Advances in Elastography Using Geometrically Focused Actuation

BY

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THESIS

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To my patient and loving wife…
ACKNOWLEDGMENTS

It goes without saying that this work is too complex to solely be my own. There are so many people without whose help, contributions, support, and leadership I would have never completed this work. It has been a true privilege to work among such great and friendly people during this time.

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SPK
CONTRIBUTION OF AUTHORS

Chapter 2 is from a previously published journal article [1], of which I was the primary author and main contributor to the experimental study. Author Altaf Khan assisted with experimental measurements and design, Zoujun Dai attributed analytical solutions, and Thomas J. Royston assisted in writing and was my thesis advisor.
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<td>CaP</td>
<td>Prostate Cancer</td>
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<tr>
<td>FOV</td>
<td>Field of View</td>
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<td>GFA</td>
<td>Geometrically Focused Actuation</td>
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<td>GFS</td>
<td>Geometrically Focused Surface</td>
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<td>MEG</td>
<td>Motion Encoding Gradients</td>
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<td>MRE</td>
<td>Magnetic Resonance Elastography</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>PSA</td>
<td>Prostate Specific Antigens</td>
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<td>ROI</td>
<td>Region of Interest</td>
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<tr>
<td>RP</td>
<td>Radical Prostatectomy</td>
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<td>SLDV</td>
<td>Scanning LASER Doppler Vibrometer</td>
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<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
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<td>TE</td>
<td>Echo Time</td>
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<tr>
<td>TR</td>
<td>Recovery Time</td>
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<td>TRUS</td>
<td>Transrectal Ultrasound</td>
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<td>OE</td>
<td>Optical Elastography</td>
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<td>SLIM or SLIM-MRE</td>
<td>Sample Interval Modulation MRE</td>
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<td>SLIM-PV</td>
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<td>SLIM-PC</td>
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SUMMARY

In this dissertation several applications of elastography have been researched. These include: in vivo skin optical elastography (OE), in vivo mouse brain sample interval modulation (SLIM) magnetic resonance elastography (MRE), ex vivo prostate MRE, and in situ Lung MRE. The novel method of geometrically focused actuation (GFA) has been included in all of the applications, when possible. GFA, is simply a method of actuation that produces a wave field of either converging surface or shear waves to a focus point. To produce the shear wave fields a sample is placed inside a vibrating hollow tube, and to produce the surface wave fields an annular ring is vibrated on the surface of a sample. The overall motivation for this work is the hope that these new applications can be used for the early detection of various disease pathologies.

For skin elastography, the aim was to develop a novel in vivo skin surface wave actuator to be used for wideband optical elastography, and to investigate the applicability of various viscoelastic models of human skin. It was found that 2 particular models stood out. In terms of variability, the fractional order models performed the best. In quality of fit, the SLS model outperformed all others. Therefore, if one needed a model to identify pathological changes of groups either the fractional Voigt or spring-pot model would be ideal, and if one needed a targeted patient specific model the SLS would be the best choice.

For mouse brain MRE, the aim was to further the development of recently invented SLIM-MRE (simultaneous motion encoding of the 3D wave field) using a novel SLIM-PV (phase varying) method and the original SLIM-PC (phase constant) method, and to test the efficacy of SLIM-MRE at ultra-high field (UHF) 9.4 T for in vivo mouse brain MRE. Both SLIM methods showed good agreement with the conventional MRE method. SLIM-PC, compares to conventional with less error in terms of the shear modulus maps, than SLIM-PV but requires an increase in TE.
For prostate MRE, the aim was to design a novel GFA for \textit{ex vivo} prostate MRE, investigate capability of MRE to accurately measure prostate material properties, and test a threshold based cancer identification method. The threshold based determination of positive and negative prostate cancer (CaP) segments correlated well with the pathology report giving a sensitivity of 85.7\% and specificity of 53.7\%. In addition, potential improvements to the study were found in terms of filter selection and pathology comparison. In order to have more accurate shear modulus results, experiments should be coincided with dynamic testing of the prostate specimen. Also, more local identification algorithms could likely increase both the sensitivity and specificity of segment CaP identification.

And finally, for lung MRE, the aim, using GFA, was to investigate the potential application of UHF proton \textit{in vivo} lung MRE. Unfortunately, it was found that proton lung MRE at 9.4 T does not provide enough signal to perform \textit{in vivo} experiments. Also, the results of the \textit{in situ} experiment that lung tissue stiffness decreased with pressure, did not agree with current literature.
1 INTRODUCTION

1.1 Motivation

Palpation is a common exam room diagnostic method. It is performed by examining the organ in question by touch and checking the stiffness, texture, and or size of the tissue. Often an organ with diseased tissue, such as a tumor, can appear harder than normal. For instance, prostate cancer [2] and breast cancer [3], are both commonly screened using palpation. However, this method is biased, and is best for detecting only significant sized tumors (potentially already metastatic) near the palpation location. The physical stiffness that the examiner is feeling is the property of elasticity or Young’s modulus and shear modulus. For instance, breast tumors have been shown to have elastic moduli 90-fold greater than normal tissue [4]. This property, the elastic modulus of tissue, can be examined in a more quantitative and qualitative way by using elastography.

Elastography techniques are numerous and continuing to evolve, but this dissertation will focus on: optical elastography (OE) [5] and magnetic resonance elastography (MRE) [6]; with each technique introduced and explained in sections 2.2 and 3.2, respectively. Both techniques are dynamic methods for imaging elasticity, and require an external vibration applied to the tissue to create a shear wave field. As will be seen in section 2.2, the equations of motion for this type of wave field are directly related to the dynamic shear modulus. So, by measuring the wave field one can now determine the material properties.

The quality of elastography data is dependent on the signal strength, SNR, of the wave, i.e. the amplitude. Complicating this, is the fact that all biological tissues are viscoelastic, which means that there will be attenuation as the shear wave propagates through the tissue. So, the deeper, or farther away, a tissue is from the source the more the signal will degrade. This is where the method
of geometrically focused actuation (GFA) comes into play. It is designed so that wave fronts converge from all surfaces, thereby reducing the propagation distance a wave travels, and benefiting from convergence of waves. GFA, will then be able to operate with larger bandwidths than a normal point source actuator. It is GFA that will be used for the first time in the applications of chapters 2, 4, and 5.

With an increased bandwidth to measure, a corresponding increase in measurement time will be needed. One method to reduce this is, sample interval modulation MRE; which encodes all three motion directions simultaneously [7]. The SLIM technique will be advanced in this dissertation through a novel phase varying gradient shifting method, and will be tested for the first time in an ultra-high field (UHF) 9.4 T small animal scanner.

1.2 Dissertation Aims

This dissertation is organized in chapters based on the specific study aim. Each chapter will start with relevant background material for the study, and followed by, if needed, a theoretical section explaining the working principles behind the study technique. The methods are outlined and then the results and discussion follow. Finally, a broad conclusion will be made of all the aims.

Aim 1: develop a novel in vivo skin surface wave actuator to be used for wideband optical elastography, and to investigate the applicability of various viscoelastic models of human skin.

Aim 2: further the development of recently invented SLIM-MRE (simultaneous motion encoding of the 3D wave field) using a novel SLIM-PV (phase varying) method and the original SLIM-PC (phase constant) method, and to test the efficacy of SLIM-MRE at ultra-high field (UHF) 9.4 T for in vivo mouse brain MRE.
**Aim 3**: design a novel GFA for *ex vivo* prostate MRE, investigate capability of MRE to accurately measure prostate material properties, and test a threshold based cancer identification method.

**Aim 4**: using GFA, investigate the potential application of UHF proton *in vivo* lung MRE.
2 MODELS OF HUMAN SKIN USING OPTICAL ELASTOGRAPHY

This chapter includes my own work which was originally published in the journal *Physics and Medicine in Biology* [1], and has been used with permission from the publisher, see Appendix A.

2.1 Background

Viscoelastic properties of human skin are affected by disease and injury; measurement of these properties can be used as a diagnostic aid for detection and monitoring of conditions that affect the epidermis and dermis. For example, Raynaud’s phenomena and scleroderma have been shown to increase shear elasticity and shear viscosity [8], [9] as well as affect the thickness of skin [10]. However, skin viscoelastic properties are also affected by ambient temperature, humidity, moisture content [11], [12], thickness, age [13]–[15], sex, and the direction of applied stress [16]. These confounders have limited the utility of viscoelasticity measurements.

Early measurement methods relied mainly on excised strips of skin and tensometer equipment [14]. These tests were accurate and could be performed alongside histological analysis to correlate the stress-strain relationship with changes in molecular structure. However, this was too invasive to be used as a diagnostic tool for skin disorders. Advances in more sensitive measuring equipment led to *in vivo* measurements of shear strain hysteresis curves [12]. Up to this point, the majority of the studies were based on static methods until [11] studied the dynamic viscoelastic properties of skin, over a frequency range of near zero to 1000 Hz, using propagating surface waves. It was found that the viscoelastic properties were dispersive (and therefore frequency-dependent). A similar study also found comparable results; using surface wave propagation, a direct measurement of the complex Young’s modulus of excised rabbit skin was made [17]. Even though it has been determined that skin is viscoelastic, static methods, such as
the suction method or indentation method, have proven reliable and practical for clinical use [16], [18]–[20]; however, they cannot measure the frequency dependence or viscous behavior.

Focusing on the dynamic response of skin, elastography techniques have been developed that use surface waves as the source for elastography imaging. Elastography applies the principle that the wavelength and attenuation of a propagating mechanical wave is dependent on the mechanical properties. Using this principle, several imaging modalities have been used to derive the Young’s modulus or shear modulus. Ultrasound shear wave elastography was used in [21], having the advantage of subsurface imaging of the skin, but was only able to acquire a single frequency per scan. Optical shear wave coherence elastography (OCE) has been used to measure skin viscoelasticity [22], and excised animal tissue [23]. OCE has the advantages of micrometer scale resolution, and 3D imaging capabilities that penetrate the surface. Optical surface wave elastography (OE), the technique employed in this dissertation, uses a LASER Doppler vibrometer (LDV) to measure the surface displacement using the Doppler effect [24], [25]. OE has the advantage of high SNR due to the sensitivity of LASER probes, but it cannot penetrate the surface. Also, current OE methods for skin use outward propagating, point source, surface waves which suffer significantly from attenuation.

All of the previous studies mentioned have been successful in measuring the viscoelastic properties of skin; yet, the standard deviations are large and with the plethora of measured parameters (i.e. wave speed, Young’s modulus, shear modulus, distention, relaxation, etc.) it is not straight forward to compare results that often require an estimate of Poisson’s ratio, which can lead to erroneous results. There is a clear need for a less variable, repeatable, and comparable viscoelastic model or parameter value of human skin for better diagnostic accuracy.
This chapter will assess a novel measurement method using optical elastography to image surface wave propagation over a large bandwidth of frequencies. By measuring large bandwidth data, viscoelastic models can be fit to shear modulus dispersion curves for detailed analysis. To accomplish this, an annular mechanical radiator has been developed that creates geometrically focused surface (GFS) waves, similar to [21] and [26]. GFS waves are surface waves that converge in a cylindrical manner to a focal point. This has the advantage of decreased attenuation and allows for a larger bandwidth than point or line sources. The only major drawback of this novel method is the inability to probe below the surface. The amplitude and phase of the surface waves are measured using a scanning LASER Doppler vibrometer (SLDV), which produces a spatial profile curve of the actual surface wave. The wave profile can then be fit to a frequency response function to estimate the complex shear modulus. A wideband frequency spectrum of the complex shear modulus can then be fit to various viscoelastic models for detailed analysis.

2.2 Theory: OE

The theoretical background used to obtain the solution of an annular radiating surface source (the GFS actuator) will be briefly described followed by a description of the viscoelastic models used. In the following, the skin is assumed to be a homogenous, isotropic, semi-infinite, viscoelastic half-space; as a consequence, the surface waves measured are assumed to represent the material properties of the skin including all of the internal layers. Displacements are small enough, on the order of μm, so that linear system theory is valid. Particle motion of the continuum is governed by Navier’s equations in the absence of body forces:

\[(\lambda + G)\nabla \cdot \mathbf{u} + \mu \nabla^2 \mathbf{u} = \rho \frac{\partial^2 \mathbf{u}}{\partial t^2}\]  \hspace{1cm} (2.1)
For a complete derivation of Eq. (2.1) refer to [27]. Definitions: $\mathbf{u}$ is the displacement vector, $\rho$ is the density of the medium, $\partial / \partial t$ denotes a derivative with respect to time, $\nabla$ is the spatial gradient operator dependent upon the chosen coordinate system, and $\lambda$ and $G$ are the Lame parameters. The Lame parameters are rate dependent and complex, where $\lambda$ and $G$ represent the volume and shear viscoelastic coefficients, respectively. There are two wave types in Eq. (2.1), compression and shear waves. The waves propagate independently of each other allowing them to be separated from Eq. (2.1). Taking the divergence of both sides of Eq. (2.1) yields:

$$\nabla^2 (\nabla \cdot \mathbf{u}) = \frac{1}{c_1^2} \frac{\partial^2 (\nabla \cdot \mathbf{u})}{\partial t^2} \quad \text{with} \quad c_1 = \sqrt{\frac{(\lambda + 2G)}{\rho}} \quad (2.2)$$

With $c_1$ representing the compression wave speed. Similarly, taking the curl of both sides of Eq. (2.1) yields:

$$\nabla^2 (\nabla \times \mathbf{u}) = \frac{1}{c_2^2} \frac{\partial^2 (\nabla \times \mathbf{u})}{\partial t^2} \quad \text{with} \quad c_2 = \sqrt{\frac{G}{\rho}} \quad (2.3)$$

With $c_2$ representing the shear wave speed. For this study it is more convenient to express the wave speeds as the wave numbers:

$$k_1 = \omega \sqrt{\frac{\rho}{\lambda + 2G}} \quad \text{and} \quad k_2 = \omega \sqrt{\frac{\rho}{G}} \quad (2.4)$$

With $k_1$ and $k_2$ representing the complex compression and shear wave numbers respectively.

Using the zero stress boundary condition on the free surface, at $z = 0$ (see Figure 1), the solutions to the equations of motion for a half-space yield the following relation between the surface wave number and shear wave number:
\[ p^3 - 8p^2 + \left(24 - 16\left(\frac{1 - 2\nu}{2(1 - \nu)}\right)p - 16\left(1 - \frac{1 - 2\nu}{2(1 - \nu)}\right)\right) \]  

(2.5)

Where \( p = (k_2/k_{su})^2 \) (see [27] page 325 for complete derivation). The surface wave number \( k_{su} \) can be related to \( k_2 \) by finding the roots of Eq. (2.5). Of the three roots of Eq. (2.5), only the real roots and solutions that satisfy the condition \( k_2/k_{su} > 1 \) are valid, leaving only one solution. For this study, \( \nu = 0.495 \) yields \( k_2/k_{su} = 0.954 \).

**Figure 1.** Schematic section view of the annular radiating surface source theoretical problem with coordinate frame; symmetry is about the line \( r = 0 \). (1) Applied periodic stress \( P = P_0\exp[i\omega t] \). (2) Annular actuator end piece with radius ‘a’. (3) Example of a typical GFS wave curve produced from source. (4) Semi-infinite medium with free surface at \( z = 0 \).
The surface source problem in Figure 1 is analogous to a known solution of a finite circular disk of radius ‘a’ oscillating on a half-space first solved by [28]. A more exact solution was found by [29]. However, this solution was a bit cumbersome so a more compact form of the solution was found in [30], and is referred to as the frequency response function (FRF) of the surface wave motion at \( r \) with respect to the surface wave motion and given by:

\[
\text{FRF} = \frac{u_x(r)}{u_x(a)} = \frac{K_0(irk_{su})}{K_0(iak_{su})} \tag{2.6}
\]

Here, \( K_0 \) is the modified Bessel function of the second kind, and \( i = \sqrt{-1} \). This expression satisfies the governing wave equation and the nonhomogeneous boundary condition imposed by the circular disk of radius ‘a’. Equation (2.6) denotes radially, outward bound surface waves; radially inward bound surface waves can be defined by replacing the modified Bessel function of the second kind, \( K_0 \), which asymptotically approaches zero as the argument increases, with the complementary modified Bessel function of the first kind, \( I_0 \), which asymptotically approaches a finite value as the argument approaches zero:

\[
\text{FRF} = \frac{u_x(r)}{u_x(a)} = \frac{I_0(irk_{su})}{I_0(iak_{su})} \tag{2.7}
\]

Equation (2.7), satisfies the new nonhomogenous boundary condition imposed by the new surface source, the annular ring of inner radius ‘a’. Furthermore, a modified Equation (2.7), described in detail in section 2.3.4, will be used as the objective function to fit to the experimental data.

Surface waves are known to travel below the surface with the penetration depth being a function of surface wave wavelength [27]. For this study, it is expected that the surface wave wavelengths will fall in the range of 2–30 mm. The low frequency waves will correspond to the larger wavelengths and will penetrate all skin layers, and beyond, even to the subcutaneous fat and
muscle, while the high frequency waves will only affect the epidermis layer. Currently, there is no known theory of how each layer will affect the wavelength and attenuation of the surface wave at the surface itself. With the focus of this chapter being on model identification of healthy human skin measured at the surface, the interactions between the layers of skin are neglected and only the skin as a whole is modeled.

Several types of viscoelastic models are used to estimate material parameters; see Figure 2 for mechanical analogies. Each of these models, mathematically represented in Table I, represent the dynamic shear modulus $G$. The fractional models—spring-pot and fractional Voigt—represent models derived from fractional derivatives and the $\alpha$ parameter represents the fraction of viscosity, 0 being purely elastic and 1 being a viscous fluid.
2.3 **Methods: Skin OE**

2.3.1 **Apparatus**

Mechanical wave motion was induced using a custom designed ring (annular disk) actuator shown in Figure 3. Three preloaded piezos (P-840.1, Physik Instrumente GmbH and Co., Karlsruhe Germany) were arrayed in 120° increments around the outside of the ring, allowing for an even distribution of displacement and clear line of sight for the LASER. The largest usable diameter ring is 62 mm and smaller sized rings could be nested concentrically within the larger ring as desired. For this study only 2 ring sizes were used: 62 mm for the Ecoflex sample, and 25.4 mm for the human subjects. The annular actuator sub assembly was then attached to a box frame composed of 6061 Al, which provided the fixed based.
Table I. Viscoelastic model parameters in the frequency domain representing the dynamic shear modulus separated into real and imaginary parts; also referred to as the storage modulus and the loss modulus, respectively.

<table>
<thead>
<tr>
<th>Viscoelastic Model</th>
<th>Storage Modulus</th>
<th>Loss Modulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxwell</td>
<td>$\frac{\omega^2 \eta^2 \mu_0}{\mu_0^2 + \omega^2 \eta^2}$</td>
<td>$\frac{\omega \eta \mu_0^2}{\mu_0^2 + \omega^2 \eta^2}$</td>
</tr>
<tr>
<td>Voigt</td>
<td>$\mu_0$</td>
<td>$\omega \eta$</td>
</tr>
<tr>
<td>SLS</td>
<td>$\frac{\mu_0 \mu_1^2 + \omega^2 \eta^2 (\mu_0 + \mu_1)}{\mu_1^2 + \omega^2 \eta^2}$</td>
<td>$\frac{\omega \eta \mu_1^2}{\mu_1^2 + \omega^2 \eta^2}$</td>
</tr>
<tr>
<td>Spring-Pot</td>
<td>$\mu_0 + \mu_1 \omega^\alpha \cos \left(\frac{\pi}{2} \alpha\right)$</td>
<td>$\mu_1 \omega^\alpha \sin \left(\frac{\pi}{2} \alpha\right)$</td>
</tr>
<tr>
<td>Fractional Voigt</td>
<td>$\mu_0 + \mu_1 \omega^\alpha \cos \left(\frac{\pi}{2} \alpha\right)$</td>
<td>$\mu_1 \omega^\alpha \sin \left(\frac{\pi}{2} \alpha\right)$</td>
</tr>
</tbody>
</table>

Early preliminary tests of the experiment revealed that approximately one wavelength should be visible inside the actuator ring for quality estimates of the shear modulus, otherwise the fitting algorithm, described later, suffers from too many possible solutions. Therefore, separate ring sizes had to be used for the phantom and human experiments to meet the requirement, as the phantom used is stiffer (longer wavelengths at the same frequency) than human skin. The scale of the apparatus in no way affects the wave pattern.
Figure 3. Schematic section view of the experimental setup. (1) Location of where the Ecoflex sample or human forearm is placed, rectangle represents a simple section view of an Ecoflex sample. (2) Al 6061 box frame. (3) Three preloaded piezos. (4) SLDV LASER. (5) Annular mechanical radiator. Not shown is the SLDV head located approximately 300 mm above the sample surface and the third piezo.

Measurement of vibrations were performed using a scanning LASER Doppler vibrometer (SLDV) (PSV-400, Polytec Inc., Hopkinton, MA) with a visible light helium-neon LASER of 632.8 nm wavelength. The PSV-A-410 close up lens was used together with the #2 diopter which resulted in a maximum field of view of 70 mm × 55 mm and a spot size of 40 μm. The SLDV uses the Doppler principle to determine surface velocity of a point in the Z-direction; see coordinate frame in Figure 111. Software and control hardware was included with the PSV-400 system, which
processed the FFT on the recorded time signal. Periodic chirp waveforms with a frequency range of 100–1000 Hz were generated using the internal PSV-400 signal generator. Surface wave displacement ranged from 50–300 nm across the entire frequency spectrum.

2.3.2 **Ecoflex Sample Preparation**

An Ecoflex phantom sample (ECOFLEX-0010, Smooth-On, Inc., Easton, Pennsylvania) was used to validate the method as it can be directly compared to similar studies [26], [30], [31]. A homogenous sample 140 mm in diameter and 20 mm thickness was used. Preparation of the sample comprised multiple steps. Parts A and B were mixed at a 1:1 ratio, then placed in a vacuum chamber to pull all the air bubbles out of the mixture. Removing the air bubbles took approximately 15 min at 51 cmHg. The bubble free mixture was then poured into the mold and allowed to cure for 24 h. The mold required use of mold release agent (Ease Release 200, Smooth-On, Inc., Easton, Pennsylvania) which was allowed to dry for 20 min before pouring of the mold.

2.3.3 **Experimental Procedure**

All scans consisted of a single line of points across the diameter of the sample inside of the ring shown in Figure 3. Specifications of each scan can be seen in Table II. Spatial resolution was chosen so that the smallest estimated wavelength, using test scans and results from [26], would have at least 10 points and thereby ensuring the Nyquist criterion was not violated. The phantom study consisted of 1 sample measured in 6 trials. The sample was positioned under the ring actuator with a slight amount of preload (approximately 1–2 mm indentation) to ensure the sample was fully seated against the actuator surface. Ecoflex scans consisted of 6 trials and human scans of 3 trials, with each trial being separated by removing the sample/subject and then replacing it back into position. This was done to allow the subject time to rest after each scan and assess repeatability. Subjects were scanned in a flat area on the volar forearm.
All testing of human volunteers was done with approval of the University of Illinois at Chicago Institutional Review Board.

### Table II. Applicable specifications used in each experiment.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Ecoflex Sample</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of View</td>
<td>63 mm</td>
<td>25 mm</td>
</tr>
<tr>
<td>Spatial Resolution</td>
<td>0.377 mm</td>
<td>0.239&lt;sup&gt;a&lt;/sup&gt; mm</td>
</tr>
<tr>
<td>Frequency Range</td>
<td>200-1000 Hz</td>
<td>100-1000 Hz</td>
</tr>
<tr>
<td>Frequency Resolution</td>
<td>25 Hz</td>
<td>12.5 Hz</td>
</tr>
<tr>
<td>Trials</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Density</td>
<td>1030 kg m&lt;sup&gt;-3&lt;/sup&gt;</td>
<td>1100 kg m&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poisson’s Ratio</td>
<td>0.495</td>
<td>0.495</td>
</tr>
<tr>
<td>Averages</td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Resolution was slightly smaller for subjects 1–3 (0.2065 mm for subjects 1, 2 and 0.2153 mm for subject 3).

*Note:* Poisson’s ratio was chosen based on [22] and chosen to be slightly less than incompressible (0.495). Ecoflex density was based on [31], and Human density was from [11], [21].

### 2.3.4 Data Post Processing

Post processing of the phantom data and skin data was performed in the following manner. First a spatial Butterworth bandpass filter was applied to remove waves larger than the actuator diameter and any high frequency noise; cutoffs were 40 mm on the low end and 2 mm on the high end. After application of the spatial filter all trials were run through the curve fitting algorithm to estimate the surface wave number which is related to the shear wave number by Eq. (2.5). Lastly, the estimated shear modulus was fit to various viscoelastic models to evaluate their quality of fit and robustness of parameters.
Experimental data was fit to Eq. (2.7) using the ‘Global Optimization’ toolbox provided by MATLAB. The algorithm used the same objective function as in the work by [26], and the objective function is given by:

\[
FRF_{obj} = X_1 e^{ix_2} \frac{I_0(iX_3(r - X_4))}{I_0(iaX_3)} + X_5
\] (2.8)

The principal parameter, \(X_3\), in Eq. (2.8) is the surface wave number. The other parameters represent the following: \(X_1\) amplitude (required to correct amplitude), \(X_2\) phase (not all measurements were made at exactly zero start phase), \(X_4\) symmetry shift (out of phase piezos could shift the center focal point of the wave pattern), and \(X_5\) zero offset (compensation for reflected compression waves). The curve fitting algorithm in this study used the nonlinear curve fit function, ‘lsqcurvefit’, with the ‘levenberg-marquardt’ search algorithm, which minimized the error function:

\[
\text{Error} = \sum_{k=1}^{n} (FRF_{obj}(X, r_k) - FRF_k)^2
\] (2.9)

With, \(k\), being each data point, and \(n\), the total number of data points. The advantage of this algorithm was the ability to estimate complex parameters, and unbounded parameters. To further increase the accuracy of the curve fit, the Jacobian of the objective function was also manually derived. With 5 complex parameters to estimate, the curve fit was sensitive to local minima. Therefore, 10 random start positions were chosen, and the best fit was decided using the highest coefficient of determination or \(R^2\). The number of random start points were chosen based on more exhaustive searches which did not yield an improvement in results.
After estimating the shear modulus, viscoelastic models were fit to each trial and the viscoelastic parameters of each trial were then averaged. The algorithm to fit the viscoelastic models was almost identical to the previous step, the only difference being rejection of outliers. Rejection of outliers was critical in the evaluation of the quality of the viscoelastic models, particularly with respect to the $R^2$ parameter, because the outliers would cause a bias that lowered $R^2$ even though visually the fit was fine. There is no standard way to remove outliers in nonlinear regression. Outliers were deemed to be data points that were 2 standard deviations from the residual error mean of the curve fit. These outliers were rejected and curve fits were rerun a second time again rejecting any outliers. This type of feedback outlier rejection is similar to the method used in [32].

2.4 Results: Skin OE

2.4.1 Ecoflex Phantom Results

Examples of a typical curve fit to Eq. (2.8) at 200, 600, and 1000 Hz are given in Figure 4. From this plot it can be seen that as the frequency increases the coefficient of determination decreases in quality of fit. The 200 and 600 Hz plots show the effect of a static offset in the results as the data does not clearly oscillate about zero. This was accounted for in the curve fit equation as a static complex offset (parameter $X_5$). For the 1000 Hz plot another phenomena that was not accounted for in the curve fit equation can be seen near the source, particularly evident in the real part. The wave near the source, $|r| \geq 15$ mm, does not oscillate about zero yet further away, $|r| < 15$ mm, the oscillation returns to oscillate about zero.
Figure 4. Curve fit of frequency response function to experimental surface wave data. From left to right is 200, 600, and 1000 Hz curve fits from trial 2 Ecoflex data. The coefficient of determination is given inside the box for each plot.

The derived shear modulus was then fit to the five viscoelastic models in Figure 5. From the coefficient of determination and visually, it can be seen that the fractional Voigt model, spring-pot, and SLS models have better fits than the Maxwell and Voigt models. For each model the outlier rejection algorithm rejected different frequencies and can be seen as missing points. However, all models started with the same data points prior to outlier rejection. The shear modulus dispersion curve is close to monotonically increasing starting from 300 Hz for the storage modulus and 400 Hz for the loss modulus. A supplemental plot was added to Figure 5 which shows the relation between the storage and loss modulus. The data, in black solid circles, has a broad linear profile in Figure 5(f); this is in contrast to the Voigt and Maxwell models which have constant and curved profiles, respectively.
**Figure 5.** Viscoelastic model fits for trial 2 of Ecoflex phantom. Plots (a)–(e) show the dispersion curve of the real and imaginary components of the estimated complex shear modulus. (f) All viscoelastic model curves including the experimental data of the loss modulus versus the storage modulus.
The mean parameter values ± the standard deviations of the viscoelastic models are given in Table III. The 2nd column in Table III is the mean $R^2$ coefficient used to evaluate mean quality of fit for all 6 trials. The fractional Voigt model and the spring-pot model have identical quality of fits; however, the viscoelastic parameters vary significantly from one another. Indentation testing measured the static shear modulus at 12.5 kPa and is used as a comparison to the accuracy of the $\mu_0$ parameter. Table IV is used to compare data to literature using the same material type and similar but not identical elastography techniques.

**Table III.** Mean viscoelastic model parameter values for Ecoflex sample.

<table>
<thead>
<tr>
<th>Viscoelastic Model</th>
<th>$R^2$</th>
<th>$\mu_0$ (kPa)</th>
<th>$\mu_1$ (kPa)</th>
<th>$\mu_\alpha$ (kPa $s^\alpha$)</th>
<th>$\eta$ (Pa s)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional Voigt</td>
<td>0.93</td>
<td>17.0 ± 5.0</td>
<td>1.33 ± 0.50</td>
<td>0.43 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring-Pot</td>
<td>0.93</td>
<td>2.35 ± 1.06</td>
<td>0.26 ± 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLS</td>
<td>0.90</td>
<td>12.5 ± 6.4</td>
<td>20.0 ± 11.5</td>
<td>3.42 ± 1.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxwell</td>
<td>0.64</td>
<td>22.2 ± 11.0</td>
<td></td>
<td>16.4 ± 7.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voigt</td>
<td>0.78</td>
<td>17.8 ± 8.4</td>
<td></td>
<td>2.01 ± 1.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note:* The plus minus error is one standard deviation. Also included is the mean correlation coefficient ($R^2$) for each model. Not all models have the same parameters; spaces are left blank where this occurs.

To analyze the variability of each parameter the coefficient of variation was used and is the standard deviation divided by the mean. The two parameter models were compared in Figure 6 left, and three parameter models in Figure 6 right. In both the 2 and 3 parameter fractional models (fractional Voigt, spring-pot) most parameters had lower coefficients of variation than the integer models.
Table IV. Comparison of Ecoflex model parameters to literature using models, standard linear solid and fractional Voigt.

<table>
<thead>
<tr>
<th>Study</th>
<th>$\mu_0$ (kPa)</th>
<th>% Error</th>
<th>$\mu_1$ (kPa)</th>
<th>% Error</th>
<th>$\eta$ (Pa s)</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>12.5</td>
<td></td>
<td>20</td>
<td></td>
<td>3.42</td>
<td></td>
</tr>
<tr>
<td>[26]</td>
<td>13.3$^a$</td>
<td>-6.4</td>
<td>35.3</td>
<td>-76.5</td>
<td>18.1</td>
<td>-429</td>
</tr>
<tr>
<td>[30]</td>
<td>13.3$^a$</td>
<td>-6.4</td>
<td>27.5</td>
<td>-37.5</td>
<td>17.8</td>
<td>-420</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>$\mu_0$ (kPa)</th>
<th>% Error</th>
<th>$\mu_\alpha$ (Pa s$^\alpha$)</th>
<th>% Error</th>
<th>$\alpha$</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>17.0</td>
<td></td>
<td>1329</td>
<td></td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>[26]</td>
<td>13.3$^a$</td>
<td>21.8</td>
<td>2038</td>
<td>-53.3</td>
<td>0.33</td>
<td>23.0</td>
</tr>
<tr>
<td>[30]</td>
<td>13.3$^a$</td>
<td>21.8</td>
<td>350.8</td>
<td>73.6</td>
<td>0.55</td>
<td>-28.0</td>
</tr>
</tbody>
</table>

$^a$This parameter was not estimated but experimentally measured using indentation method.

2.4.2 Human Results

The human in vivo results first start with the curve fitting of Eq. (2.8); typical examples of this complex curve fit can be seen in Figure 7. There does not appear to be as much static offset from zero as was observed in the phantom case. Note that the FOV for the human study is smaller than that of the phantom study; this is due to the large difference in static stiffness of the two materials. Overall, skin is softer than Ecoflex material, and therefore, needs a smaller FOV to capture multiple wavelengths in a single plot. The softer tissue of skin allowed for a slightly larger bandwidth 100–1000 Hz as compared to 200–1000 Hz for the phantom study. Looking at Figure 7(c), it can be seen that wave profile is asymmetric about the $R = 0$ line of the surface wave. Another item of note from Figure 7 is the $R^2$ coefficient decreasing as frequency increases.
Comparing subjects (along columns Figure 7), it can be visually seen, by wavelength alone, that subjects vary in stiffness at the same frequency.

\[ \text{Figure 6. Coefficient of variation of Ecoflex phantom for 2 (left) and 3 (right) parameter viscoelastic models. Parameter name is identified inside the associated bar.} \]
Figure 7. Typical curve fits for skin in vivo experiments. The columns represent 3 frequencies of 100, 600, and 1000 Hz, respectively, and the rows represent subjects. Row 1 subject 1 trial 3 ((a)–(c)), row 2 subject 3 trial 3 ((d)–(f)), row 3 subject 7 trial 2 ((g)–(i)). The y-axis is the FRF amplitude, and the x-axis is the radial coordinate. Inside each plot is the coefficient of determination to assess goodness of fit.

A typical dispersion curve of the shear modulus in shown in Figure 8, and it can be seen that the storage and loss moduli all have a generally monotonically increasing curve. The best fit, in terms of the $R^2$ coefficient, is the SLS model, and the worst fit is the Maxwell model, see Table V. From the Voigt model fit in Figure 8, it can be seen that the assumption of a constant storage modulus does not resemble the dispersion curve shown. Also, for the Maxwell model an estimate
of a loss modulus that decreases with frequency does not reflect the measured dispersion curve. The best fit models are then fractional Voigt, spring-pot, and SLS.

Figure 8. Viscoelastic models fit to complex shear modulus (human skin) of subject 3 trial 3. FV = Fractional Voigt, SP = spring-pot, SLS = Standard Linear Solid, Max = Maxwell, and V = Voigt. The $R^2$ coefficient is given in the box next to each models name.
Table V. Mean viscoelastic model parameter values for all human volunteers.

<table>
<thead>
<tr>
<th>Viscoelastic Model</th>
<th>R²</th>
<th>$\mu_0$ (kPa)</th>
<th>$\mu_1$ (kPa)</th>
<th>$\mu_\alpha$ (kPa s$^\alpha$)</th>
<th>$\eta$ (Pa s)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional Voigt</td>
<td>0.89</td>
<td>6.4 ± 5.8</td>
<td>0.78 ± 0.33</td>
<td>0.38 ± 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring-Pot</td>
<td>0.88</td>
<td>2.40 ± 1.22</td>
<td>0.27 ± 0.04</td>
<td>0.27 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLS</td>
<td>0.93</td>
<td>12.7 ± 6.8</td>
<td>19.9 ± 10.7</td>
<td>3.54 ± 1.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxwell</td>
<td>0.67</td>
<td>22.6 ± 10.8</td>
<td>16.6 ± 7.84</td>
<td>2.02 ± 1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voigt</td>
<td>0.71</td>
<td>18.1 ± 8.7</td>
<td></td>
<td>2.02 ± 1.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The plus minus error is one standard deviation. Also included is the mean correlation coefficient ($R^2$) for each model. Not all models have the same parameters, spaces are left blank where this occurs.

For an additional measurement of the variability of models, the coefficient of variation is shown in Figure 9. In Figure 9, only the models with the same number of parameters can be compared to each other. It can be seen from Figure 9 that the fractional Voigt model has parameters that are more stable than the SLS model in 2 out of 3 parameters. For the 2 parameter models, the spring-pot model is more stable in only 1 out of 2 parameters. For both the 2 and 3 parameter models the $\alpha$ parameter has the smallest variation of all.
Figure 9. Coefficient of variation of human skin for 2 (left) and 3 (right) parameter viscoelastic models. Parameter name is identified inside the associated bar.

Finally a comparison to the literature is shown in Table VI. Table VI is not exhaustive; however, it represents the literature using dynamic surface wave excitation with estimation of the shear modulus. Two types of data is can be seen in the literature, mono-frequency data that does not use a model, and multi-frequency data with a model. In order to be consistent in comparison, the fractional Voigt model, from this dissertation, is extrapolated to the single points of frequency in references [21], [22], and extrapolated to the center frequency of references [9], [25]. These extrapolations can be seen in the 5th column of Table VI, and directly compared to the reference data in the 4th column. The percent error of the current $G'$ to the reference data is given in the last column.
Table VI. Comparison of the current data presented in this dissertation to literature. Each reference (1st column) is compared to the current data (5th column) using the frequency of the referenced study (3rd column). If a model was used, the central frequency was used to be consistent with the single frequency references. The model used in the current column was the fractional Voigt model.

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Hz</th>
<th>(G') (kPa)</th>
<th>(G'') (kPa)</th>
<th>Current @ Hz</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>[21]\textsuperscript{a}</td>
<td>None</td>
<td>300</td>
<td>1980</td>
<td>17.7</td>
<td>1.107x10\textsuperscript{4}</td>
<td></td>
</tr>
<tr>
<td>[22]\textsuperscript{a}</td>
<td>None</td>
<td>50</td>
<td>33.8</td>
<td>12.1</td>
<td>178.8</td>
<td></td>
</tr>
<tr>
<td>[9]</td>
<td>Voigt</td>
<td>200</td>
<td>10.6</td>
<td>19.0</td>
<td>-34.2</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} These studies only measured the real part of the phase speed, so their \(G'\) values are an approximation.

2.5 Discussion: Skin Elastography

Diagnosing and monitoring skin diseases using a non-invasive elastography technique, such as the one developed in this dissertation, requires that a known and consistent model of healthy skin can be found and that the technique itself is repeatable. This study has shown that the proposed method is repeatable and works well enough to warrant further development. A potential repeatable model has been found using the fractional order models. These statements will be addressed by examining the quality of the fits in the phantom and skin results, and then finally looking at the stability of the models as well as comparing them to literature.

It can be seen in the phantom curve fits of Figure 4, that Eq. (2.7) can be successfully fit to the experimentally measured GFS wave curve and that the mechanical setup does produce a symmetric GFS wave. However, comparing Figures 4 and 7 it is evident that, overall, human skin
was a better fit to the objective function than the Ecoflex phantom. For both the phantom and \textit{in vivo} experiments as frequency increases quality of fit went down. However, even as the quality of fit decreased, by examining Figures 4 and 7 closely it can be seen that the wavelength is accurately estimated even though attenuation is not. This should not have affected the quality of the overall shear modulus estimate; as the storage modulus and the loss modulus are both dependent on the real and imaginary parts of $k_2$ [33]. There will still be errors associated with the inaccurate measurement of attenuation, but both the storage modulus and the loss modulus will be affected by this.

Many reasons for inaccuracies in the overall quality of fit are from known mechanical issues encountered during the study. Imperfect phase coherence between the 3 piezos led to 2 problems: the loss of symmetry in the wave profile about the $r = 0$ line, and a slight linear tilt (i.e. $Y = rx$) of the wave curve. Also, the static indentation of the actuator ring creates a static strain curve not accounted for by the objective function. For this study it was not the intention to measure the impact of these sources of error. However, they can be overcome by improvement to the mechanical setup, such as finding a minimal preload to minimize the static strain curve, and use of a single element ring piezo to remove phase incoherence. Inaccuracies from unknown phenomena could be any or none of the following: wave reflections, compression waves, and layered media. Layered media has been found to affect the Young’s modulus in [22]; however, there is to date no predictable relation between penetration depth of surface waves to the wave profile and speed at the surface. Compression waves can be easily accounted for by adding the static component to Eq. (2.7) and reflections can be minimized by averages and sample size. All three of the previously stated unknowns would likely have the largest impact on the estimation of
the loss modulus from the interference of wave patterns. Finally, other potential unknowns are the possibility of multiple surface waves [34] and complex Poisson’s ratio [35], [36].

A viscoelastic model that fit well to the complex shear modulus of skin and has minimal variability between volunteers was a goal of this study. From the results in Figure 8 and Table V the model that best meets this goal is the fractional Voigt model or the spring-pot model, both of fractional order. This conclusion is based primarily on the \( \alpha \) parameter coefficient of variation (0.14–0.15) and the model \( R^2 \) of 0.88–0.89. The remaining parameters (\( \mu_0 \) and \( \mu_\alpha \)) in these two models still have a significantly high coefficient of variation 0.48–0.90. Reasons for the high variability could be due to changes in hydration levels of the skin [11], [12], [22], or Langer lines as found in [22]. It has also been found by [13] that changes in age can lead to physical changes in the skin.

For validation of these results a comparison to literature would be a preferred method and a small comparison is found in Tables IV and VI. It is however, particularly difficult to compare a dynamic complex shear modulus as it is dependent on frequency. Also, many studies such as [16], [24], [37] use static methods or time dependence, both of which are not directly comparable to this study. It is then determined in this study that fitting a viscoelastic model to as wide a bandwidth as possible, as in [26], [30], would make comparison between dynamic elastography methods more practical. This is most evident in Table VI of references [9] and [25], where comparing even a poor fitting model such as the Voigt model results in a better comparison of viscoelastic properties between studies than just a single frequency. It is then suggested for further studies to make use of large bandwidths and viscoelastic models.

In conclusion, using GFS waves, the complex shear modulus of human skin can be measured over a large bandwidth in a noninvasive manner. It was found that using viscoelastic
models provides a reliable and robust method when comparing between different studies. The best viscoelastic model for skin in terms of variability is the fractional Voigt model. However, in terms of best curve fit the model of choice would be the standard linear solid model; but, it is not recommended due to its high variability from subject to subject. Continuation of this technology will include larger studies with more volunteers as well as volunteers with skin disease. Also, to increase model accuracy, investigation into the relationship between surface wavelength and layered material will be conducted.
3 MOUSE BRAIN MRE USING SLIM MRE METHODS

3.1 Background

Magnetic resonance elastography (MRE), is a phase contrast MRI imaging technique that can image the spatial distributions of material properties, called elastograms or stiffness maps [6]. A mechanical wave is applied to a material, and the resulting wave motion is encoded in the phase image by the motion encoding gradients (MEGs). The wave image is then processed by an inversion algorithm to produce the elastogram [38]. Contrast in the elastogram is derived from variations in the wave field. For example, a hard material has longer wavelengths than a soft tissue, and likewise a more viscous tissue will have greater attenuation. This concept has found success as a metric in characterizing pathological tissue changes in, but not limited to, the brain [39]–[42], liver [43]–[45], and prostate [46], [47].

Much success has been made using MRE as a diagnostic tool for human imaging; this is true as well for the animal model. For instance, many studies have focused on the murine model of the brain to assess multiple sclerosis [48], Alzheimer’s [49], tumors [50], and traumatic brain injury [51]. Much of the MRE work involving animal models have been conducted on tissue above the torso or in euthanized animals. Reason being, MRE imaging of in vivo animal torso requires gating or averaging due to motion artifacts, and with 4-8 temporally shifted scans for each motion direction, scan times will be significantly longer than without gating. Methods to reduce MRE scan time could then potentially increase the breadth of organ types imaged in laboratory animals.

Currently, there are methods to reduce MRE scan times already in practice. For instance, use of fast imaging pulse sequences such as EPI have been used [52], [53], or fractional encoding [54], have worked well, but all at a cost of SNR or phase encoding efficiency. Alternatively, time reduction can be made by assuming that the wave propagation is planar and, therefore, it is
necessary to encode only one motion direction, as suggested in [55]. However, this is not always practical as it depends on the type of actuator and setup used. It has also been shown possible to use multiple imaging methods simultaneously, making more efficient use of total scan time [56].

Recently, a novel method to simultaneously encode all three motion directions, called sample interval modulation (SLIM), was developed [7]. In SLIM, all three motion directions are encoded in a single MRE scan by varying the start times of the MEGs relative to the vibration actuation start time. This has the capability to reduce scan times by a third, with only a small decrease in SNR. This is due to the increase in TE time necessary for the MEG start time variation. This technique has been shown to work well in the human brain and was not impacted by the slight decrease in SNR [57]. However, it has yet to be tested in the murine model.

The purpose of this study is to assess the feasibility of the SLIM-MRE technique for in vivo mouse brain MRE, and to assess a modified SLIM method that does not require an increase in TE time. The modified SLIM technique works by varying the phase of the MEG rather than the MEG start time. Assessment will be based on the similarity of wave and elastogram images of each method to the conventional MRE method. Finally, the spatially averaged shear modulus values will be compared to conventional using the Wilcoxon rank sum test.

### 3.2 Theory: MRE

The quantity of phase accumulation \( \phi \) from vibration induced motion, at a frequency \( f \), is the principal equation in MRE, and is given by the time integral of the scalar product of the motion \( \mathbf{u} \) and motion encoding gradient (MEG) \( \mathbf{G} \) [6]:

\[
\phi(s) = \gamma \int_0^{s+\tau} \mathbf{G}(t) \cdot \mathbf{u}(t) dt
\]  

(3.1)
In conventional MRE, the total phase accumulated for each phase offset is separated into individual scans for each spatial direction. Typically, a complex phase signal is desired for inversion methods used in post processing of data. Therefore, $\phi$ is discretized by acquiring $N$ discrete time steps at a sampling frequency of $f_s = nf/N$ [7]; enabling the complex valued $\Phi(nf)$ to be determined by the Fourier transform of $\phi(t)$. The discretized solution of Eq. (3.1) is given by:

$$\phi_n = \phi_0 \cos(\theta_0 - \psi_n) \quad (3.2)$$

Here $\phi_0$ is a function of gradient strength, vibration frequency, vibration amplitude, and the number of MEGs, $\theta_0$ is the initial phase of the vibration, and $\psi_n$ is the difference in phase between the MEG and the vibration. Sampling Eq. (3.2) by:

$$\psi_n = \frac{2\pi n}{N} \quad (3.3)$$

encodes the complex phase signal in the first frequency component of $\Phi(nf)$. Two more frequency components ($n = 2, 3$) are then left empty, and can be used to encode the remaining spatial directions by altering the sampling frequency.

For SLIM-MRE, all spatial directions are acquired simultaneously resulting in a summation of Eq. (3.2) [57].

$$\phi_n = \phi_0 \sum_{j=1}^{3} \cos(\theta_0 - \psi_n) \quad (3.4)$$

With $\psi_n$ redefined as:

$$\psi_n = j \frac{2\pi n}{N} \quad (3.5)$$
Each direction \( j \) can now be sampled at a different frequency, and the Fourier transform of Eq. (3.4) will have each motion direction placed in a separate frequency bin.

For this study we are concerned with the method in which the phase difference \( \psi_n \) is achieved. Previous studies [7], [57] have varied \( \psi_n \) by delaying the start time of the MEG, but keeping the start phase of the MEG constant; we will call this method SLIM phase constant (SLIM-PC). The second method, SLIM phase varying (SLIM-PV), varies the phase of the MEG and keeps the start time constant. Figure 10, shows the direct comparison of the two methods for 8 time steps. Notice that the SLIM-PC method requires an increase in TE duration. On the other hand, SLIM-PV varies between flow compensated gradient shapes and non-flow compensated shapes.

3.3 Methods: In Vivo Mouse Brain MRE

In this study, analysis of two methods of SLIM-MRE applied to the in vivo mouse brain were compared to the conventional MRE technique. Six female C57BL/6 adult mice were used (aged 3 – 8 months), and all experimental procedures were approved by the University of Illinois at Chicago’s Institutional Animal Care and Use Committee. MRE scans were performed using an Agilent 9.4 T small animal scanner (Agilent Technologies, Santa Clara, CA) with a 38 mm inside diameter quadrature birdcage RF coil.

Animals were initially anesthetized using 4.0% isoflurane in oxygen until a lack of motor response was observed, and then anesthesia was maintained at a 1.0 – 2.0% mixture throughout the scans. A model 1030 SA animal monitoring system (SA Instruments; Stony Brook, New York) was used to measure body temperature and respiratory function. Body temperature was maintained with warm air circulated from the instrument end of the magnet.
Shear waves were induced into the brain by a bite bar actuator, Figure 11. The mouse was placed into the actuator by sliding the nose cone back towards the piezo to clear the bite bar. Then the mouse could be placed into the cradle, and once a secure bite was confirmed the nose cone would be slid back over the mouse head. The nose cone, bite bar, and piezo mount were all made from Stereolithography material (Polylactide Resin 4043D, NatureWorks® LLC, Minnetonka, MN) and were printed on a MakerBot 3D printer (MakerBot Replicator 5th Gen., MakerBot® Industries, LLC, Brooklyn, NY). Vibration was induced by a nonmagnetic amplified piezo actuator (APA60S, Cedrat Technologies, Meylan Cedex, France) which provided 50 µm peak to peak displacement for a 10 g load with a resonance at 1,500 Hz. The mouse head was only secured
at the bite bar, therefore, shear waves propagating in all of the coordinate axes of the magnet were created.

Figure 11. Bite bar actuator and anesthesia setup for MRE imaging. 1) Approximate mouse representation, 2) adjustable nose cone, 3) bite bar, 4) piezo actuator, 5) piezo attachment base, 6) respiration pillow sensor, 7) outlet and inlet anesthesia lines.

Each animal underwent five MRE scans, 3 sequential scans of each direction using conventional MRE, and 1 each of SLIM-PC and SLIM-PV. In addition, a single mouse underwent, on a separate day, two full 3D conventional MRE scans for use as a base comparison. All MRE methods were based on a spin echo pulse sequence. To scan the entire mouse brain 24-30 slices were used, depending on mouse brain size. Isotropic voxels of 0.375 mm on a side were acquired with a FOV of 24 x 24 mm and 64 x 64 pixels. The repetition time and echo time were 1000/12.1 ms for conventional MRE and SLIM-PV and 1000/13.5 ms for SLIM-PC. MRE parameters were: 8
motion encoding gradients, 250 mT/m gradient strength, 8 time steps with 180° phase offsets for static phase noise subtraction, 1000 Hz vibration, and a total scan time of 51 min for conventional MRE and 17 min for SLIM-MRE.

For data processing a 3D algebraic inversion method was employed. A Fourier transform was applied to the temporal wave images, and the complex waves, representing U, V, and W displacements, were then separated from the 2\textsuperscript{nd}, 1\textsuperscript{st}, and 3\textsuperscript{rd} frequency bins, respectively. Next, the complex wave images were 3D spatially filtered with a low pass Butterworth filter with a cut off of 3 pixels, which corresponds to shear waves with 1.12 mm wavelengths. Then the curl was applied to remove any contribution from compression waves and/or rigid body motion, and the 3D algebraic inversion was applied to the curl data in a least squares sense [38].

The metric of mean percent pixel error (MPPE) was used to compare the two SLIM encoding methods to the conventional encoding method. This measure is determined simply by directly comparing each individual pixel from all slices and then taking the mean:

\[
MPPE = \frac{1}{\text{Total No. of Pixels}} \times 100 \left( \frac{\text{Image Pixel} - \text{Reference Image Pixel}}{\text{Reference Image Pixel}} \right) \quad (3.6)
\]

The reference image in this case is always the conventional MRE images. Also, to aid in assessment of the MPPE metric a base comparison of one mouse using two conventional MRE scans was made. Finally, the spatially averaged complex shear moduli of all mice, averaged from a 3-pixel eroded visually segmented ROI of the brain tissue [58], are compared using a pairwise Wilcoxon rank sum test for each method. A failure to reject the null hypothesis (i.e. p > 0.05) signifies that the two groups can be considered to be from the same continuous distribution.
3.4 Results: *In Vivo* Mouse Brain MRE

For a more relative measure of the MRE methods in this study, a base comparison of conventional MRE to conventional MRE was performed. The results of the base compare can be seen in Table VII. From Table VII, it is clear that the variability in conventional MRE from scan to scan for this study is quite significant with similar ranges of approximately 15-24% error for both curl wave images and shear modulus maps. This demonstrates that a significant amount of noise is present for the imaging parameters used, for this study, and similar errors can be expected for the SLIM MRE methods if they compare well. Even with the significant MPPE errors, the spatially averaged shear modulus values stayed relatively stable with $G''$'s of $7.34 + i4.01$ kPa and $7.12 + i4.19$ kPa for scans 1 and 2, respectively; giving an error of -3.1% for the real part and 4.4% for the imaginary part.

**Table VII.** Conventional MRE comparison for one mouse. Listed are the MPPE for the complete set of MRE images in the following order: curl wave images real and imaginary for each direction, then the shear modulus maps for storage and loss moduli.

<table>
<thead>
<tr>
<th>Image Type</th>
<th>MPPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re[$Q_x$]</td>
<td>24.0</td>
</tr>
<tr>
<td>Im[$Q_x$]</td>
<td>17.5</td>
</tr>
<tr>
<td>Re[$Q_y$]</td>
<td>20.4</td>
</tr>
<tr>
<td>Im[$Q_y$]</td>
<td>14.8</td>
</tr>
<tr>
<td>Re[$Q_z$]</td>
<td>16.9</td>
</tr>
<tr>
<td>Im[$Q_z$]</td>
<td>17.5</td>
</tr>
<tr>
<td>$G'$</td>
<td>14.9</td>
</tr>
<tr>
<td>$G''$</td>
<td>26.8</td>
</tr>
</tbody>
</table>
Visually, from Figure 12, it can be seen that the wave images, post application of the curl (curled wave field), are similar. The variations in the images seem to be mainly associated with amplitude variations, yet there are some variations in the actual wave pattern itself, especially for the SLIM-PV case. An interesting note is that the imaginary wave images of the SLIM-PV case seem to have a more similar comparison than the real wave images. This is especially evident at the external boundaries of the brain in the real part of the curled wave field images. Table VIII, displays the MPPE for each mouse of the curled wave field images. The SLIM-PC method shows good agreement with the conventional MRE images, but MPPE errors are higher, approximately double, as compared to the base comparison results of Table VII. For the SLIM-PV case, the errors are significantly higher, however, there is a marked reduction in error in the imaginary parts.

Comparison of the complex shear modulus, Figure 13, shows a visual similarity for the SLIM-PC method and for the SLIM-PV case but with more dissimilar regions. Yet, the high and low stiffness regions do appear to be generally located in the same regions, such as, the upper right and lower left corners of the brain. Table IX, gives the MPPE of all shear modulus images. It shows that $G'$ of the SLIM-PC method is comparable in error to the base result of $G'$, and the SLIM-PV method shows significantly less error than the curled wave fields. For both methods $G''$ increased in error as compared to $G'$.

Finally, the spatially averaged shear modulus values, Table X, are assessed. Comparison of the mean shear modulus values are good with percent errors of 1.4 – 4.8%. Figure 14, shows the pair wise Wilcoxon rank sum test for each method. This method gives a good idea of how well SLIM data performs in assessing groups. Both SLIM methods do not reject the null hypothesis with p-values > 0.05 for the storage and loss modulus. This suggest that the data sets can be considered to be from the same group.
Figure 12. Comparison of the complex wave image after application of the curl for conventional MRE and SLIM-MRE methods. Conventional MRE images are along the top row, SLIM-PC images the 2nd row, and SLIM-PV images along the bottom row. Each set of images inside the boxes represent a central slice of mouse 5 for each Cartesian direction (Q_X, Q_Y, and Q_Z). Also, the real and imaginary part is shown side by side. The curled wave data is dimensionless.
Table VIII. MPPE for all mice, both SLIM methods, curled wave field for each direction, and real and imaginary parts, designated by Re, and Im, respectively. The final column is the mean of all mice for the corresponding row.

<table>
<thead>
<tr>
<th>Method</th>
<th>$Q_n$</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Re[Qu]</td>
<td>27.6</td>
<td>42.5</td>
<td>21.8</td>
<td>21.7</td>
<td>40.9</td>
<td>38.3</td>
<td>32.1</td>
</tr>
<tr>
<td></td>
<td>Im[Qu]</td>
<td>41.8</td>
<td>23.2</td>
<td>23.0</td>
<td>21.3</td>
<td>47.5</td>
<td>24.1</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>Re[Qv]</td>
<td>41.3</td>
<td>32.5</td>
<td>26.5</td>
<td>19.5</td>
<td>27.3</td>
<td>46.6</td>
<td>32.3</td>
</tr>
<tr>
<td></td>
<td>Im[Qv]</td>
<td>44.1</td>
<td>35.0</td>
<td>22.2</td>
<td>19.8</td>
<td>34.0</td>
<td>18.9</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>Re[Qw]</td>
<td>26.3</td>
<td>29.6</td>
<td>21.0</td>
<td>23.8</td>
<td>22.7</td>
<td>35.3</td>
<td>26.4</td>
</tr>
<tr>
<td></td>
<td>Im[Qw]</td>
<td>49.3</td>
<td>27.5</td>
<td>22.6</td>
<td>19.2</td>
<td>29.2</td>
<td>52.6</td>
<td>33.4</td>
</tr>
<tr>
<td>SLIM-PC</td>
<td>Re[Qu]</td>
<td>59.9</td>
<td>74.0</td>
<td>69.5</td>
<td>72.1</td>
<td>79.6</td>
<td>50.1</td>
<td>67.5</td>
</tr>
<tr>
<td></td>
<td>Im[Qu]</td>
<td>53.0</td>
<td>28.3</td>
<td>28.5</td>
<td>25.6</td>
<td>60.7</td>
<td>28.1</td>
<td>37.4</td>
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<tr>
<td></td>
<td>Re[Qv]</td>
<td>79.9</td>
<td>55.7</td>
<td>62.3</td>
<td>46.8</td>
<td>51.5</td>
<td>73.7</td>
<td>61.6</td>
</tr>
<tr>
<td></td>
<td>Im[Qv]</td>
<td>33.5</td>
<td>44.4</td>
<td>29.0</td>
<td>25.5</td>
<td>40.7</td>
<td>19.9</td>
<td>32.2</td>
</tr>
<tr>
<td></td>
<td>Re[Qw]</td>
<td>50.3</td>
<td>86.3</td>
<td>67.6</td>
<td>83.2</td>
<td>49.2</td>
<td>70.9</td>
<td>67.9</td>
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<tr>
<td></td>
<td>Im[Qw]</td>
<td>60.7</td>
<td>31.1</td>
<td>30.7</td>
<td>22.3</td>
<td>31.9</td>
<td>67.0</td>
<td>40.6</td>
</tr>
</tbody>
</table>
Figure 13. Comparison of the complex shear modulus images of conventional MRE and SLIM-MRE methods for a single central slice of mouse 5. The columns from left to right represent the storage and loss moduli, respectively, and the rows designate the MRE method used. The magnitude image for this particular slice is given for reference. The black points represent rejected pixels based on a shear modulus threshold of $>30 \text{kPa}$ or $<50 \text{Pa}$. 
Table IX. MPPE for the complex shear modulus images (G*). SLIM-PC and SLIM-PV. G’ and G’’, represent the storage and loss moduli, respectively. The last column is the mean of all errors for all mice.

<table>
<thead>
<tr>
<th>Method</th>
<th>G*</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIM-PC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G'</td>
<td>19.9</td>
<td>18.5</td>
<td>16.7</td>
<td>17.2</td>
<td>16.5</td>
<td>20.2</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>G''</td>
<td>38.6</td>
<td>31.4</td>
<td>32.3</td>
<td>28.1</td>
<td>32.6</td>
<td>33.9</td>
<td>32.8</td>
<td></td>
</tr>
<tr>
<td>SLIM-PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G'</td>
<td>24.3</td>
<td>23.7</td>
<td>21.6</td>
<td>20.1</td>
<td>21.3</td>
<td>21.2</td>
<td>22.0</td>
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</tr>
<tr>
<td>G''</td>
<td>41.9</td>
<td>39.8</td>
<td>38.9</td>
<td>35.3</td>
<td>42.0</td>
<td>38.9</td>
<td>39.5</td>
<td></td>
</tr>
</tbody>
</table>

Table X. Spatially averaged shear modulus values for each mouse and method. All units are in kPa.

<table>
<thead>
<tr>
<th>Method</th>
<th>G*</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONVENTIONAL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>G'</td>
<td>4.88</td>
<td>5.62</td>
<td>6.21</td>
<td>6.72</td>
<td>7.23</td>
<td>4.91</td>
<td>5.93</td>
<td></td>
</tr>
<tr>
<td>G''</td>
<td>2.38</td>
<td>2.84</td>
<td>3.27</td>
<td>3.23</td>
<td>3.54</td>
<td>2.44</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>SLIM-PC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G'</td>
<td>4.91</td>
<td>5.40</td>
<td>6.21</td>
<td>7.17</td>
<td>7.07</td>
<td>5.28</td>
<td>6.01</td>
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</tr>
<tr>
<td>G''</td>
<td>2.34</td>
<td>2.75</td>
<td>3.29</td>
<td>3.62</td>
<td>3.52</td>
<td>3.00</td>
<td>3.09</td>
<td></td>
</tr>
<tr>
<td>SLIM-PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G'</td>
<td>4.79</td>
<td>5.29</td>
<td>5.95</td>
<td>6.85</td>
<td>6.85</td>
<td>5.11</td>
<td>5.81</td>
<td></td>
</tr>
<tr>
<td>G''</td>
<td>2.36</td>
<td>2.76</td>
<td>3.20</td>
<td>3.60</td>
<td>3.67</td>
<td>2.92</td>
<td>3.09</td>
<td></td>
</tr>
</tbody>
</table>
Figure 14. The pairwise Wilcoxon rank sum test scatter plots. Each method is compared to the conventional method and its corresponding p-value is shown with brackets across groups. The dark line is the median and the storage modulus is shown in the left graph with the loss modulus on the right.

3.5 Discussion: In Vivo Mouse Brain MRE

In this study, we have introduced a new methodology for implementing SLIM, called SLIM phase varying, that does not require an increase in echo time to encode all three motion directions simultaneously. Also, both SLIM methods, phase constant and phase varying, are tested for their feasibility for small animal in vivo MRE. Although the SLIM-PC method was previously successfully tested on phantoms [7] and human [57], the high field (9.4 T), high frequency (1000 Hz), and in vivo environment presents a unique challenge for the SLIM concept.

The SLIM-PC and SLIM-PV methods both demonstrate similarity to the conventional MRE method. In terms of shear modulus map similarity, the SLIM-PC method comes out on top
with significantly less MPPE and is comparable to the base comparison study of conventional to conventional. However, for spatially averaged shear modulus results the two methods are not significantly discernable. The Wilcoxon rank sum test concluded that data from SLIM-PC and SLIM-PV do not reject the null hypothesis and can be considered as data from the same group.

The comparisons to conventional are not absolutely similar, as expected, but are still higher than that of conventional MRE repeated scans. This study required a total 5 consecutive scans, therefore, resolution was kept relatively low to limit the duration each mouse was anesthetized and in the scanner. At 0.375 mm voxel resolution a typical wavelength measured only about 8-10 voxels. This had the effect of making the filter characteristic very sensitive to the cut-off frequencies chosen. For instance, rejecting one less or one more pixel could vary the spatial average as much as ±1 kPa. So, the cut-off was kept at three pixels to be conservative and likely resulted in incomplete noise reduction. Future implementation (not comparison studies) of SLIM will not have this problem; as the time reduction enabled by SLIM can allow for significantly increased resolution by using the saved time for averaging or longer TR.

Even with the low spatial resolution, shear modulus data compared quite well and in agreement with previous studies. For instance [59], demonstrated mean coefficients of variation for the shear modulus of 14-30%, using an advanced iterative inversion algorithm [60]; which is comparable to the MPPE found in this study. Also, for most images the shear modulus MPPEs are less than 37%, which is a measure found to represent a significant change in liver tissue [61], and significantly less than 37% for mean shear modulus values. Furthermore, increasing the ROI by reducing the voxel resolution will increase precision of the shear modulus [58].

A consequence of the SLIM method that could not be identified theoretically, is that of phase shifts. Theoretically, the variation of the start time, SLIM-PC, or phase, SLIM-PV, should
not create a phase shift in the acquired wave fields. However, this is not the case. A noticeable phase shift was detected in both SLIM methods but could be easily corrected for. It was found that the SLIM-PC method resulted in a direction specific phase shift; for direction $j = 1, 2, 3$ the phase was shifted by $-2\pi(j - 1)/N$ for $N = 8$. To then correct the phase shift, for comparison purposes, the wave images were multiplied by this phase shift. For SLIM-PV, the phase shifted by the same factor, however, there was an additional polarity shift to the real part of the wave image. The direct cause of these phase shifts could not be identified in this study, but it can be assumed to be caused by the hardware and/or software, especially with all three gradients on at the same time. The polarity shift, though, is more likely a result of the gradient shapes varying from flow compensated to non-flow compensated. These phase shifts do not seem to have a significant effect on the spatially averaged shear modulus values, but only on the wave image comparison do they have a more pronounced effect.

Mouse brain MRE benefits from high spatial resolution, due to the shorter wavelengths encountered at such high frequencies, and from full 3D wave field acquisition. With the actuator set to induce mainly planer shear wave motion it can be seen from Figure 12 that this is not the case. There is significant wave motion in all three directions and inversion accuracy would be lost if these directions were ignored. The time reduction capabilities of SLIM-MRE allowed for the acquisition of three directions in 1/3 the time of conventional MRE. Previous studies have shown good results with 1D inversion [55], [62], but often requires directional, bandpass filtering, and an assumption that the shear waves are propagating only in the imaging plane. Using the new SLIM methods the increase in scan time for 3D encoding is no longer an issue. The only downside is that gradient strength is now distributed among 3 directions resulting in a loss of encoding efficiency.
The new SLIM method developed in this study, SLIM-PV, has the advantage of no increase in TE time. An increase in SNR using SLIM-PV is not very significant for animal studies as many MEGs are used and the percent increase in TE becomes less prominent. For instance, in this study 8 MEGs were used, and had a total duration of 8 ms. The increase in TE for SLIM-PC was 0.5 ms (25% of vibration period times two for SE), a 6.25% increase. However, for human studies this may be a more significant factor in choosing the SLIM method as human studies use less MEGs and have longer vibration periods.

This study assessed the feasibility of SLIM-MRE for in vivo mouse studies, and developed a novel SLIM method that encodes all three motion directions without an increase in TE. Both methods show good agreement with the conventional MRE method. SLIM-PC, compares to conventional with less error in terms of the shear modulus maps, but requires an increase in TE. Finally, both methods show excellent spatially averaged shear modulus results with errors of 1.4-4.8%.
4 EX VIVO HUMAN PROSTATE MRE: PRELIMINARY RESULTS

4.1 Background

Prostate cancer (CaP), according to the World Health Organization, is the fifth leading cause of death in men. Diagnosing CaP starts with a digital examination, using the method of palpation to find regions of hard tissue, and includes blood testing for prostate specific antigens (PSA) [63]. If PSA is detected follow up diagnosis may be conducted with transrectal ultrasound (TRUS) guided biopsy [64]. T2-weighted and diffusion weighted MRI may be used as well to further analyze the CaP localization [65], [66].

Even with the advanced TRUS biopsy technique, multiple negative biopsies still occur in patients with elevated PSA [67]. Having to undergo multiple procedures with negative results can be a significant burden on the patient. Additionally, prostate biopsy can lead to complications such as; erectile dysfunction, urinary incontinence, and rectal bleeding [68]. To mitigate these problems MRI guided biopsy has been designed to perform more targeted and precise biopsies [67]. This method is not widely used due to the technical difficulties and expense. Also, multiparametric imaging (mpMRI) can detect larger tumors but they need to be of greater than grade 7 [69], [70].

Eventually, the treatment for CaP is often radical prostatectomy (RP) using laparoscopic surgery, manual or robotic assisted. This procedure can lead to complications with erectile dysfunction or urinary dysfunction [71]. More accurate preoperative planning will help reduce these complications by adding spatial information about the tumor location. Additionally this would help improve tumor margins (distance between excised tissue boundary and malignant tissue).
Elastography is well suited to the detection of hard tumors as its underlying principle parallels palpation, and with the inclusion of quantitative and qualitative analysis of the complex shear modulus, is more accurate than palpation. Recently, research into the feasibility of elastography methods to detect CaP has increased. For instance, ultrasound elastography of CaP has shown a 2 times increase in tumor stiffness as compared to normal tissue [72]. Magnetic Resonance Elastography (MRE) has been proven to give a strong correlation with pathology in [47]. However, these studies were conducted on prostates post fixation in formalin, which has been shown to change the mechanical properties of the prostate gland [73]. The method proposed in this study will assess the feasibility of ex vivo prostate MRE prior to formalin fixation to identify tumor locations and potentially provide prostate gland mechanical properties for future use in in vivo studies.

In this study, MRE was performed on ex vivo prostates after RP and assessed using pathology reports. This is an ongoing study, eventually comprising 20 subjects, that currently has data from 5 subjects. Analysis methods will include contrast-based examination of segments and a threshold identification of tumors based on the MRE storage modulus maps.

4.2 Methods

4.2.1 Experimental Procedure

The prostate specimens all come from consenting patients with positive CaP diagnosis. The protocol has been approved by the Institutional Review Board at the University of Illinois at Chicago. Radical prostatectomy (RP) is the procedure used to remove the prostate gland. When completed, the study will comprise a total of 20 subjects, but as of this dissertation only seven subjects have been used with two data sets being rejected due to experimental complications. These
complications have been rectified and are not likely to occur again with the remaining subjects. So, the total sample size for analysis in this dissertation is five.

As soon as the prostate gland is removed from the patient, it is placed in a saline solution and transported directly to the MRI facility. The prostates are scanned using MRE prior to fixation in formalin by pathology, which allows for stiffness measurements much closer to the in vivo condition, as fixation tends to stiffen tissue. Because of this, the entire procedure, from removal of prostate to post MRE pathology fixation in formalin, must be completed within two hours. This window was determined by the surgeons involved to be a conservative time scale that would ensure the tissue does not degrade to the point where it is unusable by pathology. The experimental procedure is then as follows; remove prostate, optimize MRI and MRE parameters to scan entire prostate with the highest resolution possible while maintaining the 2 hour window constraint, return prostate to pathology, and process MRE stiffness and compare with pathology results.

4.2.2 MRE Imaging

The most important MRI imaging requirement, for this study, is that the entire prostate gland volume be imaged; followed by, image resolution, and then MRE actuation frequency, which should be as high as possible. Due to a large variance in prostate volume and geometry, Figure 15, it is not possible to achieve the priorities mentioned and have consistent imaging parameters. For instance, the prostates in Figure 15 vary in volume by almost double and it can be seen that the prostate on the left can be scanned at a much higher resolution than the right, while maintaining the 2 hour time window. Not only do the prostates vary in geometry but in stiffness as well. In Figure 16, it can be seen that the larger than usual prostate attenuates the 500 Hz frequency so quickly that only a single wavelength can be seen, while the 250 Hz frequency propagates through
the entire gland. In addition to all these variations, the first 3 prostates were still so unknown, in terms of material properties, that much time was spent deciding on the best settings and slice thickness had to be increased to reduce time.

**Figure 15.** Example of variation in prostate geometry and volume. A) One of the smallest prostates imaged; note the higher image resolution. B) One of the largest prostates imaged; note the low image resolution.
Figure 16. The same prostate wave fields at 2 different actuation frequencies. On the left is 500 Hz with hard tissue approximately within the black ellipse and soft tissue around the surface. On the right, is the same prostate at 250 Hz, note how the shear wave fully penetrates the entire gland.

MRI imaging was performed in an Agilent 9.4 T small animal scanner (Agilent Technologies, Santa Clara, CA) with a 62 mm inside diameter quadrature birdcage RF coil. The phase constant SLIM-MRE motion encoding method was used with a modified spin echo sequence, Figure 17, using flow compensated MEGs. The MRI and MRE parameters are given for each prostate in Table XI.
Figure 17. Pulse sequence diagram of the SLIM-MRE sequence using the phase constant method. The red boxes are the MEGs and inside is an example of how the MEGs are shifted temporally. The solid black line represents a common start time and each access is then shifted at a rate $kn\Delta t$ with $k = 1, 2, 3$ and $n$ representing the temporally shift number. Cosine shaped gradients are used for flow compensation.
Table XI. MRI and MRE imaging parameters for all prostates.

<table>
<thead>
<tr>
<th>Prostate #</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOV (mm x mm)</td>
<td>40 x 40</td>
<td>48 x 48</td>
<td>64 x 64</td>
<td>42 x 42</td>
<td>64 x 64</td>
</tr>
<tr>
<td>Resolution (mm)</td>
<td>0.3125</td>
<td>0.5</td>
<td>1</td>
<td>0.3281</td>
<td>0.5</td>
</tr>
<tr>
<td>Slice Thickness (mm)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Number of Slices</td>
<td>20</td>
<td>20</td>
<td>50</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>Number of MEGs</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Gradient Strength (G/cm)</td>
<td>15</td>
<td>18</td>
<td>15</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>500</td>
<td>500</td>
<td>250</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>25.2</td>
<td>26.1</td>
<td>25.5</td>
<td>27.6</td>
<td>27.6</td>
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<td>TR (ms)</td>
<td>750</td>
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<td>2400</td>
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<td>2000</td>
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<td>Scan Time (min)</td>
<td>25</td>
<td>18</td>
<td>41</td>
<td>75</td>
<td>68</td>
</tr>
</tbody>
</table>

For actuation, again, the geometrically focused method was used. The design of the actuator can be seen in Figure 18(B). It is simply a tube connected to a piezo actuator (P-840.1, Physik Instrumente GmbH and Co., Karlsruhe Germany) and vibrated along the central axis of the tube. To compensate for the various geometries of prostates either shims or tubes with smaller inner diameters can be used. For this study, shims were found to be most effective in terms of adaptability of setup. As can be seen in Figure 18(A), z-direction, the geometric actuation creates a focused pattern of shear waves with significant energy throughout the prostate. The actuation also produces waves in all three motion directions. This is likely due to the interface of internal tissue boundaries and the asymmetric geometry of the prostate.
4.2.3 Post Processing

The processing and analysis of MRE data was done with two objectives in mind: 1) to measure the contrast ratio of cancer positive segments to cancer negative segments, and 2) to assess the ability of a stiffness threshold criteria to identify positive and negative segments of the prostate. Both methods require the segmentation of the prostate and the pathology report.
To segment the prostate, the standard 12 region method was adopted to coincide with the pathology reports. The segmenting of the MRI images was performed manually using the urethra and the seminal vesicles for proper orientation of the images. In Figure 19(A), the image shows a front view section with 6 regions visible, and it can be seen that the prostate resembles an upside down pyramid. The base, mid, and apex regions are roughly one third each of the length of the prostate from base to apex, and the left and right anatomical sides split this into 6 total regions. The remaining 6 regions come from the split of anterior and posterior, which can be seen in Figure 19(B).
Figure 19. Anatomical schematic of the prostate with segments shown. A) Front section view of prostate. B) Left side section view along urethra plane.

Stiffness images were obtained using the 3D algebraic Helmholtz inversion of the curled wave field, $Q$:

$$G(\omega) = -\rho \omega^2 [(\Delta Q)^T \Delta Q]^{-1} (\Delta Q)^T Q$$

Here $G$ is the complex storage modulus. Finally, $G$ was smoothed using a 5 pixel cube window. Spatially averaged mean values were obtained prior to smoothing and also employed a 3 pixel eroded mask for discrete derivative errors. The mean of the absolute magnitude in each segment was then calculated and split into two groups, one for cancer positive segments, and one for cancer...
negative segments. The mean stiffness of these segments were then compared to examine the contrast ratio.

Finally, the threshold method was used to identify segments as positive or negative. The threshold used is:

\[ 10\% \text{ of Pixels} > G'_{\text{mean}} + \sigma \] (4.2)

Results of this analysis are based on assuming the pathology report being the gold standard. Segments are split into 1 of 4 criteria: true positive (TP), false positive (FP), true negative (TN), and false negative (FN). False negative is the worst, as it represents a missed identification of cancer. These categories can then give the sensitivity and specificity:

\[
\text{Sensitivity} = \frac{\sum \text{TP}}{\sum (\text{TP} + \text{FN})}, \quad \text{Specificity} = \frac{\sum \text{TN}}{\sum (\text{TN} + \text{FP})}
\] (4.3)

### 4.3 Results: Ex Vivo Prostate MRE

In Figure 20, the stiffness scale is normalized so that all of the tissue is of the same scale, and contrast is based on the two ROIs shown for soft and hard tissue. As the filter cutoff is increased a boost in contrast can be seen between the hard and soft tissue, but continuing to increase the filter cutoff reverses this effect as the soft tissue becomes stiffer. This can be seen more clearly in Figure 21, there is a specific point, 1.5 mm, at which highest contrast is achieved; after this, contrast starts to decrease rapidly. The mean tissue storage modulus, for both soft and hard tissue, monotonically increases with increasing filter wavelength cutoff.
Figure 20. Effect of filter cutoff selection on contrast. Top row is the magnitude image of a prostate phantom followed by the 2 ROIs for soft and hard tissue. The next two rows are storage modulus maps normalized to the same scale, with increasing filter cutoff wavelength.
Table XII lists the contrast results. Here we can see the mean complex amplitude of the shear modulus for all segments of all specimens (± the standard deviation). The positive column is for all segments identified as positive for cancer based on the pathology report, and likewise for the negative column. The last column is the contrast ratio and is simply the positive divided by the negative. It can be seen that the contrast ratio is not very high, and very close to a 1:1 ratio for some cases, especially specimen 5 which shows a ratio of 1:1.
Table XII. Mean complex amplitude stiffness values based on positive and negative segments. The last column is the ratio of mean positive to mean negative.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Mean Positive</th>
<th>Mean Negative</th>
<th>Contrast Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>3.6 ± 0.48</td>
<td>3.0 ± 0.67</td>
<td>1.19</td>
</tr>
<tr>
<td>P2</td>
<td>4.6 ± 0.71</td>
<td>3.6 ± 0.52</td>
<td>1.35</td>
</tr>
<tr>
<td>P3</td>
<td>5.2 ± 0.77</td>
<td>4.8 ± 0.50</td>
<td>1.08</td>
</tr>
<tr>
<td>P4</td>
<td>4.1 ± 0.45</td>
<td>3.6 ± 0.41</td>
<td>1.14</td>
</tr>
<tr>
<td>P5</td>
<td>6.0 ± 0.61</td>
<td>6.0 ± 0.85</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table XIII. represents all the segments of each prostate specimen. The segment column lists the corresponding segment name and each set of prostate results is compared to the pathology report on the left and the MRE threshold identification on the right. A plus symbol represents a positive result for cancer in that segment, and an empty cell represents a negative result. The worst case scenario is a false negative identification (meaning cancer was missed) and is highlighted with a red plus symbol. Notice, that only prostate 5 had segments with this type of identification. Overall, the sensitivity and specificity were 85.7% and 53.7%, respectively.
Table XIII. Threshold based identification results for each segment in the left column. A plus sign indicates a positive identification of cancer. The pathology and MRE results are listed side by side for each prostate. The red plus signs represent a false negative.

<table>
<thead>
<tr>
<th>Seg.</th>
<th>Path.</th>
<th>MRE</th>
<th>Path.</th>
<th>MRE</th>
<th>Path.</th>
<th>MRE</th>
<th>Path.</th>
<th>MRE</th>
<th>Path.</th>
<th>MRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAP</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LAA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LMP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LMA</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>LBP</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>LBA</td>
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<td>+</td>
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<td></td>
<td>+</td>
<td></td>
<td>+</td>
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<td>+</td>
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<tr>
<td>RAP</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>RAA</td>
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<tr>
<td>RMP</td>
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To visually understand the threshold criteria examples of storage modulus maps and the segment identifications will be assessed. There are 4 possible identifications as compared to the pathology report; true positive (TP), false positive (FP), true negative (TN), and false negative (FN). Each of these identifications are represented in the stiffness map examples, Figures 22 and 23. The figures are organized with the magnitude reference slice on the left and the corresponding stiffness map on the right. Each slice is split into the ROIs representing each segment by the dashed lines. The flags next to each segment represent the segment name and identification type for the magnitude and stiffness maps, respectively.
The first stiffness map example, Figure 22, gives a typical representation of the results with good sensitivity but poor specificity. Segments LAP and LAA, both have a clear nodule of hard tissue and are both TPs. However, segment LMP has a clearly defined hard nodule as well, but this was a FP for unknown reasons. The TN segments LMA, LBP, LBA, and RMA are good examples of normal tissue stiffness. Finally, the FPs in segments RMP, RBP, and RBA are likely due to the urethra wall, yellow line in the magnitude image, which is stiffer than normal tissue.

The second example, Figure 23, illustrates the case of FNs. The orientation of this specimen slice plane is different than that of Figure 22; it is sliced along the apex to base axis rather than left to right, therefore requiring 3 slices to represent all the segments. The FNs, RAP, RAA, and LBA, are due to either small nodules that do not encompass a large enough percentage of the segment volume, or the stiffness is too close to the mean. Comparing the positive identifications to those of the negatives gives a good idea of about the size and stiffness needed to label a segment positive.
Figure 22. Example of prostate 1 storage modulus map. Left column is the magnitude image of the left slice (top) and right slice (bottom) with segments shown and labeled. Right column is the corresponding storage modulus map with the threshold results labeled next to their respective segment.
Figure 23. Example of prostate 5 storage modulus map. Each box represents the slice listed above with the magnitude image and its corresponding storage modulus map. Each magnitude image has the segments labeled and the storage modulus maps the threshold results labeled.

4.4 Discussion: Ex Vivo Prostate MRE

This preliminary work on ex vivo prostates was developed to assess the MRE technique to identify adenocarcinoma tumors. This was assessed on a threshold based criteria and compared to the pathology results. Additionally, the contrast between positive and negative segments of the prostate, determined by pathology, was analyzed.
One of the least discussed issues in MRE is the one of filter selection. If using a direct inversion approach to process MRE data 2-3 discrete derivatives are required, depending on the method used. Discrete derivatives tend to amplify noise, so spatially filtering the MRE wave data is an absolute necessity. For the most part, this is not a significant issue as MRE studies are self-contained; meaning, the actual stiffness value is not as important as the differences observed in groups A and B. So, as long as the filters remain consistent within the study there is no issue. The problem arises when parameters from scan to scan change, and in so doing, filter parameters have to change as well, when the actual stiffness value is important and needs to be compared to other studies, or when used as reference for future in vivo work. From Figure 21, it is clear how a small change in filter parameters can drastically change the mean stiffness values. This is likely one of the major reasons for the large variances seen in MRE data from study to study. For this study in particular, validation using methods such as employed in [72] or dynamic shear loading methods would increase the feasibility of transitioning to in vivo studies.

From Table XII, it is clear that the contrast ratio from positive to negative segments is not significant. The issue is not likely associated with the filter parameter selection as care was made to ensure ideal contrast was achieved. It is, however, much more likely that this is a consequence of segments containing too much volume compared to the volume of tumors. The size of the segments could be reduced by increasing the number of regions the prostate is split into, as was done in a transperineal biopsy study [68]. This would then require a new procedure for pathology.

The sensitivity (specificity) of the threshold based segment identification of adenocarcinoma, at 85.7% (53.7%), suggests MRE is a practical method to identify prostate cancer ex vivo. It is comparable to other methods of cancer detection for the prostate such as; 85% for standard sextant TRUS biopsy up to 93% for additional targeted biopsies [74], 54-82% (46-91%)
with T2 weighted MRI [75], and in [47] with 69% (69%) for ex vivo MRE, 62-75% (62-75%) for DWI, and 78-82% (75%) for DWI+MRE.

This study has demonstrated that MRE of the ex vivo prostate prior to formalin fixation, while preserving the tissue quality for pathology, is practical. The ability of this MRE method to detect prostate cancer was comparable and in some cases better than the literature. Potential limiting factors to transitioning to in vivo studies were found in the filter parameter selection. This continuing study will hope to elucidate a solution to the above problem. It is expected as the sample size in this study increases the sensitivity and specificity results will improve.
5 ULTRA HIGH FIELD ANIMAL LUNG MRE

5.1 Background: Proton Lung MRE

Lung MRE presents a difficult technical challenge. However, there are numerous diseases that affect the lung tissue material properties. For instance some common diffuse diseases have been shown to either increase the shear modulus (asthma or bronchoconstriction [76], fibrosis [77]) or decrease the shear modulus (emphysema [78]). Therefore, there is a clinical need to identify normal lung material properties and those of diseased lungs.

MRE, in many ways, is well suited to this task. The first preliminary test of lung MRE was done in [79], and on in vivo human lungs. This study clearly established the feasibility of lung MRE in humans, and also demonstrated the correlation of lung stiffness with inflation pressure in an excised porcine lung. A further study of human lung MRE [80], compiled larger sample sizes and established base stiffness data for inspiration and expiration. With lung MRE fully demonstrated work turned to faster acquisition with EPI, and alternative measures, such as divergence of the lung [81], [82].

In addition to human lung MRE in vivo, additional animal lung MRE studies were undertaken on rat and pig models [83]–[86]. However, all of these studies were on dead animals or excised animal parts. Therefore there is a need to attempt or at least direct animal lung MRE towards in vivo experiments. This study will look at the practicality of proton lung MRE at the ultra-high field (UHF) strength of 9.4 T. First, a detailed analysis of the problems encountered in UHF proton lung imaging is made. Secondly, analysis of actuators was made, and, finally, lung MRE was performed on a euthanized rat at two inflation pressures.
5.2 **Signal at 9.4 T**

It would be expected that as magnetic field strength is increased from 1.5 T to 9.4 T there should be a corresponding increase in signal for lung parenchyma, however it is not as simple as this. At 1.5 T the T2 decay rate of lung parenchyma is 80-90 ms [87], and at 9.4 T T2 is 23-32 ms [88]. T2* also behaves in a similar way; as magnetic field strength is increased T2* time decreases. This shows us that the decay rates of transverse magnetization are very different, and can be visualized in Figure 24. In order to then make use of the signal boost from the higher magnetic field, echo times need to be decreased significantly, and possibly, due to hardware limitations, the necessary decrease in TE might not be practical [89].

There are, however, methods designed specifically to image materials with short T2, and T2* times. One branch of these methods are designated ultra-short echo time (UTE) sequences. They have such a short TE that they are capable of imaging normally MRI-invisible materials like rubber, and cork [90], [91]. Another branch, is that of swept frequency type scans such as SWIFT, which can image even thermoplastics [92]. Both of these methods have demonstrated successful application to the excised or dead mouse lung [93], [94].

There is one major theme here, and it is that TE needs to be as short as possible when imaging at high field strengths, especially UHF’s of 9.4 T, the field strength of the magnet used in this study. For MRE, this statement is counterproductive; MRE needs to add MEGs in order to encode vibration, increasing TE by anywhere from 1-20 ms depending on the frequency and number of MEGs used. For MRE to work, either fractional encoding should be used, which decreases encoding efficiency, or effort should be made to increase the amplitude of vibrations, thereby, boosting encoding efficiency.
Figure 24. Comparison of 2 transverse magnetization relaxation curves of lung parenchyma at 1.5 T and 9.4 T magnetic field strengths.

5.3 In Vivo Lung MRE

For lung MRE to be a practical research and clinical tool it needs to be performed in vivo. This presents problems related to motion from the respiration and cardiac cycles. Not only is motion an issue, but the phase of the respiration cycle effects signal intensity due to the increase and decrease in proton density during expiration and inspiration, respectively [89], [95].

To correct for motion error a common method is the use of gating; i.e. only imaging during a natural breath hold. This will allow for the use of SE sequences which are less affected by the magnetic field inhomogeneity produced by lung tissue. This is fine for pure imaging; but, for MRE
time becomes a significant factor. Still, it is within reason. MRE scan times can be from 30 min to 1.5 hours while gating. But this does not correct for all of the motion induced noise.

To test the effects of motion induced noise air on MRI lung images a female C57BL/6 mouse was imaged *in vivo* at 9.4 T (Agilent Technologies, Santa Clara, CA). Three specific pulse sequences were investigated: SE with gating, GE without gating (instead 80 averages) and minimized TE time, and GE-MRE (80 averages) with increased resolution to ensure Nyquist criteria is obeyed for shear wavelengths. Table XIV lists the specifications for each of these sequences. Images from these test scans can be seen in Figure 25. For the SE scan, Figure 25(A), the red box highlights motion induced noise from the heart; notice how it covers the majority of lung tissue. Instead of gating, many averages can be used with a GE sequence, but with a very short TE to pick up lung tissue signal; see Figure 25(B). This seems to remove all of the motion noise but at a cost of resolution. Now to perform MRE image resolution has to be increased to ensure Nyquist criteria is obeyed for shear wavelengths; it can be seen in Figure 25(C), how the lung signal quickly degrades with the increase in TE time.
Table XIV. Specifications for motion noise test scans. A, B, and C correspond to the images in Figure 25.

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Figure 25. Comparison of methods to reduce motion noise while boosting signal in the lungs (see Table XIV for imaging specifications). A) SE sequence with respiratory gating, there is signal in the lung even at this high resolution, however, inside the red box motion noise from the heart ruins the majority of the lung image. B) GE sequence with resolution reduced to get TE as short as possible, and using 80 averages without gating. There is almost no motion noise in this image and even the Tygon tubing is picked up (red circle). C) GE-MRE sequence with 80 averages, notice the signal loss in the lung tissue due to increase in TE time for MEGs.

5.4 Actuation Methods

There are two main methods of actuation that could be used: acoustic source or mechanical source.

The acoustic source may be the simplest method to setup; but, the high frequencies used in small animal MRE reduce its practical use. This is due to the attenuation of sound in air and tissue. As sound frequency is increased so does the absorption rate of sound in air \[96\]. In addition, acoustic actuation is similar to a point source, and points far from the source lack wave energy.

The preferred method for high frequencies is then a mechanical source. The first actuator developed was a bed type actuator with a cover for the anesthesia gases, see Figure 26(A1) top. An FEA analysis of this design found that a linear motion along its main axis results in an undesired motion of the bed. From Figure 26(A2-A4), it can be seen that the flexing of the walls results in a
rocking motion instead of the desired shear motion. So, instead the GFA, Figure 26(B1), method was designed and analyzed in the same manner. From Figure 26(B2-B4), the desired shearing type motion is achieved. This method also has the advantage of the source completely surrounding the specimen surface, which will mitigate attenuation.
Figure 26. Comparison of two MRE actuators. On the left is the bed type shaker, red highlight in A1 is mounting point to piezo, and the arrow shows the vibration direction. On the right is the GFA type (hollow tube), again mounting point highlighted in red. The images below each actuator are the FEA dynamic motion responses to a 1000 Hz harmonic displacement at the mounting point, with each image a time snapshot of the displacement response.

5.5 Results & Discussion: In Situ Rat Lung

The GFA method was tested on in situ lungs of a euthanized rat. This experiment was designed as a precursor for in vivo mouse and rat lung MRE. It was necessary to first establish that shear waves could be induced into lung tissue and imaged at 9.4 T, without the in vivo complication of gating or averaging. Also, the effect of lung inflation pressure on lung tissue stiffness was tested.
The specifications of this test were: TE/TR 12.92/500 ms, FOV 46 mm x 46 mm, voxels 96 x 96, slice thickness 8 mm, MEGs 2, gradient strength 30 G/cm, and actuation frequency of 250 Hz. Two inflation pressures were tested, 0.0 cmH\textsubscript{2}O and 10.0 cmH\textsubscript{2}O, with densities of 579 kg/m\textsuperscript{3} and 236 kg/m\textsuperscript{3}, respectively, derived from [86]. The complex wave data was spatially filtered using a Butterworth band pass filter. For inversion, a 2D algebraic inversion was applied assuming any compression waves were removed using the filter. Lastly, the lung ROIs were manually selected, which was used to measure the lung tissue SNR and spatially averaged shear modulus.

The results for the two inflation pressures can be seen in Figure 27, with row A representing 0.0 cmH\textsubscript{2}O and B 10.0 cmH\textsubscript{2}O. The first images from left are the magnitude images with the ROI and its corresponding SNR given above. Notice how increasing lung pressure to about half inflation cuts the SNR of the lung by 57\%, which is expected; as lung pressure increases lung density and proton density will decrease. Visually, the increase in volume can be seen, as well, by comparing the two ROIs.

For 0.0 cmH\textsubscript{2}O inflation pressure (Figure 27(A)), the wave image shows significantly strong waves throughout the entire rat torso, and the far right image displays the lung ROI and its mean shear modulus. Unexpectedly, for 10.0 cmH\textsubscript{2}O Figure 27(B), the stiffness of the tissue decreased with increasing lung pressure. This result is at complete odds with the literature [84], [85].

The results suggest that there must be a considerable amount of error in the wave field. It was evident in the magnitude images that increasing pressure resulted in a significant loss in signal, and even for the 0.0 cmH\textsubscript{2}O case, SNR of 18.3, was relatively low compared to, for instance, the heart region with a SNR of 54.7. With such a low SNR, very narrow band filters were required to
even capture a wave image, and it is possible that this wave image is partly a consequence of the
filter. Alternative inversion methods, such as; adding a directional filter, or phase gradient still
yielded the same decrease in tissue stiffness with pressure. So, it is unlikely that the results are due
to the processing method. Another item of consequence, was the very large slice thickness; at 8
mm, the slice thickness was a little over a third of entire length of the lungs. The reason for such a
large slab was that anything less produced such little signal that MRE was not practical. Perhaps
then, the waves seen were not solely from the lung tissue, but just an overlay of waves from
different tissues just above or just below the lung. With these issues in mind, for the time being, it
is concluded that proton lung MRE at 9.4 T is not practical.
Figure 27. From left to right magnitude, wave, and storage modulus images at 2 inflation pressures, A) 0.0 cmH$_2$O and B) 10.0 cmH$_2$O. The lung ROI area is outlined in yellow with the average shear modulus given above the image.
6 CONCLUSION

This dissertation has experimented with elastography applications using GFA. The direct material applications of GFA included: human skin in vivo, prostate glands ex vivo, and in situ rat lung. The exception was the in vivo mouse brain MRE study, which focused on a novel method of motion encoding. Interestingly though, the bite bar actuator produced wave patterns similar to those produced with GFA, but considering that the brain is surrounded by the skull on all sides, much like the prostate actuator, this result is not surprising. All of these applications benefited from large bandwidth or attenuation compensation of GFA as compared to a single point (small area) actuation.

In the in vivo human skin study, GFA resulted in large bandwidth measurement of the dynamic shear modulus. Various viscoelastic models were then fit to this data and evaluated based on variation and quality of fit. It was found that 2 particular models stood out in these categories. In variation, the fractional order models performed the best. In quality of fit, the SLS model outperformed all others. These conclusions lead to recommendations for use in future studies with skin diseases. If one needed a model to identify pathological changes of groups either the fractional Voigt or spring-pot model would be ideal, and if one needed a targeted patient specific model the SLS would be the best choice.

In the in vivo mouse brain MRE study, 2 methods of motion encoding for the novel SLIM sequence were examined. Both methods showed good agreement with the conventional MRE method. SLIM-PC, compares to conventional with less error in terms of the shear modulus maps, than SLIM-PV but requires an increase in TE. If SNR is not a serious concern then the SLIM-PC method would be the ideal choice. For small animal MRE the actuation frequency is much greater than that of human MRE, so the increase in SNR by using SLIM-PV is not as great as it would be
in the human case. It would then be interesting to also compare the SLIM-PV method against the SLIM-PC in human MRE.

In the *ex vivo* prostate MRE study, GFA provided strong wave energy throughout the entire prostate gland volume. The study is still ongoing, and will eventually total 20 specimens. Even with only 5 samples to date, the results of the experiment are promising. The threshold based determination of positive and negative CaP segments correlated well with the pathology report giving a sensitivity of 85.7% and specificity of 53.7%. In addition, potential improvements to the study were found in terms of filter selection and pathology comparison. In order to have more accurate shear modulus results experiments should coincide with dynamic testing of the prostate specimen. Also, more local identification algorithms could likely increase both the sensitivity and specificity of segment CaP identification.

Finally, in the *in situ* Lung MRE study, GFA, once again, proved to be the actuation method of choice. For this application, in the bed type shaker, unwanted modes of vibration were discovered and only mitigated when the GFA method was used. Unfortunately, it was found that proton lung MRE at 9.4 T does not provide enough signal to perform *in vivo* experiments. Also, the results of the *in situ* experiment that lung tissue stiffness decreased with pressure, did not agree with current literature.
APPENDIX A

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APPENDIX B

Protocol Approvals:

November 4, 2015

Dieter Klatt
Bioengineering
M/C 063

Dear Dr. Klatt:

The modifications requested in modification indicated below pertaining to your approved protocol indicated below have been reviewed and approved in accordance with the Animal Care Policies of the University of Illinois at Chicago on 11/3/2015.

Title of Application: 3D SLIM MRE of Mouse Brain
ACC Number: 13-172
Modification Number: 05
Nature of Modification: Personnel Addition: Shreyan Majumdar
Protocol Approved: 10/22/2013
Current Approval Period: 10/15/2015 to 10/15/2016

Currently protocol NOT matched to specific funding source. Modification will need to be submitted prior to Just in time or acceptance of award to match protocol to external funding source. All animal work proposed in the funding application must be covered by an approved protocol. UIC is the only performance site currently approved for this protocol.

This institution has Animal Welfare Assurance Number A3460.01 on file with the Office of Laboratory Animal Welfare, NIH. This letter may only be provided as proof of IACUC approval for those specific funding sources listed above in which all portions of the grant are matched to this ACC protocol.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,

[Signature]

John P. O'Bryan, PhD
Chair, Animal Care Committee

JPO /rs

cc: BRL, ACC File, Steven Kearney
December 3, 2014

Thomas Royston
Mechanical Engineering
M/C 251

Dear Dr. Royston:

The modifications requested in modification indicated below pertaining to your approved protocol indicated below have been reviewed and approved in accordance with the Animal Care Policies of the University of Illinois at Chicago on 12/8/14.

Title of Application: Mouse Lung Magnetic Resonance Elastography

ACC Number: 12-108

Modification Number: 3

Nature of Modification: Personnel Addition: Vidyanti Suryadevara and Yideli Lin
Addition of MRE of heart in same living animals as MRE of lungs and MRE of lungs and heart post-mortem.

Protocol Approved: 9/25/2012


Current Funding: *Currently protocol NOT matched to specific funding source. Modification will need to be submitted prior to Just in time or acceptance of award to match protocol to external funding source. All animal work proposed in the funding application must be covered by an approved protocol. UIC is the only performance site currently approved for this protocol.*

This institution has Animal Welfare Assurance Number A3460-01 on file with the Office of Laboratory Animal Welfare, NIH. This letter may only be provided as proof of IACUC approval for those specific funding sources listed above in which all portions of the grant are matched to this ACC protocol.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,

Bradley Merrill, PhD
Chair, Animal Care Committee

BM/116
cc: BRL, ACC File
February 4, 2015

Simone Crivellaro, MD
Urology
820 S. Wood Street
CSN 515, M/C 955
Chicago, IL 60612
Phone: (312) 996-9330 / Fax: (312) 413-0495

RE: Protocol # 2014-1088
“Pilot Study: Use of Magnetic Resonance Elastography and Haptics for Diagnosis of Prostate Cancer - ExVivo”

Dear Dr. Crivellaro:

Your Initial Review (Response to Modifications) was reviewed and approved by the Expedited review process on February 4, 2015. You may now begin your research. Please note the following information about your approved research protocol:

**Protocol Approval Period:** February 4, 2015 - February 4, 2016

**Approved Subject Enrollment #:** 20

**Performance Sites:** UIC

**Sponsor:** None

**Research Protocol:**

a) Pilot Study: Use of Magnetic Resonance Elastography and Haptics for Diagnosis of Prostate Cancer - ExVivo; Version 2.0, 2/3/2015

**Informed Consent:**


**Additional Determinations for Research Involving Minors:**

These determinations have not been made for this study since it has not been approved for enrollment of minors.

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories:

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or

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microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

**Please note the Review History of this submission:**

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Please remember to:

→ Use your research protocol number (#2014-1088) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,

"UIC Investigator Responsibilities, Protection of Human Research Subjects"

(http://medicine.uic.edu/depts/over/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3202. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

[Signature]
Teresa D. Johnston, B.S., C.I.P.
Assistant Director
Office for the Protection of Research Subjects

Enclosures:
1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Document:

cc: Craig Niederberger, Urology, M/C 955
Approval Notice
Amendment to Research Protocol and/or Consent Document – Expedited Review
UIC Amendment #3

February 6, 2015

Thomas Royston, PhD
Bioengineering
SEO 212
M/C 063
Chicago, IL 60612
Phone: (312) 413-7558 / Fax: (312) 996-5921

RE: Protocol # 2013-0441
"HCC: Medium: Collaborative Research: Force Feedback for Fingertips"

Dear Dr. Royston:

Members of Institutional Review Board (IRB) #3 have reviewed this amendment to your research under expedited procedures for minor changes to previously approved research allowed by Federal regulations (45 CFR 46.110(b)(2)). The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: January 29, 2013

Amendment:
Summary: UIC Amendment #3 dated 1/19/15 and received on 1/26/15 involves addition of UIC employees as a target population. The initial review application has been revised to reflect this change. The consent already contains the language pertaining to UIC employees.

Please note the Review History of this submission:

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<td>01/26/2015</td>
<td>Amendment</td>
<td>Expedited</td>
<td>01/29/2015</td>
<td>Approved</td>
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</table>

Please be sure to:
- Use your research protocol number (2013-0441) on any documents or correspondence with the IRB concerning your research protocol.
Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects" (http://tiger.uic.edu/dept/ovcr/research/protocol/review/irb/policies/0924.pdf).

Please note that the UIC IRB #3 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 355-1609. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Rahab Mwangi, MPH
IRB Coordinator, IRB # 3
Office for the Protection of Research Subjects

cc: Thomas Royston, Bioengineering, M/C 063
CITED LITERATURE


VITA

Education

**University of Illinois at Chicago**  
PhD in Mechanical Engineering  
Overall GPA: 3.91/4.00  
August 2009 – May 2016

**University of Illinois at Chicago**  
Bachelors of Science in Mechanical Engineering  
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Research & Teaching Experience

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Research Assistant  
August 2009 – December 2015  
Lemont, IL.

**University of Illinois at Chicago**  
Research Assistant – Acoustics and Vibrations laboratory  
January 2014 – December 2015  
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**University of Illinois at Chicago**  
Teaching Assistant – Experimental Methods ME 341  
August 2012 – December 2013  
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Professional Experience

**Baxter International, Inc.**  
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January 2009 – August 2009  
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Patent


Publications


