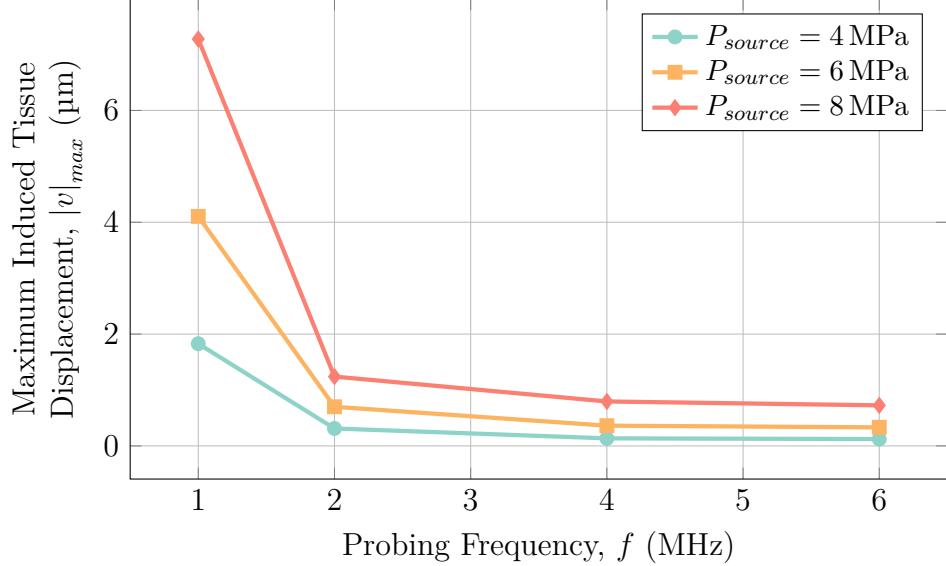


Fig. 4.10: Magnitude of deformation resulting from ARFI interrogation at various interrogation frequencies and source pressures at a depth of 6 cm with a transducer aperture of 4 cm and source pressure of 3.35 MPa.

4.3.3 Numerical Characterization of Acoustic Radiation Force Impulse Imaging

Beyond understanding the general nature of acoustic radiation forces in soft tissue, the effects of these forces in the presence of deep tissue injuries must also be characterized for ARFI imaging to become a useful diagnostic tool for such injuries. In order to investigate the suitability of ARFI imaging for the detection of DTI, the procedure outlined in Section 4.2.4 was carried out on a range of models with varying parameters of interest. The results of these characterizations are presented here.

In order to understand the effect of general lesion size on the detection sensitivity of ARFI imaging, hard-boundaried spherical lesions of various radii were placed in a soft tissue domain at a depth of 4 cm and insonated at 2 MHz with an aperture of 4 cm and pressure of 3.35 MPa for 150 μs (300 pulse cycles). The results of this characterization are presented in Fig. 4.11.

As Fig. 4.11 shows, ARFI imaging was able to detect the presence of both

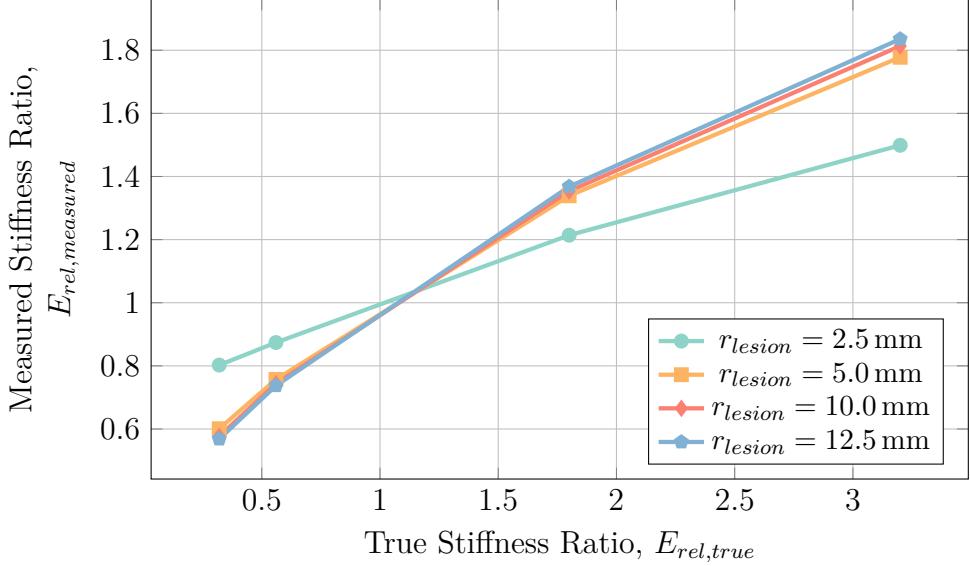


Fig. 4.11: Numerical characterization of the ARFI imaging-acquired stiffness ratios acquired with varying lesion radii for a hard-boundaried lesion at a depth of 4 cm using an ARFI probing frequency of 2 MHz.

stiff and soft lesions of all sizes, however the technique both severely underestimated the stiffness of stiff lesions and overestimated the stiffness of “soft” lesions—leading to the observation that ARFI imaging has a relatively low detection sensitivity with regards to both stiff and soft deep tissue injury lesions. Fig. 4.11 also shows that above lesion radii of approximately 2.5 mm, the lesions size does not have any appreciable effect on the detection sensitivity of the technique. Below this limit, however, lesions will be much more difficult to detect as the differences between them and the surrounding tissue are minimized.

To further corroborate these results, the mean-squared error associated with the various lesion radii was calculated according to equation 4.17 where \hat{Y}_i are the true lesion stiffness ratios and Y_i are the measured lesion stiffness ratios. The results of this calculation with regards to lesion radius are given in Fig. 4.12. Figure 4.12 explicitly depicts a greater degree of error for lesions with radii of 2.5 mm, with only marginal improvements in measurement error

resulting from increasing the lesion radius beyond 5.0 mm.

$$MSE = \frac{1}{n} \sum_{i=1}^n (\hat{Y}_i - Y_i)^2 \quad (4.17)$$

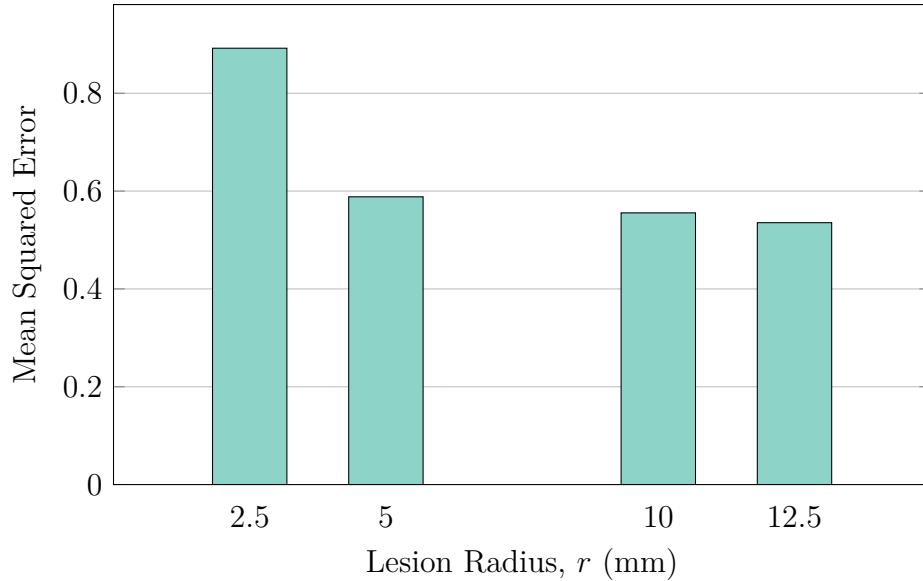


Fig. 4.12: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion radii for a hard-boundaried lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

In order to investigate the effect of lesion depth on detection sensitivity, the use of ARFI imaging to distinguish spherical hard-boundaried lesions with radii of 10 mm was investigated at a range of depths, with the results shown in Fig. 4.13. As Fig. 4.13 shows, there is almost no dependence of the detection sensitivity on the depth of the lesion. However, it must be noted that the deformations resulting from acoustic radiation force impulses will be of such small magnitudes that they will not be detectable using current ultrasound technology. To understand the limitations of depth in ARFI imaging, please refer to Section 4.3.2.

Fig. 4.14 portrays the mean-squared-error of the measured lesion stiffness across the various depths examined. Although the variance in error between

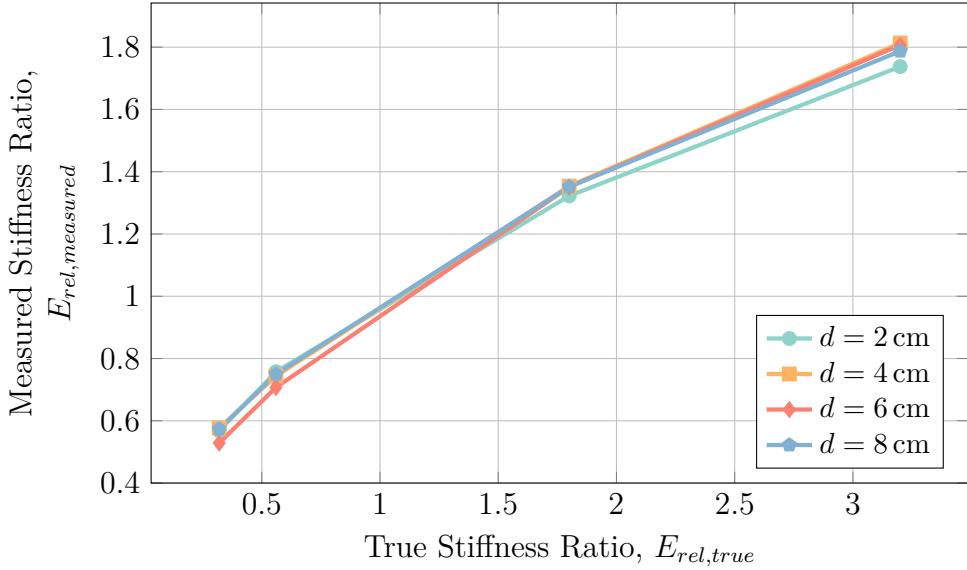


Fig. 4.13: Numerical characterization of the ARFI imaging-acquired stiffness ratios acquired with varying lesion and focal point depths for a hard-boundaried 0.5 cm radius lesion using an ARFI probing frequency of 2 MHz.

the different depths is not substantial, both very shallow—lesions at a depth of 2 cm or less—and very deep—lesions at a depth of 8 cm or more—were found to have the greatest measurement error. ^{c1}

Since the aforementioned hard-boundaried, spherical lesion cases represent simplifications of reality designed to obtain a general understanding of the ARFI technique, models representing more complicated geometry were also studied. Fig. 4.15 shows the simulated lesion stiffness ratios for a set of lesions with radii of 10 mm at a depth of 4 cm with blurred boundaries as described in Section 4.2.4. As Fig. 4.15 shows, there is no reliance of the detection sensitivity on the blur radius of the lesion, with the results shown repeating the results seen in Figs. 4.11 and 4.13.

The mean-squared error shown in Fig. 4.16 further supports this conclusion, with the error between different blur radii differing by just over 1%. This lack of sensitivity on the degree of lesion blurring presents a significant

^{c1} KH: Why?

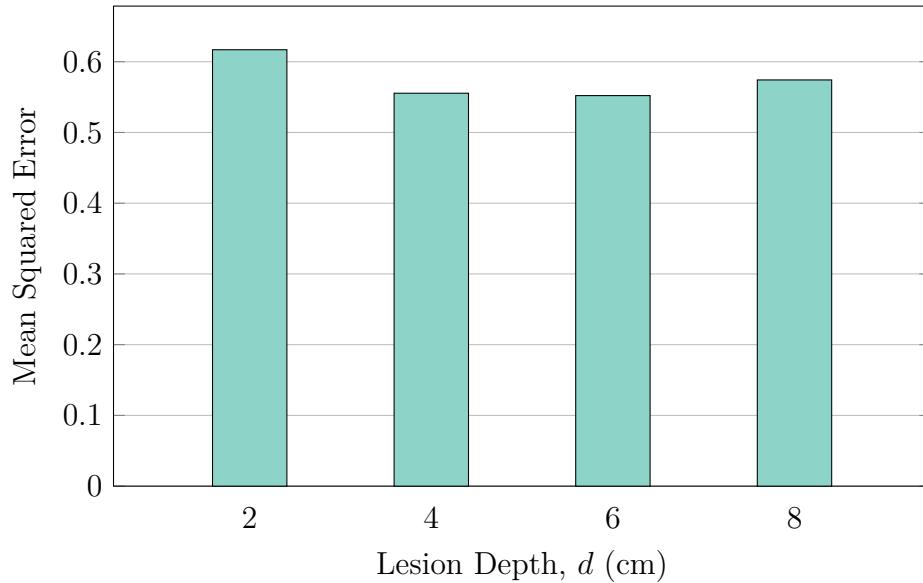


Fig. 4.14: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion depths for a hard-boundaried 0.5 cm radius lesion using an ARFI interrogation frequency of 2 MHz.

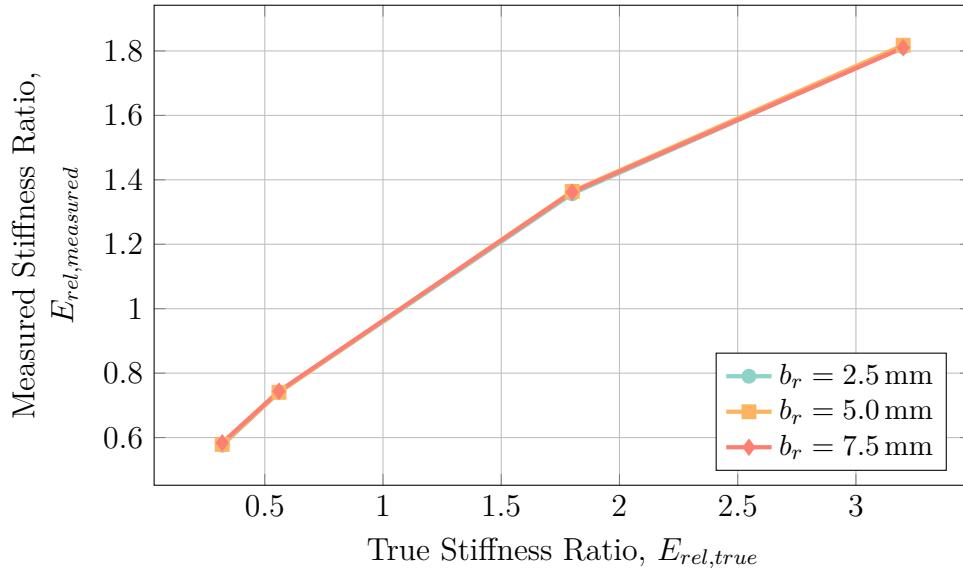


Fig. 4.15: Numerical characterization of the ARFI imaging-acquired stiffness ratios acquired with varying lesion and focal point depths for a blurred 1.0 cm radius lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

advantage over quasi-static elastography as it allows even lesions without well-defined boundaries to be detected.

It may also be possible that a diseased region of tissue is not a singular,

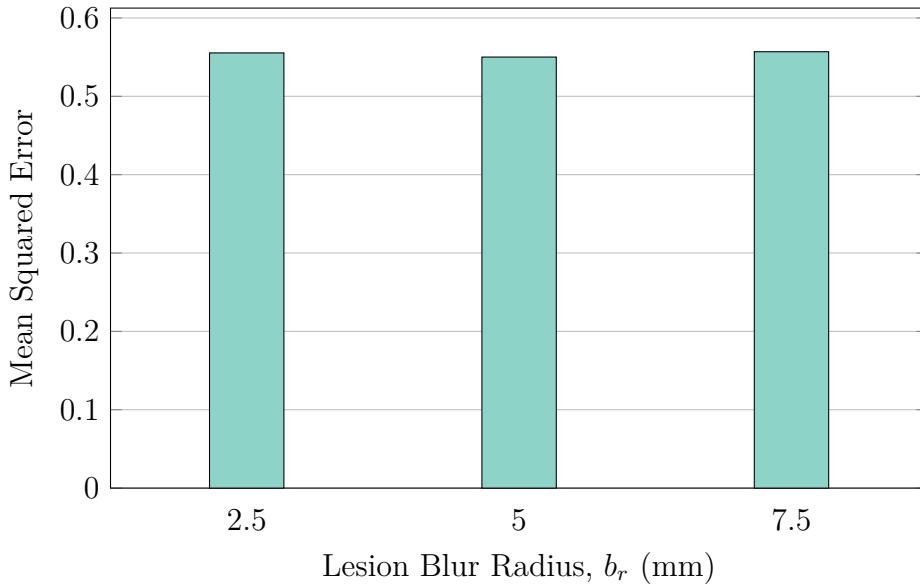


Fig. 4.16: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion depths for a blurred 1.0 cm radius lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

continuous lesionous region, but rather an amalgamation of numerous small lesions or damaged tissue which collectively compose a larger lesionous region. To investigate the effect such a phenomenon would have on the detection sensitivity of ARFI imaging, the density and size of numerous small, clustered lesions were varied in models and the resulting measured stiffness ratios were investigated. Fig. 4.17 shows the characterization of the lesion cluster density—how many lesions are present per unit area—for densities ranging from 10 cm^{-2} to 40 cm^{-2} with small lesions of radius 1.0 mm. The centre of the lesionous regions were located at a depth of 4 cm in an overall region with a radius of 10 mm.

As Fig. 4.17 shows, increasing the cluster density results in monotonically increasing the detection sensitivity of the ARFI technique. This is as expected, as increasing the cluster density increases the total area contributing to the modified tissue stiffness in the region, which in turn allows the ARFI technique to more readily distinguish the lesion. These results are further shown in by

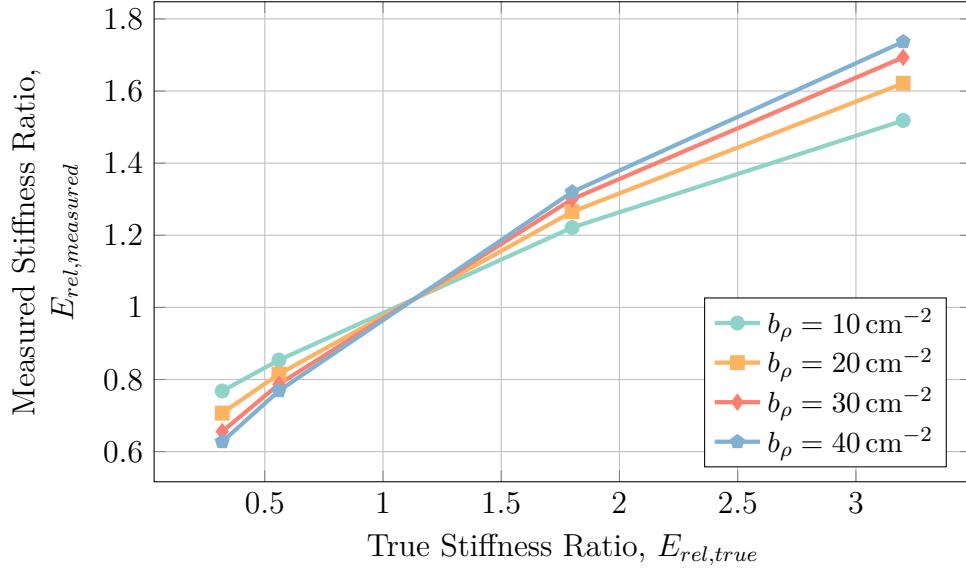


Fig. 4.17: Numerical characterization of the ARFI imaging-acquired stiffness ratios acquired with varying cluster densities for clustered 1 mm radius lesions within a 1.0 cm radius at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

the mean-squared error shown in Fig. 4.18 which shows the decrease in error attributed to increases in lesion cluster densities.

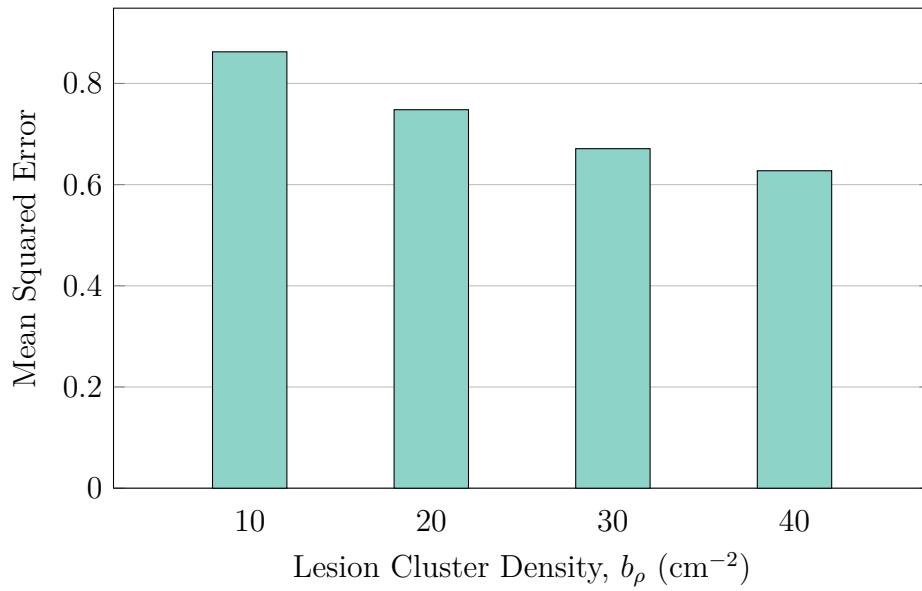


Fig. 4.18: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion cluster density for clustered 1 mm radius lesions within a 1.0 cm radius at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

Another method to alter the ratio of damaged to healthy tissue within

the lesionous region is to alter the size of the individual lesions that comprise that region. This characterization was carried out using small lesions with radii ranging from 0.5 mm to 1.5 mm at a cluster density of 30 cm^{-2} , with the results given in Fig. 4.19.

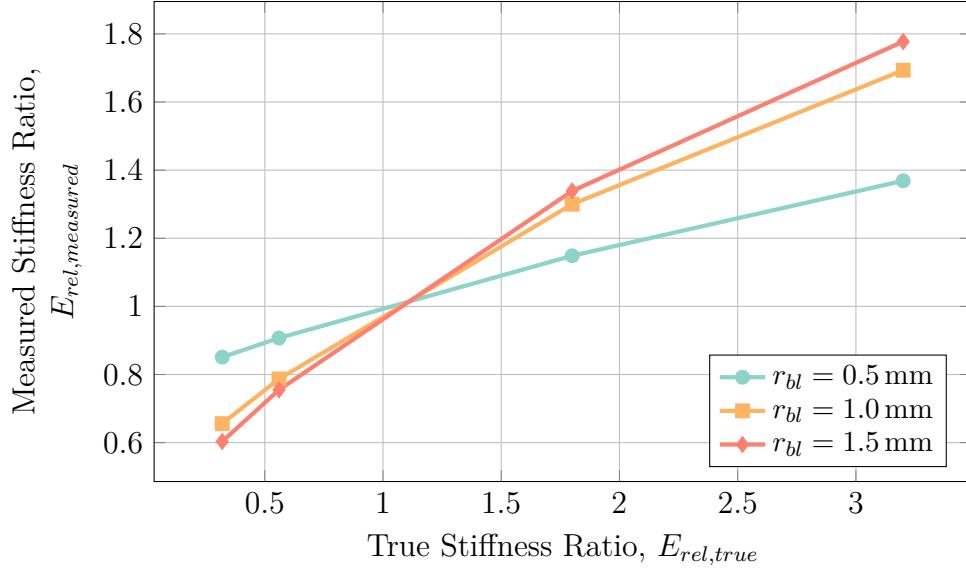


Fig. 4.19: Numerical characterization of the ARFI imaging-acquired stiffness ratios acquired with varying clustered lesion radii for clustered lesions with a density of 30 cm^{-2} within a 1.0 cm radius at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

As Fig. 4.19 shows, decreasing the individual lesion radii in the clustered model substantially decreased the detection sensitivity of the ARFI technique, again echoing the previous results where decreasing the ratio of damaged to healthy tissue in the lesionous region results in lesser detection sensitivity. This is confirmed by examining the mean-squared error of the results, which shows monotonically decreasing errors for monotonically increasing individual lesion radii.

While the aforementioned studies investigated generally spherical lesionous regions, this is unlikely to be the case in a real soft tissue domain. To further investigate ARFI imaging, a model utilizing complicated geometry arising from the combination of the MRI-acquired geometry of a deep tissue injury with

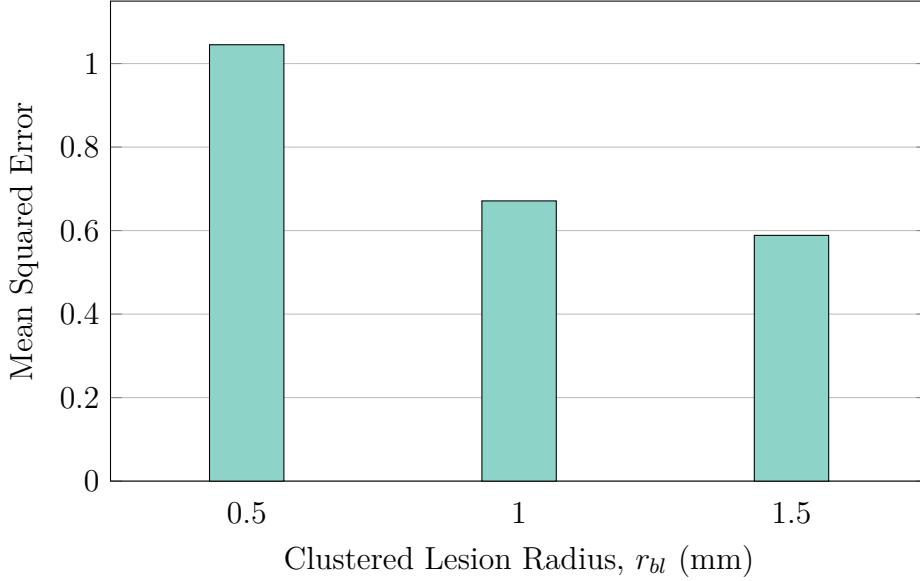


Fig. 4.20: Mean squared error between the true and measured lesion stiffness ratios for increasing clustered lesion radii for clustered lesions with a density of 30 cm^{-2} within a 1.0 cm radius at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz .

the anatomical distribution of fat, muscle, and bone obtained from the Visible Human project [110] was created as described in Section 4.2.4. To investigate the effect of lesion size in this model, the lesion size, ϕS_{lesion} , was varied between 2.5 mm and 12.5 with the lesion being placed at a depth of 6 cm . The results of this characterization are shown in Fig. 4.21.

As Fig. 4.21 shows, decreasing the lesion width in the Visible Human model resulted in a decreased detection sensitivity which was echoed by the mean-square error of the results shown in Fig. 4.22. The detection sensitivity decreases with half-widths less than 10 mm in the Visible Human model as opposed to radii of 5 mm as found with the spherical lesion embedded in general soft tissue seen in Fig. 4.11. Although the reason for this is not immediately clear, possible differences lay in the depth at which the lesions were imaged at: the Visible Human model placed the lesion at a depth of 6 cm so as to have it lay immediately superior to the ischial tuberosity while the results for

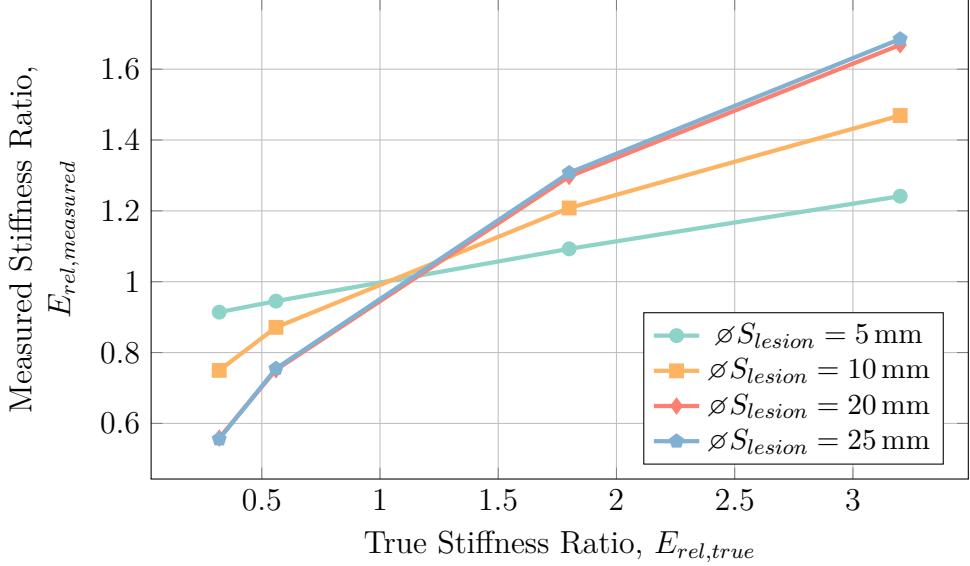


Fig. 4.21: Numerical characterization of ARFI imaging-acquired stiffness ratio with changing lesion radii for MRI-acquired lesion geometry in a Visible Human model at a depth of 6 cm using an ARFI interrogation frequency of 2 MHz.

the spherical lesion were taken at a depth of 4 cm. Further, comparing the half-width of the Visible Human lesion to the radius of the spherical lesion may introduce errors as the overall area of lesionous tissue were different.

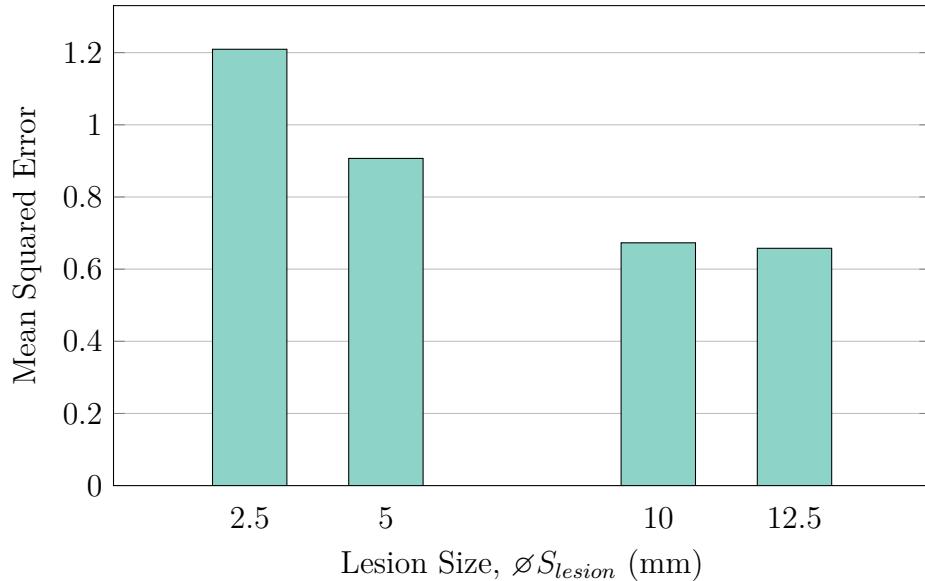


Fig. 4.22: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion radii for MRI-acquired lesion geometry in a Visible Human model at a depth of 6 cm using an ARFI interrogation frequency of 2 MHz.

4.3.4 Physical Phantom Validation

In order to determine if the results presented in Section 4.3.3 represent valid simulations, validation experiments were carried out on a physical tissue mimicking phantom as described in Section 4.2.5. Fig. 4.23 shows the result of these experiments.

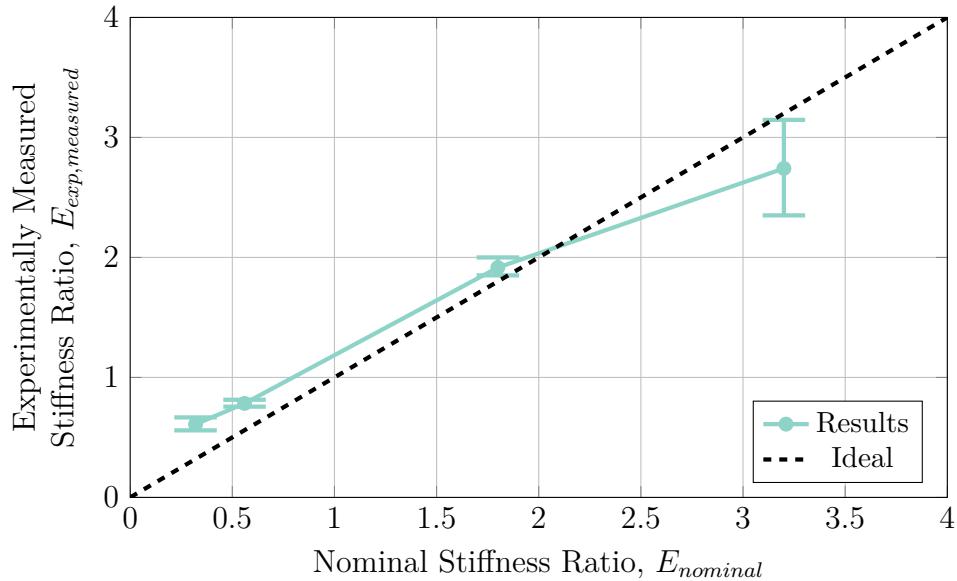


Fig. 4.23: Relation between nominally reported strain ratios of the tissue mimicking phantom and experimentally measured strain ratios for a lesion at a depth of 3.5 cm and diameter of 2.0 cm. Error bars represent the range of measurements acquired.

As the results seen in Fig. 4.23 show, ARFI imaging was found experimentally to significantly underestimate the stiffness of the stiffest lesions investigated—lesions with nominal stiffnesses of 3.2. For all other lesions investigated, ARFI imaging was shown to overestimate the lesion stiffness ^{c1}.

Fig. 4.24 compares the experimentally-acquired lesion stiffness ratios against measured stiffness ratios arising from parametrically identical simulated lesions. As Fig. 4.24 shows, although the experimentally measured stiffness ratios align well with the simulated stiffness ratios for relatively soft lesions

^{c1} KH: More

($E_{rel} < 1$), the simulated ARFI procedure was found to underestimate the stiffness of the stiff lesions that were investigated ($E_{rel} > 1$). The exact cause of this disparity is unclear ^{c2}.

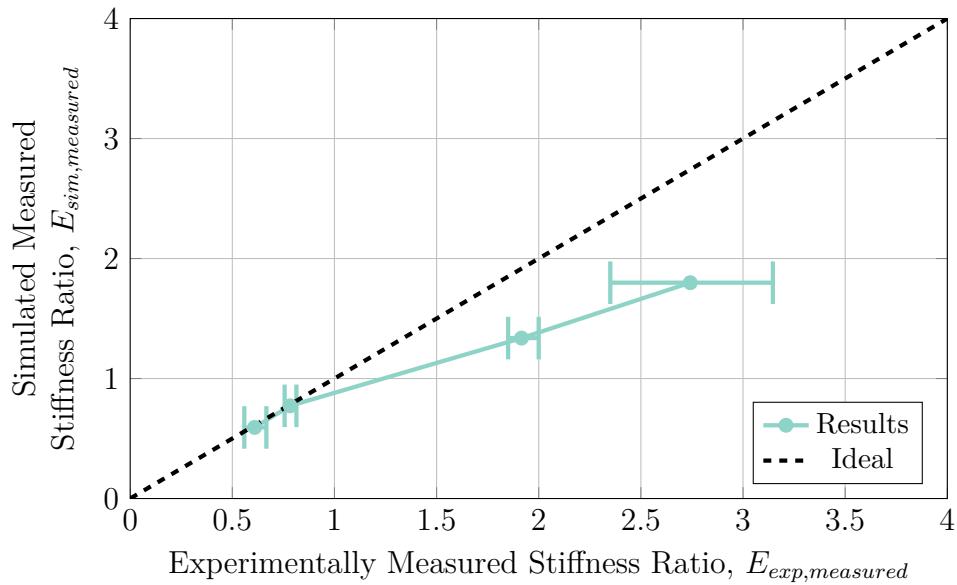


Fig. 4.24: Relation between simulated measured strain ratios and experimental measured strain ratios for a lesion at a depth of 3.5 cm and diameter of 2.0 cm.

4.4 Conclusion

The results presented in Section 4.3 represent a numerical characterization of the use of acoustic radiation force impulse imaging for the detection of deep 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

^{c2} KH: ???

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 focussed at—increasing depth was found to induce the greatest reduction in the magnitude of the 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 soft 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 soft 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 towards 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 pseudospectral 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 pseudospectral 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 speeds and tissue stiffness. This relationship between shear wave speed and tissue stiffness 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.

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

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

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

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 $\varepsilon_{ii,j} = u_{j,ij}$.

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

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

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

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

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

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.

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

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

While the above equation holds for linear elastic materials, soft tissues in the human body are generally considered viscoelastic ^{c1}. In the case of viscoelastic tissues, complex Lamé parameters must be used, such that the shear wave speed is represented by equation 5.11 ^{c2}. Note that viscoelastic shear wave speeds of viscoelastic tissues are generally acquired through empirical measurements rather than any sort of mathematical derivation ^{c3}.

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

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 soft 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 [110]. 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

^{c1} KH: Add citation

^{c2} KH: Add citation

^{c3} KH: Add citation

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
Lesion depth	d	[1, 2, 3, 4, 5, 6, 7, 8, 9] cm
Lesion diameter	ϕS	[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	ϕS	[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 lies in the the data that was extracted and processed from the time-domain finite-element models of tissue displacement. A discussion of how shear wave speeds are tracked in the finite-element model of tissue deformation is given in Section 5.3.2 by working though a sample dataset result.

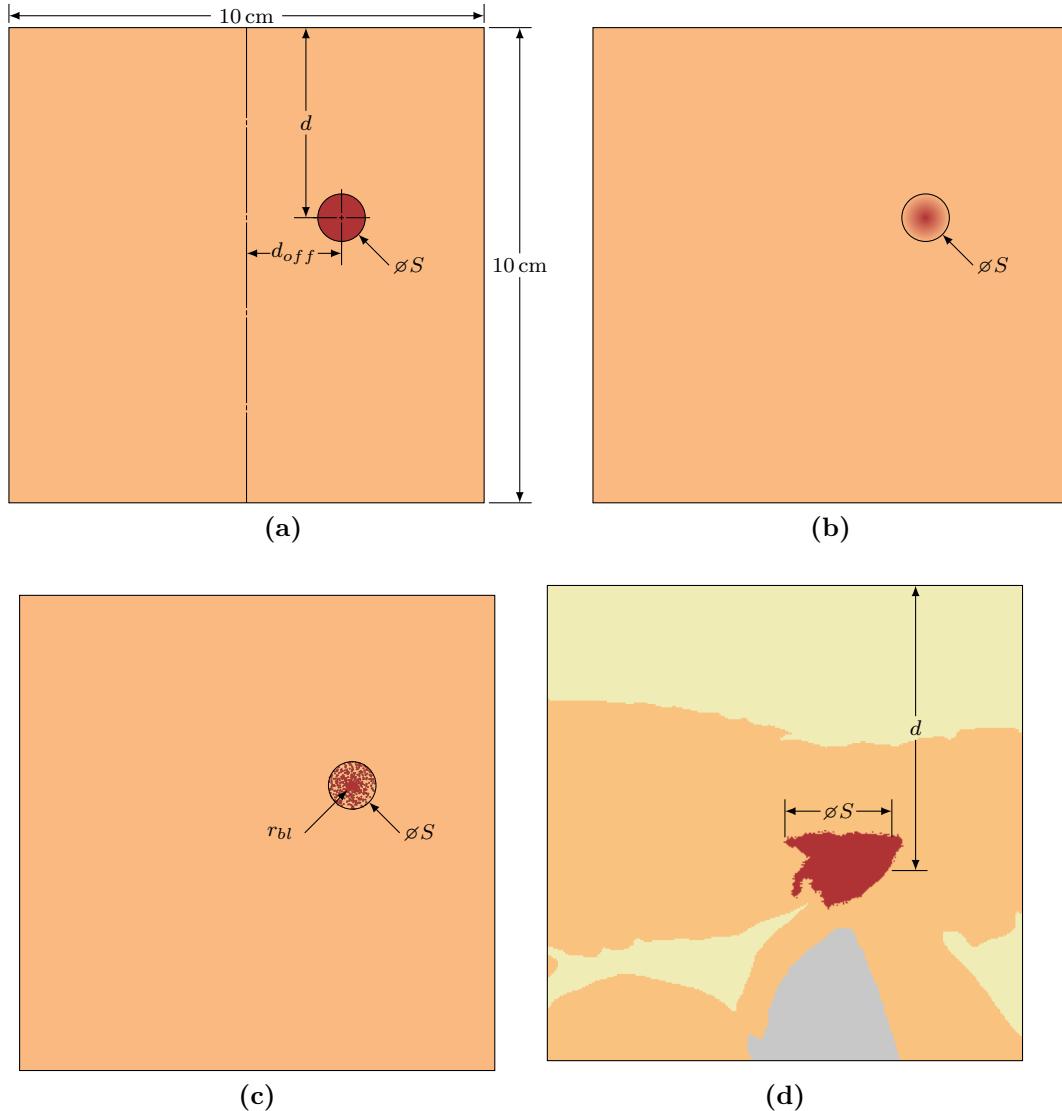


Fig. 5.1: Schematics of the lesion models that were investigated using shear wave speed quantification showing (a) a spherical hard-boundaried lesion, (b) a spherical blurred-boundary lesion, (c) a cluster of numerous small lesions composing a larger lesionous region, and (d) the geometry from an MRI-acquired deep tissue injury overlaid on a slice from the Visible Human Project such that the injury lesion was located immediately superior to an ischial tuberosity.

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 soft 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 software 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.

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.

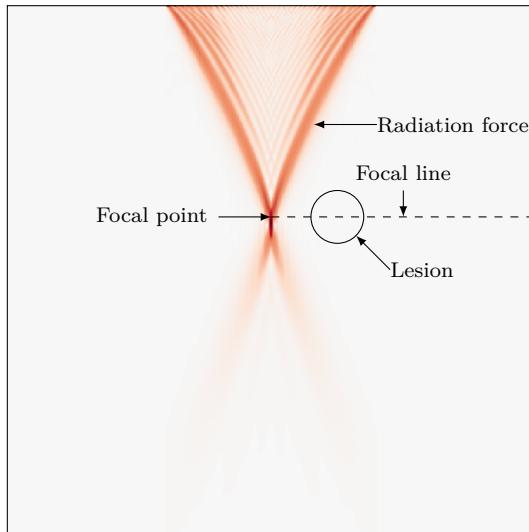


Fig. 5.2: A sample acoustic radiation force distribution shown with a schematic of the lesion's location and size in the simulated tissue domain. Note how the focal point is adjacent to the lesion, offset in this case by 1.25 cm. The focal line extends laterally from the focal point, through the lesion, to the edge of the tissue domain—this is the line that will be used to calculate shear wave speeds.

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

Lamé's second parameter for the lesion and tissue respectively, $c_{T,l}$ and $c_{T,t}$ are the shear wave speeds in the lesion and tissue respectively, and ρ is the density of the tissue and assumed to be constant between the lesion and tissue.

$$c_T = \sqrt{\frac{\mu}{\rho}} \quad (5.12a)$$

$$c_T^2 \rho = \mu \quad (5.12b)$$

$$E_{rel} = \frac{\mu_l}{\mu_t} = \left(\frac{c_{T,l}}{c_{T,t}} \right)^2 \quad (5.12c)$$

In order to determine the velocity of generated shear waves, the ARFI load-induced displacement of the soft tissue must be tracked through time along a line passing through the focal point radiating laterally outward in the finite-element model of tissue deformation. A sample result of tissue displacement through time and along such a line is presented in Fig. 5.3 where the wave can be readily visualized through time, noting that the wave travels ever further from the centerline.

The results in Fig. 5.3 represent a finite subsample of the shear wave's propagation along the focal line. For a continuous representation of the shear wave propagation, the surface shown in Fig 5.4 may be constructed. In order to track the wave through both position and time, a contour line representing a constant displacement value may be extracted. For this work, a contour line representing the mean value of the displacement over the entire position-time domain was utilized and is portrayed in Fig. 5.5.

Fig. 5.6 represents the extracted contour line. This contour line now represents a position-time trace of the shear wave, from which the velocity of the wave may be calculated by differentiating the position of the wave with respect to time as per equation 5.13. Care must be taken when numerically

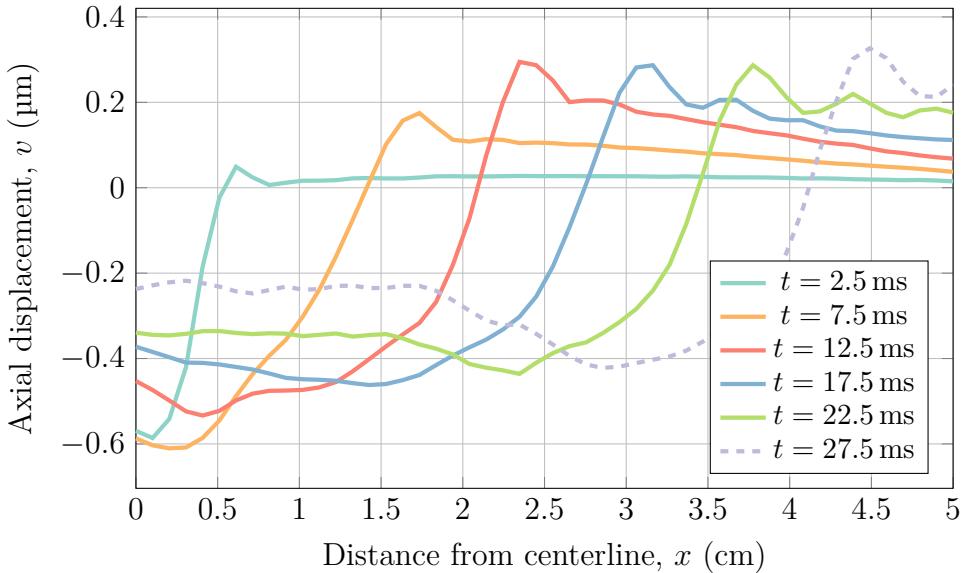


Fig. 5.3: Axial displacement induced by a shear wave traveling laterally across the focal line of an ARFI load. There is a stiff ($E_{rel} = 3.2$) lesion with a diameter of 1 cm located 1.25 cm away from the centerline, with both the focal line and the lesion located at a depth of 4 cm from the surface.

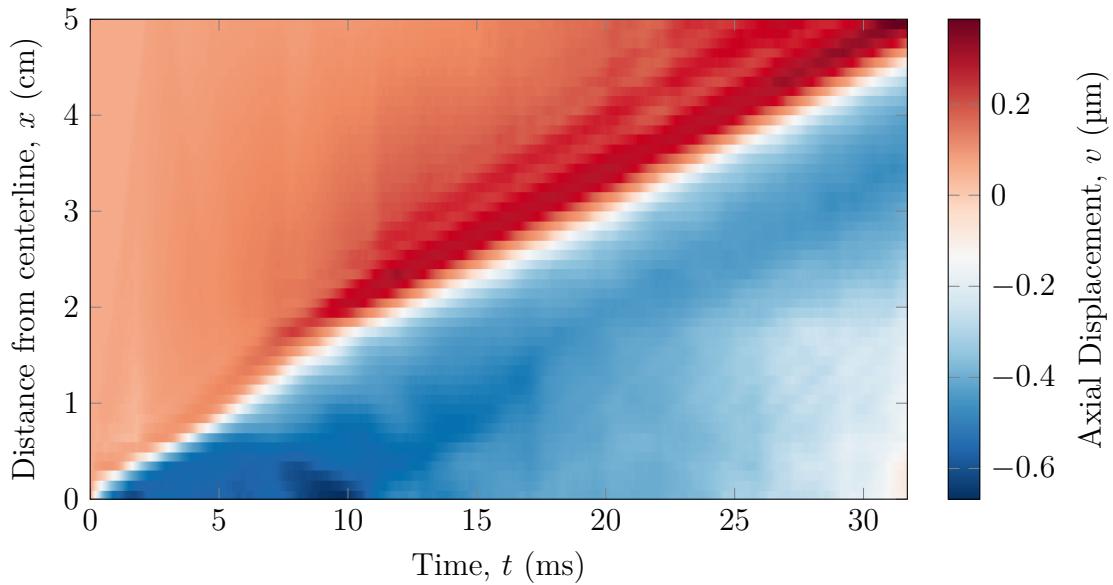


Fig. 5.4: Continuous surface plot of the shear wave induced axial displacement tracked through both time and distance from the transducer centerline. The sharp transition from negative to positive displacement marks the location of shear wave in time at any given location.

differentiating, as numerical errors are greatly amplified by differentiation. To combat this, a moving window average filter with a kernel of 5 mm was applied

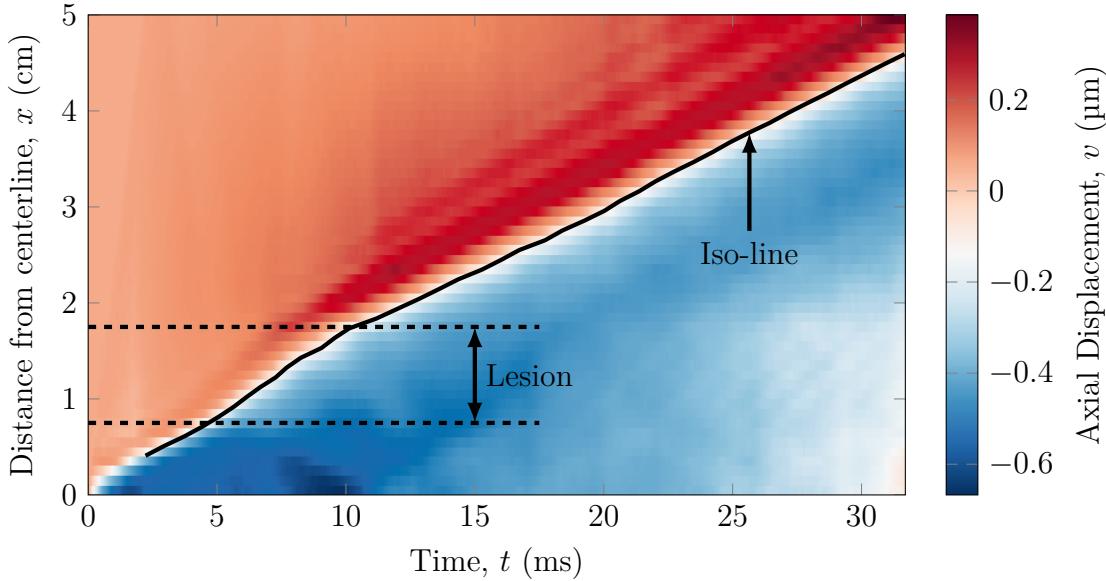


Fig. 5.5: Continuous surface plot of shear wave induced axial displacement highlighting a mean contour line representing the shear wave location as time progresses. By inspection, the slope of the contour line is greater within the lesionous region than outside of it, suggesting that the lesion is stiffer than the surrounding tissue.

to the position-time curve before center-difference differentiation was used to result in the shear wave speed graph given in Fig. 5.7.

$$c_T = \frac{dx}{dt} \quad (5.13)$$

As is shown in Fig. 5.7, the speed of the shear wave within the lesion (which was in this case 3.2 times as stiff as the surrounding tissue) is substantially greater than the shear wave speed in the regular tissue. Note that instead of an impulse response at the boundaries of the lesion as might be expected, the shear wave speed reaches a peak value approximately halfway through the lesion, indicating that the wave requires some finite amount of time to both speed up and slow down within the lesion, suggesting that the technique may have difficulty identifying small lesions as the shear wave speed will not be able to fully adjust to the lesion in the time it takes for the wave to completely pass through the lesion.

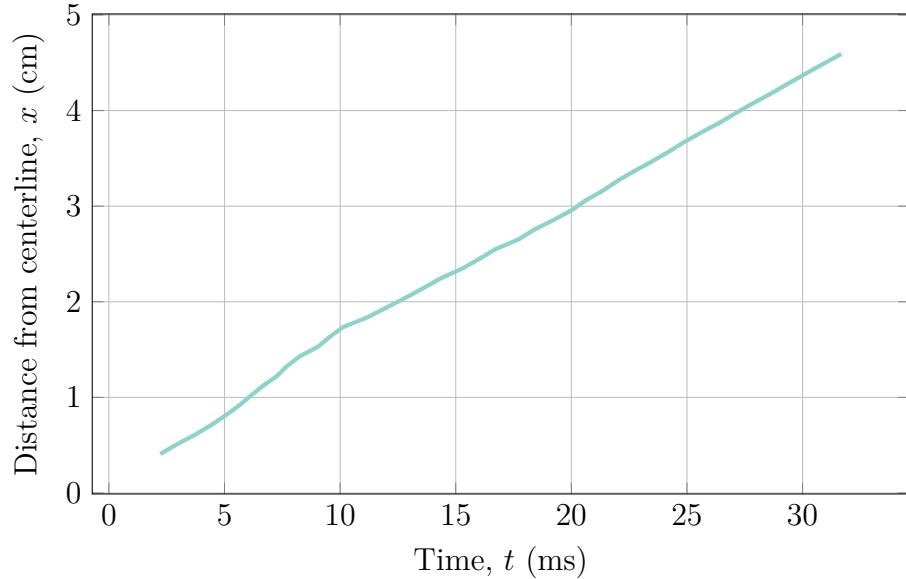


Fig. 5.6: The extracted shear wave position-time trace showing the location of the generated shear wave increases with time, albeit at different rates depending on the underlying tissue properties.

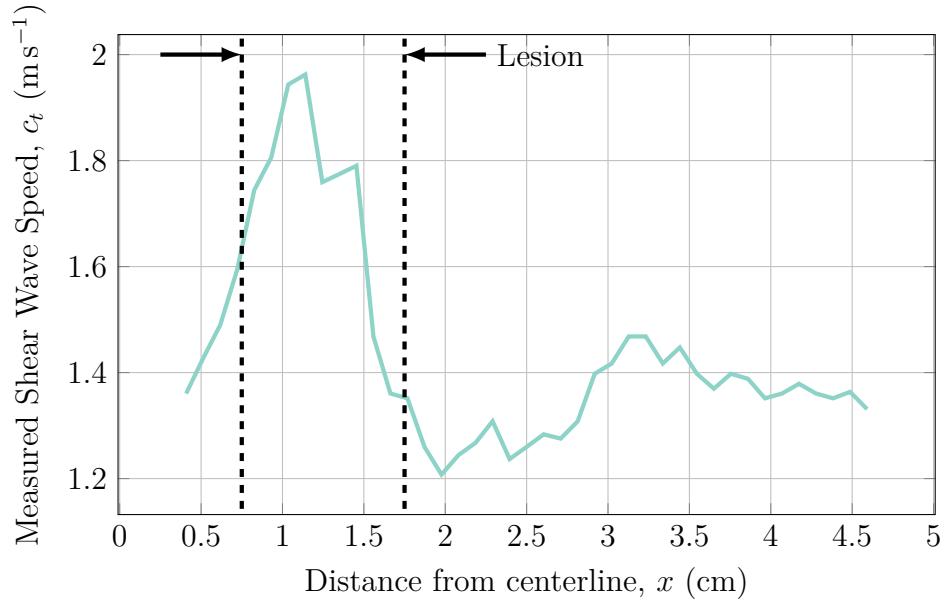


Fig. 5.7: Trace of the shear wave speed along the focal line through both lesionous and “healthy” tissue. The shear wave speed within the lesion is much greater than the shear wave speed through the “healthy” tissue, indicating that the lesion is significantly stiffer than the surrounding tissue. The shear wave speed was calculated as the numerical differentiation of the shear wave’s position through time.

5.3.3 Lesion Detection Characterization

In order to determine the detection sensitivity of shear wave speed quantification with respect to lesion size, hard-boundaried spherical lesions with varying radii were interrogated using ARFI loads while the speed of the shear waves developed along the focal line were monitored. The ARFI loads were applied using a probing frequency of 2 MHz for 150 μ s with a source pressure of 3.35 MPa using an F-number of $f/1.0$. The lesions were located at a depth of 4 cm with an offset of 1.25 cm from the focal point of the ARFI load. The results of this characterization are given in Fig. 5.8. Lesions stiffness ratios were measured by calculating the maximum or minimum shear wave speed within the lesion if the shear wave speed within the lesion was greater than or less than the surrounding tissue respectively and the mean shear wave speed without the lesion and applying equation 5.10.

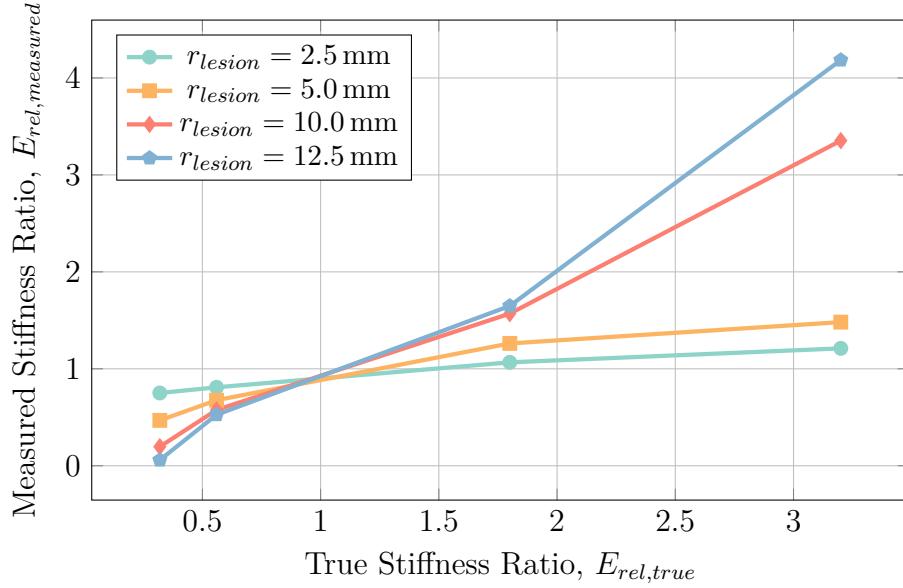


Fig. 5.8: Numerical characterization of the shear wave speed measured stiffness ratios acquired with varying lesion radii for a hard-boundaried lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

As can be seen in Fig. 5.8, small lesions with radii ≤ 5.0 mm are nearly

impossible to detect—large changes in the true lesion stiffness ratio represent very minute changes in the measured lesion stiffness ratio for these small lesions. Conversely, large lesions are much easier to detect, portraying a nearly one-to-one or better mapping between the true and measured lesion stiffness ratios. This suggests that the larger the lesion is, the more readily it may be detected while smaller lesions are more difficult to detect with a lower limit of the lesion radius approaching 5.0 mm.

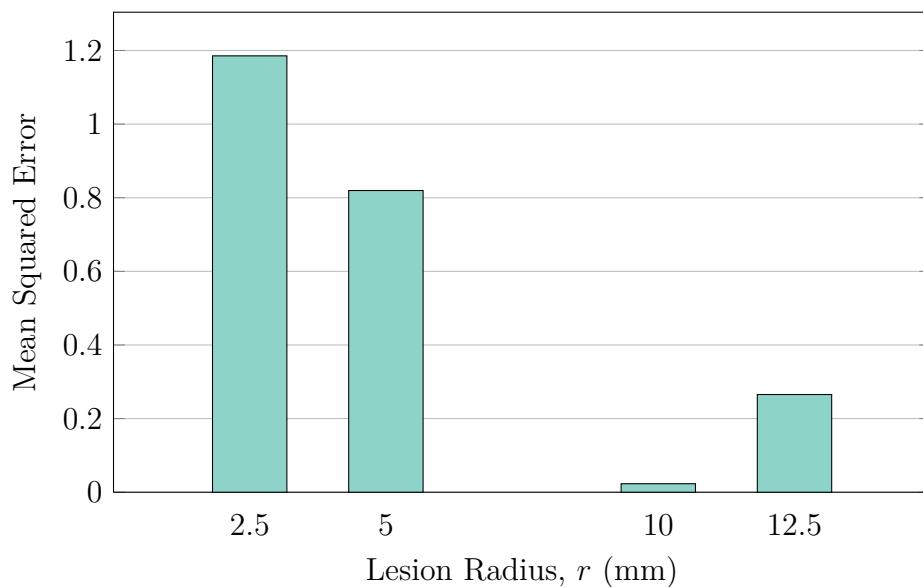


Fig. 5.9: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion radii for a hard-boundaried lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

To further investigate these results, the mean-squared error associated with varying lesion size was calculated as per equation 4.17 with the results presented in Fig. 5.9. In Fig. 5.9, it is clear to see that the error associated with small lesions is significantly greater than with larger lesions. Interestingly, the largest lesions tested (with radii of 12.5 mm) presented greater error than lesions with radii of 10.0 mm. This increase in error may be largely attributed to the over-estimation of the lesion stiffness ratio for a stiff ($3.2 \times$ basal stiffness) lesion with a radius of 12.5 mm seen in Fig. 5.8. The exact cause of this error

is unknown. ^{c1}.

One of the key parameters used in shear wave speed quantification is the distance between the focal point of the acoustic radiation force and the lesion itself. In order to adequately generate fully-formed shear waves within the lesion, the focal point of acoustic radiation force should be located adjacent to the lesion. As can be seen in Fig. 5.10, regardless of the lesion offset distance, shear wave speed quantification is able to differentiate lesions from the tissue with reasonable accuracy. The largest exception to this generalization is for very stiff lesions for which the ARFI load is focused the farthest away from the lesion. It is hypothesized that the measured stiffness ratio of these lesions is underestimated because by the time the shear wave reaches the relatively far-away lesion, its energy has substantially dissipated, disallowing the wave to remain fully cohesive and speed up appropriately.

Fig. 5.11 portrays the mean squared error between the measured and true lesion stiffness ratios with increasing lesion offset distance. As Fig. 5.11 shows, a lesion offset of approximately 2.5 cm is ideal for quantifying lesion stiffness as it produces the least amount of error between the true and measured lesion stiffness ratios which confirms the notion that the shear wave needs some time to become fully developed as it travels through the tissue. Since the error between lesion offsets of 1.25 cm and 2.50 cm is nearly negligible, it is likely that the wave is able to become fully developed even earlier than 2.50 cm and lesion offsets as small as 1.25 cm may be used. The relatively large error present for the largest lesion offset of 3.75 cm is largely due to the severe underestimation of the lesion stiffness for the stiffest lesion seen in Fig. 5.10.

Another key parameter relating to the detection of deep tissue injury lesions relates to the depth that the lesions may actually be detected—for example,

^{c1} KH: Elaborate?

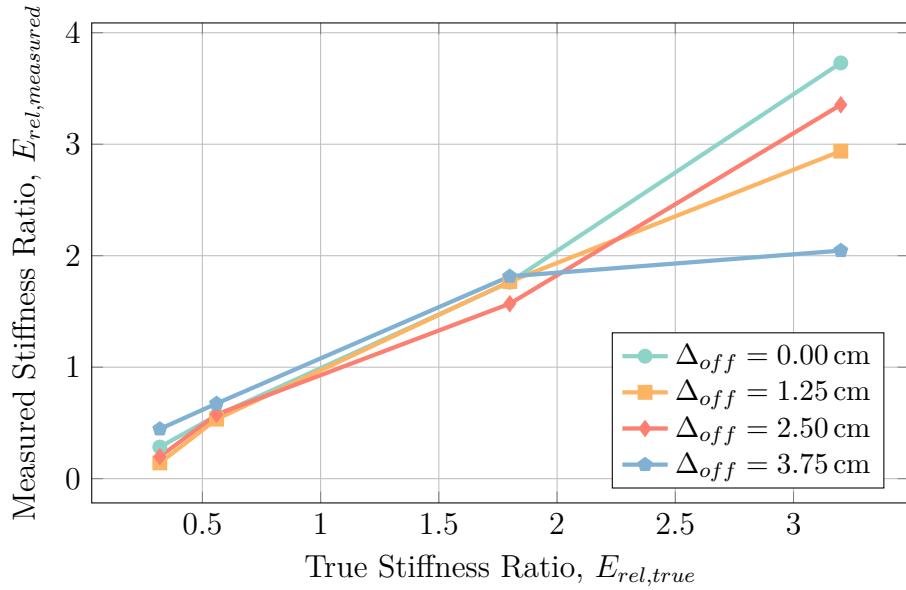


Fig. 5.10: Numerical characterization of the shear wave speed measured stiffness ratios acquired with varying lesion offsets for a hard-boundaried 0.5 cm radius lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz. The greatest error between the true and measured stiffness ratios occurred at the highest stiffness ratio of 3.2, with the large lesion offset underestimating the stiffness ratio and the negated lesion offset overestimating the stiffness ratio.

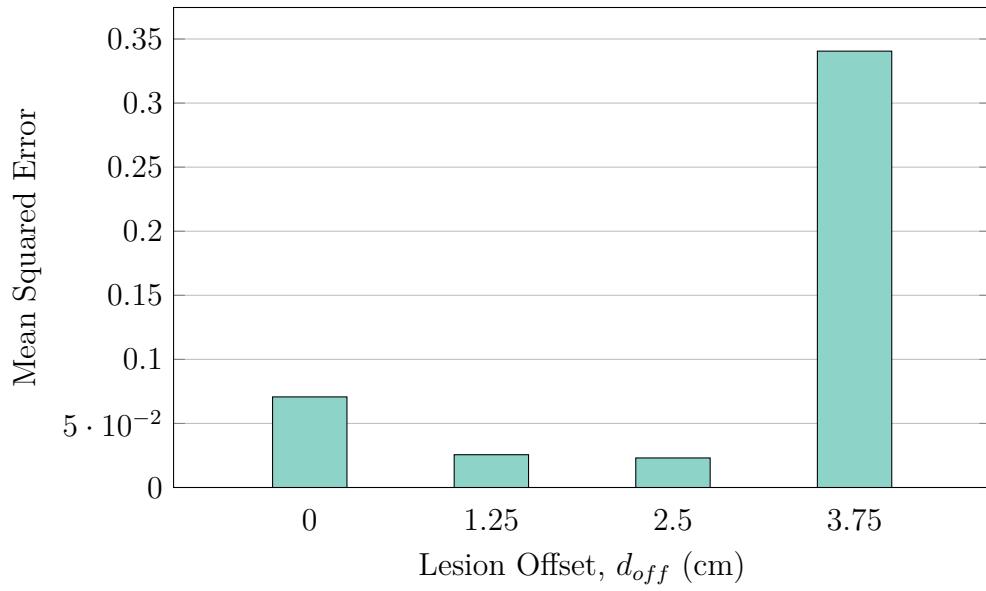


Fig. 5.11: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion offsets for a hard-boundaried 0.5 cm radius lesion at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

in people with large amounts of body fat or muscle, the distance between the surface of the skin and the boney prominence where lesions are most likely to form may be very large compared to someone with very little amounts of body fat or muscle. In order to study the effect of lesion depth on the detection sensitivity of shear wave speed quantification, simulated lesions were placed at various depths ranging from 2 cm – 8 cm below the surface of the skin with the measured stiffness ratios for these lesions calculated and shown in Fig. 5.12.

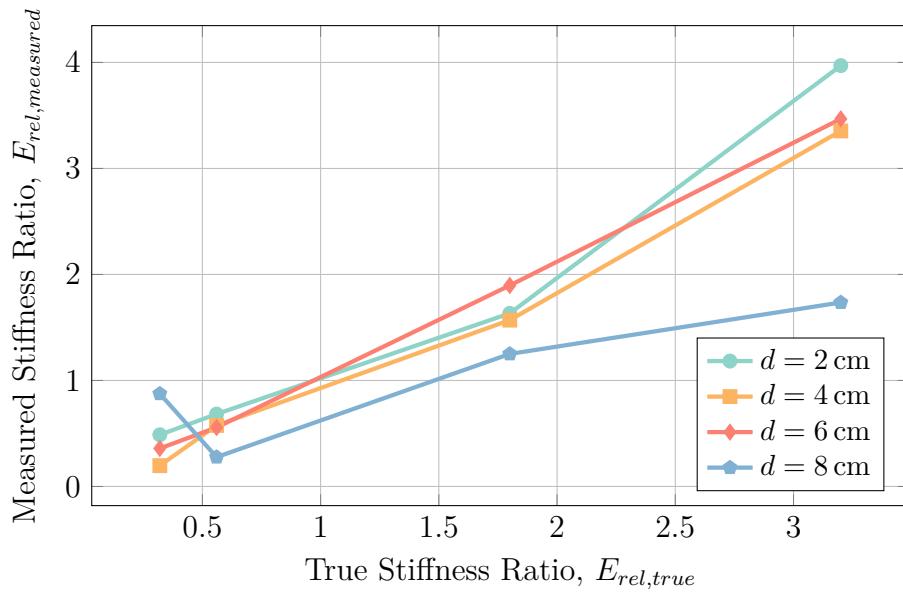


Fig. 5.12: Numerical characterization of the shear wave speed measured stiffness ratios acquired with varying lesion and focal point depths for a hard-boundaried 0.5 cm radius lesion with an offset of 2.50 cm using an ARFI interrogation frequency of 2 MHz.

As Fig. 5.12 shows, there is little dependence of shear wave speed quantifications detection sensitivity for shallow to medium-depth lesions—lesions placed at a depth of 2 cm – 6 cm presented approximately equal detection curves. Of note in Fig. 5.12 is that deep lesions—lesions at a depth of 8 cm or more—are difficult to detect as the method is not very sensitive these deeper lesions—both underestimating the stiffness of deep stiff lesions and overestimating the stiffness of deep soft lesions. The large error involved with at-

tempting to measure the stiffness of deep lesions can be seen in Fig. 5.13 where the mean squared error for the various depths examined was calculated. In Fig. 5.13, the 8 cm deep lesions present a significantly greater amount of error than their shallower counterparts. Also of note is that the shallowest lesions investigated—lesions at a depth of 2 cm—presented with greater error than the mid-depth lesions. The source of this error largely lies in the over-estimation of the stiff lesion stiffness seen in Fig. 5.12 which may be due to numerical errors in the models and calculations.

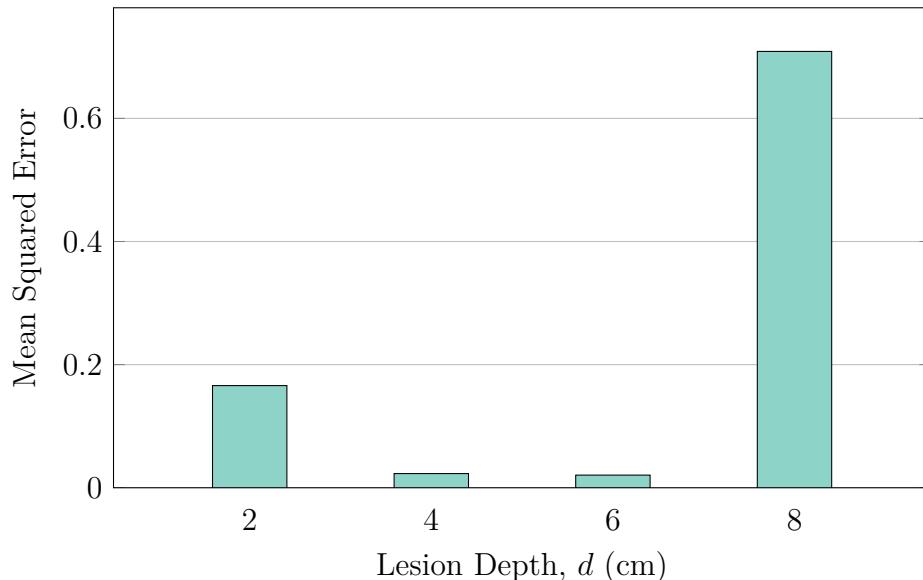


Fig. 5.13: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion depths for a hard-boundaried 0.5 cm radius lesion with an offset of 2.50 cm using an ARFI interrogation frequency of 2 MHz.

Since deep tissue injury lesions are unlikely to be perfectly round and hard-boundaried, three different models of lesion geometry were investigated—namely, lesions with blurred boundaries that “fade” into the surrounding tissue, clusters of small lesions that together make up a larger lesions region, and a lesion with mri-acquired geometry [67] embedded in geometry obtained from a Visible Human slice [110]. Although the spherical hard-boundaried lesions may not represent all the intricacies of real deep tissue injuries, the general

trends that result from analysing them may improve the general understanding of lesion detection behaviour.

In order to investigate the effect of blurring lesions into the background tissue, hard-boundaried spherical lesions were blurred with varying blur radii as described in Section 5.2.2. The results of this characterization are presented in Fig. 5.14. As can be seen in Fig. 5.14, the effect of blur radii on lesion detection ability is negligible as noted by how the detection curves of the lesions with varying blur radii are largely coincident.

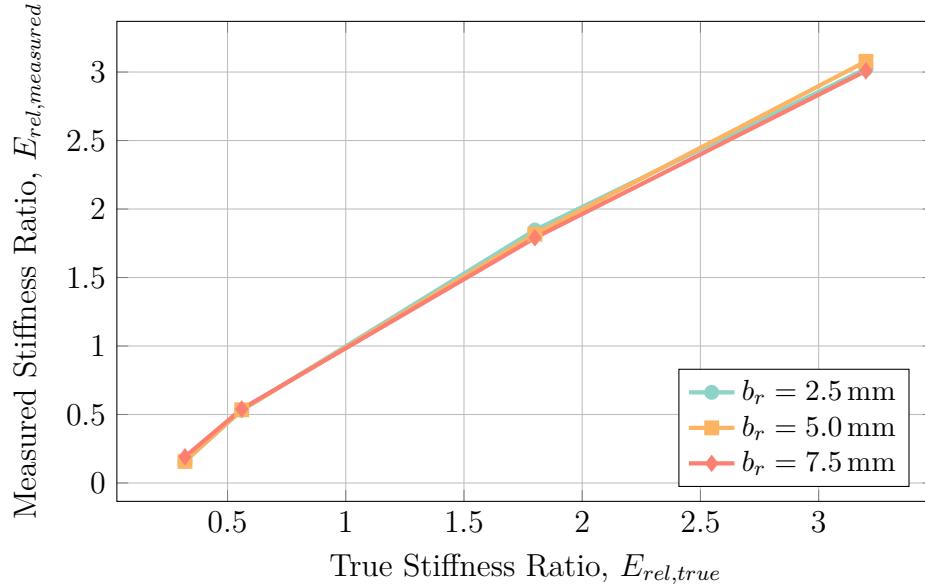


Fig. 5.14: Numerical characterization of the shear wave speed measured stiffness ratios acquired with varying lesion and focal point depths for a blurred 1.0 cm radius lesion with an offset of 1.25 cm at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

This lack of reliance of detection sensitivity on blur radius is further portrayed by the mean squared error of the results, calculated in Fig. 5.15. While there are some minor differences in the error between the various blur radii—chiefly between blur radii of 2.5 mm and 5.0 mm—the scale of these differences lie within the range of numerical error and noise and so is not significant.

The fact that detection sensitivity does not decrease with increasing blur

radii in shear wave speed quantification makes shear wave speed quantification a desirable tool for detecting deep tissue injury lesions as it means that even imperfect, newly-forming lesions can still be readily detected and monitored.

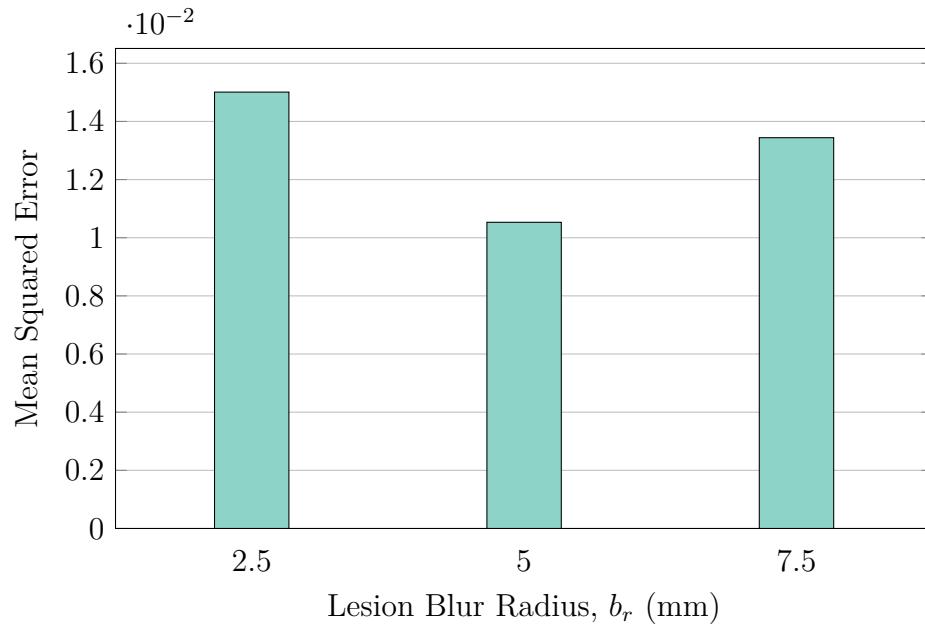


Fig. 5.15: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion depths for a blurred 1.0 cm radius lesion with an offset of 1.25 cm at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

Beyond having boundaries that “fade” into the background tissue, deep tissue injury lesions may in fact be heterogeneous in nature with a large number of small lesions clustered together to form a larger lesionous region. To investigate this phenomenon, the effect of small clustered lesion density and individual radii were investigated using shear wave speed quantification. The effect of clustered lesion density was investigated as outlined in Section 5.2.2, the results of which are shown in Fig. 5.16. ^{c1}

As Fig. 5.16 shows, decreasing the cluster density generally results in a decreasing detection sensitivity with the least dense clusters both underestimating the stiffness of stiff lesions and overestimating the stiffness of soft

^{c1} KH: Add graph of shear wave speed along focal line for clustered lesions to show lack of ability to detect individual small lesions?

lesions. This behaviour is somewhat expected—as the density of clustered lesions decreases, so too does the mean true stiffness of the lesionous region that is inspected due to the greater ratio of “healthy” tissue to lesionous tissue.

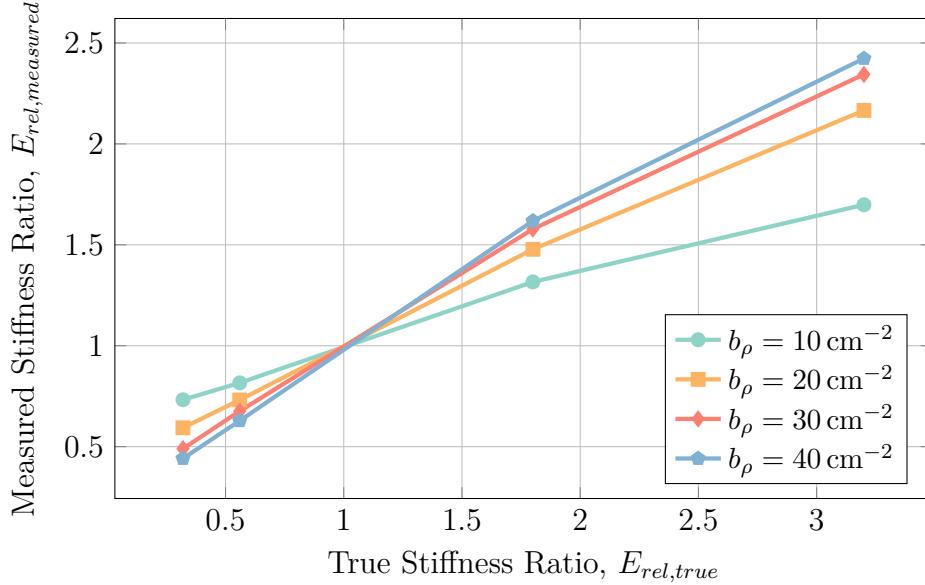


Fig. 5.16: Numerical characterization of the shear wave speed measured stiffness ratios acquired with varying cluster densities for clustered 1 mm radius lesions within a 1.0 cm radius with an offset of 1.25 cm at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

This generalization is further portrayed in by the mean squared error which is shown in Fig. 5.17. In Fig. 5.17, increasing cluster density results in monotonically decreasing error.

Beyond the cluster density, the size of individual clustered lesions within the lesionous region may affect the detection sensitivity. To investigate this parameter, the radii of the individual lesions in the clustered lesion model were varied, with the results presented in Fig. 5.18. Fig. 5.18 shows how decreasing the individual clustered lesion radii results in decreases in the detection sensitivity. This is similar to the results presented in Fig. 5.16 in that decreasing the individual lesion radii results in a decrease of the ratio between lesionous tissue and healthy tissue within the lesionous region—the greater the propor-

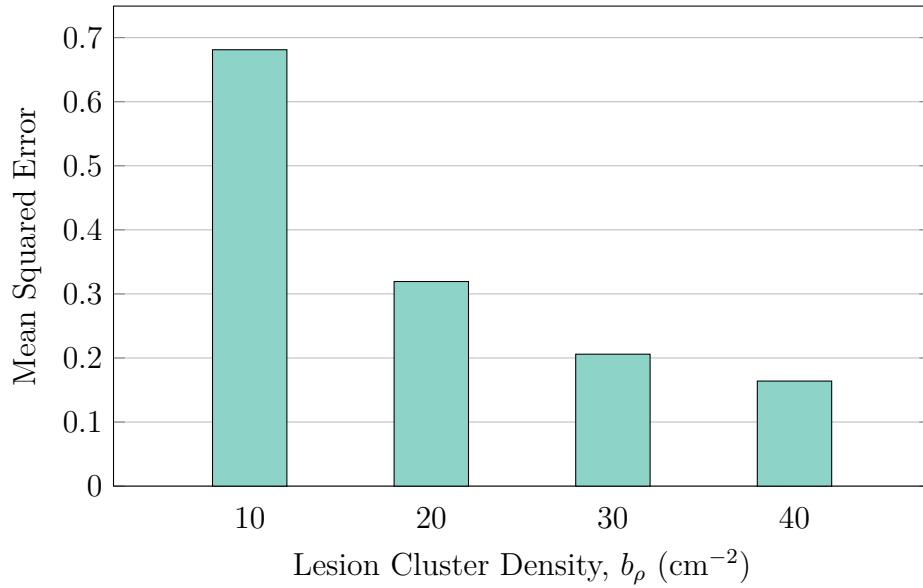


Fig. 5.17: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion cluster density for clustered 1 mm radius lesions within a 1.0 cm radius with an offset of 1.25 cm at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

tion of lesionous tissue within the investigated region, the more accurate the detection of the lesionous region.

Again, this conclusion is corroborated by the mean squared error shown in Fig. 5.19. In Fig. 5.19, increasing the individual lesion radii results in a significant decrease in the stiffness measurement error in the lesionous region.

Finally, in order to place these characterizations within the context of a real deep tissue injury situated within the geometry of a real human soft tissue domain, a numerical characterization of lesion size in the Visible Human lesion model outlined in Section 5.2.2 was carried out with the results portrayed in Fig. 5.20. Fig. 5.20 relates the change in detection sensitivity with different sized lesions and shows that small lesions (with “radii” \leq 5.0 mm) are extremely difficult to detect as the stiffness of small stiff lesions is severely underestimated and the stiffness of small soft lesions is severely overestimated. These results align with what was seen in the spherical hard-boundaried le-

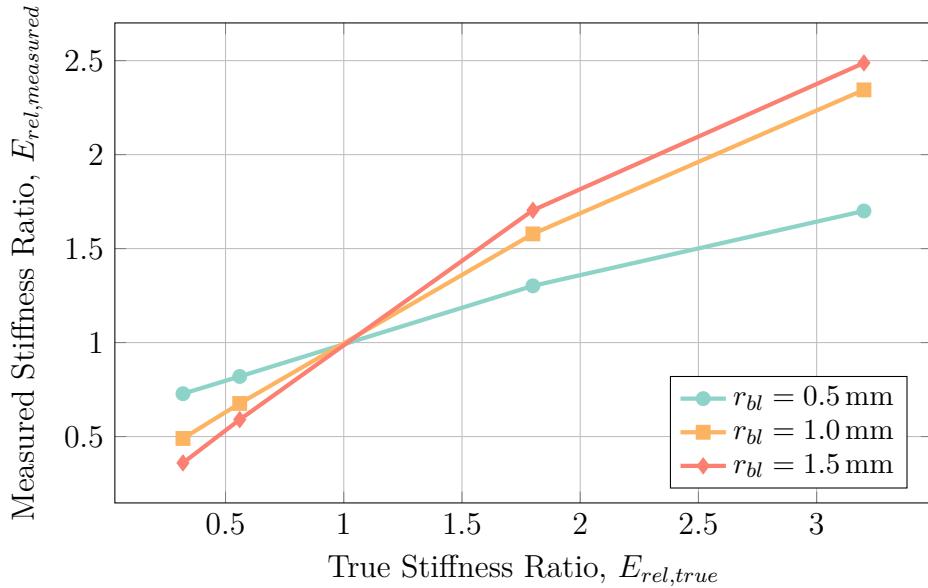


Fig. 5.18: Numerical characterization of the shear wave speed measured stiffness ratios acquired with varying clustered lesion radii for clustered lesions with a density of 30 cm^{-2} within a 1.0 cm radius with an offset of 1.25 cm at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

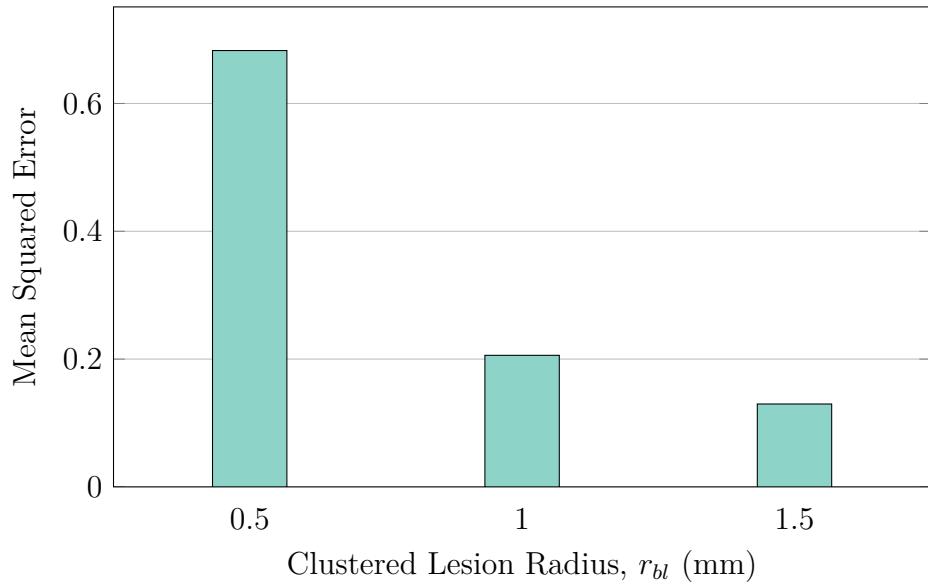


Fig. 5.19: Mean squared error between the true and measured lesion stiffness ratios for increasing clustered lesion radii for clustered lesions with a density of 30 cm^{-2} within a 1.0 cm radius with an offset of 1.25 cm at a depth of 4 cm using an ARFI interrogation frequency of 2 MHz.

sion case presented in Fig. 5.8, indicating that the simplified spherical results generally hold true for the more complex geometry results.

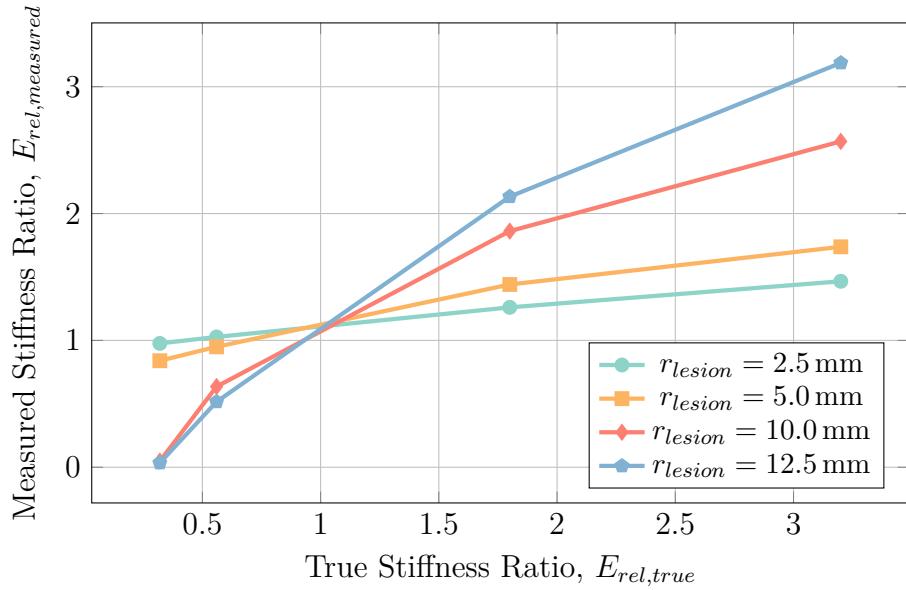


Fig. 5.20: Numerical characterization of shear wave speed measured stiffness ratio with changing lesion radii for MRI-acquired lesion geometry in a Visible Human model with an offset of 1.25 cm at a depth of 6 cm using an ARFI interrogation frequency of 2 MHz.

As expected from the results in Fig. 5.20, increasing the lesion radius results in monotonically decreasing measurement error as is shown in Fig. 5.21 with the least amount of measurement error present for the largest lesions. This means that relatively larger lesions will be easier to detect and accurately quantify and may be due to the shear wave requiring some finite period of time to speed up or slow down with a lesionous region of tissue as discussed previously.

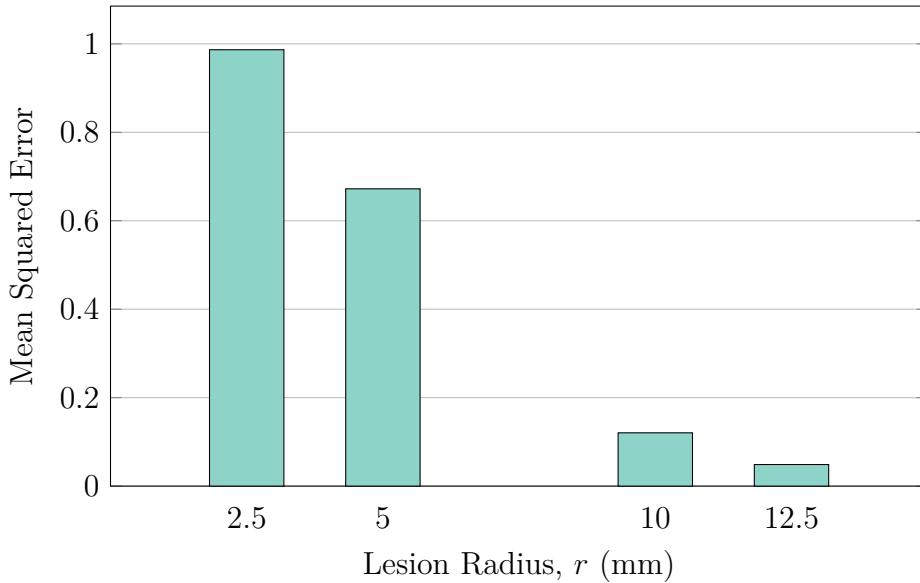


Fig. 5.21: Mean squared error between the true and measured lesion stiffness ratios for increasing lesion radii for MRI-acquired lesion geometry in a Visible Human model with an offset of 1.25 cm at a depth of 6 cm using an ARFI interrogation frequency of 2 MHz.

5.3.4 Physical Phantom Validation

In order to examine the validity of the simulations presented in Section 5.2.2 and the results presented in Section 5.3, experiments using a physical tissue mimicking phantom and an ultrasound machine were performed as described in Section 5.2.3. The results of these experiments are presented in Figs. 5.22 and 5.23 where the difference between the experimentally measured stiffness ratios of lesions were compared against their nominal and simulated stiffnesses respectively.

Fig. 5.22 shows the general agreement between the nominal and experimentally acquired lesion stiffness ratios. Of note is the increasing amount of measurement error associated with increasing nominal stiffness ratios and reflects the general underestimation of stiff lesion stiffness that was seen in the characterization of nearly all stiff lesions in Section 5.3. Further, the relatively large degree of error was due to the measurement of the shear wave speed

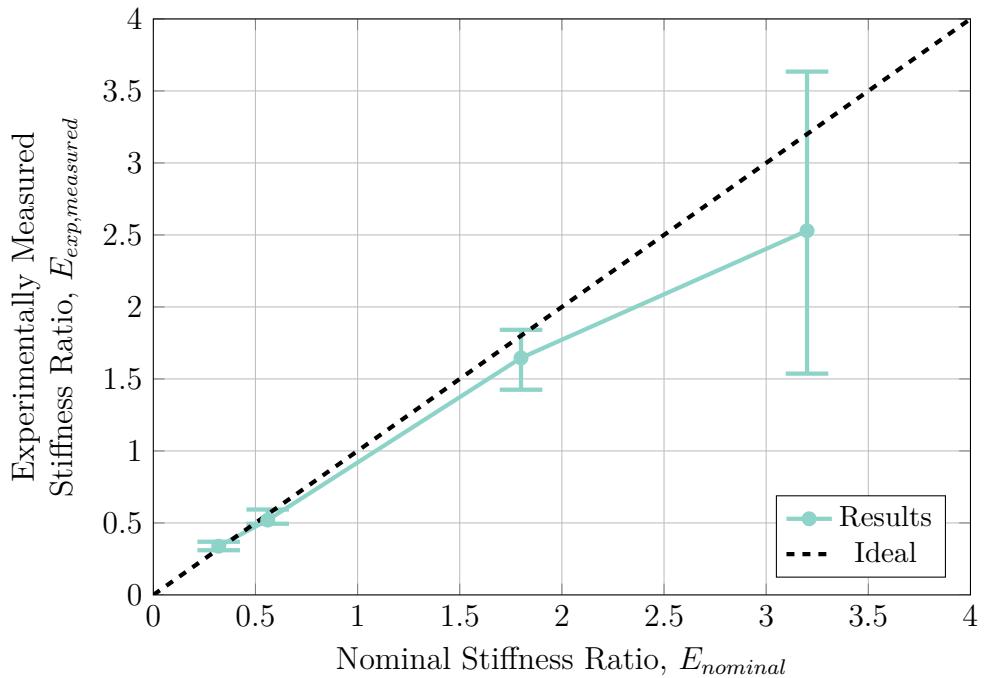


Fig. 5.22: Relation between nominally reported strain ratios of the tissue mimicking phantom and experimentally measured strain ratios for a lesion at a depth of 3.5 cm and diameter of 2.0 cm showing general agreement between simulated and experimental cases. Error bars represent the range of measurements acquired.

within the lesion rather than variability in the shear wave speed of the surrounding tissue. Nonetheless, the experimentally-acquired values lay within error of the expected nominal stiffness ratios, so the experiment was considered to produce acceptable results to compare against the simulations. The results of this comparison are shown in Fig. 5.23 where the stiffness ratios acquired through simulation are compared against experimentally-acquired stiffness ratios of parametrically identical lesions.

As expected, there is nearly a one-to-one correspondence between the experimentally measured lesion stiffness ratios and the simulated lesion stiffness ratios for the various lesions investigated. In all of the lesion cases studied, the simulated lesion stiffness ratio was slightly greater than the experimentally measured stiffness ratio. This suggests that the simulated models introduce a minor bias in the results, although as the correlation is linear this is may

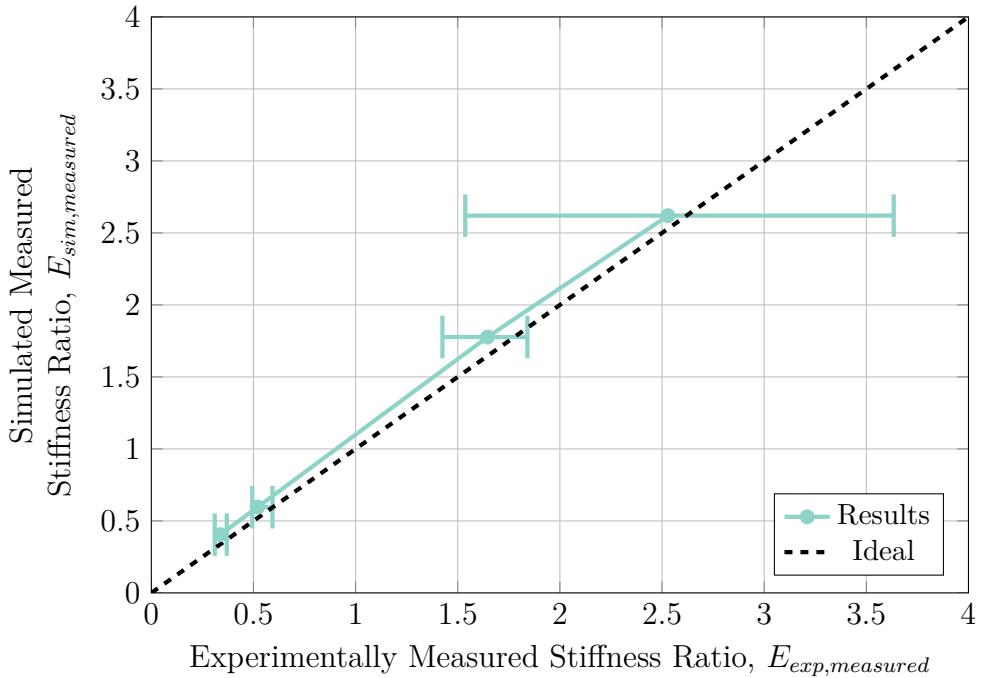


Fig. 5.23: Relation between simulated measured strain ratios and experimental measured strain ratios for a lesion at a depth of 3.5 cm and diameter of 2.0 cm showing general agreement between simulated and experimental cases.

be 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 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 [1] and present

6.1 Comparisons Between Methods

Simulated Lesions

Experimental Validations

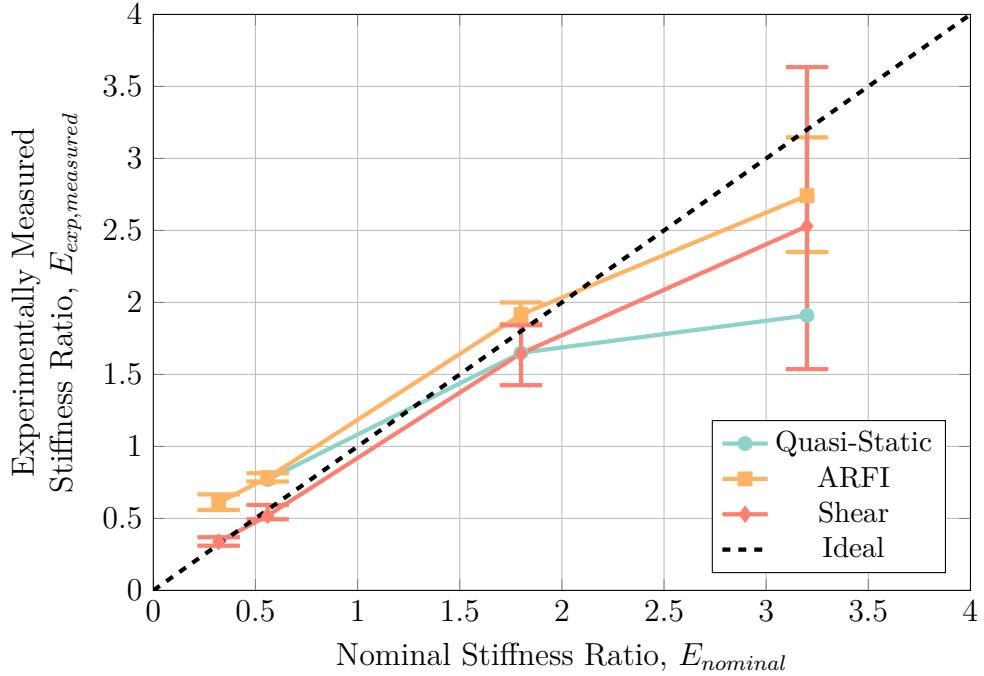


Fig. 6.1: Experimental results of the three methodologies investigated. ARFI imaging consistently overestimated the stiffness of the lesion compared to both quasi-static and shear wave speed quantification, which generally underestimated the stiffness of lesions.

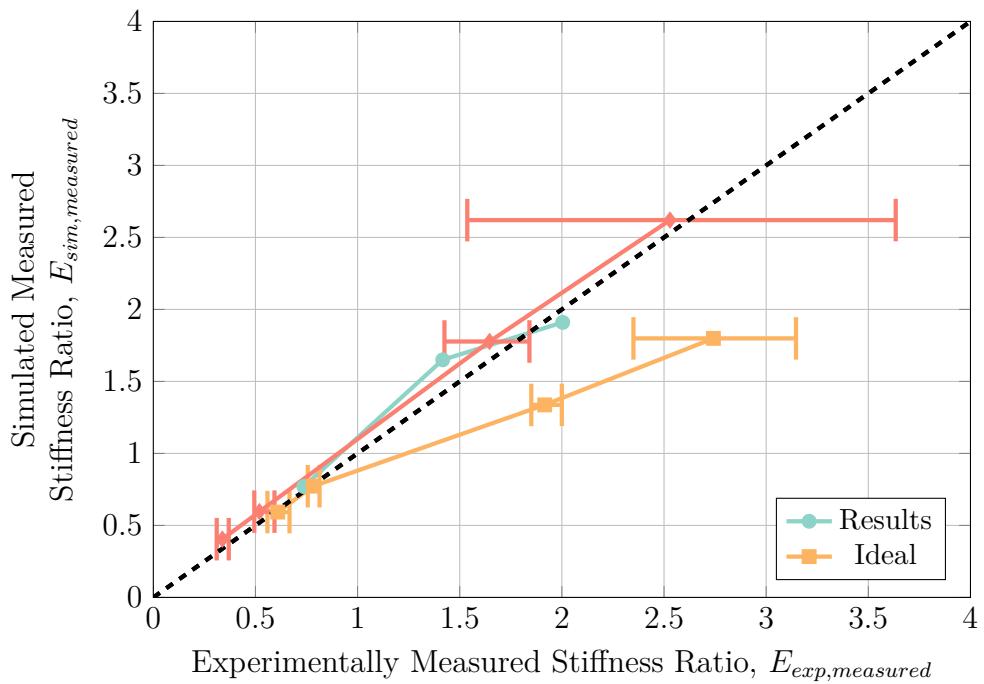


Fig. 6.2: Experimental validation of the simulation results across all three methodologies investigated. The quasi-static ultrasound elastography and shear wave speed quantification simulations most closely matched the results seen experimentally.

6.2 Future Work

References

- [1] R. M. Allman, P. S. Goode, M. M. Patrick, N. Burst, and A. A. Bartolucci, “Pressure ulcer risk factors among hospitalized patients with activity limitation.,” *JAMA : the journal of the American Medical Association*, vol. 273, no. 11, pp. 865–870, Mar. 15, 1995, ISSN: 0098-7484.
- [2] C. A. Salzberg, D. W. Byrne, C. G. Cayten, P. van Niewerburgh, J. G. Murphy, and M. Viehbeck, “A new pressure ulcer risk assessment scale for individuals with spinal cord injury.,” *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists*, vol. 75, no. 2, pp. 96–104, 1996, ISSN: 0894-9115.
- [3] N. Kanno, T. Nakamura, M. Yamanaka, K. Kouda, T. Nakamura, and F. Tajima, “Low-echoic lesions underneath the skin in subjects with spinal-cord injury.,” *Spinal cord*, vol. 47, no. 3, pp. 225–229, Mar. 2009, ISSN: 1362-4393. DOI: 10.1038/sc.2008.101.
- [4] A. Stekelenburg, D. Gawlitta, D. L. Bader, and C. W. Oomens, “Deep tissue injury: how deep is our understanding?” *Archives of physical medicine and rehabilitation*, vol. 89, no. 7, pp. 1410–1413, Jul. 2008, ISSN: 1532-821X. DOI: 10.1016/j.apmr.2008.01.012.
- [5] A. Gefen, N. Gefen, E. Linder-Ganz, and S. S. Margulies, “In vivo muscle stiffening under bone compression promotes deep pressure sores.,”

Journal of biomechanical engineering, vol. 127, no. 3, pp. 512–524, Jun. 2005, ISSN: 0148-0731.

- [6] S. Loerakker, E. Manders, G. J. Strijkers, K. Nicolay, F. P. Baaijens, D. L. Bader, and C. W. Oomens, “The effects of deformation, ischemia, and reperfusion on the development of muscle damage during prolonged loading.,” *Journal of applied physiology (Bethesda, Md. : 1985)*, vol. 111, no. 4, pp. 1168–1177, Oct. 14, 2011, ISSN: 1522-1601. DOI: 10.1152/japplphysiol.00389.2011.
- [7] J. Black, M. M. M. Baharestani, J. Cuddigan, B. Dorner, L. Edsberg, D. Langemo, M. E. E. Posthauer, C. Ratliff, G. Taler, and National Pressure Ulcer Advisory Panel, “National pressure ulcer advisory panel’s updated pressure ulcer staging system.,” *Advances in skin & wound care*, vol. 20, no. 5, pp. 269–274, May 2007, ISSN: 1527-7941. DOI: 10.1097/01.asw.0000269314.23015.e9.
- [8] C. V. Bouten, C. W. Oomens, F. P. Baaijens, and D. L. Bader, “The etiology of pressure ulcers: skin deep or muscle bound?” *Archives of physical medicine and rehabilitation*, vol. 84, no. 4, pp. 616–619, Apr. 2003, ISSN: 0003-9993. DOI: 10.1053/apmr.2003.50038.
- [9] C. W. Oomens, S. Loerakker, and D. L. Bader, “The importance of internal strain as opposed to interface pressure in the prevention of pressure related deep tissue injury.,” *Journal of tissue viability*, vol. 19, no. 2, pp. 35–42, May 2010, ISSN: 0965-206X. DOI: 10.1016/j.jtv.2009.11.002.
- [10] A. Stekelenburg, C. W. Oomens, G. J. Strijkers, K. Nicolay, and D. L. Bader, “Compression-induced deep tissue injury examined with magnetic resonance imaging and histology.” *Journal of applied physiology*

(Bethesda, Md. : 1985), vol. 100, no. 6, pp. 1946–1954, Jun. 2006, ISSN: 8750-7587. DOI: 10.1152/japplphysiol.00889.2005.

- [11] N. Aoi, K. Yoshimura, T. Kadono, G. Nakagami, S. Iizuka, T. Higashino, J. Araki, I. Koshima, and H. Sanada, “Ultrasound assessment of deep tissue injury in pressure ulcers: possible prediction of pressure ulcer progression.,” *Plastic and reconstructive surgery*, vol. 124, no. 2, pp. 540–550, Aug. 2009, ISSN: 1529-4242. DOI: 10.1097/prs.0b013e3181addb33.
- [12] M. Tanter, J. Bercoff, A. Athanasiou, T. Deffieux, J.-L. L. Gennisson, G. Montaldo, M. Muller, A. Tardivon, and M. Fink, “Quantitative assessment of breast lesion viscoelasticity: initial clinical results using supersonic shear imaging.,” *Ultrasound in medicine & biology*, vol. 34, no. 9, pp. 1373–1386, Sep. 2008, ISSN: 0301-5629. DOI: 10.1016/j.ultrasmedbio.2008.02.002.
- [13] K. König, U. Scheipers, A. Pesavento, A. Lorenz, H. Ermert, and T. Senge, “Initial experiences with real-time elastography guided biopsies of the prostate.,” *The Journal of urology*, vol. 174, no. 1, pp. 115–117, Jul. 2005, ISSN: 0022-5347. DOI: 10.1097/01.ju.0000162043.72294.4a.
- [14] L. Sandrin, B. Fourquet, J.-M. M. Hasquenoph, S. Yon, C. Fournier, F. Mal, C. Christidis, M. Ziol, B. Poulet, F. Kazemi, M. Beaugrand, and R. Palau, “Transient elastography: a new noninvasive method for assessment of hepatic fibrosis.,” *Ultrasound in medicine & biology*, vol. 29, no. 12, pp. 1705–1713, Dec. 2003, ISSN: 0301-5629.
- [15] E. Linder-Ganz and A. Gefen, “Mechanical compression-induced pressure sores in rat hindlimb: muscle stiffness, histology, and computa-

- tional models.,” *Journal of applied physiology (Bethesda, Md. : 1985)*, vol. 96, no. 6, pp. 2034–2049, Jun. 2004, ISSN: 8750-7587. DOI: 10.1152/japplphysiol.00888.2003.
- [16] L. R. Solis, A. B. Liggins, P. Seres, R. R. Uwiera, N. R. Poppe, E. Pehowich, R. B. Thompson, and V. K. Mushahwar, “Distribution of internal strains around bony prominences in pigs.,” *Annals of biomedical engineering*, pp. 1–19, Mar. 8, 2012, ISSN: 1521-6047. DOI: 10.1007/s10439-012-0539-y.
- [17] A. Gefen, “Deep tissue injury from a bioengineering point of view.,” *Ostomy/wound management*, vol. 55, no. 4, pp. 26–36, Apr. 2009, ISSN: 0889-5899.
- [18] J.-F. F. Deprez, E. Brusseau, J. Fromageau, G. Cloutier, and O. Basset, “On the potential of ultrasound elastography for pressure ulcer early detection.,” *Medical physics*, vol. 38, no. 4, pp. 1943–1950, Apr. 2011, ISSN: 0094-2405.
- [19] K. Beckrich and S. A. Aronovitch, “Hospital-acquired pressure ulcers: a comparison of costs in medical vs. surgical patients.,” *Nursing economic\$*, vol. 17, no. 5, pp. 263–271, 1999, ISSN: 0746-1739.
- [20] C. Russo, C. Steiner, and W. Spector, “Hospitalizations related to pressure ulcers among adults 18 years and older, 2006: statistical brief no. 64.,” *Agency for Health Care Policy and Research (US)*, Dec. 2008.
- [21] J. M. Zanca, D. M. Brienza, D. Berlowitz, R. G. Bennett, C. H. Lyder, and National Pressure Ulcer Advisory Panel, “Pressure ulcer research funding in america: creation and analysis of an on-line database.,” *Advances in skin & wound care*, vol. 16, no. 4, pp. 190–197, 2003, ISSN: 1527-7941.

- [22] D. K. Langemo, H. Melland, D. Hanson, B. Olson, and S. Hunter, “The lived experience of having a pressure ulcer: a qualitative analysis.,” *Advances in skin & wound care*, vol. 13, no. 5, pp. 225–235, 2000, ISSN: 1527-7941.
- [23] M. M. Baharestani, “The lived experience of wives caring for their frail, homebound, elderly husbands with pressure ulcers.,” *Advances in wound care : the journal for prevention and healing*, vol. 7, no. 3, May 1994, ISSN: 1076-2191.
- [24] M. C. C. de Freitas, A. B. F. B. Medeiros, M. V. C. V. Guedes, P. C. C. de Almeida, F. T. T. de Galiza, and J. d. M. d. e . M. Nogueira, “[pressure ulcers in the elderly: analysis of prevalence and risk factors].,” *Revista gaúcha de enfermagem / EENFUFRGS*, vol. 32, no. 1, pp. 143–150, Mar. 2011, ISSN: 0102-6933.
- [25] S. A. Aronovitch, “Intraoperatively acquired pressure ulcer prevalence: a national study.,” *Journal of wound, ostomy, and continence nursing*, vol. 26, no. 3, pp. 130–136, May 1999, ISSN: 1071-5754.
- [26] E. Jaul, “Assessment and management of pressure ulcers in the elderly: current strategies.,” *Drugs & aging*, vol. 27, no. 4, pp. 311–325, Apr. 1, 2010, ISSN: 1170-229X. DOI: 10.2165/11318340-00000000-00000.
- [27] Z. B. Niazi, C. A. Salzberg, D. W. Byrne, and M. Viehbeck, “Recurrence of initial pressure ulcer in persons with spinal cord injuries.,” *Advances in wound care : the journal for prevention and healing*, vol. 10, no. 3, pp. 38–42, 1997, ISSN: 1076-2191.
- [28] S. L. Garber and D. H. Rintala, “Pressure ulcers in veterans with spinal cord injury: a retrospective study.,” *Journal of rehabilitation research and development*, vol. 40, no. 5, pp. 433–441, 2003, ISSN: 0748-7711.

- [29] C. Campbell and L. C. C. Parish, “The decubitus ulcer: facts and controversies.,” *Clinics in dermatology*, vol. 28, no. 5, pp. 527–532, Sep. 2010, ISSN: 1879-1131. DOI: 10.1016/j.clindermatol.2010.03.010.
- [30] J. M. Black, L. E. Edsberg, M. M. Baharestani, D. Langemo, M. Goldberg, L. McNichol, J. Cuddigan, and National Pressure Ulcer Advisory Panel, “Pressure ulcers: avoidable or unavoidable? results of the national pressure ulcer advisory panel consensus conference.,” *Ostomy/wound management*, vol. 57, no. 2, pp. 24–37, Feb. 2011, ISSN: 1943-2720.
- [31] J. Maklebust, “Pressure ulcers: the great insult.,” *The Nursing clinics of North America*, vol. 40, no. 2, pp. 365–389, Jun. 2005, ISSN: 0029-6465. DOI: 10.1016/j.cnur.2004.09.015.
- [32] L. Gunningberg and N. A. Stotts, “Tracking quality over time: what do pressure ulcer data show?” *International journal for quality in health care : journal of the International Society for Quality in Health Care / ISQua*, vol. 20, no. 4, pp. 246–253, Aug. 2008, ISSN: 1353-4505. DOI: 10.1093/intqhc/mzn009.
- [33] C. T. Milne, D. Trigilia, T. L. Houle, S. Delong, and D. Rosenblum, “Reducing pressure ulcer prevalence rates in the long-term acute care setting.,” *Ostomy/wound management*, vol. 55, no. 4, pp. 50–59, Apr. 2009, ISSN: 0889-5899.
- [34] J. A. Witkowski and L. C. Parish, “Histopathology of the decubitus ulcer.,” *Journal of the American Academy of Dermatology*, vol. 6, no. 6, pp. 1014–1021, Jun. 1982, ISSN: 0190-9622.

- [35] S. M. Dinsdale, “Decubitus ulcers: role of pressure and friction in causation.,” *Archives of physical medicine and rehabilitation*, vol. 55, no. 4, pp. 147–152, Apr. 1974, ISSN: 0003-9993.
- [36] M. KOSIAK, “Etiology of decubitus ulcers.,” *Archives of physical medicine and rehabilitation*, vol. 42, pp. 19–29, Jan. 1961, ISSN: 0003-9993.
- [37] R. Labbe, T. Lindsay, and P. M. Walker, “The extent and distribution of skeletal muscle necrosis after graded periods of complete ischemia.,” *Journal of vascular surgery*, vol. 6, no. 2, pp. 152–157, Aug. 1987, ISSN: 0741-5214. DOI: 10.1067/mva.1987.avso060152.
- [38] P. E. Strock and G. Majno, “Microvascular changes in acutely ischemic rat muscle.,” *Surgery, gynecology & obstetrics*, vol. 129, no. 6, pp. 1213–1224, Dec. 1969, ISSN: 0039-6087.
- [39] M. Bliss and B. Simini, “When are the seeds of postoperative pressure sores sown?. often during surgery.,” *BMJ (Clinical research ed.)*, vol. 319, no. 7214, pp. 863–864, Oct. 2, 1999, ISSN: 0959-8138.
- [40] K. Ytrehus, O. Reikerås, N. Huseby, and R. Myklebust, “Ultrastructure of reperfused skeletal muscle: the effect of oxygen radical scavenger enzymes.,” *International journal of microcirculation, clinical and experimental / sponsored by the European Society for Microcirculation*, vol. 15, no. 4, pp. 155–162, 1995, ISSN: 0167-6865.
- [41] F. W. Blaisdell, “The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review.,” *Cardiovascular surgery (London, England)*, vol. 10, no. 6, pp. 620–630, Dec. 2002, ISSN: 0967-2109.
- [42] S. Tsuji, S. Ichioka, N. Sekiya, and T. Nakatsuka, “Analysis of ischemia-reperfusion injury in a microcirculatory model of pressure ulcers.,”

Wound repair and regeneration, vol. 13, no. 2, pp. 209–215, Mar. 2005,
ISSN: 1067-1927. DOI: 10.1111/j.1067-1927.2005.130213.x.

- [43] R. Salcido, J. C. Donofrio, S. B. Fisher, E. K. LeGrand, K. Dickey, J. M. Carney, R. Schosser, and R. Liang, “Histopathology of pressure ulcers as a result of sequential computer-controlled pressure sessions in a fuzzy rat model.,” *Advances in wound care : the journal for prevention and healing*, vol. 7, no. 5, Sep. 1994, ISSN: 1076-2191.
- [44] G. E. Miller and J. Seale, “Lymphatic clearance during compressive loading.,” *Lymphology*, vol. 14, no. 4, pp. 161–166, Dec. 1981, ISSN: 0024-7766.
- [45] T. A. Krouskop, N. P. Reddy, W. A. Spencer, and J. W. Secor, “Mechanisms of decubitus ulcer formation—an hypothesis.,” *Medical hypotheses*, vol. 4, no. 1, pp. 37–39, 1978, ISSN: 0306-9877.
- [46] N. P. Reddy and G. V. Cochran, “Interstitial fluid flow as a factor in decubitus ulcer formation.,” *Journal of biomechanics*, vol. 14, no. 12, pp. 879–881, 1981, ISSN: 0021-9290.
- [47] B. Braden and N. Bergstrom, “A conceptual schema for the study of the etiology of pressure sores.,” *Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses*, vol. 12, no. 1, pp. 8–12, 1987, ISSN: 0278-4807.
- [48] A. S. Landsman, D. F. Meaney, R. S. Cargill, E. J. Macarak, and L. E. Thibault, “1995 william j. stickel gold award. high strain rate tissue deformation. a theory on the mechanical etiology of diabetic foot ulcerations.,” *Journal of the American Podiatric Medical Association*, vol. 85, no. 10, pp. 519–527, Oct. 1995, ISSN: 8750-7315.

- [49] C. V. Bouten, M. M. Knight, D. A. Lee, and D. L. Bade, “Compressive deformation and damage of muscle cell subpopulations in a model system.,” *Annals of biomedical engineering*, vol. 29, no. 2, pp. 153–163, Feb. 2001, ISSN: 0090-6964.
- [50] Y.-N. N. Wang, C. V. Bouten, D. A. Lee, and D. L. Bader, “Compression-induced damage in a muscle cell model in vitro.,” *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of engineering in medicine*, vol. 219, no. 1, pp. 1–12, 2005, ISSN: 0954-4119.
- [51] K. K. Ceelen, A. Stekelenburg, S. Loerakker, G. J. Strijkers, D. L. Bader, K. Nicolay, F. P. Baaijens, and C. W. Oomens, “Compression-induced damage and internal tissue strains are related.,” *Journal of biomechanics*, vol. 41, no. 16, pp. 3399–3404, Dec. 5, 2008, ISSN: 0021-9290. DOI: [10.1016/j.jbiomech.2008.09.016](https://doi.org/10.1016/j.jbiomech.2008.09.016).
- [52] E. Linder-Ganz, N. Shabshin, Y. Itzchak, Z. Yizhar, I. Siev-Ner, and A. Gefen, “Strains and stresses in sub-dermal tissues of the buttocks are greater in paraplegics than in healthy during sitting.,” *Journal of biomechanics*, vol. 41, no. 3, pp. 567–580, 2008, ISSN: 0021-9290. DOI: [10.1016/j.jbiomech.2007.10.011](https://doi.org/10.1016/j.jbiomech.2007.10.011).
- [53] S. Portnoy, I. Siev-Ner, N. Shabshin, A. Kristal, Z. Yizhar, and A. Gefen, “Patient-specific analyses of deep tissue loads post transtibial amputation in residual limbs of multiple prosthetic users.,” *Journal of biomechanics*, vol. 42, no. 16, pp. 2686–2693, Dec. 11, 2009, ISSN: 1873-2380. DOI: [10.1016/j.jbiomech.2009.08.019](https://doi.org/10.1016/j.jbiomech.2009.08.019).
- [54] N. Slomka and A. Gefen, “Relationship between strain levels and permeability of the plasma membrane in statically stretched myoblasts.,”

Annals of biomedical engineering, vol. 40, no. 3, pp. 606–618, Mar. 7, 2012, ISSN: 1573-9686. DOI: 10.1007/s10439-011-0423-1.

- [55] S. Loerakker, L. R. Solis, D. L. Bader, F. P. Baaijens, V. K. Mushahwar, and C. W. Oomens, “How does muscle stiffness affect the internal deformations within the soft tissue layers of the buttocks under constant loading?” *Computer methods in biomechanics and biomedical engineering*, vol. 16, no. 5, pp. 520–529, 2013, ISSN: 1476-8259. DOI: 10.1080/10255842.2011.627682.
- [56] E. Linder-Ganz and A. Gefen, “Stress analyses coupled with damage laws to determine biomechanical risk factors for deep tissue injury during sitting.,” *Journal of biomechanical engineering*, vol. 131, no. 1, Jan. 2009, ISSN: 0148-0731. DOI: 10.1115/1.3005195.
- [57] T. Nagel, S. Loerakker, and C. W. Oomens, “A theoretical model to study the effects of cellular stiffening on the damage evolution in deep tissue injury.,” *Computer methods in biomechanics and biomedical engineering*, vol. 12, no. 5, pp. 585–597, Oct. 2009, ISSN: 1476-8259. DOI: 10.1080/10255840902788603.
- [58] A. Gefen and E. Linder-Ganz, “[diffusion of ulcers in the diabetic foot is promoted by stiffening of plantar muscular tissue under excessive bone compression].,” *Der Orthopäde*, vol. 33, no. 9, pp. 999–1012, Sep. 2004, ISSN: 0085-4530. DOI: 10.1007/s00132-004-0701-9.
- [59] D. DiMaio and Vincent, “Rigor mortis,” in *Forensic Pathology, Second Edition (Practical Aspects of Criminal and Forensic Investigations)*, V. J. Geberth, Ed., 2nd ed. CRC Press, Jun. 28, 2001, pp. 26–28, ISBN: 084930072X.

- [60] S. Portnoy, Z. Yizhar, N. Shabshin, Y. Itzchak, A. Kristal, Y. Dotan-Marom, I. Siev-Ner, and A. Gefen, “Internal mechanical conditions in the soft tissues of a residual limb of a trans-tibial amputee.,” *Journal of biomechanics*, vol. 41, no. 9, pp. 1897–1909, 2008, ISSN: 0021-9290. DOI: [10.1016/j.jbiomech.2008.03.035](https://doi.org/10.1016/j.jbiomech.2008.03.035).
- [61] K. Vanderwee, M. H. Grypdonck, D. De Bacquer, and T. Defloor, “Effectiveness of turning with unequal time intervals on the incidence of pressure ulcer lesions.,” *Journal of advanced nursing*, vol. 57, no. 1, pp. 59–68, Jan. 2007, ISSN: 0309-2402. DOI: [10.1111/j.1365-2648.2006.04060.x](https://doi.org/10.1111/j.1365-2648.2006.04060.x).
- [62] S. E. Rich, D. Margolis, M. Shardell, W. G. Hawkes, R. R. Miller, S. Amr, and M. Baumgarten, “Frequent manual repositioning and incidence of pressure ulcers among bed-bound elderly hip fracture patients.,” *Wound repair and regeneration*, vol. 19, no. 1, pp. 10–18, 2011, ISSN: 1524-475X. DOI: [10.1111/j.1524-475x.2010.00644.x](https://doi.org/10.1111/j.1524-475x.2010.00644.x).
- [63] T. A. Krouskop, P. S. Noble, J. Brown, and R. Marburger, “Factors affecting the pressure-distributing properties of foam mattress overlays.,” *Journal of rehabilitation research and development*, vol. 23, no. 3, pp. 33–39, Jul. 1986, ISSN: 0748-7711.
- [64] B. Pham, L. Teague, J. Mahoney, L. Goodman, M. Paulden, J. Poss, J. Li, L. Ieraci, S. Carcone, and M. Krahn, “Early prevention of pressure ulcers among elderly patients admitted through emergency departments: a cost-effectiveness analysis.,” *Annals of emergency medicine*, vol. 58, no. 5, Nov. 2011, ISSN: 1097-6760. DOI: [10.1016/j.annemergmed.2011.04.033](https://doi.org/10.1016/j.annemergmed.2011.04.033).

- [65] L. Rafter, “Evaluation of patient outcomes: pressure ulcer prevention mattresses.,” *British journal of nursing (Mark Allen Publishing)*, vol. 20, no. 11, 2011, ISSN: 0966-0461.
- [66] S. Gyawali, L. Solis, S. L. L. Chong, C. Curtis, P. Seres, I. Kornelsen, R. Thompson, and V. K. Mushahwar, “Intermittent electrical stimulation redistributes pressure and promotes tissue oxygenation in loaded muscles of individuals with spinal cord injury.,” *Journal of applied physiology (Bethesda, Md. : 1985)*, vol. 110, no. 1, pp. 246–255, Jan. 2011, ISSN: 1522-1601. DOI: 10.1152/japplphysiol.00661.2010.
- [67] L. R. Solis, E. Twist, P. Seres, R. B. Thompson, and V. K. Mushahwar, “Prevention of deep tissue injury through muscle contractions induced by intermittent electrical stimulation after spinal cord injury in pigs.,” *Journal of applied physiology (Bethesda, Md. : 1985)*, vol. 114, no. 2, pp. 286–296, Jan. 15, 2013, ISSN: 1522-1601. DOI: 10.1152/japplphysiol.00257.2012.
- [68] N. Greer, N. A. Foman, R. MacDonald, J. Dorrian, P. Fitzgerald, I. Rutks, and T. J. Wilt, “Advanced wound care therapies for nonhealing diabetic, venous, and arterial ulcers: a systematic review.,” *Annals of internal medicine*, vol. 159, no. 8, pp. 532–542, Oct. 15, 2013, ISSN: 1539-3704. DOI: 10.7326/0003-4819-159-8-201310150-00006.
- [69] R. L. Longe, “Current concepts in clinical therapeutics: pressure sores.,” *Clinical pharmacy*, vol. 5, no. 8, pp. 669–681, Aug. 1986, ISSN: 0278-2677.
- [70] H. Brem, D. M. Nierman, and J. E. Nelson, “Pressure ulcers in the chronically critically ill patient.,” *Critical care clinics*, vol. 18, no. 3, pp. 683–694, Jul. 2002, ISSN: 0749-0704.

- [71] B. Biglari, A. Büchler, T. Reitzel, T. Swing, H. J. Gerner, T. Ferbert, and A. Moghaddam, “A retrospective study on flap complications after pressure ulcer surgery in spinal cord-injured patients.,” *Spinal cord*, vol. 52, no. 1, pp. 80–83, Jan. 12, 2014, ISSN: 1476-5624. DOI: 10.1038/sc.2013.130.
- [72] I. Bales and T. Duvendack, “Reaching for the moon: achieving zero pressure ulcer prevalence, an update.,” *Journal of wound care*, vol. 20, no. 8, Aug. 2011, ISSN: 0969-0700.
- [73] M. Thompson, “Reducing pressure ulcers in hip fracture patients.,” *British journal of nursing (Mark Allen Publishing)*, vol. 20, no. 15, 2011, ISSN: 0966-0461.
- [74] D. Carson, K. Emmons, W. Falone, and A. M. M. Preston, “Development of pressure ulcer program across a university health system.,” *Journal of nursing care quality*, Sep. 10, 2011, ISSN: 1550-5065. DOI: 10.1097/ncq.0b013e3182310f8b.
- [75] D. Norton, R. McLaren, and A. N. Exton-Smith, *An Investigation Of Geriatric Nursing Problems In Hospital*, 5. London, UK: Churchill Livingstone, Jul. 1975, vol. 77, pp. 317+. DOI: 10.1016/s0033-3506(63)80071-2.
- [76] B. J. Braden and N. Bergstrom, “Predictive validity of the braden scale for pressure sore risk in a nursing home population.,” *Research in nursing & health*, vol. 17, no. 6, pp. 459–470, Dec. 1994, ISSN: 0160-6891.
- [77] M. Lindgren, M. Unosson, A.-M. M. Krantz, and A.-C. C. Ek, “A risk assessment scale for the prediction of pressure sore development: reliability and validity.,” *Journal of advanced nursing*, vol. 38, no. 2, pp. 190–199, Apr. 2002, ISSN: 0309-2402.

- [78] I. Fromantin, M. C. Falcou, A. Baffie, C. Petot, R. Mazerat, C. Jaouen, L. Téot, and d. Rycke, “Inception and validation of a pressure ulcer risk scale in oncology.,” *Journal of wound care*, vol. 20, no. 7, Jul. 2011, ISSN: 0969-0700.
- [79] U. Källman and M. Lindgren, “Predictive validity of 4 risk assessment scales for prediction of pressure ulcer development in a hospital setting.,” *Advances in skin & wound care*, vol. 27, no. 2, pp. 70–76, Feb. 2014, ISSN: 1538-8654. DOI: 10.1097/01.asw.0000439059.72199.41.
- [80] Y. J. J. Lee, S. Park, J. Y. Y. Kim, C. G. G. Kim, and S. K. K. Cha, “[clinical nurses’ knowledge and visual differentiation ability in pressure ulcer classification system and incontinence-associated dermatitis].,” *Journal of Korean Academy of Nursing*, vol. 43, no. 4, pp. 526–535, Aug. 2013, ISSN: 2093-758X. DOI: 10.4040/jkan.2013.43.4.526.
- [81] J. M. Levine, E. A. Ayello, K. M. Zulkowski, and J. Fogel, “Pressure ulcer knowledge in medical residents: an opportunity for improvement.,” *Advances in skin & wound care*, vol. 25, no. 3, pp. 115–117, Mar. 2012, ISSN: 1538-8654. DOI: 10.1097/01.asw.0000412908.43335.46.
- [82] E. Sloth and T. Karlsmark, “Evaluation of four non-invasive methods for examination and characterization of pressure ulcers.,” *Skin research and technology : official journal of International Society for Bioengineering and the Skin (ISBS) [and] International Society for Digital Imaging of Skin (ISDIS) [and] International Society for Skin Imaging (ISSI)*, vol. 14, no. 3, pp. 270–276, Aug. 2008, ISSN: 1600-0846. DOI: 10.1111/j.1600-0846.2008.00290.x.
- [83] T. Higashino, G. Nakagami, T. Kadono, Y. Ogawa, S. Iizaka, H. Koyanagi, S. Sasaki, N. Haga, and H. Sanada, “Combination of thermo-

- graphic and ultrasonographic assessments for early detection of deep tissue injury.,” *International wound journal*, Nov. 22, 2012, ISSN: 1742-481X. DOI: 10.1111/j.1742-481x.2012.01117.x.
- [84] C. Gehin, E. Brusseau, R. Meffre, P. M. Schmitt, J. F. Deprez, and A. Dittmar, “Which techniques to improve the early detection and prevention of pressure ulcers?” *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, vol. 1, pp. 6057–6060, 2006, ISSN: 1557-170X. DOI: 10.1109/ieemb.2006.259506.
- [85] A. Gefen, K. J. Farid, and I. Shaywitz, “A review of deep tissue injury development, detection, and prevention: shear savvy.,” *Ostomy/wound management*, vol. 59, no. 2, pp. 26–35, Feb. 2013, ISSN: 1943-2720.
- [86] J.-F. F. Deprez, G. Cloutier, C. Schmitt, C. Gehin, A. Dittmar, O. Basset, and E. Brusseau, “3D ultrasound elastography for early detection of lesions. evaluation on a pressure ulcer mimicking phantom.,” *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, vol. 2007, pp. 79–82, 2007, ISSN: 1557-170X. DOI: 10.1109/ieemb.2007.4352227.
- [87] R. Beetham, “Biochemical investigation of suspected rhabdomyolysis.,” *Annals of clinical biochemistry*, vol. 37 (Pt 5), pp. 581–587, Sep. 2000, ISSN: 0004-5632.
- [88] J. M. Sauret, G. Marinides, and G. K. Wang, “Rhabdomyolysis.,” *American family physician*, vol. 65, no. 5, pp. 907–912, Mar. 1, 2002, ISSN: 0002-838X.

- [89] W. H. Bagley, H. Yang, and K. H. Shah, “Rhabdomyolysis.,” *Internal and emergency medicine*, vol. 2, no. 3, pp. 210–218, Oct. 2007, ISSN: 1828-0447. DOI: [10.1007/s11739-007-0060-8](https://doi.org/10.1007/s11739-007-0060-8).
- [90] J. F. Greenleaf, M. Fatemi, and M. Insana, “Selected methods for imaging elastic properties of biological tissues.,” *Annual review of biomedical engineering*, vol. 5, no. 1, pp. 57–78, 2003, ISSN: 1523-9829. DOI: [10.1146/annurev.bioeng.5.040202.121623](https://doi.org/10.1146/annurev.bioeng.5.040202.121623).
- [91] Hippocrates, “On the articulations. the genuine works of hippocrates.,” *Clinical orthopaedics and related research*, no. 400, pp. 19–25, Jul. 2002, ISSN: 0009-921X.
- [92] E. Brusseau, C. Perrey, P. Delachartre, M. Vogt, D. Vray, and H. Ernert, “Axial strain imaging using a local estimation of the scaling factor from RF ultrasound signals.,” *Ultrasonic imaging*, vol. 22, no. 2, pp. 95–107, Apr. 2000, ISSN: 0161-7346.
- [93] P. Hoskins, K. Martin, and A. Thrush, Eds., *Diagnostic Ultrasound Physics and Equipment*. Cambridge, UK: Cambridge University Press, 2010, ISBN: 978-0-521-75710-2.
- [94] T. Karlas, C. Pfrepper, J. Wiegand, C. Wittekind, M. Neuschulz, J. Mössner, T. Berg, M. Tröltzscher, and V. Keim, “Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease.,” *Scandinavian journal of gastroenterology*, vol. 46, no. 12, pp. 1458–1467, Dec. 2011, ISSN: 1502-7708. DOI: [10.3109/00365521.2011.610004](https://doi.org/10.3109/00365521.2011.610004).
- [95] R. L. Maurice, J. Ohayon, Y. Frétigny, M. Bertrand, G. Soulez, and G. Cloutier, “Noninvasive vascular elastography: theoretical framework.,”

- IEEE transactions on medical imaging*, vol. 23, no. 2, pp. 164–180, Feb. 2004, ISSN: 0278-0062. DOI: 10.1109/tmi.2003.823066.
- [96] R. J. Dickinson and C. R. Hill, “Measurement of soft tissue motion using correlation between a-scans.,” *Ultrasound in medicine & biology*, vol. 8, no. 3, pp. 263–271, 1982, ISSN: 0301-5629.
 - [97] L. S. Wilson and D. E. Robinson, “Ultrasonic measurement of small displacements and deformations of tissue.,” *Ultrasonic imaging*, vol. 4, no. 1, pp. 71–82, Jan. 1982, ISSN: 0161-7346.
 - [98] E. J. Chen, J. Novakofski, W. K. Jenkins, and W. D. O’Brien, “Young’s modulus measurements of soft tissues with application to elasticity imaging,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 43, no. 1, pp. 191–194, Jan. 1996, ISSN: 08853010.
 - [99] G. Treece, J. Lindop, L. Chen, J. Housden, R. Prager, and A. Gee, “Real-time quasi-static ultrasound elastography,” *Interface Focus*, Apr. 20, 2011. DOI: 10.1098/rsfs.2011.0011.
 - [100] J. Ophir, I. Céspedes, H. Ponnekanti, Y. Yazdi, and X. Li, “Elastography: a quantitative method for imaging the elasticity of biological tissues.,” *Ultrasonic imaging*, vol. 13, no. 2, pp. 111–134, Apr. 1991, ISSN: 0161-7346.
 - [101] J.-F. F. Deprez, E. Brusseau, C. Schmitt, G. Cloutier, and O. Basset, “3D estimation of soft biological tissue deformation from radio-frequency ultrasound volume acquisitions.,” *Medical image analysis*, vol. 13, no. 1, pp. 116–127, Feb. 2009, ISSN: 1361-8423. DOI: 10.1016/j.media.2008.07.003.

- [102] J. Meunier and M. Bertrand, “Ultrasonic texture motion analysis: theory and simulation.,” *IEEE transactions on medical imaging*, vol. 14, no. 2, pp. 293–300, 1995, ISSN: 0278-0062. DOI: 10.1109/42.387711.
- [103] T. Varghese, “Quasi-Static ultrasound elastography.,” *Ultrasound clinics*, vol. 4, no. 3, pp. 323–338, Jul. 2009, ISSN: 1556-858X. DOI: 10.1016/j.cult.2009.10.009.
- [104] P.-E. Austrell, B. Enquist, A. Heyden, and S. Spanne, “Contact free strain measurement using MATLAB image processing toolbox,” Lund, Sweden.
- [105] E. Brusseau, J. Kybic, J.-F. F. Deprez, and O. Basset, “2-D locally regularized tissue strain estimation from radio-frequency ultrasound images: theoretical developments and results on experimental data.,” *IEEE transactions on medical imaging*, vol. 27, no. 2, pp. 145–160, Feb. 2008, ISSN: 0278-0062. DOI: 10.1109/tmi.2007.897408.
- [106] K. R. Nightingale, R. W. Nightingale, M. L. Palmeri, and G. E. Trahey, “A finite element model of remote palpation of breast lesions using radiation force: factors affecting tissue displacement.,” *Ultrasonic imaging*, vol. 22, no. 1, pp. 35–54, Jan. 2000, ISSN: 0161-7346.
- [107] K. R. Nightingale, M. L. Palmeri, R. W. Nightingale, and G. E. Trahey, “On the feasibility of remote palpation using acoustic radiation force.,” *The Journal of the Acoustical Society of America*, vol. 110, no. 1, pp. 625–634, Jul. 2001, ISSN: 0001-4966.
- [108] K. Nightingale, M. S. S. Soo, R. Nightingale, and G. Trahey, “Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility.,” *Ultrasound in medicine & biology*, vol. 28, no. 2, pp. 227–235, Feb. 2002, ISSN: 0301-5629.

- [109] M. L. Palmeri, K. D. Frinkley, L. Zhai, M. Gottfried, R. C. Bentley, K. Ludwig, and K. R. Nightingale, “Acoustic radiation force impulse (ARFI) imaging of the gastrointestinal tract.,” *Ultrasonic imaging*, vol. 27, no. 2, pp. 75–88, Apr. 2005, ISSN: 0161-7346.
- [110] T. U. S. National Library of Medicine, *Visible human project*, 1994.
- [111] J. C. Bamber and R. J. Dickinson, “Ultrasonic b-scanning: a computer simulation.,” *Physics in medicine and biology*, vol. 25, no. 3, pp. 463–479, May 1980, ISSN: 0031-9155.
- [112] T. A. Krouskop, T. M. Wheeler, F. Kallel, B. S. Garra, and T. Hall, “Elastic moduli of breast and prostate tissues under compression,” *Ultrasonic Imaging*, vol. 20, no. 4, pp. 260–274, Oct. 1, 1998, ISSN: 1096-0910. DOI: [10.1177/016173469802000403](https://doi.org/10.1177/016173469802000403).
- [113] A. P. Choi and Y. P. Zheng, “Estimation of young’s modulus and poisson’s ratio of soft tissue from indentation using two different-sized indentors: finite element analysis of the finite deformation effect.,” *Medical & biological engineering & computing*, vol. 43, no. 2, pp. 258–264, Mar. 2005, ISSN: 0140-0118.
- [114] A. D. Martin, M. Z. Daniel, D. T. Drinkwater, and J. P. Clarys, “Adipose tissue density, estimated adipose lipid fraction and whole body adiposity in male cadavers.,” *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, vol. 18, no. 2, pp. 79–83, Feb. 1994, ISSN: 0307-0565.
- [115] J. Y. Rho, R. B. Ashman, and C. H. Turner, “Young’s modulus of trabecular and cortical bone material: ultrasonic and microtensile mea-

- surements.,” *Journal of biomechanics*, vol. 26, no. 2, pp. 111–119, Feb. 1993, ISSN: 0021-9290.
- [116] R. Shahar, P. Zaslansky, M. Barak, A. A. Friesem, J. D. Currey, and S. Weiner, “Anisotropic poisson’s ratio and compression modulus of cortical bone determined by speckle interferometry,” *Journal of Biomechanics*, vol. 40, no. 2, pp. 252–264, Jan. 2007, ISSN: 00219290. DOI: [10.1016/j.jbiomech.2006.01.021](https://doi.org/10.1016/j.jbiomech.2006.01.021).
- [117] Y. Zheng, W. W. Lu, Q. Zhu, L. Qin, S. Zhong, and J. C. Leong, “Variation in bone mineral density of the sacrum in young adults and its significance for sacral fixation.,” *Spine*, vol. 25, no. 3, pp. 353–357, Feb. 1, 2000, ISSN: 0362-2436.
- [118] B. E. Treeby, J. Jaros, A. P. Rendell, and B. T. Cox, “Modeling non-linear ultrasound propagation in heterogeneous media with power law absorption using a k-space pseudospectral method.,” *The Journal of the Acoustical Society of America*, vol. 131, no. 6, pp. 4324–4336, Jun. 2012, ISSN: 1520-8524. DOI: [10.1121/1.4712021](https://doi.org/10.1121/1.4712021).
- [119] W. Nyborg, “Acoustic streaming,” in *Physical Acoustics*, W. Mason, Ed. New York: Academic Press Inc., 1965, vol. IIB, ch. 11, pp. 265–331.
- [120] C. Then, T. J. Vogl, and G. Silber, “Method for characterizing viscoelasticity of human gluteal tissue.,” *Journal of biomechanics*, vol. 45, no. 7, pp. 1252–1258, Apr. 30, 2012, ISSN: 1873-2380. DOI: [10.1016/j.jbiomech.2012.01.037](https://doi.org/10.1016/j.jbiomech.2012.01.037).

Appendix A

Source Code

c1

Listing A.1: Sample code used to simulate b-mode ultrasound images through the convolution of a simulated scattering center distribution with the point spread function of an ultrasound pulse.

```
1 % generate normally distributed noise across the domain
2 rng(domainSeed);
3 backgroundMap = 1 + noiseMagnitude * randn([Ny, Nx]);
4
5 % transform the background map into the domain -1 -> 1
6 backgroundMap = (backgroundMap - min(min(backgroundMap))) / (
7     max(max(backgroundMap)) - min(min(backgroundMap)));
8 backgroundMap = 2 * backgroundMap - 1;
9
10 % if a finite-element model of tissue compression is being used
11 %
12 % compress the background map
13 if model == 0
14     % extract the resultant degrees of freedom from the model
```

^{c1} KH: Add references to each of the listings in this appendix in the body text

```

13 [x, y, u, v] = extractUV([transducerWidth, depth], size(
14     backgroundMap), model);

15 % generate the domain over which interpolation will occur
16 [xx, yy] = meshgrid(x, y);

17 % interpolate the data to deform it
18 backgroundMap = interp2(xx, yy, backgroundMap, xx - u, yy - v
19 , 'spline', mean(mean(backgroundMap)));
20 end

21 % use a cosine function to create the point-spread function
22 % shape in the axial direction
23 xpsf = linspace(-windowWidth / 2, windowHeight / 2, 1 *
24     pointsPerWaveLength);
25 ypsf = linspace(0, 4 * wavelength, 2 * pointsPerWaveLength);
26 [xmpsf, ympsf] = meshgrid(xpsf, ypsf);
27 psf = cos(2 * pi * frequency * ympsf / waveSpeed);

28 % apply a lateral gaussian "filter" to the signal
29 mu = 0;
30 sigma = windowHeight / 4;
31 gauss = (1 / (sigma * sqrt(2 * pi))) * exp(-(xmpsf - mu) .^ 2 /
32     (2 * sigma ^ 2));
33 psf = psf .* gauss;

34 % apply an axial gaussian "filter" to the signal
35 mu = 2 * wavelength;
36 sigma = wavelength * 2;
37 gauss = (1 / (sigma * sqrt(2 * pi))) * exp(-(ympsf - mu) .^ 2 /
38     (2 * sigma ^ 2));
39 gauss = (gauss - min(min(gauss))) / (max(max(gauss)) - min(min(
40     gauss)));

```

```

39 psf = psf .* gauss;

41 % normalize it to -1 -> 1
psf = (psf - min(min(psf)))/(max(max(psf)) - min(min(psf)));
43 psf = 2 * psf - 1;

45 % convolve the scattering map with the point spread function
bmode = conv2(backgroundMap, psf);

47

48 % crop the image to the appropriate size
sz = size(bmode);
49 bmode = bmode(int32(floor((sz(1) - pointDepth) / 2)) : int32(
    floor((sz(1) - pointDepth) / 2) + pointDepth - 1), int32(
    floor((sz(2) - numElements) / 2)) : int32(floor((sz(2) -
numElements) / 2) + numElements - 1));

51

52 % apply classical ultrasound post-processing
53 % the signal is currently oscillating a high frequency
% - extract the envelope of the signal
54 bmode = envelopeDetection(bmode)';
55
56 % apply log compression to allow to be readily viewed
57 bmode = logCompression(bmode, 3, true);

58

59 % normalize it to 0 -> 1
bmode = (bmode - min(min(bmode))) ./ (max(max(bmode)) - min(min
(bmode)));

```

Listing A.2: Sample code used to estimate the lateral and axial strain along a given scanline of a pre- and post- compression b-mode image using quasi-static ultrasound elastography.

```

2 % calculate the number of windows along this scanline
M = maxX / deltaAx;

```

```

4 % these variables will return the alpha and tau coefficients
5 % along this scanline
6 alpha = [];
7 tau = [];
8
9 % loop through every window along this scanline
10 for m = 1:M
11
12     % calculate the locations of the two windows to start the
13     % search from
14
15     pr1 = m .* deltaAx;
16
17     pr2 = sum(deltaAx ./ alpha);
18
19
20     % extract the window in the uncompressed image
21
22     x1 = linspace(pr1, pr1 + L, numPoints);
23
24     r1 = interp1(1 : length(I1), I1, x1, 'linear', 'extrap');
25
26
27     % initialize search variables
28
29     alphas = maxAlpha:-0.001:1;
30
31     taus = zeros(size(alphas));
32
33     correlations = zeros(size(alphas));
34
35
36     % loop through the possible values of alpha
37
38     for i = 1 : length(alphas)
39
40         % keep track of which scanline gives us the best
41         % correlation
42
43         columnCorrelations = [];
44
45
46         % loop through the adjacent scanlines
47
48         for c = (column - columnRadius) : (column + columnRadius)
49
50             % make sure we have a valid scanline
51
52             if (c < 1) || (c > columns)
53
54                 continue;

```

```

34    end

36    % extract the window in the compressed image
37    x2 = linspace(round(pr2), round(pr2) + round(L),
38      numPoints);
39    r2 = interp1(1:length(I2(:, c)), I2(:, c), x2, 'linear',
40      'extrap');

42    % get the correlation for the two windows
43    columnCorrelations = [columnCorrelations, Correlate(r1,
44      r2)];
45    end

47    % pick the scanline that had the best correlation for this
48    alpha
49
50    c = -columnRadius : column + columnRadius;
51    [correlations(i), mindex] = min(columnCorrelations);
52    taus(i) = c(mindex);
53    end

55    % employ a-priori smoothing to the data
56    % in case of errant outliers
57    [~, mindex] = min(correlations);
58    if abs(alphas(mindex) - alpha(length(alpha))) > 0.02
59      alpha = [alpha; alpha(length(alpha))];
60      tau = [tau; tau(length(tau))];
61    else
62      alpha = [alpha; alphas(mindex)];
63      tau = [tau; taus(mindex)];
64    end
65  end

```

Listing A.3: Sample code used in conjunction with the K-Wave Toolbox to simulate acoustic radiation force body loads generated by an ultrasonic transducer.

```

% calculate the best grid size for computational efficiency
2 % taking into account Nyquist so that appropriate sampling is
   used

dx = medium.sound_speed / (2 * probingFrequency);
4 dy = dx;

Nx = bestFactor(domainDepth / dx + (2 * PML_X_SIZE)) - (2 *
   PML_X_SIZE);
6 Ny = bestFactor(domainWidth / dy + (2 * PML_Y_SIZE)) - (2 *
   PML_X_SIZE);

dx = domainDepth / Nx;
8 dy = domainWidth / Ny;

10 % make the grid!
kGrid = makeGrid(Nx, dx, Ny, dy);

12

13 % create the time array

14 kGrid.t_array = makeTime(kGrid, medium.sound_speed, [],

   pulseCycles / probingFrequency);

16 % beam-form the data

17 % create indices for our elements

18 numActiveElements = Ny;
elementIndices = -(numActiveElements - 1) / 2 : (
   numActiveElements - 1) / 2;

20

21 % calculate time delays for a steered and focussed beam
22 elementWidth = dy;
delayTimes = focalDepth / medium.sound_speed * (1 - sqrt(1 + (
   elementIndices * elementWidth ./ focalDepth) .^ 2 )); % [s]
23
24

```

```

% convert the delays to be in units of time points
26 delayTimes = delayTimes - min(delayTimes);
delayTimes = delayTimes ./ kGrid.dt;

28
% use the k-wave toolbox's function "toneBurst" to create the
    signal
30 inputSignal = toneBurst(1 / kGrid.dt, probingFrequency,
    pulseCycles, 'SignalOffset', delayTimes);

32 % scale the signal by the source pressure
source.p = sourcePressure .* inputSignal;

34
% truncate the input signal to the appropriate length
36 source.p = source.p(:, 1:length(kGrid.t_array));

38 % make only the nodes along the top boundary apply pressure to
    the domain
source.p_mask = zeros([Nx, Ny]);
40 source.p_mask(1, 1 : (numActiveElements)) = 1;

42 % tell the k-wave toolbox to record the pressure and intensity
    for
% the entire domain, continuously
44 sensor.mask = ones(Nx, Ny);
sensor.record = {'I', 'p'};

46
% set up simulation settings
48 inputArgs = {'PlotSim', false, 'PMLInside', false, 'PlotPML',
    false, 'PMLSsize', [PML_X_SIZE, PML_Y_SIZE], 'DataCast', ,
    'single', 'DataRecast', true, 'DisplayMask', 'off'};

50 % run the simulation

```

```

    sensorData = kspaceFirstOrder2D(kGrid, medium, source, sensor,
        inputArgs{:});

52

% reshape the output data to make sense

54 Ix = reshape(sensorData.Iy, [Nx, Ny, kGrid.Nt]);
Iy = reshape(sensorData.Ix, [Nx, Ny, kGrid.Nt]);
P = reshape(sensorData.p, [Nx, Ny, kGrid.Nt]);

58 % calculate body forces
alpha = (attenuationCoefficient * 100 * probingFrequency / 1e6)
    / (20 / log(10));
60 Fx = 2 * alpha .* Ix ./ soundSpeed;
Fy = -2 * alpha .* Iy ./ soundSpeed;

```

Listing A.4: Sample code used to calculate the speed of a shear wave generated by an ARFI force along a lateral line traversing the focal point of the applied force.

```

1 % extract the displacement along a lateral line traversing the
   focal point
%
% throughout the complete simulation time
3 [x, t, lateralCut] = getLateralFocalCutDisplacement(model);

5 % use the mean value of the displacement through time and
   location
%
% as the isoline value to track
7 targetValue = mean(mean(lateralCut));

9 % loop along the x-coordinates of the dataset
points = NaN(length(x), 2);
11 % ignore the first 4 data points which lie within the width of
   the
%
% initial radiation force
13 for xi = 5 : length(x)

```

```

% find the point in time where the displacement at the given
x-coordinate
15 % crosses the target value previously established
for ti = 2 : length(t)
17 if (lateralCut(ti, xi) < targetValue) && (lateralCut(ti -
1, xi) >= targetValue)
18 % if the cross-over point was found, store it and
19 continue with
20 % the next x-coordinate
21 points(xi, :) = [t(ti), x(xi)];
22 ti = length(t);
23 break;
24 end
25 end

27 % remove NaNs from the dataset
points = points(~any(isnan(points), 2), :);

29 % differentiate to get shear velocity
30 % (use a center-weighted moving window average filter first
31 % otherwise the data will become unusable)
32 Ct = diff(smooth(points(:, 2))) ./ diff(smooth(points(:, 1)));
33 x = linspace(min(points(:, 2)), max(points(:, 2)), length(Ct));

```