Transthoracic Measurement of Dynamic Myocardial Stiffness using Acoustic Radiation Force-Based Ultrasound Methods

by

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Leslie Collins

Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biomedical Engineering in the Graduate School of Duke University 2018
ABSTRACT

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Abstract

Heart failure is one of the most common cardiac disorders and is projected to increase in prevalence over the next few decades. It can arise from a wide variety of root causes such as coronary artery disease, hypertension, cardiomyopathy, or cardiotoxicity and can manifest as systolic and/or diastolic dysfunction. Traditionally, its diagnosis has been based on monitoring qualitative changes in cardiac structure, such as chamber geometry and wall motion patterns, or quantitative changes in indices of cardiac function, such as the blood flow velocities and ventricular ejection fraction. These parameters are assessed in clinical settings using medical imaging modalities like ultrasound and magnetic resonance imaging. Recent research into cardiac pathophysiology has indicated that the progression of cardiac disease is often accompanied by changes in the mechanical properties of cardiac muscle. Interrogation of these changes could be used to gain useful diagnostic insight into the etiology of heart failure.

Acoustic radiation force (ARF)-based techniques, such as acoustic radiation force impulse (ARFI) imaging and shear wave elasticity imaging (SWEI), provide the means to measure mechanical properties of soft tissues using ultrasound. They operate on the principle that ultrasound can be used to remotely generate as well as track micron-level vibrations in the body and thus derive mechanical properties such as tissue stiffness. ARFI and SWEI have previously been shown to capture dynamic changes in myocardial stiffness in Langendorff set-ups, open-chest experiments, and
intracardiac settings. This dissertation explores the challenges and opportunities of implementing acoustic radiation force-based methods for noninvasive applications via transthoracic imaging windows.

Transthoracic imaging of the heart using ultrasound can be challenging for a number of reasons. The two main sources of signal degradation that were hypothesized to impact ARFI and SWEI in this environment are acoustic clutter and intrinsic tissue motion. Acoustic clutter refers to incorrectly localized echoes which lead to the degradation of target conspicuity, border delineation, and image quality. Intrinsic tissue motion, on the other hand, impedes the ability to accurately measure the ARF-induced motion and consequently affects the estimation of tissue stiffness. The work presented herein focuses on quantifying the level of both sources of signal degradation under \textit{in vivo} imaging conditions and evaluating the effectiveness of strategies to minimize their impact. Lastly, the feasibility of tracking dynamic myocardial stiffness through the cardiac cycle via transthoracic imaging windows on human volunteers was investigated.

Harmonic imaging is often used to suppress acoustic clutter in clinical settings. Clutter levels are also closely tied to the choice of beamforming configuration used. Quantifying the impact of harmonic imaging and transmit beamforming (focused versus plane wave) on acoustic clutter, under \textit{in vivo} transthoracic imaging conditions is therefore important. Clutter level, for a given imaging scenario, was quantified using contrast between the cardiac chambers and the interventricular septum. Substantial variations in clutter levels were observed across as well as within volunteers. Harmonic imaging had a measurable impact in suppressing clutter under both the plane wave (2.97 dB) and focused (6.1 dB) configurations. However, even in the optimal configuration (harmonic-focused), clutter levels varied over a broad range (4 - 22 dB). These results suggest that acoustic clutter, while consistently lowered through the use of harmonic imaging, is still likely to be a major detriment to transthoracic
measurement of myocardial stiffness.

The heart exhibits complex and rapid three-dimensional motion; this could be a dominant confounder when attempting to measure micron-level ARF-induced displacements. Intrinsic cardiac motion of the interventricular septum, as observed through the parasternal long- and short-axis views, was analyzed in both the time- and frequency-domain. Two types of motion filters, frequency-based (high-pass filters) and recovery-based (polynomial filters) were compared to assess their ability to separate the axial component of cardiac motion from the ARF-induced motion. The effect of non-axial cardiac motion on speckle decorrelation was quantified using temporal coherence and related to the uncertainty of axial displacement estimation or jitter. High-pass filters with cutoffs $>75$ Hz and quadratic polynomial filters were found to be equally effective at compensating for axial tissue motion. While high-pass filters are independent of a recovery-time assumption, they introduce a downward bias to measured ARF-induced motion; this bias increases with cutoff frequency. Temporal coherence was empirically related to measured displacement estimation jitter. At end-diastole, temporal coherence was high and jitter was low (0.5 - 2.5 $\mu$m). In other phases of the cardiac cycle, however, jitter was found to increase dramatically with the span of the temporal window over which it was computed. Jitter for short spans, 2 ms, was found to be in the range of 2 - 8 $\mu$m, However, for spans of 10 ms, it could be as high as 10 - 20 $\mu$m. These results indicate that the noise-floor for micron-level axial displacement estimation in the myocardium via transthoracic imaging windows can be fairly high (compared to the magnitude of ARF-induced displacements) and can vary considerably over the cardiac cycle.

In the final study, M-mode ARFI imaging was performed on twelve healthy volunteers to track stiffness changes within the interventricular septum in the parasternal long- and short-axis views. Myocardial stiffness dynamics over the cardiac cycle were quantified using five indices: stiffness ratio, rates of relaxation and contrac-
tion, and time constants of relaxation and contraction. Yield of ARFI acquisitions was evaluated based on metrics of signal strength and tracking fidelity such as displacement signal-to-noise, signal-to-clutter level, temporal coherence of speckle, and spatial similarity within the region-of-excitation. These were quantified using the mean ARF-induced displacements over the cardiac cycle, the contrast between the myocardium and the cardiac chambers, the minimum correlation coefficients of RF signals (over a 2 ms window), and the correlation between displacement traces across simultaneously-acquired azimuthal beams, respectively. Forty-one percent of ARFI acquisitions were determined to be “successful” using a mean ARF-induced displacement threshold of 1.5 \( \mu \text{m} \). “Successful” acquisitions were found to have higher i) signal-to-clutter levels, ii) temporal coherence, and iii) spatial similarity compared to “unsuccessful” acquisitions. Median values of these three metrics, between the two groups, were measured to be 13.42 dB vs. 5.42 dB, 0.988 vs. 0.976, and 0.984 vs. 0.849, respectively. Signal-to-clutter level, temporal coherence, and spatial similarity were also found to correlate with each other. Across the cohort of healthy volunteers, stiffness ratio was measured to be 2.74 \( \pm 0.86 \); rate of relaxation was 7.82 \( \pm 4.69 \)/s and contraction was -7.31 \( \pm 3.79 \)/s; time constant of relaxation was 35.90 \( \pm 20.04 \) ms, and contraction was 37.24 \( \pm 19.85 \) ms. ARFI-derived indices of myocardial stiffness were found to be similar in both views.

In summary, despite the many challenges that are inherent to the transthoracic imaging environment, acoustic radiation force-based techniques were found to capture the dynamic trends of myocardial stiffness when appropriate conditions are met. Future work to improve the strength of ARF-excitations, better characterize or circumvent the influence of noise sources such as acoustic clutter and tissue motion, and explore the association between ARFI/SWEI-derived myocardial stiffness and traditional indices of cardiac function will be critical to realizing the diagnostic potential of acoustic radiation force-based ultrasound methods in clinical cardiology.
To Vipul and Elisabeth.
# Contents

Abstract iv  
List of Tables xiv  
List of Figures xv  
List of Abbreviations and Symbols xix  
Acknowledgements xxi  

## 1 Introduction 1  
1.1 Clinical Motivation ........................................ 1  
1.1.1 Heart Failure ........................................ 1  
1.1.2 Diagnosis ........................................ 2  
1.1.3 Cardiac Disease and Myocardial Stiffness ................. 4  
1.2 Outline ...................................................... 5  

## 2 Background 7  
2.1 Measurement of Cardiac Function .......................... 7  
2.1.1 Pressure-Volume (PV) Loops ................................ 10  
2.1.2 Time-Varying Elastance .................................. 13  
2.1.3 Elastance and Myocardial Stiffness ..................... 14  
2.2 Echocardiography ........................................ 14  
2.2.1 Ultrasound Imaging ...................................... 14  
2.2.2 Transthoracic Echocardiography ......................... 16
C A Novel Drift Compensation Algorithm for Improved Beat-to-Beat Repeatability of Myocardial Strain Imaging: Preliminary *in vivo* Results

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.1 Introduction</td>
<td>154</td>
</tr>
<tr>
<td>C.2 Methods</td>
<td>155</td>
</tr>
<tr>
<td>C.2.1 Data Acquisition</td>
<td>155</td>
</tr>
<tr>
<td>C.2.2 Strain Computation</td>
<td>155</td>
</tr>
<tr>
<td>C.2.3 Error Propagation and Drift</td>
<td>156</td>
</tr>
<tr>
<td>C.2.4 Drift Compensation</td>
<td>157</td>
</tr>
<tr>
<td>C.3 Results and Discussion</td>
<td>157</td>
</tr>
<tr>
<td>C.4 Conclusion</td>
<td>161</td>
</tr>
</tbody>
</table>

Bibliography 162

Biography 184
## List of Tables

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Contrast between anechoic targets and speckle generating background on imaging phantom (ATS Model 549)</td>
<td>37</td>
</tr>
<tr>
<td>3.2</td>
<td>Multivariate analysis with mixed effects on contrast measurements.</td>
<td>45</td>
</tr>
<tr>
<td>4.1</td>
<td>Magnitude (in dB with respect to the peak) of myocardial (IVS) velocity signals as a function of frequency in PLAX and PSAX.</td>
<td>64</td>
</tr>
<tr>
<td>4.2</td>
<td>Magnitude (in dB with respect to the peak) of simulated ARF-induced motion as a function of frequency for displacement and velocity data.</td>
<td>67</td>
</tr>
<tr>
<td>5.1</td>
<td>Parameters for M-mode ARFI Sequences.</td>
<td>93</td>
</tr>
<tr>
<td>5.2</td>
<td>Number of “successful” acquisitions across the two views for the three tracking configurations.</td>
<td>105</td>
</tr>
<tr>
<td>5.3</td>
<td>Summary of ARFI-derived indices of dynamic myocardial stiffness over all cardiac cycles acquired in “successful” acquisitions.</td>
<td>112</td>
</tr>
<tr>
<td>C.1</td>
<td>Drift in the point grid over multiple cardiac cycles across all acquisitions (n=10).</td>
<td>160</td>
</tr>
<tr>
<td>C.2</td>
<td>End-systolic radial strain over multiple cardiac cycles across all acquisitions.</td>
<td>161</td>
</tr>
</tbody>
</table>
# List of Figures

2.1 Wiggers Diagram ...................................................... 8
2.2 Pressure-volume (PV) loops ........................................ 11
2.3 Illustration of systolic and diastolic dysfunction on PV loops .... 12
2.4 Time-varying Elastance ............................................. 13
2.5 Jitter magnitude as a function of correlation coefficient for a low and a high SNR case (as predicted by the CRLB) .................. 22
3.1 Representative B-mode and M-mode images for the two transthoracic echocardiography (TTE) views used in the study. ............ 33
3.2 B-mode and M-mode images illustrating a high clutter imaging scenario compared to a low clutter case. .......................... 38
3.3 Illustration of changes in clutter level as a function of beamforming configuration in PSAX. ........................................ 39
3.4 Illustration of changes in clutter level as a function of beamforming configuration in PLAX. ........................................ 40
3.5 Contrast measurements as a function of beamforming configuration, split by cardiac chamber ........................................ 41
3.6 Distributions and associated box plots for relative contrast (matched to within each data set) compared to the fundamental-focused configuration for each cardiac chamber. .................. 42
3.7 Scatter plot of measured absolute contrast for each beamforming configuration against their corresponding value in the fundamental-focused case with overlayed linear fit. ...................... 43
3.8 Trends of contrast as a function of beamforming split by volunteer. 44
4.1 Parameters used in polynomial-based motion filtering ............ 60
5.4 Examples of displacement data over the cardiac cycle with high and low spatial similarity. ................................................. 99

5.5 Illustration of the model fitting and parameter extraction process used to compute ARFI-derived indices of dynamic myocardial stiffness. . . 101

5.6 Examples B-mode and M-mode ARFI images for a “successful” and two “unsuccessful” acquisitions. ........................................ 104

5.7 Bar graph depicting number of “successful” acquisitions across volunteers split by view. ................................................. 105

5.8 Mean ARF-induced displacements within the IVS for “successful” acquisitions in diastolic and systolic temporal windows as well as prior to each ARF excitation over the entire cardiac cycle. .................. 106

5.9 Contrast, temporal coherence, and spatial similarity for individual cardiac cycles in “successful” and “unsuccessful” acquisitions split by tracking configuration. ................................................. 108

5.10 Pair-wise relationships between metrics of tracking fidelity across all acquisitions and ROC curves for differentiation of “successful” from “unsuccessful” acquisitions using individual metrics. .................. 109

5.11 Example of a “successful” TTE M-mode ARFI acquisition in PLAX along with ARFI-derived indices of dynamic myocardial stiffness. . . 110

5.12 Example of a “successful” TTE M-mode ARFI acquisition in PSAX along with ARFI-derived indices of dynamic myocardial stiffness. . . 111

5.13 Beat-to-beat variability of ARFI-derived indices of dynamic myocardial stiffness. ................................................. 111

A.1 Effect of stationary clutter and electronic noise on displacement estimation in an ARFI ensemble. ............................................. 137

A.2 Effect of moving clutter on displacement estimation in an ARFI ensemble. ................................................. 138

A.3 Effect of stationary clutter on an in vivo M-mode ARFI image. . . 139

A.4 Effect of electronic noise (random across simultaneously acquired azimuthal angles) on an in vivo M-mode ARFI image. ............... 140

A.5 Effect of electronic noise (correlated across simultaneously acquired azimuthal angles) on an in vivo M-mode ARFI image. ............... 141
A.6 Effect of clutter moving with the ARF excitation on an *in vivo* M-mode ARFI image. .......................................................... 142

A.7 Effect of stationary clutter on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. .......................................................... 143

A.8 Effect of electronic noise (random across simultaneously acquired azimuthal angles) on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. .......................................................... 144

A.9 Effect of electronic noise (correlated across simultaneously acquired azimuthal angles) on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. .......................................................... 145

A.10 Effect of ARF-induced moving clutter on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. .......................................................... 146

B.1 Illustration of bias in ARFI-derived stiffness ratios compared to simulated ratio of Young’s modulus and shear wave speed. ................. 151

B.2 Ratios of raw FE displacements vs. displacements tracked with an F/2.6 configuration for various interrogation times. ...................... 152

B.3 Comparison of measured vs. simulated stiffness ratios for a range of reference Young’s moduli. ..................................................... 153

C.1 Consecutive end-diastolic frames with positions of the points of interest (green dots) with and without drift compensation. .............. 158

C.2 Cumulative axial as well as lateral displacements and derived radial strain of the myocardium over several consecutive cardiac cycles for the raw and compensated cases along with the concurrently acquired ECG signal. ..................................................... 159

C.3 Spatial distributions of drift and end-systolic strain as a function of beat index over a single acquisition. ...................................... 160
List of Abbreviations and Symbols

Abbreviations

ARF Acoustic Radiation Force
ARFI Acoustic Radiation Force Impulse (Imaging)
BMI Body Mass Index
CRLB Cramér-Rao Lower Bound
ECG Electrocardiogram
EDPVR End-diastolic Pressure-volume Relationship
EF Ejection Fraction
ESPVR End-systolic Pressure-volume Relationship
FOV Field-of-view
HF Heart Failure
HFpEF Heart Failure with Preserved Ejection Fraction
HFrEF Heart Failure with Reduced Ejection Fraction
IQ In-phase and Quadrature
I_{SPPA} Spatial-peak Pulse-average Intensity
I_{SPTA} Spatial-peak Temporal-average Intensity
IVS Interventricular Septum
LV Left Ventricle
MI Mechanical Index
MRI Magnetic Resonance Imaging
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE</td>
<td>Magnetic Resonance Elastography</td>
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<tr>
<td>PLAX</td>
<td>Parasternal Long-axis</td>
</tr>
<tr>
<td>PRF</td>
<td>Pulse Repetition Frequency</td>
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<td>PSAX</td>
<td>Parasternal Short-axis</td>
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<tr>
<td>PSF</td>
<td>Point Spread Function</td>
</tr>
<tr>
<td>PV</td>
<td>Pressure-volume</td>
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<tr>
<td>RF</td>
<td>Radio-frequency</td>
</tr>
<tr>
<td>ROE</td>
<td>Region-of-excitation</td>
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<tr>
<td>ROI</td>
<td>Region-of-interest</td>
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<tr>
<td>RV</td>
<td>Right Ventricle</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-noise Ratio</td>
</tr>
<tr>
<td>SWEI</td>
<td>Shear Wave Elasticity Imaging</td>
</tr>
<tr>
<td>TI</td>
<td>Thermal Index</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic Echocardiography</td>
</tr>
</tbody>
</table>
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Introduction

1.1 Clinical Motivation

1.1.1 Heart Failure

Heart disease is amongst the most prevalent causes of death in developing countries. In 2013, cardiac disorders were diagnosed in approximately 15.5 million Americans over the age of 20 and accounted for over 600,000 deaths (Mozaffarian et al., 2016). Common cardiac disorders include myocardial infarction, heart failure, angina pectoris, and stroke. Amongst these, heart failure alone affects nearly 5.7 million Americans and is projected to rise in prevalence by 46% (affecting > 8 million) over the next 15 years (Heidenreich et al., 2013).

Heart failure (HF) is a clinical syndrome characterized by an inability of the heart to maintain sufficient blood flow to meet the metabolic needs of the body. It can arise from a variety of root causes such as coronary artery disease (Gheorghiade and Bonow, 1998), cardiomyopathy (Olson et al., 1998), hypertension (Deedwania, 1997), cardiac fibrosis (Conrad et al., 1995), and cardiotoxicity (Bovelli et al., 2010). Given the diversity in the etiology of heart failure, it is often difficult to diagnose at early stages in the progression of the disease.
The aforementioned root causes of HF can manifest as systolic and/or diastolic dysfunction. Systolic dysfunction suggests an inability of cardiac muscle to efficiently pump blood to the pulmonary and peripheral vasculature, whereas diastolic dysfunction represents a failure of the ventricles to adequately relax and fill with blood (Rihal et al., 1994). The ability to accurately identify the underlying cause of disease has critical diagnostic, therapeutic, and prognostic implications.

1.1.2 Diagnosis

According to the 2013 ACCF/AHA guidelines (Yancy et al., 2013), heart failure is suspected when a patient presents with symptoms of shortness of breath (especially during physical activity), general fatigue or weakness, persistent coughing or wheezing, and swelling of the abdomen or extremities.

An initial suspicion is followed by a physical examination to determine the severity of symptoms and risk factors such as high blood pressure, irregular pulse, recent changes in body mass index (BMI), and degree of fluid retention. Other risk factors include familial or personal history of hypertension, diabetes, coronary artery disease, or congenital heart defects. Blood tests to measure the level of biomarkers associated with insult/injury of cardiac tissue, such as natriuretic peptides and cardiac troponin, can also be useful in establishing cardiac involvement (Dao et al., 2001; de Lemos et al., 2010).

Next, one or more medical imaging modalities are used to assess anatomic or physiological changes associated with progression of the disease. Chest X-ray is often used to ascertain the size and shape of the heart and identify signs of enlargement. It can also be helpful in diagnosing pulmonary congestion, edema, and presence of calcifications or pericardial effusion. However, X-ray images alone have low sensitivity and specificity and thus are complemented with other forms of imaging such as ultrasound and magnetic resonance imaging (Fonseca et al., 2004).
Ultrasound imaging of the heart, or echocardiography, is the most commonly used modality for cardiac diagnostics given its real-time, low-cost, and non-ionizing nature. Intracardiac and transesophageal echocardiography is routinely used to guide procedures in surgical settings, whereas transthoracic echocardiography is primarily used for out-patient diagnostic procedures. Ultrasound imaging provides feedback at high-frame rates and can be used for qualitative as well as quantitative assessment of cardiac structure and function. Most ultrasound-derived clinical metrics used in cardiology quantify size of the ventricular chambers, motion of cardiac walls, and blood flow through the valves (Kirkpatrick et al., 2007).

One metric of particular importance is the ejection fraction (EF), which is defined as the percentage of the ventricular volume expelled with each heart beat. Systolic dysfunction is generally diagnosed using the EF. Diastolic dysfunction, on the other hand, is not as easily identified using standard imaging modes. While systolic and diastolic dysfunction rarely occur in isolation, cases of heart failure can broadly be categorized into heart failure with preserved ejection fraction (HFrEF) and heart failure with reduced ejection fraction (HFrEF). HFrEF accounts for nearly 50% of all HF cases and has been associated with relaxation abnormalities (Owan et al., 2006; Maeder and Kaye, 2009).

Other modalities that could be used to further investigate specific structural or functional abnormalities are magnetic resonance imaging (McCrohon et al., 2003), computed tomography (Mangalat et al., 2009), and nuclear imaging (Peix et al., 2014). While these modalities provide invaluable diagnostic information, they are not available at the point-of-care, expensive in terms of cost as well as organizational effort required, and could involve exposing patients to harmful doses of radiation. For these reasons, echocardiography remains the dominant diagnostic imaging resource in the field of cardiology.
1.1.3 Cardiac Disease and Myocardial Stiffness

Pathophysiologial research into cardiovascular disorders has yielded a strong association between disease progression and changes in myocardial stiffness. (Nagueh et al., 2004; Jalil et al., 1989; Zile and Brutsaert, 2002; Díez et al., 2002). It has also been shown that both systolic and diastolic dysfunction are accompanied with significant ventricular remodeling and consequent modifications of myocardial stiffness dynamics (van Heerebeek et al., 2006; Chatterjee and Massie, 2007). These results have launched several investigations into the measurement and quantification of myocardial stiffness using noninvasive imaging techniques.

Magnetic Resonance Elastography (MRE) has been shown to capture the cyclic changes in myocardial stiffness over the cardiac cycle. Sack et al. (Sack et al., 2009) measured a diastolic-to-systolic ratio of 2.45 for the amplitude of externally induced shear waves in healthy volunteers. Kolipaka et al. (Kolipaka et al., 2010) demonstrated excellent correlation between MRE-derived myocardial stiffness and simultaneously measured chamber pressure. Despite these advantages, high cost and limited availability hinder the widespread use of MRE for diagnosis of cardiac disorders.

In 2005, Kanai (Kanai, 2005) showed that propagation of mechanical waves that are spontaneously generated in the heart walls by closure of the aortic valve could be tracked using transthoracic echocardiography. By measuring the speed of these waves, they were able to extract mechanical properties of the myocardium during isovolumic relaxation. More recently, this work has been extended to also utilize waves induced by mitral valve closure and measure myocardial stiffness at end-diastole (Vos et al., 2017; Kanai and Koiwa, 2001). These measurements, however, are limited to specific points in the cardiac cycle when intrinsic waves are present.

Acoustic radiation force impulse (ARFI) imaging and shear wave elasticity imag-
are ultrasound-based techniques that estimate tissue stiffness by using acoustic waves to generate and track micron-level displacements (Doherty et al., 2013a). In Langendorff models, ARFI and SWEI have been shown to be sensitive to changes in myocardial stiffness in response to variations in clinically relevant factors such as coronary perfusion pressure (Vejdani-Jahromi et al., 2015) and contractility (Vejdani-Jahromi et al., 2017) as well as to assess diastolic function (Vejdani-Jahromi et al., 2018). SWEI has also been shown to quantify absolute myocardial stiffness, but is only viable through transthoracic imaging in diastole (Song et al., 2016; Villemain et al., 2018).

No ultrasound-derived clinical metric to-date incorporates information about the dynamics of myocardial stiffness. A robust, reliable, and real-time ultrasound-based method for direct assessment of myocardial stiffness over the cardiac cycle would make a meaningful impact on the way disorders of the heart are diagnosed, monitored, and treated.

1.2 Outline

Given the strong potential of ARFI and SWEI to yield diagnostically relevant information about cardiac disease, there is great interest in developing these techniques for minimally invasive and noninvasive imaging of the heart. The ability to measure myocardial stiffness trends over the cardiac cycle in out-patient settings would greatly advance the diagnostic utility of echocardiography. The work presented herein builds towards that goal. This dissertation is organized as follows:

Chapter 2 elaborates on the current methods used to assess cardiac function. It describes the fundamentals of conventional ultrasound imaging, ultrasound-based stiffness measurement techniques, and introduces acoustic clutter and intrinsic tissue motion as potential challenges for transthoracic implementation of ARFI and SWEI.

Chapter 3 presents an analysis of in vivo clutter levels in transthoracic imaging.
It discusses the benefits of using harmonic imaging over the fundamental mode in both focused as well as plane wave transmit beamforming configurations.

Chapter 4 addresses the impact of cardiac motion on the ability to measure micron-level displacements using ultrasound. It presents a comparative performance evaluation of conventional polynomial motion filters versus a high-pass filtering approach to suppress axial tissue motion. It also explores the effect of non-axial tissue motion through the cardiac cycle on speckle decorrelation and uncertainty of displacement estimates.

Chapter 5 describes an *in vivo* feasibility study where dynamic myocardial stiffness was measured using ARFI on a population of healthy volunteers. It presents methodology for computation of ARFI-derived indices of dynamic myocardial stiffness and an analysis of the impact of clutter and motion on the viability of transthoracic ARFI.

Chapter 6 summarizes the findings of the aforementioned studies and provides a few potential avenues of research that could improve upon the techniques investigated.
2.1 Measurement of Cardiac Function

The most accurate method to measure cardiac function involves tracking changes in the hemodynamic characteristics of the heart over the cardiac cycle. This is accomplished by introducing catheters into specific locations within the heart and using catheter-mounted sensors to track parameters such as pressure and volume which are related to cardiac pump function. This technique is often used by researchers in basic sciences to study cardiac physiology and is considered to be the gold-standard for cardiac function quantification (Burkhoff et al., 2005). However, the invasive nature of this technique limits its clinical utility. While pressure-volume relationships can be analyzed for all four chambers of the heart, the ones associated with the left ventricle are most commonly studied because of the importance of the left ventricle in delivering oxygenated blood to the peripheral vasculature.

Hemodynamic changes over the cardiac cycle are also accompanied by cyclic electrical activity in the heart which can be measured noninvasively using the electrocardiogram (ECG). An intuitive understanding of the temporal alignment of these
Figure 2.1: The Wiggers diagram illustrates the temporal relationship between aortic, left atrial, and left ventricular pressures, left ventricular volume, and the electrocardiogram. This presentation allows for identification of individual phases of the cardiac cycle and their manifestation on the different signals. Mid-systole is highlighted in purple and mid-diastole in gold. Adapted from (Krug et al., 2013).

This phenomenon can be useful for describing cardiac mechanics. The cardiac cycle can be divided into systole and diastole; each of these can further be split into two phases. Systole is composed of isovolumic contraction and ejection, while diastole is composed of isovolumic relaxation and ventricular filling. These phases have distinct signatures on pressure, volume, and ECG traces. Figure 2.1 illustrates changes in the aortic, left atrial, and left ventricular pressures, left ventricular volume, and the ECG as a function of time over two cardiac cycles.

Ventricular pressure and volume achieve their lowest and highest values, respectively, at the end of diastole. The mitral valve (between the left atrium and ventricle) as well as the aortic valve (between the left ventricle and the aorta) are closed at this time. On the ECG, end-diastole aligns with the Q-wave.

The onset of the R-wave signifies the electrical stimulation and subsequent depolarization of the ventricular myocardium, leading to active contraction. With both
valves being closed, pressure in the ventricle increases rapidly while the volume stays constant. This phase is referred to as isovolumic contraction. On the ECG, isovolumic contraction begins at the peak of the R-wave and ends after the S-wave.

The aortic valve is forced open when the ventricular pressure surpasses that in the aorta. Opening of the aortic valve signifies initiation of the ejection phase where blood is pushed out of the left ventricle and into the peripheral vasculature through the aorta. During this phase, pressure continues to rise, achieves its maximal value, and then begins to fall slowly. Volume, on the other hand, shows a monotonic decline that slows over the duration of this phase and achieves its minimal value the end of ejection. This phase culminates when the ventricular pressure falls below the aortic pressure, thus causing the aortic valve to close. Closure of the aortic valve also marks the end of systole. On the ECG, ejection starts after the S-wave and ends in the latter part of the T-wave.

In the next phase, isovolumic relaxation, both valves are closed again and the ventricular myocardium is undergoing active relaxation. Volume stays constant at its lowest, and ventricular pressure drops precipitously. This stage ends when the ventricular pressure equals the atrial pressure and the mitral valve opens up. On the ECG, the end of isovolumic relaxation corresponds with the tail end of the T-wave.

The fourth and final phase of the cardiac cycle is ventricular filling. This phase is subdivided into three stages: rapid inflow, diastasis, and atrial systole. During rapid inflow, the myocardium is in a relaxed state and blood flows quickly from the left atrium into the left ventricle. This process continues into diastasis; however, the filling rate slows down as the volume rises. Diastasis represents the “quietest” segment of the cardiac cycle, in terms of hemodynamic, electrical, and mechanical activity. Ventricular pressure is relatively constant at a low value during rapid inflow as well as diastasis. The P-wave (on the ECG) appears near the end of diastasis, signifying atrial contraction and a momentary rise in the filling rate of the ventricles.
as blood is forced into the ventricles from the atria. Volume rises to reach its maximal value over the cardiac cycle. Atrial systole aligns with the P-Q interval on the ECG. Lastly, the mitral valve closes when the atrial pressure falls below the ventricular pressure and the cardiac cycle repeats.

2.1.1 Pressure-Volume (PV) Loops

Dynamics of pressure and volume can be analyzed as a function of time or in a parametric fashion i.e., plotted against each other. Figure 2.2(a) shows ventricular pressure and volume, plotted against each other, over one cardiac cycle. The pressure and volume trace out a closed loop in a counter-clockwise fashion (over time); this is referred to as the pressure-volume (PV) loop. End-diastole appears at the bottom right corner (high volume, low pressure), while end-systole is at the top left corner (high pressure, low volume). The four identifiable limbs of this plot correspond to the four phases of the cardiac cycle outlined in the previous section. The right limb signifies isovolumic contraction (rise in pressure at constant volume), the top limb signifies ejection (rapid decrease in volume with relatively low change in pressure), the left limb signifies isovolumic relaxation (drop in pressure at constant volume), and the bottom limb signifies filling (increase in volume at low pressure).

PV loops provide an intuitive understanding of the cardiac pump function. Stroke volume, which is defined as the difference between end-diastolic and end-systolic ventricular volume is represented by the horizontal extent of the PV loop. Cardiac output is computed by multiplying stroke volume with the heart rate and the area of the PV loop is related to the ventricular stroke work. In an ideal state, for fixed loading, inotropic, and mechanical conditions, i.e., no change in end-diastolic/end-systolic pressure or volume, an isolated heart would continue to trace out a fixed loop over multiple cardiac cycles. Note that, changes in heart-rate would impact only the rate at which the loop is transcribed.
Further insight into cardiac mechanics can be gained by varying the loading conditions, i.e., afterload as quantified by end-systolic pressure or volume and preload as quantified by end-diastolic pressure or volume, and observing changes in the shape and position of the PV loop. While it is difficult to control individual parameters independently in an \textit{in vivo} setting, they can be studied using \textit{ex vivo} isolated heart set ups. Figure 2.2(b) illustrates changes in the PV loop for varying loading conditions (at a fixed inotropic and mechanical state). The instantaneous slopes of the pressure-volume curve ($dP/dV$) at end-systole and end-diastole are referred to as the end-systolic pressure-volume relationship (ESPVR) and the end-diastolic pressure-volume relationship (EDPVR), respectively. ESPVR is used to quantify cardiac contractility which is indicative of the intrinsic contractile strength of the chamber in systole. EDPVR, on the other hand, is used to quantify cardiac lusitropy which refers to the ability of the chamber to relax during diastole.

Figure 2.3 depicts changes in the ESPVR and EDPVR for pathological states of systolic dysfunction (a) an diastolic dysfunction (b). These changes are distinct from those brought about by varying the loading conditions. Changes in loading conditions
Figure 2.3: Illustration of change in ESPVR as a result of systolic dysfunction (a) and EDPVR as a result of diastolic dysfunction (b). In both cases, the stroke-volume and therefore cardiac output as well as the area covered by the PV loop is decreased compared to the reference (normal) state. Adapted from (Klabunde, 2011).

causes the end-systolic and end-diastolic points on the PV loop to traverse along a fixed ESPVR and EDPVR, respectively. In comparison, systolic dysfunction leads to a decrease in the ESPVR, i.e., $dP/dV$ at end-systole, and suggests a decrease in the contractile strength of the heart during systole. The result is a decrease in the end-systolic pressure and as well as a decrease in the end-systolic volume. Consequently, the end-systolic point of the PV loop (top left corner) moves rightward and downward. Although the EDPVR is constant in this case, end-diastolic volume also increases due to a compensatory mechanism in the heart to partially maintain stroke volume.

Diastolic dysfunction, on the other hand, leads to an increase in the EDPVR, i.e., $dP/dV$ at end-diastole, and suggests an inability of the chamber to fully relax during diastole. This leads to a decrease in end-diastolic volume and an increase in the end-diastolic pressure. Consequently, the end-diastolic point of the PV loop (bottom right corner) moves leftward and upward. Stroke volume is also lowered.

Thus, both systolic and diastolic dysfunction result in a decrease in stroke volume, cardiac output, and ventricular stroke work.
2.1.2 *Time-Varying Elastance*

ESPVR and EDPVR refer to $dP/dV$ at two specific time points in the cardiac cycle. This slope, however, need not be limited to fixed time points and can be evaluated in a continuous fashion over the entire cycle. This concept was introduced by Suga and Sagawa (Suga and Sagawa, 1974) and is known as time-varying elastance. Figure 2.4(a) illustrates the slopes of the pressure-volume curve at various time points over the cardiac cycle. $T_1$ and $T_{10}$ align with end-diastole, while $T_6$ aligns with end-systole; the transition from $T_1$ to $T_6$ depicts contraction while $T_6$ to $T_{10}$ depicts relaxation.

Figure 2.4(b) shows $dP/dV$ as a function of time over one cardiac cycle. Elastance, as defined here, is directly proportional to $dP/dV$ throughout the cardiac cycle. Elastance achieves its maxima at end-systole and minima at end-diastole; it rises and falls during contraction and relaxation, respectively. At end-systole ($T_6$), elastance is equivalent to ESPVR and related to contractility. Similarly, elastance
at end-diastole ($T_1$ and $T_{10}$) is equivalent to EDPVR and related to lusitropy.

2.1.3 Elastance and Myocardial Stiffness

Elastance, as derived from the analysis of pressure-volume relationships, can be conceptualized as the stiffness of the chamber at various points in the cardiac cycle. Chamber properties, as measured using hemodynamic theory, however, are not directly equivalent to the mechanical properties of the material that the chamber is composed of. Chamber properties are dependent on material mechanical properties as well as the geometry of the chamber. Mechanical properties of the myocardium can be derived using elastic theory or analysis of stress-strain relationships. A vast body of research has addressed the relationship between chamber stiffness and myocardial stiffness and has found them to be closely related when the ventricular geometry is assumed to be ellipsoidal or spherical. (Mirsky, 1976).

The ultrasound-based stiffness imaging methods described in this dissertation are designed to capture material mechanical properties as derived from stress-strain relationships. Therefore, measurement of myocardial stiffness through noninvasive ultrasound-based methods have the potential to yield a correlate of time-varying elastance at the point-of-care without the need for catheterization.

2.2 Echocardiography

2.2.1 Ultrasound Imaging

Ultrasound imaging works on the principle that acoustic waves traveling through a heterogeneous medium are scattered at boundaries of acoustic impedance mismatches. The scattered waves encode the relative positions of these boundaries and can be used to create a visual representation of the underlying structures.

In the most basic form, an ultrasound system consists of a transducer, transmit/receive circuitry, beamforming/signal processing hardware, and a display.
transducer can consist of a row or matrix of piezoelectric elements that convert voltage signals into pressure waves and vice-versa. The transmit circuits drive the transducer elements with Gaussian-enveloped, sinusoidal voltage pulses (at frequencies > 1 MHz) that are emitted into the tissue as pressure waves. These circuits also control the relative timing of the signals at individual elements to have the output pressure waves constructively interfere at a specified point in the field, consequently creating a transmit focus. Echoes are generated when the forward-propagating sound waves interact with scatterers that have local acoustic impedance mismatches. The acoustic impedance ($Z$, Rayl) is a function of the density ($\rho$, kg/m$^3$), and the speed of sound ($c$, m/s) of the medium and is also related to the bulk modulus ($K$, kPa), as shown in equation (2.1).

$$Z = \rho c = \sqrt{\rho K} \tag{2.1}$$

The amplitude of the backscattered echoes is directly related to the magnitude of the impedance mismatch. The backward-propagating sound waves (echoes) impinge on the transducer and are converted into a time series of voltage signals at each element. The subsequent process of beamforming involves applying appropriate delays to these signals to account for geometric spreading of the backscattered waves, thereby focusing them on receive. The delayed signals are then summed across the transducer elements to yield pressure as a function of time, typically referred to as an A-line. The carrier frequency of a beamformed trace is removed by envelope detection and the time axis is converted to its corresponding spatial dimension, axial depth, by assuming a fixed speed of sound (1540 m/s for soft tissue). An image is created by electronically steering transmit/receive events to multiple lateral and/or elevational locations and repeating the process to sweep out a two- or three-dimensional field-of-view (FOV). Lastly, individual A-lines are stitched together to form a image
or a volume that is displayed on the screen as an echo-brightness map or a B-mode image. The axes on a B-mode image represent the spatial dimensions of the scan plane: axial, lateral, and (in the case of 3D) elevational distance from the transducer face.

Multiple images or frames can be acquired rapidly to observe the tissue over time. Images can also be created with the axial distance along one dimension and time along the other; this mode is called M-mode. Frame rates in ultrasonic imaging tend to be on the order of 10-1000 Hz depending on the spatial extent of the FOV and the number of transmit-events required to reconstruct a single image. Trade-offs can be made between spatial and temporal resolution by altering transmit and/or receive beam configurations. Weakly focused transmit beams combined with parallel processing on receive, for instance, can be used to improve the frame rate at the expense of image quality.

### 2.2.2 Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is the most popular modality for noninvasive examination of the heart due to its low-cost, real-time, and non-ionizing nature. It is well integrated into the workflow of cardiology clinics and is used in virtually every form of out-patient cardiac exam. These exams are performed using phased array transducers operating at 2-5 MHz with relatively small footprints (2x2 cm$^2$), so as to fit between the ribs. The small apertures are necessitated because bone has a high acoustic impedance; it generates strong reflections and prevents further propagation of ultrasonic pulses into the body. The four main acoustic windows (and associated imaging planes) used in TTE are parasternal (long and short axis), apical (2-chamber and 4-chamber), subcostal, and suprasternal (Otto, 2013). The basic modes of TTE include B-mode imaging (2D to 4D), M-mode imaging, pulse-wave Doppler and color Doppler (Baker et al., 1977; Miyatake et al., 1984). More recently, strain and strain-
rate imaging have also become widely available (Sutherland et al., 2004; Yip et al., 2003).

TTE is utilized for both structural as well as functional assessment of the heart. It is used to assess cardiac features such as wall thickness/motion (Devereux and Reichek, 1977; Miyatake et al., 1995), septal defects (Marx et al., 1995), and valvular abnormalities (Baumgartner et al., 2008). It can also be used to extract numerical metrics of cardiac function such as ejection fraction (Caiani et al., 2005), blood velocities through valves, and cardiac wall motions (De Zuttere et al., 1988; Gorcsan III et al., 1996). However, the accuracy and reproducibility of these metrics is highly dependent on factors such as imaging angle, geometric assumptions, and boundary tracing (Chukwu et al., 2008; Thavendiranathan et al., 2013).

2.3 Ultrasound-based Stiffness Imaging

As described in section 2.2.1, B-mode imaging yields images of local changes in density and compressibility of the propagation medium. Corollary ultrasound-based techniques can be used to extract information about mechanical properties of the medium. In this context, tissue is commonly modeled as a linear, elastic solid; the generalized Hooke’s law for such a material is stated in Einstein notation as

$$\sigma_{ij} = C_{ijkl} \epsilon_{ij},$$

(2.2)

where $\sigma$ and $\epsilon$ are second-order tensors called the Cauchy stress tensor and the infinitesimal strain tensor, respectively. They are related to each other by a fourth-order tensor termed the elasticity tensor, $C$ (Lai et al., 2009). Material moduli such as Young’s modulus ($E_Y$, kPa), shear modulus ($\mu$, kPa) and Bulk modulus ($K$, kPa) can be derived from the terms of $C$. The goal of stiffness imaging is to estimate the material moduli by observing the stress-strain response of the tissue being imaged.
2.3.1 Acoustic Radiation Force (ARF)

Acoustic Radiation Force (ARF) is a force that is associated with the propagation of an acoustic wave through a dissipative medium. This phenomenon originates due to the transfer of momentum from the acoustic wave to an absorptive or reflective medium. The force is applied in the direction of wave propagation and can be represented by equation (2.3) (Nyborg, 1965)

\[
F(\vec{r}, t) = \frac{2\alpha I(\vec{r}, t)}{c},
\]

(2.3)

where \( F \) represents the magnitude of the body force per unit volume, \( \alpha \) represents the absorption coefficient of the medium, \( I \) represents the local time-average acoustic intensity, and \( c \) is the speed of sound. In theory, ARF is induced during conventional B-mode imaging; however, its effect is negligible due to the short pulses and the low intensities used. ARF excitations used to generate displacements in soft tissue generally use longer acoustic pulses (50-500 \( \mu \)s) and high intensities (500-1000 \( W/cm^2 \)).

Equation (2.3) can be derived by starting with the balance of linear momentum as stated (in indicial form) by (Nyborg, 1965):

\[
\sigma_{ij,j} = \rho a_i.
\]

(2.4)

The acceleration term \( a \) can be expressed in terms of particle velocity \( v \) as \( a_i = \dot{v}_i + v_j v_{i,j} \). This expansion retains the time derivative of particle velocity as well as the convective acceleration term. At ultrasonic frequencies, tissue is approximated as an incompressible Newtonian fluid whose constitutive relationship is given by

\[
\sigma_{ij} = -p\delta_{ij} + \mu' D_{ii}\delta_{ij} + 2\mu J D_{ij},
\]

(2.5)
where $D_{ij}$ is the rate of deformation tensor defined as $D_{ij} = \frac{1}{2}(v_{i,j} + v_{j,i})$ and $\mu_f, \mu_f$ are the bulk and shear viscosity constants respectively. Substituting equation (2.5) into equation (2.4), combining terms of particle velocity and expressing it in vector form yields

$$\frac{\partial (\rho \bar{v})}{\partial t} + \rho \bar{v} \cdot \nabla \bar{v} + \bar{v} \nabla \cdot \rho \bar{v} = -\nabla p + (\mu' + \frac{4}{3} \mu) \nabla \nabla \cdot \bar{v} - \mu \nabla \times \nabla \times \bar{v}, \quad (2.6)$$

where $\rho$ is the tissue density, $v$ is the particle velocity, and $p$ is the pressure due to the propagating acoustic wave. Performing a perturbative expansion of equation (2.6) with respect to $p, \rho, v$, grouping second-order terms, and averaging over an integer number of cycles allows the balance of linear momentum to be expressed as:

$$\vec{F} = \rho \langle \bar{v} \nabla \cdot \bar{v} + \bar{v} \cdot \nabla \bar{v} \rangle. \quad (2.7)$$

At the focus, propagation is planar, and particle velocity can be expressed as $\bar{v} = j \omega v_o e^{-\alpha x + j(\omega t - kx)} \hat{z}$. When substituted into, (2.7) this yields:

$$|\vec{F}| = -v_o^2 e^{-2\alpha z} \rho_0 \alpha. \quad (2.8)$$

Furthermore, the time averaged intensity of an attenuating plane wave expressed in terms of particle velocity can be shown to have the form:

$$I = \frac{\rho c v_o^2 e^{-2\alpha z}}{2}. \quad (2.9)$$

Combining equations (2.8) and (2.9) yields equation (2.3). This suggests that the acoustic radiation force generated in tissue is most directly related to the local time-averaged acoustic intensity, assuming uniform attenuation and speed of sound. This
force is used as the source of mechanical excitation in radiation force-based stiffness imaging to generate stress fields within tissue and measure its strain response.

2.3.2 Wave Propagation in Elastic Solids

In section 2.3.1, tissue was modeled as a viscous fluid to analyze its behavior at ultrasonic frequencies. However, at the lower frequencies excited by an impulsive ARF excitation (0-500 Hz), tissue can be modeled as a linear, elastic solid. Furthermore, making the assumption of isotropy the constitutive relation can be expressed as:

\[
\sigma_{ij} = \lambda \epsilon_{ii} \delta_{ij} + 2\mu \epsilon_{ij}, \tag{2.10}
\]

where \(\lambda\) and \(\mu\) are the Lamé constants of the material and \(\epsilon\), the strain tensor, is defined as \(\epsilon_{ij} = \frac{1}{2}(u_{i,j} + u_{j,i})\), with \(u\) being particle displacement. Substituting (2.10) into (2.4), grouping particle displacement terms, and converting the final expression into vector form yields:

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

The displacement field \(u\) can be separated into a scalar dilational component \((\psi)\) and a vector equivoluminal or shear component \((\vec{W})\) through the Helmholtz decomposition as \(\bar{u} = \nabla \psi + \nabla \times \vec{W}\). These yield two wave equations: one for a longitudinal wave (2.12) and another for the transverse wave (2.13). \(c_L\) and \(c_T\) are then the propagation speeds of the two waves. These are indicated below:

\[
\nabla^2 \psi - \frac{1}{c_L^2} \frac{\partial^2 \psi}{\partial t^2} = 0, \quad c_L = \sqrt{\frac{\lambda + 2\mu}{\rho}}, \tag{2.12}
\]

\[
\nabla^2 \vec{W} - \frac{1}{c_T^2} \frac{\partial^2 \vec{W}}{\partial t^2} = 0, \quad c_T = \sqrt{\frac{\mu}{\rho}}, \tag{2.13}
\]
2.3.3 Displacement Estimation

ARF-induced stress fields lead to tissue deformation, or strain, which can be measured using ultrasound. In this process, regular B-mode imaging pulses are used in rapid succession (4-10 kHz) at the same spatial location to monitor the temporal strain response of tissue to the ARF-induced stress. The magnitude of induced displacements in soft tissues are on the order of 1-15 µm, or 1/10th – 1/400th of a wavelength of ultrasonic pulses (Pinton et al., 2006). These small fluctuations in the location of underlying scatterers appear in the radiofrequency (RF) and demodulated in-phase and quadrature (IQ) signals as phase-shifts. They can be computed using a variety of unbiased methods such as normalized cross correlation (Bonnefous and Pesque, 1986) and phase-based estimators (Kasai et al., 1985; Loupas et al., 1995), or biased, iterative algorithms (Pesavento et al., 1999; Byram et al., 2013). The relative performance, biases, and trade-offs of these methods have been extensively studied (Viola and Walker, 2003; Pinton et al., 2006).

The work presented herein uses Loupas’ 2-D autocorrelation algorithm which operates on the IQ data. Walker and Trahey derived a fundamental theoretical limit on the variance of unbiased time delay estimators when using partially correlated signals (Walker and Trahey, 1995). This limit, known as the Cramér-Rao Lower Bound (CRLB), is given by

\[
\sigma \geq \left[ \frac{3}{2f_c^3\pi^2T(B^3 + 12B)} \left( \frac{1}{\rho^2} \left( 1 + \frac{1}{\text{SNR}^2} \right)^2 - 1 \right) \right]^{1/2},
\]

where \(\sigma(\text{ns})\) is the standard deviation of time delay estimates, \(f_c\) (MHz) and \(B\) (%) are the tracking pulse center frequency and fractional bandwidth, \(T\) (µs) and \(\rho\) are the kernel length and correlation coefficient, and SNR is the signal-to-noise ratio of the tracking signals used. Displacement jitter can be calculated by scaling the time
Figure 2.5: Jitter magnitude as a function of correlation coefficient for a low and a high SNR case (as predicted by the CRLB). Imaging parameters used are typical for transthoracic echocardiography: \( f_c = 3\text{–}4 \text{ MHz}, B = 80\% \), \( T = 7.5 \lambda \)
delay jitter by half the speed of sound. Jitter is most sensitive to changes in SNR and the correlation coefficient; it increases dramatically for SNR<10 dB but stays relatively stable at high SNR. The relationship between jitter and the correlation coefficient is approximately linear when \( 0.7 < \rho < 0.95 \), with higher correlation coefficients corresponding to lower jitter. Jitter magnitudes for parameters relevant to transthoracic imaging (\( f_c = 3\text{–}4 \text{ MHz}, B = 80\% \), \( T = 7.5 \lambda \)) are shown in Figure 2.5. Predicted jitter for the high SNR case approaches 0 \( \mu \text{m} \) in the case of no decorrelation (i.e. \( \rho = 1 \)), but it reaches a minima around 5 \( \mu \text{m} \) for the low SNR case. This relationship suggests that even for stationary speckle patterns, low SNR systems may suffer from high variance on estimated displacements (compared to ARF-induced displacement magnitudes).

2.3.4 Acoustic Radiation Force Impulse Imaging (ARFI)

ARFI imaging is the most basic form of ARF-based stiffness imaging. It uses an ARF excitation, or a “push”, to induce displacements within tissue and monitors the response within the region of excitation (ROE) i.e. along the same axis as the excitation. It relies on the principle that the magnitude of the displacement generated in tissue (in response to a stress field) is inversely proportional to the
elastic modulus of the tissue. Given that soft tissue is not perfectly elastic, this relationship is not strictly linear, but assuming a uniform excitation force over a localized region, ARFI allows for differentiation of tissue based on inhomogeneity in local stiffness (Nightingale et al., 2002). It yields spatial (2D ARFI) or temporal (M-mode ARFI) maps of relative tissue stiffness.

Tracking of the on-axis displacement-recovery response yields multiple parameters that can be used to create ARFI images, such as displacement at a fixed time after ARF excitation, peak displacement over tracked time, time-to-peak displacement, and recovery time (Palmeri et al., 2006a). While all these metrics are inversely proportional to tissue stiffness, their accessibility and relative sensitivity is limited by application specific factors such as background motion, tracking duration and jitter. Displacement at early time steps (0.25-0.75 ms post ARF excitation) is the most commonly used metric to display ARFI images.

2.3.5 Shear Wave Elasticity Imaging (SWEI)

SWEI relies on measuring the speed of the transverse traveling shear waves that are generated in tissue as a response to ARF excitations. In its simplest implementation, SWEI utilizes broad transmit beams and several spatially distinct receive lines to track the displacement-recovery dynamics of the tissue at multiple lateral locations simultaneously (Sarvazyan et al., 1998; Nightingale et al., 2003). The speed of shear waves can be calculated from the spatio-temporal displacement data by estimating the time-of-flight (TOF) of the shear wave (Sandrin et al., 2003; McLaughlin and Renzi, 2006; Wang et al., 2010) or by using a Radon Sum Transformation approach (Rouze et al., 2010).

Similar to ARFI, SWEI can generate spatial (2D SWEI) as well as temporal (M-mode SWEI) maps of tissue stiffness. However, unlike ARFI where the images represent relative stiffness, SWEI is capable of generating quantitative information
about the absolute mechanical properties of tissue. Shear wave speeds can be converted to mechanical moduli by making simplifying assumptions about the material model of the medium. A homogeneous, linear, elastic, and isotropic model is generally used to recover tissue shear modulus (Palmeri et al., 2008). Although, several recent studies have investigated higher order models to extract tissue anisotropic and viscoelastic properties using shear waves (Gennisson et al., 2010; Tanter et al., 2008; W Urban et al., 2012).

2.3.6 Imaging Challenges for ARFI and SWEI

Challenges for ARF-based stiffness imaging modes can be broadly separated into issues of generating a substantial mechanical excitation and accurately tracking the dynamic response. The push is the source of signal for ARF-based stiffness imaging. Therefore an inability to generate displacements greater than the noise floor (as determined by the CRLB) renders both ARFI and SWEI unfeasible. Comparatively, SWEI requires a stronger displacement signal since it relies on measuring the propagation of a wave that decays rapidly from the source of excitation due to geometric spreading and attenuation. These effects become a much greater concern when imaging stiff media (> 30 kPa) at large imaging depths (> 50 mm).

On the tracking front, displacement estimation jitter (as determined by the CRLB) is the primary source of random noise for ultrasound-based motion tracking. While parameters such as pulse frequency, bandwidth, and kernel length can be chosen, the SNR and correlation coefficients are largely dependent on specific imaging scenarios. Achieving sufficient SNR at depth can be challenging due to attenuation and beam diffraction. Rapid, multi-dimensional background tissue motion can lead to speckle decorrelation. Both these effects amplify jitter and reduce the accuracy of displacement estimation.

Aside from sources of noise that increase uncertainty, there are also several sources
of bias that impact ARFI and SWEI. The presence of stationary clutter can lead to displacement underestimation; this negatively impacts both ARFI and SWEI equally. Systematic underestimation of on-axis displacements is a source of bias in ARFI and has been tied to push/track beam geometry, pulse parameters, and tissue stiffness (McAleavey et al., 2003; Palmeri et al., 2006b; Czernuszewicz et al., 2013). SWEI has additional sources of noise and bias associated with the extra processing steps of shear wave speed estimation and modulus calculation (Deffieux et al., 2012).

In recent work, speckle-induced spatial bias has also been identified as a correlated source of noise in SWEI (McAleavey et al., 2015). This effect draws a relationship between the variance in TOF estimates and the local speckle pattern under the track beam, which causes minor lateral deviations in tracking location (from the beam axis). This has led to the development of Single Track Location (STL) implementations of SWEI (Langdon et al., 2015) and their exploration as more robust stiffness imaging methods than traditional Multiple Track Location (MTL) SWEI (Hollender et al., 2015).

2.3.7 Material Models of Myocardium

Traditionally, ultrasound-based stiffness imaging techniques have employed a simplistic homogeneous, linear, elastic, and isotropic model to describe soft tissue (Sarvazyan et al., 1998). This model is applicable in elasticity phantoms and is a decent first-order approximation for large, relatively homogeneous organs such as the liver (away from vasculature); it allows for the characterization of the mechanical properties of tissue using only two material coefficients: \( \lambda \) and \( \mu \) (i.e. Lamé constants). These can be used to derive engineering moduli. However, biological tissue generally deviates from these assumptions to varying degrees (Fung, 2013).

Myocardium has been shown to have spatially varying (Novak et al., 1994), viscoelastic (Dokos et al., 2002; Huyghe et al., 1991), and anisotropic (Rohmer et al.,
2007) material properties. While ARF-based techniques are capable of differentiating local spatial inhomogeneities of tissue mechanical properties, violation of these higher order material models lead to predictable biases in the estimated tissue stiffness. Several investigations in the recent past have focused on these effects for ARFI and SWEI (Rotemberg et al., 2013; Deffieux et al., 2009; Wang et al., 2013). The effects of higher order material properties are manifested in both the on-axis displacement-recovery response as well as shear wave propagation, however, they are expected to have a much larger impact on the latter.

While these higher order properties are certainly relevant, they can only be meaningfully estimated and studied using high quality ARF-induced motion data, i.e., in environments where accuracy of displacement estimation is not a first-order concern. The work presented herein will extensively discuss specific factors that make displacement estimation challenging in noninvasive transthoracic imaging environments. Therefore, the basic material model of a linear, elastic, isotropic medium will be maintained for these analyses.
Effect of Transmit Beamforming on Clutter Levels in Transthoracic Echocardiography

The work presented in this chapter was published in the following manuscript:


3.1 Introduction

Ultrasound imaging of the heart, or echocardiography, is an extremely valuable tool in clinical cardiology. It provides structural as well as functional information about the heart in a real-time, cost-effective, and convenient manner. It can be performed via transthoracic, transesophageal, or intracardiac windows. When implemented transthoracically, it is completely noninvasive and widely used for initial screening, management, as well as follow-up exams. Transthoracic echocardiography (TTE) involves the use of two- and three-dimensional imaging as well as power- and color-
Doppler modes to survey the heart for abnormalities such as enlargement of chambers (Hauser et al., 1985), ventricular dyssynchrony (Yu et al., 2004), and regurgitant or stenotic valves (Yoshida et al., 1988; Baumgartner et al., 2008). It is also used to derive quantitative metrics of cardiac function such as chamber volumes (Lang et al., 2006), ejection fraction (Quiñones et al., 1981), and flow velocities through valves (Appleton et al., 1993). The diagnostic potential of echocardiography is rapidly expanding with increasing clinical acceptance and standardization of ultrasound-based modes such as tissue-doppler imaging (Yu et al., 2007) and myocardial strain imaging (Perk et al., 2007).

However, the benefits of TTE are contingent upon the ability to obtain good quality images. Imaging artifacts can present in echocardiograms as obscured or distorted structures and severely impact their diagnostic value (Bertrand et al., 2016; Le et al., 2016). The reliability and reproducibility of quantitative echocardiographic metrics of cardiac function are also drastically reduced for patients with poor image quality (Hoffmann et al., 1996; Tighe et al., 2007). In echocardiography, image quality is generally determined based on the visibility of endocardial borders, the extent of shadowing artifacts, and the ability to discern recognizable anatomical structures at depth. Poor quality cardiac ultrasound images, often referred to as “technically difficult echocardiograms”, are associated with factors such as obesity, scar tissue (from prior injury/surgery), and lung disease. These factors result in high acoustic clutter and limited depth of penetration.

Acoustic clutter is the diffuse haze that overlays ultrasound images. It degrades border delineation and diminishes the contrast of hypoechoic or hyperechoic targets (Lediju et al., 2008). It can arise as a result of three basic phenomenon: reverberation, off-axis scattering (due to side-lobes or grating lobes), and phase aberration (Pinton et al., 2011). While all three phenomena likely contribute to clutter under in vivo conditions, their relative contributions can be difficult to differentiate.
Properties of the propagation path (i.e. tissue through which an ultrasound image is acquired) is also a determinant of the magnitude and spatial extent of acoustic clutter. Heterogeneity in the speed-of-sound and presence of layered structures or specular reflectors has been shown to be associated with higher levels of acoustic clutter (Anderson et al., 2000; Dahl and Sheth, 2014; Fatemi et al., 2017). In the case of echocardiography, the propagation path is complex in nature and includes several tissue layers (skin, fat, muscle, and potentially ribs); these conditions can lead to the generation of a considerable amount of reverberation clutter. This form of clutter is generated in the near-field, i.e. close to the transducer face and is likely to decay with depth. Clutter can also arise from bright off-axis structures such as the pericardium and lung boundaries. Additionally, the clutter generating structures can be relatively stationary (chest wall) or ones that move with the cardiac or respiratory cycles (pericardium and lungs) (Lediju et al., 2009).

One technique that has made a tremendous impact on image quality in echocardiography is harmonic imaging. Clinically relevant image quality improvements in echocardiography using harmonic imaging have been reported by several studies (Kornbluth et al., 1998; Rubin et al., 2000; Spencer et al., 1998; Becher et al., 1998; Franke et al., 2000; Kühl et al., 1999). Harmonic imaging in ultrasound relies on non-linear propagation of sound waves through the imaging media which leads to the generation of echoes at higher harmonics of the transmit frequency (Thomas and Rubin, 1998). Echoes at these harmonic frequencies (generally second harmonic) can be isolated using band-pass filtering, pulse-inversion, or coded harmonics (Desser and Jeffrey, 2001) and reconstructed into images with improved resolution and reduced clutter. In simulations, harmonic imaging has been shown to suppress clutter due to reverberation by as much as 26 dB (Pinton et al., 2011).

The clutter suppression effect of harmonic imaging can be attributed to the fact that harmonics are preferentially generated in regions where the transmit beam pres-
sure at the fundamental frequency is highest i.e., around the transmit focus in depth and the beam axis in the azimuthal and elevation dimensions. Consequently, reverberant echoes from tissue layers in the near-field as well as echoes from off-axis targets and side-lobes are suppressed (Tranquart et al., 1999). However, harmonic imaging comes with its own set of unique challenges. Harmonic signals are 15-20 dB lower in amplitude compared to their fundamental counterparts (Schwarz et al., 1997). This limits their signal-to-noise ratio (SNR) and penetration depth. Consequently, focused beams have traditionally been used for this mode to aid harmonic generation and improve SNR. It also necessitates the use of broad-band probes to capture echoes at the higher harmonics.

Aside from image quality, frame-rate or temporal resolution is also critical when imaging a rapidly moving organ such as the heart. For a fixed field-of-view (FOV) and line density, the temporal resolution of ultrasound images is dependent on the number of receive lines being reconstructed per transmit and the number of transmits required to capture the entire FOV. These parameters can be modulated through beamforming. Beamforming involves manipulating the phase and amplitude of individual elements across an array so as to control the spatial profile of transmit or receive events. In conventional two-dimensional echocardiography, focused transmit beams are swept across the FOV and used to reconstruct one receive line per transmit. This yields frame-rates of 30-80 Hz. While these frame-rates may suffice to capture the bulk motion of the heart, they are too slow to capture phenomenon such as waves propagating in the myocardium due to valve closure and dynamics of valve motion (Kanai and Koiwa, 2001).

Frame-rates can be improved using parallel receive beamforming, wherein multiple receive lines (typically 4-64) are acquired simultaneously following a single transmit (Shattuck et al., 1984). In this configuration, the transmit beam is broadened by shrinking the active transmit aperture or using defocused beams. Multiple receive
beams are then captured across the insonified region. An extrapolation of this concept is used in “ultra-fast” imaging using plane waves (Montaldo et al., 2009). Plane wave imaging involves using a broad transmit pulse combined with extensive parallel receive beamforming. It has the benefit of being able to reconstruct entire FOVs with a single transmit event; thereby achieving extremely high frame-rates greater than 1000 Hz. Imaging at these high frame-rates is critical for the translation of transient elastography techniques into cardiac applications (Pernot et al., 2016; Song et al., 2016). Another approach to improving frame-rates is through the use of multi-line transmits wherein focused beams are transmitted simultaneously at several lateral locations (Tong et al., 2014).

However, this improvement in temporal performance comes at the cost of image quality. The lack of transmit focusing results in decreased resolution, lower SNR, and higher levels of acoustic clutter (Papadacci et al., 2014). These effects can also be attributed to lower pressure amplitudes and higher off-axis energy. While coherent summation of multiple steered plane waves has been shown to alleviate some of these challenges (Porée et al., 2016), a fundamental trade-off between image quality and temporal resolution exists.

For harmonic imaging, frame-rates have traditionally been limited due to the use of focused transmits. However, the combination of plane wave imaging and harmonic imaging has been a topic of exploration in the past few years. Recent studies have reported on the benefits of using plane waves in harmonic mode in the context of shear wave elastography (Correia et al., 2016; Song et al., 2013). The improvements are largely attributed to the clutter suppression effect of harmonic imaging and the improved temporal resolution due to plane wave imaging. While image quality improvements using the combined mode have been shown in phantoms and in limited in vivo examples, a thorough analysis of clutter levels for the various beamforming configurations has not previously been conducted.
The work presented herein aims to characterize and quantify clutter levels under \textit{in vivo} imaging conditions for a variety of factors such as beamforming configuration, imaging depth, and TTE view. The performance of focused and plane wave imaging in fundamental as well as harmonic modes is evaluated for matched imaging conditions to assess their relative benefits. These results serve to inform decisions on beamforming trade-offs so as to optimize image quality and frame-rate for ultrasound-based techniques in cardiac imaging.

3.2 Methods

3.2.1 Experimental Design

Twelve healthy volunteers were recruited and imaged under an IRB approved protocol (Duke IRB Pro00032068) at the out-patient Cardiology Clinic at Duke University Hospital. Study participants spanned an age range of 22-35 years and a body mass index (BMI) range of 20-24 kg/m$^2$. Imaging was performed by an experienced sonographer in two standard transthoracic echocardiographic (TTE) views: parasternal long axis (PLAX) and parasternal short axis (PSAX). As shown in Figure 3.1, both views capture the interventricular septum (IVS) at a depth of 50-60 mm. The chambers of the right ventricle (RV) and the left ventricle (LV) are located shallow and deep to the IVS, respectively.

A commercially available ultrasound system, Siemens Acuson SC2000$^{\text{TM}}$ (Siemens Medical Solutions Inc., Malvern, PA, USA), and an adult cardiac phased array, Siemens 4V1c, were used for imaging. The probe has a center frequency of 3.2 MHz and a bandwidth of 2.5 MHz. Custom pulse sequences were developed to acquire B-mode as well as M-mode images in a sequential fashion. B-mode images were captured in a manufacturer-optimized imaging condition native to the system for a 90$^\circ$ azimuthal FOV and a maximum depth of 100 mm.

M-mode images were acquired for a single transmit beam (down the middle of
Figure 3.1: Representative B-mode and M-mode images for the two transthoracic echocardiography (TTE) views used in the study, presented on a 35 dB dynamic range. B-mode shows a spatial map of echogenicity, while M-mode is a spatiotemporal representation along the center line of the B-mode image (dotted green line) as a function of time and spans multiple cardiac cycles. (a) and (b) show the heart in the parasternal long axis (PLAX) view while (c) and (d) depict it in parasternal short axis (PSAX). The interventricular septum (IVS) appears as the bright tissue layer at a depth of 50 – 60 mm in all four images. The hypoechoic regions shallow and deep to the IVS represent the chamber of the right ventricle (RV) and the left ventricle (LV), respectively.

the B-mode) with parallel receive beamforming to acquire five receive lines across a narrow lateral extent (1°). Clutter level was measured using all receive lines, however, the M-mode images presented herein correspond to the central angle. M-mode images were acquired for four beamforming configurations comprising combinations of fundamental and harmonic mode using focused and plane wave transmit settings. Fundamental imaging was performed at 3.2 MHz while harmonic imaging (using pulse-inversion) employed a 2 MHz transmission corresponding to a 4 MHz receive frequency. In the focused setting, the full probe aperture (18.87 mm) was used to generate a focus at a depth coinciding with the IVS, yielding F-numbers in the range of 2.65 to 3.18. For the plane wave case, the full aperture was used
again, however the focus was set to 1000 mm so as to achieve a near-planar transmit wavefront. Therefore, the four beamforming configurations were, fundamental-plane (FP), fundamental-focused (FF), harmonic-plane (HP), and harmonic-focused (HF). The mechanical index of the transmit pulses used in this study are in the range of 1.01-1.65.

For each configuration, raw M-mode echo data was acquired for a duration of 5 s at a pulse repetition frequency of 4 kHz. Beamformed, in-phase and quadrature (IQ) data (i.e. focused, summed, and demodulated signals) were acquired prior to envelope detection and log compression. Each “data set” was comprised of one B-mode and four M-mode images. M-mode images (one for each beamforming configuration) were acquired in quick succession following the acquisition of the B-mode to maintain a stable field-of-view (FOV) within each data set. Each data set was acquired over a duration of 35-40 s. Volunteers were not required to hold their breath given the prolonged duration of the acquisition. 3-8 repeated acquisitions were performed on each volunteer and in each view. Five data sets with independent speckle realizations were also acquired on a ATS imaging phantom, Model 549 (ATS Laboratories Inc., Bridgeport, CT, USA). Anechoic targets at a depth of 40 mm and 60 mm were imaged through a water path as well as in the presence of a reverberant tissue layer (pork belly).

3.2.2 Data Processing

B-mode images were used for anatomical reference to identify specific cardiac walls on the corresponding M-mode and also to confirm that standard TTE views were obtained. Spatiotemporal regions-of-interest (ROIs) representing the IVS were manually traced on each M-mode image. ROIs were also traced shallow and deep to the IVS to represent the RV and LV, respectively. These are shown as dotted green lines in Figure 3.2. ROIs were carefully chosen so as to exclude cardiac anatomical
features such as valve leaflets, papillary muscles, and chordae tendineae.

Contrast was measured as the ratio of the mean envelope-detected IQ data within ROIs representing the cardiac chambers and that of the IVS, as shown in Equation 3.1. While the ratio was computed using linear data (representing pressure signals), the contrast is presented on a logarithmic scale. On an ideal image, the IVS is hyperechoic compared to the chambers. However, contrast was defined to be a positive quantity to make the analysis intuitive.

\[
C_c = -20 \log_{10}\left(\frac{\bar{v}_c(z,t)}{\bar{v}_{IVS}(z,t)}\right),
\]

(3.1)

where \(C_c\) refers to measured contrast, \(\bar{v}_c\) stands for the spatiotemporal mean of the signal within an ROI corresponding to a particular chamber (RV or LV), while \(\bar{v}_{IVS}\) represents the spatiotemporal mean over the interventricular septum. \(z\) and \(t\) represent the spatial (depth) and temporal dimensions of the M-mode image, respectively, and \(c\) represents the specific chamber (RV or LV).

M-mode images that displayed artifacts related to breathing, such as the invasion of lung tissue into the imaging plane or the clear presence of cardiac structures in the ROIs of the RV or LV, were excluded from analysis. The final analysis was conducted on 169 data sets across the 12 volunteers. M-mode data in the fundamental-plane configuration was not acquired for 90 data sets due to experimental limitations.

3.2.3 Statistical Analysis

As discussed above, contrast data was acquired across three main parameters: beamforming configuration, cardiac chamber, and TTE view. A multivariate analysis was performed using a mixed model with fixed effects for the three parameters mentioned above and random effects across volunteers and repeated acquisitions. Magnitude as well as direction of the effects of the three main parameters on contrast and their
two-way interactions were isolated through this analysis. Repeated measures were incorporated into the model to assess inter- vs. intra-volunteer variability.

Contrast data was modeled as:

\[ C_{ijklm} = \mu + c_i + v_j + b_k + p_l + (c \cdot v)_{ij} + (v \cdot b)_{jk} + (c \cdot b)_{ik} + \epsilon_{ijklm}, \quad (3.2) \]

where \( C_{ijklm} \) is the measured contrast for the \( i^{th} \) chamber (RV or LV), \( j^{th} \) view (PLAX or PSAX), \( k^{th} \) beamforming configuration (FP, FF, HP, or HF) from the \( l^{th} \) volunteer (1-12) and the \( m^{th} \) repeated measurement (1-8). Note that an unequal number of repeated measurements were performed for each condition. The model in Equation 3.2 approximates contrast in terms of a baseline mean (\( \mu \)), which corresponds to the contrast of the RV, in PLAX using the fundamental-focused (FF) configuration. The model goes on to include the main effects of the chamber (\( c_i \)), the view (\( v_j \)), and the beamforming configuration (\( b_k \)). It also includes a random effect of the volunteer (\( p_l \)) and pairwise interactions between the three main factors. The random effect, \( p_l \), is assumed to have a zero-mean Gaussian distribution with standard deviation of \( \sigma_p \). Lastly, \( \epsilon_{ijklm} \) represents measurement error, assumed to have an independent zero-mean Gaussian distribution with a standard deviation \( \sigma_\epsilon \). The model was fit to the data by the method of restricted maximum likelihood (REML) using the \textit{nlme} package in the R computing platform (R Core Team, 2013).

3.3 Results

Table 3.1 presents mean and standard deviations of five contrast measurements made on an imaging phantom (ATS Model 549) using the four beamforming configurations. The anechoic targets were 8 mm in diameter and centered at depths of 40 mm and 60 mm. The 12 mm background speckle region between the two targets was used for reference. When imaging through a water path, the plane wave configurations showed similar performance in fundamental as well as harmonic mode with mean contrast...
Table 3.1: Contrast between anechoic targets and speckle generating background on imaging phantom (ATS Model 549)

<table>
<thead>
<tr>
<th></th>
<th>Contrast (dB)</th>
<th>Water Path</th>
<th>Reverberant Tissue Layer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40 mm</td>
<td>60 mm</td>
</tr>
<tr>
<td>Fund. Plane (FP)</td>
<td>23.53 ± 0.65</td>
<td>17.81 ± 1.68</td>
<td>6.67 ± 1.87</td>
</tr>
<tr>
<td>Fund. Foc. (FF)</td>
<td>32.59 ± 0.67</td>
<td>29.39 ± 0.74</td>
<td>8.44 ± 1.46</td>
</tr>
<tr>
<td>Harm. Plane (HP)</td>
<td>22.93 ± 1.44</td>
<td>18.83 ± 0.59</td>
<td>13.01 ± 2.39</td>
</tr>
<tr>
<td>Harm. Foc. (HF)</td>
<td>36.85 ± 1.36</td>
<td>33.17 ± 0.92</td>
<td>19.85 ± 1.99</td>
</tr>
</tbody>
</table>

ROI Diameter = 8 mm, n = 5

( across the targets) of 20.67 dB and 20.88 dB, respectively. Mean contrast was significantly higher in the fundamental-focused configuration, 30.99 dB, and highest in the harmonic-focused case, 35.01 dB. Contrast for the deep target was lower than the shallow one; on average the difference between the two was 3.92 dB.

When imaging though a reverberant tissue layer (pork belly), contrast was found to be lower for all targets and in all beamforming configurations. However, mean contrast (across the targets) in this case was found to improve across beamforming configurations. Fundamental-plane showed the lowest contrast, 6.77 dB, followed by fundamental-focused, 9.97 dB. Mean contrast in harmonic-plane and harmonic-focused configurations was 10.31 dB and 19.22 dB, respectively.

Figure 3.2 portrays a comparison of high and low clutter imaging environments in vivo. B-mode and M-mode images shown here were acquired in the PSAX view on two separate volunteers. Clutter, which appears as a diffuse haze, is noticeable within the cardiac chambers. While clutter is observable to some degree across all four images, it is especially pronounced within the RV in Figure 3.2(a) and (b). Clutter arising from stationary sources appears in the M-mode (Figure 3.2(b) and (d)) as horizontal streaks through time within the RV chamber. Contrast measurements for the RV (shallow) and LV (deep) are superimposed on the M-mode images. In the
Figure 3.2: B-mode and M-mode images illustrating a high clutter imaging scenario, (a) and (b), compared to a low clutter case, (c) and (d), in the parasternal short axis view. The dotted green lines on B-mode represent the lateral position of the M-mode, while the same on M-mode represent outlines of the ROIs for IVS, RV and LV. Measured contrast for each cardiac chamber (with respect to the IVS) over the spatio-temporal ROI is indicated on the M-mode images. Low contrast is indicative of a high clutter environment and vice-versa. Contrast, not only varies between the two imaging scenarios but also between the two cardiac chambers.

High clutter case, Figure 3.2(b), the LV shows substantially higher contrast compared to the RV.

Figures 3.3 and 3.4 demonstrate the effect of beamforming on clutter levels in PSAX and PLAX views, respectively. Each figure shows a full data set comprising the B-mode, (a), as well as M-mode images for all four beamforming configurations, (b)-(e). Contrast measurements for both cardiac chambers as a function of beamforming configuration are tabulated below the B-mode images.

A qualitative comparison of the M-mode images, in both examples, shows similar performance for both fundamental configurations (focused and plane). A reduction in clutter is observed when using the harmonic-plane mode. The harmonic-focused configuration further enhances clutter suppression and improves image quality. De-
Figure 3.3: A representative data set in parasternal short axis. (a) shows the B-mode, (b) - (e) show M-mode images for the four beamforming configurations and the table (left bottom) shows contrast measurements in RV and LV as a function of beamforming configuration. Qualitative improvements in clutter levels are evident in the sequence of M-mode images (top to bottom) while quantitative trends are captured by the contrast measurements in the table.

Increased clutter is accompanied by improved border delineation of the IVS and a cleaner representation of myocardial walls against the background of the hypoechoic cardiac chambers. Contrast measurements, presented in the tables, capture this reduction in clutter levels across beamforming configuration in a quantitative sense. Comparing fundamental-plane with harmonic-focused, the mean contrast improvement (across cardiac chambers) was 7.70 dB in PSAX and 5.56 dB in PLAX.

Contrast measurements as a function of beamforming configuration, for all repeated acquisitions, and across the twelve volunteers in the study are shown in Fig-
Figure 3.4: A representative data set in parasternal long axis. (a) shows the B-mode, (b) - (e) show M-mode images for the four beamforming configurations and the table (left bottom) shows contrast measurements in RV and LV as a function of beamforming configuration. The trend of improvement in contrast (over beamforming configurations) appear to be similar in both TTE views and for both cardiac chambers.

Figure 3.5. Within each beamforming configuration, the data are segmented by cardiac chamber; RV is presented in the light gray markers while LV is in dark gray. Box plots for the respective distributions are superimposed. The primary trend of note is that median contrast increases monotonically in response to beamforming configuration from left to right or from fundamental-plane to harmonic-focused. This effect is observed for both the RV as well as the LV. Comparing fundamental-plane to harmonic-focused, median contrast was found to increase for the RV from 6.71 dB to 13.91 dB and for the LV from 9.62 dB to 16.71 dB.

While contrast for both chambers exhibit the same trend across beamforming
Figure 3.5: Contrast measurements as a function of beamforming configuration, split by cardiac chamber. For the box plots, the horizontal marker represents the median, the edges of the box represent the 25th and 75th percentile and the whiskers mark the furthest values not considered outliers. RV (light gray markers) shows lower contrast (higher clutter) as compared to LV (dark gray markers). A monotonic trend of incremental improvements in contrast (reduction in clutter) as a function of beamforming are observed in both RV and LV.

configuration, their distributions are distinct from one another. On average, over the four beamforming configurations, median contrast for the RV is 2.96 dB lower than that for the LV; this difference is largest in the harmonic-plane configuration.

Figure 3.6 illustrates the relative trend of contrast across beamforming configuration. Relative contrast was derived in a matched sense (within each data set) by referencing the raw contrast measurements using each beamforming configuration to their counterparts in the fundamental-focused configuration. Cardiac chamber specific results are presented for the RV and the LV in light and dark shades, respectively. Relative contrast distributions highlight the dominant effect of beamforming. Compared to fundamental-focused, the fundamental-plane configuration shows a subtly lower contrast; median difference of -0.79 dB. The harmonic configurations, however showed more pronounced effects with the plane and focused cases showing improvements of 2.97 dB and 5.28 dB respectively. The difference between cardiac chambers is almost negligible in the case of relative contrast across beamforming configurations (compared to absolute contrast, i.e. Figure. 3.5).

Figure 3.7 shows a scatter plot of contrast measurements for each beamforming
Figure 3.6: Distributions and associated box plots for relative contrast (matched to within each data set) compared to the fundamental-focused configuration for each cardiac chamber. Contrast changes for the RV are represented by lighter shades and those for the LV are in darker shades. Box plots are as describe in Figure 3.5. The trend of improving relative contrast as a function of beamforming is highlighted here. No significant difference in relative contrast with beamforming configuration is observed between RV and LV.

configuration plotted against their counterpart in the fundamental-focused case, i.e. the reference mode. In this format, the abscissa indicates the contrast in the reference beamforming mode (FF, in gray), going from high clutter on the left to low clutter on the right. The ordinate indicates contrast (for a matched view from the same data set) for the other three beamforming configurations (FP, in green; HP, in red; HF, in blue). A strong positive correlation is observed between contrast in the baseline mode compared with the same in each of the other three modes. This relationship is highlighted by the linear fits derived from the multivariate model and reflected in the Pearson correlation coefficients; 0.97 for FP, 0.80 for HP, and 0.85 for HF. Vertical offsets from the diagonal indicate changes in clutter levels from the baseline. In the case of fundamental-plane, this change is subtle and in the negative direction; suggesting slightly higher clutter. Alternatively, the two harmonic modes show large positive offsets with harmonic-focused being considerably larger than harmonic-plane. This is suggestive of clutter reduction due to the use of harmonic imaging.

Contrast measurements as a function of beamforming configuration for individual
Figure 3.7: Scatter plot of measured absolute contrast for each beamforming configuration against their corresponding value in the fundamental-focused case. Linear fits are superimposed. Data points along the diagonal are contrast values in the fundamental-focused mode, the region above the diagonal represents improvements in contrast while the region below it represents degradation. The fundamental-plane case shows a small degradation in contrast while the two harmonic cases show substantial improvements.

Study participants is presented in Figure 3.8. Within each participant, beamforming configurations are placed in the following order: (from left to right) fundamental-plane, fundamental-focused, harmonic-plane, and harmonic-focused. The thin gray lines represent individual data sets while the thicker black line represents the mean. Contrast values show considerable variability between multiple acquisitions within a participant as well as across different participants. However, the general trend of increasing contrast (decreasing clutter) across beamforming, going from left to right, was observed in all cases.

Multivariate statistical modeling was used to isolate the impact of individual factors, assess their interactions, and compare these to random effects. Results from
Figure 3.8: Trends of contrast as a function of beamforming split by volunteer. Contrast measurements for individual data sets are indicated in the light gray lines, and the median trend is shown in black. Despite the range of contrast measurements, the trend of incremental improvements across the four beamforming configurations was found to be consistent for all volunteers in the study.

This analysis are presented in Table 3.2. The multivariate model described by Equation 3.2 accounts for fixed effects of chamber, view, and beamforming configuration as well as random effects across study participants and repeated measurements. The baseline condition (row 1) for this analysis was RV, PLAX, and fundamental-focused. Rows 2-6 represent changes in contrast (from baseline) as a result of independent contributions of each individual factor. Rows 7-13 represent pairwise interaction effects; these can be interpreted as added effects due to the combined contribution of two factors relative to the sum of their individual contributions. Effects were considered statistically significant for \( p \)-values under 0.01.

The effect of view, chamber, and beamforming configuration were all found to be statistically significant with \( p \)-values less than 0.0001. However, the magnitudes and directions of these effects varied. The standard deviation of contrast measurements across study participants (\( \sigma_p \)) was found to be 2.51 dB; the same across repeated measurements, i.e. within study participants (\( \sigma_e \)) was 2.57 dB. From a baseline contrast value of 6.44 dB, contrast for the LV was found to be 5.05 dB higher. Switching to the harmonic-focused configuration was shown to result in a 5.16 dB improvement in contrast. The effect of view and the two plane wave cases (fundamental and
Table 3.2: Multivariate analysis with mixed effects on contrast measurements.

<table>
<thead>
<tr>
<th>Term</th>
<th>Effect</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.44</td>
<td>0.83</td>
<td>7.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(RV, PLAX, Fund. Foc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>5.05</td>
<td>0.47</td>
<td>10.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSAX</td>
<td>2.2</td>
<td>0.49</td>
<td>4.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fund. Plane</td>
<td>-1.94</td>
<td>0.65</td>
<td>-2.99</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Harm. Plane</td>
<td>1.94</td>
<td>0.51</td>
<td>3.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Harm. Foc.</td>
<td>5.16</td>
<td>0.51</td>
<td>10.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV: PSAX</td>
<td>-3.29</td>
<td>0.45</td>
<td>-7.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV: Fund. Plane</td>
<td>0.5</td>
<td>0.73</td>
<td>0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>LV: Harm. Plane</td>
<td>0.66</td>
<td>0.58</td>
<td>1.14</td>
<td>0.26</td>
</tr>
<tr>
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<td>0.58</td>
<td>0.27</td>
<td>0.79</td>
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<tr>
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<tr>
<td>PSAX: Harm. Foc.</td>
<td>0.09</td>
<td>0.57</td>
<td>0.16</td>
<td>0.87</td>
</tr>
</tbody>
</table>

RV = Right Ventricle, LV = Left Ventricle
PLAX = Parasternal Long Axis, PSAX = Parasternal Short Axis

harmonic) also yielded statistically significant, albeit smaller effect sizes of 2.2 dB, 1.94 dB, and 1.94 dB, respectively. All interaction terms modeled herein, with the exception of the interaction of view and chamber, were found to be statistically insignificant. The combined effect of switching to LV and PSAX was 3.29 dB lower than the sum of their individual contributions.

### 3.4 Discussion

The diagnostic value of ultrasound images can be drastically degraded in the presence of acoustic clutter. This form of image degradation can be detrimental for clinically relevant tasks where border delineation is critical such as measuring thickness of tissue layers, quantifying sizes of anechoic regions, and visualizing subtle structures such as vegetations. Artifacts due to clutter from stationary as well as moving sources can not only obscure the presentation of anatomical structures but also impede the
accuracy of ultrasound-based motion tracking algorithms (Pinton et al., 2006).

In echocardiography, the dominant sources of clutter are presumed to be reverberation and off-axis scattering. Echoes generated through these two mechanisms get superimposed over echoes from structures along the beam axis because they arrive at the receive aperture simultaneously. The additive nature of clutter can, thus, make it difficult to quantify its effects under in vivo conditions where the FOVs consist mostly of speckle generating tissue e.g., liver or thyroid imaging. However, clutter levels can be estimated in cases where the FOV contains substantial anechoic or hypoechoic regions.

TTE provides one such opportunity; while the myocardial walls are composed of muscular structures, the cardiac chambers are largely filled with blood. At typical frequencies used for transthoracic imaging (2-5 MHz), echoes from blood are 40-100 dB lower in magnitude compared to those from myocardial walls such as the interventricular septum (IVS) (Bjaerum et al., 2002). Thus, in the ideal “clutter-free” image the cardiac chambers would appear nearly anechoic compared to the myocardial walls. Varying levels of contrast loss and lack of image conspicuity due to clutter is evident in all M-mode images presented here. Measuring contrast between cardiac chambers and the IVS can, therefore, provide an estimate of clutter levels. A low contrast measurement is indicative of a high clutter environment and vice-versa. Moreover, depth dependent changes in clutter levels can be readily studied in TTE by comparing clutter levels in different cardiac chambers.

The impact of clutter can be mitigated through the use of beamforming. For applications such as echocardiography where motion tracking can be just as important as the ability to visualize fine structure, beamforming strategies seek to find an optimum over a complex and interrelated set of parameters that impact image quality (spatial resolution, SNR, and clutter suppression) as well as temporal resolution, and field-of-view.
3.4.1 Phantom Trends

In the phantom, when imaging though a water path the mean contrast for the anechoic targets using the fundamental-focused configuration was measured to be 30.99 dB. Compared to this, the fundamental-plane and the harmonic-plane cases showed substantial deteriorations of 10.32 dB and 10.11 dB, respectively, while the harmonic-focused case yielded a 4.02 dB improvement. The marked decrease in contrast for the plane wave cases compared to their focused counterparts can be attributed to an increase in the contribution of off-axis scattering when using plane waves. Harmonic imaging is expected to yield improvements primarily through the suppression of reverberant echoes (Pinton et al., 2011) and to a lesser extent by limiting the contribution from the side-lobes. Given the lack of sources of reverberation in the phantom, the improvement in contrast when using harmonic-focused (compared to fundamental-focused) is most likely a consequence of the suppression of echoes from the side-lobes. However, the degradation of contrast in the harmonic-plane case suggests that, in this scenario, the increase in off-axis clutter due to the use of plane waves has a stronger impact compared to the suppression of reverberant clutter afforded by harmonic imaging. This result provides a validation of the expected relationships between the various beamforming configurations in a low reverberation environment.

In the presence of a reverberant tissue layer, mean contrast for the anechoic lesions in the fundamental-focused configuration was dramatically reduced from 30.99 dB to 9.97 dB. However, the trends across beamforming configurations in this case matched the ones observed under in vivo conditions. The harmonic-plane and harmonic-focused cases were shown to improve contrast by 0.34 dB and 9.25 dB, respectively; while the fundamental-plane case showed a 3.2 dB reduction. While a monotonic trend was observed in the contrast of the shallow lesion, the deep lesion showed a
slight reduction in contrast when using the harmonic-plane configuration. This could be attributed to a decrease in SNR as a function of depth due to lower harmonic generation when using plane waves. These results illustrate the effect of reverberant clutter as a function of beamforming configuration in a controlled environment.

3.4.2 *In vivo* Trends

Under *in vivo* imaging conditions, contrast values varied over a wide range for each beamforming configuration. Using the fundamental-focused configuration, contrast values ranged from -0.87 dB to 19.63 dB. Measurements varied not only across study participants but also between repeated acquisitions within a particular participant, as illustrated in Figure 3.8. This variability can be attributed to changes in the propagation path used for imaging. Additionally, all volunteers in this study had BMIs within a fairly narrow range. Considerably higher clutter levels (and lower contrasts) would be expected for patients with higher BMIs (Lediju et al., 2008).

Using the fundamental-focused configuration, median contrast (across chambers) was found to be 9.99 dB. The fundamental-plane showed a relatively minor deterioration of 1.23 dB, while the harmonic-plane and harmonic-focused modes showed improvements of 2.97 dB and 6.1 dB, respectively, over the fundamental-focused. These results align well with the phantom results in the presence of a reverberant tissue layer.

When imaging the phantom through a water path, the harmonic-plane configuration showed a large deterioration in contrast with reference to the fundamental-focused case. However for phantom imaging in the presence of a reverberant tissue layer as well as under *in vivo* conditions it yielded an improvement in contrast. This evidence suggests that harmonic imaging using plane waves is only likely to show contrast improvements in the presence of strong reverberation clutter. For environments where reverberation is not the primary source of image degradation, the
harmonic-plane configuration is likely to yield lower contrast as a result of lower SNR of the harmonic signals as well as increased contribution of off-axis echoes due to the use of plane waves.

Clutter levels for *in vivo* images were also found to decay substantially with depth away from the chest wall, i.e. clutter in the shallow chamber (RV) was substantially higher than that in the deep chamber (LV). The statistical significance and appreciable magnitude of this effect (2.96 dB) are also suggestive of the presence of strong clutter from near-field reverberations. Even though absolute clutter levels between the two chambers differed from each other; the trend of relative changes in clutter as a function of beamforming was found to be consistent across cardiac chambers (as shown in Figure 3.6). This suggests that beamforming driven effects dominate over other confounding factors that differentiate clutter levels between the two cardiac chambers.

The highest contrast, however, was observed in the harmonic-focused configuration; the median across chambers in this configuration was measured to be 16.09 dB. This result is consistent with the findings on the phantom and indicates that the benefits of harmonic imaging are maximized when using focused beams. This effect can be attributed to the fact that higher pressures are generated when using a focused transmit configuration which in turn yields greater harmonic generation and thus improved SNR of the received echoes.

While the results presented portray a consistent relationship between clutter levels and beamforming configuration, there are a few confounding factors that were not addressed in this study. Given that clutter can arise from stationary as well as moving structures, its magnitude is likely to fluctuate over the cardiac cycle. Contrast data presented here were averaged over 4-5 cardiac cycles to overcome potential bias from transient changes, however, the variation in clutter levels through time was not explicitly addressed. Changes in SNR as a function of beamforming were also not
studied here. SNR can be estimated on phantoms and stationary tissue by tracking speckle correlation through time. However, similar analysis on cardiac images is more likely to represent motion-induced decorrelation as opposed to the effects of SNR.

Beamforming configuration was treated as an ordinal variable in this analysis. In doing so, the interactions between fundamental vs. harmonic and focused vs. plane wave were not directly interrogated. The apparent non-linearity in the contrast improvement between adjacent pairs of beamforming configurations warrants a closer analysis into their interplay. Lastly, the comparison of focused beams and plane waves represents only a small subset over a wide spectrum of transmit beamforming configurations. Several other conditions such as diverging waves, coherent summation of steered plane waves, multi-line transmits, and other transmit configurations used in synthetic aperture techniques also aim to address the trade-offs between image quality, frame-rate, and field-of-view. Future work will look to expand the analysis of clutter levels in fundamental as well as harmonic modes to the other transmit geometries, over a wider range of BMIs, and also across more in vivo imaging environments such as fetal and abdominal imaging.

### 3.5 Conclusions

This study investigated the effects of transmit beamforming on clutter levels in the context of transthoracic echocardiography. Contrast between the cardiac chambers and the interventricular septum was used to estimate clutter levels under in vivo imaging conditions. Focused and plane wave transmit configurations were evaluated in fundamental as well as harmonic modes to assess their susceptibility to acoustic clutter. Trends in the magnitude of clutter were analyzed, in an absolute as well as relative sense, across parameters relevant to TTE imaging such as view (PLAX, PSAX), chamber (RV, LV) and beamforming configuration.
Clutter levels for the four transmit beamforming configurations were found to be significantly different from one another. In both, fundamental as well as harmonic modes, the focused case yielded higher contrast compared to its plane wave counterpart demonstrating the impact of off-axis scattering. Additionally, the harmonic-plane configuration outperformed the fundamental-focused case. Contrast was also found to improve with increasing depth away from the chest wall. These results suggest a strong contribution of reverberant clutter under \textit{in vivo} transthoracic settings.
Impact of Cardiac Motion on Signal Quality in Transthoracic Acoustic Radiation Force Impulse Imaging

4.1 Introduction

The heart is a dynamic organ that undergoes cyclic electro-mechanical changes with every beat. Over the course of a cardiac cycle, the muscular walls of the heart actively contract and relax in response to electrical stimuli and exhibit complex motion patterns consisting of elongation, thickening, rotation, and twist (Troy et al., 1972; Nakatani, 2011). Motion of the myocardial walls has been shown to be closely associated with the efficacy of cardiac pump function (Buckberg et al., 2008; Bijnens et al., 2012) and is measurably altered in diseased states. Abnormalities in global/regional wall motion or its synchronization with the electrical activity of the heart can be used to diagnose structural and functional cardiac disorders (Yun et al., 1991; Møller et al., 2006; Nagel et al., 2000; Stuber et al., 1999; Tibayan et al., 2002; Sade et al., 2004).

Cardiac motion can be studied in qualitative and quantitative ways through
a variety of techniques. These can range from highly invasive methods, where fiducial markers are implanted directly into the myocardium, to noninvasive techniques using medical imaging modalities. Invasive methods, such as sonomicrometry (Moores et al., 1984) and tracking implanted radiopaque beads using biplane fluroscopy (Tsamis et al., 2011), provide high fidelity data and are considered to be the most accurate representation of three-dimensional cardiac motion. However, they require surgical intervention and thus are unsuitable for out-patient clinical assessment. Noninvasive measurement of cardiac motion can be performed using medical imaging modalities such as ultrasound (Kapetanakis et al., 2005), magnetic resonance imaging (Osman et al., 1999), and computed tomography (Achenbach et al., 2000). A number of studies have found good agreement between the various invasive and noninvasive means to quantify cardiac motion. (Amundsen et al., 2006; Yeon et al., 2001; Ashraf et al., 2010; Edvardsen et al., 2002).

Amongst the noninvasive methods, ultrasound imaging of the heart, or echocardiography, is most widely used for diagnostic purposes in clinical cardiology. Not only is echocardiography a low cost, non-ionizing, portable, and widely available imaging modality but it also provides the unique ability to visualize the heart in real-time at extremely high frame-rates (>1000 Hz) (Cikes et al., 2014). These advantages have led to the development and clinical acceptance of ultrasound-based myocardial motion analysis tools such as strain/strain-rate imaging (D’hooge et al., 2000) and tissue-Doppler imaging (Price et al., 2000).

Myocardial motion refers specifically to the motion of the walls of the heart. Characterization of myocardial motion, however, only provides a partial picture of cardiac mechanics. In addition to complex three-dimensional motion, myocardium also exhibits dramatic changes in its elasticity or stiffness over the cardiac cycle. Healthy myocardium achieves peak stiffness following active contraction at end-systole and minimum stiffness in a relaxed state during diastole (Suga and Sagawa, 1974). Much
like cardiac motion, alterations in myocardial stiffness have also been associated with pathological states (van Heerebeek et al., 2006; Nagueh et al., 2004; Jalil et al., 1989; Zile and Brutsaert, 2002; Díez et al., 2002).

Changes in tissue stiffness, while not captured in conventional ultrasonic imaging modes, can be measured using acoustic radiation force-based ultrasonic methods such as acoustic radiation force impulse (ARFI) imaging and shear wave elasticity imaging (SWEI). These methods rely on ultrasound’s ability to remotely generate and track micron-level mechanical vibrations in soft tissue (Doherty et al., 2013a). They have been researched extensively for the past two decades and have found a plethora of potential as well as realized clinical applications for noninvasive quantification of the mechanical properties of liver, breast, and prostate. (Friedrich-Rust et al., 2012; Fahey et al., 2005; Meng et al., 2011; Lee et al., 2013; Palmeri et al., 2016). ARFI and SWEI have also been used to interrogate the heart and shown to capture the temporal changes in myocardial stiffness through the cardiac cycle in open-chest experiments (Hsu et al., 2007) and Langendorff preparations (Pernot et al., 2011; Vejdani-Jahromi et al., 2015) as well as to identify the spatial extent of ablation lesions in intracardiac imaging environments (Bahnson et al., 2014). Implementation of these techniques for transthoracic imaging has yielded promising preliminary results and is an active field of research (Song et al., 2016; Villemain et al., 2018; Kakkad et al., 2015).

A dominant source of error and uncertainty in clinical applications of ARFI and SWEI is intrinsic physiological tissue motion and/or transducer motion (Fahey et al., 2007). Acoustic radiation force (ARF) excitations or “pushes” induce motion along the propagation direction of the ultrasound beam i.e., axial dimension, and result in the generation of shear waves that travel in the orthogonal dimension i.e., lateral and elevational dimensions. The displacement magnitude of these mechanical excitations in soft tissues is generally in the range of 0-20 µm. Their temporal duration is about 5-15 ms. Thus, for a short interval following the “push”, peak axial tissue
velocities can reach values up to 2 cm/s. In comparison, myocardial velocities in the cardiac coordinate system, i.e., radial, circumferential, and longitudinal dimensions, have been reported to be as high as 6.5, 3.2, and 12 cm/s, respectively (Delfino et al., 2008). Additionally, myocardial accelerations have been measured to be on the order of 190 cm/s² (Cheung et al., 2005). These values have also been found to increase dramatically with heart rate. Accurate and precise measurement of the ARF-induced axial motion in the presence of intrinsic, multi-dimensional, physiological tissue motion can prove to be a challenging task especially in the context of transthoracic cardiac imaging.

Previous attempts to suppress intrinsic physiological tissue motion in ARF-based imaging techniques have involved using fitting-based approaches to model the temporal trend of physiological motion and subtract it out (Hsu et al., 2009). In this paradigm, the measured displacement profiles (through time) for a fixed “push” direction are extracted within two temporal windows: one prior to the “push”, referred to as the “pre” window, and another at a later time point at which the ARF-induced motion is considered to be fully decayed (>5-10 ms), referred to as the “post” window. Displacement data for these two windows are fit to either a linear or a quadratic polynomial (through time) which is designed to capture tissue motion with uniform velocity or uniform acceleration, respectively. The resultant fit is considered to capture physiological tissue motion and is subtracted off of the computed displacement profile. Deviations from the fit are thus attributed to ARF-induced motion. The process is then repeated independently at all axial pixels for a given “push” direction as well as for subsequent “pushes” which could be in a different direction in the case of 2D ARFI or the same direction in the case of M-mode ARFI. These motion filters will be referred to as “polynomial filters”.

While, these approaches have been successful at suppressing transducer motion and intrinsic physiological motion for slow-moving organs such as liver and prostate,
they have been less effective when applied to tissues that exhibit rapid and complex motion such as the heart. Moreover, the magnitude and direction of myocardial motion varies substantially over the cardiac cycle, thus the performance of motion filters can be highly dependent on the phase of the cardiac cycle being evaluated. Variations on polynomial filters have included temporal interpolation, extrapolation, and weighted fitting (Giannantonio et al., 2011). These have lead to improved performance during diastole but effective suppression of cardiac motion in systole continues to be a challenge.

Another approach to motion filtering could involve separating ARF-induced motion from intrinsic physiological motion on the basis of differences in their frequency content. Physiological motion is expected to be confined to the lower end of the frequency spectrum (<30-50 Hz). In contrast, ARF-induced motion, while substantially lower in magnitude, is expected to retain energy at much higher frequencies (>100 Hz) given its limited temporal extent.

The goal of this work is to characterize the impact of cardiac motion on the signal quality of transthoracic M-mode ARFI images. A comparative analysis of motion filtering approaches aimed at suppressing the axial component of cardiac motion and separating it from ARF-induced motion is presented. The effects of non-axial components of cardiac motion on the precision of micron-level displacement estimation is also examined.

4.2 Methods

4.2.1 Clinical Data Acquisition

*In vivo* data was acquired on five healthy volunteers at the out-patient Cardiology Clinic at Duke University Hospital following informed consent. Volunteers were recruited under an IRB approved protocol (Duke IRB Pro00032068) and imaged by an experienced cardiac sonographer. Imaging was performed to capture the inter-
ventricular septum (IVS) in the parasternal long axis (PLAX) and parasternal short axis (PSAX) views. Two datasets were acquired in each view and on each volunteer, for a total of twenty datasets. The probe was lifted off the chest and repositioned between the two repeated acquisitions so as to capture subtle positional variations within a fixed view.

The sequences used in this study were developed and implemented on a Siemens Acuson SC 2000™ (Siemens Medical Solutions Inc., Malvern, PA, USA) and an adult cardiac phased array, Siemens 4V1c. Each dataset consisted of a B-mode image, an M-mode image, and the concurrent electrocardiogram (ECG) trace. B-mode images were captured in a manufacturer-optimized imaging condition native to the system for a 90° azimuthal field-of-view (FOV) and a maximum depth of 100 mm. M-mode images were acquired for a single transmit direction down the middle of the B-mode FOV using a custom sequence that employed pulse-inversion harmonic imaging. The transmit beams were centered at 2 MHz, focused at the depth of the IVS (between 50-70 mm), and repeated at a pulse-repetition-frequency (PRF) of 4 kHz.

Echoes were captured at the harmonic frequency of 4 MHz, focused dynamically through depth, and processed using parallel receive beamforming (Shattuck et al., 1984) to synthesize seven simultaneously acquired lines across an angular span of 0.4° about a virtual apex of 300 mm behind the probe face. Pulse-inversion processing was performed using the fully-sampled approach (Doherty et al., 2013b) to maintain the temporal sampling rate of 4 kHz. M-mode data were acquired as beamformed, in-phase and quadrature (IQ) data (i.e. focused, summed, and demodulated signals) for a duration of 5 seconds, thus spanning 4-6 consecutive cardiac cycles.

4.2.2 Finite Element Simulations

The temporal response of soft tissue to an impulsive acoustic radiation force (ARF) excitation was modeled using a combination of LS-DYNA (Livermore Software Tech-
nology, Livermore, CA) and FIELD II (Jensen, 2002). This model has previously been validated by Palmeri et al. (Palmeri et al., 2005, 2017). Myocardium was modeled using a set of semi-infinite, elastic media with Young’s moduli of 3, 6, 12, 24, and 36 kPa. The transducer used for in vivo data acquisition, Siemens 4V1c, was modeled in FIELD II to generate the spatial intensity distribution of a focused beam with a 50 mm focus. This profile was scaled using a peak intensity (I_{SPPA}) of 1000 W/cm² to yield the forcing function associated with an ARF excitation or “push” at a center frequency of 2.8 MHz, an F-number of 2.7, and a duration of 180 µs. LS-DYNA was subsequently used to apply the forcing function as point-loads and record the resultant transient response of the media over a 80 mm axial and 10 mm azimuthal extent at a spatial sampling of 40 nodes/mm. These displacement profiles were then applied to scatterers in FIELD II to simulate ultrasonic tracking using tracking parameters matched to the sequences used for clinical acquisitions. The temporal response was tracked at a PRF of 10 kHz for a duration of 10 ms after the “push”. The simulated tracked echo signals were stored as radio-frequency (RF) data and demodulated to IQ data prior to displacement estimation. Five speckle realization were simulated for each Young’s modulus.

4.2.3 Displacement Estimation

Axial displacement profiles, captured in the IQ data, were computed using Loupas’ phase-based estimator (Loupas et al., 1995). This process was performed in an incremental fashion by comparing the phase-shifts between successive time points (i.e., 1→2, 2→3, 3→4...) and then cumulatively summing the result to yield displacements as a function of time. Cumulative displacements were then averaged over a 5-λ axial kernel (1.92 mm). This process was performed independently for each azimuthal angle. Velocity traces as a function of time were computed by differentiating the displacement profiles. The frequency spectra of displacement and velocity data
were computed using a 20,000-point fft function in MATLAB (The MathWorks Inc.,
Natick, MA)

4.2.4 Motion Filtering

Two approaches towards suppressing intrinsic cardiac motion were evaluated in this
work: polynomial filtering and high-pass filtering.

In polynomial filtering, cardiac motion is estimated by fitting measured displace-
ments within two temporal windows, before (“pre”) and after (“post”) the ARF
excitation, using a polynomial of a fixed order. This model is then subtracted off
the measured displacement trace to isolate the ARF-induced motion. This process
can be parameterized by: i) order of the polynomial, ii) temporal positions of the
“pre” and “post” windows ($t_{pre}$ and $t_{post}$), and iii) the temporal length of the “pre”
and “post” windows ($t_{win}$). These are illustrated in Figure 4.1. For this analysis,
$t_{win}$ was chosen to be identical for both windows; window lengths of 1, 3, and 5 ms
were evaluated here. $t_{pre}$ was fixed at -1 ms and $t_{post}$ was varied from 5 to 9 ms
in 1 ms increments. These time-points are defined with reference to the “push” at
t=0 ms. 1st- and 2nd-order polynomials i.e., linear and quadratic were evaluated in
this analysis.

In contrast, high-pass filtering aims to separate intrinsic cardiac motion and ARF-
induced motion in the frequency domain. It is implemented using a 3rd-order high-
pass Butterworth filter and parametrized using only the cutoff frequency. High-pass
filters were applied in both the forward and reverse direction to eliminate phase
distortions. Cutoff frequencies in the range of 5-150 Hz were evaluated in this study.

The performance of various motion filters was compared using the spatio-temporal
distribution of displacement data within the IVS on M-mode ARFI images i.e., M-
mode ARFI images generated using displacement profiles after application of a spe-
cific motion filter. M-mode ARFI images were reconstructed from the in vivo M-
Figure 4.1: The blue line represents a measured displacement profile which is a combination of ARF-induced motion and intrinsic cardiac motion. The gray bands indicate the temporal positions of windows used for the fitting operation. The solid and dashed black lines represent the push and the time-point used to generate the ARFI image, respectively. $t_{\text{post}}$ and $t_{\text{pre}}$ indicate the leading and trailing edges of the “post” and “pre” windows, respectively and $t_{\text{win}}$ is the window length.

Mode IQ data. The 5-second window (over which M-mode IQ data were acquired) was divided into 175 ensembles each spanning 28.5 ms. The middle time-point of each ensemble was defined to be the location of the “push” and considered to be $t=0$ ms (within the ensembles). Raw displacement profiles were computed using the raw M-mode IQ data as described above. Motion filters were then applied to the raw displacement profiles and M-mode ARFI images were reconstructed by taking the difference of two time-points; 1.5 ms after the “push” and the last time-point prior to the “push” for each of the 175 ensembles. Displacements on M-mode ARFI images greater than $\pm \lambda/10$ ($\pm 38.5 \mu$m) were considered to be outliers and excluded from the analysis.

Three metrics were used to assess the signal quality of M-mode ARFI images: accuracy, precision, and variability. Accuracy was evaluated based on the bias in M-mode ARFI images and was quantified as the mean of the spatio-temporal displacement distribution within the IVS. Precision was evaluated based on the statistical spread in M-mode ARFI images and was quantified using the standard deviation of the spatio-temporal distribution of displacements within the IVS. Lastly, variability,
which was designed to capture consistency over multiple datasets, was quantified as the standard deviation of the bias across the twenty datasets spanning five volunteers, two views, and two repeated acquisitions.

Accuracy was also evaluated for both types of motion filters using the raw *in vivo* data, i.e., in the absence of a “push”, as well as in the presence of calibrated, artificially introduced “pushes” from the FE simulations. ARF-induced motion was introduced by adding simulated displacements on to each ensemble of the displacement profiles prior to motion filtering and reconstruction of the M-mode ARFI images. ARF-induced displacements for two different Young’s moduli, 36 and 3 kPa, were used to model systole and diastole, respectively. For each Young’s modulus, two “push” magnitudes, 2 and 10 µm, were investigated. “Push” magnitude was scaled with reference to the ARF-induced displacement at the time-point being interrogated in the ARFI image i.e., 1.5 ms.

4.2.5 Temporal Coherence and Jitter Computation

Temporal coherence was used to characterize the decorrelation of myocardial speckle due to lateral, elevational, or rotational motion as well as the presence of thermal noise in the IQ data. It was measured over all pixels in depth, within narrow time windows (2-10 ms) and based on the peak correlation coefficient \( \rho \) of the normalized cross-correlation (NCC) function at each time-point in the specified window with respect to the first time-point (i.e., in an anchored sense). NCC was performed on RF data (remodulated from IQ to a sampling rate of 80 MHz) using a 5-\( \lambda \) kernel (1.92 mm) and a \( \lambda/2 \) axial search region in either direction (axially). Cumulative displacement estimates for the same data were used to reposition the search region so as to compensate for large axial displacements i.e., greater than \( \lambda/2 \). The NCC operation was also used to compute displacements (referenced to the first time-point); these were used to estimate jitter. Peak hopping artifacts corresponding to \( \lambda/2 \) and \( \lambda \)
shifts were compensated for prior to jitter computation. Jitter, then, was calculated as the standard deviation of the measured, peak hop corrected displacements over time (within the temporal windows) and used to capture the uncertainty in the displacement estimation process. Measured jitter was compared to theoretical jitter as predicted by the Cramér-Rao Lower Bound (CRLB). Temporal coherence and jitter were computed over the cardiac cycle at a sampling rate of 35 Hz i.e., temporal windows were evenly spaced every 28.5 ms.

4.3 Results

4.3.1 Myocardial Motion

Figure 4.2 illustrates B-mode images, myocardial velocity traces within the IVS (and corresponding ECG signals), and their spectra for both PLAX and PSAX. The velocity data at each time represents the mean over the depth extent of the IVS and across the simultaneously acquired azimuthal angles. The peak velocities were observed to be in the range of ±75 to ±90 mm/s. They are highly repeatable in their shape from beat-to-beat but vary between the two views. In both views, peak velocities are observed around the R-wave and following the T-wave. Late-diastole (latter half of the T-P interval) exhibits relatively slow motion. The spectra represent the average over the three cardiac cycles. They suggest that the strongest (i.e., highest magnitude) motion is confined to the lower end of the frequency spectrum; this trend is consistent across the two views. In these examples, the frequency content decays roughly linearly up to 100 Hz and then levels off around -50 dB.

Figures 4.3 and 4.4 show velocity profiles, ECG traces, and spectra (of velocity data) for two repeated acquisitions (columns) for five volunteers (rows) in PLAX and PSAX, respectively. The data represented in these figures span a range of peak velocities, specific morphology, as well as heart rates. In general, all acquisitions within a fixed view, i.e., PLAX versus PSAX, look similar to each other compared to
Figure 4.2: (a,b) B-mode images in parasternal long axis (PLAX) and parasternal short axis (PSAX) views. The green box indicates the position of the transmit focus which was placed over the interventricular septum (IVS). (c,d) Velocity as a function of time, averaged over depth within the IVS and the corresponding ECG trace over three cardiac cycles. (e,f) Mean spectra of myocardial velocities over three cardiac cycles. Velocity profiles show similar morphology from beat-to-beat but differ significantly between the two views. The frequency content in PLAX and PSAX, however, are roughly identical.

Ones in the other view. The patterns represented in the velocity data are also highly repeatable from beat-to-beat as evidenced by their alignment with ECG landmarks. However, substantial variability is observed not only across volunteers but also between repeated acquisitions on the same volunteer. Despite these dissimilarities, the spectra of velocity data showed largely consistent trends of a sharp decrease below 100 Hz and then a plateau between -40 and -60 dB.

Figure 4.5 depicts the aggregate spectra for all acquisitions and volunteers in the two views. These spectra exhibit good consistency across all acquisitions, volunteers, as well as views. Mean and standard deviation of the magnitude of the spectra at few relevant frequencies for each view are provided in the Table 4.1.
Figure 4.3: Repeatability of velocity profiles and spectra of the IVS within and across volunteers in PLAX. Rows represent five different volunteers and columns represent two repeated acquisitions. The red and blue traces on the spectra indicate the two acquisitions.

Table 4.1: Magnitude (in dB with respect to the peak) of myocardial (IVS) velocity signals as a function of frequency in PLAX and PSAX.

<table>
<thead>
<tr>
<th></th>
<th>15 Hz</th>
<th>50 Hz</th>
<th>100 Hz</th>
<th>200 Hz</th>
<th>400 Hz</th>
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<tbody>
<tr>
<td>PLAX</td>
<td>-17.09±8.68</td>
<td>-31.43±6.24</td>
<td>-36.29±4.75</td>
<td>-41.14±5.89</td>
<td>-45.64±6.34</td>
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<tr>
<td>PSAX</td>
<td>-15.94±4.67</td>
<td>-30.48±2.87</td>
<td>-42.77±6.45</td>
<td>-48.05±3.12</td>
<td>-52.07±5.98</td>
</tr>
</tbody>
</table>

PLAX = Parasternal Long Axis
PSAX = Parasternal Short Axis

64
Figure 4.4: Repeatability of velocity profiles and spectra of the IVS within and across volunteers in PSAX. Rows represent five different volunteers and columns represent two repeated acquisitions. The red and blue traces on the spectra indicate the two acquisitions.

4.3.2 ARF-induced Motion

Simulated and tracked ARF-induced on-axis displacements as well as velocities in elastic materials for a range of Young’s moduli relevant to myocardium are shown in Figure 4.6(a,b). These traces represent the average over a 5 mm axial window around the focus (50 ms) and five speckle realizations. ARF-induced displacement profiles follow the expected displacement-recovery trend with a rapid acceleration to peak displacement immediately following the “push” and a slower decay back to baseline (0 µm, in this case) over a duration of 10-15 ms. As anticipated, for a constant “push” magnitude and duration, peak displacement as well as time required to
achieve peak displacement were inversely correlated with Young’s modulus. Across speckle realizations, mean and standard deviation of peak displacements ranged from $14.32 \pm 1.02 \mu m$ for 3 kPa to $3.83 \pm 0.26 \mu m$ for 36 kPa. Across Young’s moduli, time-to-peak-displacement varied from 1.3 to 0.4 ms. Velocity traces achieved peak positive values prior to peak displacement, exhibited negative values during the slow recovery before returning to baseline. Peak ARF-induced velocities, across speckle realizations, were calculated to be of $21.01 \pm 2.63 \text{ mm/s}$ for 3 kPa and $15.21 \pm 1.64 \text{ mm/s}$ for 36 kPa.

Figure 4.6(c,d) show frequency spectra corresponding to the displacement and velocity data, respectively. Spectra of displacement signals show a strong DC component i.e., peak at 0 Hz and decay roughly linearly with frequency. Velocity spectra, on the other hand, have a null at DC, rise quickly and remain relatively stable in the range of 100-500 Hz. Subtle variations between the spectra corresponding to different Young’s moduli can be observed. In general, higher Young’s moduli show flatter spectra with substantial high frequency content. Table 4.2 presents the magnitude of displacement and velocity spectra at a few relevant frequencies.
Figure 4.6: (a,b) Simulated on-axis displacement and velocity profiles for a range of semi-infinite, elastic media. (c,d) Frequency domain representations of the displacement and velocity data.

Table 4.2: Magnitude (in dB with respect to the peak) of simulated ARF-induced motion as a function of frequency for displacement and velocity data.

<table>
<thead>
<tr>
<th></th>
<th>15 Hz</th>
<th>50 Hz</th>
<th>100 Hz</th>
<th>200 Hz</th>
<th>400 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Displacement Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 kPa</td>
<td>-0.22</td>
<td>-2.39</td>
<td>-6.57</td>
<td>-11.19</td>
<td>-18.90</td>
</tr>
<tr>
<td>12 kPa</td>
<td>-0.10</td>
<td>-1.11</td>
<td>-3.97</td>
<td>-6.31</td>
<td>-11.29</td>
</tr>
<tr>
<td>36 kPa</td>
<td>-0.09</td>
<td>-0.77</td>
<td>-1.38</td>
<td>-5.44</td>
<td>-7.45</td>
</tr>
<tr>
<td><strong>Velocity Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 kPa</td>
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<td>-4.40</td>
<td>-2.58</td>
<td>-1.21</td>
<td>-2.91</td>
</tr>
<tr>
<td>12 kPa</td>
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<td>-4.75</td>
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<td>-0.07</td>
</tr>
<tr>
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<td>-21.81</td>
<td>-12.11</td>
<td>-6.72</td>
<td>-4.77</td>
<td>-0.79</td>
</tr>
</tbody>
</table>
4.3.3 Characterization of Signal Quality versus Motion Filter Parameters

Figure 4.7 illustrates the performance of various motion filters characterized in this analysis on a representative dataset in the absence of a “push”. Performance of the filters varies, not only with the choice of filter parameters, but also as a function of the cardiac cycle. The high-pass filter with a cutoff of 15 Hz, shown in Figure 4.7(c), does a reasonable job of suppressing intrinsic cardiac motion in late-diastole, but is less effective around the QRS complex. Similar results are observed for the linear polynomial filter, shown in Figure 4.7(e). The high-pass filter with a cutoff of 75 Hz and the quadratic polynomial filter, show in Figure 4.7(d) and (f), respectively, are more effective at suppressing cardiac motion over the entire cardiac cycle. Performance of the motion filters, while dependent on cardiac phase, was found to be consistent from beat-to-beat. Given this observation, accuracy and precision of motion filters was analyzed separately for systole and diastole and averaged over consecutive beats. In this context, systole was defined as starting slightly before the R-wave and ending after the end of the T-wave while diastole was defined as the latter half of the T-P interval.

Figure 4.8 illustrates the trends in bias and statistical spread of the various motion filters analyzed across a range of parameter settings. Performance of the filters in systole and diastole is presented separately in purple and gold, respectively. The thin lines represent individual datasets while the thick lines depict the mean over all datasets. The ideal filter has low bias (high accuracy), i.e., mean of displacements close to 0 $\mu$m (in the absence of a “push”), as well as low statistical spread (high precision), i.e., standard deviation of displacements close to 0 $\mu$m). Furthermore, the ideal filter would perform equally well across all phases of the cardiac cycle and exhibit low variability, i.e., consistent performance, across volunteers and acquisitions.

High-pass filters (Figure 4.8(a,b)) exhibit low bias in systole as well as diastole
Figure 4.7: (a) B-mode image in PSAX. (b) M-mode image corresponding to the mid-line of the B-mode (shown as the dotted green line) over four cardiac cycles. (c-f) M-mode with a semi-transparent overlay of the ARFI image. Displacement data are shown in color. (c,d) show performance of high-pass filters with cutoffs of 15 Hz and 75 Hz, respectively. (e,f) show linear and quadratic polynomial filters, respectively. For the polynomial filters, $t_{win}$ was 2 ms, $t_{pre}$ was -1 ms, and $t_{post}$ was 6 ms. Performance of the filters varies, not only with the choice of filter parameters, but also as a function of the cardiac cycle.

beyond 25 Hz; mean absolute bias across all datasets in the frequency range of 25-150 Hz was found to be $< 0.06 \mu m$. Statistical spread decreases with cutoff frequency in both phases. Diastole, however, has a faster drop-off. At 75 Hz, the spread for high-pass filters was found to be is 5.28 $\mu m$ in systole and 4.05 $\mu m$ in diastole. The same at 25 Hz was 8.18 $\mu m$ in systole and 5.01 $\mu m$ in diastole. Variability of high-pass filters decreases with cutoff frequency. In systole, diastole, respectively, the variability was measured to be 0.98, 0.39 $\mu m$ at 25 Hz, 0.33, 0.21 $\mu m$ at 75 Hz, and
Figure 4.8: Accuracy (bias), precision (spread), and variability (consistency) of high-pass and polynomial filters for a variety of filter parameters in systole and diastole in the absence of an ARF-excitation. (a,b) show trends of bias and spread, respectively, for high-pass filters as a function of cutoff frequency. (c,d) show trends of the same for linear polynomial filters as a function of position of the “post” window ($t_{post}$) grouped by window length ($t_{win}$). (e,f) show similar trends for the quadratic polynomial filters. The thin purple lines represent systolic phase of individual acquisitions while the thin gold lines represent the diastolic phase. The thick purple and gold lines show the means across all acquisitions.

0.14, 0.20 $\mu$m at 125 Hz.

Linear polynomial filters (Figure 4.8(c,d)), on average, exhibit a small but systematic positive bias that increases with window position ($t_{post}$) and is stronger in systole compared to diastole. For a $t_{win}$ of 1 ms (left group), mean bias is systole was found to be 0.12 $\mu$m at a $t_{post}$ of 5 ms and 0.35 $\mu$m at a $t_{post}$ of 9 ms; the same for a $t_{win}$ of 5 ms (right group) was 0.14 $\mu$m at a $t_{post}$ of 5 ms and 0.39 $\mu$m at a $t_{post}$ of 9 ms. Statistical spread, on the other hand, increases roughly linearly with $t_{post}$ in both cardiac phases and was higher in systole. These trends were observed for all window lengths ($t_{win}$). The spread achieved a minimum value in systole, diastole, respectively, of 6.33, 4.52 $\mu$m for $t_{win}$/$t_{post}$ combination of 1/5 ms. While the magnitude of bias and spread are comparable to the high-pass filters, the performance
of linear polynomial filters across volunteers and acquisitions is highly inconsistent. Variability was observed to increase dramatically with $t_{\text{post}}$ for all values of $t_{\text{win}}$. For the $t_{\text{win}}/t_{\text{post}}$ combination of 1/5 ms, where bias and spread were minimized, the variability was measured to be in 0.41 $\mu$m in systole and 0.24 $\mu$m in diastole.

Quadratic polynomial filters (Figure 4.8(e,f)) show low bias (<0.09 $\mu$m) across all parameter combinations in both systole and diastole. The statistical spread of quadratic polynomial filters follows similar trends to linear polynomial filters; it is higher in systole compared to diastole and increases gradually with $t_{\text{post}}$ as well as with $t_{\text{win}}$. For $t_{\text{win}}/t_{\text{post}}$ of 1/5 ms (leftmost configuration), the spread is 5.19 $\mu$m in systole and 4.17 $\mu$m in diastole. On the other end (rightmost configuration), $t_{\text{win}}/t_{\text{post}}$ of 5/9 ms, the spread is 6.86 $\mu$m in systole and 4.65 $\mu$m in diastole. Variability of quadratic polynomial filters was observed to be substantially better compared to polynomial linear filters. Minimum variability was measured to be 0.21 and 0.20 $\mu$m in systole and diastole, respectively, for a $t_{\text{win}}/t_{\text{post}}$ of 1/5 ms (leftmost configuration).

### 4.3.4 Performance of Motion Filters in the presence of ARF-Induced Motion

Figure 4.9 illustrates trends in absolute and relative changes in peak displacement as well as displacement at 1.5 ms for simulated ARF-induced on-axis motion as a function of cutoff frequency of a high-pass filter. Trends are shown for all simulated Young’s moduli in the range of 3-36 kPa. Both peak displacement and displacement at 1.5 ms were found to decrease monotonically with an increase in the cutoff frequency resulting in a downward bias in the measured displacement after motion filtering when using a high-pass filter. The trend was consistent across all Young’s moduli. However, for a fixed cutoff frequency, the magnitude of the bias was larger for lower Young’s moduli. This dispersion in the magnitude of the bias was found to be more prominent in peak displacement compared to displacement at 1.5 ms. At 75 Hz, the bias in the peak displacement for 3 kPa and 36 kPa was -7.78\% and
Figure 4.9: Trends of (a) peak displacement and (b) displacement at 1.5 ms as a function of cutoff frequency of the high-pass filter for various Young’s moduli. (c,d) illustrate relative change of the displacements shown in (a,b) with respect to their values in the absence of a filter. The high-pass filters lead to a consistent downward bias in measured displacement at the peak as well as at 1.5 ms.

-0.72%, respectively; the same for displacement at 1.5 ms was -9.43% at 3 kPa and -4.41% for 36 kPa.

This effect was also observed when ARF-induced displacements were combined with cardiac motion. Simulated displacement-recovery profiles were added onto displacement data derived from the in vivo M-mode IQ data. ARF-induced displacements in systole and diastole were modeled using simulated data from 3 kPa and 36 kPa, respectively. These combined displacement profiles were then motion filtered using high-pass filters with cutoffs between 5 and 150 Hz as well as quadratic polynomial filters for a number of window length/position combinations. Filtered displacement profiles were processed to generate M-mode ARFI images to analyze their spatio-temporal distributions within the IVS. Thus, accuracy (bias) of the motion filters could be assessed in the presence of a known ARF-induced displacement. Bias for systolic and diastolic windows were evaluated for displacement magnitudes of 2 and 10 µm.

The results of this analysis are shown in Figure 4.10. The downward bias that
Figure 4.10: Displacement bias for (a) high-pass and (b) polynomial filters in the presence of simulated ARF-induced motion. Systole (purple) and diastole (gold) were modeled using 36 kPa and 3 kPa, respectively. Bias for displacement magnitudes of 2 µm are shown using closed circles while the same for a magnitude of 10 µm are shown in open circles. The dotted-lines indicate the “true” value of the added displacement. Curves represent mean displacement measured on M-mode ARFI images (for each cardiac phase) across volunteers and acquisitions as a function of cutoff frequency in the case of high-pass filters and window length/position combinations for polynomial filters.

Increases progressively with cutoff frequency is observed in all four curves in Figure 4.10(a). For a fixed “push” magnitude, the bias is observed to be more pronounced in diastole (3 kPa) compared to systole (36 kPa) - this observation is consistent with the results presented in Figure 4.9. Additionally, the bias, in an absolute sense (i.e., in units of microns), is more pronounced for the stronger “push” (10 µm). This suggests that it is a relative effect that scales with “push” magnitude.

For quadratic polynomial filters, Figure 4.10(b), there was no systematic trend of bias across combinations of window length/position. Bias was minimal in both systole and diastole for the low displacement (2 µm) case. For high displacement (10 µm), a slight downward bias was observed in diastole; this bias decreased in magnitude for higher t_{post} as well as higher t_{win}. In systole, there was a subtle overestimation of displacement for t_{win} of 1 ms.
Figure 4.11: (a) M-mode image of the IVS in PSAX. Myocardial speckle shows varying degree of temporal stability across the cardiac cycle. (b) illustrates a stable speckle pattern while (c) displays rapid change, likely due to non-axial motion. (d) Peak correlation coefficients ($\rho$) as a function of time (with respect to the first time-point) for the two windows, averaged over depth within the IVS. Error bars represent standard deviation through depth.

4.3.5 Relationship between Temporal Coherence and Jitter

Temporal coherence for two temporal windows at different points in the cardiac cycle are shown in Figure 4.11. The speckle pattern depicted in Figure 4.11(b) (outlined in green) remains stable over the 10 ms and thus shows high $\rho$ values (close to 1) and low variance through depth. The minimum correlation coefficient ($\rho_{\text{min}}$) in this case was found to be $0.97 \pm 0.05$. In contrast, the speckle pattern in Figure 4.11(c) (outlined in red) shows substantial change over the same duration; this is captured as a progressively decreasing $\rho$ as well as increased variance in the axial dimension. $\rho_{\text{min}}$ for this window was $0.51 \pm 0.21$. Temporal coherence curves, on average, were found to be monotonic. However, trends for individual spatio-temporal pixels could show complex behavior.
Temporal coherence data can be displayed in a variety of ways to gain an intuitive sense of the level of decorrelation within the myocardium over the cardiac cycle. Two possible ways to depict temporal coherence are illustrated in Figure 4.12. The spatio-temporal distribution of $\rho$ at a fixed time point (5 ms, in this example) is shown in Figure 4.12(b). The corollary is shown in Figure 4.12(c), which depicts the spatio-temporal distribution of time at which the temporal coherence function achieves a specific $\rho$ value (0.95 in this example). The two displays provide complementary information and align well with each other as well as landmarks on the ECG trace. Late-diastole (latter half of the T-P interval) is characterized by high temporal coherence i.e., stable speckle while the period surrounding the QRS complex, which is characterized by active contraction and ejection, shows low temporal coherence i.e., significant lateral, elevational, and rotational motion.
Figure 4.13 depicts the relationship between temporal coherence and displacement estimation jitter and their variations over the cardiac cycle for temporal windows with lengths varying from 2 to 10 ms. $\rho_{\text{min}}$ and jitter were computed over the cardiac cycle at 35 Hz. The curves presented here represent the mean over depth within the IVS and were median filtered through time (over the cardiac cycle) using a filter with a 5-sample (142 ms) kernel. $\rho_{\text{min}}$ and jitter are inversely correlated with each other and demonstrate similar trends from one beat to the next. Both sets of curves indicate a monotonic relationship with window length i.e., $\rho_{\text{min}}$ decreases for larger window lengths and vice versa for jitter. The rate of change of each quantity with window length, however, varies depending on the phase of the cardiac cycle. In late-diastole, $\rho_{\text{min}}$ as well as jitter are nearly identical for all window lengths. However, in the R-T interval, both quantities vary significantly as a function of window length. These trends, however, are smooth, consistent, and repeatable through time over the cardiac cycle as well as over multiple cycles.

The empirically measured relationship between temporal coherence and displacement estimation jitter and its comparison to the theoretical limit defined in the CRLB is presented in Figure 4.14. The CRLB curve was derived using a center frequency of 4 MHz, fractional bandwidth of 80%, kernel length of 5-$\lambda$, and a channel signal-to-noise ratio (SNR) of 60 dB. As also observed in Figure 4.13, $\rho$ and jitter follow an inverse relationship. Measured jitter was generally found to be higher than that predicted by the CRLB, except in the case of high temporal coherence i.e., $\rho > 0.9$. These low jitter estimates could be an artificially lower due to averaging over depth within the IVS.

4.4 Discussion

Motion tracking algorithms in ultrasound can broadly be classified into two groups: ones that operate on raw ultrasound echo signals (i.e., beamformed RF or IQ data)
Figure 4.13: (a,b) M-mode images in PLAX and PSAX, respectively along with the ECG trace. (c,d) Corresponding temporal coherence data for the septum, characterized by minimum correlation coefficient ($\rho_{\text{min}}$), for various temporal window lengths. (e,f) Displacement estimation jitter, measured within the septum, over matched temporal windows. $\rho_{\text{min}}$ and jitter demonstrate an inverse relationship and repeatable trends over consecutive beats.

Figure 4.14: Comparison of empirically measured temporal coherence and displacement estimation jitter against the theoretical limit defined in the Cramér-Rao Lower Bound (CRLB).
and ones that operate on processed ultrasound images (i.e., envelope-detected data). The former utilize the high spatial frequency information captured in the RF or the complex phase of the IQ signals and compute displacements using normalized cross correlation (NCC) in the case of RF (Bonnefous and Pesque, 1986) or phase-based autocorrelation algorithms in the case of IQ (Kasai et al., 1985; Loupas et al., 1995). The latter take advantage of the inherent texture of processed ultrasound images or speckle and extract motion using correlation-based block-matching (Blessberger and Binder, 2010) or non-rigid (elastic) image registration (Elen et al., 2008). These are commonly referred to as “speckle tracking” techniques.

NCC and phase-based techniques were originally developed to track blood flow in pulse wave- and color-Doppler modes. They were adapted to capture tissue motion and were central to the development of tissue-Doppler imaging (Heimdal et al., 1998) as well as in early implementations of strain/strain-rate imaging (D’hooge et al., 2000). More recently, speckle tracking techniques have gained popularity for myocardial strain imaging since they can easily be extended to track motion in multiple-dimensions (Byram et al., 2010). There is, however, a fundamental trade-off between the ability to track 2D or 3D motion and precision of displacement estimation. Speckle tracking techniques utilize detected image data, thus their precision is tied to the size of ultrasonic speckle and is generally on the order of millimeters in the context of echocardiography. In contrast, phase-based techniques capture local changes in the phase of the RF or IQ echo signals through depth and thus allow for measurement of motion with micron-level precision. ARFI and SWEI necessitate the use of NCC or phase-based techniques due to the small magnitudes of ARF-induced displacements (0-20 µm). The major drawback of NCC and phase-based techniques, however, is that they are limited to tracking only the axial component of motion. Non-axial components such as lateral, elevational, and rotational motion lead to decorrelation of the echo signals and consequently an increase in the uncertainty of
axial displacement estimates (Walker and Trahey, 1995).

MRI-based measurement of cardiac motion has shown that the myocardium, not only exhibits high velocity motion, but also that the magnitude of motion varies substantially with direction (Delfino et al., 2008). Highest velocities are measured in the longitudinal dimension (base-to-apex), followed by the radial dimension (changes in wall thickness), and lastly in the circumferential dimension (rotation around the central axis of the heart). For M-mode imaging of the IVS in PLAX as well as PSAX, the axial dimension of ultrasound beam corresponds with the radial dimension in cardiac coordinates. In PLAX, the lateral, and elevational dimensions align with the longitudinal and circumferential dimensions, respectively; these are reversed in PSAX. These relationships are not exact and can change slightly depending on the direction of the transmit beam as well as subtle changes in the angle of the myocardial walls over the cardiac cycle.

A thorough analysis of regional (transmural) as well as temporal (through the cardiac cycle) variations of micron-level motion in the IVS and their relationship to cardiac events such as valve closure has been reported on by Kanai et al. (Kanai and Koiwa, 2001). The results presented herein (Figure 4.2) are consistent with their observations. The temporal trends of myocardial velocity exhibit good repeatability from beat-to-beat and align well with the ECG signal. Ventricular systole (QRS complex) was characterized by high magnitude motion while late-diastole (latter half of T-P interval) exhibited lower velocities. These trends, however, showed large qualitative variations from acquisition-to-acquisition and from volunteer-to-volunteer, as illustrated in Figure 4.3 and 4.4. This result can be attributed to subtle variations in the angle between the IVS and the axial dimension of the ultrasound beam which could arise from using a fixed direction for the M-mode acquisition (down to middle of the B-mode FOV) as opposed to aligning the beam direction with anatomical landmarks. It also demonstrates the directional (angular) sensitivity of tracking my-
ocardial velocities using phase-based techniques and the level of caution necessary
in order to extract reliable quantitative information from these measurements.

The frequency content of cardiac motion, however, was found to be fairly consist-
tent across beats, acquisitions, views, and volunteers. This consistency is illustrated
in Figure 4.5 and Table 4.1. Velocity spectra decayed rapidly from DC (0 Hz) to
about 100 Hz and then plateaued between -40 to -60 dB, thus supporting the hy-
pothesis that the frequency content of intrinsic physiological motion is concentrated
towards the lower end of the frequency spectrum.

In contrast, the frequency content of ARF-induced motion retains significant en-
ergy at higher frequencies, as shown in Figure 4.6. ARF-induced displacements have
a peak at DC due to their positive mean value and decay relatively slowly compared
to cardiac motion. ARF-induced velocities have a null at DC and peak at frequen-
cies higher than 150 Hz. Frequency content of ARF-induced motion can depend on
a variety of factors such as Young’s modulus, duration of the excitation pulse, and
spatial extent of the ARF-excitation (Palmeri et al., 2014). “Push” pulses that are
narrower in space and shorter in time are closer to the ideal impulsive excitation
and generate higher frequency content. Tracking parameters such as beam-width
and pulse repetition frequency can also impact the spectral range over which motion
is faithfully represented. While there are subtle variations between the frequency
content of ARF-induced motion as a function of Young’s modulus, these differences
are significantly smaller compared to the difference between the frequency content
of cardiac motion and ARF-induced motion.

The comparative performance analysis of the two families of motion filters (Fig-
ure 4.8) suggests that: i) filter performance varies significantly between systole and
diastole, ii) quadratic polynomial filters outperform linear polynomial filters, iii)
high-pass filters and quadratic polynomial filters show similar performance.

Both sets of polynomial filters trended towards higher bias, spread, and variabil-
ity for longer window lengths ($t_{\text{win}}$) as well as for farther post-excitation window position ($t_{\text{post}}$). This could be attributed to the increase in displacement estimation jitter which rises progressively with time due to speckle decorrelation (Figure 4.13). Thus, the farther time-points could lead to erroneous model-fits thereby degrading the performance of polynomial filters. Quadratic polynomial filters, however, showed much higher stability across parameter combinations and more uniform performance between the two cardiac phases suggesting that they better represent myocardial motion over these temporal windows. Their performance was also relatively unchanged in the presence of ARF-induced motion (Figure 4.10). While bias was marginally higher for the 10 $\mu$m cases, there was no clear trend in this bias with respect to parameter combinations.

In the case of high-pass filters, the bias is negligible beyond 25 Hz in the absence of ARF-induced motion in both phases. The statistical spread decreases faster (as a function of cutoff frequency) in diastole compared to systole suggesting that the systolic phase has higher frequency content compared to the diastolic phase. This aligns well with the observation of higher myocardial velocities in the systolic phase. Above 75 Hz, the spread in both phases, however, is nearly identical and similar the optimal quadratic polynomial filter combination ($t_{\text{win}}/t_{\text{post}}$ of 1/5 ms).

In the presence of ARF-induced motion, high-pass filters show a downward bias that increases with cutoff frequency. This was demonstrated using FE data (Figure 4.9), as well as by combining in vivo motion profiles with simulated ARF-induced motion (Figure 4.10). This bias is a consequence of the high-pass filter suppressing part of the frequency content of the ARF-excitation; it impacts materials with lower Young’s moduli more since they have relatively higher low frequency content compared to materials with higher Young’s moduli. Thus diastolic displacements, while expected to be higher in magnitude, are likely to experience a stronger downward bias compared to systolic displacements. The magnitude of this bias, however,
is <10\% for cutoff frequencies below 75\,Hz. Additionally, the linear behavior of high-pass filters allows for compensation of this bias and recovery of the expected displacement.

Even for the optimal filter parameter configurations, the statistical spread of both filters remains high (around 5\,\mu m). This could be reduced using jitter filters through time that suppress the highest frequency components of tracked displacements (>1000\,Hz), by employing statistical outlier rejections schemes, or by using nonlinear operations such as spatio-temporal median filtering.

The main drawback of polynomial filters is that they require an assumption about when the ARF-induced motion is considered to be fully decayed. While assuming a $t_{\text{post}}$ of 5\,ms may be a decent assumption along the axis of the “push”, it is not the case for laterally offset tracking beams that are required in SWEI. The time (with respect to the “push”) at which shear waves appear and decay at laterally offset beams will certainly be later than the on-axis excitation and also depend on the location of the beam as well as the Young’s modulus of the material (which impacts the shear wave speed). Given the degradation in performance of polynomial filters with increasing $t_{\text{post}}$, they may not be well suited for this application. High-pass filters, on the other hand, are independent of “recovery-time” and perform as well as the optimal quadratic polynomial filter with the lowest $t_{\text{win}}/t_{\text{post}}$ combination of 1/5\,ms. Consequently, high-pass filters can be applied identically across all lateral beams and thus likely to perform equally well at suppressing intrinsic tissue motion at multiple lateral locations. Future work will aim to compare the performance of these filters at multiple, simultaneously-acquired lateral locations and study their impact on the estimation of shear wave speeds.

The aforementioned discussion addresses the ability to isolate ARF-induced axial displacement from measured axial motion; the effects of intrinsic tissue motion in other dimensions, however, must also be considered. While neither the magnitude
nor direction of lateral, elevational, or rotational motion may be measured using phase-based techniques, their impact on the uncertainty of axial displacement estimation can be gauged using the relationship between temporal coherence and jitter. As shown in Figure 4.11, temporal coherence captures the progressive decorrelation of speckle patterns in the myocardium for temporal windows lengths that are relevant for ARFI and SWEI (2-10 ms). On average, temporal coherence tends to be monotonic over these intervals and thus could be quantified using $\rho_{\text{min}}$; jitter is quantified as the standard deviation of axial displacements through time. The relationship of temporal coherence and jitter over the cardiac cycle can provide an adaptive indication of the varying noise-floor for axial displacement estimation as a function of window length (Figure 4.13).

ARFI, which only requires tracking for 2-4 ms to make a viable measurement, may experience maximum jitter levels on the order of 5-10 $\mu$m in systole. SWEI necessitates tracking of ARF-induced motion at multiple lateral locations for up to 6-10 ms. In this case jitter along each lateral line could be higher than 15 $\mu$m at later time-points, thereby severely complicating the task of tracking a propagating wave with decaying displacement amplitude. Jitter in late-diastole, however, was observed to be low across all window lengths suggesting that a SWEI measurement is most likely to yield a measurable result in this phase of the cardiac cycle.

While the CRLB places a fundamental limit on jitter for unbiased displacement estimators, better precision can be achieved using non-linear iterative algorithms (Pesavento et al., 1999) or biased Bayesian approaches to measure micron-level motion (Byram et al., 2013). Speckle decorrelation and consequently jitter could potentially also be reduced through multi-stage displacement estimation techniques that combine phase-based approaches with correlation-based block matching (Porras et al., 2014).
4.5 Conclusions

The effects of multidimensional intrinsic cardiac motion on the signal quality of transthoracic ARFI images were studied. To this end, three different analyses were performed. The goals of these were: i) to determine the frequency content of \textit{in vivo} myocardial motion and compare it to that of simulated ARF-induced motion for relevant Young’s moduli (3-36 kPa), ii) to characterize the performance of frequency-based motion filters versus polynomial motion filter, both in the presence and absence of ARF-induced motion, for a range of parameter configurations, and iii) to determine the impact of non-axial cardiac motion on speckle decorrelation and associated displacement estimation jitter through the cardiac cycle.

The conclusions of this work are:

i) The spectrum of myocardial motion was fairly consistent across the study population; it was found to be dominant at lower frequencies and decayed rapidly. The strength at 100 Hz was roughly -40 dB compared to the peak. In contrast, ARF-induced motion contained significant energy at high frequencies. Thus, frequency-based approaches could be used to distinguish cardiac motion from ARF-induced motion.

ii) Quadratic polynomial filters outperformed linear ones. High-pass filters performed at par with quadratic polynomial filters. Bias, precision, and variability (across datasets) were used to quantify performance. The performance of high-pass filters as a function of cutoff frequency was benchmarked against linear and quadratic polynomial filters for several window length/position combinations. While frequency-based filters have the advantage of being independent of assumptions about recovery of ARF-induced motion, they introduce a downward bias in measured displacements that increases with cutoff frequency.

iii) Temporal coherence of myocardial speckle was found to vary substantially
over the cardiac cycle and align well with empirically measured displacement estimation jitter. This relationship could potentially be used to adaptively determine the expected level of noise in acoustic radiation force-based applications.
Noninvasive Measurement of Dynamic Myocardial Stiffness using Acoustic Radiation Force Impulse Imaging

5.1 Introduction

Congestive heart failure (CHF) affects nearly 5.7 million people in the United States alone (Mozaffarian et al., 2016) and is projected to increase by 46%, impacting over 8 million over the next 15 years (Heidenreich et al., 2013). CHF can arise from a variety of root causes such as hypertension (Levy et al., 1996), coronary artery disease (Gheorghiade and Bonow, 1998), several forms of cardiomyopathy (McCrohon et al., 2003; Harris et al., 2006; Ng et al., 2005; Maron et al., 2006), as well as chemotherapy-induced cardiotoxicity (Kremer et al., 2001; Swain et al., 2003). In most cases, the structural and functional changes in the heart due to CHF are accompanied by alterations in the stiffness of the cardiac muscle (Watanabe et al., 2006; Borbély et al., 2005; Conrad et al., 1995; Zile et al., 2015; Westermann et al., 2008).
5.1.1 *Myocardial Stiffness and Cardiac Function*

Cardiac muscle or myocardium is an active tissue that exhibits complex changes in its mechanical properties over the cardiac cycle. These dynamics are induced by a combination of electrical, chemical, and mechanical stimuli that all impact cardiac function. Myocardial stiffness is considered to be one such important mechanical property and has traditionally been estimated using hemodynamic parameters such as pressure and volume which can be graphed in a parametric fashion over time to yield pressure-volume (PV) loops (Burkhoff et al., 2005).

Slopes of the end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) are used to estimate myocardial stiffness at the respective cardiac phases. These have been shown to be associated with the systolic and diastolic function of the heart, respectively (Sunagawa et al., 1983; Zile and Brutsaert, 2002). This analysis can also be extended to model dynamics of myocardial stiffness over the entire cardiac cycle using the concept of time-varying elastance (Suga and Sagawa, 1974). This model has been applied to study changes in the peak rates of ventricular pressure rise (during contraction) and fall (during relaxation) as a function of heart-rate, inotropic states, and loading conditions (Suga et al., 1973; Little, 1985).

PV loop analysis is widely considered to be the gold standard for the characterization of cardiac function. Myocardial stiffness estimates derived from PV loops are indirect in the sense that they require a closed-chamber and are dependent on the hemodynamic parameters. They provide a global estimate of chamber properties, and do not represent regional variations. While PV loop analysis provides a wealth of information to guide cardiovascular pathophysiological studies, their clinical utility is limited by their invasive nature. Tracking temporal changes in pressure and volume with high precision requires cardiac catherization and thus renders this technique...
unsuitable as a diagnostic procedure.

5.1.2 Noninvasive Measurement of Myocardial Stiffness

a noninvasive manner, have been the topic of significant research over the last two decades. They can be implemented using ultrasound (Doherty et al., 2013a) as well as magnetic resonance imaging (MRI) (Mariappan et al., 2010).

Magnetic resonance elastography (MRE) uses MRI to track waves induced in soft tissues due to externally-coupled mechanical actuators. These vibrations are tracked in all three-dimensional and fit to mechanical models to compute stiffness moduli. Through a combination of open- and closed-chest experiments on animals, MRE has been shown to capture cyclic trends of myocardial stiffness over the cardiac cycle (Kolipaka et al., 2010) as well as quantify changes in end-diastolic stiffness due to variations in loading conditions (Kolipaka et al., 2011) and end-systolic stiffness due to variations in contractility (Kolipaka et al., 2012). More recently, the diagnostic potential of MRE has been investigated in porcine models of amyloidosis (Arani et al., 2016), hypertension (Mazumder et al., 2017b), and myocardial infarction (Mazumder et al., 2017a; Arunachalam et al., 2018). Initial results have also been demonstrated on human volunteers (Sack et al., 2009; Wassenaar et al., 2016).

Ultrasound-based transient elastography methods such as acoustic radiation force impulse (ARFI) imaging and shear wave elasticity imaging (SWEI) have also been investigated in a variety of experimental settings. In open-chest experiments on canine and ovine subjects, both ARFI and SWEI have been demonstrated to be sensitive to temporal trends of myocardial stiffness through the cardiac cycle (Hsu et al., 2007; Couade et al., 2011). Similar results have also been presented using catheter-mounted intracardiac echocardiography probes (Hollender et al., 2012, 2013). ARFI has also been shown to be useful for near real-time monitoring of cardiac ablation procedures on human subjects (Bahnson et al., 2014). Short-term changes in ARFI-
and SWEI-derived myocardial stiffness in response to inotropic agents and variations in coronary perfusion pressure have also been demonstrated using rodent hearts in Langendorff set-ups (Pernot et al., 2011; Vejdani-Jahromi et al., 2015). ARFI- and SWEI-derived indices of dynamic myocardial stiffness have also shown to be well correlated to each other (Vejdani-Jahromi et al., 2016).

5.1.3 Acoustic Radiation Force Impulse (ARFI) Imaging

Ultrasound waves, when propagating through a medium, are partially absorbed. The absorption results in a transfer of momentum and the generation of acoustic radiation force (ARF); the magnitude of this force is linearly related to the time-integrated, local acoustic intensity over the pulse duration. In soft tissues, the resultant ARF for prolonged acoustic pulses, on the order of 50-500 µs, leads to a mechanical excitation or “push” in the form of a micron-level (1-30 µm) displacement in the direction of sound propagation, along the axis of the push beam as well as generation of shear waves in the orthogonal plane (Nightingale et al., 2003). These mechanical perturbations can be monitored using a subsequent sequence of short-duration, diagnostic ultrasound pulses (“tracks”) and used to discern the local mechanical properties of the tissue. Steering the push and track beams across a spatial extent allows for the interrogation of spatial variations in tissue stiffness (i.e., 2D ARFI or SWEI). Similarly, temporal variations in tissue stiffness can be measured by repeating the push and track pulses over time at a fixed spatial location (i.e., M-mode ARFI or SWEI).

For a fixed acoustic intensity and pulse duration, the magnitude of ARF-induced displacement is inversely proportional to tissue stiffness (Palmeri et al., 2006a). ARFI imaging exploits this relationship to yield relative estimates of tissue stiffness by tracking the displacement-recovery trend along or near the axis of the push beam for a duration of 1-3 ms after the push. SWEI, on the other hand, aims to measure absolute stiffness based on the shear wave speed and an assumed mechanical model.
Estimation of the shear wave speed requires tracking the displacements across a field-of-view in azimuth or elevation for 5-10 ms following the push. This proves to be a challenging task in cases where the background tissue is also moving, such as the heart which exhibits rapid, multi-dimensional motion. Additionally, the amplitude of shear waves decays with distance away from the axis of the push beam, making them increasingly difficult to track in stiff and highly attenuating media. Lastly, the curved geometry of the heart walls and spatial (transmural or base-to-apex) changes in the fiber orientation make it difficult to track the polarization of propagating shear waves at large azimuthal angles. These effects introduce noise and/or bias in shear wave speed estimates. Despite these challenges, implementations of SWEI for transthoracic imaging have shown promising preliminary results on human subjects. Song et al. demonstrated the feasibility of measuring the passive mechanical properties of myocardium at end-diastole using SWEI in pediatric volunteers (Song et al., 2016). Additionally, Villemain et al. showed changes of passive myocardial stiffness in adults as a function of age as well as differentiation between healthy volunteers and patients with hypertrophic cardiomyopathy (Villemain et al., 2018). However, transthoracic implementations of SWEI have been limited to a single phase of the cardiac cycle: end-diastole. In principle, SWEI could be used throughout the cardiac cycle. However, technical limitations related to tracking shear waves in rapidly moving and stiff materials have made the implementation of SWEI in other phases of the cardiac cycle challenging.

In contrast to SWEI, ARFI imaging uses higher amplitude on-axis displacements and requires a relatively short duration to compute a stiffness estimate. ARFI could be used to overcome some of the technical obstacles that impede successful tracking of shear waves in challenging imaging environments such as transthoracic echocardiography as well as in moving targets such as the myocardium across the full cardiac cycle. The primary goal of this study is to assess the feasibility of tracking dynamic
myocardial stiffness using M-mode ARFI through the cardiac cycle via transthoracic imaging windows. We also present ARFI-derived indices to characterize the temporal trends of myocardial stiffness, and analyze beat-to-beat repeatability and consistency in a cohort of healthy volunteers.

5.2 Methods

5.2.1 Sequence Design

Custom beam sequences were developed to acquire M-mode ARFI data on a clinical ultrasound scanner, Siemens Acuson SC2000™ (Siemens Medical Solutions Inc., Malvern, PA, USA), and implemented using an adult cardiac phased array, Siemens 4V1c. B-mode imaging was performed in a manufacturer-optimized setting native to the system with a maximum imaging depth of 100 mm, an azimuthal angular span of 90°, and at a frame-rate of 40 Hz. This mode was used for live image guidance; upon achieving the desired view, the M-mode ARFI sequences were initiated.

M-mode ARFI data were acquired in three configurations differentiated by the parameters of the tracking transmit beams. The first configuration used focused beams in the fundamental mode; this will henceforth be referred to as “fundamental-focused” (FF). The second two configurations employed pulse-inversion harmonic imaging using either a focused transmit beam, “harmonic-focused” (HF), or a plane wave transmission, “harmonic-plane” (HP). In all three cases, the ARF excitation (or push) was generated using a focused beam. In the focused configurations (FF and HF), the focal depth of the tracking transmit beam was set to be the same as that of the push beam, while in the plane wave configuration (HP) the focus of the tracking transmit was set to 1000 mm, so as to achieve a near-planar transmit wavefront. All other parameters of the three sequences were identical.

Parallel receive beamforming (Shattuck et al., 1984) was used to synthesize seven simultaneously-acquired and dynamically focused beams on receive. These were
uniformly spaced over a 0.4° angular span using a virtual apex of 300 mm behind the probe face. This configuration resulted in 70% spatial overlap of the -6 dB beamwidth between adjacent receive beams at a 50 mm focus and limited their azimuthal extent to within 1.16 mm on either side of the axis of the push beam.

Each of the three M-mode ARFI sequences was comprised of 175 ARFI ensembles that were repeated along the center-line of the B-mode field-of-view (FOV). Individual ARFI ensembles were 28.5 ms long and included a 300 µs push with 112 tracking pulses (56 before and after the push). The ensembles were temporally contiguous so as to achieve continuous tracking at a pulse repetition frequency (PRF) of 4 kHz and a push PRF of 35 Hz. Each M-mode ARFI sequence thus spanned 5 s.

Push beams were centered at a frequency of 2.8 MHz and focused between 45-65 mm, yielding F-numbers between 2.38 to 3.44. In the fundamental-focused (FF) configuration, the tracking was performed at a center frequency of 3.2 MHz. The two harmonic configurations (HP and HF) used a 2 MHz transmission with a receive frequency of 4 MHz. In the pulse-inversion harmonic cases, echoes from alternate transmit pulses were combined using the fully-sampled approach (Doherty et al., 2013b) to maintain the temporal sampling rate of 4 kHz. The mechanical index (MI) and the spatial-peak pulse-average intensity (I_sppa) for the push beams were measured to be below 1.65 and 430 W/cm², respectively. MI and I_sppa were computed using a fixed attenuation value of 0.5 dB/cm/MHz. The same voltage was used for push and track beams. The temperature rise at the face of the probe for individual M-mode ARFI sequences was measured to be under 3°C.

Table 5.1 provides a summary of the sequence parameters. A complete dataset was acquired over the span of 60 s and consisted of a B-mode cine clip and beam-formed in-phase and quadrature (IQ) data (i.e. focused, summed, and demodulated signals) for the three tracking configurations. The B-mode cine clip was used for anatomical reference while the raw M-mode echo data were used for displacement
estimation as well as computation of signal quality metrics.

Table 5.1: Parameters for M-mode ARFI Sequences.

<table>
<thead>
<tr>
<th></th>
<th>Push</th>
<th>Track</th>
</tr>
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<tbody>
<tr>
<td>Frequency</td>
<td>2.8 MHz</td>
<td>Fundamental: 3.2 MHz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harmonic: 2 MHz (transmit)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 MHz (receive)</td>
</tr>
<tr>
<td>Pulse Duration</td>
<td>300 µs</td>
<td>Fundamental: 0.7 µs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harmonic: 2.5 µs</td>
</tr>
<tr>
<td>Transmit Focus</td>
<td>45-65 mm</td>
<td>Focused: 45-65 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plane Wave: 1000 mm</td>
</tr>
<tr>
<td>Receive Configuration</td>
<td></td>
<td>7:1 parallel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apex = -300 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angular Span = 0.4°</td>
</tr>
<tr>
<td>Pulse Reposition Frequency</td>
<td>35 Hz</td>
<td>4 kHz</td>
</tr>
<tr>
<td>MI</td>
<td>&lt; 1.65</td>
<td>Fundamental: &lt; 1.66*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harmonic: &lt; 1.08*</td>
</tr>
<tr>
<td>$I_{sppa}$</td>
<td>&lt; 430 W/cm²</td>
<td>Fundamental: &lt; 494* W/cm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harmonic: &lt; 132* W/cm²</td>
</tr>
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</table>

MI = Mechanical index
$I_{sppa}$ = Spatial-peak pulse-average intensity
* Derived using transducer impulse response and measurements for the push beam.

5.2.2 Clinical Data Acquisition

The sequences described above were used to acquire data on twelve healthy volunteers with no history of cardiovascular disease at the out-patient Cardiology Clinic at Duke University Hospital. Imaging was performed by an experienced cardiac sonographer after receiving informed consent from study participants in accordance an IRB-approved protocol (Duke IRB Pro00032068). As part of recruitment into the study, participants were given an abbreviated cardiac ultrasound exam performed by the sonographer to screen for structural or functional abnormalities. All participants were found to be asymptomatic. No exclusions were made based on image quality. Study participants spanned an age range of 22 - 35 years and a body mass index (BMI) range of 20 - 24 kg/m². They showed heart-rates in the range of 48 - 98 bpm
and left ventricular ejection fractions in the range of 55–68%.

Data acquisition was performed in two standard transthoracic echocardiographic (TTE) views: parasternal long-axis (PLAX) and short-axis (PSAX). In both views, the myocardial wall of interest was the interventricular septum (IVS). Up to three repeated acquisitions were performed in each view. Study participants were not asked to hold their breath given the prolonged duration of the acquisitions. In addition to B-mode cine clips and raw M-mode echo data, trigger output signals from the ultrasound scanner (corresponding to each transmit event) and the electrocardiogram (ECG) were also acquired simultaneously. These signals were used to retrospectively align the M-mode ARFI acquisitions with the cardiac cycle. Imaging was performed in normal sinus rhythm and no arrhythmias were observed during or after ARFI acquisitions.

5.2.3 Data Processing

Beamformed IQ data for the M-mode ARFI sequences were acquired over axial range, time (spanning the 175 ensembles), and azimuthal angle (corresponding to the seven simultaneously-acquired receive beams). Data for the different azimuthal angles was processed independently. Figure 5.1(a,b) shows conventional B-mode and M-mode images in the PSAX view. The region-of-excitation (ROE) of the push beam is indicated by the green rectangle on the B-mode image. The M-mode image is presented for the central azimuthal angle over a 1200 ms segment and shows the IVS around a depth of 50 mm. The dotted green lines on the M-mode image indicate the temporal positions of ARF pushes. The ECG corresponding to the M-mode image is shown in Figure 5.1(c).

Axial displacements were computed using a phase-shift estimator (Loupas et al., 1995) and averaged over a 5-λ axial kernel, corresponding to a 1.92 mm axial extent. Incremental displacement estimates were calculated by comparing the phase-shifts
between successive tracking events (i.e., 1→2, 2→3, 3→4...). These were then cumulatively summed through time to yield the raw displacement traces over the duration of the acquisition. Data from the four tracking events immediately following each ARF push were not used for displacement estimation due to the presence of high amplitude echoes from the push pulse.

Background tissue motion was suppressed by applying a 3rd-order high-pass Butterworth filter with a cutoff frequency of 75 Hz through time (Kakkad et al., 2015). The filter was applied in the forward and reverse directions to minimize phase distortions. Motion-filtered displacement traces in the IVS for two representative ensembles, in mid-diastole (gold) and mid-systole (purple), are shown in Figure 5.1(d). The time vectors of the displacement traces are aligned such that the push, indicated by the gray band, begins at 0 ms. Closed circles represent measured displacements while open circles represent quadratically-interpolated estimates for time steps that were excluded from the displacement estimation process.

M-mode ARFI images, as shown in Figure 5.1(e), were generated by taking the difference between the measured displacement at 1.5 ms (shown in the solid black line) and the last tracking event prior to the push pulse. The systematic decrease in amplitude of the push away from the center of the ROE was compensated for by scaling the displacement data across the azimuthal angles based on a parabolic fit about the central angle. M-mode ARFI images were computed for all seven angles within the ROE, however, images presented herein represent only the central angle. Spatio-temporal regions-of-interest (ROIs) in the IVS were manually outlined using the conventional M-mode images. These ROIs, indicated by the green dotted lines in Figure 5.1(e), were superimposed onto the M-mode ARFI images and used to extract displacement data constrained to the myocardium.
Figure 5.1: (a) B-mode image in the parasternal short-axis (PSAX) view with the region-of-excitation of the ARF push (green rectangle) placed over the interventricular septum (IVS). (b,c) M-mode image in the same view and the corresponding ECG signal over a full cardiac cycle. Gross axial motion of the IVS as well as subtle variations in its speckle texture through time are observed. The temporal positions of ARF pushes are indicated by the dotted green lines. The gold and purple rectangles indicate ARFI ensembles in mid-mechanical diastole and systole, respectively. (d) Motion-filtered displacement profiles over the two ensembles. The gray band indicates the push; closed circles represent measured displacements while open circles represent interpolated estimates. Measured displacements at a fixed time (1.5 ms) are used to generate the M-mode ARFI image. (e) M-mode ARFI image (as a color overlay over the M-mode image) with outlines of the IVS indicated in the green dotted lines. Significantly higher displacements in mechanical diastole (compared to systole) are observed.
Figure 5.2: M-mode images over one cardiac cycle for (a) high and (b) low signal-to-clutter cases in the parasternal short axis (PSAX) view. Contrast between the right ventricular (RV) cavity and the interventricular septum (IVS) is used as a surrogate for signal-to-clutter level and measured to be 20.67 dB in (a) and 5.66 dB in (b).

5.2.4 Metrics of Signal Strength and Tracking Fidelity

M-mode ARFI data within the spatio-temporal ROI representing the IVS were averaged through range, azimuth, and time over individual cardiac cycles to yield $u_{cyc}$. This metric quantifies the mean ARF-induced displacement in the myocardium (after filtering out background motion) and was used as an indicator of signal strength. Acquisitions with a mean $u_{cyc}$ over all cardiac cycles $\leq 1.5 \mu m$ were considered to be “unsuccessful”. This threshold was determined using the Cramér-Rao Lower Bound (Walker and Trahey, 1995), which predicts the uncertainty in displacement estimation using partially-correlated signals. For the parameters defined in Table 5.1, the predicted standard deviation of individual displacements estimates (jitter) is approximately equal to $1.5 \mu m$.

Quantitative metrics to assess the level of acoustic clutter and out-of-plane motion were also derived using the raw M-mode echo data. Contrast in echo magnitude between the right ventricular (RV) cavity and the myocardium in the IVS was used to estimate the signal-to-clutter level (Kakkad et al., 2018). The RV cavity, which appears shallow to the IVS in the PLAX as well as PSAX views, was outlined manually. Contrast was defined as the ratio of the mean envelope-detected IQ data (prior to log compression) within the spatio-temporal ROIs representing the IVS divided
Figure 5.3: M-mode images over a cardiac cycle for (a) high and (b) low temporal coherence case in the parasternal long axis (PLAX) view. High temporal coherence indicates minimal speckle decorrelation due to out-of-plane motion and temporal noise. Mean $\rho_{\text{min}}$ within the IVS was measured to be 0.987 and 0.968 in (a) and (b), respectively.

The temporal coherence of speckle was used to determine the level of decorrelation from lateral, elevational, and rotational motion as well as temporal noise. IQ data for 2 ms temporal windows were remodulated to radio-frequency at a sampling frequency of 80 MHz and processed through a normalized cross-correlation operation anchored to the first time step in the window. A 5-$\lambda$ kernel (1.92 mm) and 1/2-$\lambda$ axial search range (0.19 mm) were used. Large axial displacements ($> 1/2-\lambda$) were compensated for by adjusting the axial location of the search range using cumulative displacements. The minimum correlation achieved over each temporal window ($\rho_{\text{min}}$) was used to quantify the level of speckle decorrelation. The process was repeated for several uniformly-spaced 2 ms windows across the cardiac cycle and synthesized into M-mode maps of temporal coherence. The 2 ms window length was chosen to represent a reasonable duration over which an ARFI measurement can be acquired. Figure 5.3(a,b) shows M-mode maps for high and low temporal coherence cases, respectively. High $\rho_{\text{min}}$ within the IVS over the entire cardiac cycle as well as a clear distinction between the myocardium and the cardiac chambers is observed in Figure 5.3(a). Comparatively, Figure 5.3(b) shows a more uneven spatio-temporal
Figure 5.4: Mean displacements within the IVS over a cardiac cycle for all seven azimuthal angles across the ROE in cases with (a) high and (b) low spatial similarity. Under the assumption of uniform myocardium over the ROE, high spatial similarity indicates low jitter and vice versa. $\rho$ within the IVS was measured to be 0.994 for (a) and 0.856 for (b).

Signal quality was also measured based on spatial consistency or similarity of the displacement trends within the ROE i.e., across the simultaneously acquired beams in azimuth. Assuming structural uniformity of the myocardium across the ROE, this metric is indicative of the mechanical signal-to-noise ratio. This was quantified by correlating traces of mean displacement through range within the IVS across the seven azimuthal angles and reported using the mean Fisher-transformed Pearson correlation coefficients ($\rho$). This metric is referred to as the spatial similarity and was also computed on a beat-by-beat basis. Figure 5.4(a) and 5.4(b) depict examples with low- and high-spatial similarity, respectively.

The performance of each metric at distinguishing “successful” from “unsuccessful” acquisitions was analyzed using receiver-operator-characteristic (ROC) curves and quantified using the area under the curve (AUC).

Indices of Dynamic Myocardial Stiffness

Five indices characterizing the temporal dynamics of myocardial stiffness over the cardiac cycle were derived from the M-mode ARFI data. These indices are: stiffness ratio, rates of relaxation and contraction ($\text{rate}_R$ and $\text{rate}_C$), and time constants of relaxation and contraction ($\tau_R$ and $\tau_C$). ARFI-derived indices of myocardial stiff-
ness were computed for the IVS on a beat-by-beat basis between successive systolic intervals.

The stiffness ratio was calculated by dividing the mean displacements within the IVS over successive pairs of diastolic and systolic temporal windows. The positions of these windows were defined using ECG landmarks and chosen to capture the myocardium in mid-mechanical diastole and systole i.e., in its most relaxed and contracted states, respectively. The diastolic window, indicated by the gold bands in Figure 5.5(a,b), was centered at 85% of the T-P interval while the systolic window, indicated by the purple bands in Figure 5.5(a,b), was centered over the T-wave. The width of each window was set to 10% of the R-R interval. Mean displacement in diastole \( u_D \) and systole \( u_S \) are shown in Figure 5.5(b) as horizontal dotted lines. Stiffness ratios were computed independently for each azimuthal angle.

Mean displacements over axial range (within the IVS) for all measured time points over the cardiac cycle and for all azimuthal angles (seven around the ROE) are depicted in the shaded circles in Figure 5.5(b). A 5-point median filter through time (corresponding to 142 ms) was used to suppress outliers. Rates and time constants were derived by modeling segments of this curve using the four-parameter logistic model shown in equation 5.1.

\[
\hat{u}(t) = u_S + \frac{u_D - u_S}{1 + e^{(t-t_0)/\tau}},
\]

where, \( u_S \) and \( u_D \) represent the displacement in systole and diastole, respectively, \( t_0 \) represents the temporal center of the logistic function, and \( \tau \) represents its time constant.

The transition from systole to diastole indicates mechanical relaxation of the myocardium while diastole to systole indicates active contraction. The fitting operation was performed using MATLAB’s fit function (The MathWorks Inc., Natick, MA) which implements a constrained, robust, nonlinear least squares Trust-Region algo-
algorithm. Representative fits for relaxation and contraction are shown in Figure 5.5(b) in solid red and blue lines, respectively. Rates of relaxation and contraction were computed by taking the peak of the derivative of the corresponding fit. The vertical dotted lines in Figure 5.5(b) indicate the positions at which the peak derivatives were extracted. Time constants of relaxation and contraction were defined as the time constant of the logistic equation for the respective transition.

Temporal consistency i.e., beat-to-beat variability of ARFI-derived indices of myocardial stiffness was assessed using the median average deviation (MAD) from the median and reported as a percentage.

**Figure 5.5:** (a) ECG signal over a cardiac cycle with mid-mechanical diastolic and systolic windows marked using gold and purple bands, respectively. (b) Median displacements within the IVS for all azimuthal angles at multiple ARFI ensembles over the duration of the cardiac cycle (gray circles). Four-parameter logistic model to fit myocardial relaxation (red curve) and contraction (blue curve). Horizontal dotted lines indicate mean diastolic displacement ($u_D$) and mean systolic displacement ($u_S$). Vertical dotted lines indicate temporal position of the peak rate of relaxation ($\text{rate}_R$) (red) and the peak rate of contraction ($\text{rate}_C$) (blue). Time constant of relaxation ($\tau_R$) and contraction ($\tau_C$) are reflected by the curvature of the respective fits.
5.3 Results

A total of 204 M-mode ARFI acquisitions were collected in the study across twelve volunteers, in two TTE views (PLAX and PSAX), and using three tracking configurations (FF, HP, and HF). Acquisitions were considered to be “unsuccessful” if mean displacement within the IVS over all cardiac cycles in the acquisition ($u_{cyc}$) was $< 1.5 \mu m$, or if the conventional M-mode image showed significant artifacts due to breathing or gross motion. Acquisitions where the ARF push was unable to generate a measurable displacement or where extra-cardiac structures corrupted the echo data from the myocardium were rejected.

Examples of “successful” and “unsuccessful” acquisitions are presented in Figure 5.6. ARFI displacements in Figure 5.6(b) show a consistent and cyclic pattern over the cardiac cycle, as evidenced by the alignment to the ECG as well as the motion profile of the valve (in the lower third of the M-mode image). Measured displacements are relatively homogeneous across depth within the IVS. In comparison, Figure 5.6(d) shows consistently low displacements in all phases of the cardiac cycle with some spatio-temporal heterogeneity in the systolic phases. Mean displacement within the IVS over the full acquisition was $3.85 \mu m$ in Figure 5.6(b) and $0.83 \mu m$ in Figure 5.6(d). In Figure 5.6(f), breathing artifacts can be observed over substantial segments of the acquisition (0-1900 ms and 2600-4500 ms). These artifacts are not aligned with the cardiac cycle, manifest as transient high amplitude echoes on the conventional M-mode image, and obscure the IVS.

Figure 5.7 presents a bar graph of the number of M-mode ARFI acquisitions collected in the study across volunteers split by TTE view (in shades of gray). The number of acquisitions that were determined to be “successful” are indicated in green. Out of the twelve volunteers, at least one “successful” acquisition was acquired on eight volunteers in PLAX and six volunteers in PSAX. Six volunteers yielded
“successful” acquisitions in both views while no “successful” acquisitions could be performed on four volunteers. Table 5.2 provides a summary of the acquisition yield as a function of tracking configuration and TTE view. Yield was slightly lower for PLAX (38%) compared to PSAX (44%). The two focused configurations (FF and HF) showed higher yield (45% each) compared to the HP case (32%). All combined, 84 out of 204 acquisitions (41%) were determined to be “successful”.

Metrics of signal strength, tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness were computed and analyzed on a beat-to-beat basis. These are presented here using the median and interquartile range (IQR). Statistical significance for select comparisons was determined using a Mann-Whitney U-test and reported using the p-value. The 84 “successful” acquisitions contained 343 cardiac cycles. Within “successful” acquisitions, by tracking configuration, there were 125 (36%) cardiac cycles in FF, 93 (28%) in HP, and 125 (36%) in HF. By view, there were 158 (46%) in PLAX and 185 (54%) in PSAX. The 120 “unsuccessful” acquisitions contained 491 cardiac cycles. These were distributed by beamforming configuration as 148 (30%) in FF, 191 (39%) in HP, and 152 (31%) in HF and by view as 275 (56%) in PLAX and 216 (44%) in PSAX.

5.3.1 Displacement Signal-to-Noise

Figure 5.8 illustrates a comparison between mean ARF-induced displacements within the IVS for “successful” acquisitions in diastolic and systolic temporal windows. These displacements are measured after the application of the motion filter and each data point represents an individual cardiac cycle. Mean displacements over the entire cardiac, prior to the ARF push (for matched cardiac cycles) is also shown for reference. The diastolic and systolic displacements are computed using the first track after the push (1.5 ms) while the “pre-push” displacement was extracted 10 ms prior to it. The “pre-push” displacements serve as an indication of the noise floor in this
Figure 5.6: B-mode and M-mode images for examples of “successful” (a,b) and “unsuccessful” (c,d,e,f) acquisitions. M-mode ARFI data are presented as a semi-transparent color overlay (between the dotted green lines) on the conventional M-mode image. The mean and standard deviation of diastolic and systolic displacements in (b) are $4.88 \pm 0.58 \mu m$ and $1.42 \pm 0.06 \mu m$, respectively. The same for (d) are $1.03 \pm 0.03 \mu m$ and $0.71 \pm 0.21 \mu m$. (f) illustrates an M-mode ARFI image that was corrupted by breathing/motion artifacts. These artifacts are not aligned with the cardiac cycle and present as high amplitude echoes on the conventional M-mode image and high displacements on the M-mode ARFI data.

context. Figure 5.8(a) compares displacements across tracking configuration while (b) compares them based on TTE view.

Combining the sub-groups, the median and IQR of the displacements were measured to be $3.04 (1.59) \mu m$ in diastole, $1.19 (0.33) \mu m$ in systole, and $0.03 (0.12) \mu m$ prior to the push. These were statistically distinct from each other ($p < 0.0001$). Diastolic displacements were slightly lower in the HP configuration, $2.50 (1.23) \mu m$,
compared to FF, 3.37 (1.66) $\mu$m (p < 0.0001), and HF, 3.18 (1.39) $\mu$m (p < 0.001). Diastolic displacements were also found to be slightly higher in PLAX, 3.34 (1.88) $\mu$m compared to PSAX, 2.85 (1.24) $\mu$m (p < 0.01). Systolic displacements across the tracking configurations and between the two views were found to be roughly identical.

5.3.2 Metrics of Tracking Fidelity

“Successful” and “unsuccessful” acquisitions were compared on the basis of the proposed metrics of tracking fidelity: contrast, temporal coherence, and spatial similarity. Figure 5.9 presents a comparison of these metrics between the two groups.
Figure 5.8: Mean ARF-induced displacements within the IVS for “successful” acquisitions in diastolic and systolic temporal windows as well as prior to each ARF excitation over the entire cardiac cycle. The three groups are presented split by (a) track configuration and (b) TTE view. Box plots are as described in Figure 5.9. “Pre-push” displacements show minimal bias and a relatively narrow spread, 0.03 (0.12) µm. ARF-induced displacements in all cardiac phases exceed this noise floor. Displacements in diastole, 3.04 (1.59) µm are significantly higher than those in systole, 1.19 (0.33) µm.

Each group is further sub-divided based on the tracking configuration used. Tracking fidelity is not expected to vary preferentially with TTE view, thus the two views were combined in this analysis for brevity. Each data point represents an individual cardiac cycle.

Contrast across all “successful” acquisitions was measured to be 13.17 (7.11) dB. For “unsuccessful” acquisitions contrast was substantially lower, 5.42 (7.31) dB. This difference was statistically significant with a p < 0.0001. For each group, contrast was found to be higher for the two configurations that employed harmonic imaging (HP and HF). Within the “successful” group, contrast using FF, HP, and HF was measured at 11.07 (5.14) dB, 14.12 (8.48) dB, and 16.62 (7.05) dB, respectively.

Temporal coherence, quantified using $\rho_{\min}$, was measured at 0.988 (0.007) for “successful” acquisitions. The same for “unsuccessful” acquisitions was 0.976 (0.018). However, unlike in the case of contrast where both groups displayed a large degree of variability, temporal coherence for “successful” acquisitions exhibited a relatively low variance. Across the tracking configurations, $\rho_{\min}$ for “successful” acquisitions had
IQRs of 0.008, 0.006, and 0.004 in FF, HP, and HF, respectively. For “unsuccessful” cases the same were 0.014, 0.021, and 0.015. Temporal coherence achieved the highest values and lowest variability in “successful” acquisitions in the HF configuration; $\rho_{\text{min}}$ in this case was 0.991 (0.004).

Spatial similarity ($\rho$) was found to follow trends similar to temporal coherence. In the case of “successful” acquisitions, across the three tracking configurations, $\rho$ was calculated to be 0.989 (0.021), 0.958 (0.043), and 0.988 (0.021) for FF, HP, and HF, respectively. “Unsuccessful” acquisitions exhibited lower $\rho$ values of 0.890 (0.115), 0.806 (0.171), and 0.856 (0.147) for FF, HP, and HF, respectively. Spatial similarity exhibited a larger range of values as compared to temporal coherence.

The three metrics of tracking fidelity were found to be partially correlated. Figure 5.10(a,b,c) depicts the relationships between each pair of metrics for both “successful” and “unsuccessful” acquisitions. Temporal coherence and spatial similarity values were Fisher-transformed (Silver and Dunlap, 1987) for this analysis to represent them as continuous un-bounded variables. All pairs show a moderate positive trend with linear correlation coefficients of 0.675 for contrast vs. temporal coherence, 0.474 for contrast vs. spatial similarity, and 0.591 for temporal coherence vs. spatial similarity. ROC curves for individual metrics are shown in Figure 5.10(d). AUC was 0.81 when using only contrast, 0.85 when using only temporal coherence, and 0.91 when using spatial similarity. The optimal cut-offs for each metric, i.e., where efficiency of classification is maximized were found to be 9.48 dB for contrast, 0.985 for temporal coherence, and 0.953 for spatial similarity. These cut-offs are indicated in the horizontal and vertical lines in Figure 5.10(a,b,c). As observed previously, “successful” acquisitions showed high values for all three metrics and thus were clustered in the upper right quadrant of these graphs.
Figure 5.9: (a) Contrast, (b) temporal coherence, and (c) spatial similarity for individual cardiac cycles in “successful” and “unsuccessful” acquisitions split by tracking configuration. For the box plots, the horizontal marker represents the median, the edges of the box represent the 25th and 75th percentile and the whiskers mark the furthest values not considered outliers. All three metrics were significantly higher for “successful” acquisitions compared to “unsuccessful” ones.

5.3.3 Indices of Dynamic Myocardial Stiffness

ARFI-derived indices of dynamic myocardial stiffness were computed on a beat-by-beat basis for all cardiac cycles in “successful” acquisitions. Figure 5.11 and 5.12 illustrate examples of “successful” acquisitions in PLAX and PSAX, respectively.

In both cases, the B-mode and M-mode images exhibit good border delineation of the IVS and a clear distinction between the myocardium and the cardiac chambers. Contrast, temporal coherence, and spatial similarity in both case are substantially greater than the optimal cut-offs determined using the ROC curves. M-mode ARFI data, displayed in the semi-transparent color overlay, shows a cyclic pattern with high displacements during diastole and low displacements in systole. These trends are further exemplified by the alignment of the ECG signal with the trace of mean displacements through range within the IVS. Diastolic temporal windows, indicated by gold bands, and systolic temporal windows, indicated by purple bands, generally capture the peak and trough of the M-mode displacement traces through the cardiac cycle. The five ARFI-derived indices of dynamic myocardial stiffness are displayed in the table below the B-mode image.

Table 5.3 presents a statistical summary of the five ARFI-derived indices of dy-
Figure 5.10: (a,b,c) Pair-wise relationships between metrics of tracking fidelity across all acquisitions. A moderate positive trend was observed for all three pairs of metrics with good differentiation between “successful” and “unsuccessful” acquisitions. (d) ROC curves for individual metrics. All three metrics, used individually, do a good job of separating “successful” from “unsuccessful” acquisitions. The optimal cut-offs for the metrics were found to be 9.48 dB for contrast, 0.985 for temporal coherence, and 0.953 for spatial similarity.

dynamic myocardial stiffness divided by TTE view. These were computed using all cardiac cycles in “successful” acquisitions. Statistically significant differences between the two views were not observed for any of the indices computed in this study.

Figure 5.13 depicts the level of temporal consistency or beat-to-beat variability for the ARFI-derived indices. For this analysis, tracking configurations acquired sequentially, i.e., as part of a single dataset, were combined provided the individual acquisitions were considered to be “successful”. Median absolute deviations (MAD) as a percentage of the median are presented for datasets with 10 or more cardiac
cycles. Stiffness ratios were found to be the most consistent from beat-to-beat with average MAD of 12.26%. Rates and time constants, however, exhibited a significantly higher level of temporal variability, with average MADs in the range of 30.62 - 33.28%.

Figure 5.11: Example of a “successful” acquisition in PLAX. (a) B-mode image with the ROI (green box) placed over the IVS. (b) conventional M-mode image with ARFI data in the semi-transparent color overlay. (c) concurrent ECG signal and (d) mean displacement over depth within the IVS for all azimuthal angles. Diastolic and systolic temporal windows are indicated on (c) and (d) by gold and purple bands, respectively. The table below the B-mode image presents estimated indices of dynamic myocardial stiffness and metrics of signal quality. Displacement trends align well with the ECG and show good repeatability from beat-to-beat.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness Ratio</td>
<td>2.96 (0.13)</td>
</tr>
<tr>
<td>Rate_a (1/s)</td>
<td>10.74 (5.43)</td>
</tr>
<tr>
<td>Rate_c (1/s)</td>
<td>-4.24 (0.97)</td>
</tr>
<tr>
<td>( \tau_a ) (ms)</td>
<td>23.25 (7.78)</td>
</tr>
<tr>
<td>( \tau_c ) (ms)</td>
<td>58.84 (11.15)</td>
</tr>
<tr>
<td>Signal Strength (( \mu )m)</td>
<td>2.63 (0.11)</td>
</tr>
<tr>
<td>Contrast (dB)</td>
<td>16.62 (0.25)</td>
</tr>
<tr>
<td>Temporal Coherence</td>
<td>0.994 (0.001)</td>
</tr>
<tr>
<td>Spatial Similarity</td>
<td>0.995 (0.002)</td>
</tr>
</tbody>
</table>

5.4 Discussion

This study had three main objectives: i) to assess the feasibility of tracking the temporal dynamics of myocardial stiffness using ARFI imaging in a noninvasive manner, ii) to extract quantitative indices from M-mode ARFI data that characterize changes in myocardial stiffness over the cardiac cycle, and iii) to evaluate the temporal consistency of these indices under in vivo conditions and establish reference values in a
Figure 5.12: Example of a “successful” acquisition in PSAX. Description of the panels is as described in Figure 5.11. Estimates of stiffness ratio and rates of relaxation and contraction show good repeatability over the five cardiac cycles, however estimates of the time constants are found to be more variable.

Figure 5.13: Beat-to-beat variability of ARFI-derived indices of dynamic myocardial stiffness. The temporal variability as quantified by the median absolute deviation (MAD) as a percentage of the median (of the particular index through time) is presented for “successful” acquisitions with ten or more cardiac cycles. The temporal consistency of stiffness ratios is substantially better than rates and time constants.
Table 5.3: Summary of ARFI-derived indices of dynamic myocardial stiffness over all cardiac cycles acquired in “successful” acquisitions.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stiffness Ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAX</td>
<td>2.81</td>
<td>0.81</td>
<td>[2.68  2.94]</td>
</tr>
<tr>
<td>PSAX</td>
<td>2.67</td>
<td>0.91</td>
<td>[2.54  2.81]</td>
</tr>
<tr>
<td><strong>Rate(_R) (1/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAX</td>
<td>8.07</td>
<td>5.16</td>
<td>[7.22  8.92]</td>
</tr>
<tr>
<td>PSAX</td>
<td>7.61</td>
<td>4.25</td>
<td>[6.97  8.25]</td>
</tr>
<tr>
<td><strong>Rate(_C) (1/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAX</td>
<td>-7.02</td>
<td>3.81</td>
<td>[-7.65 -6.40]</td>
</tr>
<tr>
<td>PSAX</td>
<td>-7.58</td>
<td>3.76</td>
<td>[-8.16 -6.99]</td>
</tr>
<tr>
<td><strong>(\tau(_R) (ms))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAX</td>
<td>35.26</td>
<td>20.97</td>
<td>[31.71 38.81]</td>
</tr>
<tr>
<td>PSAX</td>
<td>36.42</td>
<td>19.29</td>
<td>[33.49 39.35]</td>
</tr>
<tr>
<td><strong>(\tau(_C) (ms))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAX</td>
<td>40.65</td>
<td>21.94</td>
<td>[37.11 44.21]</td>
</tr>
<tr>
<td>PSAX</td>
<td>34.34</td>
<td>17.43</td>
<td>[31.74 36.94]</td>
</tr>
</tbody>
</table>

PLAX = Parasternal Long-Axis  
PSAX = Parasternal Short-Axis  
Std. = Standard Deviation  
CI = Confidence Interval

cohort of healthy volunteers.

5.4.1 Challenges for Transthoracic ARFI and Potential Solutions

The transthoracic imaging environment presents several obstacles for ARF-based techniques such as ARFI and SWEI. The main challenges are: i) generating strong ARF pushes in the myocardium, ii) tracking micron-level displacements in an accurate and precise manner in the presence of acoustic clutter and out-of-plane motion, and iii) separating ARF-induced displacements from the background cardiac motion.

M-mode ARFI acquisitions were categorized as “successful” or “unsuccessful” based on the mean ARF-induced displacement over the duration of the acquisition, i.e., across multiple cardiac cycles. ARF-induced displacements above the threshold of 1.5 \(\mu\)m were only observed in 41% of the 204 acquisitions. This low yield can be attributed to a variety of factors that are discussed here. ARF-induced displacements
are directly proportional to the acoustic intensity generated in the target tissue of interest (Nightingale et al., 2002); thus conditions that allow for the use of tightly focused beams through a low attenuation acoustic path are favorable for ARFI imaging. The ability to focus ultrasound beams is governed by aperture size and target depth. In TTE, the azimuthal and elevational aperture sizes are limited by the intercostal spaces to 18-20 mm. However, the targets of clinical interest such as the IVS and LV free wall appear at depths of 50-70 mm and 110-130 mm, respectively. This combination results in weakly focused beams with F-numbers on the orders of 2.5-3.5 at the IVS and 5.5-6.5 at the LV free wall. While a substantial portion of the propagation path, in TTE, consists of weakly attenuating blood, the chest wall, which appears in the near-field, is composed of highly attenuating structures such as muscle and connective tissue (Mast, 2000). Thus, a large fraction of the acoustic energy in the push pulses is absorbed in the near field and does not contribute to the mechanical excitation. These factors limit the ability to generate large ARF-induced displacements at the targets of interest.

Displacement signal strength could be improved by using longer push pulses and/or higher voltages i.e., acoustic pressures. The push pulses used in this study were 300 µs long with an MI of 1.65. These were limited due to the scanner power supply hardware and probe heating considerations. For most soft tissues, ARF excitations of up to 1 ms are still considered to be impulsive (Palmeri et al., 2006a). Thus, for a fixed MI, utilizing a 1 ms push pulse would lead to an increase in the push strength by three times compared to the sequences used in this study. Likewise, stronger push pulses could also be generated by increasing the pressures up to the FDA-enforced MI limit of 1.9 (Barnett et al., 2000). The use of longer pulse durations and elevated pressures will have to be calibrated against the increased power output and potential for tissue and transducer face heating (Bouchard et al., 2009) as well as the risk of inducing cavitation (Apfel and Holland, 1991).
Tracking of micron-level displacements using ultrasound is generally performed using normalized cross-correlation, on radio-frequency (RF) signals or using phase-shift algorithms in the case of in-phase and quadrature (IQ) data. Acoustic clutter and multi-dimensional background motion of the targets of interest can severely impact the precision as well as accuracy of tracked displacements. In simulations, clutter in the form of stationary echoes has been shown to introduce bias into displacement estimates (Pinton et al., 2006). The superposition of stationary echoes with a strength of -5 dB resulted in a 24% bias in tracked displacement. In the context of TTE, reverberation between tissue layers in the near-field can generate a substantial level of high amplitude stationary echoes and consequently corrupt M-mode ARFI data. Moreover, non-stationary clutter can also arise from structures that move with the cardiac or respiratory cycles, such as off-axis myocardium, pericardium, and lung tissue.

Tracked axial displacements represent a combination of background myocardial motion as well as ARF-induced displacements. Suppression of background motion in ARFI applications has traditionally been accomplished using quadratic motion filters. However, the performance of these filters can be sensitive to the specific combination of parameters used (Giannantonio et al., 2011). Frequency-based filters have been shown to be equally effective at suppressing background myocardial motion for transthoracic applications (Kakkad et al., 2015) and were utilized here. As shown in Figure 5.8, “Pre-push” displacements over the full cardiac cycle showed minimal bias and low variance after application of a 3rd-order high-pass Butterworth filter with a cutoff frequency of 75 Hz. For “successful” acquisitions, measured displacements in all phases of the cardiac cycle were found to be distinct from the noise floor. In diastole, displacements were always higher than systole (for “successful” acquisitions). The subtle decrease in diastolic displacements in the harmonic-plane wave configuration could be attributed to a spatial averaging effect as a result of the
broader point-spread function of the tracking transmit beam (Czernuszewicz et al., 2013).

Measurement uncertainty for unbiased displacement estimators is defined by the Cramér-Rao Lower Bound (Walker and Trahey, 1995) which relates the standard deviation of displacement estimates, or jitter, to ultrasonic tracking parameters such as frequency, bandwidth, kernel length, SNR, and speckle correlation. While axial displacements can be tracked using the techniques mentioned above, translational motion in other dimensions (azimuth and elevation) or rotational motion lead to speckle decorrelation and a consequent amplification of jitter. For typical parameters used in TTE, 3.5 MHz center frequency, 80% bandwidth, 5-λ kernel, and 60 dB channel SNR, and a correlation coefficient of 0.992, jitter is predicted to be 1.52 µm. However, jitter is sensitive to speckle decorrelation and rises quickly to 3.1 µm at a correlation coefficient of 0.97; these values represent the uncertainty associated with a single displacement estimate. In practice, however, displacements are averaged across partially overlapping spatio-temporal kernels to suppress variance at the cost of reduced resolution.

The results presented herein focus on measuring the stiffness of the IVS through the PLAX and PSAX views. M-mode ARFI, in principle, could also be used to interrogate other segments of the heart through different views; the apex and the IVS could be accessed in the apical 4-chamber or 2-chamber views. In previous unpublished work, we have attempted to use apical views to target the apex but were hampered by reverberant acoustic clutter due to the proximity of the apex to the chest wall. In the case of the IVS through apical views, the myocardium appears in a vertical orientation and exhibits substantial lateral motion which causes it to move in-and-out of the region-of-excitation (ROE). While this was a challenge for this implementation of M-mode ARFI where the ROE was fixed in azimuth, it could be overcome in the future by following the gross lateral motion of the myocardial
walls using (2D speckle tracking techniques) and adaptively adjusting the angle of
the ARF ensembles accordingly.

Acoustic clutter and speckle decorrelation due to multi-dimensional tissue motion
are, to some degree, inherent to the physics of cardiac ultrasound imaging. However,
their detrimental impact on M-mode ARFI is dependent on the specific magnitude
of each source of signal degradation. As shown here, coarse estimates of the signal-
to-clutter level can be generated using contrast between the myocardium and the
cardiac chambers, while motion-induced speckle decorrelation can be quantified using
temporal coherence. These metrics are extracted from the same echo data used for
ARFI processing and thus have potential to serve as adaptive indicators of signal
quality. Similarly, spatial similarity of displacement traces across simultaneously-
acquired beams within the ROE captured the effect of acoustic SNR as well as jitter
using the tracked displacement signals. Not only were all three metrics found to
be significantly higher for “successful” acquisitions vs. “unsuccessful” acquisitions,
they were also found to be correlated with each other. As illustrated in Figure
5.10(a,b), decreasing contrast was associated with a general decrease in temporal
coherence as well as spatial similarity. This suggests that “low contrast” could be
attributed to either poor acoustic SNR (i.e., poor penetration) or a high level of
non-stationary clutter from moving sources. In comparison, reduced contrast due to
stationary clutter from static sources would maintain high temporal coherence and
spatial similarity.

The three metrics can individually be used to categorize acquisitions into “suc-
cessful” or “unsuccessful”. Their ability to do so was quantified using AUC of the
ROC curves. All three metrics performed did a good job of separating the two groups
with spatial similarity doing the best (AUC = 0.91). While these metrics are highly
correlated, they do inherently represent different “failure modes” and could be com-
bined to form an adaptive, displacement-magnitude independent method to assess
the reliability of M-mode ARFI acquisitions.

For instance, the combination of contrast and temporal coherence can serve as an indicator to distinguish between acquisitions that are corrupted due to an inability to accurately track displacements from those where a viable ARF excitation could not be generated. 49 of the 491 (9.98%) cardiac cycles in “unsuccessful” acquisitions were found to be above the optimal cut-offs for contrast and temporal coherence determined using the ROC analysis, i.e., 9.48 dB for contrast and 0.985 for temporal coherence. In these cases, while tracking conditions were favorable, the mean tracked displacements were measured to be below the 1.5 \( \mu \)m cutoff. Thus, stronger ARF-excitation could yield viable M-mode ARFI data for such acquisitions. Using the theoretical estimates, a contrast threshold of 10 dB and a temporal coherence threshold of 0.985 would limit the bias due to stationary echoes to < 10% and jitter to < 2 \( \mu \)m. Spatial similarity was found to be the most efficient differentiator. It inherently combines the effects of acoustic SNR, jitter, as well as low ARF-induced displacement while making the assumption of uniformity over the ROE. Lastly, as employed here, the mean displacement over the cardiac cycle could also be used as an indicator of “success”.

5.4.2 Temporal Dynamics of Myocardial Stiffness

In acquisitions where a measurable ARF-displacement was able to be generated and the tracking conditions were favorable, M-mode ARFI, implemented on a clinical ultrasound system and an adult cardiac phased array, was successful at tracking changes in stiffness of the interventricular septum (IVS) over the cardiac cycle. These trends were captured in both transthoracic echocardiographic (TTE) views studied here.

Figure 5.8(a) shows a decrease in the magnitude of the ARF-induced diastolic displacement for the harmonic plane wave case, compared to the two focused cases.
This could be attributed to a spatial averaging effect of the (laterally) broader point spread function of the tracking beam when using plane waves (McAleavey et al., 2003). This result was also observed when using the same sequences to measure elasticity phantoms. Mean ARF-induced diastolic displacements were also found to be lower in PSAX versus PLAX, as shown in Figure 5.8(b). Diastolic shear wave speeds have been found to be faster in PSAX compared to PLAX (Song et al., 2016). Similarly, ARF-induced displacements have also been shown to be impacted by material anisotropy (Hossain et al., 2017). Thus, this result could be a manifestation of the change in fiber orientation between the two views. Systolic displacements did not show such subtle trends, potentially due to lower displacement magnitude and thus lower SNR. These hypotheses were not explicitly addressed in this in vivo study and could be better characterized through controlled experiments on ex vivo myocardium.

Temporal trends in the M-mode ARFI data exhibited excellent alignment with the expected physiological changes over cardiac cycle as indicated by the ECG. ARF-induced displacements, which are inversely proportional to tissue stiffness, were highest during the latter half of the T-P segment which is marked by low electrical as well as mechanical activity. During this phase of the cardiac cycle, also referred to as diastasis, pressure in the left ventricle is at its lowest and the myocardium is in a relaxed state (Stouffer, 2017). In contrast, low displacements, indicating high stiffness, were measured in the S-T segment i.e., during ejection; pressure is expected to hit its peak in this phase following active contraction of the myocardium. Smooth transitions were observed between these two extremes. Active contraction manifests in the M-mode ARFI data as a steady decrease in displacement immediately following the R-wave; while relaxation is seen as a gradual increase in displacement after the T-wave. These findings are consistent with previous implementations of ARFI and SWEI in animals using open-chest preparations (Hsu et al., 2007), intrac-
ardiac echocardiography (ICE) (Hollender et al., 2013), as well as in Langendorff experiments (Pernot et al., 2011; Vejdani-Jahromi et al., 2015).

Heart-rate dependent changes in the relative duration of systole and diastole are also reflected in the M-mode ARFI data. The diastolic duration has been shown to have an inverse relationship with heart-rate (Chung et al., 2004) while the systolic duration has been found to be less sensitive (Cui et al., 2008). In the example portrayed in Figure 5.12(b), the heart-rate is 70 bpm and the fraction of the cardiac cycle with high displacements (diastole) and low displacements (systole) are roughly equal. In contrast, Figure 5.6(b) and Figure 5.11(b) show longer segments where the displacement is consistently high; heart-rate in these cases was 53 and 55 bpm, respectively. The temporal trends of myocardial stiffness and their correlation with the ECG signal were found to be highly repeatable from beat-to-beat as well as across different volunteers. These trends could be used to augment current diagnostic methods for detection of regional conduction abnormalities that may not be captured on the global ECG.

ARFI-derived indices, especially rates and time constants showed a substantial degree of beat-to-beat variability. This could be attributed to a broad set of factors related to technical limitations of the ultrasound-based elastography methods as well as physiological changes in cardiac function due to autonomic reflexes. Even under tightly controlled experimental conditions, hemodynamic parameters extracted from interventricular pressure changes have been found to show inherent variability (Freeman et al., 1993).

5.4.3 Limitations and Future Work

This study outlines some of the fundamental challenges of performing M-mode ARFI acquisitions through transthoracic windows. However, it does not explicitly address a number of factors associated with cardiac anatomy, physiology as well as higher-order
technical limitations that could contribute to bias and variability in ARFI-derived indices of myocardial stiffness.

Given the reliance of ARFI on accurate tracking of micron-level displacements, even subtle movements of volunteers due to breathing or probe motion can lead to substantial artifacts. 41 out of 204 (20.1%) of acquisitions collected in this study had to be excluded on account of artifacts due to breathing and/or gross motion. Multidimensional motion (contraction and torsion) of the heart could also lead to some degree of spatial uncertainty in M-mode measurements of myocardial stiffness. Limiting ARFI acquisitions to shorter durations, performing them under breath-holds, and using 2D or 3D speckle tracking techniques to adaptively adjust the direction of the ARF ensembles could help improve yield and maintain spatial registration in future implementations.

Sampling rate is a critical factor when estimating a time-varying signal. In this study, temporal dynamics of myocardial stiffness were sampled at a push PRF of 35 Hz; this provided 28 stiffness estimates over the cardiac cycle at a heart-rate of 75 bpm. While this sampling rate allows for visualization of smooth transitions in myocardial stiffness between the various cardiac phases at the heart-rates tested here (48 - 98 bpm), it may not be sufficient at higher heart-rates. Undersampling the temporal trends of myocardial stiffness could mask critical features and lead to errors in the estimation of rates and time constants. Future work will look to address the accuracy of these indices as a function of sampling rate. Thermal safety considerations and hardware limitations could place a cap on the maximum achievable push PRF. However, multi-beat synthesis or gated-acquisitions could be used to boost the effective sampling rate over the cardiac cycle at the expense of assuming uniformity across multiple heart beats. Violation of this assumption could lead to increased standard deviation of computed indices.

While metrics of signal quality presented herein provide good differentiation be-
between “successful” and “unsuccessful” acquisitions, they exhibit substantial variability within acquisitions that were identified as being “successful”. Changes in these metrics over successive cardiac cycles could, in part, contribute to the beat-to-beat variability in ARFI-derived indices of myocardial stiffness. A thorough analysis addressing the various noise sources in TTE and determining their relationship to the metrics of signal quality as well as the precision and accuracy of ARFI-derived indices will be the focus of future work.

Lastly, anatomical and physiological considerations such as body habitus, myocardial fiber orientation, higher-order material characteristics such as viscoelasticity, hemodynamic parameters (loading conditions), and spatial uniformity of myocardial mechanical properties (between the epicardial to endocardial segments and from apical to basal segments within the IVS) are likely to contribute to variability in the measurement of ARFI-derived indices of myocardial stiffness and warrant further investigation.

5.5 Conclusions

The results presented herein demonstrate the feasibility of using M-mode ARFI to measure temporal trends of myocardial stiffness through the cardiac cycle via transthoracic imaging windows. Dynamic myocardial stiffness of the IVS was captured in both TTE views tested in this study and quantified using the stiffness ratio as well as rates, time constants of contraction and relaxation. The yield of “successful” acquisitions, however, was limited; this was attributed to the inability to generate a measurable mechanical excitation in the myocardium as well as unfavorable conditions for tracking micron-level displacements. Metrics of tracking fidelity such as signal-to-clutter level, temporal coherence of speckle, and spatial similarity of displacement traces within the ROE were found to differentiate “successful” from “unsuccessful” acquisitions. ARF-derived indices of dynamic myocardial stiff-
ness were found to be similar across the two views. Stiffness ratios exhibited good beat-to-beat repeatability while rates and time constants were less consistent. The values presented here were measured on healthy volunteers and serve as a reference for future studies aimed at noninvasive characterization of myocardial stiffness using ARFI in patients with clinical symptoms of cardiomyopathy.
6

Conclusions

6.1 Summary

The overarching goal of the work presented in this dissertation was to assess the feasibility of using acoustic radiation force-based techniques to measure dynamic myocardial stiffness through the cardiac cycle via transthoracic imaging windows. Prior research had hypothesized that acoustic clutter and cardiac motion were likely to be the major impediments to the success of this application. Building upon these ideas, the first two studies were designed to quantify the level of signal degradation from each source and evaluate strategies to minimize their impact. The third study was an in vivo evaluation of the concepts developed and a demonstration of the methods on a cohort of healthy volunteers.

The first study was centered around assessing the level of acoustic clutter in the transthoracic imaging environment and evaluating the impact of harmonic imaging and transmit beamforming on suppressing clutter. Contrast between the myocardium and the cardiac chambers was used to quantify the magnitude of clutter. Across volunteers contrast was found to be in the range of -2 to 22 dB. Clutter level also varied significantly across repeated acquisitions on any given volunteer. Har-
monic imaging was found to improve contrast (reduce clutter) in both the plane wave (2.97 dB) as well as the focused (6.1 dB) cases. Across all configurations, clutter level in the shallow chamber (RV) was found to be higher than the deep chamber (LV), suggesting strong reverberation from the chest wall. While the combination of harmonic imaging and focused transmit beamforming were found to be effective at suppressing clutter, the wide variation of measured contrast even in the harmonic-focused configuration (4 - 22 dB) indicated that acoustic clutter would continue to be a significant hurdle for the transthoracic implementation of ARFI and SWEI.

The second study focused on assessing the role of cardiac motion in introducing bias and uncertainty into the reconstruction of M-mode ARFI images. Two aspects of cardiac motion were considered: axial motion, which can be tracked and compensated for through motion filtering approaches, and non-axial motion, which cannot directly be measured using phase-based displacement estimators, but has a quantifiable impact on the quality of axial displacement estimates. To suppress intrinsic cardiac motion in the axial dimension, frequency-based high-pass filters were compared against tradition recovery-based polynomial filters. Cardiac motion and simulated ARF-induced motion were found to have significant separation in the frequency domain. Consequently, high-pass filters were effective at suppressing axial cardiac motion. Their performance, however, was at par with quadratic polynomial filters, but with the advantage of not requiring a recovery-time assumption.

The effects of non-axial motion were captured by tracking the temporal coherence of the myocardial speckle over limited durations (2-10 ms) throughout the cardiac cycle. Temporal coherence was found to vary predictably; it was high in diastole and low in systole. Displacement estimation jitter, as predicted by CRLB, was found to be negatively correlated with temporal coherence. Jitter i.e., the standard deviation of displacement estimates, was found to be in the range of 0.5-8 µm for 2 ms windows, but could be as high as 10-20 µm for 10 ms windows. This result indicated the level
of variation of the displacement estimation noise-floor over the cardiac cycle and potential challenges for the success of SWEI in systole.

The third study demonstrated that despite these noise sources, acoustic radiation force impulse imaging was successful at capturing the dynamic variations in myocardial stiffness through the cardiac cycle when the appropriate conditions were met. Low clutter (contrast > 9.48 dB), high temporal coherence ($\rho_{\text{min}} > 0.985$), and high spatial similarity ($\rho > 0.953$) were associated with “successful” acquisitions. Five ARFI-derived indices of dynamic myocardial stiffness were computed: (diastolic-to-systolic) stiffness ratio, rates of relaxation and contraction, and time constants of relaxation and contraction. Statistical distributions as well as an analysis of beat-to-beat repeatability of these indices for a set of healthy volunteers were presented.

These results support the hypothesis that acoustic radiation force-based methods can be used to measure dynamic myocardial stiffness through transthoracic imaging windows. While this technique certainly presents novel opportunities for diagnostic cardiology, there are several factors that must be addressed before this technology is ready to be used to drive decision-making in clinical environments.

6.2 Future Work

Acoustic radiation force-based ultrasound methods involve three fundamental steps: i) generating a mechanical excitation using ultrasound, ii) tracking the temporal dynamics of the mechanical response, also using ultrasound, and iii) deriving mechanical properties of the medium based on the measured response. As evidenced by the studies presented in this dissertation, all three steps face significant challenges in the transthoracic imaging environment. The discussion below presents a few potential avenues of research, with respect to each of the three aforementioned steps, that could meaningfully contribute to improving the yield, reliability, and accuracy of these techniques.
6.2.1 Generating Mechanical Excitations

The ideal mechanical excitation, for the purposes of ARFI and SWEI would be highly localized in all three spatial-dimensions (within the myocardium for cardiac applications), impulsive in time, and stronger in magnitude compared to the expected level of measurement uncertainty.

Spatial localization of the “push” can be achieved through aggressive focusing, i.e., using low F-numbers, which requires large apertures or shallow imaging depths. The studies presented in this dissertation were performed using an 18.89 x 13.1 mm (lateral x elevational) aperture to generate “pushes” at focal depths of 45 to 65 mm; this resulted in depths-of-field in the range of 24.92 - 52.06 mm. The depth extent of the IVS, in PLAX and PSAX, is generally only 10 - 15 mm. Thus, a substantial fraction of the “push” energy was expended on tissues outside the ROI i.e., the blood pool or tissues shallow and deep to the IVS. This issue was compounded in cases where the tissues shallow to the ROI generated reverberant clutter which was set in motion by the mechanical excitation. The ability to spatially localize the “push” to the desired ROI could be improved upon by using larger apertures that fit parallel to the ribs or by using views where the ROI appears at shallower depths. One caveat to the latter strategy, however, is that shallower ROIs, such as the apex from the apical two- or four-chamber views, are also closer to the chest wall and likely to be corrupted by strong reverberant clutter.

The magnitude of the mechanical excitation, on the other hand, is directly related to its temporal duration and pulse intensity. The practical limits of these parameters are dictated by concerns of tissue/transducer face heating and inducing adverse bio-effects such as cavitation (Bouchard et al., 2009), respectively. For cardiac imaging, specifically, there is also a risk of inducing pre-ventricular contractions (PVC) (Dalecki et al., 1991). In these studies, “push” pulses were 300 µs long and
limited to $I_{sppa} < 430 \text{ W/cm}^2$ and $\text{MI} < 1.65$. At a PRF of 35 Hz for a duration of 5 s, this generated a 3°C rise at the transducer face. No evidence of PVCs was observed during in vivo data acquisitions. While this configuration was well below the FDA limits of $I_{sppa} < 720 \text{ W/cm}^2$ and $\text{MI} < 1.9$, the transducer face heating approached an uncomfortable level for the volunteers. Other groups have previously used excitation pulses as long as 800 µs for transthoracic tracking of shear waves in the myocardium (Song et al., 2013). Longer excitation pulses have the potential to skew the temporal dynamics of ARF-induced motion (Palmeri et al., 2006a), but pulses up to 1000 µs could still be considered impulsive. Thus, ARF-induced displacement magnitude could be improved by as much as a factor of three (3 x) by utilizing longer “pushes”. Similar improvements in mechanical SNR could also be achieved by increasing the pulse pressure from 430 W/cm$^2$ to 720 W/cm$^2$ (1.6 x).

Transducer face heating could be limited by striking a balance between “push” PRF and the duration of the acquisition. Additionally, advances in transducer technology and lens design such as probes with active-cooling capabilities could help circumvent this issue in the future (Deardorff and Diederich, 2000). Given the interdependent nature of these parameters, they are best optimized on an application-by-application basis and must be closely monitored so as to not exceed safety limits.

6.2.2 Tracking Dynamic Mechanical Response

The ability to track local, micron-level mechanical vibrations using ultrasound depends upon i) reliably isolating echoes corresponding to scatterers at specific spatial locations in the field and ii) comparing subtle changes in the position of these scatterers (as captured by the echoes) over time i.e., successive transmit-receive events. The studies described in this dissertation indicate how clutter and intrinsic multidimensional tissue motion complicate both these tasks.

In transthoracic imaging, reverberant clutter from the chest wall is often super-
imposed over the echoes of the myocardium. Therefore, the signals that are spatially
gated to represent the myocardium could represent a combination of echoes from
scatterers in the myocardium as well as scatterers in the clutter generating tissues.
Estimates of motion computed using these echoes, thus, represent a weighted combi-
nation of the myocardial motion as well the motion of the clutter generating tissues.
Moreover, as indicated previously, clutter could arise from stationary or moving tis-
sues and thus can lead to an increase in bias or variance of the computed motion.
While harmonic imaging provides some degree of clutter suppression, it was found
to be insufficient in a number of cases analyzed here. Techniques aimed at suppress-
ing clutter while retaining RF or IQ data such as spatio-temporal filtering (Demené
et al., 2015), blind-source separation (Gallippi and Trahey, 2002), or model-based
approaches (Byram et al., 2015) could be investigated in the future to “de-clutter”
raw echoes prior to motion tracking.

Even in the absence of acoustic clutter, speckle decorrelation due to non-axial
tissue motion can dramatically increase displacement estimation uncertainty. This
is especially a challenge given the nature of cardiac mechanics. These detrimental
effects could be minimized by employing higher-order displacement estimators such
as iterative (Pesavento et al., 1999) or biased, Bayesian algorithms (Byram et al.,
2013). Multi-dimensional motion estimation schemes based on correlation across
simultaneously acquired lateral and/or elevational beams could also be explored to
improve temporal coherence and consequently limit jitter.

Another approach could be to monitor the level of signal degradation from these
noise sources and adaptively “select” imaging windows where their impact is likely
to be low. Metrics such as contrast and temporal coherence that were shown to
correlate with the level of acoustic clutter and displacement estimation jitter, could
be computed in a real-time fashion and used to guide ARFI and SWEI acquisitions.
The yield of “successful” acquisitions could be improved by implementing such an
6.2.3 Deriving Mechanical Properties

The final step of this process hinges on the ability to fit the measured mechanical response to an appropriate material model and derive one or more mechanical properties of clinical interest. The accuracy of the derived mechanical properties can be greatly impacted by the choice of material model as well as the quality of the measured signal. In this work, the myocardium was treated as a linear, elastic, isotropic, homogeneous, and semi-infinite medium that changes only in its Young’s modulus over the cardiac cycle. This assumption, however, is a gross over-simplification of the reality.

Myocardium is a curved layer that is composed of muscular strands that have a highly organized fiber orientation (Rohmer et al., 2007). It has been shown to have viscoelastic properties that can change over the cardiac cycle (Dokos et al., 2002; Huyghe et al., 1991). Violations of these assumptions can be a significant source of noise or bias and can impact ARFI-derived relative stiffness and SWEI-derived absolute stiffness differently. Characterization of the magnitude of these effects through tightly controlled simulation and ex vivo experiments could partially explain the measurement variability that was empirically observed in these studies.

6.3 Physiological Considerations

Aside from the aforementioned factors, there are several physiological considerations that are unique to cardiac imaging and should be accounted for in future experiments. Below are a few examples:

i) Heart-rate: The temporal dynamics of the heart are closely tied to the length of the cardiac cycle. Even for healthy volunteers, the relative durations of systole and diastole can vary with changes in heart-rate. In these studies, myocardial stiffness
measurements were made at 35 Hz; this results in 30 samples over a cardiac cycle at a hear-rate of 70 bpm, but only 21 samples at 100 bpm. The optimal sampling rate in time or the number of samples over a cardiac cycle required to accurately capture the temporal dynamics of myocardial stiffness remains an open question. This is likely to be a salient factor if myocardial stiffness measurements are to be implemented alongside a cardiac stress exam where heart rates can be as high as 180 bpm.

ii) Loading Conditions: Myocardial stiffness trends represent the dynamic changes in mechanical properties of the muscle itself and are expected to be independent of loading conditions i.e., the specific end-diastolic and end-systolic pressure and volume co-ordinates. This hypothesis, however, remains to be tested and will likely play a major role in determining the diagnostic utility of myocardial stiffness as a marker of cardiac disease.

iii) Transmural Variations: The analysis here considered the IVS to be uniform in its mechanical properties across its thickness i.e., from the RV side to the LV side. Observed ARF-induced displacements, however, showed a consistent trend of higher displacements or lower apparent stiffness on the RV side compared to the LV side. This could be a manifestation of several confounding factors such as the RV side being the proximal (shallower) end in both views, boundary conditions (fluid-to-solid on the RV side versus solid-to-fluid on the LV side), or true differences in mechanical properties of the IVS (perhaps due to the drastically different pressures in the LV and the RV). These hypotheses could be investigated in future experiments.

Developing a clear understanding of the impact of such factors as well as how they are likely to vary in healthy versus diseased states will be critical before in vivo measurement of dynamic myocardial stiffness can be used for diagnostic decision-making.
Appendix A

Characterizing the Influence of Clutter and Electronic Noise on Transthoracic Acoustic Radiation Force Impulse Imaging

A.1 Introduction

Artifacts in ultrasound imaging can broadly be categorized into two groups: acoustic clutter and electronic noise. Clutter represents improper localization of received echo signals i.e., a discrepancy between the spatial location of the scatterers that generate echoes and their reconstructed position on the processed (beamformed) data or image. It can arise from a variety of sources such as reverberation between tissue layers, presence of strongly scattering (bright) off-axis structures, and phase-aberration in received echo signals due to local mis-matches in the speed of sound (Pinton et al., 2011). Alternatively, electronic noise is a result of poor penetration of ultrasound into the body and amplification of thermal noise within the analog circuitry. This leads to decreased signal-to-noise ratio of the received echo signals due to greater relative contribution of electronic noise.

Acoustic clutter appears as a stable haze on B-mode and can resemble the char-
acteristic speckle texture of ultrasound images. Sources of clutter are abundant in
the transthoracic imaging environment; the chest wall is composed of several tissue
layers (skin, muscle, and bone) which can result in strong reverberation as well as
phase aberration. Additionally, the heart is surrounded by highly scattering tissues
such as bone, lung, and pericardium. While clutter is largely considered to be a
stationary phenomenon in the case of abdominal imaging, this is not necessarily true
for cardiac imaging. Clutter, in echocardiography, can also arise from cardiac as well
as extra-cardiac structures that move with the respiratory and/or the cardiac cycles
(Lediju et al., 2009).

Electronic noise, in comparison, has a spatially and temporally random, “twin-
kling” appearance on B-mode images. It is most noticeable when imaging at large
depths (>10 cm) or in anechoic or hypoechoic structures such as cardiac chambers.
It is a consequence of the attenuation of ultrasound as it propagates through the
body. In the case of transthoracic imaging, the propagation path includes highly
attenuating tissue of the chest wall (Mast, 2000). Thus, electronic noise could also
appear at shallower imaging depths.

For traditional echo amplitude-based ultrasonic imaging modes, such as B-mode
and M-mode, both acoustic clutter and electronic noise lead to loss of contrast, degra-
dation in border delineation, and consequently a lowering of image quality. Their
impact on ultrasound imaging modes that involve motion tracking, however, can be
quite different. In simulation, stationary clutter has been shown to introduce a bias
into micron-level displacement estimates (Pinton et al., 2006). Electronic noise, on
the other hand, lowers the correlation coefficient between successive tracking pulses
(through time) and can lead to a dramatic increase in the variance of displacement
estimates (Walker and Trahey, 1995).

The work presented herein, demonstrates the impact of acoustic clutter and elec-
tronic noise on acoustic radiation force impulse (ARFI) imaging. The influence of

132
clutter, generated from both stationary and moving tissues, as well as electronic noise is demonstrated on an single ARFI ensemble acquired on an elasticity phantom and on \textit{in vivo} transthoracic M-mode ARFI images.

A.2 Methods

ARFI acquisitions were performed using the system outlined in Chapter 5. ARFI ensembles are shown for phantom data acquired on a CIRS, Model 039 elasticity phantom (CIRS Inc., Norfolk, VA, USA) with a Young’s modulus of 3 kPa. \textit{In vivo} transthoracic M-mode ARFI data was taken, for a single cardiac cycle each, from three “successful” acquisitions as described in Chapter 5.

Stationary clutter i.e., clutter generated from stationary scatterers/tissue layers, was modeled using IQ data acquired on a uniform speckle generating phantom. Axially moving clutter was modeled by imparting an axial displacement through time to the IQ data acquired on the uniform speckle generating phantom. Non-axially moving clutter was modeled by manually moving the probe in the lateral/elevational direction during the acquisition on the speckle generating phantom. Clutter moving with an ARF-induced motion profile was modeled using IQ data from M-mode ARFI acquisitions performed on a CIRS Model 039 elasticity phantom with a Young’s modulus of 12 kPa. Electronic noise was modeled using complex white gaussian noise. Five speckle realizations of each type of noise were generated.

The magnitude of clutter/electronic noise were scaled to a desired noise level with respect to the magnitude of the “uncorrupted” IQ data for the 3 kPa phantom acquisition or the \textit{in vivo} acquisitions (constrained to within the septum). The scaled noise signals were added to the “uncorrupted” IQ data to generate “noisy” IQ data which was then used for all subsequent processing steps. Displacement estimation, motion filtering, and reconstruction of M-mode ARFI images was performed exactly as described in Chapter 5. In the case of the \textit{in vivo} data, metrics of signal strength

133
(mean ARF-induced displacement over the cardiac cycle), tracking fidelity (contrast, temporal coherence, and spatial similarity), and ARFI-derived indices of dynamic myocardial stiffness (ratio, rates and time constants of relaxation and contraction) were also computed. Trends of these quantities as a function of noise level, ranging from -40 to 20 dB, for each type of noise were analyzed.

A.3 Results and Discussion

Figures A.1 illustrates the impact of stationary clutter and electronic noise on the displacement profiles in an ARFI ensemble. As observed in previous simulation studies, the addition of stationary clutter, which has no axial displacement and is perfectly correlated across time, leads to a consistent downward bias in the estimated displacement. The magnitude of this bias is observed to be directly proportional to the level of stationary clutter and independent of displacement amplitude. Stationary clutter does not appear to impact the uncertainty of the displacement estimates. In contrast, electronic noise, which is random through time and therefore uncorrelated, leads to jitter in the displacement estimates without introducing any systematic bias. Additionally, jitter level is correlated with the magnitude of the electronic noise.

Figures A.2 depicts the same trends for moving clutter. The effects of moving clutter can vary depending on the direction and velocity of the clutter generating scatterers/tissue layers. Clutter generated by moving tissues could potentially move in all three dimensions. For simplicity, only uni-directional motions were considered here. Axially moving clutter was differentiated from clutter moving in the lateral/elevational (non-axial) directions since axial motions are captured when using phase-based displacement estimators while non-axial motions lead to speckle decorrelation. Clutter generated from tissues moved by the ARF excitation represents a special case of axially moving clutter.

Axially moving clutter, both due to intrinsic and ARF-induced motion, remains
correlated through time, provided the kernel used to compute the correlation coefficient is allowed to move (in the axial direction) so as to capture the peak correlation. Much like stationary clutter, it leads to a bias in the estimated displacement. The magnitude of this bias is again directly related to the clutter level. Its direction, however, can be upward or downward depending on the axial motion profile of the clutter generating scatterers/tissue layers.

Clutter moving in the lateral/elevational directions leads to incremental speckle decorrelation. The rate of this decorrelation is related to the velocity of non-axial motion as well as the speckle size (which in turn is determined by the spatial profile of the tracking beam) (Friemel et al., 1998). Compared to electronic noise, where the jitter level is independent of time and related only to the noise level, the jitter level for non-axially moving clutter increases incrementally with the level of speckle decorrelation. Additionally, given its partially correlated nature through time, it also introduces a downward bias to the estimated displacement.

The biased motion profile that is introduced due to clutter that moves as a result of intrinsic tissue motion (as opposed to ARF-induced motion) is likely to be compensated by motion filters. However, this is not the case for clutter that moves due to ARF-induced motion. The temporal trend of the biased motion profile, in this case, is similar to the ARF-induced motion profile in the underlying “uncorrupted” IQ data and thus likely to pass through the both frequency- or recovery-based motion filters.

Figure A.3, A.4, A.5, and A.6 depict the qualitative impact of stationary clutter, electronic noise (random and correlated across simultaneously acquired azimuthal angles), and ARF-induced moving clutter, respectively, on an in vivo M-mode ARFI dataset. The biasing effect of both forms of clutter and the amplification of jitter due to electronic noise on the spatio-temporal consistency of the M-mode ARFI images as well as the displacement trend over the cardiac cycle can be observed.
Figure A.7, A.8, A.9, and A.10 illustrate trends of signal strength as quantified by the mean ARF-induced displacement (within the septum over the cardiac cycle), metrics of tracking fidelity (contrast, temporal coherence, and spatial similarity), and indices of dynamic myocardial stiffness (ratio, rates, and time constants of relaxation and contraction) as a function of noise level for stationary clutter, electronic noise (random and correlated across simultaneously acquired azimuthal angles), and ARF-induced moving clutter, respectively, on three \textit{in vivo} M-mode ARFI datasets.

A.4 Conclusion

These results demonstrate that the various sources of noise in the transthoracic imaging environment can have a range of effects on motion tracking-based ultrasonic applications such as ARFI. Clutter leads to bias in the measured displacements. The direction of bias is determined by the axial motion profile (or lack thereof in the case of stationary clutter) of the clutter generating tissues as well as their relative magnitude compared to the echoes of the targets of interest. Clutter that moves in the lateral/elevational directions as well as electronic noise lead to speckle decorrelation and a consequent increase in jitter. Contrast was found to be degraded regardless of the type of noise being added. Temporal coherence and spatial similarity, on the other hand, trended differently based on the type of noise added. While the individual noise types were analyzed separately here, they are unlikely appear in isolation under \textit{in vivo} imaging environments. An unpredictable and weighted combination of all these noise sources could be present in any given imaging scenario. The combination of these metrics could be used to differentiate between and assess the level of different types of noise in transthoracic ARFI.
Figure A.1: Effect of stationary clutter and electronic noise on displacement estimation in an ARFI ensemble. IQ data (converted to RF) for the “uncorrupted” signal (left column) and stationary clutter/electronic noise (middle column top/bottom) are shown in black. Profiles of axial displacement and correlation coefficient (through time) for the same are shown below the corresponding echo plots. The right column shows displacement trends computed using the “noisy” IQ data for a number of noise levels; noise level increases incrementally from green to blue. The addition of stationary clutter leads to a downward bias in the measured displacement which increases with the magnitude of stationary clutter. In the case of electronic noise, increasing the noise level yields an increase in jitter.
Figure A.2: Effect of moving clutter on displacement estimation in an ARFI ensemble. Echo plots, displacement profiles, and correlation coefficient trends are laid out as described in Figure A.1. Increasing the magnitude of axially moving clutter as well as clutter moving with ARF-induced motion results in a systematic bias towards the motion profile represented in the clutter signal. The addition of clutter moving in the lateral/elevational directions leads to a downward bias as well as a progressive increase in jitter through time.
Figure A.3: Effect of stationary clutter on an 

in vivo M-mode ARFI image. The B-mode image is shown at the top. The M-mode image with ARFI overlay (in color), the ECG trace, and ARF-induced displacement (mean over depth) within the septum (for all seven simultaneously acquired azimuthal angles) are shown for various noise levels. Clutter magnitude with respect to the magnitude of the septum (in the “uncorrupted” IQ data) is shown in the top right hand corner of the M-mode images. A clear cyclic trend of ARF-induced displacement over the cardiac cycle is observed in the “uncorrupted” data. The downward bias due to stationary clutter starts to become noticeable at a noise level of -12 dB and increases sharply beyond that (with increasing noise level). The ARF-induced displacement trend is nearly imperceptible at a noise level of 6 dB. Displacements at all simultaneously acquired azimuthal angles show an identical trend.
Figure A.4: Effect of electronic noise (random across simultaneously acquired azimuthal angles) on an *in vivo* M-mode ARFI image. The subplots are laid out as described in Figure A.3. The increase in jitter with increasing magnitude of electronic noise is evident in the spatio-temporal variance on the ARFI overlay as well as the displacement traces.
Figure A.5: Effect of electronic noise (correlated across simultaneously acquired azimuthal angles) on an *in vivo* M-mode ARFI image. The subplots are laid out as described in Figure A.3. The presentation of jitter in this case is mostly similar to Figure A.4. The only difference is that, at high noise levels, the jitter realization, while random through time, is correlated across the simultaneously acquired azimuthal angles. This is best depicted at a noise level of 12 dB.
Figure A.6: Effect of clutter moving with the ARF excitation on an *in vivo* M-mode ARFI image. The subplots are laid out as described in Figure A.3. Increasing clutter magnitude, in this case, leads to a bias towards the ARF-induced displacement in the clutter (6 μm). Similar to the stationary clutter, it becomes noticeable at a noise level of -12 dB and rises rapidly.
Figure A.7: Effect of stationary clutter on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. The three traces (red, blue, and black) represent M-mode ARFI data from one cardiac cycle on three different volunteers. The lines and shaded regions represent the mean and standard deviation for each quantity over the five speckle realizations of noise. Increasing the level of stationary clutter leads to a decrease in the measured displacement i.e., signal strength. It also leads to a decrease in contrast and spatial similarity, but does not impact temporal coherence.
Figure A.8: Effect of electronic noise (random across simultaneously acquired azimuthal angles) on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. Layout of plots is as described in Figure A.7. Increasing the level of random electronic noise does not show a significant bias in the measured displacement. Higher variance across speckle realizations, however, is observed for high noise levels. Contrast, temporal coherence, and spatial similarity all show a monotonic decrease with increasing noise level.
Figure A.9: Effect of electronic noise (correlated across simultaneously acquired azimuthal angles) on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. Layout of plots is as described in Figure A.7. Increasing the level of correlated electronic noise shows similar trends as the random electronic noise with the exception of spatial similarity which is found to decrease slightly and then reverse course for high noise levels. This trend can be attributed to the deterministic nature of the displacement estimation process. At high noise levels, even though the measured displacement has high jitter, the correlated electronic noise yields an identical realization of jitter at all azimuthal angles, thereby increasing their spatial similarity.
Figure A.10: Effect of ARF-induced moving clutter on signal strength, metrics of tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness as a function of noise level. Layout of plots is as described in Figure A.7. Increasing the level of ARF-induced moving clutter results in a spurious increase in signal strength. Contrast, again, is found to decrease monotonically. Temporal coherence and spatial similarity, however, remain relatively high and are observed to be insensitive to the level of ARF-induced moving clutter.
Appendix B

Parameters Impacting Accuracy of Acoustic Radiation Force Impulse Imaging-derived Stiffness Ratios: A Simulation Study

B.1 Introduction

Characterization of the mechanical properties of myocardium has been a topic of significant research over the last few years. Several ultrasound-based methods, such as ARFI and SWEI, have been employed to measure myocardial stiffness in a variety of settings from highly invasive environments such as open-chest preparations to non-invasive procedures such as transthoracic imaging. While SWEI allows for assessment of tissue mechanical properties in an absolute sense, in the context of cardiac imaging it has only been shown to be feasible in diastole. ARFI, on the other hand, provides a relative estimate of tissue mechanical properties and has been shown to be viable over the entire cardiac cycle. One metric of myocardial performance that has been investigated is the ARFI-derived diastolic-to-systolic stiffness ratio. While this ratio is indicative of the change in stiffness of the myocardium over the cardiac cycle, its quantitative relationship to absolute material properties has yet to be thoroughly
ARFI images can be presented in a variety of ways: using peak displacement, time to peak displacement, displacement at a fixed time, or by quantifying the rate of recovery. Peak displacement is the preferred display metric. However, in practice, peak displacement may not be available due to limitations related to the sampling rate or the duration of high-amplitude reverberations from the ARF excitation pulses. In their absence, displacement at the earliest possible time point is used to display ARFI images. Given that, materials with different Young’s moduli achieve peak displacement at slightly different times and show variations in the rates of recovery, a quantitative stiffness ratio derived using displacement at a fixed time could suffer from systematic inaccuracies. This work aims to investigate some potential factors that could introduce bias into ARFI-derived stiffness ratios and quantify their impact.

B.2 Methods

Finite-element (FE) simulations were performed to study the parameters governing the relationship between ARFI-derived stiffness ratios and absolute material properties. ARF-excitations were simulated in elastic, isotropic materials over a range of Youngs moduli relevant to myocardial mechanics (3 kPa to 36 kPa). The dynamic response of these excitations (both on-axis displacement-recovery and shear wave propagation) were tracked in Field II using focused as well as plane wave tracking configurations. ARFI-derived stiffness ratios, for each case, were compared with known material elasticity ratios for a variety of relevant parameters. The details of the simulation parameters were as described in Chapter 4. Bias in measured stiffness ratios with reference to simulated stiffness ratios were analyzed using the raw FE data as well as displacement data after ultrasonic tracking. The effect of interrogation time, ultrasonic tracking, and reference Young’s modulus are presented.

Stiffness ratio, in this context, refers to the ratio of Young’s moduli ($R_E$). For
incompressible, elastic materials the ratio of shear wave speed ($R_c$) is the square root of the ratio of Young’s moduli.

B.3 Results and Discussion

Figure B.1(a) depicts simulated ARF-induced FE displacement profiles (not tracked) for materials with Young’s moduli of 3 kPa and 12 kPa. The stiffer material not only shows lower peak displacement but also achieves peak displacement earlier in time. Figure B.1(b) shows the ratio of the two curves as a function of time. The solid red, green, and blue vertical lines correspond to three fixed interrogation times (0.5, 1.5, and 2.5 ms, respectively). The solid and dashed cyan lines indicate the temporal position of the peak displacement for the 3 kPa and 12 kPa material, respectively. The horizontal lines in represent the ratio of elasticity ($R_E$) and ratio of shear wave speed ($R_c$). Figure B.1(c) shows a comparison of the simulated versus measured ratios for all materials using 3 kPa as the reference. Stiffness ratio is severely underestimated when using the early time point, 0.5 ms (shown in red). The magnitude of underestimation increases with the intrinsic ratio. For the later two time points, 1.5 ms (green) and 2.5 ms (blue), there appears to be minor overestimation; its magnitude, however, is below 20% for ratios <3.5. Ratio of peak displacement aligns well with the ratio of shear wave speed over the range of simulated materials.

Figure B.2 shows a comparison of the ratios computed using raw FE displacement data versus after ultrasonic tracking. Ultrasonic tracking can introduce subtle changes into displacement-recovery trends due to averaging over the tracking point-spread-function and speckle bias. The error bars for the ratios computed using tracked displacements represent the standard deviation over 25 speckle realizations (i.e., all combinations of 5 speckle realization for the numerator and denominator). Ratios computed using the tracked displacements are slightly lower than the ones computed using raw FE displacements. For the 1.5 ms case, this underestimation
leads to improved alignment with the simulated stiffness ratio for the range of materials tested. Ratios of the peak displacement using FE versus tracked displacements do not show any significant deviation.

Figure B.3 shows the effect of varying the reference stiffness on the relationship between measured versus simulated stiffness ratios. Bias in the measured stiffness ratio is observed to be dependent on the reference stiffness used. Using stiffer reference materials leads to a larger overestimation of the stiffness ratio.

B.4 Conclusion

These results indicate that: i) ARFI-derived stiffness ratios are impacted by: time of interrogation, tracking configuration, and absolute elasticity, ii) Ratio of peak displacement is indicative of the ratio of shear wave speeds, and iii) For materials in the range of 3 - 36 kPa, ARFI-derived stiffness ratios using tracked displacements interrogated at 1.5 ms align well with simulated stiffness ratios.
Figure B.1: Displacement-recovery profiles for a pair of representative materials (3 kPa, 12 kPa) (a), ratio over time (b) and comparison of measured vs. simulated stiffness ratio for all combinations of simulated materials as a function of interrogation time (c). Vertical lines in (a) and (b) represent the interrogation times evaluated; fixed times in red, green and blue and $t_{peak}$ in cyan. Horizontal lines in (b) represent the ratio of elasticity ($R_E$) and ratio of shear wave speed ($R_c$). Shaded regions in (c) represent $\pm 20\%$ uncertainty in measured ratios. Ratio is underestimated at the earliest time point and overestimated at the latter two, the effect is exacerbated for larger ratios. Ratio of peak displacement aligns well with shear wave speed ratio.
Figure B.2: Ratios of raw FE displacements vs. displacements tracked with an F/2.6 configuration for the interrogation times in Figure B.1 (a,b,c,d). Error bars represent uncertainty over 25 speckle realizations. Ratios from tracked displacements at 1.5 ms align well with the simulated stiffness ratios while those from peak displacements align well with shear wave speed ratios. Magnitude of uncertainty due to speckle realizations is significantly smaller than the ±20% (shown in the shaded regions).
Figure B.3: Comparison of measured vs. simulated stiffness ratios for a range of reference Young’s moduli (denominator). Measured ratio is progressively overestimated with increases in reference stiffness. The overestimation is within ±20% error for ratios below 3 but is more pronounced for larger ratios.
Appendix C

A Novel Drift Compensation Algorithm for Improved Beat-to-Beat Repeatability of Myocardial Strain Imaging: Preliminary in vivo Results

C.1 Introduction

Strain imaging is rapidly gaining traction as a means to assess cardiac function by tracking the cyclic deformation of the myocardium. Compared to traditional measures such as ejection fraction, global myocardial strain has been shown to be have superior prognostic value for detection of adverse cardiac events (Kalam et al., 2014). Similarly, regional myocardial strain has been shown to be useful for identifying ischemia (Edvardsen et al., 2001) and myocardial infarction (Weidemann et al., 2003).

Myocardial strain can be measured with ultrasound using three main techniques: tissue doppler imaging (TDI) (Heimdal et al., 1998), speckle tracking (Kaluzyński et al., 2001; Tanaka et al., 2010), and elastic image registration (Elen et al., 2008). Recent results have shown that elastic image registration has potential to outperform speckle tracking and yield more reliable strain measurements (Heyde et al., 2013). While the techniques mentioned above use mathematically distinct algorithms to
compute displacements and strains from raw ultrasound images; their reliability is hampered by similar drawbacks such as angular dependence, speckle decorrelation and heart rate variability. The major consequence of these effects is the introduction of drift in the tracked displacements over multiple cardiac cycles. Given that strain is computed as a derivative of the tracked displacements, it is heavily impacted by drift and is therefore rendered unstable for prolonged acquisitions.

In this work, we present a method to improve the stability and repeatability of displacement tracking and strain estimation over multiple consecutive cardiac cycles using a displacement-based drift compensation algorithm. The performance of this algorithm was evaluated under *in vivo* imaging conditions on healthy volunteers.

C.2 Methods

C.2.1 Data Acquisition

A clinical ultrasound system (Siemens *SC 2000*™) and a cardiac phased array (4V1c) were used to acquire B-mode cine clips on 10 healthy volunteers. Cine clips were acquired in the parasternal long and short axis views, recorded at a frame rate of 40 Hz and were 5 seconds long (so as to encompass multiple consecutive heart beats). Data collection was performed at the out-patient cardiology clinic in accordance with an IRB approved protocol (Duke IRB Pro00032068)).

C.2.2 Strain Computation

Myocardial displacements and strains were derived from the B-mode cine clips using an elastic image registration algorithm (Heyde et al., 2013). This technique operates on successive pairs of B-mode frames denoted as reference and floating frames. In this method, non-rigid deformations are applied to the floating frame so as to spatially match it to the reference frame. This framework is implemented as an optimization problem and yields a spatial transformation which is used as the inter-frame displace-
ment field. The inter-frame displacement field consists of both the axial and lateral components of motion for each pixel in the pair of frames. Inter-frame displacement fields are then combined in a cumulative fashion to generate two-dimensional displacement data over the entire cine loop.

Displacements are combined starting with the inter-frame displacement field at the first end-diastolic (ED) frame within the acquisition. The heart is assumed to return to the origin (zero cumulative displacement for each pixel) after each complete cardiac cycle i.e. at every subsequent ED frame. Radial, longitudinal and circumferential strains are computed by taking spatial derivatives of the displacement fields in the two orthogonal directions with respect to the orientation of the myocardial wall of interest. The parasternal long axis view yields radial, longitudinal strains while the short axis view yields radial, circumferential strains.

C.2.3 Error Propagation and Drift

Uncertainty in displacement tracking using elastic image registration can be introduced through three potential mechanisms: tracking error, accumulation error and re-positioning error. Tracking errors arise from decorrelation of speckle between a pair of frames likely due out-of-plane motion or large in-plane motion (compared to speckle size). Accumulation errors are introduced through the process of cumulatively summing independent inter-frame displacements, each of which can have a small random component. This effect is exacerbated for longer acquisitions (with many frames) and largely contributes to drift in the tracked displacements. Lastly, re-positioning errors occur when the assumption of stationarity between successive ED frames is found to be invalid i.e. when the heart wall does not return perfectly to its initial position at the end of every cardiac cycle. Displacement drift is the manifestation of one or more of these error mechanisms.
C.2.4 Drift Compensation

In this work, we propose a drift compensation scheme that aims to suppress the effect of accumulation and re-positioning errors.

It addresses accumulation errors by altering the process of combining inter-frame displacements from a simple cumulative sum to a weighted cumulative sum of displacement fields computed in the forward and backward direction. In this modified formulation, inter-frame displacement fields are computed twice per pair of frames, with each frame serving as the reference as well as the floating frame. The combined displacement is then computed as a linearly weighted combination of the two displacement fields over individual cardiac cycles, i.e. from one ED frame to the next. This process is independently repeated for each successive cardiac cycle to span the entire acquisition.

Re-positioning errors are addressed by explicitly testing the assumption of stationarity between adjacent ED frames. This is performed by computing displacement fields between pairs of adjacent ED frames using the same elastic image registration technique. When the assumption of stationarity is valid the resultant displacement field is negligible; however if there is substantial motion between adjacent ED frames then it is captured and accounted for by adjusting the position of the tracked points of interest by the inter-diastolic displacement field. The final cumulative displacement trace is then computed as a combination of weighted cumulative sums over individual cardiac cycles and spatial adjustments to the point grid at each end-diastole.

C.3 Results and Discussion

Displacement drift over successive cardiac cycles is illustrated in Figure C.1. The B-mode images show the inter-ventricular septum (in a parasternal long axis view) at four successive ED frames, with the tracked positions of the points of interest
Figure C.1: Consecutive end-diastolic frames with positions of the points of interest (green dots) with and without drift compensation; panel (a) and (c) respectively. Panel (b) shows the ECG trace with the black lines indicating the temporal position of the frames. Panel (a) depicts substantial warping of the point grid which gets incrementally worse with each cardiac cycle. This effect is largely rectified after applying drift compensation, resulting in a spatially stable point grid over the duration of the acquisition.

marked in green dots. The top row represents the raw case, while the bottom row shows the result after applying displacement-based drift compensation. The ECG signal is shown in the middle row with vertical black lines indicating the temporal position of the ED frames. Warping of the point grid is evident as early as ED 2 in the case of raw processing and appears to get incrementally worse at subsequent ED frames. In contrast, after compensation, the point grid maintains its spatial integrity at the end of every cardiac cycle in the acquisition. Minor deviations in the positions of the points of interest can be observed in the bottom row; this can be attributed to tracked relative motion of the myocardium between successive ED frames.

The temporal evolution of drift over multiple cycles and its effects on radial strain are further demonstrated in Figure C.2. Both axial and lateral displacement traces (of the individual points of interest) appear to diverge from each other over the four cardiac cycles. This drift leads to erroneous strain estimates by artificially introducing spatial gradients in the tracked positions. The compensation algorithm
Figure C.2: Cumulative displacements in the axial (panels (a), (b)) and lateral (panels (c), (d)) dimensions for the raw as well as compensated case. Panels (g) and (h) show the corresponding radial strain; while the ECG trace is represented in panels (e) and (f). Each displacement trace represents a single tracked point in the region of interest. The strain curve and shaded region represents the spatial distribution of radial strain at each time point. Drift between individual points is appreciable in both the axial and lateral displacements in the raw case and is largely mitigated after compensation. The strain looks similar for the first cardiac cycle but degrades rapidly in the absence of drift compensation.

largely corrects for this effect and yields significantly more repeatable strain trends between each cycle. The vertical black lines indicate the times in each cardiac cycle at which end-systolic strain is computed.

In the simplest sense, drift can be quantified on a point-by-point basis within an acquisition as the absolute value of the difference between the position of a point in ED frame n compared back to its position in ED frame 1. Analyzing the distribution of this quantity across all points within the ROI and at successive ED frames can give us a sense of the degree to which the point grid has translated and/or warped. Drift, quantified in this manner is shown in Figure C.3 (a). In the raw case, the dramatic rise of the mean and standard deviation of drift over each heart beat suggests
significant warping of the point grid. For the compensated case, the stability of the point grid results in comparatively smaller changes in the drift.

Lastly, the impact of drift-compensation can be summarized by analyzing the end-systolic radial strain ($\text{ESS}_R$). $\text{ESS}_R$ is a commonly used clinical metric derived from strain imaging and associated with left ventricular function. Figure C.3 (b) shows the spatial distribution of $\text{ESS}_R$ over five successive cardiac cycles. The increase in standard deviation of strain over the acquisition (in the raw case) is predominantly an effect of drift. The compensated case, on the other hand shows a highly stable strain distribution across beats.

Table C.1: Drift in the point grid over multiple cardiac cycles across all acquisitions (n=10).

<table>
<thead>
<tr>
<th>Drift (mm)</th>
<th>Beat 1</th>
<th>Beat 3</th>
<th>Beat 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw</td>
<td>-</td>
<td>3.97 ± 1.9</td>
<td>5.17 ± 3.06</td>
</tr>
<tr>
<td>Compensated</td>
<td>-</td>
<td>2.28 ± 1.49</td>
<td>1.85 ± 1.06</td>
</tr>
</tbody>
</table>

The mean and standard deviation of drift over all acquisitions in the study (n=10) are shown in Table C.1. In the raw case, drift is found to increase by 30% from beat 3 to beat 5. Post-compensation, the mean drift at beats 3 and 5 is roughly half of its value in the raw case. A non-zero drift in the compensated case could be indicative of either real motion of heart from one beat to the next or tracking error associated
with computing displacements between ED frames.

Table C.2: End-systolic radial strain over multiple cardiac cycles across all acquisitions.

<table>
<thead>
<tr>
<th>ESS$_R$ (%)</th>
<th>Beat 1</th>
<th>Beat 3</th>
<th>Beat 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw</td>
<td>38.47 ± 16.8</td>
<td>63.24 ± 36.82</td>
<td>78.64 ± 47.89</td>
</tr>
<tr>
<td>Compensated</td>
<td>37.43 ± 17.44</td>
<td>38.33 ± 19.75</td>
<td>39.44 ± 24.69</td>
</tr>
</tbody>
</table>

Table C.2 shows end-systolic strain radial strain (ESS$_R$) across all acquisitions (encompassing both parasternal long and short axis views) (n=10) as a function of beat index for the raw and compensated cases. The ESS$_R$ is nearly identical between the raw and compensated cases at beat 1. However, in the raw case the mean and standard deviation vary dramatically at beat 3 and 5; whereas as they stay stable and consistent in the compensated case. This demonstrates the improved beat-to-beat repeatability of strain estimates after the application of displacement-based drift compensation.

C.4 Conclusion

These results demonstrate the efficacy of displacement-based drift compensation in improving beat-to-beat repeatability and consistency of strain measurements made using elastic image registration. Application of this method can thereby allow for the characterization of regional myocardial strain over prolonged multi-beat acquisitions. This could open new opportunities for myocardial strain imaging wherein sensitivity to changes in strain patterns over short durations is valuable.

Future work in this direction will look to investigate a "fully-sampled" approach to drift compensation wherein more than one phase of the cardiac cycle (only ED in the current implementation) are used to ascertain spatial stability of the points of interest and also adaptive strain-based localization of cardiac phases.
Bibliography


Biography

Vaibhav (V) Rajesh Kakkad was born July 23, 1988 in Nagpur, India. He grew up in India as well as Oman and moved to the United States in 2006 to attend college at the University of Rochester where he was awarded a Genesee Scholarship. He completed a B.S. in Biomedical Engineering in 2010 with highest departmental distinction and was inducted to Tau Beta Pi (National Engineering Honor Society). He remained at the University of Rochester through 2011 on a Take Five Scholarship to study sociology and psychology. Subsequently, he moved to Duke University to pursue a Ph.D. in Biomedical Engineering with a focus on novel clinical applications of diagnostic ultrasound. Under the mentorship of Dr. Gregg Trahey, he specifically studied acoustic radiation force-based elasticity measurement methods for cardiac applications and spatial coherence-based imaging techniques for fetal scanning. At Duke, he was awarded the Fritz Thurstone Graduate Fellowship, was part of the Duke Scholars in Cardiovascular Medicine Program, and served as a Tech Transfer Fellow at the Duke Office of Licensing and Ventures.

Selected Other Publications
