Resolution Estimation and Bias Reduction in Acoustic Radiation Force Impulse Imaging

By

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Submitted in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy

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2010
Curriculum Vitae

Manoj Menon was born in Rochester, New York on September 26th, 1982. He began attending the University of Rochester in 2000 and received a Bachelor of Science degree in Biomedical Engineering in 2004. In 2003, he joined the Center for Visual Science as a research assistant where he contributed to customized vision correction research until 2005. He enrolled in the Biomedical Engineering graduate program in 2004 and received his Masters of Science Degree in 2006. Mr. Menon began research in the field of ultrasound imaging under the supervision of Professor Stephen McAleavey in 2005. He served as a research assistant in Professor McAleavey’s laboratory from 2005 to 2010.
Acknowledgements

I have spent nearly a decade in the presence of amazing individuals in the Department of Biomedical Engineering at the University of Rochester. It was not only the books, the classes, or even the research that has helped me accomplish my goals, but also the experiences and the personal relationships that have influenced my learning. These relationships and experiences have helped me become the scholar and scientist I am today.

First and foremost I would like to thank my graduate advisor, Professor Stephen A. McAleavey. As his first graduate advisee I have had the pleasure of building a laboratory with him. His youthful genius and excitement for the field of ultrasound imaging is truly inspirational. His unbridled curiosity can only be described as contagious.

The members of my thesis committee have been integral in the completion of this thesis. Professor Diane Dalecki first introduced me to the world of biomedical engineering as an undergraduate student, and later to the fundamentals of ultrasound as a graduate student. She has been the one constant positive mentor throughout my experience at this university and has been a driving force in the continuation of my academic development. Professor Sheryl Gracewski has graciously offered her time and infinite wisdom in the development of numerical and analytical models. Dr. Deborah Rubens has provided the clinical prospective that was invaluable in maintaining the medical relevance of this thesis.

I would like to thank the Department of Biomedical Engineering support staff and other faculty. I cannot give enough thanks to Sally Child and Carol Raeman. Together, they have assisted me on a number of experimental procedures fundamental in the field of ultrasound. The technical assistance of Art Salo, Paul Osborn, and Ken Adams has been critical in the development of phantom mechanical testing procedures. Professor Amy Lerner graciously allowed me to use her materials testing
room and provided invaluable materials testing knowledge. I could not have endured stringent requirements of the undergraduate program and the confusing formalities of the graduate program without the help of our program coordinators, Dottie Welch and Donna Porcelli. Thank you for your constant encouragement and unsurpassed patience.

A truly heartfelt thanks goes to my fellow graduate students and friends. Tony Chen and Sarah Lancianese joined the graduate program with me an eternity ago and will always remain two of my closest friends. Graduate student mentors who have provided invaluable guidance in my early graduate years include Ben Casteneda, Ken Hoyt, and Man Zhang. I would like to thank my labmates, including Etana Elegbe, Johnathan Langdon, and Viabhav ‘V’ Kakkad for numerous joint procedures and countless practice presentations. Many thanks are extended to Carlos Sevilla, Kelley Garvin, Dan Roy, Brenden Morse, Nick Berry, Kristen Hovinga, Erin Collins and Karla Mercado. This group has made these years without a doubt my most memorable.

I would not be where I am today if it was not for my family and loved ones. My parents, my brother Sajay, and my fiancé Angela have tirelessly supported me with their unconditional love and support. This dissertation is dedicated to them, because without them, this would have not been possible. Thank you.
Abstract

Pathological conditions give rise to mechanical changes in tissue that can be exploited for the purpose of diagnosis and treatment of disease. Elasticity imaging is a field developed to create images of tissue stiffness by mechanically exciting tissue and tracking the tissue response. Acoustic Radiation Force Impulse (ARFI) imaging is one such modality that measures the micron–scale displacements induced in tissue by local acoustic radiation forces using high intensity ultrasound pulses generated by a standard diagnostic ultrasound scanner. Ultrasound pulses track displacements that are quantified using conventional correlation–based speckle-tracking methods. Generated displacement images can exhibit improved contrast of diseased tissue than conventional ultrasound techniques.

In this thesis, the spatial resolution of ARFI imaging has been measured using novel simulation and experimental techniques. The full-width, half-maximum (FWHM) of the point-spread function (PSF), a measure of the resolution limit of an imaging system, was extracted by imaging a tissue-mimicking phantom composed of two bonded materials of differing modulus. The ARFI image of the material interface was an estimate of the step response of the system. The ARFI imaging resolution limit was further explored using FEM/acoustic field simulations and linear shift invariant (LSI) models. The ARFI imaging resolution limit was 0.5 mm to 1 mm, but was highly dependent on imaging parameters. ARFI axial resolution was limited by the correlation window length and tracking pulse parameters. When the correlation window length was less than 1 mm, FEM and LSI models suggest the mechanical
response of the tissue influences the resolution, resulting in a larger FWHM than
would be predicted by imaging and signal processing parameters alone. ARFI lateral
resolution limit corresponded to the lateral two-way beamwidth of the tracking beam.
Measuring ARFI imaging resolution capabilities on small phantom inclusions and
tissue ablation lesions proved the validity of the step-response based estimated
resolution limits on objects of relevant, circular geometry. ARFI imaging resolution
was again primarily a function of imaging and signal processing parameters, in good
agreement with modulus step phantom derived results. To improve the ability of
ARFI imaging to resolve targets near bright boundaries, a method called envelope-
weighted normalization (EWN) was developed to reduce amplitude modulation of
ultrasound signals, thereby reducing displacement estimation bias.
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The following chapter of this dissertation was jointly produced. My participation and contribution to the research is as follows:

I am the primary author of Chapter 6. I collaborated with Professor Stephen McAleavey and with fellow graduate student Jonathan Langdon. This chapter has been accepted for publication in Ultrasonic Imaging.
Chapter 1 Introduction

Mechanical changes in tissues due to pathological or thermal processes can be exploited for treatment and diagnostic purposes. Elasticity imaging is a field developed to create images of tissue stiffness by mechanically exciting tissue and tracking its response. Acoustic Radiation Force Impulse (ARFI) imaging is one such modality that measures the micron-scale displacements induced in tissue by local acoustic radiation forces using high intensity ultrasound pulses generated by a standard diagnostic ultrasound scanner. Displacements are estimated by tracking micron-scale shifts in the ultrasound speckle pattern.

The goals of this thesis are to develop a novel approach to estimate ARFI imaging spatial resolution through simulation and experiment, and to reduce echo amplitude-dependent displacement estimation bias to allow better resolution of objects of interest near bright boundaries. This is achieved through the assessment of the ARFI imaging system’s ability to resolve the boundary between two bound materials of differing shear modulus. The ARFI image of the boundary serves as an estimate of the ARFI imaging step response, and the derivative is the point spread function (PSF) of the system. The full-width half-maximum (FWHM) of the PSF is used to quantify the resolution limit. The estimate of the step response is corrupted by noise due to speckle-tracking variability, which is only augmented when the derivative is calculated to estimate the width of the PSF. A nonlinear least squares fitting routine is used instead to fit a sigmoid function to the step, and the derivative of this fitting function was used as an estimate of the true PSF.

The ARFI imaging system is modeled as linear shift invariant (LSI) system. The axial PSF is modeled by convolving the correlation window length with the ultrasound
tracking pulse length, and the FWHM of the resulting function is calculated to estimate resolution. The lateral FWHM is compared to the lateral beamwidth of the tracking beams. Simulations are developed using coupled FEM/acoustic field simulations to better understand these parameters that fundamentally limit ARFI imaging resolution. The results from the LSI model and FEM simulation are compared to experimental estimates of the ARFI imaging resolution.

ARFI imaging resolution measurements are corroborated by imaging small, stiff inclusions in otherwise compliant tissue-mimicking phantoms and thermal lesions in excised porcine liver tissue. Cross-sections of a stiff conical phantom inclusion are imaged with diameters close to the ARFI imaging resolution limit (0.5 mm to 1.5 mm). Image contrast measurements between the stiff cross-sections and the more compliant background material are compared to results of a 2D LSI model, in which circles are convolved with a PSF, derived from imaging parameters. Cross-sections of the cylindrical ablation lesions, generated by passing a current through high-resistance wire threaded through porcine liver tissue, will also be imaged to demonstrate ARFI imaging resolution capabilities \textit{ex vivo}.

To reduce displacement estimation bias due to large changes in the underlying echo amplitude, a novel pre-processing approach is developed to locally diminish these strong signals called envelope weight normalization (EWN). A parametric simulation study is conducted that uses standard ARFI imaging specifications and experimental conditions to quantify the reduction in displacement bias and generation of jitter errors. Following the simulation study, radio-frequency (RF) data for ARFI images of a porcine hepatic vessel are preprocessed using the EWN prior to displacement estimation to demonstrate the technique’s bias reduction capabilities.
1.1 Organization of the Report

The purpose of this thesis is to aid in the improvement of the ARFI imaging technique through the development of new resolution estimation techniques and bias reduction methods, as highlighted by the following goals:

1. Develop finite element and acoustic field based simulations to estimate ARFI resolution.

2. Estimate ARFI imaging axial and lateral resolution using a tissue mimicking modulus step phantom.

3. Image small lesions near the resolution limit of our ARFI Imaging system to validate the step-response based resolution estimates on objects of relevant, circular geometry.

4. Reduce displacement estimate bias in ARFI images due to amplitude modulation in tracking echoes by implementing an envelope-weighted normalization technique.

Chapter 2 is a review of the basic concepts underlying ARFI imaging, along with the detailed methodology of standard ARFI imaging sequences. The acoustic radiation force is described, followed by the beam sequences implemented on an ultrasound scanner utilized to generate the forces. Tracking of resulting ARFI induced displacements are subsequently detailed along with alternative methods. In addition, safety considerations are addressed in terms of potential thermal and cavitation effects.

Chapter 3 provides a brief review of the impulsive dynamics of displacements induced in a homogeneous medium by an acoustic radiation force and details a coupled FEM/acoustic field simulation program used to estimate ARFI imaging axial and lateral resolution. The goal is to extract the point-spread function (PSF) of the system and quantify the resolution as the full width half maximum value of the PSF.
The PSF is derived by taking the spatial derivative of the step response of the system. The system step response is estimated by imaging the boundary between two bound materials of distinct shear modulus. A finite element model is developed that simulated this bimaterial and its response to a high intensity “pushing” beam. The fabrication and imaging of a “modulus step phantom” is described and experimental data are shown to corroborate simulation results.

Chapter 4 presents a novel experimental methodology by which to estimate ARFI imaging axial and lateral resolution using a modulus step phantom. The step phantom, as described in Chapter 3, allows the estimation of the PSF. Errors in ARFI images, called jitter errors, provide a number of challenges that are addressed in order to measure the FWHM of the ARFI imaging system PSF. In Chapter 5, these estimates are compared to ARFI imaging performance when imaging small lesions in tissue-mimicking phantoms and ablated porcine hepatic tissue \textit{ex vivo}.

Chapter 6 introduces a novel signal processing technique called envelope-weighted normalization (EWN) that reduces high amplitude regions of an echo signal, thereby reducing amplitude-dependent biasing of displacement estimates. Often times strong reflections exist at tissue boundaries, such as the walls of a blood vessel, that can dominate a displacement estimate and compromise ARFI imaging’s ability to resolve objects close to the wall. A parametric analysis was performed and the results suggest that this algorithm can improve ARFI images in the presence of strong reflections. Chapter 7 discusses how the tools developed in this thesis can be used to improve ARFI imaging and proposes future work motivated by these contributions.
Chapter 2 Background

2.1 Clinical Motivation

Pathological conditions give rise to mechanical changes in tissue that can be exploited for the purpose of diagnosis and treatment of disease. For hundreds of years, physicians have used manual palpation to interrogate suspicious stiff masses that are often an indication of cancerous tumors. In fact, digital rectal exams (DRE) are still a standard screen tool to identify prostate cancer in its early stages, and supplement other predictive measures that are recommended by the American Cancer Society, such as the prostate-specific antigen (PSA) test. Women are encouraged to regularly perform breast self-examinations (BSE) to detect potentially cancerous breast lesions, in addition to a regular mammography, because malignant masses are often detectable through palpation due to higher fibrous tissue content [1-4]. Nevertheless, these manual palpation techniques often fail to find growths that have low stiffness contrast relative to surrounding healthy tissue, that are very small, or that are located deep in the tissue. DRE has been shown to have a sensitivity of 55% to 68% in asymptomatic men and a positive predictive value of only 6% to 30% [5-7], leaving many cancer sufferers undiagnosed.

Changes in tissue stiffness are not only associated with malignant growths, but also characterize the progression of other common conditions, such as liver fibrosis and atherosclerotic plaque formation, and therapies such as thermal ablation treatments. Cirrhosis, the end stage of liver fibrosis, is a condition that affects an estimated 900,000 patients in the United States alone, resulting in an estimated 30,000 deaths per year [8]. Cirrhosis is presently diagnosed by liver biopsy, a highly invasive procedure that suffers from as much as 20% interobserver variability in evaluating the
degree of fibrosis [8]. A number of studies observed that liver stiffness is strongly correlated with fibrosis level, and has the potential to monitor its progression [9-14]. Atherosclerosis has long been linked to cardiovascular disease, and is typically diagnosed using invasive techniques, including angiography and intravascular ultrasound (IVUS), and noninvasive measures, such as carotid intima-media thickness (CIMT) [15-18]. These methods may be complimented by data regarding the altered mechanical properties of arteries with plaque formation [19, 20]. Thermal treatments that purposefully ablate diseased tissue cause local stiffening through protein denaturation, coagulation, inflammation and necrosis. Thorough treatment of the tissue target can be crucial in achieving disease remission, requiring adequate real-time monitoring of the treatment area.

Correlations between diseased and ablated tissues and changes in the mechanical properties motivate the development of elasticity imaging techniques. These methods serve to noninvasively assess the tissue stiffness to provide complementary information in an effort to improve the diagnosis, characterization, and treatment of disease. One such modality, and the focus of this thesis, is Acoustic Radiation Force Impulse (ARFI) imaging. In ARFI imaging, high intensity ultrasound beams are used to apply localized impulsive forces to tissue while monitoring the tissue response using ultrasonic techniques. The tissue response is inextricably linked to underlying tissue mechanical properties and can create high contrast images of diseased tissue. The next section describes ARFI imaging in detail as well as other elasticity imaging techniques.

2.2 Elasticity Imaging Modalities

With the advent of modern imaging modalities, such as ultrasound imaging and magnetic resonance (MR) imaging, tracking of tissue displacements has been widely investigated. Tissue displacements are related to the tissue mechanical properties,
which can change as a result of pathological processes in the tissue [1-4, 9, 17-20]. The range of elastography modalities can be differentiated by the method by which displacements are induced, including a variety of time harmonic, static, transient, or natural mechanisms. With knowledge of the forcing function and the corresponding tissue response, it is possible to extract information regarding the underlying tissue mechanical properties. In the following section elasticity imaging modalities are reviewed. For comprehensive reviews of the field of elasticity imaging please refer to Gao et al. [21], Greenleaf et al. [22], and Parker et al. [23].

2.2.1 Compression Elastography

Quasi-static external compression methods were used by Ophir et al. [24] to create strain images for what is now called compression elastography. In short, this method applies a uniform compression to tissue and estimates local tissue deformation by comparing ultrasound images before and after compression. These types of methods avoid the problems of vibratory techniques that can suffer from artifacts due to standing waves, reflections, and mode patterns. Furthermore, this method also simplifies the generalized one-dimensional discrete viscoelastic equation of force motion [24]:

\[ M\frac{d^2x}{dt^2} + R\frac{dx}{dt} + Kx = F_0e^{j\omega t}, \]

where \( M \) is the inertial controlled term, \( R \) is the viscous controlled term, \( K \) is the stiffness controlled term, \( x \) is the displacement, \( F_0 \) is the force amplitude, and \( \omega \) is the angular vibrational frequency. When the load is uniaxial and quasi-static the angular frequency \( (\omega) \) is zero. Since \( x \) is constant, the velocity and acceleration terms vanish, eliminating the inertial and viscous terms, respectively. The Hookean equation \( (Kx = F_0) \) remains, allowing for direct extraction of the Young’s modulus by estimating the displacements before and after application of a force. The equivalent Hooke’s Law is:
\[ \varepsilon E = \sigma \] (2.2)

where \( E \) is the Young’s modulus, \( \varepsilon \) is strain, and \( \sigma \) is the applied stress. Ophir et al. [24] computed displacements, and thereby strains, by using cross-correlation based speckle-tracking techniques. Knowledge of the applied compression and the boundary conditions can be used to generate images of tissue modulus. A constant stress field as a function of position is required to infer the elastic modulus distribution from the strain image directly. The most interesting, and clinically relevant tissue targets are elastically heterogeneous, therefore imposing additional boundary conditions. These boundary conditions influence the apparent stiffness of the tissue, making interpretation of strain images nontrivial [22, 25].

Compression elastography has been used in applications such as prostate, breast, and ablation lesion imaging. Good correlation was found between elastographic images and histology of excised canine prostates [26]. In vivo studies were performed by Garra et al. [27] to evaluate the plausibility of breast lesion detection. Cancerous tissues were found to be statistically significantly darker (lesser strain) than fibroadenomas, and a majority of cancers were differentiated from fibroadenomas and stiff benign masses. Righetti et al. [28] found ablation lesions induced by HIFU lesions were differentiable from surrounding healthy canine liver tissue. For RF ablation imaging, one study used a traditional compression plate [29], while another found the RF needle could be used as a more effective compression source [30]. A third RF study found compression elastography more successful at detecting RF ablation lesions that CT [31].

2.2.2 Sonoelastography

Tissue elasticity mapping can also be achieved by monitoring tissue response to a time harmonic, external vibration source in real-time using a pulsed Doppler ultrasound system, as first proposed by Krouskop et al. [32] and Lerner et al. [33].
The stiffness is inversely proportional to the amplitude of tissue vibration. A technique similar to color Doppler ultrasound is used to determine the vibration amplitude. Taylor et al. provided the following expression for the scattered ultrasound signal \(s(t)\) from a vibrating target [34]:

\[
s(t) = A \sum_{n=-\infty}^{\infty} J_n(\beta) \cos(\omega_0 t + n(\omega_L t + \phi)),
\]

where \(\beta\) is the modulation parameter of Bessel function \(J_n\), \(A\) is spectral amplitude, \(\omega_0\) (rad/s) is the angular frequency of the ultrasound signal, \(\omega_L\) (rad/s) is the angular frequency of the target vibration, and \(\phi\) is the vibration phase. Huang et al. [35] found a relationship between the modulation parameter of the Bessel function (\(\beta\)) and the standard deviation of the Doppler power spectrum of the received ultrasound echoes:

\[
\beta = \frac{\sqrt{2} \sigma_s}{\omega_L},
\]

where \(\sigma_s\) (Hz) is the standard deviation of the Doppler power spectrum. In other words, the vibration amplitude, given by \(\sigma_s\), is linearly related to the vibration amplitude, given by \(\beta\). An advantage of a Doppler-based displacement estimate is that it can be easily implemented in many modern ultrasound systems. A limitation to this method is that the low frequency excitation creates continuous shear waves that undergo reflection and diffraction at tissue boundaries, creating complex, difficult to interpret, interference patterns in the sonoelastographic images [22].

Sonoelastography has been used for a variety of applications including imaging of cancerous prostate tissues, non-invasive imaging of liver tissue, and thermal lesion imaging. Taylor et al. [36] explored tumor detection using 3D sonoelastography by collecting tomographic images of human excised prostates, outlining the tumor boundary, and performing 3D reconstructions. The study found that 3D volumes created using sonoelastography when compared to those using B-mode ultrasound
images showed better agreement with histological data. Sanada et al. [37] evaluated liver tissue non-invasively using sonoelastography. Positive correlations were found between shear wave velocity and liver fibrotic rate (ratio of proportion of fibrosis to whole liver), suggesting sonoelastography could be used to monitor liver fibrosis. Thermal ablation lesions in porcine liver tissue were imaged in real-time in a study by Zhang et al. [38]. The investigators found good agreement between volumetric sonoelastography data and gross pathology. Zhang et al. [38] also found sonoelastography to outperform B-mode imaging and concluded that sonoelastography techniques could potentially be used for thermal therapy evaluation.

2.2.3 Magnetic Resonance Elastography (MRE)

Displacement tracking for the purpose of elasticity imaging is not limited to ultrasound imaging techniques, but has also been performed using MR imaging methods. MR imaging can be used for displacement tracking of both statically and dynamically induced tissue displacements and is typically called magnetic resonance elastography (MRE). Dynamic MRE utilizes phase-contrast MRI to track shear waves and create a map of elasticity derived from shear wave velocities. For example, if a sinusoidal stress is applied to the tissue externally, the position of the nuclear spins, \( \mathbf{r}(t) \), can be modeled as [39]:

\[
\mathbf{r}(t) = \mathbf{r}_0 + \tilde{\xi}(\mathbf{r}, f),
\]  

(2.5)

\[
\tilde{\xi}(\mathbf{r}, \theta) = \tilde{\xi}_0 \cos(k \cdot \mathbf{r} - \omega t + \theta),
\]  

(2.6)

where \( \mathbf{r}_0 \) is the mean position of the nuclear spin, \( \tilde{\xi}(\mathbf{r}, \theta) \) is the displacement of the spin about its mean position, \( k \) is the wave vector, \( \theta \) is an initial phase offset, and \( \omega \) is the angular frequency of the mechanical excitation. The phase distribution \( \phi \) of the MR image is [39]:
\[ \phi = \gamma \int_{0}^{\tau} G_r(t) \cdot r(t) dt, \]  

(2.7)

where \(G_r(t)\) is an oscillating magnetic gradient, \(\tau\) is the time duration of the gradients after excitation, and \(\gamma\) is the gyromagnetic ratio (the ratio of the magnetic dipole moment to the angular momentum). When \(\tau\) is chosen such that [39]:

\[ \int_{0}^{\tau} G_r(t) dt = 0, \]  

(2.8)

the phase shift is given by [39]:

\[ \phi(\mathbf{r}, \theta) = \gamma \int_{0}^{\tau - NT - TE} G_r(t) \cdot \mathbf{\xi}(\mathbf{r}, \theta) dt = \frac{2\gamma NT (G \cdot \mathbf{\xi}_0)}{\pi} \sin(\mathbf{k} \cdot \mathbf{r} + \theta). \]  

(2.9)

where \(N\) is the number of gradient cycles, \(T\) is the period of the mechanical excitation, \(TE\) is the time at which the MR signal is received, and \(\omega = 2\pi T\). By collecting spatial phase information at a number of time points, quantitative measurements of wave velocity can be used to estimate shear modulus, given the following expression, relating shear wave velocity and shear modulus:

\[ c_s = \sqrt{\frac{G}{\rho}}, \]  

(2.10)

where \(c_s\) is the shear wave velocity, \(G\) is the shear modulus, and \(\rho\) is density.

Limitations of this technique include long acquisition time (on the order of minutes) and high cost [40].

MRE has been used to measure the mechanical properties of a variety of tissue types, including prostate, liver, breast, and muscle [41-47]. In preliminary work by Kruse et al. [42], shear stiffness and shear viscosity were calculated using multiple frequency
MRE data. Shear wave velocity was found to increase with an increase in tissue stiffness. Evidence was found of shear anisotropy in skeletal muscle and shear isotropy in liver tissue [42]. Sinkus et al. [48] also investigated viscoelastic shear properties of breast tissue by applying the MRE technique during the course of a standard MR mammography to study breast lesions in vivo. Shear modulus images showed differentiation between malignancies and benign fibroadenomas, suggesting MRE can aid in the diagnosis of breast cancer. Rouvier et al. [45] imaged patients with and without liver fibrosis and found a significant difference in the estimated mean liver shear stiffness, concluding that MRE shows promise in the assessment of liver disease.

### 2.2.4 Transient Elastography

Unlike time harmonic and static excitation mechanisms, transient elastography tracks tissue response to transient mechanical stimuli, reducing the impact of boundary conditions and motion artifacts. The method was first introduced by Catheline et al. [49] to avoid displacement estimation bias due to wave reflections. The investigators first demonstrated transient elastography in beef muscle using a piston source. An inversion algorithm is used to convert the measured shear wave displacements to shear modulus values. The dynamics equation for a linear, isotropic, piece-wise homogeneous medium can be described with the following expression [50]:

\[
\frac{\rho \partial^2 \vec{u}}{\partial t^2} = (\lambda + \mu \nabla \cdot \vec{u}) + \mu \nabla^2 \vec{u},
\] (2.11)

where \( \lambda \) and \( \mu \) are the Lamé constants and \( u \) is displacement. Two types of waves result from a transient excitation, shear waves and longitudinal waves, which are linked to the shear and bulk properties of the tissue, respectively. Since the bulk stiffness of the tissue is orders of magnitude greater than the shear modulus, longitudinal waves travel much faster than shear waves. Longitudinal waves
propagate out of the region of interest instantaneously relative to shear wave propagation speeds and can therefore be neglected. Displacements can only be estimated along the ultrasound beam, therefore only the z-component can be determined, leaving the following reduced basic equation for inversion [51]:

$$\rho \frac{\partial^2 u_z}{\partial t^2} = \mu \Delta u_z$$

(2.12)

where $\Delta$ represents the Laplacian operator. To cope with the lack of estimates of x- and y-components of the displacement field, the authors make the assumption that the displacements in the elevation dimension are much less than those in the imaging plane (axial and lateral dimensions) to reduce this expression to [51]:

$$\rho \frac{\partial^2 u_z}{\partial t^2} = \mu \left( \frac{\partial^2 u_z}{\partial x^2} + \frac{\partial^2 u_z}{\partial z^2} \right)$$

(2.13)

This expression can be readily used to estimate the shear modulus [51]:

$$\mu(x,z) = \rho \frac{\frac{\partial^2}{\partial t^2} u_z(x,z,t)}{\frac{\partial^2}{\partial x^2} u_z(x,z,t) + \frac{\partial^2}{\partial z^2} u_z(x,z,t)}$$

(2.14)

Bercoff et al. [51] used transient elastography to measure the stiffness of breast lesions by tracking low-frequency shear waves using an ultrafast ultrasound scanner. Sandrin et al. [52] developed a transient elastography system called the Fibroscan® to assess liver fibrosis in vivo, and found shear stiffness measurements to correlate well with fibrosis grade (METAVIR scale). This elasticity imaging modality is limited to applications near the surface of tissues that allow shear wave penetration from transient external excitation.
2.2.5 Remote Palpation Imaging

Rather than using an external vibration source, elasticity imaging can be performed using high intensity focused ultrasound beams to remotely generate local acoustic radiation force induced displacements that act as transient or time harmonic vibration sources near the region of interest (ROI). Micron-scale displacements are typically induced and displacements are tracked using ultrasonic methods. The displacements are related to the magnitude of the acoustic radiation force and the tissue mechanical properties.

Acoustic radiation force is employed by a number of groups to extract information related to tissue mechanical properties. Sugimoto et al. were among the first groups to investigate the use of acoustic radiation for the measurement of tissue “hardness” [53]. Nightingale et al. induced streaming using acoustic radiation force [54] to differentiate fluid from solid cysts, and later developed Acoustic Radiation Force Impulse (ARFI) imaging to generate displacements in tissue with focused ultrasound beams using a diagnostic ultrasound scanner [55]. Vibro-acoustography applies a local low frequency vibration (kHz range) to an object using confocal ultrasound beams that create oscillatory acoustic radiation forces [56]. The resulting acoustic emission is detected and provides information regarding the object’s elastic response to the harmonic stimulation. Supersonic Shear Imaging (SSI), Shear Wave Elasticity Imaging (SWEI), and Spatially Modulated Acoustic Radiation Force (SMURF) imaging monitor the propagation of shear waves induced by local impulsive acoustic radiation forces thereby estimating the shear modulus of the medium and have applications in the characterization of liver tissue [57-59]. Kinetic Acoustic Vitreoretinal Examination (KAVE) is a technique that applies an acoustic radiation force to the vitreous of the eye and estimates the resulting steady-state displacements ultrasonically [60]. Details descriptions of these methods are presented later in this chapter.
2.3 Acoustic Radiation Force Impulse Imaging

Acoustic Radiation Force Impulse (ARFI) imaging is a technique that uses a diagnostic ultrasound scanner to create images related to tissue stiffness. Transmitting a high intensity, short duration ultrasound pulse into the region of interest creates local acoustic radiation forces that induce tissue displacements. Momentum is transferred from the propagating pressure wave to an absorptive medium, such as tissue, in the direction of wave propagation. The magnitude of the acoustic radiation force is given by the following expression [55]:

$$ F = \frac{2\alpha I}{c} $$

(2.15)

where $F$ is the acoustic radiation force in the form of a body force, $\alpha$ is the absorption coefficient, $c$ is the sound speed, and $I$ is the temporal average intensity. High intensities ($I_{sppa} \sim 1000 \text{ kW/cm}^2$) can generate forces large enough to displace tissue ($\alpha \sim 1 \text{ dB/cm/MHz}$, $c \sim 1540 \text{ m/s}$) on the order of 10’s of microns [55]. The magnitudes of the displacements are related to the stiffness of the tissue and can therefore monitor the advancement of diseases characterized by tissue stiffening [61].

The primary goal of this section is to provide a basic understanding of the concepts underlying ARFI imaging. In Section 2.3.1, a typical ARFI imaging sequence is presented. Section 2.3.2 reviews displacement estimation techniques that allow for tracking of micron-scale shifts in the speckle pattern. Section 2.3.3 explains image formation from the displacement data set. Section 2.3.4 discusses the safety considerations when using high intensity ultrasound beams to induce measurable displacements in tissue.
2.3.1 ARFI Imaging Beam Sequences

ARFI imaging typically utilizes short duration (on the order of 100’s of microseconds), high intensity ($I_{sppa} \sim 1000 \text{ kW/cm}^2$) ultrasound pulses to create an acoustic radiation force [55]. Equation 2.15 shows that, assuming the medium has a relatively constant absorption coefficient and speed of sound, the force is directly proportional to the temporal average intensity and therefore has the same spatial extent as the intensity profile. An ultrasound frequency must be chosen that is high enough to create a significant acoustic radiation force, as the acoustic radiation force is a function of frequency dependent attenuation (Eq. 2.15). If the frequency is too high, however, frequency dependent attenuation will reduce ultrasound penetration, limiting the depth at which ARFI imaging can be performed. By using a focused beam, greater penetration can be achieved. Therefore, it is important that the ultrasound frequency is chosen such that the focal gain is dominant over attenuation. For example, consider a simple focused piston source. An approximation of the axial pressure profile is [62]:

$$p_z = p_0 G \frac{R \sin X}{z}$$  \hspace{1cm} (2.16)

given

$$X = \frac{G(\frac{R}{2} - 1)}{2(\frac{R}{z} - 1)}$$  \hspace{1cm} (2.17)

$$G = \frac{\pi a^2}{\lambda R}$$  \hspace{1cm} (2.18)

where $p_0$ is the source pressure, $G$ is the focal gain, $a$ is the radius of the aperture, $R$ is the focal length, and $\lambda$ is the ultrasound wavelength. Once the effect of attenuation is included, the expression for on axis pressure is [62]:

$$P = p e^{-\alpha z}$$  \hspace{1cm} (2.19)
where \( \alpha \) (dB/cm/MHz) is the attenuation coefficient. In Figure 2.1, pressure profiles are plotted for several frequency and attenuation coefficient values.

![Figure 2.1: Normalized acoustic pressure of a focused piston transducer on-axis for a range of frequencies (a), and attenuation coefficients (b). The radius of the piston is 1 cm and the focal length is 2 cm. For (a), the attenuation is 0.7 dB/cm/MHz, and in (b) the ultrasound frequency is 4 MHz.](image1.png)

Figure 2.1(a) shows that as frequency increases, the peak intensity increases and is located closer to the focal point. This is advantageous because a higher pressure amplitude results in a greater acoustic radiation force, and a deeper peak pressure implies better penetration. Figure 2.1(b) shows that an increase in the attenuation results in a decrease in the acoustic pressure, and pushes the peak pressure slightly closer to the transducer. These plots illustrate that choosing the optimal frequency, given tissue attenuation and desired imaging depth, is critical in creating ideal beam for the generation acoustic radiation forces.

Tracking is performed coaxially using standard B-mode ultrasound pulses (on the order of 0.1 – 1 microseconds). A schematic of a typical ARFI imaging sequence is shown in Figure 2.2.
Figure 2.2: Schematic of an ARFI imaging system, showing (a) the ARFI imaging setup, and (b) the pulse sequence. In (a) the transducer applies a high intensity, focused ultrasound (US) pushing beam to the tissue. In a homogeneous, absorbing medium, the maximum displacement is located on axis, generally in the vicinity of the focus. In (b), the pulse sequence is plotted, with the abscissa representing “slow time”, on the order of the pulse repetition period (PRP), and the ordinate representing “fast time”. The dotted line represents the beginning of each pulse period. Notice that the pulse used for the push is generally the same amplitude, but much longer than the tracking pulses. The displacement induced by the push causes a greater delay in retrieval of an echo from a particular scatterer until relaxation is complete, as shown by the change in the delay times of the received pulses.

Although the methodology reviewed here was used throughout this body of work, an ARFI imaging sequence is not limited to this pulse sequence. In an early study, Nightingale et al. [55] investigated the use of a range of pushing pulse durations and pushing pulse repetition frequencies. Using a series of pushing pulses while tracking increased the pushing pulse repetition frequency. Increases in pushing pulse duration and PRF increased the induced displacement, and consequently generated higher SNR ARFI images. For artery imaging, Trahey et al. [63] also implemented multiple pushing pulses with interspersed tracking pulses to exploit the higher displacements generated. On the other hand, for a similar application, Dumont et al. [64] used...
longer duration pushing pulses rather than a series of pulses. Transducer heating was reduced by utilizing a “wiper-blading” sequence in which beam sequences were laterally alternated rather than employing a left to right set of beam sequences.

### 2.3.2 Displacement Estimation

Displacements due to acoustic radiation force can be measured by utilizing well-established speckle-tracking techniques. Displacement estimation techniques were first proposed to measure blood flow velocities [65-67]. These methods were later adopted and modified for the purpose of estimating displacements in solid tissues [24, 68]. Now speckle-tracking techniques are widely employed by a diverse field of tissue stiffness imaging modalities, including static and time harmonic elastographic imaging [24, 30, 36, 46, 69-78], and acoustic radiation force excitation based imaging [53, 56-60, 79-82].

The “speckle pattern” refers to the granular quality of ultrasound images that can be exploited for the purpose of displacement estimation. The speckle pattern arises from the coherent nature of the source, resulting in the constructive and destructive interference of the acoustic contributions of densely packed, randomly distributed scatterers [83]. In the case of ultrasonic sources and tissue targets, in which the scattering sources comprise a uniform random distribution of an infinite number of Rayleigh scatterers, the SNR of the echo is 1.91 [83]. In practice, ten or more scatterers per resolution cell yields “fully developed” speckle [84, 85]. The speckle size and statistics are primarily dependent on the characteristics of the source when scatterers are randomly distributed [85].

Due to the variability of the speckle pattern in otherwise homogeneous tissue, pattern-matching techniques such as normalized cross-correlation, have been used to estimate local shifts in the tissue due to mechanical excitation. Tracking echoes, acquired during and after mechanical excitation, are compared to reference echoes, acquired before excitation. Windows corresponding to the same time after pulse transmission
in the reference and tracking signals are compared by performing normalized cross-correlation, given by the following expression for the normalized correlation coefficient [86]:

\[ R_N(\tau) = \frac{\int_{-T/2}^{T/2} f(t)g(t+\tau)dt}{\sqrt{\int_{-T/2}^{T/2} (f(t))^2 dt \int_{-T/2}^{T/2} (g(t+\tau))^2 dt}} \]  

(2.20)

where \( f(t) \) and \( g(t) \) represent the reference and tracking signals, \( T \) is the correlation window length, and \( \tau \) is the window shift in units of time. This operation is performed for a range of window shifts (i.e. \( \tau_{\text{min}} \leq \tau \leq \tau_{\text{max}} \)) along the tracking pulse. The value of \( \tau \) corresponding to the peak cross-correlation coefficient is the estimated time delay and can be converted into a distance (\( \Delta z \)) using \( \Delta z = c \tau/2 \), where \( c \) is the speed of sound in tissue.

Noise in the displacement estimate is characterized as either false peak errors or jitter errors [86]. False peak errors occur when a secondary correlation peak appears larger in magnitude than the true peak, due to noise, finite window length, and signal decorrelation effects. These errors are often greater than a quarter wavelength, and can be reduced by using nonlinear (e.g. median) filtering techniques [86]. A second type of displacement error is called jitter and is also attributed to signal decorrelation, noise, and finite window lengths. Jitter errors, unlike false peak errors, are characterized by small shifts of the primary correlation peak [86]. Jitter cannot be removed and represents a fundamental limit on displacement estimation performance.

A theoretical expression has been developed to estimate the lower limit of standard deviation of jitter errors known as the Cramer-Rao Lower Bound (CRLB) [86]. The CRLB is the lower bound on the performance of a unbiased displacement, or delay, estimator [86]. A delay estimator is unbiased when, on average, the estimator will yield the true value of the delay [87]. The CRLB model assumes that jitter errors are accrued when comparing two broad band signals with flat power spectra that have
been corrupted by electronic noise and decorrelation due to non-rigid deformation and shearing within the tracking beam. The CRLB has the following definition [88]:

\[
\sigma(\Delta t - \Delta't) \geq \sqrt{\frac{3}{2f_0^3\pi^2T(B^3 + 12B)}}\left(\frac{1}{\rho^2}\left(1 + \frac{1}{SNR^2}\right) - 1\right)
\]

(2.21)

where \(\sigma\) is the standard deviation of the jitter errors, \(\Delta t\) is the time delay, \(f_0\) is frequency, \(B\) is the fractional bandwidth, \(\rho\) is the correlation coefficient, and \(SNR\) refers to the signal to noise ratio of the echo signals. For a delay estimated using a reference signal and delayed signal, the CRLB is valid when the signals are relatively similar [86]. By appropriately adjusting tracking parameters, the lower bound of the standard deviation of jitter errors can be reduced.

Numerous other methods have previously been developed to estimate displacements. Examples of commonly used displacement estimators include sum square difference [89], sum absolute difference [90], hybrid-sign correlation [89, 91, 92], polarity-coincidence correlation [89, 91, 92], and the Meyr-Spies method [93-95]. Many of these methods simplify the original signal through a transformation to reduce the computational cost of the displacement estimate. For example, the hybrid-sign correlation transforms the original signal into a series of -1 and 1 values depending on the sign of the original signal. With loss of signal amplitude information, additional jitter errors are generated. Although normalized cross-correlation is computationally expensive, it is considered the gold standard because its performance matches the CRLB.

### 2.3.3 Image Formation

ARFI images are created by combining displacement data that correspond to a certain time after the application of the acoustic radiation force excitation [55]. After displacement calculation, an image is constructed from the collective group of ARFI
image lines. For each time delay (corresponding to a tracking pulse after the push), the displacement profile at each lateral location was combined to create a 2D ARFI image [Figure 2.3(a)]. The resulting image stack is a movie of the tissue response to acoustic radiation force excitation [Figure 2.3(b)]. Filtering techniques can be implemented to reduce noise, such as false peak errors, in the displacement estimates. Masking of the correlation coefficients and median filtering [96] of displacement data can discard outliers [97].

**Figure 2.3:** Schematic of ARFI image formation, showing (a) the ARFI imaging setup, and (b) the image stack. In (a) the transducer applies a high intensity, focused ultrasound (US) pushing beam to the tissue at a number of lateral locations (L₁-Lₙ). In (b) a stack of 2D images are generated. For each tracking pulse (t₁ – tₙ), the displacement profiles at all of the lateral locations are stitched together to create a single image. The set of images can be combined to create a movie of ARFI displacements.

Displacement data after acoustic radiation force excitation can be utilized to create images of a variety of different time-dependent parameters [61]. Images of time-to-peak and recovery velocity have been calculated in breast tissue by groups such as Nightingale et al. [61]. Spatial mapping of these various transient responses gives additional information regarding tissue mechanical properties and may also be used to differentiate tissues of differing stiffness [61].
2.3.4 Safety Considerations

Safety must be addressed when using high intensity ultrasound beams to create displacements for ARFI imaging. Two major bioeffects that can result from the exposure of tissues to high intensity ultrasound are cavitation and heating [62]. The potential damage to tissues as a result of cavitation and other non-thermal bioeffects is regulated by the United States Food and Drug Administration (FDA) by limiting the mechanical index (MI) to a value of 1.9 [98]. The MI has the following definition:

\[
MI = \frac{p_{r,3}}{\sqrt{f}},
\]

(2.22)

where \( p_{r,3} \) is the peak rarefractional pressure, measured at the location of peak pulse intensity derated by 0.3 dB/cm/MHz and \( f \) is the pulse frequency [99]. The spatial peak pulse average intensity (\( I_{spfa} \)) of ARFI pushing pulses is typically on the order of 1000 W/cm\(^2\) [55, 61, 100]. Assuming the pulse is long, sinusoidal, and of uniform amplitude at the location of maximum intensity, the pressure can be estimated using the expression of the intensity of a sinusoidal ultrasound wave:

\[
I = \frac{p^2}{2\rho c},
\]

(2.23)

where \( p \) is the acoustic pressure (Pa), \( \rho \) is the density (kg/m\(^3\)), and \( c \) is the sound speed (m/s). Given a pulse average intensity of 1000 W/cm\(^2\), the pressure is 5.5 MPa. By substituting the pressure calculated and pulse frequencies greater than 4.21 MHz result in MI values are less than 1.9, within the FDA limit. This is a conservative estimate, because in tissue, pulses of such high intensity are asymmetric, with rarefractional pressure amplitudes less than the compressional pressure amplitude.

The FDA regulates ultrasound dosage by enforcing intensity limits. The spatial peak temporal average intensity limit, derated by an attenuation coefficient of 0.3 dB/cm/MHz (\( I_{spta,3} \)) is 0.72 W/cm\(^2\) [101]. The FDA also limits either a pulse average
intensity ($I_{SPPA,3}$) of less than 190 W/cm$^2$ or an MI of 1.9. Since an MI of 1.9 can result in an $I_{SPPA,3}$ much greater than 190 W/cm$^2$, there is no effective limit on the $I_{SPPA,3}$. To understand how the FDA limit on the $I_{SPTA,3}$ affects the ARFI pushing pulse intensity, consider a train of ARFI pulses. If $I_{SPPA,3}$ is the spatial peak intensity averaged over a single pulse and $I_{SPTA,3}$ is the spatial peak intensity averaged over the pulse repetition period (PRP) [102]:

$$I_{SPPA,3} = \frac{I_{SPTA,3}}{t \cdot PRF},$$

(2.24)

where $t$ is the pulse length of the ARFI pulses and $PRF$ is the pulse repetition frequency. The FDA limit on the $I_{SPTA,3}$ requires the following expression to be satisfied:

$$I_{SPPA,3} < \frac{0.72}{t \cdot PRF} W/cm^2,$$

(2.25)

Assuming an $I_{SPPA,3}$ value of 1000 W/cm$^2$, the maximum allowable duty factor ($t \cdot PRF$) must be less than $7.2 \times 10^{-4}$. In this thesis, the pushing pulses were 200 cycles in length. For pulses with center frequencies of 4.21 MHz and 6.67 MHz pulses, the PRF’s must be less than 15 Hz and 24 Hz, respectively. A single image includes adjacent beams (not coaxial), and therefore only a single pushing pulse is applied to a particular focal location for a single image. This is only true close to the focus, where the -6 dB beamwidth is less than the line spacing of the images. Images are only collected at a rate as high as one image per minute in this thesis, corresponding to a frequency of only 0.02 Hz at the focus. The FDA does not presently specify the time over which the $I_{SPTA,3}$ must be averaged [102].

Heating is another consequence of the use of high intensity ultrasound pulses in tissue. The FDA also requires the calculation of the temperature index (TI), which diagnostic ultrasound scanners must display when the index exceeds 1, indicating the
potential for 1 °C of tissue heating. To calculate tissue heating due to a typical ARFI pulse used in this thesis, we can use the following expression [62]:

\[
\frac{dT}{dt} = \frac{2\alpha I}{4.18\rho c'}
\]

(2.26)

where \(\alpha\) is the absorption coefficient, and \(C\) is specific heat cal/g/°C, \(I\) is the temporal average intensity, and \(\rho\) is the density. For typical soft tissue, consider \(f = 6.67\) MHz, \(\alpha = 0.54\) Np/cm, \(\rho = 1000\) kg/m³, \(c = 1540\) m/s, and \(t = 30\) µs, the expected increase in temperature rise is 0.08 °C, well below the 1 °C TI requirement. Although ARFI pushing pulses are high intensity, their short duration results in little heating.

The expression presented in Equation 2.26 is an over-simplification for heating that results from ultrasonic imaging because 2D imaging involves complex source geometries and overlapping intensity fields. Palmeri et al. [100] computed the heat generated during ARFI imaging by using a finite element method (FEM) model composed of thermal elements, accounting for thermal characteristics of tissue such as heat capacity and thermal diffusivity. For details on the FEM simulation please refer to Palmeri et al. [100]. The study found that during ARFI imaging of tissue, heating did not exceed 1 °C [100]. Temperature increases less than 1 °C are deemed acceptable for diagnostic ultrasound scanning [98, 103], suggesting that ARFI imaging does not impose an increased risk to patients than that of conventional ultrasound techniques.

2.3.5 ARFI Imaging Applications

ARFI imaging has been used for a multitude of applications since Nightingale et al. first used acoustic radiation force to differentiate fluid filled cysts from solid lesions [54, 104], and showed its efficacy in tissue stiffness imaging [55]. ARFI imaging was implemented in an endocavity probe for gastrointestinal imaging, and proved effective at imaging at depth [105, 106]. Arteries were imaged by Trahey et al. [63],
Dumont et al. [64] and Behler et al. [97] showed ARFI imaging can distinguish mechanical changes associated with artherosclerosis. Behler et al. [97] demonstrated the feasibility of *in vivo* hemostasis assessment postcardiac catherization. Zhai et al. [107] performed prostate ARFI imaging and showed promise in differentiating internal structures and suspicious lesions. To aid regional anesthesia procedures, Palmeri et al. [108] investigated the feasibility of using ARFI imaging to aid in needle guidance. Hepatic shear modulus was measured in healthy humans [109], and in a rat model with fibrosis [109, 110], by implementing a modified version of ARFI imaging called the Time-To-Peak (TTP) algorithm that measures shear wave propagation speed to estimate the shear modulus. Cardiac ARFI imaging [111, 112] was achieved despite gross tissue motion by implementing a novel motion filter that subtracted the relatively slow, cyclic cardiac motion from the faster, transient response of the tissue to the impulsive acoustic radiation force.

### 2.4 Other Remote Palpation Imaging Modalities

ARFI imaging is only one of a number of elasticity imaging modalities that measure displacements induced remotely using focused ultrasound beams. Although all of these remote palpation techniques share a common method of mechanical excitation through remote generation of local acoustic radiation forces, the implementation is quite varied. These techniques were briefly summarized in the previous chapter and are reviewed in this section in greater detail.

#### 2.4.1 Kinetic Acoustic Vitreoretinal Examination (KAVE)

KAVE imaging uses acoustic radiation forces to generate steady-state displacements and estimates the displacements ultrasonically [60]. Through mechanical modeling, parametric images of relative mass, relative elasticity, and relative viscosity have
been generated. Viola et al. [113] developed a simple model consisting of an inertial component in series with a Voigt model:

\[
m \dddot{x}(t) + \mu \ddot{x}(t) + kx(t) = F(t),
\]

(2.27)

In their study, Viola et al. [113] transmitted 5000 ultrasonic pulses to the same location in a vitreous-mimicking phantom, at a pulse interval much shorter than the time constant of the mechanical response of the tissue, generating a step-like forcing function [113]:

\[
F(t) = AH(t),
\]

(2.28)

where \( A \) is the force amplitude and \( H \) is the Heaviside unit step function. Substituting Equation 2.27 into Equation 2.28 yields [113]:

\[
x(t) = \xi + \frac{\xi}{2\sqrt{\xi^2 - 1}} e^{(-\xi + \sqrt{\xi^2 - 1})t} + \frac{\xi}{2\sqrt{\xi^2 - 1}} e^{(-\xi - \sqrt{\xi^2 - 1})t} + s,
\]

(2.29)

where \( \xi \) is the damping ratio, \( \omega \) is the natural frequency (rad/s), and \( s \) is the static sensitivity. Since the force amplitude \( A \) is unknown, because it depends on the unknown properties of the tissue, the time-dependent data can only be used to solve relative parameters [113]:

\[
\xi = \frac{\mu_r}{2\sqrt{k_r^3 m_r}}, \quad \omega = \sqrt{\frac{k_r}{m_r}}, \quad s = \frac{1}{k_r},
\]

(2.30)

where \( k_r = k/A, \mu_r = \mu/A, \) and \( m_r = m/A. \) In this way, KAVE imaging exploits not only the amplitude of the displacements induced by the radiation force, but also excitation and relaxation behavior of the tissue target to extract viscoelastic parameters. This imaging modality has promise in aiding the diagnosis of vitreoretinal disorders, in which changes in the mechanical properties of the vitreous humor can be indicative of age-related degradation or disease [113].
2.4.2 Vibro-acoustography

Vibro-acoustography is a method by which dynamic, oscillating radiation force is induced in an object of interest, and the object’s response is recorded, providing information regarding material properties. Two interfering, continuous wave, confocal ultrasound beams produce the oscillatory force. If the frequencies of the two beams are $f_0$ and $f_0 + \Delta f$, in the vicinity of the foci, the combined ultrasound fields interfere, creating a sinusoidally modulated force, or oscillation, with a frequency of $\Delta f$. The coaxial foci create a very small vibrating source, which in turn creates an acoustic emission. The resolution is a function of the size of the vibrating source. The emitted wave travels through the tissue at a temporal frequency of $\Delta f$. The ultrasound beam is scanned throughout the ROI and the acoustic emission is detected by a hydrophone. The hydrophone data are recorded and mapped into an image. Fatemi et al. [56, 80, 114, 115] found vibro-acoustography capable of detecting small objects such as submillimeter glass spheres and calcifications in excised arteries.

2.4.3 Shear Wave Elasticity Imaging (SWEI)

SWEI imaging generates an amplitude modulated acoustic radiation force in a tissue target using high intensity focused ultrasound beams and monitors resulting shear wave motion ultrasonically to extract viscoelastic parameters [58]. Saravazyan et al. [58] described two ways in which the shear waves can be detected. The first method described uses ultrasound imaging transducers for shear wave detection and tissue imaging. The imaging transducers can either be incorporated in the transducer used for shear wave generation, or positioned on another side of the tissue. Another possible configuration for SWEI is to induce a low frequency shear wave such that low-frequency acoustic sensors can detect ultrasonically generated shear waves at the tissue surface. By solving the inversion problem, reconstruction of the mechanical features of the medium is possible.
It is also possible to determine the shear modulus (μ) by estimating the time necessary for the displacement at the focus to reach a maximum value after pulse excitation, assuming a Gaussian beam profile [58]:

$$\mu = \rho \left( \frac{aD}{t_{\max}} \right)^2,$$

(2.31)

$$D = \frac{d}{x_d},$$

(2.32)

$$x_d = \frac{\omega a^2}{2c},$$

(2.33)

where \(a\) is the diameter of the aperture, \(D\) is the diffraction, \(d\) is the focal length, \(x_d\) is the diffraction length, \(\omega\) is the ultrasound frequency, and \(t_{\max}\) is the time required to achieve the maximum displacement. In addition, the time it takes for the tissue to relax to a certain level can be used to determine the shear viscosity of the tissue [58]. By modeling and experimentally validating shear wave generation and propagation induced by acoustic radiation forces, SWEI imaging laid the foundation for a number of other acoustic radiation force shear wave monitoring modalities [56, 57].

### 2.4.4 Supersonic Shear Imaging (SSI)

In SSI imaging, acoustic radiation forces are used to generate vibration sources radiating low-frequency shear waves moving at speeds greater than the tissue shear wave speed along the imaging axis [57]. This can be achieved by successively focusing the ultrasonic high intensity pushing beams at different depths. A “Mach cone” results from the contributions of the moving source due to constructive interference, characterized by two planar shear waves. These waves show relatively high displacement amplitude compared to other radiation force-based imaging modalities because of the constructive interference (40 μm – 100 μm), especially important in very stiff or viscous tissues. The angle between the forcing axis and the
planar waves depends on the speed of the source. By tracking the 1D displacement field ultrasonically, the tissue stiffness is mapped quantitatively by utilizing inversion algorithms. Shear modulus can also be mapped by estimating the shear wave speed ($c_s$) using the time of flight of the shear wave between two spatial points ($\mu = \rho c_s^2$).

For details regarding the inversion algorithm, refer to Section 2.2.4. By changing the shear wave angle, spatial compounding can be used to improve elasticity images. Images are acquired at very high speeds through implementation of parallel receive beams. SSI has been used \textit{in vivo} to map the viscoelastic parameters of human bicep muscle [116], human liver [116], and human corneal tissue [117].

2.4.5 Spatially Modulated Ultrasound Radiation Force (SMURF)

Imaging

SMURF imaging creates shear modulus images of tissue by inducing spatially modulated radiation forces and tracking the resultant shear wave ultrasonically [59]. SMURF imaging can be performed in one of three ways. A single, spatially modulated shear wave can be induced using focal Fraunhofer or intersecting plane wave methods which exploit the constructive and destructive interference of the ultrasound beams to create a spatially modulated displacement profile. A third method to create the spatial modulation is to sequentially push in adjacent locations. This is feasible because of the large difference (three orders of magnitude) between the ultrasound and shear wave velocities, and the relatively short duration of the pushing pulses (30 µs) relative to the shear wave periods (0.5 – 2 ms). A tracking beam is utilized adjacent to the pushing location, the displacement field is tracked, and the temporal frequency estimated. A higher temporal frequency is an indication of a stiffer material, as shown in the following expression:

$$\mu = \rho (\lambda f)^2, \quad (2.34)$$
where $\lambda = \frac{2\pi}{k}$, $k$ (m$^{-1}$) is the spatial frequency, and $f$ (Hz) is the temporal frequency of material vibration.

A second modified version of SMURF imaging applies an acoustic radiation force at a single location and tracks the displacements from that pulse at an adjacent location. Later, another acoustic radiation force is applied at a second location, and the displacements are tracked at the same location as the previous pulse. The difference in arrival times can be used to estimate the shear modulus. As in ARFI imaging, a standard diagnostic scanner may be used for the implementation of this technique, but unlike the ARFI imaging, SMURF imaging can provide quantitative information regarding the shear modulus of the tissue. The SMURF imaging technique has estimated stiffness in tissue mimicking gelatin phantoms of various shear moduli and shows good agreement with estimates using quasistatic material testing techniques [59].

### 2.5 Elasticity Imaging and Resolution

A number of groups investigated lesion delectability in elastographic images using both tissue-mimicking phantoms and finite element method (FEM) simulations. Nightingale et al. [96] studied lesion displacement contrast as functions of time after force application, stiffness ratio, lesion diameter, focal position, and force duration in ARFI imaging. The studies were performed in hydrogel tissue-mimicking phantoms with matching FEM simulations. Palmeri et al. [118] studied the dynamic response of lesions of various Young’s modulus ratios (4:12 kPa, 4:24 kPa, 8:24 kPa, and 8:48 kPa) and diameters (14 mm to 20 mm) to acoustic radiation force. Parker et al. [119] investigated the detectability of lesions using vibration sonoelastography by measuring displacement contrast as functions of vibration frequency, lesion size, and modulus ratio using FEM simulations and corroborating the results with Zerdine phantom data.
The spatial resolution limit is one method by which image quality is quantified for a number of elastographic techniques. Alam et al. [120] measured elastographic axial resolution as a function of window length and shift by simulating a phantom composed of a stiff 1D wedge in a compliant background. The resolution limit was defined as the widths of the wedge at which the strain profile dropped below the average of the high and low strains. This was essentially an estimate of the axial dimension of the point spread function (PSF) of the system. Fatemi et al. [115] measured the resolution of their vibro-acoustography system by imaging a glass bead on a thin latex sheet and found the measured PSF to match the theoretical PSF based on excitation frequency, transducer dimensions, and target location. Others have created more sophisticated simulations to include the mechanical parameters that can impact elastographic image resolution. Righetti et al. measured both axial [121] and lateral [122] resolution by simulating two stiff lesions in a compliant, homogeneous background. Strain was simulated in a finite element (FE) model, and displacement tracking was simulated using the acoustic field simulation program FIELD II [123, 124]. The width of the PSF was estimated by measuring the width of the peak in displacement between the two lesions at the -6 dB threshold. In both cases the entire measurement was simulated and the method of tissue deformation was static, global strain.
Chapter 3 Coupled Finite Element and Acoustic Field Simulation for ARFI Resolution Estimation

3.1 Introduction

This chapter presents previous work focused on modeling displacements in inhomogeneous media due to an impulsive acoustic radiation forces, followed by novel numerical finite element and acoustic simulations used to estimate ARFI resolution. Section 3.2 first reviews the equations that describe the mechanical response of a homogeneous continuum to an impulsive radiation force, as described by Palmeri et al. [125], and then details previous work regarding the more complicated response of a bimaterial to such forces. Section 3.3.1 describes numerical FEM simulations developed to quantify the ARFI imaging axial resolution. For both lateral and axial resolution FIELD II is used to simulate the ultrasonic tracking parameters involved in the ARFI imaging system that can also determine the resolution. In Section 3.3.2, the FEM simulations are experimentally validated using gelatin-based tissue mimicking phantoms.

3.2 Background

3.2.1 The Acoustic Radiation Force

The acoustic radiation force can be described as a unidirectional force due to a transfer of momentum from an acoustic wave to an attenuating medium [55]. The
acoustic radiation force per unit area in an absorbing, Rayleigh scattering medium is given by [55, 126]:

\[ F_{\text{total}} = (\Pi_a + \Pi_s)(E) \]  

(3.1)

where \( F_{\text{total}} \) is the total force per unit volume experienced by the target, \( \Pi_a \) is the power absorbed per unit incident intensity, \( \Pi_s \) is the power scattered per unit incident intensity, and \( \langle E \rangle \) is the temporal average energy density of the acoustic wave. The contribution of absorption (\( \Pi_a \)) to attenuation of acoustic waves in tissue is much larger than that of scattering (\( \Pi_s \)) [127], therefore scattering can be neglected in the calculation of the acoustic radiation force. By using a plane wave approximation, the radiation force in tissue is [55, 128, 129]:

\[ F = \frac{2\alpha I}{c} \]  

(3.2)

where \( F \) is the acoustic radiation force in the form of a body force, \( \alpha \) is the attenuation, \( c \) is the sound speed, and \( I \) is the temporal average intensity. Equation 3.2 shows that an acoustic radiation force can be generated with the appropriate acoustic intensity from the source and absorption characteristics of the medium, resulting in the local displacement of the medium.

### 3.2.2 Displacements in Continua

The governing elastodynamic equations presented in this section follows the derivation by Achenbach [130], and later by Palmeri et al. [125] The displacement equation for a linearly elastic, isotropic solid can be expressed in vector form as [130]:

\[ (\lambda + \mu) \nabla (\nabla \cdot \vec{u}) + \mu \nabla^2 \vec{u} = \rho \ddot{\vec{u}}, \]  

(3.3)
where $\lambda$ and $\mu$ represent the Lame constants for the material [131] and $\rho$ [kg/m$^3$] is the material density. The decomposition of the displacement field can yield [130]:

$$\vec{u} = \nabla \xi + \nabla \times \vec{W},$$  \hspace{1cm} (3.4)

where $\xi$ represents the dilatation (longitudinal) displacement component, and $\vec{W}$ represents the equivoluminal (transverse) displacement component. The substitution of the displacement field (Equation 3.4) into the displacement equation (Equation 3.3) is given by the expression:

$$\nabla \left[ (\lambda + 2\mu)\nabla^2 \xi - \rho \frac{\partial^2 \xi}{\partial t^2} \right] + \nabla \times \left[ u\nabla^2 \vec{W} - \rho \frac{\partial^2 \vec{W}}{\partial t^2} \right] = 0$$  \hspace{1cm} (3.5)

The longitudinal and transverse displacement components in Equation 3.5 are separable and individually take the form of the wave equation [130]. These equations can be expressed in one direction ($\hat{x}$) [125]:

$$\nabla^2 \vec{W} = W_x(x,t)$$  \hspace{1cm} (3.6)

$$\frac{\partial^2 W_x}{\partial x^2} - \frac{1}{c_T^2} \frac{\partial^2 W_x}{\partial t^2} = 0,$$  \hspace{1cm} (3.7)

$$\frac{\partial^2 \xi}{\partial x^2} - \frac{1}{c_L^2} \frac{\partial ^2 \xi}{\partial t^2} = 0,$$  \hspace{1cm} (3.8)

$$c_L = \sqrt{\frac{(\lambda + 2\mu)}{\rho}},$$  \hspace{1cm} (3.9)

$$c_T = \sqrt{\frac{\mu}{\rho}},$$  \hspace{1cm} (3.10)
where $c_L$ represents the longitudinal wave speed, and $c_T$ represents the transverse wave speed. These constants reveal that the transverse and longitudinal wave speeds are functions of the Lame constants of the material. While the longitudinal wave speed is dependent on both constants, the transverse wave speed is only dependent on the shear modulus. Although gelatin-based phantoms are typically elastic, tissue often exhibits viscous properties. The viscous properties cause the tissue to exhibit a time-dependent response to a stimulus that can be expressed by including complex terms in the Lame constants.

### 3.2.3 Displacements in Bimaterials

The utility of elastography comes in the ability to distinguish one material from another by acquiring mechanical property information. ARFI imaging generates displacements within the ROI that are related to the stiffness of the material. If there are local changes in material stiffness, changes in displacement amplitude can be expected. An imaging metric that can quantify the ability of ARFI imaging to differentiate media of varying stiffness is resolution. The ARFI image resolution is the ability to distinguish detail in the estimated displacement profile, which can be limited by imaging, signal processing, and material properties.

ARFI imaging resolution can be estimated by imaging an interface separating two bonded materials, or a “bimaterial” of differing stiffness. The ARFI image of the bimaterial interface is the step response of the system. The spatial derivative of the step response is the point spread function (PSF). The width of the PSF can be used to quantify the resolution. In the following chapters, ARFI resolution is estimated axially and laterally, requiring two different orientations of the bimaterial interface and the transducer. These orientations motivate the following analyses of transient displacements in axially and laterally oriented bimaterials. Propagation of displacements in an unbounded continuum is well understood, however, when a
boundary between two media is introduced, reflections are generated at the interface making the transient response more complicated.

The local acoustic radiation force primarily generates shear (transverse) waves that propagate away from the region of interest, in a direction perpendicular to the direction of the force. In ARFI imaging the pushing pulse generates 3D, spatially varying forces. These forces are not all orthogonal to the interface and can therefore result in complicated shear wave interactions such as reflection and refraction across the interface. Understanding the transient response of layered media has been of interest in the field of seismology for decades. A number of groups have determined exact solutions for using tools such as generalized ray (GR) [132] and Cagniard deHoop methods [133, 134]. Although a number of groups have developed exact solutions for a force at some distance from a bimaterial interface, these displacement fields can be quite complicated, and specific to particular sources and configurations.

3.2.4 Finite Element Method

Finding an analytical expression for the transient response of a bimaterial to an impulsive, spatially varying force is non-trivial. As was described in the previous section, reflections are generated at the interface making the transient response quite complicated. Mathematical models developed to determine the mechanical response of homogeneous tissues to acoustic radiation force, such as the Khokhlov-Zabolotskaja-Kuznetson (KZK) equations [58, 72, 135] and Greens function analyses [57, 136], cannot represent the complex displacement fields in these bimaterials. In addition, modeling the material response due to an ARFI excitation of a solid given a particular transducer geometry and configuration lends itself to numerical methods.
3.3 Methods

3.3.1 Finite Element Model for Axial Resolution Estimation

Mesh Generation

A Finite Element Method (FEM) model was developed to estimate ARFI imaging axial resolution. The model accounted for the dynamic, spatially varying pushing pulse following the method developed by Palmeri et al. [125], in addition to the inhomogeneous nature of the medium. Finite element software (FEMLAB, Comsol Inc., Burlington, MA) was used to create a 3D transient linear elastic model. While Palmeri et al. [125] presented models of homogeneous elastic solids and spherical inclusions, a two material model with a planar interface is presented here. In the model, the two materials only differed in shear modulus, and the planar interface was located in the lateral-elevation plane (parallel to the face of the transducer) at the lateral focal depth of 2 cm.
Figure 3.1: Plots of the FE solid mesh. The mesh consists of a total of 17,520 Lagrange quadratic, 8-noded brick elements. Plane symmetry was used in the elevation dimension (y). The top surface of the model, the contact area of the transducer, was fixed in the lateral (x) and elevation dimensions. The bottom surface was fixed in all dimensions. The finest mesh was in the shadow of the transducer (0.2 mm axially and 0.5 mm laterally) in the vicinity of the elastic step (1.5 cm to 2.5 cm axially).

An elastic solid was modeled by generating a mesh composed of 17,520 Lagrange quadratic, 8-noded, brick elements, as shown in Figure 3.1. The dimensions of the model were 10 mm, 16 mm, and 30 mm in the elevation, lateral and axial directions, respectively. Dimensions were chosen to allow for wave propagation and dissipation, such that reflected waves from the model edge minimally affect the displacements at in the ROI. The top surface of the model (closest to the transducer) was fixed in the lateral and elevation dimensions, consistent with the experiment in which the transducer was in contact with the top of the phantom. The bottom surface was fixed in all directions. The front axial-lateral plane was fixed in the elevational dimaension to exploit elevational symmetry, thereby reducing the computational cost of the model.
The Young’s modulus was defined as stiffer 2 cm to 3 cm from the transducer, with a shear modulus of 6.3 kPa, and compliant from 0 cm to 2 cm from the transducer with a shear modulus of 4.0 kPa. The orientation of the bimaterial interface perpendicular to the axis was chosen to measure axial resolution. Shear modulus values were chosen based on stiffness estimates of a phantom used to validate the model. A Poisson’s ratio of 0.499 was chosen to approach the incompressibility conditions while maintaining numerical stability. Node spacing was 0.5 mm in the elevation direction, but varied in the axial-lateral plane. The finest mesh was in the shadow of the transducer (0.2 mm axially and 0.5 mm laterally) in the vicinity of the elastic step (1.5 cm to 2.5 cm axially). Small element sizes near the elastic step were critical in accurately modeling the complex displacements at the interface.

Forcing Functions

To compute the 3D intensity field in the region of interest (ROI), the VF7-3 transducer was simulated using FIELD II [123, 124]. The transducer had a single row of elements, a 5.33 MHz center frequency, 4.21 MHz excitation frequency, a F/5 focal configuration in elevation, a F/3.1 focal configuration laterally, and a focal depth of 2.0 cm. The attenuation was defined as that of the tissue-mimicking phantom (0.7 dB/cm/MHz). The radiation force was approximated to be proportional to the acoustic intensity (Equation 3.2), and was converted to a spatially varying forcing function.

FEM Model Solution

Displacements were computed numerically for a 3D elastic solid using commercially available finite element software (FEMLAB, Comsol Inc., Burlington, MA). The forcing function was imported by the FE program and applied as a force for the duration of a pushing pulse (48 µs). The 3D, spatially varying force was applied in the axial direction downward (away from the transducer), given that displacements
induced by acoustic radiation forces primarily occur in the axial direction. FEMLAB bases its implementation on the equilibrium equations expressed in global stress components. Given the initial transient forcing conditions, the program calculated the stress field by satisfying Newton’s Second Law (F = ma) using a standard linear conjugate gradients method at predefined time steps. The simulation solved for displacements for 10 time points with interval spacing of 0.15 ms after cessation of the 48 µs pushing force. The interval spacing was chosen to match the experimental tracking pulse repetition period. The solution was converted to displacements as a function of time by FEMLAB using stress-strain and strain-displacement relationships. The resulting displacement profile peaks were normalized to peak displacement estimated experimentally.

3.3.2 Experimental Validation

ARFI Beam Sequences and Displacement Estimation

ARFI beam sequences consist of transmitting one or more reference pulses, followed by a pushing pulse and a series of tracking pulses for each image line. ARFI Imaging was performed with a Siemens SONOLINE Antares™ (Siemens Medical Solutions USA, Inc., Issaquah, WA, USA) using the VF7-3 linear array and the imaging parameters matched those used in the FEM simulation. The aperture remained unapodized to maximize acoustic output of the transducer. Pushing pulses were 48 µs (200 cycles at 4.21 MHz) in duration, and a 50% system output was used to avoid overheating of the phantom and the transducer. The displacements induced by the pushing pulse were tracked by a series of 5 µs (2 cycles at 4.21 MHz) pulses with a pulse repetition frequency (PRF) of 6.7 kHz for 4.8 ms after the pushing pulse. This sequence was repeated at 27 lateral locations with 0.71 mm spacing.

Pushing and tracking beam profiles were chosen for accurate displacement estimation. McAleavey et al. [137] showed that the displacement estimates
determined using a tracking beam is the average of the displacement values across the beam. When the pushing beamwidth is wide compared to the tracking beam, the region that is averaged across the tracking beam is close to the peak displacement. In this thesis, the pushing beams were generated using an F/3.1 focal configuration with a 2 cm axial focal length. The tracking beams were created using an F/2 focal configuration with a 2 cm axial focal length on transmit and dynamic focus on receive. Tracking beams were apodized using a Hamming window to reduce sidelobes and for improved contrast resolution. The pushing beam aperture remained unapodized to allow for maximum intensity, and therefore maximum displacement in the ROI.

Displacements were estimated with sub-sample precision. After determining the correlation coefficients for a range of window shift values, a continuous fitting function is used to predict a peak in correlation that may exist between interpolated samples. In the studies completed in this thesis, a lowpass interpolation was used of a factor of 8 before cross-correlation, allowing for sub-sample delay estimates. An adequate interpolation factor was empirically determined by increasing the factor until no significant change in the displacement estimate was observed between factors. An interpolation factor of 8 was adequate to reduce this interpolation noise below the noise floor. A parabolic fit of the correlation coefficients was used to estimate displacements with further sub-sample precision.

**Tissue-Mimicking Phantom**

The phantom was fabricated to include a compliant cylinder embedded in a stiff background material, as shown in Figure 3.2. The background was created using 300 Bloom gelatin at a concentration of 61 g/L in deionized, degassed water and 4% weight 2-propanol (Mallinckrodt Baker, Inc., Phillipsburg, NY, USA). Cornstarch (Wegmans Food Markets, Rochester, NY, USA) was added to the gelatin mixture at a concentration of 185 g/L to provide ultrasound scattering and attenuation (0.7
dB/cm/MHz). 1% weight gluteraldehyde (Amresco, Inc., Solon, OH, USA) was added just before the gelatin mixture was poured into molds to increase the melting point. The phantoms were roughly cylindrical with a mean diameter and height of 7 cm. The phantom background was fabricated around a rod attached at the base of the cap of the mold. After removing the rod, the same procedure was used to create the embedded, compliant cylinder using 100 Bloom gelatin. The procedure was adapted from Hall et al. [138].

**Figure 3.2:** Tissue mimicking phantom (left) and the schematic (right), which includes the internal geometry of the phantom. The total diameter and height were approximately 7 cm. The gray regions are compliant and the surround region are stiff. The cylindrical inclusion was imaged in order to measure the step response of the ARFI imaging system and was subsequently removed for mechanical testing. The conical inclusion was used in later studies as a resolution target. The shear modulus of the stiff inclusion was $6.3 \pm 0.1$ kPa and the shear modulus of the compliant background was $4.0 \pm 0.1$ kPa.

Core samples were obtained and the modulus was estimated using an MTS-1/S Material Testing Workstation (MTS Systems Corporation, Eden Prairie, MN, USA). Young’s modulus (E) of the phantoms was estimated by performing unconfined cyclic loading from 5% to 10% strain. Young’s modulus is related to shear modulus (G) through the relationship $G = E/3$ assuming incompressibility. Shear moduli of $6.3 \pm 0.1$ kPa and $4.0 \pm 0.1$ kPa were calculated for the cylinder and the background, respectively.
**Experimental Setup**

The tissue-mimicking phantom was imaged in deionized, degassed water in a Plexiglas tank. The transducer was fixed above the phantom and the phantom was placed on a 1 in thick rubber absorber to mitigate reflections from the bottom of the tank. The compliant core was closest to the face of the transducer and the interface between the stiff and compliant materials was positioned at the 2 cm focus. Representative displacement profiles were collected for comparison with simulation results. Immediately after imaging, the phantom was mechanically tested, as was detailed in the previous section, and the Young’s modulus values were used for the FEM simulation.

**3.4 Results**

**3.4.1 ARFI Intensity Fields**

The ARFI intensity field of the pushing pulse was computed using FIELD II. The axial profile is given on the transducer axis and the lateral profile is given at an axial position of 18.9 mm, the location of peak intensity, in Figure 3.3. The axial peak occurs slightly shallower than the 20 mm below the transducer face (lateral focus) of the transducer due to attenuation effects. The -6 dB beamwidth is approximately 1 mm at the focus. The tracking beam is narrow relative to the pushing beam with this configuration, as illustrated in Figure 3.4, using FIELD II.
Figure 3.3: Plots of ARFI intensity (a) in 2D, (b) axial, and (c) lateral dimensions, and in all cases centered in the elevation dimension. FIELD II was used to generate these patterns by simulating the VF7-3 transducer ($\alpha = 0.7$ dB/cm/MHz, center frequency of 5.33 MHz, excitation frequency of 4.21 MHz, lateral focal depth of 20 mm and F/3.1 focal configuration). The axial profile is given on the transducer axis (lateral position is 0 mm) and the lateral profile is given at an axial position of 18.9 mm, the location of peak intensity.

Figure 3.4: Simulated tracking and pushing beam profiles at the 2 cm axial focal depth. In (a) an excitation frequency of 4.21 MHz is used to generate the profiles, and in (b) an excitation frequency of 6.67 MHz is used. The pushing beams were generated using an F/3.1 focal configuration with a 2 cm axial focal length. The tracking beams were created using an F/2 focal configuration with a 2 cm axial focal length on transmit and dynamic focus on receive. The pushing pulse aperture was unapodized, while the tracking beam used Hamming apodization.

3.4.2 ARFI Displacement Fields in a Bimaterial

Finite element method (FEM) model displacements are illustrated in Figure 3.5 showing displacement fields plotted in the imaging plane of the transducer for
multiple time points. The shear modulus was 4.0 kPa between the transducer (top) and 2 cm on axis and was 6.3 kPa from 2 cm to 3 cm on axis. Brighter pixels indicate higher magnitude displacements in the direction away from the transducer (axially). Notice for the first time point ($t = 0.15$ ms), the displacement amplitude is greater in the stiffer medium (2 cm to 3 cm). During later time points ($t = 0.45$ ms, 0.75 ms) the stiffer medium includes displacements of lesser amplitude that spread more rapidly than those in the compliant medium (0 cm to 2 cm).

**Figure 3.5:** Displacement fields plotted in the plane of the transducer for three time points from the FEM simulation. Brighter pixels indicate higher magnitude displacements in the direction away from the transducer (axially). The medium shear moduli are 4.0 kPa for the compliant region between 0 mm and 20 mm from the transducer axially, and 6.3 kPa for the stiff region between 20 mm and 30 mm axially.

Displacements, as computed by the FEM simulation, were compared to experimental data in Figure 3.6(d-f) for time points up to 1.65 ms after the ARFI pushing pulse. The displacement profiles are normalized to their respective peak displacements.
within 1 cm of the geometric focus (1.5 cm to 2.5 cm), allowing a comparison of
displacement profile spatial and temporal variation. The bimaterial interface is
located at the axial focal depth of 2 cm. The experimental ARFI data is the mean of
using adjacent sequences (n = 27), with a 0.71 mm lateral spacing.

The displacement field induced across the bimaterial interface, or the “displacement
step response”, is an important component of the total ARFI imaging step response,
which also includes imaging parameters involved in tracking the displacements and
signal processing parameters for displacement estimation. The derivative of the step
response is the point spread function (PSF), used to quantify the resolution. The
displacement step response is a function of both spatial stiffness variation of the
bimaterial and the spatial variation of the intensity of the pushing force due to the
focal pattern of the ARFI pushing pulse.

One method by which to minimize spatial changes in the displacement profile due to
the intensity focal profile is the Time Gain Control (TGC) method [111]. TGC refers
to the time-delay dependent gain added to ultrasonic signals to minimize otherwise
relatively large variation due to the focal profile. The effect of the focal profile alone
can be estimated by collecting displacement profiles in a homogeneous medium. For
the experimental data, 270 axial displacement profiles (10 images composed of 27
lines) collected from compliant portions of the phantom were averaged and divided
from each bimaterial displacement profile. Displacements from the FEM simulation
were compared to experimental data in Figure 3.6(a-c) for the homogeneous,
compliant data.
Figure 3.6: Comparison of normalized FEM simulation displacement data and experimental displacement estimates at times up to 0.75 ms after the pushing pulse in (a-c) a homogeneous, compliant medium, and (d-f) a bimaterial. The displacement profiles are normalized to their respective peak displacements within 1 cm of the geometric focus (1.5 cm to 2.5 cm). The solid line represents FEM data and the dashed lines represent the experimental data (mean of 27 independent trials). The axial position indicates the distance, on axis, from the transducer. The measured experimental shear modulus is $6.3 \pm 0.1$ kPa for the stiff medium and $4.0 \pm 0.1$ kPa for the compliant medium.
The ARFI resolution limit can be estimated by measuring the width of the PSF, the spatial derivative of the step response. Displacement step responses, after implementing the TGC method are shown in Figure 3.7(a-c). The spatial derivatives of the displacement profiles are given in units of strain in Figure 3.7(d-f), and represent the PSF of the system. Experimental data is too noisy to visualize the PSF. In Chapter 4 a nonlinear-least squares fitting algorithm is introduced that is used to approximate the PSF as the derivative of a sigmoid function.

Figure 3.7: FEM simulation displacement (a-c) and strain (e-f) data of bimaterial interface after using the TGC method, using the displacement profile in the homogeneous, compliant region. The axial position indicates the distance, on axis, from the transducer. The medium shear moduli are 4.0 kPa for the compliant region between 0 mm and 20 mm from the transducer axially and 6.3 kPa for the stiff region between 20 mm and 30 mm axially.
3.5 Discussion

3.5.1 ARFI Intensity Fields

Simulated ARFI intensity field profiles for the pushing pulse are shown in Figure 3.3. Assuming a constant attenuation, Equation 3.2 shows acoustic radiation force is directly proportional to the acoustic intensity, and therefore can be used as the forcing for an FEM simulation. Parameters were chosen to simulate the characteristics of the VF7-3. The location of peak intensity on axis is 1.89 cm, shallower than both the focal depths from lateral and elevation focal configurations (2 cm and 3.75 cm, respectively) because, with attenuation (\( \alpha = 0.7 \) dB/cm/MHz), the focal point tends to move toward the transducer. A majority of the acoustic intensity is located between 1.5 cm and 2.5 cm on axis.

3.5.2 ARFI Displacement Fields in a Bimaterial

Phantoms were created that included two bonded materials, or bimaterials, with differing modulus values, estimated using and MTS system. Shear modulus values of 4.0 ± 0.1 kPa and 6.3 ± 0.1 kPa were achieved by using 100 Bloom and 300 bloom gelatin, respectively. This approach was followed as opposed to increasing/decreasing the gelatin concentration of a single bloom-type to avoid a change in the apparent modulus due to an osmotic gradient across the bimaterial interface. The modulus was estimated using core samples extracted from the phantom immediately after ARFI imaging at a low frequency (0.01-0.03 Hz) unconfined cyclic loading. Timely mechanical testing avoids variability of the stiffness estimate due to stiffening over time that occurs in gluteraldehyde solutions [138]. Low frequency cyclic loading was used to avoid friction effects and bulging at the slip boundaries.
Simulated displacement fields in 2D are illustrated in Figure 3.5. The displacements are given in the axial-lateral plane, centered in the elevation dimension. Figure 3.5(a) shows the displacement field 0.15 ms after the excitation takes the shape of the initial acoustic radiation force focal pattern shown in Figure 3.3(a). At this early time point, the stiffer material reacts faster to and displaces more initially from the ARFI excitation without appreciable shear wave propagation. In Figure 3.5(b) the displacements have increased more in the compliant material than in the stiff material given by the visible change in brightness at the bimaterial interface (axial depth of 2 cm). Figure 3.5(c) shows displacements 0.75 ms after the excitation, after significant shear wave propagation. The displacements in the stiff material are not only lower in magnitude (from 2 cm to 3 cm axially) but also show greater lateral spreading than the displacements induced in the compliant material due to a greater shear wave speed.

Displacement profiles across the bimaterial interface from the FEM simulation show good agreement with experimental data from the phantom in Figure 3.6. The raw data was divided by spatial and temporal peak displacements in the FEM simulation and experimental displacement fields. Displacement profiles are shown for a range of time points after the ARFI excitation. The bimaterial interface is located at an axial position of 2 cm. The displacements in the stiff medium (axial positions greater than 2 cm) begin to decrease after 0.45 ms, while those in the compliant medium only decrease after the 0.75 ms. Lower shear wave speeds in compliant media can result in slower propagation of displacements out of the ROI. After the 0.45 ms time point, there is a noticeable change in the slope of the displacement profile close to the bimaterial interface (2 cm) due to the combined effects of differing displacement magnitude and shear wave speeds of the two media.

To estimate the step response of the ARFI system, large variations in the displacement amplitude due to the focal configuration of the ARFI pushing pulse were first minimized using the TGC method. The TGC method involves dividing a
displacement profile by a reference profile, collected in a homogeneous medium. In the present investigation, reference profiles were collected in the compliant portion of the phantom, and simulated using a FEM model of compliant elastic solid. The reference profiles from the FEM and the experiment are compared in Figure 3.6 show good agreement. The displacement profiles continue to increase in magnitude up to 0.75 ms after excitation, after which the average displacement magnitude decreased, suggesting similar shear moduli.

The displacement step response is shown at times after the ARFI excitation from the FEM simulation in Figure 3.7(a-c), and the corresponding PSF is shown in Figure 3.7(d-f). The PSF is the spatial derivative of the step response, so it is shown in units of strain rather than displacement. Notice in the change in displacement slope at the bimaterial interface corresponds to a trough in strain in Figure 3.6(d-f) presumably due to an abrupt change in shear modulus of the material. Notice the spatial extent of the strain trough increases with time. 0.45 ms after the excitation [Figure 3.7(b)] the PSF of the system is comprised of strains in both the stiff and compliant regions. In contrast, 0.75 ms after the excitation [Figure 3.7(c)] the strain in the compliant region (< 2 cm) corresponds to a majority of the total strain between the stiff and compliant portions of the phantom, and can therefore be considered itself the primary contributor to the PSF. In Chapter 4, the PSF width will be estimated by fitting a sigmoid to the step response. The derivative of the sigmoid will be an estimate of the PSF. Although the true PSF is irregular in shape, this fit can be considered an adequate approximation. In Chapter 5, this irregular FEM-derived PSF will be used in a convolution model to derive simulated displacement data for comparison with experimental data.

3.5.3 Limitations of the FEM simulation and Future Work

The present model requires scaling of computed displacement to the displacements measured experimentally from phantoms. Other groups have approximated the
intensity of ARFI pushing pulses by using a hydrophone at low acoustic pressures, to avoid saturation in water. Intensities in the phantom were estimated by scaling the measured values linearly by the ratio of displacements observed using transducer output voltage, and high transducer output voltage. Such empirically-determined, linearly extrapolated fields have been shown to overestimate the true focal intensity [139] and induce higher simulated displacements possibly due to nonlinear absorption effects [125]. In this study, instead of measuring intensity values, peak displacements from the FEM simulation were scaled to match those of the experimental study.

The geometry of the model does not capture the complexity of the displacement field induced in objects of a variety of shapes. The present model describes the step response of two bonded semi-infinite media. In practice, objects can be closely spaced, resulting in the constructive and destructive interference of shear waves within the ROI, having significant effects on the visibility of boundaries. Time points soon after the excitation (<1 ms), before appreciable shear wave propagation, were utilized for the resolution estimation and therefore can represent the resolution limit for small objects as well.

The measurement of lateral resolution is difficult using this model. For a lateral resolution measurement, the boundary must be parallel to the transducer axis. In this configuration, the pushing locations are at various distances from the interface, requiring an individual 3D FEM simulation for every pushing location. For the large number of pushing locations necessary for adequate sampling of the lateral PSF, the number of FEM simulations would necessitate a large amount of computing time and was therefore not performed.

Tissues can exhibit viscoelastic properties that can impact the step response of a material to an impulsive acoustic radiation force. Viscoelastic properties describe the time dependent strain rate and resulting dispersion of the displacement field of a material. In this simulation and phantom study, these effects are not included. In later chapters, small porcine liver ablation lesions are imaged using ARFI imaging
techniques to demonstrate ARFI resolution capabilities in viscoelastic materials. In the future, these viscous material parameters can be extended to simulations to study viscosity’s impact on ARFI resolution.

3.6 Summary and Conclusions

A theoretical framework and FEM simulation for the response of a bimaterial interface to an ARFI excitation was presented in this chapter to estimate the ARFI imaging axial resolution. The simulated ARFI excitation was generated using FIELD II, and was applied in a finite element model. The model simulated the response of a 3D isotropic, linear elastic solid with a planar interface separating two materials with differing shear moduli. The displacement field across the interface was the displacement step response of the system. Experimental displacement data from a gelatin phantom showed good agreement with FEM simulation displacement data. The simulated axial PSF was plotted for multiple time points by taking the spatial derivative of the displacement profiles. The width of the PSF is the axial resolution in the absence of ultrasonic tracking parameters.
Chapter 4 Experimental Estimation of ARFI Imaging Resolution

4.1 Introduction

In this chapter, the spatial resolution of an ARFI imaging system is measured by imaging a modulus step phantom consisting of two bonded materials of distinct shear modulus. This is accomplished by extracting the imaging system step response. The point-spread function (PSF) can be estimated by calculating the spatial derivative of the step response. The full-width half-maximum (FWHM) of the PSF is reported to quantify the resolution. Jitter noise in the displacement profiles resulting from ultrasonic tracking corrupts the step response, and is amplified when calculating the derivative of the step response to determine the PSF. This noise makes measurement of the FWHM difficult, thus the FWHM is not calculated directly from the displacement data. Instead, a curve-fitting algorithm is applied to the step profile to estimate the noise-free step response. The spatial derivative of the curve fit is calculated to estimate the PSF.

This chapter presents the experimental ARFI imaging resolution estimation technique and compares these results to those obtained from a FEM simulation and a linear shift invariant (LSI) model. Section 4.2 discusses the ultrasound, displacement estimation, and mechanical parameters that fundamentally limit both axial and lateral ARFI resolution. A description of the experimental setup is provided in Section 4.3. The nonlinear least squares fitting model used to minimize the effect of jitter in the displacement estimate is introduced. To test the hypothesis that the resolution of the ARFI imaging system is dependent on ultrasound and displacement estimation parameters, a LSI model is proposed. In sections 4.4 and 4.5, experimental resolution
estimates are compared to estimates obtained from a matching FEM simulation (Chapter 3), and to LSI model results.

4.2 Background

The resolution of elastography modalities, such as strain imaging, that use correlation based displacement estimation, have been shown to be functions of ultrasonic and signal-processing parameters [121]. Ultrasonic parameters, such as beamwidth and pulse length, describe the ultrasound beams and echoes that are used in displacement tracking. These beams are used to track the movement of scatterers for displacement estimation and therefore influence the resolution of displacement images. For example, Righetti et al. showed lateral resolution is limited by the tracking beamwidth in elastographic strain images [122]. Within the beam, a number of individual scatters contribute to the overall detected echo signal. Therefore, displacements estimated in adjacent lateral location are difficult to distinguish if they are less than a beamwidth apart.

The tracking pulse length and the correlation window length can limit axial resolution. Tracking pulse length can limit axial resolution in displacement images because scatterers located within this length are difficult to distinguish and are therefore difficult to individually track. Righetti et al. [121] found axial resolution in elastography to be limited by the bandwidth of the tracking pulses. The bandwidth can limit the tracking pulse length. Correlation window length is integral to the process of windowed cross-correlation based displacement estimation because a single displacement estimate is the average displacement experienced by the scatterers within the correlation window [86]. This averaging causes additional blurring to the axial PSF, thereby reducing axial resolution with an increase in window length as demonstrated in elastography by Alam et al. [120], and Righetti et al. [121]. Although the mechanism of displacement of the tissue/phantom is
fundamentally different between Elastography and ARFI imaging (impulsive rather than static), the imaging and tracking parameters are the same, and can also therefore influence ARFI imaging resolution.

4.2.1 ARFI Image Resolution and the Step Response

In ultrasonic imaging, axial resolution depends on bandwidth and wavelength while lateral resolution depends on beamwidth. The resolution can be measured by an instrument’s ability to resolve two reflecting boundaries that are closely spaced [127]. For estimating the resolution of ARFI imaging, the disadvantage of utilizing two closely spaced boundaries is that it would require a phantom with a very thin layer of distinctly different modulus, which can be difficult to fabricate with the precision required for an accurate estimate of resolution. Instead, in this study a step response is used to measure the PSF FWHM. A drawback of this method is that the derivative of the displacement estimates is very noisy, which is why a curve-fitting routine is implemented to calculate the PSF from a noise-free step response.

4.2.2 Temporal Variation of ARFI Imaging Step Response

A standard acoustic radiation force pushing pulse duration is on the order of 10 to 100’s of microseconds. Tissue response times are much slower, on the order of milliseconds, making the radiation force relatively impulsive. The tissue response time to the radiation force excitation is inextricably linked to tissue stiffness. Stiffer tissues respond more quickly than more compliant tissues. A consequence of this stiffness-dependent temporal response is a temporally varying step response.

The difference in wave propagation speeds in the stiff and compliant media improves the ability to resolve objects of different shear moduli depending on the elastic contrast. For example, if there were two adjacent regions with a shear modulus contrast of $C_s$, the relative displacement maxima have a ratio of $1/ C_s$. The
displacement induced is inversely proportional the stiffness of the medium. The relationship between the shear modulus and shear wave velocity is given in Equation 3.9, the relative wave speeds will have a ratio of $\sqrt{\text{Cs}}$. Initially, the stiffer of the two media responds to the acoustic radiation force more quickly due to the greater shear wave speed resulting in a lower contrast interface between the stiff and compliant regions and a potentially wider PSF. As time progresses, the displacements in the stiff region propagate away as those in the compliant region reach their peak within the ROI. This evolution in displacements is illustrated in Figure 3.5. At this point maximum displacement contrast and resolution is reached. In the range of physiologically relevant values of shear modulus (1-10 kPa [140]) this dynamic process occurs within the first few milliseconds of acoustic radiation force excitation. In this study, we chose a time period that included this critical temporal displacement evolution and therefore report the estimated optimal ARFI resolution. An example measurement of the ARFI resolution limit as a function of time after the pushing pulse is presented in Section 4.4.2.

### 4.2.3 Spatial Variability of the Displacement Field due to ARFI

The step response of the ARFI imaging system is both a function of ARFI focal intensity profile and the underlying modulus. The acoustic radiation force used to displace the medium is generated using a focused beam that has a spatially varying intensity with the highest intensities present on axis in the vicinity of the geometric focus. The acoustic radiation force at a particular spatial location is proportional to the acoustic intensity of the beam at that location, assuming a constant attenuation throughout the medium. Therefore the largest displacements will also occur in the vicinity of the focus when the focal effects are dominant with respect to attenuation effects. To minimize the large variation in the displacement profile due to these focal effects, a method is proposed to normalize the step response with a “reference
profile”, called the time gain compensation (TGC) method [111] which was first introduced in Chapter 3, and is discussed in the Section 4.3.

4.3 Methods

4.3.1 Scan parameters

Imaging was performed with a Siemens Sonoline Antares Ultrasound Scanner (Siemens Medical Solutions USA, Inc., Issaquah, WA, USA). A VF7–3 linear array transducer with a 2 cm lateral focal length and 4.21 MHz excitation frequency was used for the pushing and tracking pulses. Beam sequences included a 0.5 μs reference pulse, followed by a 48 μs pushing pulse, and 30 – 0.5 μs tracking pulses (at a pulse repetition frequency (PRF) of 6.8 kHz) and data was acquired at a 40 MHz sampling rate. System parameters were chosen based on values typical of those used in ARFI imaging studies. In Table 4.1, Table 4.2, and Table 4.3 are pulse, imaging and focal parameters used throughout this thesis (Study 1 and Study 2). Also included in this table are ARFI imaging parameters used in a simulation study conducted by Palmeri et al. [100] to compute the expected temperature rise during ARFI imaging. In the Results section, the results of the simulation study will be discussed and compared to the ARFI imaging exposures used in this set of studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>f (MHz)</th>
<th>Pulse Duration (μs)</th>
<th>Pulse Number</th>
<th>Burst (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmeri et al.</td>
<td>7.2</td>
<td>28</td>
<td>6</td>
<td>0.92</td>
</tr>
<tr>
<td>Study 1</td>
<td>6.67</td>
<td>30</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Study 2</td>
<td>4.21</td>
<td>48</td>
<td>1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 4.2: Focal Parameters
Resolution measurements were made using the parameters listed in Table 4.4. A range of tracking pulse lengths, correlation window lengths, and frequencies are investigated for axial resolution, while lateral resolution was measured as a function of depth. The default parameters, unless otherwise specified, are an ultrasound frequency of 4.21 MHz, tracking pulse length of 0.4 mm (2\(\lambda\)), correlation window length of 0.8 mm, and a depth of 2 cm.

### Table 4.4: Imaging and Displacement Estimation Parameters

<table>
<thead>
<tr>
<th>Dimension</th>
<th>(f) (MHz)</th>
<th>Window (mm)</th>
<th>Tracking Pulse (mm)</th>
<th>Depth (cm)</th>
<th>Lines</th>
<th>(F/#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>4.21 - 20</td>
<td>0.2 - 1.9</td>
<td>0.4 - 1.8</td>
<td>2</td>
<td>27</td>
<td>F/2</td>
</tr>
<tr>
<td>Lateral</td>
<td>4.21</td>
<td>0.8</td>
<td>0.4</td>
<td>1.5 - 2.1</td>
<td>945</td>
<td>F/2</td>
</tr>
</tbody>
</table>

Note, from hereon, tracking pulse lengths are reported using round trip time (\(d = ct/2\), \(c = 1540\) m/s) for direct comparison with correlation window lengths. The impact of tracking frequency (4.21 MHz – 20 MHz) on axial resolution is also investigated using the FEM simulation and LSI model.
4.3.2 Safety Considerations

Intensity measurements of the 6.67 MHz setup were measured using a hydrophone. To avoid saturation of the high intensity pulses in the water tank, an insertion method was performed using a hydrogel phantom. The phantom was fabricated with absorption coefficient of 0.7 dB/cm/MHz. For phantom fabrication details, refer to section 3.3.2. The experimental parameters are provided in Tables 4.1-4.3 as “Study 1”. A 2 cm slice of the phantom was inserted between the transducer (VF10-5, Siemens Medical Solutions USA, Inc., Issaquah, WA, USA) in a tank of deionized, degassed water. A needle hydrophone (ONDA Corporation, Sunnyvale, CA, USA) was used to measure the peak pressure close to the phantom surface, near the geometric focus.

4.3.3 Tissue-Mimicking Phantoms

The tissue-mimicking phantom fabrication and mechanical testing is detailed in Section 3.3.2. For the phantoms used in these measurements, the background was created using 300 Bloom gelatin at a concentration of 61 g/L and the compliant inclusions used a mixture of 100 Bloom and 200 Bloom gelatin at concentrations of 31 g/L. Shear moduli of 6.3 ± 0.1 kPa and 4.0 ± 0.1 kPa were measured for the background and the cylinder, respectively, using mechanical testing procedures (Section 3.3.2). The stiffness values were chosen to be representative of healthy and cancerous breast tissue, respectively [141, 142].

4.3.4 Experiment

Axial Resolution Measurement Setup

The phantom was imaged in a tank of degassed, deionized water positioned on a 1 cm thick rubber slab to reduce reverberations. Images for axial resolution measurements
were acquired with the phantom positioned on its side, such that the compliant
cylinder was at the top of the phantom, parallel to the face of the transducer. The
boundary between the compliant and stiff regions was positioned at the lateral focal
depth of 2 cm [Fig 4.1(a)]. At a single imaging location, an image was captured for
each set of parameters investigated. The transducer was then repositioned at 3
different positions at least 5 mm apart in order to sample independent speckle regions
(n = 3), such that the stiffness boundary remained at the 2 cm focal depth.

![Figure 4.1: Orientation of phantom and transducer for (a) the axial resolution measurement and (b) the lateral resolution measurement. The gray region is the more compliant, 4.0 ± 0.1 kPa, inclusion, and the white region is the stiffer, 6.3 ± 0.1 kPa background material. The scan plane is in the plane of the page.](image)

**Lateral Resolution Measurement Setup**

For lateral resolution estimation, images were acquired with the phantom positioned
upright and the compliant cylinder perpendicular to the transducer face [Fig 4.1(b)].
Again, the phantom was imaged in a tank of degassed, deionized water positioned on
a rubber slab to reduce reverberations. The stiff-compliant boundary was centered in
the axial-lateral transducer plane.

The allowable number of pushing pulses per unit time was limited by potential
transducer heating. As a result, the lateral sampling of the displacement field using
our ARFI sequence (beam spacing = 0.7 mm) is too sparse to measure the FWHM of
the submillimeter PSF. Sufficient sampling of the lateral PSF was achieved by up-sampling through mechanical translation of the transducer. The transducer was attached to a motorized 3-axis positioner (Newport Corporation, Irvine, CA) to capture 35 laterally offset images, to achieve a 20 μm line spacing (Table 4.1).

A one-minute off-time between sequences for heat dissipation was used to avoid potential transducer overheating and phantom damage. Phantom motion was avoided during transducer translation by maintaining a 1 mm gap between the phantom and transducer. This procedure was repeated three times in different locations to acquire three independent measurements (n = 3).

4.3.5 Data Collection and Processing

Displacement estimation was performed on the raw RF data using the procedure detailed in Section 2.3.2. For the axial resolution estimate, all lines in each of the three displacement images were averaged. Jitter in the displacement profiles required averaging for accurate resolution estimation. If the stiffness boundary was tilted with respect to the transducer face, averaging could lead to blurring of the step and an underestimation of resolution. The total lateral width of the 27 image lines was 1.9 cm. A tilt of only 1 mm across the 27 lines would result in a blur on the order of the PSF. Proper alignment was ensured before averaging by applying a range of tilts to the data. A “tilt” required shifting each image line. Each image pixel, with a lateral coordinate of x and axial coordinate z, was shifted in the z-direction by a pixel value equal to K⋅x, where K is a constant. For each K value, all of the lines were averaged and the width of the PSF was estimated using the algorithm described in the next section. A K value was chosen that corresponded to the minimum PSF width estimate. A matching FEM/acoustic field simulation generated simulated ARFI RF data. For a detailed description of the simulation, refer to Section 3.3.1. In Figure 4.2, a single displacement profile and a profile that is the result of averaging 27 profiles are plotted.
The displacement data were normalized using the TGC method. This method applies an axially varying gain to displacement profiles, normalizing for the focal gain and the depth-dependent attenuation of the pushing pulse. Two hundred and seventy axial displacement profiles were collected and averaged from homogeneous, compliant portions of the phantom to generate a "reference profile". This reference profile was divided from the step displacement profile. At early time points, the "reference profile" is a good approximation of the early tissue response of both materials. As time passes, however, the shape of the displacement profiles begin to deviate, as shear waves in the stiffer medium propagate out of the ROI at faster speeds than those in the compliant medium. Therefore, this method is only valid at early time points, before significant shear wave propagation. Plots of a representative step displacement profile, reference displacement profile, and the resulting step response are provided in Figure 4.3.
Figure 4.3: The TGC method is the dividing of the (a) original averaged displacement profile by a (b) reference profile from the homogeneous, compliant region. The resulting step response is shown in (c), and is used to estimate the FWHM of the PSF.

Tilting and averaging of displacement profiles was also used for the lateral resolution estimate. Tilt was calculated for image lines oriented laterally, parallel to the transducer face. In this case, each image pixel, with a lateral coordinate of $x$ and axial coordinate $z$, was shifted in the $x$-direction by a pixel value equal to $L \cdot z$, where $L$ is a constant. For each $L$ value, all of the lines were averaged for profiles for a depth range of 1.5 to 2.1 mm, close to the focus. The PSF width was estimated for each $L$ value, and the $L$ value that corresponded to the smallest FWHM was applied. Displacement data was subsequently averaged axially using a 0.5 mm window before resolution estimation to reduce noise.

**Step-Fitting Algorithm**

The FWHM of the PSF was estimated by calculating the derivative of the step response. As expected, the displacement estimates were corrupted by jitter. The process of taking the derivative of a noisy function amplifies the noise. The FWHM is very difficult to measure from a noisy estimate of the PSF. A moving average filter for noise reduction is avoided because blurring of the step response would cause a gross underestimation of the highest achievable resolution.
A nonlinear least squares fitting routine (NLSF) was employed to fit a sigmoid function to the step, and the derivative of the fitted function was used to estimate the FWHM of the PSF (Figure 4.4). A sigmoid was chosen because it is a continuous function that describes the transition from one constant value to another. In this case, the sigmoid closely describes the blurring of displacement estimates across the boundary between the two materials of varying stiffness ($R^2 > 0.9$). Notice in Figure 4.4(b), although the sigmoid is a relatively smooth function, the displacement profile demonstrates a change in slope at the bimaterial interface, similar to the one seen in Figure 3.7(b). As seen in Figure 3.7(e), the true PSF of the underlying displacements (from the FEM model) is irregular, so the derivative of the sigmoid is an approximation of this irregular function. In the experiment, the displacements are estimated using ultrasound data and are therefore effectively blurred. It is expected that this blurring smooths the irregularities, making the sigmoid approximation a more accurate representation of the ARFI imaging PSF. The NLSF routine uses an iterative gradient descent method to converge on the function that minimizes the sum of the squared residuals between the curve fitting function and the displacement profile [143].

![Image](image.png)

**Figure 4.4:** NLSF curve-fitting and FWHM resolution estimation using an ARFI image of a step phantom. An (a) ARFI image is acquired, and (b) a sigmoid function is fit to the displacement profile using a NLSF curve-fitting algorithm and represents the system step response. The (c) PSF is the derivative of the curve fit function, and the FWHM is reported as the ARFI resolution.
The location of the step was estimated as the location of local maximum value of the derivative of the displacement profile after using a 2 mm averaging window along the profile to smooth the data. A 1 cm segment, large enough to include the entirety of step response, of the original (unsmoothed) displacement profile centered at the estimated step location was selected for curve fitting. A second order polynomial was fit to the data segment and subtracted, and a tilted sigmoid was fit to the remaining data. The curve fit function is a tilted sigmoid, given by the expression:

\[ y = a + bx + \frac{c}{1 + e^{-nx+m}}, \]  

(4.1)

where \( a \) is the vertical shift, \( b \) is the tilt, \( c \) is the amplitude of the sigmoid, \( n \) is the rate of decay of the exponential term, and \( m \) is the horizontal i.e. \( x \) shift. An initial guess is chosen for the parameters in the curve fit function based on raw displacement data. The initial guess for \( a \) was equal to the average displacement in the low-displacement part of the step response and the guess for \( c \) was the average displacement in the high-displacement part of the step minus \( a \). The initial guess for the tilt \( b \) and horizontal shift \( m \) was zero and the initial guess for \( n \) was chosen such that the FWHM of the PSF would be equal to 1 mm (on the order of the anticipated FWHM). The derivative of the sigmoid was calculated and the FWHM of the resulting PSF is reported.

Subtracting the second order polynomial prior to curve fitting facilitated better convergence of the NLSF algorithm. In the PSF domain, the second order polynomial is simply a “tilt” of the PSF. This is evident in the following expressions:

\[ D(x) = S(x) + Ax^2, \]  

(4.2)

\[ \frac{dD(x)}{dx} = \frac{dS(x)}{dx} + 2Ax, \]  

(4.3)

where \( D \) represents a displacement profile composed of a sigmoid \( S \) and a second order polynomial \( Ax^2 \), where \( A \) is a constant. In Equation 4.3, the derivative of the
displacement in the $x$ direction is shown and is the sum of the derivative of the sigmoid function and a line of slope $A$. The line is the tilt of the PSF. Subtracting this tilt has no effect on the width of the PSF, as illustrated in Figure 4.5.

![Image of PSF before and after subtraction of tilt]

**Figure 4.5**: The PSF before and after subtraction of tilt. The dotted function represents the ARFI imaging system PSF. The solid line represents the PSF after subtraction of the tilt. Notice the width of the PSF remains the same before and after the removal of tilt.

### Axial Linear Shift Invariant (LSI) Model

Assuming a perfect step in the displacement field between the two materials, and that the ARFI imaging system is linear and shift invariant (LSI), the axial PSF can be modeled by convolving the expected shape of the tracking pulses with that of the correlation window. This convolution-based approach is consistent with modeling of imaging system responses in ultrasound literature [137, 144-147]. A rectangular function accurately describes the correlation window length while the tracking pulse can be approximated as a Gaussian enveloped sinusoid. The convolution results in the PSF, as given below:

$$PSF(x) = W_r(x) * T(x),$$  

(4.4)

$$W_r(x) = \begin{cases} 1 & |x| \leq \tau/2 \\ 0 & |x| > \tau/2 \end{cases}$$  

(4.5)
\[ T(x) = e^{-x^2/2\sigma^2}, \quad (4.6) \]

\[ \sigma^2 = \frac{-2\log(1/2)}{(\pi B f)^2}, \quad (4.7) \]

where \( W \) is the correlation window function, \( T \) is the tracking pulse envelope function, \( \tau \) is the correlation window length, \( B \) is the fractional bandwidth, and \( f \) is the ultrasound frequency.

Tracking pulses generated by the VF7-3 linear array transducer were measured using an ONDA HNV-0200 needle hydrophone (ONDA Corporation, Sunnyvale, CA, USA) in degassed water. The bandwidth of the pulse was calculated and used to define the Gaussian envelope (bandwidth = 0.5) of the model tracking pulse (Figure 4.6). The pulse was convolved with a function representing the impulse response of the transducer (center frequency of 5.33 MHz, and 0.5 fractional bandwidth) and then convolved with a rectangular function that represented the correlation window length. The FWHM of the result is measured as the model estimate of the axial resolution limit.

**Figure 4.6:** Tracking pulse pressure amplitude vs. time. The tracking pulse (a) was measured in a water tank, was 2-cycles and had an excitation frequency of 4.21 MHz. An LSI model was developed to model the ARFI imaging PSF in which the tracking pulse (b) was modeled as a Gaussian enveloped sinusoid.
4.4 Results

ARFI imaging axial and lateral resolution estimates are reported from the experiment, FEM simulation and LSI model. The mean and standard deviation of the resolution estimate for three individual profiles (n = 3) are reported. For all data sets, 95% confidence intervals (CI) were calculated. The estimated FWHM is reported at the focus of the transducer (z = 2 cm) for axial resolution and near the focus (z = 1.5 cm to 2.5 cm) for lateral resolution.

4.4.1 Safety Considerations

Pulse waveforms measured were asymmetric, with an ISPPA of 630 W/cm², rarefractional peak pressure of 4 MPa, and a compression peak pressure of 5 MPa. These values fall under the 1000 W/cm² used for the calculations presented in Section 2.3.4 using Equation 2.22, and therefore also abide by the FDA limits. However expression presented in Equation 2.22 is an over-simplification for heating that results from ultrasonic imaging because 2D imaging involves complex source geometries and overlapping intensity fields. Palmeri et al. [100] computed the heat generated during ARFI imaging by using a finite element method (FEM) model composed of thermal elements and found that during ARFI imaging of tissue, heating did not exceed 1 °C [100]. Temperature increases less than 1 °C are deemed acceptable for diagnostic ultrasound scanning.

This simulation study is a conservative estimate for heating produced in the course of this thesis because higher frequencies, lower F/#'s, and closer line spacings were implemented by Palmeri et al. [100] Also note that bursts of six 28 μs pulses are used in the simulation. The 150 μs between the six pushing pulses in the simulation was not long enough for appreciable cooling. The six pulse sequence therefore can result in the same tissue heating as one, long 168 μs pulse [100], much longer than pushing pulses used in this thesis. However, the authors of the simulation study mention
although nonlinear distortion is minimal when using a 7.2 MHz source frequency due to attenuation, when lower frequencies are employed these nonlinear effects have a greater impact. More specifically, pulses of lower frequencies are less attenuated in tissue. Less tissue attenuation means higher pulse pressures, resulting in nonlinear distortion of the ultrasound waves and generation of harmonics, which are subsequently absorbed, generating additional heat. The heat generated by absorbed harmonics in this thesis is expected to be small relative to the additional heat generated by the greater absorption of the higher frequency, more highly focused beams generated in the simulation study by Palmeri et al. Creating a thermal FEM simulation is beyond the scope of this study, but may require future investigation.

4.4.2 Axial Resolution Estimates

Figure 4.7 is a plot of the axial resolution as a function of time after the pushing pulse excitation. As described in the background section, the step response of the system evolves over time. This evolution is due to shear wave propagation. In all cases, the minimum FWHM was measured at 0.75 ms after the pushing pulse. Although this minimum FWHM time is consistent within this phantom, this time may change with a change in the relative stiffness of the compliant and stiff regions.
Figure 4.7: Estimated ARFI axial resolution (FWHM) as a function of time after the pushing pulse. A gelatin phantom was used to create a step function with a compliant core ($\mu = 4.0$ kPa) and stiff background ($\mu = 6.3$ kPa). The center frequency was 4.21 MHz, tracking pulses were 0.37 mm ($2\lambda$) in length, and correlation window spacing was one sample ($c = 1540$ m/s, sampling frequency = 40 MHz). The time at which the FWHM reaches its minimum is chosen to quantify ARFI resolution, which is 0.75 ms after the pushing pulse excitation.

Figure 4.8 shows axial resolution as a function of correlation window length. The FWHM reached a minimum 0.75 ms after the pushing pulse, so data at this time is used. The means of the resolution estimates ranged from 0.8 mm to 1.9 mm for window lengths from 0.2 mm to 1.9 mm. While the increase in the mean of the resolution estimates at 0.8 mm is significantly lower than that at 1.9 mm, the resolution means are not significantly different below a window length of 0.8 mm. The LSI model predictions show good agreement with the experimental measurement (within the 95% CI).
Figure 4.8: Estimated ARFI axial resolution (FWHM) as a function of window length for the experiment, LSI model, and FEM simulation. A gelatin phantom was used to create a step function with a compliant core ($\mu = 4.0$ kPa) and stiff background ($\mu = 6.3$ kPa). The center frequency was 4.21 MHz, tracking pulses were 0.37 mm ($2\lambda$) in length, and correlation window spacing was one sample ($c = 1540$ m/s, sampling frequency = 40 MHz). The FWHM is reported 0.75 ms after the pushing pulse, the time at which it reached its minimum value for three images ($n = 3$).

The effect of tracking pulse length on axial resolution is shown in Figure 4.9. The resolution estimate means ranged from 0.8 mm to 2.7 mm for tracking pulse lengths from 1.0 mm to 3.7 mm. The LSI model only shows an increase in the FWHM beyond a tracking pulse length of 0.8 mm because at short lengths the correlation window length limits the FWHM values.

This trend is also seen in the experimental and simulation data (95% confidence level). Although tracking pulse lengths greater than 0.8 mm show an increasing trend, this trend is not statistically significant due to large variability in the FWHM estimates.
Figure 4.9: Estimated ARFI axial resolution (FWHM) as a function of tracking pulse length. The center frequency was 4.21 MHz and correlation window length was 0.77 mm. The FWHM is reported 0.75 ms after the pushing pulse, the time at which it reached its minimum value for three images (n = 3).

The axial FWHM as a function of tracking frequency is shown in Figure 4.10. The window length was proportional to the frequency (4.2 $\lambda$). As expected the FWHM decreases as the tracking frequency increases. The LSI model shows good agreement with simulated FWHM estimates. The FWHM decreases by over 50% between frequencies of 6 MHz and 15 MHz. The FWHM decrease between 15 MHz and 20 MHz is, on the other hand, minimal (<5 %).
Figure 4.10: Estimated ARFI axial resolution (FWHM) as a function of frequency. The window length was proportional to the frequency (4.2 $\lambda$). The FWHM is reported 0.75 ms after the pushing pulse, the time at which it reached its minimum value for three images (n = 3).

4.4.3 Lateral Resolution Estimates

Figure 4.11 shows lateral resolution as a function of axial depth. The mean and standard deviation of measurements from 3 different imaging locations was calculated. At most depths, the modeled beamwidth shows agreement with the resolution measurements within the 95% CI. The resolution change as a function of depth showed no statistical significance (95% confidence level).
Figure 4.11: Estimated ARFI lateral resolution (FWHM) as a function of depth. The axial focal depth of 2 cm was used. The center frequency was 4.21 MHz and correlation window length was 0.77 mm. The FWHM is reported 0.75 ms after the pushing pulse, the time at which it reached its minimum value for three images (n = 3).

4.5 Discussion

In Figure 4.8 axial FWHM is shown as a function of correlation window length. For values greater than 1 mm, the FWHM increases with window length. The resolution limits predicted by the LSI model are within the 95% confidence interval of the experimental and simulation estimates of the FWHM. Below a 1 mm window length the resolution estimates are not significantly different from each other. Righetti et al. [121] also found axial resolution to improve with a decrease in window length, but as the window length approached the tracking pulse length, the dependence of resolution on window length diminished. For simplicity, consider two rectangular functions of different widths. The PSF can be equated to the convolution of the two rectangular
functions. The FWHM of the resulting shape is equal to the width of the wider of the functions (Figure 4.12).

**Figure 4.12:** The solution of the convolution of two rectangular functions of equal amplitude and lengths $a$ and $b$, where $b$ is the larger of the two values. The FWHM is labeled and is equal to $b$.

Below a correlation window length of 1 mm, the measured FWHM values in the experiment and simulation are greater than the FWHM values predicted by the LSI model. A contributor to this positive bias in the resolution estimate is the approximation that the strain response PSF is much smaller than the window length and tracking pulse length, and therefore can be modeled as an impulse. This assumption loses validity when shorter windows and tracking pulses are utilized, in which case the PSF of the system would more accurately be modeled as the convolution of not only the tracking pulse and correlation window, but also the displacement response. The FEM simulation, on the other hand, matches the experimental results when using window lengths below 1 mm. The LSI model only uses correlation window length and tracking pulse length to determine the FWHM of the PSF, while the FEM simulation includes the material response to the acoustic radiation force. This validates the claim that the strain profile plays an important role in accurate FWHM estimates when short correlation windows and tracking pulses are employed.

As expected, the axial FWHM increased with tracking pulse length, but the trend was not statistically significant (Figure 4.9). The LSI model correctly predicted that for tracking pulse lengths shorter than the 0.8 mm window length, the FWHM did not decrease significantly. With increased tracking pulse length, the mean FWHM
estimate increased, as did the variance. A longer tracking pulse (smaller bandwidth) is accompanied by a jitter increase, resulting in an increased variability in the FWHM estimates. Righetti et al. [121] also found that the relationship between tracking pulse length and axial resolution in elastography was not statistically significant when using excitation frequencies lower than 15 MHz.

With a frequency increase of the tracking pulses, a decrease in FWHM was observed in Figure 4.10, in good agreement with LSI model predictions. These results imply an increase in frequency from 4.21 MHz to 20 MHz considerably improves axial resolution. Although higher frequencies result in improved resolution, the frequency-dependent attenuation of tissue will reduce the penetration of the pushing pulses, thereby limiting ARFI imaging to shallower depths. A window length of $2\lambda$ was chosen because above this value, there was a strong dependence of FWHM on window length (Figure 4.8). Righetti et al. [121] also found the correlation window length for optimal resolution scales with ultrasound wavelength. Little improvement in resolution is noticed between 15 MHz and 20 MHz, as would be expected, because the change in wavelength is smaller at these higher frequencies.

Lateral FWHM is shown as a function of depth in Figure 4.11. Using FIELD II, a beamwidth of approximately 1 mm was calculated, agreeing well with the lateral resolution estimates. Other groups studying lateral resolution, in elastography [122] and resolution in axial shear strain elastography [148], also found the lateral resolution limit to correspond to the tracking beamwidth. Although measurements agreed with the theoretical estimate within a 95% CI, a positive bias and increased variability is observed with increasing depth. This is due to the decreased SNR of the displacement estimates away from the peak focal intensity of the pushing and tracking pulses.
4.6 Summary and Conclusions

Elastographic resolution has been extensively studied and quantified using ultrasonic theory and simulations. In this chapter, a novel method to measure ARFI spatial resolution experimentally was presented and matching simulations were developed to better understand the effects of the underlying ultrasound, signal processing, and mechanical parameters that affect spatial resolution. The resolution measurement technique is the first method proposed to experimentally quantify ARFI resolution. This was a new approach to resolution estimation in elasticity imaging in which the step response of the system was derived from the ultrasonic estimates of displacements induced in a bimaterial consisting of differing moduli. The derivative of this step response is the PSF of the system, and the FWHM was reported.

The ARFI imaging axial resolution limit was shown to be proportional to correlation window length and inversely proportional to frequency as predicted by the LSI model. The model suggested that the longer of the window length and the tracking pulse length would limit axial resolution. FEM simulation resolution estimates agreed well with LSI model predictions, suggesting that the mechanical response of the material was not a limiting factor above a correlation window length of 1 mm. The axial FWHM showed a positive bias in the FEM simulation below this 1 mm value when compared to the LSI predictions, suggesting that below this value, the mechanical response of the medium influences the axial resolution because the LSI model does not include material parameters. The increase in axial FWHM with tracking pulse length did not show statistical significance due to the high amount of variance in the FWHM estimates. Lateral FWHM was found, as predicted, to be equal to the -6 dB beam width. These results suggest that in many cases, ultrasonic and signal processing parameters limit ARFI imaging resolution. This methodology can be valuable in quantifying the resolution capabilities of ARFI imaging systems.
Chapter 5  ARFI Imaging of Small Phantom Inclusions and Tissue Ablation Lesions

5.1 Introduction

In Chapter 4, resolution estimates of an ARFI imaging system were determined by calculating the FWHM of the PSF from the step response. In this chapter, resolution estimates are determined from the contrast and blurring of circular lesions. There is a fundamental limit to the resolution capabilities, defined by ultrasound, displacement estimation and mechanical parameters discussed in Chapter 4. These parameters can generate the 2D PSF of the system. Image formation can be modeled by convolving the 2D PSF with the object.

The purpose of this chapter is two-fold: to demonstrate the validity of methods of resolution measurement proposed in previous chapters, and to demonstrate that ARFI imaging can image small, stiff circular lesions. To achieve the first goal, the cross-section of a large, stiff cylindrical inclusion is imaged in the hydrogel phantom. The transformation of a physical signal to an electronic signal in ultrasound imaging systems can be modeled as the 2D convolution of the input signal with the expected PSF [124, 137, 144, 145, 147]. A 2D convolution model generates simulated ARFI images using simulated displacement profiles (Chapter 3), and imaging parameters [beam profiles (Chapter 3) and a LSI model (Chapter 4)]. The axial and lateral profiles of the ARFI image are compared to those generated using the 2D PSF.

To achieve the second goal of this chapter, the contrast of small, stiff targets is measured, and compared to a 2D LSI model. Every LSI imaging system has a
characteristic PSF, and if the PSF is larger, the resolution decreases, and the image becomes increasingly blurry. In section 5.2, a 2D LSI model illustrates that as a target becomes small relative to the PSF, the contrast of that target relative to the background begins to decrease due to increased relative blurring. Small (on the order of a millimeter), stiff lesions are mimicked experimentally by imaging cross-sections of a stiff conical inclusion in an otherwise compliant hydrogel phantom and cross-sections of a cylindrical ablation lesion in porcine liver tissue ex vivo. Changes in contrast will be compared to those observed using the 2D LSI model.

5.2 Methods

5.2.1 2D LSI Models

The first goal of the phantom study was to illustrate that the width of the PSF of the ARFI imaging system, estimated using a modulus step phantom in Chapter 4, is an accurate estimate of the resolution limit. In Chapter 4, axial resolution was found to be a function of correlation window length (displacement estimation), the envelope of the tracking pulses, and the displacement profile across the interface between two materials of varying shear modulus values. The axial PSF modeled as a linear shift invariant (LSI) system using the convolution of the 0.8 mm correlation window length, 2 cycle tracking pulse assuming a 50% fractional bandwidth, a 4.21 MHz excitation frequency, and the displacement profile between two materials (as calculated using a FEM simulation presented in Chapter 3). The lateral PSF was modeled as the lateral beam profile of the tracking beam, assuming a 2 cm fixed lateral focus (F/2 laterally), a dynamic receive focus (F/2 laterally). The expressions for the axial \( PSF_A \) and lateral \( PSF_L \) PSF’s are:

\[
PSF_A(z) = S(z) \ast W(z) \ast T(z), \quad (5.1)
\]

\[
PSF_L(x) = B(x), \quad (5.2)
\]
where $S$ is the strain profile across the modulus step, $W$ is the rectangular function that represents the correlation window length, $T$ is the Gaussian envelope of the tracking pulse, and $B$ is the lateral beam profile. The tracking pulse center frequency was 4.21 MHz, the pulse length was 0.5 µs ($2\lambda$) with a fractional bandwidth of 50%.

The lateral PSF was modeled as the lateral profile of the two-way sensitivity function, i.e., the product of the transmit beam and receive beam profiles. The beams were simulated in FIELD II [123, 124], using the same parameters as the axial PSF, with a 2 cm fixed axial focus (F/2) on transmit, and dynamic receive focus (F/2). The beam profile at the 2 cm lateral focal depth was used as the lateral PSF. The axial and lateral PSF’s were multiplied in 2D to generate the 2D PSF:

$$PSF(x,z) = PSF_A(z) \cdot PSF_L(x),$$

(5.3)

The target objects were lesions modeled simply as dark circles set against a light background. The brightness of the pixels were 1 and 2, to match the stiffness ratio of the stiff and compliant regions of the phantom to be imaged. A 2D convolution was performed between the circles and the PSF’s to create the final images. For this comparison, a circle with a 1.2 cm diameter was convolved with the step-response derived PSF to generate a simulated image to compare with experimental results.

The LSI model can also model the decrease in contrast of small, stiff lesions due to the blurring effect of the 2D PSF. In this 2D LSI model, the displacement profile was not included in the axial PSF, based on the finding in Chapter 4 suggesting that axial resolution is primarily dependent on tracking pulse length and correlation window length:

$$PSF_{Ax}(z) = W(z) \ast T(z),$$

(5.4)

Circle diameters used in this study were 1.5 mm, 1.0 mm, and 0.5 mm. Diameters were chosen close to the resolution limit estimated in Chapter 4.
5.2.2 Phantom Fabrication and Inclusion Imaging

The tissue-mimicking phantom fabrication and mechanical testing is detailed in Section 3.3.2. The stiff regions used a 300 Bloom gelatin at a concentration of 61 g/L, and the background was fabricated using a mixture of 200 Bloom and 100 Bloom gelatin of equal concentrations of 31 g/L. The stiffness values measured using unconfined cyclic loading were 2.6 ± 0.1 kPa for the compliant region and 6.6 ± 0.1 kPa for the stiff region.

Cross-sectional ARFI images of the base of the phantom conical inclusion were acquired and averaged. A VF7-3 transducer was attached to a motorized 3-axis positioner (Newport Corporation, Irvine, CA). The phantom was imaged on its side with the profile of the cone in the imaging plane. The base of the stiff cone (d = 1.2 cm) was imaged sequentially in 10 image planes with 2 mm out-of-plane spacing. 10 images, each offset by 70 µm, were acquired for each plane and combined to create an image with a higher sampling rate in the lateral dimension. To avoid phantom motion during imaging, a 1 mm gap was maintained between the phantom and the transducer. The 10 images were averaged to reduce the amplitude of jitter errors.
Figure 5.1: Orientation of phantom and transducer for cross-sectional imaging of the stiff conical inclusion. In (a), the profile of the cone is imaged, and a wire is inserted into the phantom as a pointer to the base of the taper. The phantom is then rotated 90° (b) for cross-sectional imaging.

The second goal of this study was to image small lesions to demonstrate ARFI imaging resolution capabilities. A phantom was fabricated using a 100 Bloom gelatin at a concentration of 61 g/L and a stiff conical inclusion using a mixture of 100 Bloom and 200 Bloom gelatins of equal concentrations of 31 g/L. The stiffness values were 1.4 ± 0.1 kPa shear modulus for the compliant region and 2.7 ± 0.1 kPa for the stiff region. Bright reflections visibly outlined the edges of the conical inclusion when the axial profile was imaged using B-mode.

Figure 5.2: B-mode image of the profile of an phantom conical inclusion. The bright reflections at the edges were used to position a wire inserted into the phantom to later serve as a pointer.
A segment of 0.2 mm diameter steel wire was inserted into the phantom, next to the cone, such that the tip of the wire was located at the base of the cone [Figure 5.1(a)]. This location calibration later allowed us to estimate the diameter of cross-sections of the cone. The phantom was rotated 90 degrees to image the cone trans-axially [Figure 5.1(b)]. Cross-sectional ARFI images were acquired 0.75 µs after the pushing pulse for cone diameters of 1.5 mm, 1 mm, and 0.5 mm. The diameters were determined from the geometry of the cone. For each cross-section, images were combined as they were for the lateral resolution images, resulting in line spacing of 0.07 mm. By using the wire pointer as a reference, the center and diameter of each cross-section was estimated. The contrast of the lesions was measured by dividing the average value of the displacement estimates in the lesions by the average of those at the same range of depths located outside of the lesions. The dimensions of the lesions in the ARFI images were estimated by measuring the axial and lateral diameters of the visibly darker regions.

5.2.3 Tissue Ablation Imaging

Liver was acquired from a slaughtered pig and submerged in room temperature 0.9% saline solution. A 1 in x 1 in x 3 in section was removed from the liver, and a 0.14 mm Nichrome resistance wire threaded through the specimen while submerged in saline. Both ends of the wires were attached to a Proteck® Dual DC Power Supply (ProTek Devices, Tempe, AZ, USA). The VF7-3 transducer was fixed above the sample for real-time B-mode imaging. A 1.5 A current using a voltage of 0.3 V was applied until the region around the wire started to visibly change in brightness, presumably due to boiling. A steel needle was inserted below the lesion as a marker, and the wire was removed. The wire was then reinserted in an adjacent region, 1 cm away and the procedure was repeated. The time required for this local brightening
was 6 minutes and 34 seconds for the larger lesion (d ~ 2.1 mm) and 4 minutes and for the smaller lesion (d ~ 0.5 mm).

**Figure 5.3:** Experimental setup for porcine liver tissue ablation. A Siemens VF7-3 transducer was used to monitor tissue ablation, performed by passing a 1.5 A, 0.3 V current through a high resistance Nichrome wire threaded through the tissue and connected to a DC power supply.

The tissue was placed in a cold room (10 °C) overnight for further degassing. The following day the tissue was submerged in room-temperature saline and allowed to warm to room temperature, the transducer was positioned above each lesion using the needle markers such that the imaging plane was perpendicular to the axis of the cylinder. Because of degassing, the lesions were otherwise indiscernible from the background tissue in B-mode images. ARFI images were captured and the tissue was subsequently dissected. Photographs were taken of cross-sections of each of the cylindrical lesions next to a metric ruler. The ablated region was of a lighter color due to local tissue heating, allowing for measurement of the lesion diameter using Image J (National Institutes of Health, USA). The center of the lesion was approximated in the ARFI image, and the contrast was calculated as the average displacement estimated inside the lesion in the ARFI image divided by the average displacement estimate at the same range of depths outside of the lesion. The widths of both the ARFI images were simply estimated by estimating the axial and lateral diameters from the visibly darker lesion.
5.3 Results

Profiles of the 1.2 cm diameter base of the stiff embedded phantom cone are shown in Figure 5.4. The simulated data were scaled with regard to displacement magnitude to match the experimental data. Both axial and lateral profiles showed good agreement between experimental displacement profiles and LSI model displacement profiles.

![Figure 5.4: Axial (a) and lateral (b) displacement profiles for a 1.2 cm diameter cross-section of a stiff cone in a compliant background phantom. The simulated displacement profiles were generated assuming a 0.8 mm correlation window length, 4.21 excitation frequency, 2 cycle tracking pulse, 0.5 fractional bandwidth, 2 cm lateral focal depth (F/2) for the transmit beam, and dynamic focusing for the receive beam (F/2).](image)

Figure 5.5 illustrates the PSF, along with the circles of diameters from 0.5 mm to 1.5 mm. The PSF was convolved with the circles to create the simulated images. As the circle diameter decreases, the contrast between the circle image and the background image decreases (Figure 5.7).
Figure 5.5: Simulated images of lesions using the 2D LSI model. The point spread function (PSF) (a) was convolved with circles with diameters of (b) 1.5 mm, (c) 1.0 mm, and (d) 0.5 mm to generate (e-g) the expected images. The pixel brightness values are normalized. The 2D PSF assumed a 4.21 MHz excitation frequency, 50% fractional bandwidth, and 2 cycle tracking pulse for the axial dimension. Laterally, the beams were generated with a 2 cm fixed focus, and a dynamic receive focus (F/2 laterally).

ARFI images of cross-sections of the compliant cone in an otherwise stiff background material are shown in Figure 5.6. Brightness contrast and width in terms of axial and lateral dimensions are listed in Table 5.1 for a correlation window length of 0.8 mm and Table 5.2 for a correlation window length of 1.5 mm. In both cases, the brightness contrast decreased with a decrease in cross-sectional diameter. Image axial diameters were 9% to 166% larger and lateral diameters were 2% to 35% larger than the true diameter of the cross-section when using a window length of 0.8 mm.
(Table 5.1). Image axial diameters showed a greater increase of 34% to 282% when using a longer window length of 1.5 mm, while increases in lateral diameter of 7% to 33% show little change (Table 5.2). The image axial diameter of the lesion increased noticeably (approximately 0.5 mm) when the correlation window length was increased from 0.8 mm to 1.5 mm, while the change in lateral diameter was negligible.
Figure 5.6: Cross-sectional images of a stiff cone ($\mu = 2.7$ kPa) in a compliant background ($\mu = 1.4$ kPa) material for diameters of 0.5 mm to 1.5 mm. In the top row are the B-mode images. The middle and bottom rows are ARFI images in which correlation window lengths of 0.8 mm and 1.5 mm were used, respectively. The center frequency was 4.21 MHz, and the tracking pulse length was $2\lambda$. The displacements are given in microns 0.75 ms after the pushing pulse. The crosshairs represent the measured widths of the lesion in the ARFI image. When using a 0.8 mm correlation window, the lengths of the vertical cross-hairs in the ARFI images are 1.64 mm, 1.52 mm and 1.35 mm, for the 1.5 mm, 1.0 mm, and 0.5 mm diameter lesions, respectively, and the lengths of the horizontal cross-hairs in the ARFI images are 1.53 mm, 1.35 mm and 0.61 mm, for the 1.5 mm, 1.0 mm, and 0.5 mm diameter lesions, respectively. When a 1.5 mm correlation window was used, the lengths of the vertical cross-hairs in the ARFI images are 2.01 mm, 1.97 mm and 1.91 mm, for the 1.5 mm, 1.0 mm, and 0.5 mm diameter lesions, respectively and the lengths of the horizontal cross-hairs in the ARFI images are 1.61 mm, 1.33 mm and 0.55 mm, for the 1.5 mm, 1.0 mm, and 0.5 mm diameter lesions, respectively.

Table 5.1: Contrast and dimensional measurements of phantom lesion images (window = 0.8 mm)

<table>
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<th>1.0 mm</th>
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<td>1.20</td>
<td>1.18</td>
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<td>Axial Width</td>
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<td>1.52 mm</td>
<td>1.33 mm</td>
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<tr>
<td>Lateral Width</td>
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<td>1.35 mm</td>
<td>0.61 mm</td>
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Table 5.2: Contrast and dimensional measurements of phantom lesion images (window = 1.5 mm)

<table>
<thead>
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<th>1.0 mm</th>
<th>0.5 mm</th>
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<td>Brightness Contrast</td>
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<td>1.16</td>
<td>1.17</td>
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<tr>
<td>Axial Width</td>
<td>2.01 mm</td>
<td>1.97 mm</td>
<td>1.91 mm</td>
</tr>
<tr>
<td>Lateral Width</td>
<td>1.61 mm</td>
<td>1.33 mm</td>
<td>0.55 mm</td>
</tr>
</tbody>
</table>

Contrast values were calculated from the convolution images of circular targets [Figure 5.5(e-f)] and for ARFI images of cross-sections of the conical phantom inclusions (Figure 5.6). Contrast values were calculated in the simulation by dividing the background brightness by the average pixel value within the true area of the target. Contrast values were plotted as a function of target diameter from Figure 5.6. Contrast values are plotted in Figure 5.7 for window lengths of 0.8 mm and 1.5 mm. Notice contrast increases with an increase in the diameter of the target, and with a decrease in the correlation window length.

Figure 5.7: Measurements of displacement contrast (ratio of background displacement to lesion displacement) as a function of cross-sectional diameter of a circular target. The stiffness ratio between the stiff and compliant regions in the phantom experiment was 2.0 (2.7 kPa to 1.4 kPa). The LSI model included a circle target with a brightness of 1, and a background brightness of 2. LSI model results are compared to experimental results (a) for correlation window lengths of 0.8 mm and 1.5 mm. Contrasts are computed for a larger range of diameters (b) using the LSI model.

To validate the 2D LSI results, ARFI images were collected of small ablation lesions in porcine liver tissue *ex vivo* using the aforementioned ablation technique (Figure 5.8) to measure changes in contrast as a function of lesion diameter. Photographs, B-mode images, and ARFI images of cross-sections of ablation lesions in porcine liver
are illustrated. It is clear that with this set of parameters, typical of ARFI imaging sequences, both the 2.1 mm diameter lesion and the 0.5 mm diameter lesion are visible in the ARFI images. These regions correspond to the necrotic brighter regions in the photographs. Although both lesions are clearly visible in the ARFI displacement images, notice the lower contrast in the smaller cross section in Table 5.3 (1.72, as compare to 2.09 for the larger lesion). Also, the PSF blurring again results in an augmentation of the apparent lesion size. The widths reveal an increase in axial diameter of 27% to 92%, and an increase in lateral diameter of 1% to 82% for the larger and smaller cross-sections, respectively.

Figure 5.8: Images of ablation lesions with diameters of 2.1 and 0.5 mm. The center frequency was 4.21 MHz, the tracking pulse length was 0.7 mm, and the correlation window length was 0.8 mm. Notice the lesions are not visible in the B-mode image, but are clearly visible in the ARFI image, and the cross-sectional photographs. The displacements are given in microns 0.75 ms after the pushing pulse. The crosshairs represent the measured widths of the lesion in the ARFI image and in the cross-sectional photographs. The lengths of the horizontal and vertical cross-hairs are 2.66 mm and 2.12 mm, respectively, in the ARFI image of the lesion measured to have a 2.1 mm diameter (horizontal and vertical) in the cross-sectional photograph. The horizontal and vertical lengths of the cross-hairs in the are 0.96 mm and 0.91 mm, respectively, in the ARFI image of the lesion measured to have a 0.5 mm diameter (horizontal and vertical) in the cross-sectional photograph.
Table 5.3: Contrast and dimensional measurements of tissue ablation images (window = 0.8 mm)

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<td>Brightness Contrast</td>
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<td>1.72</td>
</tr>
<tr>
<td>Axial Width</td>
<td>2.66 mm</td>
<td>0.96 mm</td>
</tr>
<tr>
<td>Lateral Width</td>
<td>2.12 mm</td>
<td>0.91 mm</td>
</tr>
</tbody>
</table>

5.4 Discussion

In many ultrasound-based systems, a linear shift invariant (LSI) model can be used to describe the output of the system given a particular input using convolutions [137, 144-147]. One method to test the validity of this model is to convolve the expected 2D PSF with a target of relevant geometry, and compare this with experimental displacement profiles. In this chapter, results from a LSI model were compared to axial and lateral displacement profiles of a 1.2 cm diameter cross-section of a stiff inclusion. Figure 5.4 shows good agreement between simulated and experimental results (differences between the profiles were generally less than 0.2 µm), suggesting the LSI model can be used as an appropriate model for ARFI imaging. In the axial direction, the asymmetry in the simulated, LSI model profile matches closely that of the experimental displacement profile. The lateral profile also closely matched the experimental data, even though no finite element method based profile was used in the lateral dimension convolution, suggesting the beamwidth is the primary limiting factor for lateral resolution.

As the size of the circle target decreases, a matching decrease in the circle contrast is observed in both the LSI model and experimental data. This can be expected because as the relative size of the 2D PSF to the target is larger, increase in blurring of the target results. Images of cone cross-sections are shown in Figure 5.6. Notice that the highest contrast cross-section is that in which the shortest window length is used to visualize the largest diameter cross-section, where the displacement contrast between the lesion and the background is 1.44 (Table 5.1). This is because the PSF is smaller
in the axial direction relative to the lesion diameter. Conversely, when the longer window is used, a larger axial PSF results. When this longer window is used to estimate the displacements, the smallest cross-section shows a decreased contrast of 1.17 (Table 5.2) due to greater blurring. Also, notice the apparent increase in size of the cross-section. This is expected, since we expect a broadening of the system PSF with an increase in the window length and tracking pulse length. When the window length is increased, the axial diameter increases as well, with a negligible increase in lateral diameter.

In Figure 5.7(a), the LSI model and experimental results both show elastic contrast values increasing from 1 to 1.5 for lesion diameters of 0.5 mm to 1.5 mm and a target contrast of 2 suggesting the LSI based 2D PSF is a representative model of the experimental PSF. In Figure 5.7(b), the diameter of the LSI model target was increased in the model and as the diameter approached 10 mm, the contrast began to plateau above a contrast level of 2. This result shows in the limit, when the PSF becomes very small relative to the diameter of the lesion, the image contrast will approach the true target contrast.

Figure 5.8 shows decreases in contrast and increases in apparent ablation lesion size of porcine ablation lesions, suggesting that the PSF size is on the order of the lesion sizes. Another possible explanation for the increase in displacement contrast is a greater stiffening of the larger lesion, which is possible result of longer exposure to the electric current. The contrast increases 22% when imaging the 2.1 mm diameter lesion compared to the 0.5 mm diameter lesion. Also notice the variability in the displacement estimates makes differentiating the smaller lesion from the background difficult. As the size of the lesion drops below the size of the spatial variability in the displacement estimates, the lesion become difficult to differentiate from the background. In this case, an improvement in resolution does not improve lesion detection.
5.5 Summary and Conclusions

The validity of an LSI model of an ARFI imaging system was demonstrated through a comparison of experimental ARFI images of stiff, circular lesions with model images generated with the step-phantom derived PSF found in Chapter 4. The correlation window length, tracking pulse envelope, and FE-derived displacement profile were convolved to generate the axial component of the 2D PSF. The lateral PSF was modeled as the lateral beam profile, and was computed using FIELD II. The 2D PSF was the product of the lateral and axial PSF’s. A tissue mimicking phantom with a stiff, conical inclusion was fabricated. The cylindrical base of the cone (d = 1.2 cm) was imaged and the axial and lateral profiles showed good agreement (point by point differences in the profiles < 0.2 µm), providing evidence that the LSI model is appropriate in describing the ARFI imaging system.

To demonstrate ARFI imaging capabilities on millimeter-scale objects, small cross-sections of the stiff phantom cone were imaged. Cross-sectional sizes ranged from 0.5 mm to 1.5 mm. A 2D convolution model, in which the expected PSF was convolved with dark circle targets, was also performed to show that an LSI model can accurately describe the decrease in contrast and reduced resolution observed when imaging these small lesions. The LSI model showed that as the lesion size became large relative to the size of the PSF, additional increases in size resulted in minimal increases in contrast. A decrease in contrast of 13% to 18% when comparing images of the 1.5 mm phantom cone cross-section to the 0.5 mm diameter cross-section was observed, suggests the PSF is not much smaller than the diameters of the lesions imaged. In addition, phantom lesion images showed an increase in the axial diameters from 9% to 282% with an increase in correlation window length from 0.8 mm to 1.5 mm due to the augmentation of the axial PSF width, resulting in additional blurring of the lesion. In all cases, the lesions were visible, although discerning the smallest, 0.5 mm diameter lesions was quite difficult due to a much lower contrast of approximately 1.2. To corroborate these results in tissue, small porcine ablation lesions were imaged.
A decrease in contrast of 22% was observed between the large 2.1 mm diameter lesion and the smaller 0.5 mm diameter lesion suggesting that the size of the 2D PSF is on the order of the lesion diameters. LSI model and experimental results both show elastic contrast values increasing from 1 to 1.5 for lesion diameters of 0.5 mm to 1.5 mm and a target contrast of 2. These results suggest that ARFI imaging can be modeled accurately as LSI, and has the capacity to image millimeter scale lesions.
Chapter 6 Partial Echo Normalization for Minimization of Bias due to High Amplitude Reflections

6.1 Introduction

Current tissue motion tracking techniques are very effective at estimating displacement with fully developed, homogeneous speckle. When high amplitude reflections exist within the region of interest (ROI) these bright reflections are tracked to the exclusion of other, lower amplitude reflections. As a consequence, stiffness information of objects close to these bright boundaries is lost. In this chapter, a novel pre-processing algorithm named “Envelope-Weighted Normalization” (EWN) is described and is shown to be a robust solution for the high amplitude reflection problem.

A number of groups have recently developed methods for elastographic imaging of blood vessels [63, 64, 149-151], and in these applications accurate displacement estimation can prove to be difficult where reflection amplitude is high at the vessel-tissue boundary. In the presence of significant acoustic impedance mismatches, strong reflections occur at the vessel wall. 1D cross correlation-based techniques are commonly employed to estimate displacement with a defined signal window. The estimated displacement is considered to be the average of the displacements within that window with the assumption that the underlying speckle is fully developed without large variations in reflection amplitude. However, local high-amplitude signals tend to dominate the displacement estimate. The result is displacement bias
that spatially corresponds to the high amplitude region of the echo in the vicinity of the reflective boundary.

To minimize displacement estimation bias, several authors developed log compression methods to reduce the relative amplitude of the bright reflections [152, 153]. Logarithmic compression reduces the fluctuation in the echo signal before displacement estimation, thereby reducing the relative weighting of the correlation function. Bias was successfully reduced while improving the jitter of the displacement estimates. Further investigation by Alam et al. [153] found the signal waveform approached that of a square wave with greater log compression, and the autocorrelation of a square wave is a triangular wave. Typically, continuous functions (e.g., parabolic and cosine) are used to estimate the correlation peak for sub-sample displacement estimation. Attempting to estimate a “triangularized”, discontinuous function with a continuous function was shown to result in a cyclic bias in the displacement estimate [153].

One method to minimize displacement estimation bias without drastically changing the sinusoidal shape of the waveform is the process of normalization. Soft limiting, as proposed by Alam et al. [153], normalized signal amplitude every half cycle. Signal normalization can also be achieved by dividing a signal by its envelope, preserving the phase content of the signal while reducing amplitude modulation. A drawback of signal normalization is the increase in jitter magnitude (a measure of the precision of the displacement estimation). Local signal-to-noise ratio (SNR) is diminished because of a relative increase in amplitude of low amplitude, low SNR portions of the signal, and a relative decrease in amplitude of initially high amplitude, high SNR portions of the signal. A decrease in SNR results in an increase in jitter magnitude [86].

In this chapter, a novel envelope-weighted normalization (EWN) technique is used to lessen the high-amplitude reflections without critically affecting the quality of the rest of the signal. If the echo’s envelope is used to weight the normalization, then the larger amplitude values within the echo are reduced more than smaller amplitude
Section 6.2 provides a brief review of the fundamentals of displacement estimation and discusses bias due local high amplitude echo signals. The EWN algorithm is introduced as a method to avoid bias that results from these variations in signal amplitude. In Section 6.3, to verify the utility of this technique, a parametric analysis was performed to quantify the improvement in the displacement estimation bias and the jitter magnitude. The performance of the algorithm was demonstrated by imaging a porcine hepatic blood vessel \textit{ex vivo}.

### 6.2 Theory

Normalized cross-correlation based displacement estimation is widely employed in the field of elastography [55, 56, 58, 59, 119, 154]. The standard form of the cross-correlation between two echoes is given below:

\[
\rho(\tau) = \int_{-T/2}^{T/2} f(t)g(t+\tau)dt
\]  

(6.1)

where \( T \) is the correlation window length. When the reflection amplitudes of scattering sources in the medium are equal, the populated echo amplitudes result in a Rayleigh distribution [Figure 6.1(a)], and displacement estimates generally represent the average displacement that occurs within a correlation window.
Typically, for displacement estimation, a search region is defined over which a correlation window is shifted a signal, while the window is stationary on some “reference” signal. The shift at which the largest correlation coefficient occurs is used to estimate the displacement. However, this may result in higher correlation between a portion of a signal and an indiscriminate bright spot because Equation 6.1 is maximized by the total energy of the product of the two functions involved. To combat this artifact, normalized cross correlation is commonly implemented [86]:

\[
NCC(\tau) = \frac{\int_{-T/2}^{T/2} f(t)g(t+\tau)dt}{\sqrt{\int_{-T/2}^{T/2} (f(t))^2 dt \int_{-T/2}^{T/2} (g(t+\tau))^2}}
\]  

(6.2)

This expression normalizes the result of cross correlation by the product of signal squared, thereby accounting for any large changes in amplitude. Normalized cross-correlation is most useful when the search region is large relative to the window length, allowing for the comparison of windows with very different brightness profiles. Nevertheless, when there is a local bright region within a correlation window, this definition still implies that the value of the correlation coefficient, albeit normalized, is weighted by the high amplitude portions of the signal.
One approach to minimize the bias is to pre-normalize the echoes by dividing the echo by its envelope before performing standard normalized cross-correlation. Unfortunately, the normalization process increases the relative magnitude of the low amplitude portions of the echo, decreasing signal SNR and therefore increasing jitter error. A second option is to weight the signal after signal normalization as a function of signal amplitude. For low amplitude values, the weighting is proportional to the amplitude. For high amplitude values, the weighting function approaches a limiting value. As a result, low amplitude signals remain minimally affected, while higher amplitude signals are more normalized. The hyperbolic tangent is a function that has this quality, given in Eq. (6.3) below:

\[ n = \tanh \left( \frac{A_e}{C} \right) \tag{6.3} \]

where \( A_e \) is the envelope of echo signal \( A \), and \( C \) (the “normalization coefficient”) affects the values at which \( n \) approaches unity [Figure 6.1(b)]. In this study, the default value used for \( C \) is a multiple of the median of the echo envelope. The median of a Rayleigh distribution is proportional to the standard deviation of the echo [155]. The median was used rather than a constant because this would adjust the convergence of the \( n \) function according to the relative magnitude of the high amplitude region. The second step of the algorithm requires the normalization and then scaling of the signal by \( n \):

\[ A_n = n \frac{A}{A_e} \tag{6.4} \]

By using these EWN echoes \( (A_n) \), increases in jitter error as well as amplitude-dependent bias are reduced. Figure 6.2 illustrates the advantage of using the EWN technique before displacement estimation. A hydrogel tissue-mimicking phantom was created with a compliant cone in a stiffer background medium using the procedure detailed in Section 3.3.2. Notice, the EWN technique avoids the bias seen in the
image created using the original echo signals, and the jitter generated when normalized echoes are employed.

Figure 6.2: B-mode (log-compressed) and ARFI images of a stiff hydrogel phantom with a compliant conical inclusion using cross-correlation (a) without normalization, (b) EWN, and (c) full normalization. The center frequency is 5.33 MHz, the correlation window length was 0.77 mm, and the tracking pulse length was 2 λ. The image represents a time point 0.75 ms after the pushing pulse.

6.3 Methods

Two simulations were developed, one to estimate the ability to accurately represent the displacement between two bright regions (and in turn quantify displacement estimation bias), and the second to estimate jitter error before and after echo normalization. Simulations followed the procedure detailed in the simulation study by Walker et al. [156]. All calculations were performed in MATLAB (Mathworks Inc., Natick, MA). Signals were generated by convolving white noise with sinc-enveloped sinusoids given by:
\[ psf(t) = \frac{\sin(\pi Bf_0 t)}{\pi Bf_0 t} \sin(2\pi f_0 t) \]  

(6.5)

where \( B \) is the fractional bandwidth and \( f_0 \) is the center frequency. This particular point spread function was chosen to match the conditions used to determine the Cramer-Rao lower bound (CRLB) that is used to calculate the minimum achievable jitter error magnitude [86]:

\[ \sigma(\Delta t - \hat{\Delta t}) \geq \sqrt{\frac{3}{2 f_0^3 \pi^2 T(B^2 + 12B) \rho^2 \left(1 + \frac{1}{SNR^2}\right) - 1}} \]  

(6.6)

where \( T \) is the correlation window length and \( \rho \) is the density. The CRLB is discussed in detail in Section 2.3.2. The default parameters used in this study were a 6.67 MHz center frequency, a 40 MHz sampling frequency, a 0.5 fractional bandwidth, 0.77 mm correlation window length, a normalization coefficient of 0.6 times the median values, and a 2:1 ratio between the echo amplitude of the simulated reflective boundaries and the remaining scatterers. These value ranges are typical of those used in ARFI imaging correlation-based displacement estimation.

Simulations were employed to investigate the effect of correlation window length from 0.4 mm to 1.2 mm, brightness contrast range of 1 (no contrast) to 8, normalization level from 0.2 to 0.8 (in multiples of the echo envelope median), and center frequencies from 3 MHz to 8 MHz on the displacement estimation bias and jitter errors. The echoes generated were left unmodified in their original form, normalized by the signal envelope, or processed using the EWN algorithm. The resulting original, normalized and EWN echoes were then used to estimate the applied echo shift using normalized cross-correlation displacement tracking. Following up-sampling by a factor of 8, normalized cross-correlation was performed using a 0.77 mm window length with a search region size of 19 µm in both directions. A single sample (19 µm) window shift was used after each estimate. The location of the peak in the correlation
function was used to estimate axial displacement. Sub-sample peak estimation was achieved using parabolic interpolation.

### 6.3.1 RMS Error Estimation and Bias

For each condition analyzed, 500 scatterers were defined at random locations along a line that represented a distance of 2 cm \((c = 1540 \text{ m/s}, f_0 = 6.67 \text{ MHz}, f_s = 40 \text{ MHz})\). The amplitude of the scatterers was set to unity, and a uniform 10 µm shift was applied except for the center 2 mm of the echo and no shift was applied to the scatterers. In this center 2 mm, and the scatter amplitude was set to 2 (unless otherwise defined) before convolution with the PSF. The RMS error was calculated between the applied and tracked displacements in a 5 mm window at the center of the echo, a window long enough to include the biasing effects that are a function of window length and tracking pulse width. Each RMS error calculation was repeated for 1000 echo realizations, and the 95% confidence intervals of the means were computed assuming a normal distribution [157]:

\[
x - 1.96 \frac{\sigma}{\sqrt{n}} \leq \mu \leq x + 1.96 \frac{\sigma}{\sqrt{n}}
\]  

(6.7)

where \(x\) is the sample mean, \(\mu\) is the true mean, \(\sigma\) is the standard deviation, and \(n\) is the number of samples.

Bias was quantified by subtracting the applied displacement from the tracked displacement as shown in Figure 6.3. To reduce jitter, 10 displacement profiles were averaged from 10 independent speckle realizations. For each set of conditions, the bias was plotted as a function of position [Figure 6.3(b)].
Figure 6.3: Bias is measured by subtracting the applied displacement profile (a) from the tracked displacement profile and is plotted in (b). In this example, a 6.67 MHz center frequency, a fractional bandwidth of 0.5, and a normalization level of 0.6 times the median were used for both estimates and a correlation coefficient of 0.998, an amplitude contrast of 2. Jitter errors were reduced by averaging 10 displacement profiles from independent speckle realizations.

6.3.2 Jitter Error Estimation

500 scatterers were created to generate speckle along a line that represented a distance of 2 cm. The default SNR was 30 dB and the correlation coefficient of 0.998 was defined using Cholesky factorization of the cross correlation matrix, following the protocol described by Walker et al. [86] The signal in the final 2 mm of the echo were defined to have an average amplitude of 2, while the remainder of the signal had an average amplitude of one. The jitter error was estimated by calculating the standard deviation of the displacement estimates at the beginning of each of 1000 realizations of echo signals, with 0 µm displacement. The 95% confidence intervals of the standard deviation of jitter errors were computed assuming a normal distribution [157]:

\[
\frac{s}{1+1.96/\sqrt{2\cdot(n-1)}} \leq \sigma \leq \frac{s}{1-1.96/\sqrt{2\cdot(n-1)}}
\]  

(6.8)
where $s$ is the sample standard deviation, $\sigma$ is the true standard deviation, and $n$ is the number of samples.

### 6.3.3 Tissue Imaging Ex Vivo

A porcine hepatic artery was imaged to demonstrate the performance of EWN as compared to unmodified echoes ex vivo. Imaging was performed with a Siemens Sonoline Antares Ultrasound Scanner (Siemens Medical Solutions USA, Inc., Issaquah, WA, USA). A VF10–5 linear array transducer with a 2 cm lateral focal depth and 6.67 MHz excitation frequency was used for the pushing and tracking pulses. Beam sequences included a 0.30 μs reference pulse, followed by a 30 μs pushing pulse, and 30 – 0.3 μs tracking pulses (at a pulse repetition frequency (PRF) of 12.7 kHz) and data was acquired at a 40 MHz sampling rate.

The tissue was imaged while submerged in 0.9% saline and the brightness ratio between the artery wall and the surrounding liver was approximately 6. A lumen mask was applied by using a threshold of the correlation coefficient in which the value of 0 was defined for the lumen pixel. The empirically derived threshold of 0.997 was used. At this threshold level, values in the center of the vessel fell under the threshold, while those geometrically outside of the vessel remained above the threshold. Displacement estimates were compared with and without using the EWN technique. The widths of the vessels in both ARFI images were then compared to the width of the vessel measured from the B-mode image.

### 6.4 Results

The results are presented for displacement estimates using original (unmodified), EWN, and normalized echoes. Jitter and RMS errors are presented for all three sets of displacement estimates as functions of correlation window length, center frequency,
amplitude contrast, normalization coefficient, and SNR. In the case of jitter error, the CRLB was plotted. In addition, bias was plotted as a function of position for two parameter values for each parameter investigated.

The effect of correlation window length on the standard deviation of jitter errors, RMS error, and bias are presented in Figure 6.4 and Figure 6.5. Displacements estimates from original, EWN, and normalized echoes all show a decrease in jitter errors with increasing correlation window length within a range of window lengths from 0.4 mm to 1.12 mm [Figure 6.4(a)]. The increase in jitter magnitude when using normalized echoes was 25%. In contrast, when the EWN algorithm was employed, the increases in jitter magnitude were only 5% (<0.1 µm). The RMS error showed an increasing trend as a function of correlation window length under all three conditions, as shown in Figure 6.4(b). Displacement estimation using EWN echoes resulted in the least RMS error as compared to original, and normalized conditions. Bias is plotted in Figure 6.5 as a function of position for correlation window lengths of 0.4 mm and 1.2 mm. While the profiles for all three conditions closely match when using the short, 0.4 mm window, when a longer 1.2 mm window is employed, increases in bias magnitude and the spatial extent of the bias is observed.
Figure 6.4: Jitter magnitude (a) and RMS error (b) as a function of correlation window length. The error bars represent the 95% confidence intervals (n = 1000). A 6.67 MHz center frequency, a fractional bandwidth of 0.5, and a normalization level of 0.6 times the median were used for both estimates and a correlation coefficient of 0.998, an amplitude contrast of 2 and an SNR of 30 dB were used for jitter error estimates.

Figure 6.5: Bias as a function of position for correlation window lengths of (a) 0.39 mm and (b) 1.16 mm. A 6.67 MHz center frequency, a fractional bandwidth of 0.5, a normalization level of 0.6 times the median, and an amplitude contrast of 2 were used for both estimates.
Figure 6.6 depicts the standard deviation of jitter errors and RMS error, while Figure 6.7 shows bias, as functions of amplitude contrast. Amplitude contrast is defined as the ratio of the average amplitude of the signal in the higher amplitude region of the signal to that of the lower amplitude region of the signal. Under all three conditions tested, no significant change in jitter errors was measured within the amplitude contrast range of 1 (no contrast) to 8 [Figure 6.6(a)]. RMS error increased with amplitude contrast for all three sets of signals, but was consistently lower in the normalized and EWN cases than when using the original signals [Figure 6.6(b)]. The bias is shown in Figure 6.7 for amplitude contrasts of 1 and 8 as functions of position. Under all three conditions the difference between the displacement estimates are minimal when no amplitude contrast is applied.
Figure 6.6: Jitter magnitude (a) and RMS error (b) as a function of amplitude contrast; defined as amplitude of the bright region (the amplitude of the surrounding region is unity). The error bars represent the 95% confidence intervals ($n = 1000$). A center frequency of 6.67 MHz center frequency, a correlation window length of 0.77 mm, and a fractional bandwidth of 0.5 were used for both estimates and a correlation coefficient of 0.998, and an SNR of 30 dB were used for jitter error estimates.

Figure 6.7: Bias for amplitude contrast values of (a) 1 and (b) 8 defined as amplitude of the bright region (the amplitude of the surrounding region is unity). A 6.67 MHz center frequency, a fractional bandwidth of 0.5, correlation window length of 0.77 mm, and a normalization level of 0.6 times the median.
The standard deviation of jitter errors and RMS errors are presented in Figure 6.8, and bias in Figure 6.9, as functions of the normalization coefficient ($C$, Eq. 6.3). As $C$ increases, the jitter magnitude decreases. The increase in jitter magnitude after using the EWN algorithm is significant, but when $C$ is greater than 0.3 times the median ($M$, Eq. 6.3), the increase in jitter error is less than 20%. The increase in jitter magnitude as a result of complete normalization is nearly 40%. RMS error using the EWN algorithm is approximately 25% lower than that measured when using the original echoes at all values of $C$ from 0.3-0.9. The difference in RMS error when using normalized and EWN echoes was small at all values of $C$ ($< 0.1 \, \mu m$), and fall within their 95% confidence intervals for normalization coefficients greater than 0.6 times the median of the echo amplitudes. The bias is given in Figure 6.9 for normalization coefficients of 0.3 and 0.9. Notice although there a negligible difference in the bias between the normalized and EWN conditions when the normalization coefficient is 0.3, at a value of 0.9, the bias profile for the EWN echo falls between the profiles of bias using normalized and original echoes.
Figure 6.8: Jitter magnitude (a) and RMS error (b) as a function of normalization coefficient C, or a fraction of the median amplitude value (Equation 1). The error bars represent the 95% confidence intervals (n = 1000). A center frequency of 6.67 MHz center frequency, a correlation window length of 0.77 mm, and a fractional bandwidth of 0.5 were used for both estimates and a correlation coefficient of 0.998, an amplitude contrast of 2, and an SNR of 30 dB were used for jitter error estimates.

Figure 6.9: Bias for normalization coefficients (C in Equation 1), of (a) 0.3 and (b) 0.9 (in fractions of the median echo amplitude value). A 6.67 MHz center frequency, a fractional bandwidth of 0.5, correlation window length of 0.77 mm, and an amplitude contrast of 2 were used.
Figures 6.10 and 6.11 show the standard deviation of jitter errors, RMS error and bias as functions of center frequency. The jitter magnitude decreases with an increase in frequency when original, EWN, and normalized echoes are employed. The increase in the jitter magnitude due to EWN remains small, less than 1 µm for frequencies greater than 3 MHz, and is approximately 50% (in all cases > 0.1 µm) when normalized echoes are utilized. A decreasing trend was observed in RMS error with an increase in frequency in all three cases. The decrease in RMS error when using the EWN echoes ranged from 10% to 15%. Bias was plotted for signals with center frequencies of 3 MHz and 8 MHz. Although the bias profiles showed little variation between the three profiles when a center frequency of 3 MHz was used, the bias was noticeably greater when original echoes were employed with a center frequency of 8 MHz.
Figure 6.10: Jitter magnitude (a) and RMS error (b) as a function of center frequency. The error bars represent the 95% confidence intervals (n = 1000). A correlation window length of 0.77 mm, a fractional bandwidth of 0.5, a correlation coefficient of 0.998, a brightness contrast of 2 and an SNR of 30 dB were used.

Figure 6.11: Bias for central frequencies of (a) 3 MHz and (b) 8 MHz. A fractional bandwidth of 0.5, correlation window length of 0.77 mm, a normalization level of 0.6 times the median, and a brightness contrast of 2.
The standard deviation of jitter errors is presented as a function of SNR in Figure 6.12. The increase in the jitter magnitude due to EWN is small for SNR values above 11 dB (< 0.1 µm). When echoes are normalized, increases in jitter magnitude range from 25% to 30% (> 0.1 µm).

**Figure 6.12**: Jitter magnitude as a function of SNR. The error bars represent the 95% confidence intervals (n = 1000). A center frequency of 6.67 MHz center frequency, a correlation window length of 0.77 mm, a fractional bandwidth of 0.5, a brightness contrast of 2, and a correlation coefficient of 0.998 was used.
A porcine hepatic artery was imaged *ex vivo* to demonstrate the utility of the EWN method in tissue. Figure 6.13 shows B-mode and displacement images of porcine hepatic arteries before and after using the EWN algorithm. Notice the artifact in the displacement image in Figure 6.13(c), in which the walls appear thicker than in the B-mode images.

**Figure 6.13:** Images of porcine hepatic arteries *ex vivo*. The B-mode image is given in (a). A representative profile of the cross-correlation coefficients at a lateral position of 1.4 cm is plotted in (b), with the cut-off value of 0.997 that was used for luminal masking. In the bottom row are the displacement images 0.6 ms after an ARFI pushing pulse using the original (c) and EWN normalized (d) echoes. The frequency was 6.67 MHz, the correlation window length was 0.77 mm, the fractional bandwidth was 0.5, and the B-mode brightness contrast between the artery wall and the surrounding liver was approximately 6:1. The grayscale corresponds to displacement amplitude (µm) in the ARFI images (c and d). The average differences between the widths of the blood vessels as measured from the masked ARFI images and the B-mode image (-6 dB drop in intensity approaching the lumen) were 0.81 ± 0.39 mm when using the original echoes and 0.46 ± 0.40 mm when EWN echoes are employed.
This artifact is diminished in Figure 6.13(d), where the width of the lumen more accurately depicts the size of the lumen represented in the corresponding B-mode image. The average differences between the widths of the blood vessels as measured from the masked ARFI images and the B-mode image (-6 dB drop in intensity approaching the lumen) were $0.81 \pm 0.39$ mm when using the original echoes and $0.46 \pm 0.40$ mm when EWN echoes are employed. Given that the B-mode image accurately represents the lumen of the vessel, when EWN echoes are employed, the ARFI images mask the lumen more accurately. Figure 6.14 shows a representative echo signal and corresponding correlation coefficient profiles.

![Figure 6.14](image_url)

**Figure 6.14:** Representative (a) original echo signal and (b) correlation coefficient values as functions of depth of a porcine hepatic artery *ex vivo*. In (b), correlation coefficient is plotted for displacement estimates using both original and EWN echoes. The 0.997 correlation coefficient used for luminal masking is also marked. The frequency was 6.67 MHz, the correlation window length was 0.77 mm, the fractional bandwidth was 0.5, and the brightness contrast between the artery wall and the surrounding liver was approximately 6:1. A lumen mask was used in which a correlation threshold of 0.997 was implemented.
6.5 Discussion

The use of correlation-based displacement estimation in ultrasonic elastography is quite common, but it is used under the assumption that the underlying speckle is relatively homogeneous in amplitude. When this assumption is not true, a bias in the estimated displacement may result. The goal of this study was to minimize this “echo amplitude dependent” bias without significantly increasing the jitter magnitude. Bias reduction was quantified using an estimate of RMS error.

In the case of echo normalization, a large increase in the jitter magnitude was also observed. Echo signals include a certain level of system noise. During the normalization process the local echo SNR decreases around higher amplitude, higher SNR regions and around lower amplitude, lower SNR regions. The result is an increase in the jitter magnitude. In order to avoid this artifact, an algorithm was developed that would more strongly weight the normalization in regions of higher amplitude, minimizing the augmentation of system noise in regions of lesser amplitude.

6.5.1 Correlation Window Length

Figures 6.4 and 6.5 showed little increase in the standard deviation of jitter errors for all correlation window lengths (< 0.05 µm) and a significant decrease in RMS error ranging from 0.1 µm to 0.4 µm (6% to 18%) for window lengths of 0.4 mm to 1.2 mm, and the bias showed noticeable differences in the profiles when using EWN echoes and the original echoes when using a 1.2 mm window length. When echoes were normalized, the increase in jitter was greater than 0.1 µm for all window lengths (> 25%), and the decrease in RMS was less than that observed when using EWN echoes, especially at lower window lengths in which the jitter errors presumably began to dominate the RMS errors. The EWN algorithm results in little augmentation of noise in the regions of lesser brightness because it does not flatten the low
amplitude regions and therefore generates smaller jitter errors. The increase in RMS with window length is greatest when using the original echoes, suggesting that when the original echoes are used, RMS error is more greatly dependent on the correlation window length. This greater dependence is a result of amplitude-dependent bias, as illustrated in Figure 6.5. Once a higher-amplitude region of a signal falls within a correlation window, the displacement that corresponds to that region will dominate the estimate, causing bias. In other words, as the window length increases, the local, high amplitude region will bias more of the displacement profile, resulting in greater bias in the region corresponding to the low amplitude echo region, and a slightly lower bias in the region of higher echo amplitude. The net result is a lower overall bias when using the EWN algorithm.

6.5.2 Echo Amplitude

In Figure 6.6 and Figure 6.7, as echo amplitude contrast increased from 1 to 8, no significant change was noticed in jitter errors when original, EWN and normalized echoes were used, a decrease in RMS error was observed when EWN echoes were utilized, and only small differences in bias were observed for the higher amplitude contrast value of 8. Although jitter errors were not found to be strongly dependent on amplitude contrast, there remains a significant 0.2 µm increase in jitter with normalization, and only a small increase of less than 0.1 µm when EWN echoes are used. RMS generally increased from 1.5 µm to 3.5 µm for all three sets of echoes. The greatest decrease between profiles using original and EWN echoes was found to occur for an amplitude contrast of 4. When the amplitude contrast value is small, little biasing occurs. When the amplitude contrast is too high, the sidelobes of the echo response of the bright scatterers dominate the surrounding signal. This reduces the effectiveness of EWN. In Figure 6.7, notice the larger bias values are generated when the amplitude contrast equal to 8, as is expected because a greater echo amplitude is expected to result in greater biasing of the displacement estimates, especially in the
absence of normalization or EWN. These algorithms serve to reduce the relative amplitude of these high amplitude regions, thereby limiting displacement bias.

6.5.3 Normalization Coefficient

Standard deviation of jitter errors decreases and RMS error increases as a functions of normalization coefficient (C, Eq. 6.3), as shown in Figure 6.8, and the associated bias is illustrated in Figure 6.9. The magnitude of the jitter errors decreased by 13% with an increase in the normalization coefficient from 0.3 to 0.9. The RMS error, on the other hand, showed a small increase with normalization coefficient of less than 3%. As a value of 0.3 is approached, the RMS error approaches that of the fully normalized condition, as expected. A decrease in C also results in an increase in the standard deviation of the jitter errors. For this range of C values (0.3-0.9) the difference in the jitter magnitude between the original data and the EWN data is significant, and ranges from less than 10% when C is 0.9 to 25% when C is 0.3. The jitter magnitude is 40% larger when the echoes are fully normalized, which is significantly higher than both the original and EWN conditions. The results here suggest that under these conditions, a C value of 0.6 is appropriate for an improvement in RMS error while avoiding a large increase in the jitter magnitude, for this set of common parameters. In Figure 6.9, with an increase in C, we see the EWN echo displacement profile shows bias that approaches that of the original echoes.

6.5.4 Frequency

Figure 6.10 shows the effects of varying the frequency from 3 MHz to 8 MHz on the standard deviation of jitter errors, and RMS error, and Figure 6.11 depicts bias as a function of for frequencies of 3 MHz and 8 MHz. For all frequencies tested, the increase in the standard deviation of jitter error was approximately 50% when the echoes were normalized, and 5% (< 0.1 µm) when the EWN algorithm was employed. This suggests that percentage increase in the jitter magnitude is
independent of frequency. This result is intuitive because although frequency effects jitter, that effect would affect all three conditions equally. As the frequency increases, the difference between the RMS error using EWN echoes and the original echoes increases from 5% to 20% (0.1 µm to 0.4 µm). Greater decreases in RMS error suggest that the EWN algorithm performs better at higher frequencies. The reason for greater success of the EWN algorithm at higher frequencies is that the wavelength is shorter. As a result, the reflections from the high amplitude region of the signal only impact the local speckle. As the wavelength increases, the region over which the high amplitude reflections contribute to the surround speckle increases. Even after normalization, this contribution results in an increase in the RMS error. The bias plots in Figure 6.11 also corroborate that at the higher frequency of 8 MHz, the original profile shows visibly more bias than the EWN profile.

6.5.5 SNR

Since the normalization process tends to augment noise in the echo signal, the jitter magnitude was measured for the original, EWN and normalized echoes over a range of SNR values (Figure 6.12). The absolute value of the SNR decreases with an increase in SNR between 11 dB and 41 dB. In the case of the normalized echoes, the difference in the jitter magnitude from that of the original echoes decreases from 0.7 µm to 0.2 µm between 11 dB and 41 dB SNR. When the EWN algorithm was applied the difference in the jitter magnitude decreases from 0.2 µm to less than 0.1 µm in the same range. These results imply that the EWN algorithm does not increase the standard deviation of jitter error by a large amount, even when using signals with low SNR.

6.5.6 Tissue Images

Figures 6.13 and 6.14 illustrate the result of using this algorithm when imaging tissue. In our porcine hepatic artery experiment, a luminal mask was applied because in an
ARFI image the lumen appears as noise due to radiation force induced streaming of the fluid. As expected, the walls of the vessel seem thicker in the displacement image [Figure 6.13(c)], and these thicker regions correspond to the strong reflection at the vessel wall that result in amplitude-dependent displacement estimation bias. When this EWN algorithm is applied, this bias is diminished by approximately 50%. After normalization, when applying the luminal mask, the apparent width of the vessel in the normalized case matches the width of the lumen in the B-mode image, while the original ARFI Images shows appreciable narrowing. The EWN algorithm shows promise in imaging these smaller diameter vessels, when the lumen diameter and blood vessel wall are small relative to the window. Using the original signals for small vessels can result in a loss of much of the displacement data of the vessel wall due to bias, as shown in Figure 6.14(c). An increase in displacement estimate variability is visible in Figure 6.14(d) when compared to Figure 6.14(c) due to a small increase in jitter. Bias is also reduced, allowing for more local, more accurate displacement estimates. Although no increase in jitter is ideal, this simulation study suggests that reduction in bias due to the EWN method justifies this increase. Future studies in a clinical setting will be required to test this tradeoff. In Figure 6.14, a representative echo signal is plotted along with correlation coefficient as a function of depth. The decrease in correlation coefficient using EWN echoes is local to the walls of the vessel, outlined by the two high amplitude regions of the echo signal. The spatial extent of the decrease in correlation coefficient is greater for distal artery wall due to the higher amplitude signal. The 0.997 correlation coefficient cut-off value for luminal masking is indicated. A value was chosen that masks the lumen without eliminating displacement estimates in the surrounding tissue. A change in the cut-off value would result in little relative change in the apparent lumen diameter, as can be seen by the steep decreases in correlation coefficients when original and EWN echoes were employed.
6.6 Conclusions

An algorithm has been successfully developed to reduce amplitude-dependent bias in displacement estimates while avoiding a large increase in the jitter magnitude. The algorithm involves an envelope-weighted normalization of an echo. A parametric analysis was conducted in order to find the optimum conditions in which this partial normalization technique could be implemented. The results were also compared to the unmodified case, and the case in which the echoes were first fully normalized. It was found that under these conditions, application of this particular EWN algorithm resulted in an improvement in RMS error of at least 10% when longer correlation window lengths (> 0.6 mm) and higher frequencies (> 3 MHz) are used. Echo amplitude contrast had little impact on the relative improvement of separation distance. When a normalization level of 0.6 times the median was used, the increase in the standard deviation of the jitter errors was negligible (<5%). It was demonstrated that the EWN technique reduces displacement estimation bias under conditions typical of ARFI imaging without a large increase in jitter errors. This algorithm shows promise in the imaging of blood vessels, for example, that exhibit a change in mechanical properties that has been associated with the onset of atherosclerosis and plaque formation [19, 20], and the monitoring of ablation treatments, in which strong reflections are also prevalent.
Chapter 7 Conclusions and Future Work

7.1 Summary and Conclusions

The first goal of this thesis was to develop a protocol to accurately estimate the limits of an ARFI imaging system’s spatial resolution. The second goal of this thesis was to reduce echo amplitude-dependent displacement estimation bias to allow better resolution of objects of interest near bright boundaries. This was accomplished using a combination of experimental studies imaging hydrogel phantoms and porcine tissue, LSI modeling, FE-based simulations, and novel signal processing techniques.

The spatial resolution of an ARFI imaging system has been measured and modeled as a function of several system parameters and target contrast levels using novel simulation and experimental techniques. The step response of the system was experimentally extracted by imaging a tissue-mimicking phantom composed of two bonded materials. The ARFI imaging resolution limit was further explored by developing a coupled 3D FEM/acoustic field model. In addition, a LSI model of ARFI imaging was developed. This model estimated resolution from the dimensions of the PSF, which in turn was derived from measured/simulated step response.

The axial and lateral resolution estimates of an ARFI imaging system were primarily functions of imaging and displacement estimation parameters. ARFI axial FWHM decreased with an increase in ultrasound frequency. No significant decrease was observed for frequencies greater than 15 MHz. The increase in axial FWHM with tracking pulse length did not show statistical significance due to the high FWHM estimate variability. An increase in the FWHM was observed with an increase in
correlation window length. In all cases, the experimental results agreed with LSI model results, within the measurement variability, suggest correlation window length and tracking pulse lengths are the primary determinants of the axial resolution limit. FE-simulation resolution estimates matched LSI model predictions as well, implying that the mechanical response of the material was not a limiting factor above a correlation window length of 1 mm. Below this value, the axial FWHM showed a positive bias when compared to the LSI predictions, suggesting that below this value, the mechanical response of the medium influences the axial resolution and reduces the improvement otherwise expected from imaging and displacement estimation parameters alone. The axial FWHM was, on average, equal to the longer of the tracking pulse and the correlation window, as predicted by the LSI model. The axial FWHM was on average 0.5 mm to 1 mm because window lengths and tracking pulse lengths between 0.5 mm and 1 mm were used. The ARFI lateral resolution limit corresponded to the 1 mm lateral two-way beamwidth of the tracking beam at all depths.

ARFI imaging LSI models were validated by comparing experimental ARFI images to images generated from the step-phantom based PSF derived earlier in this thesis. The 2D PSF for the first comparison study included was a function of the correlation window length, tracking pulse envelope, and lateral beam profile. The displacement profile of a 1.2 cm cross-section of the base of a stiff-conical hydrogel inclusion showed good agreement with the LSI based profile (point by point differences < 2 µm).

For the second comparison study, the displacement contrast of small lesions with diameters of 0.5 mm to 1.5 mm measured and compared with LSI model results. The 2D PSF in this study only included imaging and displacement estimation parameters, based on the finding earlier in the thesis suggesting resolution is primarily a function of these parameters. The LSI model showed that as the lesion size became large relative to the size of the PSF, additional increases in size resulted in minimal
increases in contrast. A decrease in contrast of 13% to 18% when comparing images of the 1.5 mm phantom cone cross-section to the 0.5 mm diameter cross-section, suggesting the PSF is not much smaller than the diameters of the lesions imaged. In addition, phantom lesion images showed an increase in the axial diameters from 9% to 282% with an increase in correlation window length from 0.8 mm to 1.5 mm due to the augmentation of the axial PSF width, resulting in additional blurring of the lesion. The LSI model and experimental results both show elastic contrast values increasing from 1 to 1.5 for lesion diameters of 0.5 mm to 1.5 mm and a target contrast of 2. To corroborate these results in tissue, small porcine ablation lesions were imaged. A decrease in contrast of 18% was observed between the large 2.1 mm diameter lesion and the smaller 0.5 mm diameter lesion suggesting that the size of the 2D PSF is on the order of the lesion diameter. These results imply the step-phantom derived 2D PSF is a valid model of the experimental ARFI imaging PSF.

The ability of ARFI imaging to resolve targets near bright boundaries was improved by a method called envelope-weighted normalization (EWN) that reduces amplitude modulation of tracking echoes, thereby reducing displacement estimation bias. A parametric simulation study was conducted to quantify the reduction in displacement estimation bias. It was found that under these conditions, application of this particular EWN algorithm resulted in an improvement in RMS error of at least 10% when longer correlation window lengths (> 0.6 mm) and higher frequencies (> 3 MHz) are used. Echo amplitude contrast had little impact on the relative improvement of separation distance. When a normalization level of 0.6 times the median was used, the increase in the standard deviation of the jitter errors was negligible (<5%). Porcine hepatic blood vessels were imaged ex vivo to demonstrate the EWN pre-processing technique’s ability to reduce bias in an ARFI image of tissue with the vessel acting as a strong reflector. The EWN algorithm resulted in a 50% more accurate measurement of the diameter of the lumen.
7.2 Novel Contributions

In this chapter, a novel method to measure ARFI spatial resolution experimentally was presented and matching simulations were developed to better understand the effects of the underlying ultrasound, signal processing, and mechanical parameters that affect spatial resolution. The resolution measurement technique is the first method proposed to experimentally quantify ARFI resolution. This was a new approach to resolution estimation in elasticity imaging in which the step response of the system was derived from the ultrasonic estimates of displacements induced in a bimaterial consisting of differing moduli. The derivative of this step response is the PSF of the system, and the FWHM was reported.

The novel methodologies developed to measure and improve ARFI imaging spatial resolution through the completion of this thesis are enumerated below:

1. For the first time, a coupled FEM/acoustic field model that simulated the displacement of a bimaterial due to the application of the radiation force, tracking of the displacements ultrasonically, and displacement estimation was developed for the purpose of ARFI imaging resolution estimation.

2. The first technique was proposed to measure ARFI imaging axial and lateral resolution experimentally. A modulus step phantom was imaged to extract the step response. A tilted sigmoid was fitted to the resulting displacement profile using a NLSF algorithm, and the PSF was the spatial derivative of the sigmoid. The FWHM of the PSF was measured to quantify resolution.

3. First time small, stiff phantom inclusions and tissue ablation lesions were imaged near the ARFI imaging resolution limit to demonstrate ARFI imaging resolution capabilities. The contrast ratio of the ARFI images lesions and the background were compared to the 2D convolution of the ARFI imaging 2D PSF and circular targets.
4. A new signal processing technique was developed called envelope-weighted normalization (EWN) that preferentially diminished high amplitude signals that reduces amplitude dependent bias, avoids significant increases in jitter. Unlike other nonlinear techniques, this technique avoided a cyclic bias by simply normalizing the signal by its envelope rather than employing log compression. In addition ARFI images generated using EWN echoes more accurately represented the width of a porcine hepatic blood vessel ex vivo.

7.3 Future Work

7.3.1 Slip and Partial-Slip Boundary Conditions

The model of the ARFI imaging step response used in this thesis involved imaging of two bonded materials of differing material stiffness. This model is appropriate for elasticity imaging applications in which the stiffer diseased or necroosed tissues are well connected to the surrounding healthy tissue, and include tissue ablation imaging and imaging of metastatic infiltrating malignancies. Tissue boundaries exist, however, in which the two adjacent tissues of mismatched stiffness are not well connected, such as benign lesions and multilayered tissue fascia which may have slip or partial-slip boundaries.

The boundaries characterized by slip, or partial-slip conditions do not always require continuity of the displacement field at the interface, and therefore may result in improved ARFI imaging resolution. In the set of studies presented in this thesis, imaging parameters primarily limited the axial and lateral resolution. In other ARFI imaging systems where imaging parameters are characterized by shorter tracking pulse lengths, higher frequencies, and/or shorter correlation window lengths the underlying displacement field will provide ARFI imaging with a fundamental resolution limit. In FE model data, connected materials that require continuity of the
displacement field show some measureable width of the FWHM of the strain field. When the interface between the two materials is disconnected (slip boundary), the two materials react to the radiation force independently, potentially resulting in a strain profile that has a smaller FWHM, and therefore improved resolution. This hypothesis requires investigation.

### 7.3.2 Imaging Blood Vessels and EWN

Bias in ARFI images that resulted from amplitude modulation of the echo signals was reduced by EWN signal processing technique was illustrated in tissue ex vivo, but repeatability must be investigated. The study presented in this thesis, a porcine liver was imaged using B-mode and ARFI imaging while immersed in saline solution. This methodology can be repeated. The average change in the apparent lumen width can be recorded. Assuming that the range in echo contrast between the vessel walls and the surround tissue is quite large, the change in lumen diameter can be plotted as a function of echo contrast. Given the results of the simulation study, it can be expected that the apparent change in lumen diameter (due to amplitude dependent bias) will decrease when EWN is employed.

The EWN technique and can be further validated in vivo. An animal model could be used to image atherosclerotic plaques. The ARFI images of the plaques can be compared before and after using the EWN technique. For validation, the images can be compared to B-mode images and histological stains, similar to the methodology implemented by Behler et al. [97, 158], for example, determining the correlation between stiffness and collagen content. A better correlation is expected when the EWN algorithm is employed due to bias reduction. In the ex vivo measurements conducted in Chapter 6 the mismatch in acoustic impedance between the saline and surrounding vessel resulted in strong reflections at the interface causing a displacement estimation bias.
In vivo, the blood flows through these hepatic vessels. Blood has different acoustic impedance characteristics than saline. Specifically, the mismatch in impedance will be lower between blood and the vessel. Nevertheless, these weaker reflections are still expected to cause displacement estimation bias, given that blood vessels are often clearly outlined in B-mode images. Furthermore, smaller, but significant improvements were observed in the simulation studies when the reflection amplitude was only twice that of the surrounding tissue, suggesting that the EWN algorithm can reduce bias, even when the reflections are weak. The clinical significance of this reduction in bias requires further investigation and highlights the importance of an in vivo study. EWN algorithm might also be used for Doppler applications as part of a wall filter to reduce the amplitude of surrounding tissue without significantly distorting signals from the blood.
Bibliography


