2.1.2 Prevention and Treatment

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

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

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

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

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

2.1.3 Detection

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

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

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

cost-effective manner.

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

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

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

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

2.2 Ultrasound Elastography

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

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

2.2.1 Quasi-Static Ultrasound Elastography

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

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

2.2.2 Acoustic Radiation Force Impulse Imaging

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

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

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

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

2.2.3 Shear Wave Speed Quantification

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

$$c_T = \sqrt{\frac{\mu_{tissue}}{\rho}} \tag{2.1}$$

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

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

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

2.3 Conclusion

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

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

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

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

Chapter 3

Numerical Characterization of Quasi-Static Ultrasound Elastography

3.1 Introduction

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

3.2 Method

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

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

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

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

Table 3.1: Range of values of investigated parameters

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