

University of Alberta

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

by

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Abstract

^{c1}Deep tissue injuries are subcutaneous regions of extreme tissue breakdown generally induced by the application of significant mechanical pressure over extended periods of time through the biological mechanisms of ischemia and cell deformation causing rupture. These wounds are commonly suffered as a secondary wound or disease, often formed due to extended periods of motionless such as stationary sitting in spinal cord injured patients or those undergoing surgery. ^{c2}

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^{c2} KH: Abstract should be <= 150 words and give a decent summary of everything

Acknowledgements

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Nomenclature

Symbol	Meaning
σ	Stress

Abbreviations

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

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. 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 are presented in Chapter ??.

blurb about ARFI here..

blurb about shear here..

Finally, the results presented in this work and their implications along with suggestions for future work are discussed in Chapter ??.

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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.

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 [1], [2] while only a minute fraction of that is spent toward pressure ulcer research [3]. Compared to hospital stays for all other conditions, pa-

tients 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 [2]. 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 [4], [5]. ^{c1}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) [6]—approximately 80 % of people with spinal cord injuries (SCI) will develop at least one pressure ulcer during their lifetime [7] and approximately 19 % of elderly patients in long-term care facilities will develop one [8]. Pressure ulcers exist throughout the entire health-care system and are often formed when undergoing hospitalization [9]. These injuries have a tendency to become chronic, non-healing wounds and many patients die from complications related to them [10]. Further, patients who have developed at least one pressure ulcer in their life are at a significantly greater risk of developing a second [11]. Pressure ulcers and deep tissue injuries generally form at the bone-muscle interface deep in the tissue [12] with approximately 64 % occurring over the ischial tuberosities, trochanter, or sacrum [13]. In general, these injuries are characterized by a some manner of tissue loss through necrosis of the tissue, though there is currently some debate on the exact nature of these wounds as well as the accuracy of the clinical descriptions attributed to them by the National Pressure Ulcer Advisory Panel (NPUAP).

The NPUAP defines pressure ulcers as a “localized injury to the skin and / or underlying tissue usually over a bony prominence, as a result of pressure, or

^{c1} KH: I already mentioned this in the introduction, verbatim. Where should it go?

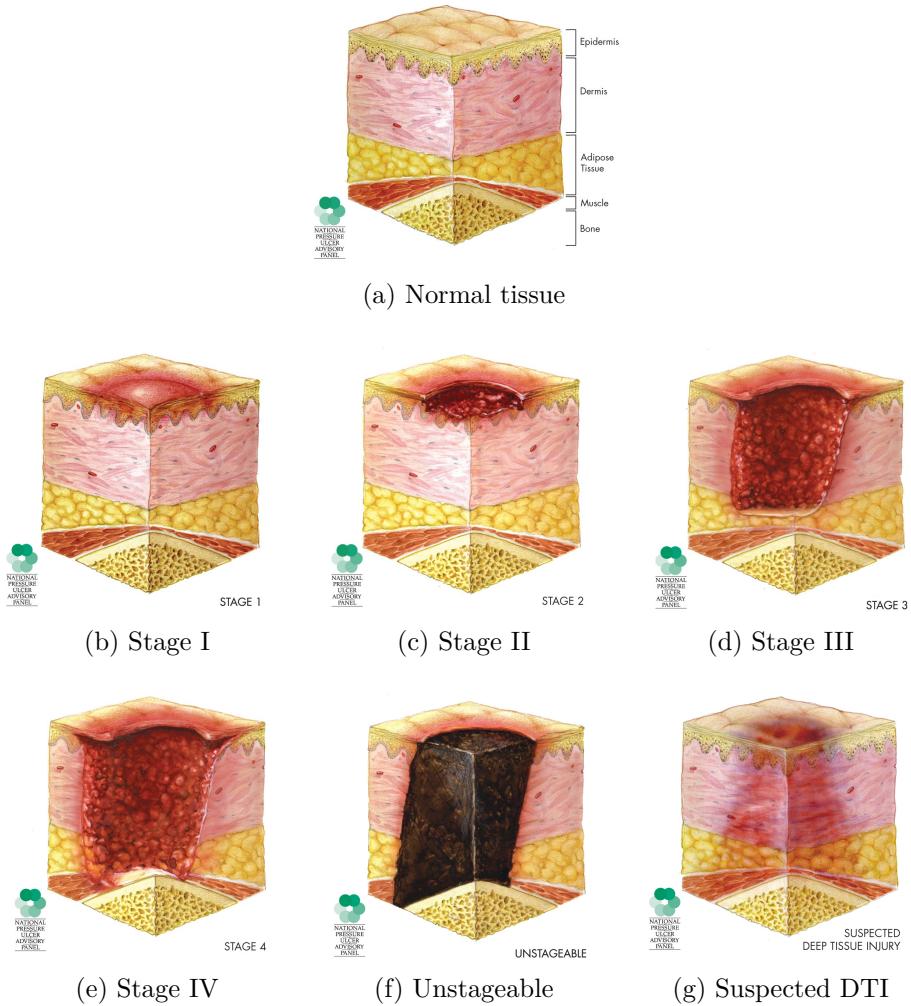


Figure 2.1: The NPUAP staging guideline illustrations of the various stages / severities of pressure ulcers.

pressure in combination with shear and / or friction” and are generally staged according to a tiered system of increasing damage [14]. 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 [15]. 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 [16]. 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 [17], [18] and one of the largest hurdles to preventing and treating DTI is the lack of any substantial early detection ability [19], [20].

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 [21].

For quite some time, ischemia was regarded as the chief acute risk factor for developing late-stage pressure ulcers [22]–[24]. Although studies have shown that healthy tissue is able to survive complete ischemia for approximately 4 hours before severe necrosis set in [25], [26], deep tissue injuries are clinically found when loading times are substantially less than this [9], [27]. 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 [28]–[30]. 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 [29]. 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 [30], [31]. 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 [32]. Once lymphatic drainage ceases, cell waste accumulates in the tissue and is thought to initiate necrosis in the cells [33]–[35]. 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 [36]–[38]. It has constantly been observed that tissue regions which eventually form deep tissue injuries exhibit signs of locally increased strains

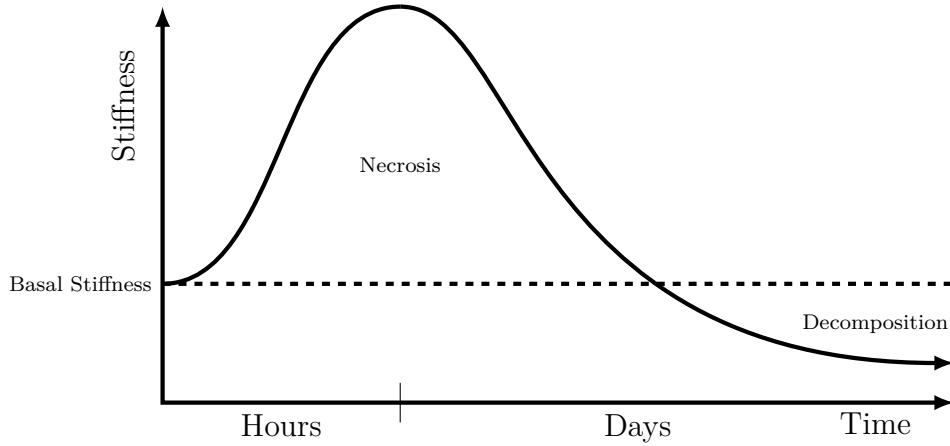


Figure 2.2: Schematic representation of the time course of tissue stiffness changes in a deep tissue injury site. The estimate for the time-course for local rigor mortis was obtained from animal model studies [52] and the estimate for the time-course for tissue decomposition was obtained from the forensic literature [51]. (Adapted from Gefen [15])

[39]–[43], 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 [44]. 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 [45]–[48]. 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 [49] with immediate 1.6-fold to 3.3-fold stiffening of the tissue occurring immediately after injury [46], [50]. Further, the stiffness of tissue severely drops below that of healthy tissue when it begins to decompose [46], [51], leading to a relationship between injury progression and stiffness as shown in Fig. 2.2 (adapted from [15]).

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 [21]. 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 [53]. There is also significant evidence in the literature that suggests that the current NPUAP definitions of PU and DTI are unacceptable 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 [15], [16].

2.1.2 Detection

As previously mentioned, there is a lack of means for detecting the early onset of deep tissue injuries in a clinical setting [19], [20]. 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” [54]–[56]. 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 % [57]. Other studies have shown that nurses have great difficulty detecting and diagnosing suspected deep tissue injuries given the current frameworks they are provided [58], while physicians are even worse [59]. 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 [39], [43], [60]. T_2^* -weighted MRI is able to detect deep tissue injury by investigating oedema within given tissues as a proxy for the stiffening and swelling that occurs during their formation. 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, patients with implants such as pacemakers and who make up a large proportion of the at-risk population cannot undergo MRI scans due to the large magnetic forces involved and / or the need to relocate from their hospital bed to the 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 [12], [61], [62], however the results from these studies are

^{c1} KH: Citation needed!

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 [63]. 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 [15], [64], [65]. 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 [66], [67]. While these studies show promise, they are only the beginning for the adoption of ultrasound elastography as a viable clinical detection modality for deep tissue injuries.

Recently, another possible avenue for DTI detection has arisen which lies in the biochemical markers present in a patient's blood or urine. (look at gefen13 for references for this).

2.1.3 Prevention and Treatment

- [68]
- Prevention of deep tissue injury through muscle contractions induced by intermittent electrical stimulation after spinal cord injury in pigs [69]
- The importance of internal strain as opposed to interface pressure in the prevention of pressure related deep tissue injury [70]
- New methodology for preventing pressure ulcers using actimetry and autonomous nervous system recording [71]
- Pressure ulcers: the great insult [18]

- Reaching for the moon: achieving zero pressure ulcer prevalence, an update [72]
- Distribution of Internal Pressure around Bony Prominences: Implications to deep tissue injury and effectiveness of intermittent electrical stimulation [68]
- Distribution of internal strains around bony prominences in pigs [43]
- Reaching for the moon: achieving zero pressure ulcer prevalence, an update. [72]
- Reducing pressure ulcers in hip fracture patients [73]
- Reducing pressure ulcer prevalence rates in the long-term acute care setting [20]
- Development of pressure ulcer program across a university health system [74]
- Assessment and management of pressure ulcers in the elderly: current strategies [10]
- Pressure ulcers: the great insult [18]
- Intermittent electrical stimulation redistributes pressure and promotes tissue oxygenation in loaded muscles of individuals with spinal cord injury. [75]

2.2 Ultrasound Elastography

2.2.1 Quasi-Static Ultrasound Elastography

- A new method for the visualization and quantification of internal skin elasticity by ultrasound imaging [76]

2.2.2 Acoustic Radiation Force Impulse Imaging

- derp

2.2.3 Shear Wave Speed Quantification

- derp

2.3 Numerical Characterization / Finite-Element Modelling

2.4 Conclusion

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Appendix A

Data Tables

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A.1 Quasi-Static Ultrasound Elastography

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A.2 Acoustic Radiation Force Impulse Imaging

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A.3 Shear Wave Speed Quantification

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Appendix B

Source Code

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B.1 Quasi2DUltrasound

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