INNOVATIONS IN ULTRASOUND SHEAR WAVE ELASTOGRAPHY

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Abstract

Tissue stiffness is a strong biomarker of the state of tissue health. Accurate assessment of tissue stiffness provides significant clinical values for early detection, diagnosis and prognosis of diseases such as cancer and fibrosis. In the last two decades, ultrasound shear wave elastography (SWE) has emerged as a promising imaging tool that is capable of noninvasively, quantitatively and directly estimating tissue stiffness. Ultrasound SWE has showed great promises in numerous clinical applications such as early detection of breast cancer and accurate noninvasive staging of liver fibrosis. However, ultrasound SWE also suffers from technical challenges that undermine its diagnostic value and limit its clinical applications. The overall goal of the research reported in this thesis, therefore, is to overcome these technical challenges and make ultrasound SWE a faster and better approach. This thesis research identified the key challenges that reside in the shear wave generation, shear elasticity map reconstruction, shear wave detection and SWE implementation of ultrasound SWE, and proposed four novel techniques including Comb-push Ultrasound Shear Elastography (CUSE), fast shear compounding, shear wave detection with harmonic imaging, and Time Aligned Sequential Tracking (TAST) to address these challenges, respectively. These novel techniques developed in this thesis research have great potentials to substantially improve the performance of ultrasound SWE and widen its spectrum of clinical applications.
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Chapter 1

Introduction

1.1 Background

In 400 B.C., Hippocrates described the correlation between tissue stiffness and tissue pathology in "The Book of Prognostics":

“… then, as are painful, hard, and large, indicate danger of speedy death; but such as are soft, free of pain, and yield when pressed with the finger, are more chronic than these…”

Hippocrates’ discoveries revealed an important medical fact that tissue stiffness is a strong indicator of tissue health state. He also practiced and described the art of palpation (“pressed with the finger”) and showed its usefulness in disease diagnosis. For over two millennia, Hippocrates’ theory of tissue stiffness has been vetted by numerous clinical practices and scientific research. The technique of palpation is still a widely used diagnostic tool in the clinic until today. Modern scientific and technical advancements in biology elucidated Hippocrates’ tissue stiffness theory and found that pathology induced tissue stiffness change is caused by exudation of fluids from the vascular system into the extra- and intracellular space causing an increase in interstitial pressure
that causes in turn the increased stiffness, or replacement of the tissue damaged by disease processes with a stiff collagen-based matrix which is a precursor to fibrosis [1]. This stiffness change can be as large as 90-fold in breast cancer tumors [1]. The tissue stiffness change is also a common symptom in a wide spectrum of diseases such as breast cancer, thyroid cancer, liver fibrosis, prostate cancer, and heart failure [1-8].

Measuring such pathology induced tissue stiffness change is of paramount clinical significance for early detection, diagnosis and prognosis of diseases. While palpation still remains as the easiest and most popular way of assessing tissue stiffness, its diagnostic value is undermined by its low sensitivity and repeatability. Biopsy is the standard for diagnosis of many cancerous and fibrotic diseases thanks to its capability of microscopically examining the histological architecture of the tissue cell. However, biopsy is an invasive technique that can cause discomfort and complications to patients [9]. Biopsy is also a partial approach that only samples a tiny portion of the tissue and is therefore limited by sampling variability [10].

Motivated by the clinical significance and necessity of sensitively, consistently, and noninvasively assessing tissue stiffness, a new branch of imaging called “elastography” emerged about two decades ago. The term “elastography”, which means elasticity imaging, was created by Professor Jonathan Ophir, who described an approach of using ultrasound to estimate strain and elastic modulus
of soft tissues [11]. Professor Ophir’s work triggered an avalanche of research works in the field of elastography, yielding hundreds of publications and dozens of techniques across various imaging modalities [2]. To date, the body of elastography research is still consistently growing and has found its clinical impact in a variety of applications. A systematic review of all elastography techniques has been established by Professors Greenleaf and Sarvazyan [1, 2]. This dissertation work focuses on developing novel techniques to improve a specific yet important branch of elastography that uses acoustic radiation force-induced shear waves to characterize tissue mechanical properties. The next two sections will give a brief review of this branch of elastography techniques.

1.2 Theory of shear wave elastography

The ultimate goal of elastography is to quantitatively and noninvasively assess tissue mechanical properties. Among all the elastography techniques that have been developed so far, shear wave elastography (SWE) is arguably the best approach that fulfills this goal. The physical parameter measured by SWE that describes tissue stiffness is Young’s modulus (\(E\)), which is given by:

\[
E = \frac{\sigma}{\varepsilon}
\]  

(1.1)

where \(\sigma\) is stress, and \(\varepsilon\) is strain. One can see that by applying a stress on the tissue and measuring the stress-induced tissue deformation (strain), one can recover the Young’s modulus of tissue using Eq. (1.1). Such a process is essentially like palpation. The field of static elastography or strain imaging used
this approach and use ultrasound to measure the tissue response to a given stress. Static elastography and strain imaging measures the tissue deformation induced by externally produced stress (e.g. using the ultrasound probe to press the tissue) or intrinsic tissue deformation (e.g. heart muscle contraction in systole), and assesses tissue stiffness based on the fact that under the same stress, softer tissue deforms more than harder tissue [11, 12]. Such methods can provide a two-dimensional (2D) or three-dimensional (3D) strain map which shows the contrast between the soft and the hard tissue that can be used for disease diagnosis [13]. One limitation of this approach, however, is that the stress term in the numerator of Eq. (1.1) is very challenging to measure and cannot always be assumed to be uniform. With unknown stress, such methods cannot provide direct measures of Young’s modulus of the tissue based on Eq. (1.1), and thus only provide relative and qualitative assessment of tissue mechanical properties. This undermines its clinical usefulness because with different stress situations (e.g. different pressure applied by different operators or different cardiac loading conditions), the strain measurement can be variable and unstable.

An alternative way to estimate mechanical properties of tissue is to use propagating shear waves in the tissue. The study of correlation of the physical properties of shear waves and the mechanical properties of tissue was pioneered by Professor Sarvazyan back in the 1960s [14]. The theory of shear wave
propagation starts with the wave equation. Given an isotropic, elastic, and locally homogeneous medium, shear wave propagation is governed by the wave equation [15, 16]:

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

(1.2)

where \(\mu\) is shear modulus, \(u\) is shear wave displacement, \(\lambda\) is bulk modulus, \(\rho\) is density, and \(t\) is time. Assuming that the wave is divergence-free (the propagating wave is pure shear wave), \(\nabla \cdot u = 0\). Then Eq. (1.2) can be simplified to the Helmholtz equation [15]:

\[
\mu \nabla^2 u = \rho \frac{\partial^2 u}{\partial t^2}
\]

(1.3)

or

\[
\mu = \frac{\rho \frac{\partial^2 u}{\partial t^2}}{\nabla^2 u}
\]

(1.4)

One can see the similarity between Eq. (1.4) and Eq. (1.1): the left side of the equation in both represents the mechanical properties of the tissue in terms of modulus. The right side of the equation in both is expressed in the form of a division. The numerator of Eq. (1.4) is essentially density times the acceleration of the shear wave (second derivative of shear wave displacement gives acceleration), which gives stress. The denominator of Eq. (1.4) is the spatial Laplacian transform of the shear wave displacement, which is essentially a measure of the tissue deformation (i.e., strain) induced by the propagation of the
shear wave. Therefore Eq. (1.1) and Eq. (1.4) are essentially describing the
same physical phenomenon of tissue reaction to a given form of stress. By
introducing a shear wave stress, one can measure both the numerator and
denominator of Eq. (1.4) and obtain the shear modulus of the tissue, which is a
true quantitative measure of tissue mechanical property. Furthermore, in isotropic
materials, Young's modulus ($E$) and shear modulus $\mu$ are related by [16]:

$$\mu = \frac{E}{2(1+\nu)} \quad (1.5)$$

where $\nu$ is Poisson's ratio. Because in soft tissues $\nu$ is very close to 0.5, Eq.
(1.5) becomes to:

$$\mu \approx \frac{E}{3} \quad (1.6)$$

Therefore by measuring shear modulus of the tissue using shear waves, one can
also obtain Young's modulus of the tissue using Eq. (1.6).

The technique that solves Eq. (1.4) is called algebraic direct inversion [17]. In
practice, although both the numerator and the denominator of Eq. (1.4) can be
readily measured in the laboratory, it is still quite challenging to solve Eq. (1.4)
using ultrasonically tracked shear waves due to signal noise [17-19]. The
denominator term of Eq. (1.4) is very vulnerable to noise because second
derivatives have to be taken along the spatial dimension of the shear wave data,
which is typically contaminated by heavy ultrasound speckle noise. In magnetic
resonance imaging (MRI), however, thanks to the relatively lower noise level in
the spatial domain as compared to ultrasound, algebraic direct inversion of Eq. (1.4) is feasible [15, 17].

Another approach to solve for shear modulus of the tissue based on shear wave propagation is to measure the shear wave propagation speed. Using the wave equation, Vappou et al. proposed that [20]:

\[ G = \rho \frac{\omega^2}{k^2} \] (1.1.7)

where \( G \) is the complex modulus of the soft tissue, \( \omega \) is the shear wave frequency, \( k \) is the complex wave number, and \( c_s \) is the shear wave speed. Ignoring the viscous term of tissue (i.e. assuming tissue is pure elastic), Eq. (1.7) can be simplified to:

\[ \mu = \rho c_s^2 \] (1.8)

where \( c_s \) is the shear wave propagation speed. Eq. (1.8) indicates that by measuring shear wave propagation speed, the shear modulus of the tissue can be recovered. Equation (1.8) is the basic equation used by a majority of the current shear wave elastography techniques including the ones that will be proposed in this thesis work. It is worth mentioning that the derivations leading to Eq. (1.8) make assumptions including local homogeneity, isotropy, incompressibility, and pure elasticity. While the homogeneity, isotropy, and incompressibility assumptions hold well in most soft tissues, research has found that most soft tissues are not purely elastic. Research has shown that the
viscosity of the tissue can be nontrivial and measuring viscosity may possess significant clinical value in addition to elasticity measurements such as shear modulus [6, 21-28]. Tissue viscosity gives rise to shear wave velocity dispersion which makes shear modulus $\mu$ and shear wave speed $c_s$ functions of shear wave frequency. This thesis work mainly focuses at recovering the tissue elastic modulus (or the effective modulus of the tissue) using shear waves because a much larger body of research has shown the significance of measuring the shear modulus for disease diagnosis. Meanwhile, tissue viscosity analysis largely resides in the post-processing part of shear wave elastography and uses the same shear wave signals that are used for shear elasticity analysis. Because most of the techniques developed in this thesis focus on the imaging portion of shear wave elastography, the shear waves can be readily used for viscosity analysis as well as elasticity analysis. Only shear elasticity will be considered in this thesis work and it will be presented in terms of the shear modulus $\mu$ or the shear wave speed $c_s$. Equation (1.8) is used throughout the thesis to convert measured shear wave speed to shear modulus.

1.3 Current techniques of ultrasound shear wave elastography

With knowledge of how to estimate tissue stiffness with shear waves, it is now a task to engineer the process and develop approaches to induce shear waves into the tissue. In the last two decades a variety of approaches have been developed by researchers around the world, and in the shear wave elastography
community, these various techniques are largely categorized by the way the shear wave is produced in the tissue. Figure 1.1 shows the majority of current shear wave elastography techniques that are categorized by the shear wave excitation methods.

Figure 1.1 – Current shear wave elastography techniques categorized by shear wave excitation method. This thesis research focuses at developing novel techniques in acoustic radiation force based shear wave elastography (within the dashed box).
Under the category of mechanical excitation, a mechanical apparatus is typically used to externally produce shear waves into the tissue. Magnetic Resonance Elastography (MRE) typically uses an acoustic driver that vibrates at a certain frequency (50 ~ 200 Hz) to produce shear waves [29-32]. Transient Elastography fixes a mechanical shaker onto the ultrasound probe and uses the same ultrasound probe to both produce and track shear waves [33-37]. Sonoelastography uses two mechanical shakers that vibrate at different frequencies to generate a special wave pattern called crawling waves which can be used to assess tissue mechanical properties [38-40]. This technique has also been realized with acoustic radiation force-induced shear waves [41, 42].

Under the category of intrinsic physiological excitation, researchers have shown the feasibility of using intrinsic shear waves that are being produced inside the body to recover tissue mechanical properties. In the heart, Kanai et al. demonstrated the feasibility of using pulsive waves in the myocardium that are produced by the opening of aortic valves during systole to estimate heart wall stiffness [43, 44]. Also in the heart, Dr. Konofagou’s group developed electromechanical wave imaging (EWI) which is capable of noninvasively and transmurally mapping the activation sequence of the heart by tracking the transient strains occurring in response to the cardiac electrical activation [45-49]. Recently Benech et al. and Gallot et al. demonstrated the feasibility of using passive physiological motions to estimate tissue mechanical properties by the
time-reversal approach [50, 51]. In MR elastography, Olsen et al. showed that the heart beat could produce shear waves in the liver and estimated liver stiffness using the intrinsic shear waves [52]; Weaver et al. showed that the blood vessel pulsation can induce harmonic motion in the brain which can be used to estimate brain mechanical properties [53].

This thesis research falls under the category of shear wave elastography that uses acoustic radiation force (ARF) as a source of shear wave excitation. Compared to mechanical excitation approaches, ARF allows shear wave imaging with a single ultrasound probe and does not require a separate mechanical actuator. This is very close to the standard clinical setup of an ultrasound exam and thus very convenient to be used by sonographers and physicians. In addition, no motion artifact to the probe and less out-of-imaging-plane waves that can bias speed measurement will be produced by ARF as compared to mechanical excitations. This greatly simplifies the post-processing of shear waves and provides more reliable estimate of tissue stiffness. Meanwhile, compared to mechanically induced waves, ARF-induced shear waves are transient, sharp and broadband, which provides better spatial resolution and favors shear wave dispersion analysis. Compared to intrinsic shear wave approaches, ARF-based shear wave elastography is more consistent and reliable in producing shear waves into the tissue, and it does not have to be limited to a specific region that must have intrinsically produced shear waves.
Also, shear waves induced by intrinsic physiological motions are typically with very low temporal frequency as compared to the ARF-induced shear waves, which compromises the spatial resolution of the intrinsic shear waves.

Before introducing the different ARF-based shear wave elastography techniques shown in Fig. 1.1, let us take a look at the common components of these approaches. ARF-based shear wave elastography typically uses a long ultrasound “push” pulse on the order of several hundreds of microseconds to produce a shear wave [54, 55]. The push pulse (Fig. 1.2(a)) is similar to a standard ultrasound imaging pulse except that the push pulse duration is much longer (a standard ultrasound imaging pulse is on the order of several tens of microseconds). The long push pulse exerts a force called acoustic radiation force on the tissue. The intensity of the push pulse \( I \) and the resulting acoustic radiation force density \( F \) follow the equation below [56]:

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

where \( \alpha \) is frequency dependent ultrasound attenuation [57] and \( c \) is the ultrasound speed. The exertion of acoustic radiation force in the tissue is like dropping a stone on the surface of a still lake: one can observe waves being produced and propagating away from the location where the stone entered the water. In tissue, a shear wave is produced and propagates away from the push beam (Figs. 1.2(b)-(c)). Figure 1.2 shows that in a typical 2D ultrasound imaging plane, one can see two shear waves – one propagates to the left of the push
beam and the other one propagates to the right of the push beam. It is these shear waves that are tracked and measured to estimate tissue mechanical properties in ARF-based shear wave elastography.

![Figure 1.2](image)

**Figure 1.2 – Ultrasound push pulse and the resulting shear waves.** (a) An ultrasound push pulse in the form of a single focused ultrasound beam. (b) – (c): snapshots of the shear wave propagation movie at different time instants. The shear wave particle velocity signals are shown. Two shear waves were produced on the right and left sides of the push beam and then propagated away from the push beam. Intensity of the shear wave motion was plotted on the same scale.

The second common component of ARF-based shear wave elastography methods is shear wave detection or shear wave tracking. The shear waves shown in Fig. 1.2 were tracked ultrasonically by ultrasound detection beams, which are essentially the same as the ultrasound B-mode imaging beams. There are several different shear wave detection schemes with different detection beams and detection sequences, which will be introduced in more detail in Chapter 5. Regardless of the type of the detection beam and the detection sequence, however, one common physical principle shared by these methods is the shear wave induced scatterer motion estimation using ultrasound. As shown
in Fig. 1.3, shear wave propagation causes local scatterer perturbations. These perturbations can be tracked by pulse-echo mode ultrasound. In two consecutive frames of pulse-echo, the amount of ultrasound radio-frequency (RF) signal shift along the time direction (\( \delta t \)) can be measured by the normalized cross-correlation of RF signal \( s(t_1) \) and RF signal \( s(t_2) \) [58, 59]:

\[
\delta t = \frac{s(-t_1) \ast s(t_2)}{\text{std}[s(t_1)] \text{std}[s(t_2)]} \tag{1.10}
\]

where \( \ast \) denotes convolution and \( \text{std} \) denotes standard deviation. Given that the scatterer moves at a speed of \( v \), the amount of shear wave displacement \( \Delta d \) from time \( t_1 \) to \( t_2 \) is:

\[
\Delta d = v(t_2 - t_1) \tag{1.11}
\]

Given a RF signal shift of \( \delta t \) in time, the amount of RF signal shift in space \( \Delta s \) is:

\[
\Delta s = \frac{c \cdot \delta t}{2} \tag{1.12}
\]

Equating (1.11) and (1.12), one has:

\[
v = \frac{c \cdot \delta t}{2(t_2 - t_1)}. \tag{1.13}
\]

The term \( t_2 - t_1 \) is called pulse-repetition-period, which is related to the pulse-repetition-frequency (PRF) by \( \text{PRF} = 1/(t_2 - t_1) \) in pulse-echo ultrasound and thus Eq. (1.13) can be written as:
\[ v = \frac{c \cdot \delta t}{2PRF}. \]  

(1.14)

The process from Eq. (1.10) to Eq. (1.14) is essentially how the measure of RF signal shift can be converted to shear wave motion in terms of scatterer motion velocity of shear wave particle velocity \( v \). One can easily integrate \( v \) to get shear wave particle displacement \( d \).
In practice, ultrasound RF signals are typically sampled by in-phase/quadrature (IQ) demodulation. The resulting IQ signal can be used to estimate shear wave motion. A number of methods have been proposed [60-63].

Figure 1.3 – Schematic plots of shear wave motion tracking with ultrasound. (a) A shear wave is propagating from right to left under the transducer. The shear wave moves a scatterer (black dot) from position 1 to position 2, within the time interval from $t_1$ to $t_2$. (b) In two consecutive insonifications, the ultrasound radio-frequency signal shifts along the time direction due to the shear wave-induced scatterer movement. The amount of signal shift $\delta f$ can be measured to determine the shear wave motion.

In practice, ultrasound RF signals are typically sampled by in-phase/quadrature (IQ) demodulation. The resulting IQ signal can be used to estimate shear wave motion. A number of methods have been proposed [60-63].
for such processing. In this thesis work we used Kasai’s 1D autocorrelation approach [60, 63]:

\[
v = \frac{c}{4\pi f_{PRF}} \arctan \left( \frac{\sum_{n=0}^{N-2} \sum_{m=0}^{M-1} Q(m,n) \sum_{m=0}^{M-1} I(m,n+1) \sum_{m=0}^{M-1} Q(m,n+1)}{\sum_{n=0}^{N-2} \sum_{m=0}^{M-1} I(m,n) \sum_{m=0}^{M-1} I(m,n+1) + \sum_{m=0}^{M-1} Q(m,n) \sum_{m=0}^{M-1} Q(m,n+1)} \right)
\] (1.15)

where \( f_{c} \) is the center frequency of ultrasound RF signal, \( I \) and \( Q \) are the real and imaginary part of the ultrasound IQ signal, respectively, and \( M \) and \( N \) are the total number of IQ samples.

All ARF-based shear wave elastography techniques shown in Fig. 1.1 have the “shear push” and “shear detect” components in their configurations. Differences among these techniques reside in the details of how the push beam is constructed and implemented and how the detection beam and sequence are configured. Again, details of the differences in the detection part of these techniques will be introduced in Chapter 5. Here we focus on the push beam part.

Figure 1.4 shows schematic plots of the various ARF-based techniques summarized in Fig. 1.1. Shear Wave Elasticity Imaging (SWEI) [54] and Acoustic Radiation Force Impulse (ARFI) Shear Wave Imaging [55] both use a single focused ultrasound push beam to generate shear waves. By tracking shear waves at different time instants (e.g., \( t_1, t_2, t_3, \) and \( t_4 \)), one can estimate shear wave propagation speed with a time-of-flight or time-of-arrival approach [3, 64-
Supersonic Shear Imaging (SSI) produces quasi-planar shear waves by sequentially transmitting multiple focused push beams at different depths [18, 70, 71]. The resulting shear waves from each push beam will constructively interfere to produce a quasi-planar shear wave that has good range of depth for shear wave imaging. A similar time-of-flight or time-of-arrival approach as used in SWEI and ARFI shear wave imaging can be used to reconstruct the quasi-planar shear waves. Shearwave Dispersion Ultrasound Vibrometry (SDUV) uses a repetitive ultrasound push beam at the same spatial location to produce harmonic shear waves with different frequencies, from which both shear elasticity and viscosity can be recovered using the Voigt model [22]. Spatially Modulated Ultrasound Radiation Force (SMURF) imaging uses a beamforming approach to produce multiple push beams with certain distance in between to produce multiple shear waves simultaneously. A single tracking line is used to measure the difference of time-of-arrival of the resulting shear waves, which can be combined with the known distance between shear wave sources and to estimate the average shear wave speed under the push beam region [72, 73].

The ARFI shear wave imaging technique has been commercialized by Siemens Healthcare. The Virtual Touch IQ function on the ACUSON S3000 ultrasound system uses ARFI shear wave imaging for 2D shear elasticity imaging (www.healthcare.siemens.com). The SSI technique has been commercialized by Supersonic Imagine and is available on the Aixplorer scanner.
(www.supersonicimagine.com). The SSI technique can provide 2D/3D shear elasticity imaging. The SDUV technique has been commercialized by Philips Healthcare and is available on the iU22 scanner (www.healthcare.philips.com). Only 1D measurement is currently available on the iU22.
1.4 Motivation

With nearly two decades of development, shear wave elastography has been translated from the laboratory to the clinic and is now available on many clinical ultrasound scanners. Shear wave elastography is arguably the first truly quantitative tissue mechanical property characterization technique for ultrasound (personal communication with Dr. Greenleaf) and has been showing great potential in numerous clinical applications [2].

As a newborn imaging modality, however, shear wave elastography also suffers from many technical challenges that severely undermine its clinical diagnostic value. These challenges exist in the shear wave generation and shear wave detection parts of shear wave elastography as introduced above, as well as in the shear elasticity map reconstruction and shear wave elastography implementation (e.g. high hardware requirements for the scanners). Addressing these challenges is vital for the field of shear wave elastography and can substantially facilitate the translation of ultrasound shear wave elastography from laboratory to clinic and the implementation of shear wave elastography in a
variety of clinical applications. Motivated by the necessities of addressing these challenges, this thesis research aims at developing novel techniques in four key components of shear wave elastography: shear wave generation, shear elasticity map reconstruction, shear wave detection, and shear wave elastography implementation. The overall goal is to develop faster and better shear wave elastography techniques that are compatible with existing clinical scanners to ensure a clear path to clinical implementations. Specific goals and detailed motivations will be given in each chapter of the thesis.

1.5 Summary of chapters

From Chapter 2 to Chapter 5, the thesis is divided into four branches of research projects corresponding to the four components of shear wave elastography: shear wave generation, shear elasticity map reconstruction, shear wave detection, and shear wave elastography implementation. Each chapter addresses one or more challenges or limitations in one key component of shear wave elastography. Figure 1.5 shows the outline and the topics of thesis.
Chapter 2 will introduce a novel method named Comb-push Ultrasound Shear Elastography (CUSE), which addresses the shear wave generation challenge. CUSE is a fast shear wave elastography technique that can reconstruct a full field-of-view (FOV) shear elasticity map with a single push-detection data acquisition. CUSE also introduces the concept of producing multiple shear waves to fill the FOV and using the directional filter to solve the complex wave field.

Chapter 3 will introduce a fast shear compounding approach that utilizes 2D shear wave speed calculation and multi-directional filtering to address the shear elasticity map reconstruction challenge. The fast shear compounding can provide
high quality shear elasticity maps with better shaped inclusions with less geometric distortion and higher signal-to-noise-ratio (SNR).

Chapter 4 will describe a new shear wave detection method with ultrasound harmonic imaging that addresses the poor shear wave detection challenge. Instead of using the ultrasound fundamental signal, we proposed to use the tissue harmonic signal to estimate shear wave motion, which can substantially improve the shear wave signal quality and realize shear wave elastography in challenging applications such as cardiac shear wave elastography.

Chapter 5 will introduce a Time Aligned Sequential Tracking (TAST) technique that addresses the challenge of implementing shear wave elastography on a conventional ultrasound scanner. Shear wave elastography demands high ultrasound frame rate for the rapid tracking of the fast propagating shear waves, which is difficult to realize with conventional ultrasound scanners. TAST proposes a sequential shear wave tracking technique that enables conventional scanners to perform shear wave elastography.

Chapter 6 will conclude the thesis with discussion and summaries. This chapter will detail the contributions within this thesis work and their impact to the field of shear wave elastography. Directions for future work will also be explored. Finally, academic accomplishments of this thesis work will be listed.
Chapter 2

Innovations in Shear Wave Generation – Comb-push Ultrasound Shear Elastography (CUSE)


Abstract

This chapter introduces a novel shear wave elastography approach termed CUSE. The chapter starts with the background and motivation of doing CUSE, followed by the Methods section where details of the CUSE methods are given. In the Experiments and Results section, systematic studies of the performances of different CUSE methods are conducted, the ultrasound safety measurements are given, in vivo case studies using CUSE are shown, and a CUSE map quality
control and CUSE resolution study are performed. The CUSE idea is then generalized to the “rain-push” approach in the Future Directions section. Finally, the Discussion and Summary section gives in-depth analysis of the CUSE methods, a comparison study with the other shear wave elastography methods, and the limitations of CUSE.

2.1 Introduction

This chapter of the thesis addresses a common shear wave generation challenge existing in the ARF based shear wave elastography techniques introduced in Chapter 1, which can result in a push beam artifact due to absence of shear waves at the push beam region and poor shear wave signal-to-noise-ratio (SNR) due to shear wave attenuation.

In ARF based shear wave elastography, shear waves are produced by ultrasound push beams and propagate away from the push beam in opposite directions (Fig. 2.1(a)). Due to absence of shear waves in the push beam region, shear wave speed cannot be recovered here, and as a result, there will be a push beam artifact in the reconstructed 2D shear elasticity map (Fig. 2.1(b)). This push beam artifact cannot be removed unless another push beam at a different location is used to produce another shear wave that can cover the push beam artifact region. Therefore more than one push-detect data acquisition is necessary to cover the full field-of-view (FOV).
The second challenge of ARF based shear wave elastography is that as shear waves propagate in tissue, significant shear wave attenuation will occur in areas that are far away from the push beam region (Fig. 2.2), which results in poor shear wave SNR and consequently noisy shear elasticity maps. Note that the elasticity map shown in Fig. 2.1(b) was reconstructed from a phantom which has much less attenuation than tissue; therefore the map could still be well reconstructed in the area that is far away from the push beam. Similar to the solution of the first challenge, multiple push-detect data acquisitions with a push beam at different lateral locations are necessary to obtain strong shear wave

Figure 2.1 – (a) A schematic plot of a ultrasound push beam and the resulting shear wave propagation direction. The focused ultrasound push beam (indicated by the red shape) produces two shear wave fronts propagating away from the push beam (indicated by the two red arrows pointing at opposite directions) in a homogeneous phantom. (b) A shear elasticity map of this phantom was reconstructed by calculating the shear wave propagation speed at each imaging pixel location. The area marked by the red rectangular indicates the artifact caused by absence of shear waves at the push beam region.
signals across the FOV so that high quality shear elasticity maps can be obtained.

![Image](a) The same shear elasticity map as in Fig. 2.1 (b). The blue dashed line indicates the path of shear wave propagation. (b) the maximum shear wave amplitude along the blue dashed line in (a).

Such a solution to push beam artifact and shear wave attenuation requires multiple push-detect data acquisitions, in order to obtain different shear elasticity maps with the push beam artifact and poor shear wave SNR region at different locations, and to concatenate these elasticity maps into a final map [3]. This process can significantly slow down the shear wave imaging frame rate, induce motion artifacts (e.g. physiological motion of the tissue) in between different data acquisitions, and may cause overheating of tissue due to excessive amount of acoustic energy being deposited. Ideally in shear wave elastography, fast data acquisition and rapid reconstruction of a shear elasticity map is desired for monitoring tissue dynamic mechanical properties in real time and minimizing motion artifacts. The theoretical frame rate (ignoring tissue heating, probe
heating, and computational cost) of full field-of-view (FOV) two-dimensional (2D) shear elasticity imaging should only be limited by shear wave propagation speed within the tissue. Such multiple data acquisition approach cannot satisfy these requirements.

Motivated by the demands of improving shear wave imaging frame rate and achieving full FOV shear wave imaging with a single push-detect data acquisition, the idea of comb-push emerged. The central principle of comb-push is that instead of exciting push beams at different locations at different times, one can excite multiple push beams at different locations simultaneously, so that the entire FOV can be filled with high SNR shear waves and all the push beam regions can be recovered by shear waves as well. This will allow a full FOV reconstruction with a single push-detect data acquisition with no push-beam artifacts.

In this thesis, the comb-push idea was first realized in the form of simultaneous transmission of multiple unfocused push beams. Our previous work in shear wave generation using an unfocused ultrasound beam [77] showed that consistent shear wave speed measurements can be obtained at different depths using unfocused push beams. Because only one sub-aperture of transducer elements (8 to 16 elements) is used for each unfocused push beam, multiple sub-apertures of elements at different spatial locations can be used to simultaneously transmit unfocused push beams, which was called “comb-push”
This version of comb-push utilized unfocused push beams and therefore was named “unfocused comb-push”. Later various configurations of push beams were tested and two new versions of comb-push were developed: “focused comb-push” which transmits multiple focused ultrasound push beams simultaneously, and “marching comb-push” which transmits multiple large-aperture focused push beams by quickly marching the push beams in the lateral direction. The focused comb-push and marching comb-push effectively increase the penetration of comb-push and thus increase the depth of shear wave imaging. These various comb-push techniques were further developed into a novel 2D shear elasticity imaging method called comb-push ultrasound shear elastography (CUSE). Categorized by different types of comb-push beams used, the CUSE that uses unfocused comb-push is called U-CUSE; the CUSE that uses focused comb-push is called F-CUSE; and the CUSE that uses marching comb-push is called M-CUSE. In all CUSE methods, shear waves produced by each push beam can be treated as an independent realization of a single push beam. Shear waves from different push beams interfere with each other and eventually fill the entire FOV. To solve for this complex shear wave field and achieve robust shear wave speed estimation, a directional filter [78] was used to extract left-to-right (LR) propagating shear waves and right-to-left (RL) propagating shear waves from the interfering shear wave patterns. A time-of-flight based shear wave speed estimate method [3] was used to recover local
shear wave speed at each pixel from both LR waves and RL waves. A final shear wave speed map is then composed from the LR speed map and RL speed map. CUSE produces shear wave motions with sufficient amplitude at all image pixels including the push beam areas, so not only can shear wave speed in “source free” areas be recovered, but shear wave speed in the push beam area can be recovered as well. This enables a full FOV 2D reconstruction of shear elasticity map with only one data acquisition (less than 35 msec).

This chapter of the thesis is structured in the following way: Section 2.2 will introduce the principles of U-CUSE, F-CUSE, and M-CUSE, including Field II simulations of the acoustic field; the principles of the directional filter and the 2D map reconstruction. Section 2.3 will first show ultrasound safety measurements of the comb-push beams, followed by tissue-mimicking phantom results including homogeneous and inclusion phantoms, as well as in vivo case studies of using CUSE on human biceps, breast, thyroid, and liver. Section 2.3 will also show a quality control method of the CUSE elasticity maps and a spatial resolution study of CUSE. Future directions of the study will be given in Section 2.4. Section 2.5 concludes this chapter with discussions and summaries.

2.2 Methods

2.2.1 Principles of U-CUSE, F-CUSE, and M-CUSE

A Verasonics ultrasound system (Verasonics Inc., Redmond, WA) was used in this study to produce comb-push beams and track shear wave motions with a
linear array transducer L7-4 (Philips Healthcare, Andover, MA). Schematic plots of U-CUSE, F-CUSE and M-CUSE are shown in Fig. 2.3. For all CUSE methods, the transducer elements were divided into subgroups, i.e. subgroups 1 to 9 for U-CUSE. In U-CUSE, subgroups 1, 3, 5, 7, and 9 simultaneously transmit unfocused push beams (center frequency = 4.09 MHz, push duration = 600 µs) while subgroups 2, 4, 6 and 8 are turned off. There are 12 elements in each push beam and 17 elements in between push beams. For F-CUSE, the transducer elements were divided into four subgroups and each subgroup has 32 elements. All subgroups transmit focused ultrasound beams simultaneously (center frequency = 4.09 MHz, push duration = 600 µs). For M-CUSE, the transducer was divided into four subgroups as well but with overlapping elements. Each subgroup has 64 elements. Subgroup 1 transmits a single focused push beam (center frequency = 4.09 MHz, push duration = 200 µs) at time $t_1$, and then marches to subgroup 2 to transmit the second focused push beam at time $t_2$. The marching continues through subgroups 3 and 4 and terminates. The time interval between the end and start of consecutive push beams was 15 µs due to hardware limitations. Note that each focused beam for M-CUSE has 200 µs push duration, which is one third that of both U-CUSE and F-CUSE. This is because the center portion of the transducer elements are transmitting three times, as shown in Fig. 2.3(c). A 200 µs push duration was used for M-CUSE so that the
maximum push duration for these center elements would still be 600 µs, to allow a fair comparison to both U-CUSE and F-CUSE in terms of transducer heating.

Figure 2.3 – Schematic plots of different CUSE imaging sequences. (a) U-CUSE: transmit multiple unfocused ultrasound push beams simultaneously at time $t_1$. (b) F-CUSE: transmit multiple focused ultrasound beams simultaneously at time $t_1$. (c) M-CUSE: transmit single focused ultrasound beam using element subgroup 1 at time $t_1$, then march laterally to push with subgroup 2 at time $t_2$, subgroup 3 at time $t_3$, and subgroup 4 at time $t_4$. The time interval between the end and start of consecutive push beams was 15 µs.

The Field II simulation tool [79] was used to simulate the acoustic radiation force field produced by different CUSE imaging sequences. A 128 element linear array transducer (L7-4) with element size of 7 mm × 0.283 mm (height × width) and kerf width of 0.025 mm was simulated. Each element was numerically divided into 5 × 5 sub-elements. The elevational focus was fixed at 25 mm depth. The center frequency was 4.09 MHz and frequency dependent attenuation was 0.5 dB/cm/MHz. For U-CUSE, the same 5-subgroup comb-push as shown in Fig. 2.3(a) was simulated: each subgroup has 12 elements and transmits unfocused
push beams simultaneously, while the elements in between teeth are turned off. 
For F-CUSE, the same 4-subgroup comb-push as shown in Fig. 2.3(b) was
simulated: each subgroup has 32 elements and transmits focused push beams
simultaneously. The focal depth was 25 mm. For M-CUSE, each focused push
beam transmitted by 64 elements was simulated separately and summed up to
form a final acoustic intensity map. The focal depth was 25 mm. The simulated
pressure field is calculated in a 40 mm × 20 mm × 40 mm (lateral (x) ×
elevational (y) × axial (z), axial direction starts from 2 mm) space with a spatial
resolution of 0.2 mm. The sampling frequency was 100 MHz. The excitation
signal was a sinusoidal wave with 20 µs duration. The intensity \( I \) of the pressure
field is derived by

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

(2.1)

where \( p \) is the pressure, \( \rho \) is density, and \( c \) is ultrasound speed. The acoustic
radiation force density \( F \) was given by Eq. (1.9).

The simulated acoustic intensity fields (normalized) of x-z (mid-elevational)
direction for different CUSE methods are shown in Fig. 2.4. The simulation
results indicate that for U-CUSE and F-CUSE, no beam-to-beam interferences
will occur between comb-push subgroups. F-CUSE uses 32 elements for each
focused push and the beams are not as tightly focused as in M-CUSE. The push
beams of F-CUSE are elongated in the axial direction which is more favorable to
generate more planar shear waves.
2.2.2 Shear wave motion estimation

For all CUSE methods, after comb-push transmission, the Verasonics system immediately switched to plane wave imaging mode using all transducer elements (center frequency = 5 MHz). A plane wave imaging (see Chapter 5.1 for details of the difference between plane wave imaging and traditional line-by-line imaging) compounding method was used to improve the signal-to-noise-ratio (SNR) of shear wave tracking [80]. Three frames at three different steering angles (−4°, 0°, 4°) were used to obtain one imaging frame, with a spatial resolution of one ultrasound wavelength (~0.308 mm assuming ultrasound speed = 1540 m/s) and effective frame rate of 3.9 kHz.

The shear wave propagation induced axial particle velocity (v) was evaluated from in-phase/quadrature (IQ) data of consecutive frames tracked by the

![Figure 2.4](image)

Figure 2.4 – Field II simulations of the acoustic radiation force field produced by different CUSE methods. (a) Normalized intensity in x-z view for U-CUSE. (b) Normalized intensity in x-z view for F-CUSE. (c) Normalized intensity in x-z view for M-CUSE.
Verasonics system. The one-dimensional autocorrelation method [60] was used to calculate $v$ for each imaging pixel. The shear wave motion was obtained from three pixels in space and two sampling points in the slow time direction. Then a $3 \times 3$ pixel spatial median-filter (0.92 mm $\times$ 0.92 mm) was used on each frame of the shear wave motion image to remove noise spike points. Figure 2.5 shows the snapshots of shear wave motions at different time steps for U-CUSE in a homogeneous phantom. Figure 2.6 shows the snapshots of shear wave motions at different time steps for F-CUSE and M-CUSE in a homogeneous phantom.
(a) $V_z$ at 0.219 ms

(b) $V_z$ at 1.02 ms

(c) $V_z$ at 2.088 ms

(d) $V_z$ at 4.758 ms

(e) $V_z$ at 7.428 ms

(f) $V_z$ at 10.098 ms
Figure 2.5 – Plots of particle axial velocity at different time steps (movies available online). The shear waves constructively and destructively interfere with each other until all shear waves have passed through the FOV (only part of the shear wave propagation plots are shown here for succinctness). The black arrows indicate the left-to-right propagating shear wave front from the leftmost tooth (subgroup 1) of the comb-push. The color-bar is in unit of mm/s and is different for each time point. (a) initial positions of shear waves produced by 5 teeth, black arrow is at the shear wave front from subgroup 1 of the comb-push, (b) shear waves from each push beam begin to propagate away from the push beam on opposite directions, the right-propagating shear wave from subgroup 1 was pointed by the black arrow, (c) the right-propagating shear wave from subgroup 1 merged with the left-propagating shear wave from subgroup 3, (d) the right-propagating shear wave from subgroup 1 merged with the left-propagating shear wave from subgroup 5, (e) the right-propagating shear wave from subgroup 1 merged with the left-propagating shear wave from subgroup 7, (f) the right-propagating shear wave from subgroup 1 merged with the left-propagating shear wave from subgroup 9.
2.2.3 Directional filtering and local shear wave speed calculation

The typical 2D shear wave speed or elasticity map reconstruction technique proposed by Tanter et al. [3] uses shear wave signals from neighboring pixels to estimate local shear wave speed for each imaging pixel. For example, Fig. 2.7 shows that in order to estimate local shear wave speed at pixel B, shear wave signals from neighboring pixels A and C are used, from which an arrival time delay of shear wave between the two pixels ($\Delta t$) can be calculated using normalized cross-correlation (Eq. (1.10), Fig. 2.7(e)).
Before we can implement such local shear wave speed estimation method in CUSE, however, there is a problem of shear wave interferences caused by multiple shear waves being produced simultaneously in the FOV and propagating at different directions. As shown in Fig. 2.8(b), the two shear waveforms from neighboring pixels have large discrepancies and cannot be used for cross-

Figure 2.7 – (a) – (c): snapshots of a single shear wave propagation movie with three pixels of interest. Pixel B is the targeting pixel where local shear wave speed estimate is desired. Shear wave signals at neighboring pixels A and C are used (d). A normalized cross-correlation of curve A and curve C (e) gives the estimate of time delay \( \Delta t \), which can be used to get shear wave speed with known distance \( \Delta d \) between pixel A and pixel C.
correlation to estimate shear wave speed. The shear wave interference has to be removed in order to obtain robust local shear wave speed calculation.

To remove the shear wave interferences, a directional filter similar to \[78, 81\] was used to separate the left-to-right (LR) and right-to-left (RL) propagating shear waves. The shear wave field data has two dimensions in space (lateral dimension (x) and axial dimension (z)) and one dimension in time (slow time (t)).

Fig. 2.9(a) shows a slice of the F-CUSE shear field data with axes of lateral dimension (x) and slow time (t). The depth of the slice is at the focal plane of the focused push beams (25 mm). The 2D Fourier transform of the shear wave field yields a symmetric spectrum as shown in Fig. 2.9(b), with the first and the third
quadrants corresponding to the LR shear waves and the second and the fourth quadrants corresponding to the RL shear waves. By designing a mask as shown in Fig. 2.9(c), one can extract the LR shear waves (Fig. 2.9(d)) by preserving the first and third quadrants of the spectrum while masking out the second and the fourth. A complementary mask to Fig. 2.9(c) will extract the RL shear waves by preserving the second and the fourth quadrants of the spectrum while masking out the first and the third. The mask edges of the directional filters have been apodized to minimize ripples [81].
Another example of separating the LR and RL shear waves from a 5-tooth U-CUSE shear wave field is shown in Fig. 2.10.
Figure 2.10 – Shear wave motion plots along slow-time and lateral dimensions before and after directional filtering. (a) Before directional filtering, the complex shear wave field shear wave interferences can be observed. (b) LR shear waves extracted by directional filter. All shear waves are propagating from left to right and no interference with RL waves can be observed. (c) RL shear waves extracted by directional filter. Again all shear wave interferences have been removed.

Going back to reexamine the shear waveforms in Fig. 2.8(b) after directional filtering, as shown in Fig. 2.11, one can see that the shear wave interferences are gone and one can easily estimate the time delay between the two waveforms using cross-correlation.

Figure 2.11 – Two shear waveforms from two neighboring pixels (a) before and (b) after directional filtering. One can see after directional filtering the interferences are gone and the two waveforms have similar shapes. Cross-correlation can be used to estimate the delay of shear wave arrival times between the two locations.
In the local shear wave speed calculation process, two pixel points separated by 8 ultrasound wavelengths (8 pixels) at the same depth are used to calculate the local shear wave speed of the pixel in the middle [3]. The particle velocity profiles were Tukey windowed (the ratio of tapered section to constant section is 0.25 [82]) so that both ends of the signal were forced to be zero, facilitating more robust cross-correlation. The velocity profiles were interpolated by a factor of five before cross-correlation (using the ‘interp’ function in MATLAB).

### 2.2.4 2D shear wave speed map reconstruction

An important advantage of CUSE imaging as introduced above is that only one data acquisition is required to reconstruct a full FOV 2D shear wave speed map. Thanks to the directional filter, as shown in Figs. 2.12(a) and (b), one can observe that the LR waves propagate through subgroups no. 3, 5, 7, and 9 and RL waves propagate through subgroups no. 7, 5, 3, and 1. Because the push beam areas are covered by shear waves from other subgroups during wave propagation, shear wave speed at these areas can be recovered as well. One may notice that LR waves cannot cover tooth no. 1 region and RL waves cannot cover tooth no. 9 region due to absence of shear wave. The LR speed map and RL speed map are therefore combined so that a full FOV speed map can be obtained, as shown in Fig. 2.12 (c). Subgroup 1 region is reconstructed using the RL wave and subgroup 9 is reconstructed using the LR wave. Images of the
regions in the middle were reconstructed by averaging the shear wave speed estimates from both LR and RL waves.

Figure 2.13 shows final map reconstruction process for F-CUSE, which is similar to the process for U-CUSE shown in Fig. 2.12. Recon1 (Fig. 2.13(a)) is reconstructed from the LR shear wave field and Recon2 (Fig. 2.13(b)) is reconstructed from the RL shear wave field. The final map (Fig. 2.13(c)) has the middle portion averaged from Recon 1 and Recon 2, part of subgroup 1 area from Recon 2 and part of subgroup 4 area from Recon1. The same reconstruction principles apply to M-CUSE.
Figure 2.14 shows two examples of combining LR and RL shear wave speed maps in a homogeneous phantom and an inclusion phantom using F-CUSE. The push beam locations are the same as shown in Fig. 2.13.

Figure 2.13 – Schematic plots of 2D shear wave speed map reconstruction in F-CUSE. (a) Shear wave speed map reconstructed using LR waves (indicated by black arrows), (b) shear wave speed map reconstructed using RL waves, (c) final shear wave speed map combined by Recon1 and Recon2.
An alternative approach to combine the LR and RL shear wave speed maps instead of averaging is to weighted sum the overlapping regions of the two maps with the cross-correlation coefficient obtained from the local shear wave speed calculation step. In this part of the thesis only averaging was used because the LR and RL shear waves typically have the same amount of energy. The weighted sum approach will be introduced in detail in Chapter 3.

2.3 Experiments and Results

2.3.1 Ultrasound safety measurements
To evaluate the safety of the proposed CUSE methods, both ultrasound pressure generated by comb-push and temperature rise during the entire CUSE sequence were measured. For ultrasound pressure measurement, a needle hydrophone (HGL-0200, Onda Corporation, Sunnyvale, CA) was used. The output of the needle hydrophone was measured with a digital oscilloscope with a 50 Ω input impedance. Only one tooth of the comb-push beams was measured because all beams can be assumed to have the same acoustic pressure, as shown in the Field simulations. The ultrasound transmit voltage was ± 90 V which is the maximum voltage the system can provide. The needle hydrophone was centered both laterally and elevationally to the push beam. The ultrasound pressure from 2 to 42 mm with 5 mm step size was measured. The mechanical index ($MI$), which provides an indicator for the likelihood of mechanical effects, was calculated by

$$MI = \frac{p_{r,0.3}}{\sqrt{f_0}}$$

(2.2)

where $p_{r,0.3}$ is the peak rarefractional pressure derated at a rate of 0.3 dB/cm/MHz in MPa and $f_0$ is the ultrasound frequency in MHz. The Food and Drug Administration (FDA) sets the limit for $MI$ at 1.9 [83]. The derated spatial peak time average intensity $I_{SPTA,0.3}$ is given by [83]

$$I_{SPTA,0.3} = I_{SPTA,0.3} \cdot PD \cdot PRF$$

(2.3)
where $PRF$ is the pulse-repetition-frequency (here 1 Hz), and $I_{SPPA,0.3} = PII_{0.3} / PD$.

The parameter $I_{SPPA,0.3}$ is the derated spatial peak, pulse average intensity. The FDA sets the limit for $I_{SPPA,0.3}$ at 190 W/cm$^2$, and $I_{SPTA,0.3}$ at 720 mW/cm$^2$. $PII$ is the pulse intensity integral [84]

$$PII = \frac{\int_{t_1}^{t_2} v_h^2(t) dt}{10^4 \rho c M_{LM}(f_c)}$$

(2.4)

where $v_h$ is the measured hydrophone voltage, $t_1$ is the beginning of the toneburst, $t_2$ is the end of the toneburst, $\rho$ is the medium mass density, $c$ is the sound speed of the medium, and $M_{LM}(f_c)$ is the hydrophone sensitivity at frequency $f_c$, and the $10^4$ factor is added to convert from W/m$^2$ to W/cm$^2$. The pressures were derated by 0.3 dB/cm/MHz for the calculations of $MI_{0.3}$, $I_{SPPA,0.3}$, and $I_{SPTA,0.3}$. The pressure waveforms were not linear and an example of the waveform with the highest intensity measured is depicted in Fig. 2.15. A few cycles have been shown to demonstrate the nonlinearity of the signal. Equation 2.4 does not assume a linear waveform.
To measure temperature rise during the CUSE sequence, a 30 gauge type T thermocouple (Omega Engineering Inc., Stamford, CT) was sandwiched between the transducer and a piece of pork tenderloin (12 cm by 7 cm by 5 cm). The thermocouple was positioned in the center of the push beam. A full CUSE sequence was executed. Five repeated measurements were taken for each CUSE sequence. In addition, the maximum temperature increase ($\Delta T$) within tissue associated with a comb-push tooth was calculated using the following equation from Palmeri et al. [85]:

$$\Delta T = \frac{2\alpha I}{c_v} t$$

(2.5)

where $\alpha$ is the frequency dependent ultrasound attenuation, $I$ is the $I_{SPPA}$ intensity, $t$ is the time of the ultrasound transmission, and $c_v$ is the heat capacity.
per unit volume \((c_v = 4.2 \text{ J/cm}^3/\text{°C})\). The equation neglects cooling due to heat conduction and blood perfusion, and therefore provides a worst case estimation. To be conservative, we used non-derated intensity and a \(\alpha\) value of 0.7 dB/cm/MHz to calculate maximum heating in Eq. (2.5). The FDA regulates the temperature rise \((TR)\) of tissue to be no more than 6 °C [86].

For U-CUSE, the values of \(MI\), \(I_{SPPA}\) and \(I_{SPTA}\) measured from 2 mm to 42 mm depth with 5 mm step size are plotted in Fig. 2.16. Different derating values of 0.3, 0.5, and 0.7 dB/cm/MHz have been used to demonstrate what the \textit{in situ} intensities might be in tissues with varying levels of ultrasound attenuation. As shown in Fig. 2.16, \(MI\), \(I_{SPPA}\) and \(I_{SPTA}\) decreased with depth and have the highest values about 7 mm from the transducer surface.
The measured safety parameters of U-CUSE, F-CUSE, and M-CUSE as well as the FDA regulatory limits are summarized in Table 2.1. All safety parameters are below FDA regulatory limits [83] for all CUSE methods.

Figure 2.16 – Acoustic output results for different levels of deration (0.3, 0.5, 0.7 dB/cm/MHz). (a) MI, (b) $I_{SPPA}$, (c) $I_{SPTA}$.
Table 2.1 – Summary of measured safety parameters of all CUSE methods compared with FDA regulatory limit

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Maximum Values Measured</th>
<th>FDA Regulatory Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U-CUSE</td>
<td>F-CUSE</td>
</tr>
<tr>
<td>$M_{I_{0.3}}$</td>
<td>0.9</td>
<td>0.45</td>
</tr>
<tr>
<td>$I_{SPPA_{0.3}}$ (W/cm$^2$)</td>
<td>109.4</td>
<td>33.6</td>
</tr>
<tr>
<td>$I_{SPTA_{0.3}}$ (mW/cm$^2$)</td>
<td>65.63</td>
<td>20.1</td>
</tr>
<tr>
<td>TR ($^\circ$C)</td>
<td>0.005</td>
<td>0.018</td>
</tr>
</tbody>
</table>

2.3.2 Homogeneous phantom experiments

Two homogeneous elasticity phantoms (CIRS Inc., Norfolk, VA) with different shear moduli were used to test the accuracy of U-CUSE, F-CUSE and M-CUSE for shear wave speed measurements. The nominal Young’s modulus of phantom 1 is 5.8 kPa (shear wave speed of 1.39 m/s calculated from Eq. (1.8)), phantom 2 is 9.7 kPa (shear wave speed of 1.80 m/s). Both phantoms have ultrasound attenuation of 0.4 dB/cm/MHz, density of 1030 kg/m$^3$ and sound speed of 1539.0 m/s. The shear wave speeds were measured by magnetic resonance elastography (MRE) and 1D transient elastography (1D TE) and were found to be in good agreement in a previous study [87]. These are regarded as reference values for this study. The details of MRE and 1D TE experiments have been described in [87]. Figure 2.17 shows the 2D shear wave speed maps of phantom 1 using U-CUSE, F-CUSE and M-CUSE. No spatial smoothing filter was applied to these maps. The lateral FOV is the same as the transducer width (about 39 mm). The data acquisition for each map was less than 25 ms. A region-of-interest (ROI) from 5 mm to 35 mm in lateral direction and from 10 mm to 35 mm
in axial direction was selected on each shear wave speed map to measure the mean and standard deviation values of shear wave speed measurements, as shown by the red rectangular box in Fig. 2.17(a). Five acquisitions at five different locations in the phantoms were measured by each CUSE method. The five measurements from different CUSE methods are compared with values from MRE (30 mm by 60 mm ROIs from five different planes) and 1D TE (25 mm line ROI along axial direction and 5 measurements from different lateral locations). The final results are summarized in Table 2.2. The measurements showed good agreements among different methods. All CUSE methods produced consistent measurements with low variances among different locations.

Figure 2.17 – 2D shear wave speed maps of phantom 1 from different CUSE methods: (a) U-CUSE, (b) F-CUSE, and (c) M-CUSE. The red box in (a) indicates the measurement ROI for all three methods. The measured shear wave speeds within the ROI from (a) is $1.55 \pm 0.05$ m/s, (b) is $1.55 \pm 0.06$ m/s, (c) is $1.57 \pm 0.05$ m/s. All speed maps use the same color scale. No spatial smoothing filter was applied to these maps.
Table 2.2 – Shear wave speeds of phantom 1 and phantom 2 measured by MRE, 1D TE, U-CUSE, F-CUSE and M-CUSE.

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Location 1</th>
<th>Location 2</th>
<th>Location 3</th>
<th>Location 4</th>
<th>Location 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE</td>
<td>1.55 ± 0.04</td>
<td>1.53 ± 0.03</td>
<td>1.50 ± 0.03</td>
<td>1.52 ± 0.03</td>
<td>1.51 ± 0.04</td>
</tr>
<tr>
<td>1D TE</td>
<td>1.49 ± 0.02</td>
<td>1.45 ± 0.01</td>
<td>1.45 ± 0.01</td>
<td>1.50 ± 0.01</td>
<td>1.51 ± 0.02</td>
</tr>
<tr>
<td>U-CUSE</td>
<td>1.55 ± 0.05</td>
<td>1.54 ± 0.06</td>
<td>1.54 ± 0.06</td>
<td>1.54 ± 0.06</td>
<td>1.54 ± 0.06</td>
</tr>
<tr>
<td>F-CUSE</td>
<td>1.55 ± 0.06</td>
<td>1.55 ± 0.06</td>
<td>1.54 ± 0.06</td>
<td>1.55 ± 0.06</td>
<td>1.55 ± 0.06</td>
</tr>
<tr>
<td>M-CUSE</td>
<td>1.57 ± 0.05</td>
<td>1.57 ± 0.05</td>
<td>1.57 ± 0.05</td>
<td>1.58 ± 0.05</td>
<td>1.58 ± 0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Location 1</th>
<th>Location 2</th>
<th>Location 3</th>
<th>Location 4</th>
<th>Location 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE</td>
<td>1.84 ± 0.03</td>
<td>1.85 ± 0.04</td>
<td>1.83 ± 0.04</td>
<td>1.81 ± 0.04</td>
<td>1.85 ± 0.04</td>
</tr>
<tr>
<td>1D TE</td>
<td>1.90 ± 0.01</td>
<td>1.81 ± 0.02</td>
<td>1.97 ± 0.02</td>
<td>1.93 ± 0.02</td>
<td>1.84 ± 0.02</td>
</tr>
<tr>
<td>U-CUSE</td>
<td>1.94 ± 0.07</td>
<td>1.94 ± 0.07</td>
<td>1.94 ± 0.07</td>
<td>1.94 ± 0.07</td>
<td>1.94 ± 0.07</td>
</tr>
<tr>
<td>F-CUSE</td>
<td>1.94 ± 0.07</td>
<td>1.93 ± 0.07</td>
<td>1.93 ± 0.07</td>
<td>1.93 ± 0.07</td>
<td>1.93 ± 0.07</td>
</tr>
<tr>
<td>M-CUSE</td>
<td>1.97 ± 0.06</td>
<td>1.97 ± 0.06</td>
<td>1.96 ± 0.06</td>
<td>1.97 ± 0.06</td>
<td>1.97 ± 0.06</td>
</tr>
</tbody>
</table>

2.3.3 Inclusion phantom experiments

Inclusion phantom experiment I

A CIRS inclusion phantom (Model 059, CIRS Inc., Norfolk, VA) was tested in this study. This phantom is a breast elastography phantom (sound speed of 1540 m/s, ultrasound attenuation of 0.5 dB/cm/MHz, and density of 1030 kg/m³) which has 13 spherical masses with different sizes and locations. The stiffness of the inclusions is about three times greater than the stiffness of the background. The nominal value of the moduli of this phantom is not available from CIRS. Using Eq. (1.8), the shear wave speed of the inclusion is thus about 1.73 times greater than that of the background. The same U-CUSE sequence as used in the homogeneous phantoms was performed in this experiment. To test if CUSE is sensitive to relative positions between the inclusion and the push beams, a mechanical stage was used to move the transducer horizontally so that the same
inclusion is at different lateral locations with respect to the transducer, as shown in Fig. 2.18. For each position, the transducer was adjusted to be aligned with the central slice of the inclusion. Then a CUSE sequence was executed and a 2D shear wave speed map was reconstructed, as shown in Fig. 2.19.

Figure 2.18 – A CIRS breast elastography phantom was imaged using CUSE. The ultrasound transducer was mounted on a mechanical stage. By translating the transducer, the inspected inclusion will change its relative position to the transducer.
As shown in Fig. 2.19, ROIs were selected to estimate shear wave speeds of the inclusion and background. The measured mean and standard deviation (std.) values of shear wave speed are summarized in Table 2.3. Table 2.3 also shows the calculated ratio of inclusion shear wave speed and background shear wave speed. Using data from Table 2.3, we can calculate that the average shear wave speed of the inclusion from 6 different positions is 3.37 m/s, background is 1.78 m/s, and the average ratio of inclusion to background is 1.90. In addition, a
contrast-to-noise-ratio (CNR) between the inclusion and background for each imaging position was calculated, which is given by [88]:

$$CNR = \frac{|C_I - C_B|}{\sigma_B}$$

(2.6)

where $C_I$ and $C_B$ are the mean shear wave speed of the inclusion and background, respectively; $\sigma_B$ is the standard deviation of the shear wave speed of the background. $C_I$, $C_B$ and $\sigma_B$ were measured using the same ROIs as in Fig. 2.19. The measured CNR values are converted to dB using $10 \log_{10}(CNR)$ and are summarized in Table 2.3. The CNR values are all greater than or equal to 25 dB, which suggests good contrast between the inclusion and background.

<table>
<thead>
<tr>
<th>Position</th>
<th>Inclusion (m/s) mean ± std.</th>
<th>Background (m/s) mean ± std.</th>
<th>Inclusion/Background</th>
<th>CNR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position 1</td>
<td>3.32 ± 0.48</td>
<td>1.72 ± 0.09</td>
<td>1.93</td>
<td>25</td>
</tr>
<tr>
<td>Position 2</td>
<td>3.95 ± 0.49</td>
<td>1.73 ± 0.07</td>
<td>2.28</td>
<td>30</td>
</tr>
<tr>
<td>Position 3</td>
<td>3.41 ± 0.34</td>
<td>1.75 ± 0.07</td>
<td>1.95</td>
<td>28</td>
</tr>
<tr>
<td>Position 4</td>
<td>3.26 ± 0.40</td>
<td>1.88 ± 0.08</td>
<td>1.73</td>
<td>25</td>
</tr>
<tr>
<td>Position 5</td>
<td>3.19 ± 0.46</td>
<td>1.82 ± 0.07</td>
<td>1.75</td>
<td>26</td>
</tr>
<tr>
<td>Position 6</td>
<td>3.11 ± 0.46</td>
<td>1.79 ± 0.06</td>
<td>1.74</td>
<td>27</td>
</tr>
</tbody>
</table>

*Inclusion phantom experiment II*

The same CIRS breast elastography phantom (Model 059, CIRS Inc., Norfolk, VA) as used in the previous experiment was tested in this study. An inclusion situated about 25 mm away from the phantom surface was located and imaged
by U-CUSE, F-CUSE and M-CUSE. F-CUSE and M-CUSE used beams focused at 25 mm. The initial push duration was 600 µs for U-CUSE and F-CUSE, and was 200 µs for M-CUSE as discussed in the Materials and Methods session. The push duration was then gradually reduced to 450, 300, 150, 120, 90, 60, 30, and 15 µs for U-CUSE and F-CUSE and 150, 100, 50, 40, 30, 20, 10, and 5 µs for M-CUSE. For each push duration, a 2D shear wave speed map was reconstructed from the three CUSE methods. As shown in Fig. 2.20, 2D shear wave speed maps from a 600 µs push (U-CUSE and F-CUSE) and a 200 µs push (M-CUSE) are provided (no spatial smoothing filter applied). All three CUSE methods were capable of providing smooth shear wave speed maps with good contrast between the inclusion and the background. The edges of the inclusions are sharp, and there are no significant artifacts throughout the speed maps. As shown in Fig. 2.20(a), ROIs of inclusion and background were selected to quantitatively measure the mean and standard deviation of shear wave speeds of the inclusion and background for all CUSE methods with different push durations. The measured results are plotted in Fig. 2.21. All CUSE methods were able to provide stable shear wave speed estimates of the phantom background throughout different push durations. F-CUSE and M-CUSE were able to provide robust estimates of shear wave speed of both the inclusion and background for all push durations, while U-CUSE failed below 30 µs, indicated by an increased measurement of standard deviation in the inclusion.
Figure 2.20 – 2D shear wave speed maps of the breast inclusion phantom using (a) U-CUSE, (b) F-CUSE, and (c) M-CUSE. All shear wave speed maps use the same color scale and no spatial smoothing filter was applied. Push duration was 600 µs for U-CUSE and F-CUSE, and 200 µs for M-CUSE. The ROIs shown in (a) were selected for all speed maps to measure the mean and standard deviation values of the background (red box) and the inclusion (black circle).
To provide a quantitative estimate of the performance of different CUSE methods, the SNR of shear wave speed measurements is calculated for the shear wave speed values given in Fig. 2.21. SNR is given by [89]:

\[
SNR = \frac{\bar{x}}{\sigma_x}
\]  

(2.7)

where \( \bar{x} \) is the mean value of shear wave speed and \( \sigma_x \) is the standard deviation.

To achieve consistent estimate of SNR, the same mean value of shear wave speed from the 600 \( \mu \)s push of each CUSE method was used to estimate SNR. The SNR measurements versus push duration of different CUSE methods are summarized in Fig. 2.22. Similar to the observations from Fig. 2.21, the SNR of inclusion measurements from U-CUSE started to decrease at 60 \( \mu \)s, and the background started to decrease at 30 \( \mu \)s. F-CUSE and M-CUSE, however, provided consistent SNRs throughout all push duration set-ups. This indicates that F-CUSE and M-CUSE require shorter push durations to achieve shear wave speed maps with comparable SNR to U-CUSE.
Inclusion phantom experiment III

Another CIRS inclusion phantom (Elasticity QA Phantom, Model 049, CIRS Inc., Norfolk, VA) was used in this study to compare the penetration of different CUSE push beams. The sound speed of this phantom is $1545 \pm 10$ m/s and frequency dependent attenuation is $0.5 \pm 0.05$ dB/cm/MHz. In order to compare the robustness of different CUSE methods, the most challenging inclusion of this phantom was imaged, which has a nominal Young’s modulus of $80 \pm 8$ kPa and whose bottom is about 50 mm away from the phantom surface, as shown by the B-mode image in Fig. 2.23(d). The nominal Young’s modulus of the phantom background is $25 \pm 4$ kPa. Assuming that the shear modulus is equal to one third of Young’s modulus [17] and using Eqn. (1), the nominal shear wave speed values for the background and inclusion are $2.89 \pm 0.22$ m/s and $5.16 \pm 0.26$ m/s,
respectively. Both U-CUSE and F-CUSE transmitted push beams with 600 µs duration and M-CUSE transmitted push beams with 200 µs duration. The focal depth was 40 mm for both F-CUSE and M-CUSE. The reconstructed shear wave speed maps are shown in Fig. 2.23. All shear wave speed maps were median-filtered with a 3 × 3 pixel spatial window. Both F-CUSE and M-CUSE provided smooth speed maps with good contrast between the inclusion and background. Compared with the B-mode image of Fig. 2.23(d), the shape of the inclusion was well preserved with sharp boundaries and no significant artifacts. For U-CUSE, however, since the inclusion is very stiff and deep, it was difficult to generate sufficient shear wave motion within the inclusion. Consequently, the shear wave estimate inside the inclusion was noisy and the inclusion is not delineated well. ROIs for the background and inclusion were selected to quantitatively measure the mean and standard deviation values of the shear wave speed of the inclusion and background, as shown in Fig. 2.23(a). The measured results are plotted in Fig. 2.24.
Figure 2.23 – Reconstructed shear wave speed maps and the B-mode image for the inclusion in the CIRS phantom. (a) Shear wave speed map reconstructed using U-CUSE. The red rectangular box is the ROI for background shear wave speed measurement; the black circular ROI is for inclusion shear wave speed measurement. The same ROIs were used for both F-CUSE and M-CUSE. (b) Shear wave speed map reconstructed using F-CUSE. (c) Shear wave speed map reconstructed using M-CUSE. (d) B-mode image of the inclusion phantom.
Fig. 2.24 shows that all CUSE-methods provided robust shear wave speed estimates of the background with excellent agreement to the nominal value. Moreover, F-CUSE and M-CUSE produced accurate estimates of the inclusion shear wave speed compared with the nominal value, while U-CUSE could not because of the noisy image of the inclusion. This indicates that both F-CUSE and M-CUSE have better penetration than U-CUSE and thus should be used in elasticity imaging of deep tissues (e.g., liver and kidney).

**Inclusion phantom experiment IV**

To evaluate the near field performances of different CUSE methods, a shallow inclusion from the same CIRS breast elastography phantom as in “Inclusion
Phantom Experiment I & II” was used. The center of the inclusion is about 15 mm away from the surface of the phantom. The same set-ups were used for all CUSE methods except that the focal depth was set to be 15 mm for both F-CUSE and M-CUSE. The reconstructed shear wave speed maps are shown in Fig. 2.25. No spatial smoothing filters were applied to these maps. All CUSE methods could provide good contrast between the inclusion and background with sharp boundaries. The measured shear wave speed values within the ROIs as shown in Fig. 2.25 of U-CUSE are: 1.76 ± 0.09 m/s for background, 3.24 ± 0.36 m/s for inclusion; F-CUSE: 1.71 ± 0.09 m/s for background, 3.34 ± 0.31 m/s for inclusion; M-CUSE: 1.74 ± 0.08 m/s for background, 3.75 ± 0.47 m/s for inclusion. To quantitatively evaluate the preservation of the shape of the inclusion by different CUSE methods, the diameter of the inclusion was measured using both B-mode images of the phantom and CUSE shear wave speed maps. Five measurements were made for B-mode and each CUSE method, as indicated by the five dashed lines in Fig. 2.25(a). The mean and standard deviation values of these measurements are summarized in Table 2.4. Table 2.5 shows the $p$ values of Student's $t$-tests for the diameter measurements among different methods. The results showed that the diameter measurements were statistically different between M-CUSE and the other methods. This is in accordance with the observation from Fig. 2.25 that both U-CUSE and F-CUSE well preserved the inclusion shape while M-CUSE generated a more square-shaped inclusion.
Table 2.4 – Inclusion diameter measurements by B-mode and CUSE shear wave speed maps

<table>
<thead>
<tr>
<th></th>
<th>B-mode</th>
<th>U-CUSE</th>
<th>F-CUSE</th>
<th>M-CUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>7.5 ± 0.34</td>
<td>7.4 ± 0.61</td>
<td>7.4 ± 0.36</td>
<td>8.3 ± 0.72</td>
</tr>
</tbody>
</table>

Table 2.5 – p values of Student’s t-tests for the diameter measurements

<table>
<thead>
<tr>
<th></th>
<th>F-CUSE</th>
<th>M-CUSE</th>
<th>B-mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-CUSE</td>
<td>0.43</td>
<td>p &lt; 0.05</td>
<td>0.32</td>
</tr>
<tr>
<td>F-CUSE</td>
<td>p &lt; 0.05</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>M-CUSE</td>
<td>p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inclusion phantom experiment V

The CIRS inclusion phantom (Elasticity QA Phantom, Model 049, CIRS Inc., Norfolk, VA) was used to compare Supersonic Shear Imaging (SSI) (Aixplorer, SuperSonic Imagine, Aix-en-Provence, France) with F-CUSE and M-CUSE. As mentioned before, this phantom is challenging to image in a sense that both the inclusion and the background are stiff (about 80 kPa Young’s modulus for the
inclusion and 25 kPa Young’s modulus for the background) and the inclusion is deep (about 38 mm from the phantom surface). The focal depth for F-CUSE was 42 mm and for M-CUSE was 45 mm. SSI used an L10-2 transducer. The PEN (penetration) mode was used for SWE with Persistence = high and Smoothing = 9. The parameter Persistence controls the amount of frame averaging and the parameter Smoothing controls the strength of the smoothing filter (9 is the maximum smoothing index).

The shear elasticity maps produced by F-CUSE, M-CUSE and SSI are shown in Fig. 2.26. The maps of F-CUSE and M-CUSE were filtered by the Non-Local Means method [90] to improve smoothness. Both F-CUSE and M-CUSE could produce comparable shear elasticity maps to SSI with good contrast and sharp boundaries between the inclusion and background. ROIs were selected to measure the shear elasticity of the inclusion and background, as shown in Fig. 2.26. The results and acoustic outputs are summarized in Table 2.6. Shear elasticity measurements of both the inclusion and background showed good agreements among F-CUSE, M-CUSE, SSI, and the nominal values. M-CUSE and F-CUSE produced lower mechanical index ($MI$) and heating than SSI.
Table 2.6 – Shear elasticity, $MI$, and heating measurements for F-CUSE, M-CUSE, and SSI.

<table>
<thead>
<tr>
<th></th>
<th>F-CUSE (kPa)</th>
<th>M-CUSE (kPa)</th>
<th>SSI (kPa)</th>
<th>Nominal value (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>79.1 ± 9.6</td>
<td>81.6 ± 9.9</td>
<td>84.8 ± 14.9</td>
<td>80 ± 8</td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td>23.9 ± 0.8</td>
<td>24.1 ± 1.4</td>
<td>26.1 ± 1.6</td>
<td>25 ± 4</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>0.94</td>
<td>0.96</td>
<td>1.4</td>
<td>-</td>
</tr>
<tr>
<td><strong>Heating</strong></td>
<td>0.018 °C</td>
<td>0.006 °C</td>
<td>2.9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Single image</td>
<td>Single image</td>
<td>(displayed TI)</td>
<td></td>
</tr>
</tbody>
</table>

2.3.4 *In vivo* case studies

To demonstrate the feasibility of implementing CUSE on real tissue elasticity imaging, a series of *in vivo* case studies were conducted on human biceps muscle, thyroid, breast, and liver.

Figure 2.27 shows the elasticity maps of the biceps muscle before and after extension by use of U-CUSE. Shear wave speed increased about two-fold: 2.14
\[ \pm 0.33 \text{ m/s} \text{ before extension and } 4.01 \pm 0.51 \text{ m/s} \text{ after passive extension (Fig. 2.27). The acquisition time was less than 20 ms for both maps.} \]

\[ \text{Figure 2.27} - \text{In vivo human biceps study. (a) imaging setup: the transducer was fixed on top of the biceps muscle. (b) 2D shear wave speed map of the biceps in flexed position. (d) 2D shear wave speed map of the biceps in extended position. (c) Shear wave speed measurements of the biceps in flexed and extended positions. The values used in the measurement were from the ROIs indicated by the black dashed boxes in (b) and (d).} \]

\[ \text{Figure 2.28 shows the shear elasticity maps of an in vivo thyroid (Fig. 2.28(a)), breast (Fig. 2.28(b)), and liver (Fig. 2.28(c)). M-CUSE was used for thyroid and U-CUSE was used for breast and liver. A curved linear array C4-2 transducer (Philips Healthcare, Andover, MA) was used for the liver study. The acquisition} \]
time was less than 25 ms for all studies. ROIs were selected as shown in Fig. 2.28 and the calculated shear elasticity for thyroid is $6.5 \pm 2.2$ kPa, breast is $3.02 \pm 0.57$ kPa, and liver is $2.35 \pm 0.31$ kPa. All in vivo results showed good agreements with literature values [3, 30, 91, 92] (Table 2.7). A breast nodule (yellow ROI) with shear elasticity of $5.36 \pm 1.59$ kPa was also observed in Fig. 2.28(b).

Figure 2.28 – Shear elasticity maps of in vivo thyroid (a), breast (b), and liver (c). The red and yellow dashed boxes/circles indicate the ROI selected for shear elasticity measurement.
Table 2.7 – Shear elasticity measurements of in vivo tissues by CUSE and literature values

<table>
<thead>
<tr>
<th></th>
<th>CUSE (kPa)</th>
<th>Literature (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps</td>
<td>4.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>6.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Breast</td>
<td>3.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Liver</td>
<td>2.4</td>
<td>2.2</td>
</tr>
</tbody>
</table>

2.3.5 CUSE map quality control

Shear elasticity maps reconstructed by shear wave elastography provides physicians and clinicians with intuitive and informative 2D/3D maps of the tissue, which possess significant diagnostic values. From the standpoint of technical development, it is crucial to design quality control mechanisms to rule out unreliable shear elasticity measurements and display maps only with pixels that have true robust shear elasticity estimates.

Deffieux et al. [93] and Wang et al. [66] described statistical and mathematical modeling of the noise propagation in shear wave elastography. Deffieux’s model is comprehensive and built in all the components of shear wave imaging including ultrafast imaging acquisition and beamforming, tissue velocity estimation, and time of flight estimation. An equation of the variance of the final reconstructed shear modulus map $\sigma_{\mu}^2$ was derived and given in [93]:

74
\[
\sigma_\mu^2 \approx \mu_0^3 \frac{1}{dr^2 2\pi^2 \cdot F^2 \cdot BW \cdot T} \left\{ \frac{1}{\text{SNR}_v \left( x - \frac{dr}{2}, z \right)} + \frac{1}{\text{SNR}_v \left( x + \frac{dr}{2}, z \right)} \right\} - 1
\]

(2.8)

where \(\mu_0\) is shear modulus, \(dr\) is the distance between the two pixels used for local shear wave speed calculation, \(F\) is the shear wave center frequency, \(BW\) is the shear wave bandwidth, \(T\) is the total data acquisition time, and \(\text{SNR}_v\) is the signal-to-noise-ratio of the shear wave motion estimation (i.e. Eq. (1.15)). \(\text{SNR}_v\) is given by shear wave motion energy divided by shear wave motion variance \(\sigma_v^2\):

\[
\text{SNR}_v = \frac{\int_{T} v(x, z, t)^2 dt}{\sigma_v^2}
\]

(2.9)

and \(\sigma_v^2\) is given by:

\[
\sigma_v^2 \approx \frac{c^2 \cdot \text{FPS}^2}{32\pi^2 F_{\text{us}}^2} \left( \frac{2}{\text{SNR}_{\text{uf}}} \right)
\]

(2.10)

where \(c\) is ultrasound speed, \(\text{FPS}\) is frames per second or \(\text{PRF}\), \(F_{\text{us}}\) is the ultrasound center frequency, and \(\text{SNR}_{\text{uf}}\) is the signal-to-noise-ratio of ultrasound (ultrasound signal intensity divided by electric noise).

To test the theory proposed in [93], we acquired a set of homogeneous phantom data with U-CUSE. Five CIRS custom made elasticity homogeneous phantoms (CIRS Inc., Norfolk, VA) with different stiffness were tested. The five
phantoms have Young’s modulus of 3 kPa, 6.75 kPa (Phantom 2), 12 kPa (Phantom 3), 48 kPa, and 108 kPa. Figure 2.29 shows the raw left-to-right (LR) shear wave speed maps of these phantoms acquired using U-CUSE. One can see that without quality control, the noisy data points (e.g. the push beam region on the left edge of the maps and the deep region on the bottom of the maps) get blended into the maps. The goal is to remove these noisy data points with certain quality control mechanisms.

Figure 2.29 – Raw 2D LR shear wave speed maps acquired by U-CUSE for the five CIRS elasticity phantoms.

To implement the quality control method in Eq. (2.8), we have to first estimate the ultrasound signal noise to obtain ultrasound SNR. Figure 2.30 shows the electric noise maps of the ultrasound acquisition system (Verasonics) for the five
phantoms. Figure 2.31 shows the SNR maps of ultrasound given by ultrasound B-mode intensity divided by the electric noise.

![Figure 2.30 - Electric noise maps of the ultrasound system.](image)

Figure 2.30 – Electric noise maps of the ultrasound system.
Figure 2.13 provides an estimate of $\text{SNR}_{Uf}$ in Eq. (2.10). Given the results in Fig. 2.31, one can calculate the shear wave motion variance $\sigma_v^2$ using Eq. (2.10). The results are shown in Fig. 2.32.
Given these shear wave motion variance maps, we can calculate shear wave SNR (SNR_v) using Eq. (2.9). The results are shown in Fig. 2.33.

Figure 2.32 – Shear wave motion variance maps.
One can see from Fig. 2.33 that the softer the phantom, the higher the shear wave SNR given the same push, which makes sense since softer phantoms give larger shear wave motion and thus larger shear wave energy. One can also see that since unfocused push beams were used, the shear wave energy is concentrated in the shallow portion of the phantom. The shear wave SNR decays rapidly along depth direction.

Using shear wave SNR, we can quality control the shear wave speed maps in Fig. 2.29 by setting up a cutoff threshold of 10 dB: all pixels that have shear wave SNR under 10 dB will be removed from the final map. The quality controlled maps are shown in Figure 2.34. One can see that the deep region where shear wave SNR is low was well controlled by the algorithm. The push beam region is not very well controlled because the shear wave energy is high close to the push.
beam. The control algorithm also removed some pixels inside the good estimate region. This makes sense because the shear wave $SNR$ calculation involves ultrasound noise estimation, which brings in ultrasound speckle noise that typically has a pattern like the ones shown in Fig. 2.34.

![Shear wave speed maps](image)

Figure 2.34 – Quality controlled shear wave speed maps. The shear wave $SNR$ was used as the controlling factor. Pixels with shear wave $SNR$ lower than 10 dB were removed.

Theoretically Eq. (2.8) should be used as the quality control algorithm. However in reality it is very challenging to estimate local shear wave bandwidth and local shear wave frequency at each pixel. Also $a priori$ knowledge of tissue stiffness $\mu_0$ is required by Eq. (2.8), which is challenging to obtain and implement in practice.
An alternative way of estimating the quality of the shear wave speed calculation, which is a missing component of the above process that only uses shear wave SNR, is to use the cross-correlation coefficient produced in the local shear wave speed calculation process. The cross-correlation coefficient reflects the quality of the local shear wave speed calculation and may potentially serve as a surrogate to the shear wave bandwidth and shear wave center frequency measures required in Eq. (2.8). Figure 2.35 shows the cross-correlation coefficient (CC) maps of the five phantom speed maps. One can clearly see that at the poor shear wave speed estimation area, e.g. the push beam region on the left edge and the deep region on the bottom, cross-correlation coefficient is significantly lower than the good shear wave speed estimation area.

Figure 2.35 – Cross-correlation coefficient maps.
Using CC to quality control the shear wave speed maps in Fig. 2.29, one can see from Fig. 2.36 that almost all the pixels with poor shear wave speed estimates were removed. The threshold for the correlation coefficient cutoff was set to 0.6. As compared to the quality controlled maps in Fig. 2.34, CC controlled maps have comparable performance to the shear wave SNR controlled maps, while CC controlled maps do not show the spike noise points inside the good estimate region. This makes sense because CC quality control does not have an ultrasound signal component built in. Nevertheless, in phantoms, ultrasound signal quality may not contribute significantly to the shear wave motion estimate because of the good scattering conditions. Figure 2.36 shows that using CC alone can quality control the CUSE maps well enough in phantoms.
In real tissue, however, using CC alone as a quality control factor may not be sufficient. This is because in real tissue, shear wave motion can be significantly weaker and shear wave signal quality can be significantly poorer than in a phantom. Weak shear wave motion or poor shear wave signal does not necessary give low cross-correlation coefficient values because the two neighboring pixels may have similar noise profiles, which may still produce a high cross-correlation coefficient without the presence of shear waves. To evaluate the impact of shear wave motion on quality control, a set of in vivo human liver shear wave data was used for the study. Figure 2.37 shows snapshots of the shear wave propagation movie of the liver.
Three types of quality control mechanisms were used to reconstruct the 2D shear elasticity map of the liver, as shown in Figs. 2.38(a)-(c). By use of shear wave SNR, the controlled map (Fig. 2.38(d)) preserves the same characteristics as in the phantom: the controlled map has many spike noise points. Using correlation coefficient (Fig. 2.38(f)), one can see that the majority of the noisy estimates from the deep region where the shear wave signal quality is low (as indicated by Fig. 2.37) can be removed. However, the null regions out of the FOV (indicated by the white circle in Fig. 2.38(f)) cannot be removed: one can see from Fig. 2.38(c) that the correlation coefficient is actually high in these null regions. This is because, as mentioned above, pixels with no shear wave signal can output high correlation coefficient as well. Using shear wave energy (i.e. the numerator of Eq. (2.9)), as shown in Fig. 2.38(e), most of the noisy points could be removed including the null regions. However, the area indicated by the white circle where there was a vessel could not be removed because blood signal can
be regarded as high “wave energy” due to the large motions of blood flow, as shown in Fig. 2.38(b).

Figure 2.38 – Maps of the quality control factors as well as the quality controlled shear wave speed maps of the liver. (a) Shear wave SNR map in dB scale. (b) Shear wave energy map in dB scale (normalized to the maximum shear wave energy). (c) Correlation coefficient map. (d) Quality controlled by shear wave SNR (threshold = 20 dB). (e) Quality controlled by shear wave energy (threshold = -20 dB). (f) Quality controlled by correlation coefficient (threshold = 0.6).

Observing the performances of the three quality control mechanisms, one can see that by combining shear wave energy with correlation coefficient, the null region that could not be removed by CC can be removed by shear wave energy; while the vessel region that could not be removed by shear wave energy can be removed by CC. Figure 2.39 shows the result of combining shear wave energy with CC as the quality control factor. One can see that the map is well controlled.
with most of the noisy pixels removed. The null region was also removed together with most of the vessel region. In real tissues where shear wave signal can be poor and noisy, one needs to use a mechanism that includes both the information of the actual shear wave energy at a certain pixel as well as the quality of the shear wave speed estimation as quality control metrics. Other metrics included in Eq. (2.8) may also be needed for different types of applications. As this study indicates, combining shear wave energy with correlation coefficient is a good metric for quality control of the elasticity maps.

Figure 2.39 – Quality controlled 2D shear elasticity map of the liver using shear wave energy and correlation coefficient. Pixels with CC < 0.6 or shear wave energy less than -20 dB were removed.

2.3.6 CUSE resolution study

Similar to ultrasound imaging where the spatial resolution of ultrasound is determined by the length of the transmitted pulse, the spatial resolution of shear wave imaging is determined by the length of the shear wave, or shear wave
wavelength. There are several spatial resolutions in shear wave imaging which need to be clarified (personal communication with Dr. Manduca):

- The pixel resolution: the resolution of the 2D shear elasticity maps. For example, the pixel size of the 2D maps presented in Fig. 2.14 is 0.31 mm. The pixel resolution is determined by ultrasound imaging resolution, which has nothing to do with the shear wave imaging resolution.

- The shear wave imaging resolution: the minimum inclusion size that can be detected by a shear wave. For example, in Fig. 2.14, the size of the inclusion in Fig. 2.20(b) is about 10 mm. The inclusion could be well imaged by the shear wave. Therefore the shear wave wavelength was no longer than 10 mm, and the shear wave imaging resolution is at least 10 mm.

The concept of shear wave imaging resolution in the second bullet point above is a relaxed condition in defining spatial resolution, in which the shear wave speed of the object does not have to be accurately determined. For example, one can still discern an inclusion whose stiffness is different from the background when the shear wave wavelength is larger than the inclusion size. However, the true stiffness of the inclusion may not be accurately estimated using such large shear wave. Theoretically, to accurately measure the shear wave speed or shear elasticity of an inclusion object, one has to rigorously satisfy the local homogeneity assumption that was made in the wave equation derivation in
Chapter 1. To satisfy local homogeneity, the shear wave wavelength has to be smaller than the size of the inclusion. In other words, the same shear wave cannot experience two types of materials with different stiffness at the same time. Otherwise the wave equation will be violated and the shear wave will not propagate at the right speed inside the inclusion [94]. Note that the processing window size for local shear wave speed estimation is not taken into account here. It is assumed that the minimum-sized processing window is used so that no blurring effect induced by processing window is introduced.

Figure 2.40 shows a finite element modeling (FEM) simulation experiment of an inclusion embedded inside a soft background. A plane shear wave was simulated to propagate from the left edge of the FOV to the right edge of the FOV. Standard CUSE processing algorithms were used to reconstruct the 2D shear wave speed maps. The processing window size was 1 pixel, which is the smallest window size in this setup in order to minimize the blurring effect of the window. Two medium types were simulated: pure elastic (Figs. 2.40(a) & (b)) and viscoelastic (Figs. 2.40(c) & (d)). One can see in the pure elastic case, the shear wave speed at the transition area was lower than the simulated value of 4 m/s, and it took the shear wave about 5 mm of propagation to reach the correct shear wave speed of 4 m/s. This transition shows that shear wave cannot propagate at the correct speed unless the whole shear wave enters the inclusion region and thus the local homogeneity assumption holds. In the viscoelastic case, however,
because shear wave becomes wider and wider when propagating in a viscoelastic medium which gradually broadens the shear wave, the shear wave speed never reached the correct speed of 4 m/s inside the inclusion and the whole inclusion stiffness was underestimated, as shown in Fig. 2.40(c). Nevertheless, the inclusion can still be reconstructed using this shear wave and one can clearly observe the contrast between the inclusion and the background. In medical imaging, the contrast between malignant tissue and normal tissue is significant for disease diagnosis, and the exact shear elasticity value of the lesion might not be as important as the contrast. However, if possible, a very sharp shear wave with very high shear wave imaging resolution that can not only provide the contrast, but also provide accurate measure of the lesion stiffness is always greatly desired. Such a sharp shear wave, however, is very challenging to obtain due to the viscoelastic nature of tissue that tends to substantially broaden the input shear wave [28]. This limitation exists in all shear wave based approaches for shear elasticity imaging of the tissue.
With understanding of the shear wave imaging resolution, a study was conducted to systematically study the resolution of CUSE and compare CUSE’s
resolution with SSI. A CIRS phantom with stepped-size cylindrical shaped inclusions (Model 049A, CIRS Inc., Norfolk, VA) was used for the study. An F-CUSE sequence on a L7-4 linear array transducer was used to image 4 different sized inclusions with stiffness of 80 kPa (Young’s modulus). For each inclusion, 5 different data acquisitions were conducted with the probe leaving the surface of the phantom and relocating the inclusion. 2D shear wave speed maps were reconstructed using the standard CUSE processing algorithm. Figure 2.41 shows representative 2D shear wave speed maps of the inclusions. One can see that as the inclusion size gets smaller and smaller, the apparent stiffness of the inclusion gets softer and softer even though the stiffness is the same for all the inclusions. This corroborates with the simulation results showed above: as the shear wave wavelength gets comparable to the size of the inclusion, even though the inclusion can still be depicted, the shear elasticity measurement is no longer accurate. CUSE could well resolve the smallest inclusion with 4.1 mm diameter. Note that in this study the processing window size was 8 pixels (corresponding to about 2.46 mm) for the 2D map reconstruction. Therefore there was potential window blurring effect on the edges of the inclusions, as opposed to the FEM simulation study. Nevertheless for the inclusions with 6.5 mm and 10.4 diameters, the underestimate bias was primarily from the comparable sizes of the inclusion and the shear wave.
To compare with SSI, bias and precision of the CUSE measurements of the inclusions were calculated. The bias and precision calculation process followed the Aixplorer’s user’s manual: shear wave speed estimation bias was derived as the difference between the mean of five independent shear wave speed measurements and the nominal shear wave speed, normalized by the nominal shear wave speed and expressed as a percentage. Shear wave speed estimation precision was derived as the standard deviation of five independent shear wave speed measurements normalized by the mean of the five independent shear wave speed measurements, and expressed as a percentage. The bias and precision measurements together with the results of SSI from Aixplorer’s user’s manual are summarized in Table 2.8.

Figure 2.41 – CUSE shear wave speed maps of different sized inclusions. The inclusions are with the same stiffness (nominal values = 80 ± 12 kPa. Each map was obtained from only one CUSE sequence (no frame averaging), which took about 25 ms. No spatial smoothing filters were applied to these maps. The PRF of the sequence was about 4.1 kHz.
Table 2.8 – Comparisons of precision and bias in inclusion stiffness measurement between CUSE and SSI

<table>
<thead>
<tr>
<th>Target Diameter (mm)</th>
<th>SSI (SL15-4)</th>
<th>CUSE (L7-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias (%)</td>
<td>Precision (%)</td>
</tr>
<tr>
<td>4.1</td>
<td>-24.5</td>
<td>2.3</td>
</tr>
<tr>
<td>6.5</td>
<td>-12.5</td>
<td>0.9</td>
</tr>
<tr>
<td>10.4</td>
<td>-0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>16.7</td>
<td>8.8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 2.8 shows that both SSI and CUSE follow the same trend of bias with different sized inclusions. The amount of bias is comparable. It was challenging to set all imaging parameters to be completely equivalent between the two methods. However, both methods show underestimation biases when the inclusion gets small, which again, corroborates with the discussion about shear wave resolution above. In terms of precision, both methods provide excellent precision for all the measurements, which suggests that the bias is stable and cannot be corrected by methods such as frame averaging. A good precision is important for clinical diagnosis.

2.4 Future directions

2.4.1 CUSE in vivo patient studies of breast cancer and thyroid cancer

Currently CUSE is being used for several in vivo patient studies, including diagnosis of breast cancer [95] and thyroid cancer [96]. To facilitate the clinical studies of CUSE, a home-made “real-time” CUSE imaging sequence was built on the Verasonics system. The sequence has real-time B-mode imaging as the guidance for CUSE imaging. After the target region is confirmed by B-mode, the user can click on the B-mode image to select the focal depth of the comb-push...
beams. The system configures the number of teeth and the F/# of the push beams as well as the types of the comb-push based on the selected focal depth. For example, if the selected focal depth is shallower than 20 mm, then a 4-tooth F-CUSE will be executed; if the selected focal depth is deeper than 30 mm, then M-CUSE will be activated. After confirming the push beam configuration, the system will execute a full CUSE sequence, the resulting shear waves will be displayed on the screen, followed by an online reconstruction of the shear waves and the display of the final 2D shear elasticity map superimposed on top of the B-mode image. The total post-processing time is about 20 seconds using Matlab scripts. The imaging sequence loops back to real-time B-mode imaging after display of the final 2D shear elasticity map. Figure 2.42 shows two examples of using the CUSE sequence for breast and thyroid imaging. One can clearly see that the lesions are stiffer than the background tissue. Both lesions were later diagnosed as cancer by biopsy.
Figure 2.42 – In vivo breast and thyroid study results using CUSE. The top row shows the B-mode image of the breast with the target lesion indicated by the red dashed region, and the CUSE image on the left showing the lesion region with high stiffness compared to the background normal tissue. The lesion was later diagnosed as infiltrating ductal carcinoma Grade III by biopsy. The bottom row shows the B-mode image of the thyroid on the right, with the target lesion indicated by the red dashed region. On the left is the CUSE image of the thyroid. The lesion region is shown to be with high stiffness. The lesion was later diagnosed as papillary thyroid carcinoma by biopsy.

Ongoing studies are being conducted on breast and thyroid using CUSE. As will be introduced in Chapter 5, CUSE has been licensed and commercialized by a large ultrasound company. CUSE is now available on the company's
ultrasound scanner. Future clinical studies of breast, thyroid, liver, kidney, and other tissues using CUSE will be conducted using this commercial system.

2.4.2 “Rain-push” CUSE

The concept of CUSE can be generalized to an idea of solving for a complex shear wave field with many shear waves propagating at different directions. CUSE is driven by the motivation of filling the FOV with as many shear waves as possible so that each imaging pixel will always have a shear wave source close by and thus shear wave SNR will be higher and more robust shear elasticity maps can be reconstructed. In ARF based shear wave elastography approaches, CUSE is limited by the number of push beams that can be produced simultaneously in the FOV with one shot.

Both M-CUSE and SSI use a method of sequentially marching or moving the push beams to create multiple shear waves. SSI marches in the axial direction in order to constructively build the resulting shear waves to form a quasi-planar shear wave (Fig. 1.4(b)), while M-CUSE marches in the lateral direction to produce multiple shear waves simultaneously without the demands of constructive interferences of the shear waves. By marching axially, SSI gains strength in the axial imaging direction by producing a shear wave with strong amplitude throughout a wide range of depth; by marching laterally, M-CUSE gains strength in the lateral imaging direction by distributing multiple shear wave sources along the shear wave propagation path (F-CUSE shares the same
advantage as M-CUSE). While both techniques have their unique advantages, it is possible to combine the two techniques by marching the push beams both in lateral and axial directions to distribute a grid of shear wave sources throughout the FOV. Specifically, there are two ways of realizing this.

The first method is depicted in Fig. 2.43 (a). Four groups of push beams were excited to simultaneously produce 8 total shear wave sources in the FOV. Each group of push beams has two push beams that were focused at different depths but transmitted simultaneously (push duration = 200 μs). The first group has the left push beam focused at 5 mm and the right push beam focused at 35 mm; the second group has the left one focused at 15 mm and the right one focused at 25 mm; the third group has the left one focused at 25 mm and the right one focused at 15 mm; and the last group has the left one focused at 35 mm and the right one focused at 5 mm. The push beam groups quickly marches from group 1 to group 4 with 15 μs transition time. The resulting shear waves are shown in Figs. 2.43(b)-(d). One can see that the whole FOV is filled with shear waves with both good range of depth and range of width. Such a push beam configuration looks like rain and therefore is named “rain-push”.

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The second method is shown in Fig. 2.44. This setup sequentially transmits multiple F-CUSE push beams along the axial direction. The first group of push beams contains 4 teeth with push duration of 150 μs; the second group of push beams contains 3 teeth with push duration of 250 μs; the third group of push beams contains 2 teeth with push duration of 300 μs; and the fourth group of push beams contains 1 tooth with push duration of 400 μs.

Figure 2.43 – (a) Schematic plot of rain-push CUSE setup 1. A total of 8 push beams were excited to produce 8 shear wave sources. The push beams that are transmitted simultaneously are marked by the same color. Four groups of push beams were excited. Each group of push beams lasted 200 μs and was 15 μs apart. (b)-(c): snapshots of the shear wave propagation movie from a homogeneous phantom of rain-push CUSE.
beams contains 2 teeth with push duration of 400 \( \mu \)s. This setup allows variations in the push beam duration so that we can use shorter push pulses in shallow tissue and longer push pulses in deep tissue. This is because shallow tissue has less attenuation than deep tissue and therefore the push pulse does not have to be as long as that of the deep tissue to produce comparable shear wave motion. The resulting shear waves are shown in Figs. 2.44(b)-(c). One can see that again, this rain-push setup can produce shear waves filling the entire FOV with good range of depth and width. Both rain-push setup 1 and setup 2 have total push durations of 800 \( \mu \)s and both setups use all the transducer elements throughout the push process. This suggests that both setups deposit the same amount of acoustic energy into the tissue. One has to be cautious when using such rain-push setups because the probe heating can be significant.
The typical CUSE post processing algorithm can be used to separate the left-to-right (LR) and right-to-left (RL) shear waves for the rain-push, and reconstruct a final 2D shear elasticity map by blending the LR and RL maps. Figure 2.45
shows an example of using rain-push to reconstruct shear elasticity maps of a homogeneous phantom and an inclusion phantom.

The potential advantage of implementing rain-push CUSE is that by distributing a large number of shear wave sources inside the FOV, the energy and SNR distribution of shear waves are more uniform. Therefore the SNR of the final shear elasticity map should also be more uniform. The rain-push distributes multiple shear wave sources both along the axial direction (like SSI) and along the lateral direction (like CUSE), which can increase the range of both depth and width for shear wave imaging. Thanks to the directional filter, one can robustly reconstruct such complicated shear wave fields robustly which ensures that only one push-detection data acquisition is necessary and therefore the shear wave imaging frame rate does not need to be sacrificed. However, in practice, one has to carefully evaluate the impact of tissue heating and probe heating of rain-push. One can also better distribute the shear wave sources and the timing of the push transmissions so that the resulting shear waves are better constructed to form a more uniform shear wave field. These directions remain in the future studies of rain-push.
This chapter of the thesis introduces a novel shear wave elastography technique, Comb-push Ultrasound Shear Elastography (CUSE). CUSE aims at addressing the issues of the push beam artifact and shear wave attenuation by distributing multiple shear wave sources inside the FOV so that each imaging pixel will always have a shear wave source close by, including the push beam region. Current 2D shear elasticity imaging techniques typically require multiple data acquisitions of the shear wave field with different push beam locations to reconstruct a full FOV 2D map because of the absence of shear waves in the push beam area and attenuation far from the push beam area. CUSE is capable of filling the full FOV with shear waves without any “blind areas” by introducing multiple unfocused push beams at different spatial locations simultaneously. This study shows promising results of using CUSE to reconstruct a full FOV 2D shear
wave speed map from only one data acquisition. Robust estimates of shear wave speed, computed using the cross-correlation method, are enabled by a directional filter that enables CUSE to separate the LR waves and RL waves so that no shear wave interferences occur. Results of this study show that CUSE is able to accurately recover shear wave speed for all pixels within the FOV in less than 35 ms, providing a fast snapshot of the tissue mechanical property. Such quick measurements reduce motion artifact and provide methods of measuring dynamic changes in tissue properties such as during flexion of muscles. In vivo case studies showed great promise for implementing CUSE in a variety of clinical applications such as breast and thyroid cancer and liver fibrosis staging. The CUSE technique has been licensed and commercialized and will be available to clinicians and researchers worldwide.

*Phantom Experiments*

The homogeneous phantom experiments showed that all three CUSE methods were capable of providing smooth 2D shear wave speed maps (Fig. 2.17) with shear wave speed estimates in good agreement to MRE and 1D TE (Table 2.2). Shear wave speed measurements from CUSE are slightly higher than those from MRE and 1D TE. One possible reason for this is the diffraction effect as described by Catheline *et al.* [97]. The diffraction effect similar to 1D TE may also exist in shear waves induced by CUSE. Each push beam of CUSE can be treated as an aperture with non-negligible size compared with shear
wavelength. Shear waves induced by such apertures may have increased shear wave speed near the push beam area. Since multiple push beams were used in CUSE, higher shear wave speed may exist within a narrow neighborhood around each push beam. However, more than one shear wave from multiple push beams are produced and shear waves from a distant push beam do not have a diffraction effect and so there are no obvious overestimate patterns surrounding the push beam area. Nevertheless, one may still expect a slight increase of shear wave speed estimate because of the diffraction effect. Further FEM studies and phantom experiments are needed to obtain more insights and provide possible corrections to the CUSE measurements.

The first inclusion phantom experiment showed that CUSE was able to provide good contrast (CNR ≥ 25 dB) between inclusion and background. The results indicate that CUSE is not sensitive to relative positions between the inclusion and push beams: at all six different lateral positions, the inclusion can be well reconstructed and there is no artifact in the background. The inclusion was designed to be spherical and thus the image cross-section should be circular. The reconstructed inclusion is elliptical with shorter diameter along the lateral dimension. This could be caused by the 8-pixel window in lateral direction used in local shear wave speed recovery. Smaller windows give better spatial resolution but provide less robust shear wave speed estimates [98]. Thus the choice of an 8-pixel window is a tradeoff between spatial resolution and robust
shear wave speed estimation. The inclusion appears noisier and more oblong in shape in imaging positions 5 and 6 in Fig. 2.19. One possible reason is that the imaging plane did not align elevationally with the center of the inclusion at imaging position 5 and 6. The imaging plane was adjusted in the elevational direction to overlap with the center of the inclusion at position 1 and then moved to the following positions. Since the inclusion is spherical with a diameter of only 10 mm and the phantom surface is not level, it is possible that imaging planes 5 and 6 (with largest translations) were off-center to the inclusion along the elevational direction of the transducer. Consequently, the shape of the inclusion may not be well preserved and the inclusions may appear to be noisier. The measured ratio of shear wave speed of the inclusion and background is 1.9, which is higher than the designed ratio of 1.73. This is caused by the overestimation of shear wave speed within the inclusion at several inclusion reconstructions, for example, position 3. The overestimation might be caused by the same diffraction effect as discussed above when the inclusion is positioned very close to or directly under the push beam. Moreover, when the inclusion is positioned right under the unfocused push beam, different modes of shear waves with different velocities may be excited within the inclusion. Shear wave reflections within the inclusion and push-beam-induced compressional waves might also cause the overestimation of shear wave speed of the inclusion. Future study is needed to investigate these issues.
The second inclusion phantom experiment showed that all CUSE methods were capable of producing smooth shear wave speed maps with good contrast between the inclusion and background as well as sharp inclusion boundaries. There is no significant artifact in the speed maps. All CUSE methods were able to provide consistent estimates of shear wave speeds for both inclusion and background with decreased push durations (Fig. 2.21). Both F-CUSE and M-CUSE could sustain decreased push duration better than U-CUSE and were able to keep consistent SNR output (Fig. 2.22). Since no focusing occurs in the unfocused push, significant push beam energy is dissipated in the near-field and thus unfocused pushes usually require push beams with longer durations to produce comparable shear wave amplitudes to focused push. Therefore, when reducing the push duration, U-CUSE suffered from lack of shear wave motion first and failed to provide robust shear wave speed maps below 60 μs push duration.

The third inclusion phantom experiment demonstrated that greater push beam penetration and deeper imaging depths can be gained by using F-CUSE and M-CUSE. It is noticeable that this inclusion phantom is very challenging for elasticity imaging because the background shear modulus is close to 9 kPa, while the inclusion is close to 26 kPa and is about 5 cm from the transducer surface. Both F-CUSE and M-CUSE were able to preserve the shape of the inclusion and accurately estimate the shear wave speed values (Figs. 2.23 and 2.24), although
the lower boundary of the inclusion was not well separated from background in Figs. 2.23(b) and (c) because of weak shear wave motion in this region. U-CUSE was not able to produce shear waves with sufficient amplitude in the inclusion and was only able to recover the shallow upper part of the inclusion.

The shallow inclusion test showed that U-CUSE and F-CUSE better preserved the shape of the inclusion than M-CUSE in shallow imaging. One possible reason for this is that the push beam out of the focal plane is greatly diverged when a large aperture for push is used [87]. The diverged push beam generates shear waves with long wavelengths with low spatial resolutions. This results in smearing of the inclusion corners and distortion of the inclusion shapes. For F-CUSE, however, since only 32 elements were used for each push beam, the divergence of the push beam is less than in M-CUSE and therefore less distortion of the inclusion shape occurred. One may have to further reduce the number of elements for each push beam for F-CUSE to image an even shallower inclusion, i.e. 20 elements for each push beam. The decreased shear wave energy due to reduced number of elements can be compensated for by using a larger number of push beams, i.e. 6 push beams with 20 elements for each push beam. For U-CUSE, the push beam divergence is minimal because the push beams are unfocused. Since shear waves generated by unfocused push beams are more planar and have stronger intensity in near field, U-CUSE is ideal for shallow tissue imaging. One can also change the number of elements for each
push beam as well as the total number of push beams for U-CUSE. Theoretically, a smaller aperture for the unfocused push will give narrower shear waveforms with shorter shear wavelengths and thus higher spatial resolution up to a point. Although shear wave amplitude will be lower with the smaller aperture of unfocused push, less attenuation occurs in near field and therefore it is feasible to decrease the aperture size. Meanwhile, reduced aperture size allows a larger number of push beams which can compensate for the loss of shear wave amplitude. Future study is needed to systematically optimize the comb-push beam set-ups for different tissue applications.

The focused comb-push and marching comb-push extend the imaging range of depth and flexibility of the CUSE method. The U-CUSE method has no control of ultrasound intensity and shear wave amplitude along the depth direction. Typically with unfocused comb-push, shear wave amplitude decreases with depth, with maximum amplitude occurring close to the transducer surface. F-CUSE and M-CUSE provide the flexibility to control the distribution of shear wave energy along the depth direction. This change, although conceptually not complicated, has important practical value. As shown in the second inclusion phantom experiment, they allow effective delivery of comb-push energy to a depth larger than what is achievable with U-CUSE. This beneficial feature will be important for applications such as liver imaging.
Comparison with SSI and ARFI Shear Wave Imaging

The marching comb-push in M-CUSE divides the transducer elements into several overlapping sub-apertures to transmit multiple focused push beams sequentially for shear wave generation. While this is similar to the push beams used in SSI [6, 18, 71, 99-101] which is implemented in the Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France) and ARFI shear wave imaging [55, 67], there are several significant differences: 1. M-CUSE does not require shear wave detection between push beams, unlike ARFI shear wave imaging. The detection starts after the transmission of the last push beam and it is the comb-shaped shear wave field that marching comb-push is aiming to produce, not individual shear waves from each push beam. 2. M-CUSE distributes consecutive focused push beams in the lateral direction, unlike SSI in which consecutive focused push beams are distributed along the axial direction. 3. M-CUSE does not require a priori knowledge of the medium shear wave speed to chase down or go faster than the shear wave front to enhance the shear wave as introduced in [71]. In fact the marching speed of consecutive focused push beams was set to be as short as possible in order to detect the comb-shaped shear wave field as soon as possible. 4. M-CUSE can arbitrarily alter the push beam sequences, e.g. the order of the subgroup activations as in Fig. 2.3(c), because the order of the push beam transmissions is irrelevant to producing a comb-shaped shear wave field with multiple shear waves. This is
different from SSI in which the consecutive focused push beams must be excited from top to bottom or from bottom to top, to construct a *single* shear wave with specific Mach number.

Note that all three CUSE methods produce a complex shear wave field with *multiple* shear waves to reconstruct a full FOV shear elasticity map with *only one* push-detection acquisition, while SSI and ARFI shear wave imaging require multiple push-detection acquisitions to reconstruct a full FOV map because of (1) absence of shear waves at the push beam region and (2) significant shear wave attenuation in areas that are far from the push beam region. Therefore, for full FOV 2D shear wave imaging, the frame rate of the CUSE methods will be higher than SSI and ARFI shear wave imaging. This higher frame rate will be important for imaging a beating heart or contracting skeletal muscle. SSI and ARFI shear wave imaging produce and analyze a *single* shear wave front at a time, while the CUSE methods produce and analyze *multiple* shear wave fronts *simultaneously* thanks to the directional filter which can differentiate shear waves propagating at different directions. The cross-correlation of multiple shear wave fronts (as shown below), also gives a narrower correlation peak for the CUSE methods than SSI and ARFI shear wave imaging, which suggests a more robust shear wave speed estimate from the CUSE methods.

To illustrate the differences described above, a direct comparison of reconstructed shear wave speed maps from each imaging sequence, imaging
speed and shear wave signal between M-CUSE, SSI and ARFI shear wave imaging (on the Verasonics system used for this study) was conducted on phantom 1. For M-CUSE, the same sequence introduced in the section 2.2.1 was used to image the phantom. The single data acquisition was about 25 ms. The reconstructed shear wave speed map is shown in Fig. 2.46(a). Figure 2.46(b) also shows a typical pair of shear wave particle velocity waveforms after directional filtering that were used to recover local shear wave speed. Note that the four shear waves from the four push beams were used simultaneously for the cross-correlation calculation. The frame rate of the 2D shear wave speed map reconstructed by M-CUSE can reach approximately 1/25ms = 40 Hz in real-time imaging in principle (ignoring computational cost, thermal safety and transducer heating).

For SSI, four consecutive focused push beams with focal depths of 6 mm, 14 mm, 22 mm, and 30 mm were transmitted. The F-number of each push beam was fixed to be 1. The push duration of each push beam was 150 μs. The time interval between consecutive push beams was 15 μs. Data acquisition started after the transmission of the last push beam and lasted for about 25 ms. The first set of SSI push (SSI Sequence 1) was positioned on the left side of the FOV, followed by a 25 ms data acquisition, and the reconstructed shear wave speed map is shown in Fig. 2.46(c). The second set of SSI push (SSI Sequence 2) was positioned on the right side of the FOV, followed by a 25 ms data acquisition, and
the reconstructed shear wave speed map is shown in Fig. 2.46(d). Note that the push beam area in Figs. 2.46(c) and (d) could not be properly recovered within each SSI sequence due to absence of shear waves in the push beam region. A final full FOV shear wave speed map (Fig. 2.46(e)) was then reconstructed by concatenating Figs. 2.46(c) and (d). The concatenation was done by averaging the areas of Sequences 1 and 2 without the push beams, filling the push beam area of Sequence 1 with Sequence 2 data, and filling the push beam area of Sequence 2 with Sequence 1 data. Since two SSI sequences were needed to reconstruct the full FOV shear wave speed map, the total data acquisition time needed was at least 25 + 25 = 50 ms. Consequently, the real-time imaging frame rate of SSI would be 20 Hz, half that of M-CUSE. According to [3], three SSI push sequences are typically needed to reconstruct a full FOV shear wave speed map – bringing the total data acquisition time to 25 + 25 + 25 = 75 ms, further reducing the frame rate. Also, as shown in Fig. 2.46(f), SSI processes a single shear wave front from each SSI sequence for cross-correlation, as opposed to M-CUSE (Fig. 2.46(b)).

For ARFI shear wave imaging, a single focused push beam with aperture size of 64 elements, focal depth of 25 mm (same as the individual focused push in M-CUSE) and push duration of 600 μs was used for each imaging sequence. The push duration was longer than in M-CUSE and SSI because only one push beam was transmitted. Data acquisition started immediately after the transmission of
the push and lasted for 25 ms. The first ARFI push (ARFI Sequence 1) was transmitted on the left side of the FOV, followed by a 25 ms data acquisition, and the reconstructed shear wave speed map is shown in Fig. 2.46(g); the second ARFI push (ARFI Sequence 2) was transmitted on the right side of the FOV, followed by another 25 ms data acquisition, and the reconstructed shear wave speed map is shown in Fig. 2.46(h). Similar to SSI, ARFI shear wave imaging cannot reconstruct a full FOV shear wave speed map with only one push-detection acquisition. A similar concatenation method as used for SSI above was used to combine Figs. 2.46(g) and (h) into a final full FOV shear wave speed map (Fig. 2.46(i)), bringing the total data acquisition time to 50 ms, and a single shear wave front (Fig. 2.46(j)) was used for cross-correlation, as opposed to M-CUSE (Fig. 2.46(b)).
A major difference between M-CUSE and SSI and ARFI shear wave imaging is that multiple shear waves are produced and processed simultaneously by M-CUSE, as shown in Fig. 2.46(b), Fig. 2.46(f) and Fig. 2.46(j). This allows more robust cross-correlation calculations of shear wave speed. Figure 2.47 (a) shows a direct comparison of the normalized correlation coefficient plots from the shear wave signals of M-CUSE (Fig. 2.46(b)), SSI (Fig. 2.46(f)) and ARFI shear wave imaging (Fig. 2.46(j)). M-CUSE has a narrower correlation peak than SSI and ARFI, which suggests a more robust shear wave speed estimate from M-CUSE. To show that this relationship holds at different spatial locations, the cross-correlation function width of all imaging pixels within the black ROIs in Fig. 2.46 were calculated for M-CUSE, SSI and ARFI shear wave imaging. The width is
given by measuring the full width at half maximum (FWHM) of the cross-correlation function. Figure 2.47(b) shows the mean and standard deviation values of the measured cross-correlation function widths among different modalities. Note that similar to the result in Fig. 2.47(a), M-CUSE has a narrower cross-correlation function width than SSI and ARFI shear wave imaging. One possible reason is that M-CUSE cross-correlates multiple shear wave fronts, which should narrow the cross-correlation width. Another possible reason is that as the shear wave propagates away from the push beam, the high frequency component attenuates faster than the low frequency component, which widens the shear wave motion signal and consequently broadens the cross correlation function. Because M-CUSE distributes multiple focused push beams along the lateral direction so that each imaging pixel always has a shear wave source close by, the dominant shear wave front has a narrower time profile and consequently narrows the final cross-correlation function.
This brief comparison study is not comprehensive, and future study is needed to fully investigate the differences among these methods. Table 2.9 summarizes the differences between M-CUSE, SSI and ARFI shear wave imaging (F-CUSE is included as well, since the conclusions for M-CUSE discussed above also apply to F-CUSE).
Table 2.9 – Summary of the differences between F-CUSE/M-CUSE and SSI and ARFI shear wave imaging

<table>
<thead>
<tr>
<th></th>
<th>Number of push beams per acquisition</th>
<th>Push beam distribution</th>
<th>Push beam order</th>
<th>Data acquisition</th>
<th>Push beam area recovered from one push-detect</th>
<th>Number of shear waves per acquisition</th>
<th>Potential Frame rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F-CUSE</strong></td>
<td>Multiple</td>
<td>Simultaneously along lateral direction</td>
<td>Simultaneous</td>
<td>Single push-detect</td>
<td>Yes</td>
<td>Multiple</td>
<td>40 Hz</td>
</tr>
<tr>
<td><strong>M-CUSE</strong></td>
<td>Multiple</td>
<td>Sequentially along lateral direction</td>
<td>Arbitrary</td>
<td>Single push-detect</td>
<td>Yes</td>
<td>Multiple</td>
<td>40 Hz</td>
</tr>
<tr>
<td><strong>SSI</strong></td>
<td>Multiple</td>
<td>Sequentially along axial direction</td>
<td>Shallow to deep or opposite</td>
<td>Multiple push-detect</td>
<td>No</td>
<td>Single</td>
<td>&lt; 20 Hz</td>
</tr>
<tr>
<td><strong>ARFI shear wave imaging</strong></td>
<td>Single</td>
<td>N/A</td>
<td>N/A</td>
<td>Multiple push-detect</td>
<td>No</td>
<td>Single</td>
<td>&lt; 20 Hz</td>
</tr>
</tbody>
</table>

**Limitations**

One potential drawback of M-CUSE is that a shorter push duration (200 μs instead of 600 μs) has to be used, if maximum transducer heating is to be controlled at the same level for all CUSE configurations, because the center transducer elements are excited three times during the M-CUSE sequence. Shorter push duration suggests a weaker shear wave signal from each push beam, which will reduce the SNR of the shear wave signal and the robustness of the shear wave speed estimate. One can increase the push duration by reducing the number of push beams, i.e. having fewer overlapping beams. This will increase the amplitude of the shear wave signal from each push beam but reduce the total number of “teeth” in the comb-push beams. A future study is
needed to balance the trade-off between the single shear wave amplitude and the total number of push beams.

One potential drawback of F-CUSE is that the total amount of acoustic energy is spread over all pushes that are transmitted simultaneously, which may cause the energy of individual push beam in F-CUSE to be lower than the push in conventional shear wave imaging methods [18, 54, 55]. However, the advantage of the simultaneous laterally distributed push beams is the significant increase in the frame rate of shear wave elasticity imaging. There is a trade-off between frame rate and the quality of the shear wave speed maps (i.e. the \( SNR \) of the shear wave which is related to the acoustic energy of the push beam). Conventional shear wave imaging methods like SSI have higher acoustic energy for the push beam but lower frame rate, while CUSE has higher frame rate but lower acoustic energy for each push beam. One can decrease the number of simultaneous focused push beams to increase the aperture size of each push beam in F-CUSE to increase the acoustic energy of individual push beams.

Because CUSE is not creating a constructively interfering diffraction pattern as in SSI, the individual shear wave \( SNR \) from CUSE may be lower than SSI. However, CUSE effectively increases the frame rate and overall \( SNR \) of shear wave imaging by distributing multiple push beam sources along the lateral direction to create multiple shear waves so that each imaging pixel will always have one or more push beam sources close by.
As shown in Fig. 2.20 and Fig. 2.21, the shear wave speed estimate for the inclusion is high for U-CUSE. This may be caused by the direct push beam on the inclusion: the inclusion was positioned directly under the center push beam. Different modes and complex interferences of shear waves with higher velocities may be excited within the inclusion with direct pushing, which may result in the overestimation. Also, although the directional filter used in this study can remove the artifacts caused by horizontally reflected shear waves as shown in [81], shear wave fronts can still be disturbed by the boundaries of the inclusions and thus propagate in various directions. This may result in artifacts because a lateral propagation direction of shear waves was assumed in this study when calculating local shear wave speeds. Future work including a finite element modeling (FEM) study is needed to address these issues. Also, all experiments in this study were conducted in phantoms. *In vitro* and *in vivo* tests on various soft tissues are needed in the future to optimize CUSE for different types of applications.

For safety measurements, the temperature rise and $I_{SPTA}$ were measured from only one push-detection acquisition. One may expect an increased $TR$ and $I_{SPTA}$ when repeating CUSE measurements in real time. The temperature rise ($TR$) measurement of M-CUSE did not consider the fact that when transmitting multiple overlapping push beams, one can get peak heating in the near field of overlapping and adjacent acoustic radiation force excitations, especially in highly-attenuating media [85, 102]. Since the $TR$ measurement of M-CUSE from a
single push was only 0.006 °C and only 4 overlapping focused push beams spaced out over a relatively large lateral range were excited per image acquisition, one may still expect a low temperature rise even if the peak heating location would occur in the near field. Future study is needed to investigate the TR in continuous M-CUSE imaging where maximum heating is more likely to occur in near field. Finally, the safety measurements in this paper did not account for the effect of transducer surface heating. For the current set-up where the accumulated "ON" time for each element per acquisition was kept below a fixed duration $D_{\text{max}}$ ($D_{\text{max}}$ was equal to 600 μs in this paper), F-CUSE should produce the highest amount of transducer surface heating in continuous imaging because all the transducer elements are excited for $D_{\text{max}}$ for every acquisition. M-CUSE has lower transducer surface heating than F-CUSE because only some of the overlapping elements are excited for $D_{\text{max}}$ while the other elements are excited for less than $D_{\text{max}}$. U-CUSE should also have lower transducer surface heating than F-CUSE because only part of the elements are excited per unfocused comb-push. Moreover, because only 60 elements are excited per comb-push, one can alternate different combinations of unfocused push beams that are distributed at different lateral locations, which should reduce the transducer surface heating of U-CUSE. Future study will be needed to fully understand the transducer surface heating during continuous imaging.
Conclusions

Based on this study, U-CUSE and F-CUSE can be optimized for shallow tissue elasticity imaging, such as breast, skeletal muscle like biceps, and thyroid; F-CUSE and M-CUSE can be optimized for deeper tissue elasticity imaging, such as liver, kidney, spleen and heart. One can combine different CUSE methods to obtain strong shear wave signals in both near and far fields. Moreover, CUSE methods can also be implemented on other types of ultrasound transducers like curved and phased arrays, which have lower ultrasound center frequencies for better penetration.

The in vivo case studies showed that CUSE could provide good quality shear elasticity maps in biceps muscle, breast, thyroid, and liver. The CUSE implementation on breast and thyroid cancer also showed great promise for using CUSE in cancer diagnosis. Sharing the same goal with other shear wave elastography techniques, in the long-term CUSE aims at reducing the number of biopsies in the clinic, which will be a great contribution to humanity (personal communication with Dr. Callstrom). CUSE has been licensed and commercialized and is currently available on a popular commercial ultrasound system. The CUSE technique will soon be available to clinicians and researchers all over the world. With the advantage of the high shear wave imaging frame rate and high shear elasticity map quality, CUSE will have a great and positive impact to the field of ultrasound and medicine.
Chapter 3

Innovations in Shear Elasticity Map Reconstruction – Fast Shear Compounding


3.1 Introduction

The fast shear compounding approach presented in this chapter aims at addressing the technical challenges that reside in the shear elasticity map reconstruction process of shear wave elastography and achieve the goals of accurate imaging of inclusion shape and reconstructing high SNR shear elasticity maps without sacrificing the frame rate of shear wave imaging. The idea of shear compounding originates from ultrasound spatial compounding. Ultrasound spatial compounding techniques are widely used in ultrasound imaging to suppress speckle noise and improve image quality [18, 80, 105]. Ultrasound spatial compounding coherently sums the backscattered signals from ultrasound insonifications with different incident angles [105]. Similarly, shear compounding
coherently compounds the shear elasticity maps from shear wave fields that are illuminated by shear waves with different incident angles [18]. Shear compounding improves the signal-to-noise-ratio (SNR) of shear elasticity maps because random noise can be suppressed by averaging multiple reconstructed maps. Shear compounding also improves the contrast of shear elasticity maps for inclusions with complex geometries and various inhomogeneities, because differently angled shear waves can illuminate and produce good elasticity maps of different parts of the inclusion, which can then be compounded to obtain a robust elasticity map of the whole inclusion.

In practice, however, there are some challenges involved with shear compounding. First, shear compounding requires multiple cycles of transmission and detection of differently angled shear waves in several separate events [18]. This can significantly reduce the frame rate of shear wave imaging and substantially compromise the efficacy of shear compounding for in vivo applications because of the non-negligible amount of gross physiological motion between separate data acquisitions. Second, when the shear wave is angled and thus oblique, one can no longer assume that the shear wave propagates in a direction parallel to the lateral dimension of the ultrasound imaging field. Therefore, conventional shear wave speed estimation methods that assume a lateral propagation direction produce biased estimates of shear wave speed [3, 64, 65, 69]. To address these challenges, this study proposes a fast shear
compounding method that: 1. uses a comb-push [74, 75] to produce multiple differently angled shear waves simultaneously to achieve shear compounding with only one push-detect data acquisition, so that shear wave imaging frame rate is preserved and motion artifacts are minimized; 2. uses a multi-directional filter to isolate shear waves with different propagation directions and a robust two-dimensional (2D) shear wave speed calculation method to accurately reconstruct 2D shear wave speed maps from each direction which are then compounded into a final map.

This chapter is structured as follows: we describe (1) a validation study of the proposed robust 2D shear wave speed calculation method on a homogeneous phantom and an inclusion phantom, (2) an inclusion phantom study that systematically compares the performance of the proposed fast shear compounding method to the conventional shear compounding method, and finally (3) demonstration of the fast shear compounding to reconstruct a full FOV 2D shear wave speed map with multiple different types of inclusions with different stiffness. The chapter closes with discussion and conclusions.

3.2 Methods

3.2.1 Robust 2D shear wave speed calculation

To realize shear compounding using acoustic radiation force excitation, shear waves with different propagation angles need to be induced and detected. When the shear wave propagates at an oblique angle from wave front 1 to 2 to 3 as
shown in Fig. 3.1(a), the actual shear wave speed $c_s$ is $a / \Delta t$, where $\Delta t$ is the time interval from 1 to 2 and 2 to 3. However if we only measure the shear wave speed along the $x$-direction as in Fig. 3.1(a), the apparent shear wave speed $c_s'$ will be $b / \Delta t$, which is higher than the real shear wave speed $c_s$. Therefore, when the measurement direction is not aligned with the shear wave propagation direction, the estimated shear wave speed will be biased high. To measure the correct shear wave speed, a 2D calculation is needed, as shown in Fig. 3.1(b). Let the shear wave signal detected at pixels $a$, $b$, and $c$ be $S_a(t)$, $S_b(t)$, and $S_c(t)$, respectively, where $t$ is time. Let $t_{ab}$ be the time delay between $S_a(t)$ and $S_b(t)$ (calculated by finding the delay associated with the peak of the cross-correlation of $S_a(t)$ and $S_b(t)$), and $t_{ac}$ the time delay between $S_a(t)$ and $S_c(t)$ (calculated by finding the delay associated with the peak of the cross-correlation of $S_a(t)$ and $S_c(t)$). Let the distance between pixels $a$ and $c$ be $L_{ac}$, and between pixels $a$ and $b$ be $L_{ab}$. Then $V_x = L_{ac} / t_{ac}$, and $V_z = L_{ab} / t_{ab}$. Considering the dimensions of the triangle defined by $a$, $b$, and $c$, the true shear wave speed $V$ can be calculated by:

$$V = \frac{V_x V_z}{\sqrt{V_x^2 + V_z^2}} \quad (3.1)$$

or
\[ V = \frac{L_{ac}L_{ab}}{\sqrt{L_{ac}^2t_{ac}^2 + L_{ab}^2t_{ab}^2}} \]  

Equation (3.2) is more stable than Eq. (3.1) when either \( t_{ac} \) or \( t_{ab} \) is zero (if the wave propagation direction is aligned with axis \( z \) or \( x \)). This 2D vector shear wave speed calculation given by Eqs. (3.1) and (3.2) does not require \textit{a priori} knowledge of the direction of shear wave propagation, which can be difficult to know in practice. Note that a similar approach for 2D shear wave speed calculation was used for crawling waves generated by external mechanical shakers [106]. Note also that such 2D methods still assume that the wave propagation is in the imaging plane, and a similar bias will result if some component of the wave propagation is out of the imaging plane [87].

Figure 3.1 – 2D shear wave speed calculation. (a) Schematic plot of shear wave propagating at an oblique direction that can bias the shear wave speed measurement. (b) Shear wave speeds along both the \( V_X \) and \( V_Z \) directions are calculated to obtain the true shear wave speed \( V \).
Two methods were developed to increase the robustness of the 2D shear wave speed calculation method while preserving the spatial resolution of the shear wave speed maps. First, an algorithm used in numerical differential calculation developed by Anderssen and Hegland [107] was adapted to calculate local shear wave speed. Conventional local shear wave speed measurement techniques as introduced in [3] are performed by cross-correlating two shear wave signals from two imaging pixels (denoted by $S(m - w/2, n, t)$ and $S(m + w/2, n, t)$, where $m$ is the lateral dimension, $n$ is the axial dimension, $t$ is the slow time dimension, and $w$ is the window size) that are a fixed distance apart (distance is equal to window size $w$), as shown in Fig. 3.2(a), to estimate the shear wave speed of the center pixel at location $(m, n)$. The normalized cross-correlation is calculated by [63]:

$$CC(j) = \frac{\sum_{i=-M/2}^{M/2} [S(m - w/2, n, i) - \bar{S}(m - w/2, n)] [S(m + w/2, n, i + j) - \bar{S}(m + w/2, n)]}{\sqrt{\sum_{i=-M/2}^{M/2} [S(m - w/2, n, i) - \bar{S}(m - w/2, n)]^2 \sum_{i=-M/2}^{M/2} [S(m + w/2, n, i + j) - \bar{S}(m + w/2, n)]^2}}, \quad (3.3)$$

where $CC$ is normalized correlation coefficient and $M$ is number of shear wave signal data points along slow time direction. Temporal delay ($\Delta t$) between the two shear wave signals is then given by

$$\Delta t = \frac{[\arg \max_j CC(j)]}{PRF}, \quad (3.4)$$
where $PRF$ is the pulse repetition frequency. Local shear wave speed $V$ of the center pixel at location $(m, n)$ is given by

$$V(m, n) = \frac{w \cdot \Delta x}{\Delta t},$$

(3.5)

where $\Delta x$ is the spatial resolution of the imaging pixels.

A more robust approach as introduced in [107] uses a sliding patch of size $p$ that is smaller than the window size $w$ to calculate normalized cross-correlations between each pair of shear wave signals at spatial locations that are $p$ pixels apart, as shown in Fig. 3.2(b). A window size $w$ of 8 and patch size $p$ of 5 were used throughout this study. Each pair of signals for which normalized cross-correlation is applied produces an estimate of local shear wave speed with a corresponding normalized cross-correlation coefficient. The final shear wave speed at the center pixel is given by summing these speed estimates with weights based on their normalized cross-correlation coefficients.

Figure 3.2 – (a) Conventional local shear wave speed recovery method. One cross-correlation is calculated between shear wave signals from the left-edge pixel and right-edge pixel of the window. (b) Proposed local shear wave speed estimation method. Multiple normalized cross-correlations are calculated. The final shear wave speed at the center pixel is given by summing these speed estimates with weights based on their normalized cross-correlation coefficients.
speed at the center pixel \( V(m,n) \) is then given by the weighted sum of these speed estimates \( V(k,n) \) by their normalized correlation coefficients \( CC(k,n) \):

\[
V(m,n) = \sum_{k=1}^{w_x-1} V(k,n) \cdot CC(k,n)
\]  

(3.6)

Equation (3.6) can be used along both the \( x \)-axis (lateral dimension) and the \( z \)-axis (axial dimension) to obtain \( V_x \) and \( V_z \), which can then be substituted into Eq. (3.2) to get the true 2D shear wave speed \( V \), as shown in Fig. 3.3(a) (the blue triangles indicate \( V_x \) and the green squares indicate \( V_z \)).

The second method for increasing the robustness of the 2D shear wave speed calculation is to use a 2D processing window instead of one-dimensional (1D) processing lines, again as in [107]. Conventional methods use 1D processing lines to calculate shear wave speed, as shown in Fig. 3.3(a), where only the pixels on the lines that cross the center pixel (indicated by the red circle) are used. In the 2D window processing technique, as shown in Fig. 3.3(b), all pixels within the 2D window (shaded area in light blue in Figs. 3.3(a) and (b)) are used to estimate shear wave speeds \( V_x \) along the \( x \)-direction (indicated by blue triangles) and \( V_z \) along the \( z \)-direction (indicated by green squares). The final \( V_x \) and \( V_z \) at the center pixel \((m,n)\) indicated by the yellow circle are given by combining these estimates (triangles and squares) weighted by the square of cross-correlation coefficients and the reciprocal of distance \( r \) to the center pixel of the 2D window:
\[ V_x(m,n) = \sum_{i=m-h'}^{m+h'} \sum_{j=n-h'}^{n+h'} \left\{ V_x(i,j) \cdot \frac{CC_x(i,j)^2 / r(i,j)}{\sum_{i=m-h'}^{m+h'} \sum_{j=n-h'}^{n+h'} CC_x(i,j)^2 / r(i,j)} \right\}, \quad h' = \frac{w-p}{2} \]

\[ V_z(m,n) = \sum_{i=m-h'}^{m+h'} \sum_{j=n-h'}^{n+h'} \left\{ V_z(i,j) \cdot \frac{CC_z(i,j)^2 / r(i,j)}{\sum_{i=m-h'}^{m+h'} \sum_{j=n-h'}^{n+h'} CC_z(i,j)^2 / r(i,j)} \right\}, \quad h' = \frac{w-p}{2} \]

(3.7)

where

\[ r(i,j) = \begin{cases} 
1, & \text{if } i = m \text{ and } j = n \\
\sqrt{(i-m)^2 + (j-n)^2}, & \text{else}
\end{cases} \]

(3.8)

The final 2D shear wave speed at the center pixel \( V(m,n) \) can be obtained by substituting Eq. (3.7) into Eq. (3.1). The final correlation coefficient of the center pixel \( CC(m,n) \) is given by the minimum of \( CC_x \) and \( CC_z \), where \( CC_x \) and \( CC_z \) are the average of all normalized correlation coefficients along the \( x \) and \( z \) directions, respectively. A 2D shear wave speed map and 2D correlation-coefficient map can be obtained by iterating the calculations through all imaging pixels.
3.2.2 Generation and detection of multiple differently angled shear waves

Because the shear wave propagates in a direction that is perpendicular to its polarization direction [54], a steered push beam is needed to produce angled shear waves for shear compounding. In this study a curved linear array transducer C5-2v (Verasonics Inc., Redmond, WA, center frequency = 3 MHz) was used to produce differently angled shear waves by using different parts of the curvature of the probe. A comb-push technique as introduced in [74, 75] was

Figure 3.3 – (a) Conventional 1D processing window. The algorithm shown in Fig. 3.2(a) is used along both axial and lateral directions to get $V_X$ and $V_Z$, respectively. The green curve indicates the pair of pixels used to get the shear wave speed estimate for the upmost square. The blue curve indicates the pair of pixels used to get the shear wave speed estimate for the leftmost triangle. Note that only pixels on lines that cross the center pixel (indicated by the red circle) are used. (b) All pixels within the blue shaded area are used to get estimates of $V_X$ and $V_Z$. The blue triangles indicate the spatial locations of estimated $V_X$. The green rectangles indicate the spatial locations of estimated $V_Z$. The red gradient shading indicates the distance weighting: higher weights are assigned to estimates that are closer to the center pixel (indicated by darker red).
used to transmit multiple push beams simultaneously at different parts of the curvature of the probe so that multiple differently angled shear waves can be produced in the FOV at the same time. A Verasonics ultrasound system (Verasonics Inc., Redmond, WA) was used to produce the ultrasound push beam and track the resulting shear wave motion. The push pulse center frequency was 2.5 MHz and the duration was 600 μs. The Verasonics system immediately switched to ultrafast plane wave imaging mode with all transducer elements to track shear wave motion after transmitting the push beam. A plane wave imaging compounding method was used to improve the SNR of shear wave displacement tracking [80]. Three different steering angles (−4°, 0°, 4°) were used for plane wave detection compounding in this study, producing an effective frame rate of shear wave tracking of 2.77 kHz given the original frame rate of 8.31 kHz (effective frame rate = original frame rate/number of compounding angles). The pixel oriented beamforming by the Verasonics [108] was used to beamform the plane wave signal. The spatial resolution (both axial and lateral) was given by the transmission wavelength, which was equal to 0.51 mm given a transmission frequency of 3 MHz and an ultrasound speed of 1540 m/s. The shear wave particle velocity signals (v) caused by shear wave propagation were used as the shear wave motion signal in this study, which was calculated from in-phase/quadrature (IQ) data of consecutive frames using a 1D autocorrelation method [60]. The raw shear wave motion signal was averaged using three pixels.
in the axial spatial dimension and two sampling points in the slow time direction. A 3 x 3 pixel spatial median filter (1.53 mm x 1.53 mm) was finally used on each frame of the shear wave signal to remove noise spike points.

3.2.3 Multi-directional filtering and fast shear compounding

To decompose the complex shear wave field with multiple differently angled shear waves produced by the comb-push, a multi-directional filter was designed corresponding to each direction of the shear wave propagation. The details of the directional filter design are given in [78]. The power of the spatially directional component of the directional filter was 3, which controls the angular width of the filter. After directional filtering, the original shear wave data set was decomposed into Ω separate data sets with Ω shear waves propagating in Ω different directions. For each direction, a 2D shear wave speed map ($M_{SW}$) at each pixel ($m,n$) can be reconstructed using the 2D shear wave speed calculation method introduced above. A final shear wave speed map can then be reconstructed by weighted summing these Ω maps:

$$M_{SW}(m,n) = \sum_{d=1}^{\Omega} M_{SW}(m,n,d) \cdot \frac{SE(m,n,d) \cdot CC(m,n,d)^2}{\sum_{d=1}^{\Omega} SE(m,n,d) \cdot CC(m,n,d)^2},$$

(3.9)

where $CC$ is the correlation coefficient map and $SE$ is the shear wave energy in each direction. $SE$ is given by the sum of the squares of the shear wave particle velocity signal ($v$) over total time duration ($T$) at each imaging pixel [93]:

$$SE = \sum_{t=1}^{T} v(t)^2$$
\[ SE = \int v^2(x, z, t) dt, \quad (3.10) \]

Note that all presented shear wave speed maps were not smoothed by any spatial smoothing filters.

3.3 Experiments and Results

3.3.1 Validation studies for the robust 2D shear wave speed calculation

**Homogeneous phantom study**

A homogeneous elasticity phantom (CIRS Inc., Norfolk, VA) was used to validate the proposed robust 2D shear wave speed calculation method. The C5-2v curved array was used to transmit three differently angled shear waves (0°, 20°, 30°) separately using an unfocused ultrasound push beam [77] for a planar shear wave, as shown in Fig. 3.4. For each push beam angle, 5 measurements were taken at 5 different locations of the phantom to test repeatability. Both conventional 1D shear wave speed calculation (i.e. \( V_\lambda \) only) and the proposed 2D robust shear wave speed calculation (i.e. \( V \)) were used to reconstruct 2D shear wave speed maps from these differently angled shear waves. The 0° push beam was regarded as the ground truth because the resulting shear wave is not angled and therefore both 1D and 2D methods were expected to give the same shear wave speed estimates.
The 2D maps reconstructed by the 1D and 2D methods using the 30° push beam are shown in Fig. 3.5. One can clearly see an elevated biased estimate of shear wave speed in the 1D method compared with the 2D method, which can be explained by the phenomenon described in Fig. 3.1 above. Regions-of-interest (ROIs) with a spatial dimension of 25 mm x 25 mm were used to analyze all shear wave speed maps reconstructed from various angled shear waves using the two different methods.
The mean and standard deviation values of shear wave speed calculated from the 5 independent tests are shown in Fig. 3.6. Student's t-tests were conducted on the shear wave speed measurements and the p values are summarized in Table 3.1. Results from Fig. 3.6 and Table 3.1 demonstrate that: Given a 0° push beam, 1D and 2D measurements are very similar because the shear wave is not oblique and thus the dominant component of $V$ is $V_X$; When the push beam is steered and the resulting shear waves are angled, the measurements by the 1D method are statistically significantly different from the 2D measurements and the ground truth measurements (0°), while the 2D measurements are not significantly different.
different from ground truth. These results validated the proposed robust 2D shear wave speed calculation method as an effective tool of correctly estimating shear wave speed when the shear wave propagation is angled and oblique.

**Figure 3.6** – Bar plots of the mean and standard deviation values of shear wave speed measured by 1D and 2D methods from 5 independent tests at 5 different locations in the phantom. The error bars were plotted from the standard deviation values from the 5 trials for each method.
Table 3.1 – \( p \) values of Student’s \( t \)-tests for shear wave speed measurements

<table>
<thead>
<tr>
<th>( t )-test 1</th>
<th>0(^\circ) push 2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0(^\circ) push 1D</td>
<td>( p = 0.31 )</td>
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<tr>
<th>( t )-test 2</th>
<th>20(^\circ) push 2D</th>
<th>0(^\circ) push 1D</th>
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<tbody>
<tr>
<td>20(^\circ) push 1D</td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>20(^\circ) push 2D</td>
<td>( p = 0.07 )</td>
<td>( p = 0.15 )</td>
<td></td>
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<table>
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<th>( t )-test 3</th>
<th>30(^\circ) push 2D</th>
<th>0(^\circ) push 1D</th>
<th>0(^\circ) push 2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>30(^\circ) push 1D</td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>30(^\circ) push 2D</td>
<td>( p = 0.40 )</td>
<td>( p = 0.38 )</td>
<td></td>
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</tbody>
</table>

**Inclusion phantom study**

This study was designed to test the performance of the robust 2D shear wave speed calculation in inclusion phantom reconstruction. When shear waves hit the surface of an inclusion which has different shear stiffness to the background medium, shear waves can be deflected and reflected. The directional filter can remove the reflected shear waves that are propagating at opposite directions to the incident shear wave. However, the deflected shear waves cannot be removed by the directional filter. The direction of the deflection is determined by the geometry of the inclusion and the stiffness ratio between the inclusion and the background, and thus can be arbitrary and hard to predict. The overall effect on shear wave speed calculation is similar to the angled shear waves introduced in the previous session, which can produce overestimate bias and distortion of...
the inclusion shape. Figure 3.7 shows an example of propagating a shear wave through an inclusion in a CIRS inclusion phantom (Model 049A, type IV). One can clearly see the process of shear wave being bent by the inclusion and the complicated and abrupt change of shear wave propagation direction at different time instants.

![Figure 3.7 – (a) – (d): Snapshots of a movie of a shear wave propagating through a stiff inclusion embedded in a soft homogeneous background. The white dashed circle indicates the position of the inclusion. The black arrows indicate the shear wave propagation direction.](image)

If using the conventional 1D shear wave speed calculation method as in Fig. 3.2(a), the reconstructed inclusion shape can be severely distorted (Fig. 3.8(a)) due to the variations of the shear wave propagation direction at the inclusion. Specifically, one can see that the inclusion is elongated along the axial direction. The elongation is caused by overestimation of the shear wave speed at the top and bottom part of the inclusion, where the shear wave is most significantly deflected as shown in Fig. 3.7. Moreover, the overestimate bias spread into the background region (Fig. 3.8(a)) where the shear wave propagation direction is no longer horizontal, again as shown in Fig. 3.7.
If using the proposed 2D shear wave speed calculation, one can immediately see an improvement of the inclusion shape reconstruction in Fig. 3.8(b): the inclusion is much rounder than it was in Fig. 3.8(a). The overestimate bias in the background region is also ameliorated in Fig. 3.8(b) compared to Fig. 3.8(a). The difference image in Fig. 3.8(c) clearly shows that the 2D algorithm successfully removed the overestimate bias at the top and bottom part of the inclusion as well as the background.

To show more details of the inclusion profile in the 2D shear wave speed maps, the 1D shear wave speed profiles of the inclusion along the horizontal and vertical directions were plotted in Fig. 3.9. The profiles were averaged by 5 independent data acquisitions of the inclusion and the standard deviations of the 5 measurements were also plotted in Fig. 3.9. From the lateral profile plots in Fig. 3.9, one can see that 1D and 2D methods essentially produced the same results.
for the inclusion. This corroborates with the theory presented above that the 2D shear wave speed calculation method with the Anderssen-Hegland algorithm does not decrease the spatial resolution of the shear wave speed map. Because the shear wave does not change its propagation direction along the central line of the inclusion (Fig. 3.7), $\nu_z$ is 0 and therefore both 1D and 2D methods produce the same result. Looking at the axial profile, however, there is a clear difference between the two reconstruction methods. The 1D method significantly elongated the inclusion shape in the axial direction as indicated by the red curve, while the 2D method was able to remove this elongation artifact and produce a diameter of the inclusion that is comparable to the one of the lateral profile plot. Inside the inclusion, both 1D and 2D methods produce the same results in the axial direction. This again, demonstrated that the proposed 2D shear wave speed calculation approach does not deteriorate the spatial resolution of the shear wave speed map.
Together with the homogeneous phantom experiment, this part of the study showed that the proposed robust 2D shear wave speed calculation method could correctly calculate shear wave speed from oblique and tilted shear waves and robustly reconstruct better shaped inclusion images without the elongation and background overestimate artifacts.

3.3.2 Comparison of the proposed fast shear compounding method to the conventional shear compounding method
A CIRS elasticity QA phantom (Model 049, CIRS Inc., Norfolk, VA) with different types of spherical inclusions was used to systemically compare the performance of the proposed fast shear compounding method to the conventional method. The type IV inclusion with a diameter of 20 mm was imaged, as shown in Fig. 3.10. For the conventional method, four focused push beams (focal depth = 40 mm, F/# = 2.63) with angles of -33.79°, -16.31°, 16.31° and 33.79° were separately transmitted (Fig. 3.10) and the resulting shear waves of each push beam were separately detected, which brought the total data acquisition time to 4 x 44 ms = 176 ms. The shear wave speed from each push beam was reconstructed using the 2D calculation method and the 2D shear wave speed maps are shown in Fig. 3.11(a). A final compounded shear wave speed map was reconstructed using Eq. (3.9), as shown in Fig. 3.11(a). For the fast shear compounding method, the same four angled push beams were transmitted simultaneously and the resulting shear waves of all push beams were detected all at once, which brought the total data acquisition time to 44 ms (4X less than the conventional method). Four directional filters were designed for the four shear wave propagation directions and decompose the original shear wave data into 4 sets of data with differently angled shear waves, as shown in Fig. 3.11(b). Shear wave speed maps were reconstructed from each direction and compounded to get a final map (Fig. 3.11(c)). Both the conventional shear compounding method and the fast shear compounding method could reconstruct
the inclusion well with sharp boundaries and excellent contrast to the background. One can clearly observe the shape change of the inclusion with respect to the direction of the shear wave propagation and the improved inclusion shape in the compounded images. The shear wave speed of the inclusion within the indicated ROI is 4.49 ± 0.26 m/s for the conventional compounding method, and 4.55 ± 0.34 m/s for the fast compounding method, both agreeing well with the nominal value of 5.16 ± 0.52 m/s. Figure 3.12 shows the difference image between the conventional compounded and fast compounded images; the mean squared error (MSE) within the ROI is 0.03 m²/s², which is very small. These results indicate that the fast shear compounding method can achieve comparable performance to the conventional shear compounding method while preserving the shear wave imaging frame rate by using only one cycle of shear wave generation and detection.
Figure 3.10 – Plot of the push beam setup on top of the B-mode image of the inclusion phantom. Four focused push beams with different angles were transmitted separately and simultaneously for the conventional shear compounding method and the fast shear compounding method, respectively. Four shear waves with different directions (numbered 1, 2, 3, and 4) were produced to propagate through the inclusion area. The arrows indicate the shear wave propagation direction.
(a) Conventional shear

(b) Multi-directional filters for fast shear

(c) Fast shear compounding
3.3.3 Fast shear compounding for multiple inclusions

The same CIRS inclusion phantom as used in the previous example was used to test the capability of the proposed fast shear compounding method for
reconstructing multiple inclusions with different stiffness with only one push-detect cycle. The type II, III, and IV inclusions with diameters of 20 mm were located and imaged. The B-mode image is shown in Fig. 3.13. Five focused push beams (focal depth = 40 mm, F/# = 3.23) with different angles (-30.29˚, -15.15˚, 0˚, 15.15˚, 30.29˚) were simultaneously transmitted to produce 8 shear waves with 8 different propagation directions, as shown in Fig. 3.13, so that each inclusion would experience multiple differently angled shear waves. All shear waves were detected together and the total data acquisition time was 44 ms.
Corresponding to the 8 propagation directions, 8 directional filters were designed to fit each propagation direction (Fig. 3.14(a)) and used to decompose the original shear wave data into 8 data sets. Shear wave speed maps were reconstructed using each data set and the results are shown in Fig. 3.14(b). These maps were then compounded into a final map using Eq. (3.9), as shown in Fig. 3.14(c). In Fig. 3.14(c), one can clearly resolve the three targeted inclusions with good contrast to the background and sharp boundaries. The type I inclusion
was even resolvable from the compounded map although it was not discernible from the B-mode image.
Figure 3.14 – (a) Multi-directional filters designed for the 8 propagation directions of shear waves. The numbering of the filters is the same as that of the shear waves in Fig. 3.13. (b) Shear wave speed maps reconstructed from the 8 directions. (c) Final shear compounded map. The dashed box and circles indicate the ROIs selected for shear wave speed measurements.
ROIs were selected to measure the shear wave speed of the inclusions and background, which were then converted to Young’s modulus by $E=3\rho V^2$, where $\rho$ is density and was assumed to be 1000 kg/m$^3$. The results are listed in Table 3.2. All measurements showed good agreements with the nominal values of the phantom.

Table 3.2 – Young’s modulus measurements of the CIRS inclusion phantom

<table>
<thead>
<tr>
<th></th>
<th>Measured values (kPa)</th>
<th>Nominal values (kPa)</th>
</tr>
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<tbody>
<tr>
<td><strong>Type II</strong></td>
<td>14.95 ± 1.50</td>
<td>14 ± 4</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>40.96 ± 3.07</td>
<td>45 ± 5</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>72.84 ± 11.02</td>
<td>80 ± 8</td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td>27.10 ± 2.54</td>
<td>25 ± 4</td>
</tr>
</tbody>
</table>

3.4 Discussion and Conclusions

This chapter presents a fast shear compounding method to realize shear compounding while preserving the shear wave imaging frame rate and minimizing motion artifacts. The proposed fast shear compounding method uses a comb-push to transmit multiple differently angled shear waves simultaneously into the tissue, a multi-directional filter to break down the complex shear wave field into different propagation directions, and a robust 2D shear wave speed calculation method to correctly estimate the speed of the angled shear waves and reconstruct 2D shear wave speed maps. The homogeneous phantom and inclusion phantom experiments validated the proposed 2D robust shear wave speed method as an effective tool to correct for the overestimate bias caused by oblique shear wave propagation. The first inclusion phantom study showed that
the proposed fast shear compounding method could achieve comparable performance to the conventional method in reconstructing a well-shaped inclusion image while preserving the shear wave imaging frame rate by reducing the total data acquisition time by a factor of 4. The second inclusion phantom experiment showed that the proposed fast shear compounding method could accurately reconstruct multiple different types of inclusions with good contrast and shape preservation, thanks to the multiple differently angled shear waves that enabled shear compounding at each inclusion. This experiment was also done with only one push-detect data acquisition (duration = 44 ms), preserving the shear wave imaging frame rate.

Ideally, shear waves from all directions surrounding the inclusion are needed for shear compounding to reconstruct a well-shaped inclusion. However, this is not feasible in reality due to limited amount of beam steering of ultrasound probes and some inaccessible directions such as from the bottom of the inclusion. If shear wave sources other than acoustic radiation force are used, which allow shear waves to be simultaneously generated surrounding the inclusion, the proposed fast shear compounding principles should still apply and may perform even better.

The 2D shear wave speed calculation method introduced in [106] was implemented on a continuous crawling wave pattern based on a phase estimator approach. While the same principle of 2D calculation was used in this study, the
robust 2D shear wave speed calculation method presented here integrated the cross-correlation and the Anderssen-Hegland methods into the algorithm to robustly estimate the speed of transient shear waves induced by acoustic radiation force, which is different from the method presented in [106].

For the validation study of the 2D shear wave speed calculation, note that given the case of a homogeneous medium and known push beam angle, one can use the angle correction technique as used in spectral Doppler [57] to obtain the true shear wave speed. Also if the tracking beam is adjusted to be parallel to the push beam and the resulting shear wave, then the overestimate bias can be corrected as well. However, in the case of inhomogeneous media such as tissues with lesions and inclusion phantoms, the shear wave propagation angle can vary significantly from one location to another due to wave deflection and reflection, which: 1) undermines the angle correction based approach since the shear wave angle is different and unknown at different spatial locations; 2) makes it very challenging to locally adjust the tracking beam direction to ensure parallel tracking of the shear waves. The proposed 2D shear wave speed calculation approach, however, does not need a priori knowledge of the shear wave propagation angle or the tracking beam to be parallel to the push beam and shear wave, and therefore can robustly handle locally variant shear wave angles, which is a more flexible and reliable approach than the angle correction method and the adjusting tracking beam method.
Figure 3.15 shows the standard deviation values of the shear wave speed of the inclusion versus number of compounding angles for both the comparison study (Fig. 3.15(a)) and the multi-inclusion phantom study (Fig. 3.15(b)). As shown in Fig. 3.15, the standard deviation of the shear wave speed estimate decreases with increased number of compounding angles for all inclusions. A comprehensive analysis of noise deduction for shear compounding will be conducted in future studies, because as suggested by [93], noise modeling for shear elasticity map reconstruction is rather complicated.
Another important function of shear compounding is to remove the structural artifacts caused by shear wave propagation direction and therefore reconstruct better shaped inclusions. As shown in Figs. 3.11 (a) and (c) and Fig. 3.14 (b) and (c), the standard deviation of the shear wave speed value of the inclusions indicated by the ROIs in the figures decreases as the number of compounding angles increases for both the conventional and fast shear compounding methods. Figure 3.15 (a) shows the plots for Type II and Type III inclusions on the secondary axis colored in green.

Figure 3.15 – (a) Plot of standard deviation of the shear wave speed value of the inclusion indicated by the ROI in Fig. 3.11 (a) versus number of compounding angles for both the conventional and fast shear compounding methods. (b) Plot of standard deviation of the shear wave speed value of the inclusions indicated by the ROIs in Fig. 3.14 (c) versus number of compounding angles for the three types of inclusions. Note that plots for Type II and Type III inclusions are on the secondary axis colored in green.
(c), the shape of the inclusion changes with the incident angle of the shear waves, causing unwanted deformation of the inclusion. After shear compounding, one can see an improved shape of all inclusions. This feature of shear compounding is different from ultrasound spatial compounding and is another benefit of this technology.

This study used a curved linear array to produce differently angled shear waves thanks to the various beam angles at various locations of the probe. To obtain more flexible control of the beam angle, one can steer the ultrasound push beam by adjusting the phase delay profile of the aperture. Beam steering is necessary for linear array and phased array probes to produce differently angled shear waves for shear compounding. Note that with beam steering on the linear array there is a chance for grating lobes. With the phased array, this should not occur. Push beam steering will be investigated in future works.

For the multi-directional filter used in this study, we empirically chose a power of 3 to balance the tradeoff between the directionality of the filter and the “streaking” artifact in a direction that is perpendicular to the filter direction. As introduced in [78], the higher the power of the filter, the narrower the angular width of the filter and thus the stronger the directionality. However, if a very narrow directional filter is used, high frequency components along perpendicular direction will be filtered out and an artificial vertical streak along the perpendicular direction will be created. If the filter is too wide, the directionality will be bad and
shear waves from different directions will not be separated. To overcome this limitation in filter design, ideally we would like to have push beam angles that are sufficiently separated so that design of directional filters that have little or no overlap is possible, and therefore each directional filter can output independent shear waves with different angles. In practice, however, this would require further steering the push beams in addition to the angles provided by the curvature of the probe. As mentioned above, push beam steering will be investigated in future work to provide more flexibility of the angle of the shear waves.

The number of shear waves of different directions that can be produced in a single comb-push cycle is limited by the transducer aperture size if a focused comb-push is used, which transmits multiple focused push beams simultaneously [75], as used in this study. Given a certain push beam F/# and probe aperture size, shallower depth allows a higher number of push beams than deeper depth, and therefore a higher number of different directional shear waves in shallower depth than in deeper depth. If a marching comb-push is used where push beams at different angles are transmitted sequentially [75], one can transmit a higher number of different directional shear waves at deeper depths compared to using focused comb-push. In this case the limiting factor to the number of push beams and number of different directional shear waves would be heating on the overlapping transducer elements that are being excited multiple times. This study was using focused comb-push as a proof of concept for the proposed fast shear
compounding method. Future studies will be conducted to test the feasibility of using marching comb-push for shear compounding.

The processing speed of fast shear compounding is faster than the conventional compounding method. On a general desktop PC with Intel Core2 Duo CPU at 3 GHz, the time cost for conventional compounding (Fig. 3.11(a)) was about 125 seconds, while for fast shear compounding it was about 90 seconds in MATLAB (The Mathworks, Natick, MA). The reason why post-processing for fast shear compounding is faster is because: 1) as in Fig. 3.11(a), the conventional method also requires calculating same number of differently angled shear wave fields (in this case 4 different angles) as the fast compounding method; 2) the conventional compounding method extracts shear wave motion from separate sets of IQ data from multiple data acquisitions (in this case 4 data acquisitions), while the fast compounding method only needs to do this once; 3) a directional filter is also needed for the conventional method to remove the reflected shear waves from the inclusion for each shear wave field, as introduced in [81]. With more advanced programming (e.g. C++) and parallel processing (e.g. graphical processing unit (GPU)), the processing time is expected to be substantially reduced. Our initial tests show a typical processing time around 0.25 ~ 0.5 sec for the fast shear compounding method.
Limitations

One limitation of this study is that only phantoms were used to test the proposed method. Real tissues typically cause more shear wave attenuation than phantoms, which means some of the differently angled shear waves would attenuate before reaching a given position. For example, in the multi-inclusion phantom experiment, shear wave no. 1 (Fig. 3.13) may not have been able to reach the rightmost type IV inclusion due to attenuation. Thus, the rightmost type IV inclusion would not have experienced as many differently angled shear waves as in the phantom case. Thus, if this experiment had been done in real tissues, the overall shear compounding efficacy may have been compromised. Nevertheless, each inclusion would still have experienced at least two differently angled shear waves thanks to the multiple push beam sources. Moreover, because the compounding is achieved with only one push-detect cycle, motion artifacts caused by breathing and other physiological motions are minimized, which is a substantial improvement over the conventional shear compounding method.

Conclusions

To summarize, this chapter presented a fast shear compounding method capable of achieving shear compounding while preserving the shear wave imaging frame rate, thus minimizing motion artifacts. The fast compounding method combines comb-push, multi-directional filtering, and a robust 2D shear
wave speed calculation technique to realize transmission and processing of multiple differently angled shear waves simultaneously, and reconstructing accurate 2D shear wave speed maps from each direction. Comparable performances to the conventional method were achieved using the fast shear compounding method while the total acquisition time was reduced by a factor of 4. Multiple inclusions with different stiffness values could be simultaneously resolved in a full FOV 2D map using the proposed method, while only one push-detect cycle of shear waves was needed. Future study includes implementing the fast shear compounding technique for investigation of in vitro and in vivo tissues.
Innovations in Shear Wave Detection – Shear Wave Detection with Harmonic Imaging


Abstract

This chapter introduces a method of using the harmonic signals of ultrasound to track shear wave motion. The benefit of using the harmonic signal is the substantial improvement of the signal quality. The Introduction section gives the background and motivations of this study, followed by the Methods section which gives the details of the shear wave detection with harmonic imaging technique. Experiments and results from gelatin phantoms to *in vivo* human heart study were conducted, followed by discussion of the results. Future directions for the harmonic imaging detection technique are given in the end of the chapter.

4.1 Introduction

This chapter of the thesis focuses at addressing a critical challenge in shear wave elastography (SWE): poor shear wave motion detection from challenging tissues such as heart. Shear wave motion detection is a vital component of shear wave elastography (SWE). As shown in Fig. 4.1, if the push beam is like a light bulb that emits light (or shear wave), then shear wave motion detection can be
compared to a human eye which is supposed to see the light (or see the shear wave). If the eye cannot see the light, there are two possible causes: one is that the light bulb is not bright enough (in other words, the push beam is not strong enough to generate sufficient shear waves), and the other reason is that there is a barricade in between the eye and the light bulb which keeps the light from going into the eye (in this case, the barricade is the ultrasound noise). While it is true that for *in vivo* applications in deep tissues such as heart, liver and kidney, the light bulb may not be bright enough (shear wave motion is weak), the ultrasound detection signal, on the other hand, is also heavily contaminated by various sources of noise and therefore the “barricade” effect as in the eye analogy may also be pronounced. In these challenging *in vivo* tissues, shear wave motion is weak due to significant attenuation of the acoustic radiation force, so shear wave motion detection can be very challenging [27, 69, 110-113]. To address these issues, many efforts have been made to improve shear wave generation [18, 69, 74, 75], develop more robust shear wave motion calculation techniques [63, 114-116], investigate better methods of shear wave speed measurement [3, 64, 65, 69, 98], and increase the signal-to-noise-ratio (SNR) of the ultrasound signal [80, 117]. While the field of SWE has been greatly advanced by these works, the issue of noise-contaminated (e.g. clutter noise, phase aberration noise, and ultrasound reverberation noise) ultrasound signals still remains unsolved and applications such as closed-chest cardiac elasticity imaging still largely remain as unfulfilled goals for SWE.
Tissue harmonic imaging has emerged as a standard B-mode imaging technique thanks to its dramatic improvement of ultrasound image quality [118-121]. Figure 4.2 shows an example of imaging the left ventricle with fundamental imaging and harmonic imaging. One can immediately see that the heart wall is much better delineated by harmonic imaging than by fundamental imaging. The harmonic B-mode image also has substantially less clutter noise than the fundamental B-mode image.

Harmonic imaging provides better spatial and contrast resolution and suffers less from noise sources such as phase aberration and ultrasound reverberation [122, 123]. Among various harmonic imaging techniques, pulse-inversion harmonic imaging adds echoes from phase-inverted transmission pulses to
cancel odd numbered harmonic components and double even numbered harmonic components, which is often preferred due to improved SNR of the second harmonic [122-126]. Recently, Doherty et al. showed that for acoustic radiation force impulse (ARFI) imaging, pulse-inversion harmonic imaging improved the displacement tracking by reducing jitter and enhancing feature detection [127]. For SWE, however, there has been no report on using the harmonic imaging to track shear wave propagation. In this chapter, we propose to implement pulse-inversion harmonic imaging in ultrasound SWE to track shear wave motion with phase-inverted and high frame-rate diverging beam pulses. The first hypothesis of this work is that compared to fundamental shear wave tracking, harmonic shear wave tracking is advantageous in obtaining more robust shear wave motion estimation under the presence of severe ultrasound signal noise. The second hypothesis is that referring to the eye analogy shown in Fig. 4.1, for closed-chest cardiac SWE applications, the light bulb is actually on: it is the ultrasound clutter noise that has been blocking the light. In other words, the shear wave is actually being produced on the heart wall by the push beam – it is the poor shear wave detection that sabotages the shear wave signal.

In this chapter, a phantom study with a gelatin phantom covered by an excised section of pork belly will be conducted to systematically compare the performance of shear wave motion tracking using either the fundamental or harmonic ultrasound signal. Another ex vivo experiment was conducted to further comparing the two imaging methods on a closed-chest pig heart within the first 35 minutes after sacrifice. Lastly, an in vivo human heart study using the
The proposed method to estimate the diastolic left ventricular wall stiffness in seven healthy volunteers with transthoracic ultrasound will be introduced. In the Future Direction session, an improved harmonic imaging detection technique will be introduced which has better harmonic signal and thus better shear wave signal. The chapter will be finalized with discussion and conclusions.

4.2 Materials and Methods

4.2.1 Shear wave tracking sequence with pulse-inversion harmonic imaging

A Verasonics ultrasound system (Verasonics Inc., Redmond, WA) and a phased array P4-2 (Philips Healthcare, Andover, MA) with 64 elements and center frequency of 2.5 MHz were used for shear wave generation and detection. For shear wave generation, all 64 elements were excited to transmit a single focused ultrasound push beam with center frequency of 2 MHz and push duration of 800 μs. For the harmonic sequence, after transmitting the push beams, the Verasonics system immediately switched to flash imaging mode with excitation of all 64 elements and emitted phase-inverted pulses (center frequency = 2 MHz, pulse duration = 2 cycles) at a pulse repetition frequency (PRF) of 7.69 kHz, as shown in Fig. 4.3(a). For each pair of the phase-inverted pulses, a positive pulse is first transmitted and the backscattered data are received; then a negative pulse with 180° phase shift is transmitted, and the backscattered data from that transmission are received and added to the data backscattered from the positive pulse transmission. The PRF is thus effectively reduced by a factor of 2 after the summation (final effective PRF = 3.85 kHz). After the addition of the
positive and negative pulses, the fundamental signal will be cancelled and the second harmonic signal will be doubled. The second harmonic signal is used for shear wave motion calculation. The term harmonic sequence and harmonic imaging (HI) sequence are both referring to this approach hereinafter. A diverging beam with the focal depth at the virtual apex of the P4-2 (-28 mm from the probe surface) was used in this study due to improved performance in the far field when compared to transmitting plane waves [128]. The focal depth of the diverging beam was adjusted to -288 mm for more concentrated energy delivery to enhance harmonic generation in the ex vivo pig and in vivo human study. For the fundamental sequence, the transmitting frequency was also centered at 2 MHz, with the same PRF as in the harmonic sequence. Every two frames were then averaged to form a fundamental frame set to improve SNR and maintain an effective PRF equivalent to that of the harmonic sequence, as shown in Fig. 4.3(b). The in-phase/quadrature (IQ) data of consecutive frames was used to estimate axial particle velocity ($v$) caused by shear wave propagation. The one-dimensional autocorrelation method [60] as in Eq. (1.15) was used to calculate $v$. 

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4.2.2 Ex vivo pork belly/gelatin phantom experiment

To compare the performance of shear wave motion detection between the fundamental and harmonic sequences, an experiment was designed in which a gelatin phantom (9% gelatin, 10% glycerol and 1% cellulose) was covered with a piece of excised pork belly and the ultrasound probe was placed on top of the excised tissue section, as shown in Fig. 4.4. A fresh piece of pork belly with a thickness of about 2.5 cm was used to simulate the body wall for evaluation of in vivo shear wave detection. The pork belly section had clearly delineated layers including skin, muscle, and subcutaneous fat. A thin layer of distilled water was poured between the pork belly and the phantom surface to ensure good acoustic
coupling. In this experiment, in order to obtain ground truth for the shear wave signal, a linear array (L7-4, Philips Healthcare, Andover, MA) was operated by one Verasonics machine (Verasonics1) to produce shear waves from the bottom of the phantom (a hole was cut in the container's bottom) so that both the push beam and detect beam of the L7-4 were not affected by the pork belly and thus the shear wave signal obtained from L7-4 could be used as ground truth. The phased array P4-2 was operated by a second Verasonics machine (Verasonics2) to track shear wave motions produced by the L7-4 from the top of the phantom. The two probes were carefully aligned without the phantom and pork belly and then the P4-2 was translated upwards by the mechanical stage (Fig. 4.4(a)) so that the alignment was maintained throughout the translation. The imaging sequence is shown in Fig. 4.4(b): Verasonics1 drove the L7-4 to emit a push pulse (center frequency = 4.09MHz, push duration = 600 μs), after which a trigger signal was sent to Verasonics2 to initiate the shear wave detection pulses by the P4-2. The same setup was used for both the fundamental and harmonic detection sequences. To obtain the ground truth signal from L7-4, a separate sequence with the L7-4 detecting its own shear waves was conducted without the detection pulses from the P4-2. To test repeatability, five measurements at five different locations of the pork belly were made for both the fundamental and the harmonic sequences. To perform this repeatability test, the position of the probes was maintained and the phantom/pork belly was moved.
4.2.3 *Ex vivo closed-chest heart experiment*

To further compare the performance of shear wave tracking by harmonic imaging and fundamental imaging, we conducted an experiment on a freshly sacrificed pig to image the stiffness of the left ventricular myocardium through the intact chest. The absence of breathing and cardiac motion allowed us to compare the performance of fundamental detection and harmonic detection under the same conditions while simulating in vivo shear wave measurements in heart. A pig weighing 44.6 kg was anesthetized by Telazol-xylazine, and then was injected with 4.5 cc of heparin for anticoagulation, followed by 10 cc of Fatal-Plus® solution for euthanasia. After death, ultrasound B-mode imaging was used as guidance to locate the left ventricular wall with a short-axis view, after which the P4-2 probe was fixed at the chest surface using a clamp. A 48 scan-line B-mode imaging scheme provided by the Verasonics was used to improve the
quality of the B-mode image, which is called “Guidance B-mode” hereinafter. The phased array P4-2 was used to both produce and track shear waves with the fundamental sequence and harmonic sequence (as introduced in part A of this section). The ultrasound push beam was focused at the anterior wall of the left ventricle, which was about 34 mm away from the probe surface. Five trials were done for both the harmonic sequence and the fundamental sequence, at the same fixed position. The entire experiment finished within 35 minutes after the death of the pig.

4.2.4 In vivo human heart study in healthy volunteers

To test the feasibility of using the proposed harmonic shear wave tracking sequence for in vivo studies, we recruited seven healthy volunteers to produce and track shear waves in the heart from a transthoracic approach with the phased array P4-2 (same push and detection setup as in section 4.2.3) and measure the shear wave propagation speed in end-diastole. The experiment protocol was approved by the Mayo Clinic Institutional Review Board and written informed consent was obtained prior to scanning. The experiment was conducted under the guidance of a cardiologist who also performed the ultrasound scan on the volunteers. The left ventricle was imaged using a short-axis view. The harmonic imaging sequence was combined with the same Guidance B-mode imaging sequence used in the ex vivo pig study so that real-time B-mode imaging could be used as a guide to select the imaging plane for shear waves, locate the focal depth of the ultrasound push beam, and trigger the shear wave imaging sequence in a real-time fashion. The Verasonics system was synchronized with
the ECG signal from the subject in order to produce and track shear wave motion in end-diastole. Because the Guidance B-mode imaging sequence uses 48 scan lines which requires much longer data acquisition time, and the shear wave imaging sequence has to be precisely triggered by the ECG signal, the Guidance B-mode sequence could not be integrated into the shear wave imaging sequence. Thus, the Guidance B-mode images were not synchronized with the ECG signal (i.e. the Guidance B-mode images were not necessarily acquired at end-diastole). Nevertheless, each shear wave imaging sequence saved one Guidance B-mode image which can be used as an offline data analysis reference.

The mechanical index ($MI$) and spatial peak time average intensity ($ISPTA$) regulated by the Food and Drug Administration (FDA) were measured for all the ultrasound beams used in this study. Both $MI$ and $ISPTA$ were derated at a rate of 0.3 dB/cm/MHz and the measured values were summarized in Table 4.1. For succinctness, the experiment is not described here and one can refer to section 2.3.1 of Chapter 2 for details. The frame rate used for $ISPTA$ calculation was 1Hz for the shear wave detection beams and the push beams, and 16 Hz for the Guidance B-mode beam. All values used in this study are under the FDA regulatory limits of 1.90 and 720 mW/cm$^2$ for the $MI_{0.3}$ and $ISPTA_{0.3}$, respectively [83]. Note that for depths shallower than 45 mm, the push beam pulse width modulation (PWM) was reduced to as low as 27% to avoid exceeding the $MI$ limit (the output power of the Verasonics transmit waveform is regulated using PWM and can be varied to obtain acoustic output levels that meet FDA regulatory
limits), which significantly reduced the power of the push beam and consequently the amplitude of the shear waves. This results in poor shear wave generation in the anterior left ventricular wall which typically locates at depths shallower than 45 mm, as will be discussed in the Results session.

Due to breathing and cardiac motion, it cannot be guaranteed that each acquisition was made in the same part of the myocardium through the same path through the fat and muscle layers. Therefore, a comparison with fundamental detection was not done here, because it was difficult to control these confounding factors for a fair comparison.

<table>
<thead>
<tr>
<th>Guidance B-mode</th>
<th>Diverging beam (focused at -288 mm)</th>
<th>Diverging beam (focused at -28 mm)</th>
<th>Push beam focused at 45 mm</th>
<th>Push beam focused at 60 mm</th>
<th>Push beam focused at 65 mm</th>
<th>Push beam focused at 70 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI_{0.3}</td>
<td>1.24</td>
<td>1.51</td>
<td>1.19</td>
<td>1.60</td>
<td>1.11</td>
<td>1.00</td>
</tr>
<tr>
<td>I_{SPTA,0.3} (mW/cm²)</td>
<td>6.8</td>
<td>51.7</td>
<td>21.3</td>
<td>225.5</td>
<td>98.6</td>
<td>80.1</td>
</tr>
</tbody>
</table>

### 4.3 Results

#### 4.3.1 Ex vivo pork belly/gelatin phantom experiment

Figure 4.5 shows the plots of the shear wave particle velocity signal ($V_\text{Z}$) at the focal depth of the focused push beam of the L7-4 for both the harmonic imaging (HI) sequence and the fundamental sequence at five different locations of the phantom/pork belly. Figure 4.5 also shows the B-mode images reconstructed by the detection beams (named Detection B-mode hereinafter) for both the fundamental and harmonic sequences, and the shear wave generation and analysis regions. Both the harmonic and fundamental sequences could detect
discernible shear wave motions. However, the amplitude of the shear waves tracked by the harmonic sequence is consistently higher than that tracked by the fundamental sequence. Moreover, the shear waves tracked by the harmonic sequence are also better delineated than with the fundamental sequence.

To quantitatively compare the performance of the harmonic and fundamental sequences, we first measured the maximum shear wave particle velocity ($V_{z,\text{MAX}}$) for each plot in Fig. 4.5. The $V_{z,\text{MAX}}$ was measured for the shear waves propagating in the $-x$ direction and $+x$ direction separately. We then used a

Figure 4.5 – Plots of the shear wave particle velocity signal at the focal depth of the push beam. Upper row: B-mode images reconstructed by the harmonic and fundamental detection beam sequences. The red dashed boxes indicate the shear wave generation and analysis regions. Shear wave signal was averaged along depth direction within the region (region thickness = 2.7 mm). The green dashed box indicates the area of pork belly. Middle row: shear wave motion tracked by the harmonic imaging (HI) sequence at 5 different locations of the phantom/pork belly. Lower row: shear wave motions tracked by the fundamental sequence at the same 5 locations as in HI. All plots use the same color scale with units of mm/s.
Radon transform to convert the plots of shear wave motion signal into sinograms from which the shear wave speed \( c_s \) can be calculated [65, 129]. For example, Fig. 4.6(a) shows the plot of the shear wave motion produced and tracked by the L7-4 probe (the ground truth signal). Figure 4.6(b) shows the sinogram of Fig. 4.6(a) with an angular resolution of 0.18° obtained from the MATLAB function “radon.m”. There are two peaks in the sinogram corresponding to the two shear waves in Fig. 4.6(a): the peak around 21° corresponds to the shear wave going toward the +x direction; the peak around 159° corresponds to the shear wave going toward the -x direction. These peak sinogram angles can be converted to shear wave speed \( c_s \) by:

\[
c_s = \frac{\Delta x}{\Delta t} \tan(\theta)
\]  

(4.1)

where \( \Delta x \) and \( \Delta t \) are the pixel sizes along the \( x \) and \( t \) directions (Fig. 4.6(a)); and \( \theta \) is the peak sinogram angle. The derivation of Eq. (4.1) is shown in Fig. 4.6(a): the peak sinogram angle \( \theta \) is indicated as the angle between the shear wave trajectory and the horizontal direction, which is given by

\[
\tan(\theta) = \frac{N_x}{N_t}
\]  

(4.2)

where \( N_x \) and \( N_t \) are the number of pixels of the shear wave trajectory along the \( x \) and \( t \) dimensions, respectively. Given:

\[
N_x = \frac{x}{\Delta x}
\]

\[
N_t = \frac{t}{\Delta t}
\]  

(4.3)

and
\[ c_s = \frac{x_s}{t_s} \]  

(4.4)

where \( x_s \) is the actual shear wave propagation distance and \( t_s \) is the shear wave propagation duration, one can easily derive to Eq. (4.1) by substituting Eqs. (4.3) and (4.4) into (4.2).

The same analyses were performed on all the harmonic sequence data and fundamental sequence data. The \( V_{Z\text{MAX}} \) and shear wave speeds \( c_s \) were recorded, as shown in Table 4.2. The signal-to-noise ratio (SNR) of the shear wave signal was also calculated. The SNR is given by:

\[ SNR = \frac{\bar{x}}{\sigma} \]  

(4.5)

where \( \bar{x} \) and \( \sigma \) are the mean and standard deviation values of the \( V_{Z\text{MAX}} \) measurements. Table 4.2 also shows the values measured by the L7-4 probe, which were regarded as ground truth in this study.
Figure 4.6 – (a) Plot of the shear wave particle velocity \( (V_2) \) signal produced and tracked by the L7-4 probe. The black dashed lines indicate the shear wave propagation trajectories. \( N_t \) and \( N_x \) are the number of pixels of the shear wave trajectory along the \( t \) and \( x \) directions, respectively. (b) Radon transform of (a). The values are normalized by the length of the projection vector \( X_p \). The black arrows indicate the positions of the peak sinogram values.
Table 4.2 – Maximum shear wave particle velocity ($V_{Z\text{MAX}}$) and shear wave speed ($c_s$) measurements by the L7-4 probe, the harmonic sequence (by P4-2) and the fundamental sequence (by P4-2)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parameters</th>
<th>Position 1</th>
<th>Position 2</th>
<th>Position 3</th>
<th>Position 4</th>
<th>Position 5</th>
<th>Mean</th>
<th>Std.</th>
<th>SNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>L7-4 (ground truth)</td>
<td>$V_{Z\text{MAX}}$ (mm/s)</td>
<td>-x</td>
<td>+x</td>
<td>-x</td>
<td>+x</td>
<td>-x</td>
<td>+x</td>
<td>-x</td>
<td>+x</td>
</tr>
<tr>
<td></td>
<td>$c_s$ (m/s)</td>
<td>2.19</td>
<td>2.23</td>
<td>2.21</td>
<td>0.03</td>
<td>2.21</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harmonic sequence</td>
<td>$V_{Z\text{MAX}}$ (mm/s)</td>
<td>39.3</td>
<td>38.1</td>
<td>34.3</td>
<td>41.8</td>
<td>59.0</td>
<td>57.7</td>
<td>50.9</td>
<td>40.8</td>
</tr>
<tr>
<td></td>
<td>$c_s$ (m/s)</td>
<td>2.17</td>
<td>2.30</td>
<td>2.25</td>
<td>2.25</td>
<td>2.28</td>
<td>2.17</td>
<td>2.25</td>
<td>2.27</td>
</tr>
<tr>
<td>Fundamental sequence</td>
<td>$V_{Z\text{MAX}}$ (mm/s)</td>
<td>7.20</td>
<td>4.70</td>
<td>10.5</td>
<td>5.56</td>
<td>4.27</td>
<td>4.92</td>
<td>11.2</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>$c_s$ (m/s)</td>
<td>2.13</td>
<td>2.03</td>
<td>3.42</td>
<td>2.18</td>
<td>2.06</td>
<td>2.10</td>
<td>2.13</td>
<td>2.10</td>
</tr>
</tbody>
</table>

*Std. denotes standard deviation*
From Table 4.2, compared to the mean $V_{2\text{MAX}}$ value measured by the L7-4, both the harmonic sequence and the fundamental sequence provided significant underestimates of the shear wave peak motion due to the presence of the pork belly as the noise source. However, the mean $V_{2\text{MAX}}$ using the harmonic sequence is over 6 times greater than the mean $V_{2\text{MAX}}$ found using the fundamental sequence. Moreover, the $V_{2\text{MAX}}$ found using the harmonic sequence is biased low by 37.2% compared to the ground truth value, while the $V_{2\text{MAX}}$ found using the fundamental sequence is biased low by 90%: almost a 3-fold less underestimation by the harmonic sequence than the fundamental. There is also an almost 2-fold increase of shear wave signal SNR using the harmonic sequence instead of the fundamental sequence. For the shear wave speed calculation, the harmonic sequence provided more consistent shear wave speed measurements than the fundamental sequence, evidenced by a 1.78% standard error (given by the ratio of standard deviation to mean) of the harmonic sequence compared to an 18.8% standard error of the fundamental sequence. These results all together indicate a significant improvement of shear wave motion tracking by the harmonic sequence.

4.3.2 Ex vivo closed-chest heart experiment

Shear wave motion at the focal depth of the ultrasound push beam as well as the B-mode images indicating the location of shear wave generation and analysis are shown in Fig. 4.7. The top row of Fig. 4.7 shows the relationship between the Guidance B-mode imaging area and the shear wave detection beam area. This same imaging set up was used for the in vivo human heart study in the next
session. The middle row of Fig. 4.7 shows the shear wave motion detected by the harmonic imaging sequence and the bottom row shows the shear wave motion detected by the fundamental sequence. One can see that the harmonic sequence consistently tracked a propagating shear wave with clear boundaries for all five trials, while the fundamental sequence could not. The same Radon transform method as used in the previous section was used to estimate shear wave speed using the plots in Fig. 4.7. A shear wave speed limit of 0.5 – 10 m/s [112] was set by restricting the search range of the Radon transform angle as in Eq. (4.1) so that estimates beyond the limit would be rejected. The results are summarized in Table 4.3. In accordance with the observations from Fig. 4.7, harmonic imaging could provide consistent measurement of shear wave speed while the fundamental sequence failed due to the absence of detected shear wave motion. The mean and standard deviation value of the shear wave speeds measured by the harmonic sequence is 1.19 ± 0.03 m/s, which is in good agreement with the diastolic myocardium stiffness measurements of pig hearts in [26, 113, 130]. The clutter noise in the heart severely contaminated the fundamental pulses and consequently deteriorated the shear wave signal. The harmonic pulses, however, are less vulnerable to such clutter noise and thus could provide more robust shear wave motion estimates compared to the fundamental pulses.
Table 4.3 – Shear wave speed ($c_s$) measurements of the left ventricular wall in an \textit{ex vivo} closed-chest pig

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Trial 4</th>
<th>Trial 5</th>
<th>Mean</th>
<th>Std.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI</td>
<td>1.16</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>1.24</td>
<td>1.19</td>
<td>0.03</td>
</tr>
<tr>
<td>Fundamental</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>1.24</td>
<td>1.19</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Std. denotes standard deviation

Figure 4.7 – Plots of the shear wave particle velocity signal at the focal depth of the push beam in the left ventricular wall of an \textit{ex vivo} close-chest pig. Upper row: Guidance B-mode images and Detection B-mode images of the left ventricular wall for both the harmonic imaging sequence (HI) and fundamental sequence. The regions indicated by the green dashed boxes are the shear wave detection region by the high PRF diverging beam. The red dashed boxes on the Detection B-mode images indicate the shear wave analysis region. Shear wave signal was averaged along depth direction within the region (region thickness = 2.7 mm). Middle row: shear wave motions tracked by the HI sequence out of 5 trials at a fixed position. Lower row: shear wave motions tracked by the fundamental sequence out of 5 trials at the same fixed position as in the HI sequence. All plots are on the same color scale with units of mm/s.
4.3.3 *In vivo* human heart study in healthy volunteers

A total of five measurements were made out of five cardiac cycles in each volunteer (one acquisition per cardiac cycle). The left ventricular wall was located under the short-axis view in Guidance B-mode imaging (Fig. 4.8) and then the focal point of the ultrasound push beam was set either at the anterior or posterior left ventricular wall. Due to the reduced PWM level required by the *MI* limit at depths shallower than 45 mm as discussed in the Materials and Methods section, no discernible shear waves could be produced at the anterior left ventricular wall. Therefore only the posterior left ventricular wall was scanned in this study. The shear wave motions at the focal depth of the five trials for volunteers 1, 2, 3, 4, 6, and 7 are plotted in Fig. 4.8 (volunteer 5 was not plotted because no shear waves could be detected), which shows that the harmonic image could consistently detect discernible shear wave motions. The Radon transform method was again used to estimate shear wave speed from the plots in Fig. 4.8, with shear wave speed limit of 0.5 – 10 m/s [112]. The reconstructed shear wave speed trajectories calculated by the Radon transform were also plotted in Fig. 4.8. Note that in trial 3 for volunteer 1 and trial 4 for volunteer 6, the Radon transform method misfit one branch of the shear wave. The fit would have been better had the data been truncated along the time direction (e.g. only analyzing the shear wave towards $-x$ direction from 0 to 3 ms for trial 3 of volunteer 1). However, in this study, we used the same temporal window size for both branches of shear waves to maintain consistency in the analysis. The shear wave speed measurements together with the mean and standard deviation
values for all the tests are summarized in Table 4.4. Table 4.4 also shows the Body Mass Index (BMI) of each volunteer. From Table 4.4, in general, 56 out of 70 measurements provided shear wave speed estimates that were within the speed limit, corresponding to a success rate of 80%; the success rate was 93.3% (56 out of 60 trials) when excluding volunteer 6 whose BMI exceeds 25. The overall mean shear wave speed of these 56 measurements is 1.56 m/s, with a standard deviation of 0.36 m/s, which shows good agreement to the diastolic left ventricle stiffness measurement in sheep [112] and pigs [113, 130]. The ratio of the standard deviation to the mean value varies from 8.6% (volunteer 2) to 30.3% (volunteer 1) for all the subjects, with a mean value of 18.6%. These results showed that the harmonic imaging sequence provided consistent measurements of shear wave speed in diastolic left ventricular myocardium. This is, to our knowledge, the first reported shear wave speed measurements of the left ventricular myocardium stiffness on in vivo, closed-chest human subjects with shear waves induced transthoracically by acoustic radiation force. Previous in vivo and closed-chest tests have only been done in pigs [131].
Figure 4.8 – Plots of the shear wave particle velocity signals transthoracically produced and tracked by the harmonic sequence in *in vivo* human heart under diastole for the seven recruited volunteers. The leftmost column shows the Guidance B-mode images of the short-axis view of the left ventricle, with red dashed boxes indicating the shear wave generation and analysis regions. Shear wave signal was averaged along depth direction within the region (region thickness = 2.7 mm). Shear wave motion data of the seven volunteers are shown in each row of the plot. The black dashed lines indicate the angles of shear wave propagation obtained by the Radon transform. The failed shear wave speed measurements (not within the 0.5 ~ 10 m/s range) were not plotted. Results of volunteer 5 are not shown because no discernible shear waves could be detected.
Table 4.4 – Shear wave speed ($c_s$) measurements of the left ventricular wall in end-diastole

<table>
<thead>
<tr>
<th>BMI</th>
<th>Trial 1 $c_s$ (m/s)</th>
<th>Trial 2 $c_s$ (m/s)</th>
<th>Trial 3 $c_s$ (m/s)</th>
<th>Trial 4 $c_s$ (m/s)</th>
<th>Trial 5 $c_s$ (m/s)</th>
<th>Mean $c_s$ (m/s)</th>
<th>Std. $c_s$ (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol* 1</td>
<td>22.7</td>
<td>1.03</td>
<td>1.34</td>
<td>1.24</td>
<td>1.81</td>
<td>0.71</td>
<td>2.14</td>
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<td>Vol. 2</td>
<td>23.6</td>
<td>1.79</td>
<td>1.65</td>
<td>1.58</td>
<td>1.63</td>
<td>1.53</td>
<td>1.33</td>
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<td>1.66</td>
<td>1.16</td>
<td>1.23</td>
<td>-</td>
<td>1.38</td>
</tr>
<tr>
<td>Vol. 5</td>
<td>27.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vol. 6</td>
<td>21.5</td>
<td>1.65</td>
<td>2.28</td>
<td>1.74</td>
<td>1.88</td>
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<td>Vol. 7</td>
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<td>1.36</td>
<td>0.70</td>
<td>1.29</td>
<td>1.09</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Std. denotes standard deviation
** Vol. denotes volunteer
4.4 Discussion and Conclusions

This chapter investigated the implementation of pulse-inversion harmonic imaging for the task of shear wave tracking in ultrasound shear wave elastography, with the hypothesis that harmonic imaging can improve shear wave motion tracking in the presence of severe noise sources based on the principles that apply to general ultrasound B-mode imaging. The *ex vivo* pork belly phantom experiment showed significant improvement of shear wave tracking by the harmonic imaging sequence, indicated by an almost 3-fold less underestimation of shear wave motion, 2-fold increase of shear wave SNR, and more consistent shear wave speed calculation than the fundamental sequence. The experiment on an *ex vivo* closed-chest pig further demonstrated this improvement by showing that harmonic imaging could consistently track the shear wave motion and provide robust shear wave speed estimates while the fundamental sequence completely failed. Finally, the *in vivo* human heart study proves the feasibility of implementing the proposed harmonic tracking technique in *in vivo* applications.

There are several possible explanations why harmonic imaging works better than fundamental imaging for shear wave tracking. First, harmonic imaging suffers significantly less from phase aberration than fundamental imaging, as explained in [119, 121]. Under the presence of phase aberration, such as the pork belly and the chest walls of the pig and human, the inhomogeneous
distribution of ultrasound speed can significantly disturb the ultrasound RF signal and misregister the position of the scatterers. This can cause a partial volume effect in which echoes from the moving and non-moving scatterers are mixed and the overall effect is a "smearing" of the sharp and high shear wave motion such that what is detected is blurred and low shear wave motion. Because harmonic imaging is less affected by phase aberration, this "smearing" effect is less pronounced than fundamental imaging, evidenced by the observations from the pork belly experiment in which the underestimation of motion is much less by the harmonics than the fundamental. A second possible reason is the finer resolution cell and weaker side lobes for the harmonic component compared with the fundamental. This can help ameliorate the partial volume effect as proposed in the first reason because harmonic imaging is capable of examining a smaller and finer cell of scatterer motion [132, 133]. Another reason is based on the fact that in general, harmonic imaging is effective in suppressing clutter noise, especially for cardiac applications where the heart wall is usually contaminated by heavy clutter noise [120]. The clutter noise can completely ruin the fundamental ultrasound RF signal and cause failure of the shear wave motion detection, as observed in the heart experiment on the ex vivo closed-chest pig. Harmonic imaging, however, suffers less from clutter noise and thus could still provide robust shear wave tracking and shear wave speed estimate.
An alternative approach of doing harmonic imaging is to filter the fundamental signal to extract a harmonic signal at twice the frequency of the fundamental, which is named filter-based harmonic imaging. When receiving at the center frequency of the transmission frequency (e.g. 2 MHz in this study), the filter-based harmonic imaging method requires a minimum of 200\% receiving bandwidth to avoid cutting off the second harmonic signal at 4 MHz. The Verasonics system used in this study, however, imposes a default input band-pass filter with a bandwidth of 128\% to filter the backscattered RF signal and suppress noise, significantly lower than the required 200\% bandwidth. Therefore, it is difficult to extract a reliable second harmonic signal directly from the fundamental signal and perform the filter-based harmonic imaging approach, due to the limitation of Verasonics. Harmonic imaging on the Verasonics is achieved by setting the receiving center frequency to the frequency of the harmonics such that the harmonic signal can pass the input band-pass filter. In other words, Verasonics can perform either fundamental or harmonic imaging, but not both at the same time.

For the proposed harmonic imaging detection method, there is a tradeoff between the detection frame rate and harmonic excitation. If one were to use a focused beam as in conventional B-mode imaging to excite more harmonics, the frame rate would have to be sacrificed because line-by-line scanning is required to track shear wave propagation. If one were to use a high frame rate diverging
beam as used in this study to provide sufficient frame rate for shear wave tracking, the harmonic excitation would have to be compromised due to the dispersed distribution of the acoustic energy. To compare the harmonic excitation among different types of detection beams, we used a CIRS elasticity homogeneous phantom (CIRS Inc., Norfolk, VA) and three different types of detection beams to excite the harmonics: a focused beam with a focal depth of 45 mm (regarded as the beam used in conventional B-mode imaging); the narrow diverging beam with a focal depth of -288 mm used in the ex vivo pig study and in vivo human study; and the wide diverging beam with a focal depth of -28 mm used in the pork belly phantom study. All beam configurations were the same for the three types of beams except for the focal depth. The frequency spectrum of the RF signal is plotted in Fig. 4.9. Figure 4.9 indicates that the narrow diverging beam was able to excite comparable amount of harmonics to the focused beam in the shallow and deep fields, while the focused beam could excite significantly more harmonics than both diverging beams around its focal depth where the energy was mostly concentrated. The narrow diverging beam produces more consistent amount of harmonics through all depths compared to the other two beams. Meanwhile Table 4.1 shows that the narrow diverging beam has an MI of 1.51, which corresponds to a 2.14 MPa negative pressure given a 2 MHz transmission frequency. Therefore the intensity of the diverging beam used in this study was strong enough to excite sufficient harmonics for
shear wave detection purposes while preserving a high frame rate of several kilohertz.

Figure 4.9 – Plots of the frequency spectrum of three types of ultrasound beams at three depths. Ten cycles of radio-frequency (RF) signal backscattered from the CIRS phantom were Fourier transformed to obtain the spectrum. The focused beam stands for the conventional B-mode imaging beam which was focused at 45 mm. The narrow diverging beam is the diverging beam focused at -288 mm used in the ex vivo pig study and in vivo human study for shear wave detection. The wide diverging beam is the diverging beam focused at -28 mm used in the pork belly phantom study for shear wave detection.

**In vivo human heart study**

In the in vivo human heart study, five acquisitions were performed with one acquisition per cardiac cycle during end-diastole. Acquisitions were not performed other than at end-diastole because the motion of the heart poses two major challenges to shear wave generation and detection. First, the focal point of the push beam had to be pre-positioned onto the location of the left ventricular myocardium in end-diastole to ensure shear wave generation. The position of the left ventricular myocardium varies significantly during one cardiac cycle and thus the location of the focal point has to be changed accordingly, which is very challenging to realize in practice. Second, because heart contraction follows a complicated “twisting” motion and the ultrasound scan is two-dimensional in
nature, the shear wave may propagate out of the imaging plane and disappear from the field-of-view. Meanwhile the bulk motion of the heart can cause decorrelation of the ultrasound signal from consecutive frames and results in poor shear wave motion estimation. In end-diastole, however, the heart is moving more slowly and it is therefore less challenging to produce and detect shear waves.

The failed test in the in vivo human heart study was on the subject with the highest BMI of 27.5, which indicates that obesity still remains as an issue with the proposed method, as with shear wave elastography in general on cardiac applications. The absence of shear waves in the failed test could be caused by significant attenuation to the ultrasound push beam and consequently weak or no shear wave production at the left ventricular wall; or by severe phase aberration and ultrasound attenuation to the harmonic detection beams which results in an unreliable shear wave motion estimate. Since one-third of adults and almost 17% of youth in the US are obese [134], the success rate of SWE with harmonic imaging on the heart could be significantly lower than 80% as reported in this paper. Nevertheless, this study showed a significant improvement of shear wave detection and the first report of the SWE application on in vivo and closed-chest human heart using the pulse-inversion harmonic imaging approach.
Limitations

One limitation of this study is that the pulse-inversion harmonic imaging sequence could have been implemented in a sliding-window-sum fashion as proposed in [127] such that the original frame rate is preserved instead of reduced by a factor of 2 as in this study. However, due to system limitations of the Verasonics, for now we could only sum the echoes as shown in Fig. 4.3(a). This limitation was due to the way the Verasonics scanner was configured and was not fundamental. The current configuration of Verasonics enables online processing of the IQ data so that the operator can observe the resulting shear waves immediately after the push and detection. This setup is very convenient in practice, especially for in vivo studies. This online processing requires the sum of the RF signals from phase-inverted pulses to be done before the beamforming and IQ demodulation processes, therefore the original positive and negative frames shown in Fig. 4.3 are not accessible anymore and Doherty’s sliding-window-sum approach cannot be implemented. One can use the sliding-window-sum technique before the beamforming and IQ demodulation process, however the Verasonics does not support duplicate use of the same frame: e.g. once a frame A is assigned to be added to another frame B, this frame A cannot be used anymore. A potential solution is to save all the positive and negative frames and perform offline beamforming and shear wave calculation, so that the sliding-window technique can be done without the restriction of the Verasonics system.
However, this approach would disable the real-time feedback of shear wave motion information and can be very inconvenient for in vivo studies.

In this study, only the phased array transducer P4-2 was used for harmonic detection. However, the same principle can be applied to other types of ultrasound probes such as curved and linear arrays for a wide range of elasticity imaging applications. To perform the harmonic imaging appropriately, the transducer being used must have adequate bandwidth to incorporate both the fundamental and harmonic frequencies.

Conclusions

To conclude, this chapter developed and demonstrated a novel shear wave detection method that utilizes pulse-inversion harmonic imaging and second-harmonic signal to estimate shear wave motion. The proposed method was shown to be able to provide significant improvement of shear wave motion tracking under the presence of severe noise sources such as phase aberration, ultrasound reverberation, and clutter noise. Harmonic imaging detection was able to reduce the underestimation bias of shear wave motion and improve the consistency of shear wave speed measurement in an experiment using a section of excised pork belly tissue. Harmonic imaging also provided robust shear wave tracking on an ex vivo closed-chest pig heart while conventional fundamental imaging failed. This chapter also showed the feasibility of using the proposed harmonic imaging detection method to transthoracically measure diastolic left
ventricular myocardium stiffness in 6 out of 7 healthy volunteers. These promising results indicate that the second harmonic imaging approach can be used for improving shear wave motion detection for shear wave imaging in a wide spectrum of shear wave applications.

4.5 Future Directions

4.5.1 Multi-zone harmonic imaging detection

Figure 4.9 shows that the efficacy of harmonic excitation increases by narrowing the detection beam. As discussed above, however, narrowing the detection beam decreases the width of the imaging FOV and shortens the available shear wave tracking region. To increase the harmonic excitation without sacrificing the size of the shear wave tracking region, one can use multiple detection zones distributed at different locations of the FOV. For example, as shown in Fig. 4.10, if using the diverging beam, the FOV can be covered with a single-zone; if using a higher energy wide beam which has stronger harmonic excitation, then one can use 3 zones with steered wide beams to cover the FOV. Such multi-zone detection scheme allows sufficient FOV size for shear wave imaging with stronger harmonic excitation and thus better ultrasound and shear wave signal.
To implement the multi-zone harmonic imaging detection method shown in Fig. 4.10(b), we can transmit phase-inverted pulses at each detection beam location and sequentially fire different detection zones, as shown in Fig. 4.11. The actual firing sequence iterates from beam 1 to beam 6. Beams 1 and 2 are transmitted toward the same direction but with inverted phases. The same setup applies to beams 3 and 4, and beams 5 and 6. Beams 1 and 2 are then summed to get second-harmonic signal and form Zone 1. Beams 3 and 4 are summed to
form Zone 2, and beams 5 and 6 are summed to form Zone 3. The time delay caused by the sequential tracking among different zones can be corrected by the TAST technique that will be introduced in the next chapter.

Figure 4.11 – Multi-zone harmonic imaging detection sequence.

To concatenate shear waves detected by the three zones as shown in Fig. 4.11, one has to account for the overlapping areas among different zones. Otherwise the same shear wave may be detected by multiple zones multiple times, and may introduce artifacts to the final shear wave signal if one just simply adds the shear wave signals from different zones. A method was developed to concatenate shear waves from different zones based on the intensity of the detection beam. Figure 4.12 shows that the three zones have overlapping areas.
at a certain depth. Given a spatial location inside the FOV \((x, z)\), the intensity \(I\) at this point from any beam \(i\) is \(I(x, z, beam(i))\). One can calculate a weighting function \(w\) at point \((x, z)\) by:

\[
    w(x, z, beam(i)) = \frac{[I(x, z, beam(i))]^2}{\sum_{i=1}^{N}[I(x, z, beam(i))]^2}
\]  

(4.6)

where \(N\) is the total number of detection beams.
The weighting parameter \( w \) at any spatial location sums to be 1 given Eq. (4.6), so that shear wave signals from different zones can be combined by use of the weighting parameter without introducing artifacts. For example, the weighting coefficients for the three intensity profiles shown in Fig. 4.12(b) are shown in Fig. 4.13(a). At any given lateral location, the sum of the weighting coefficient equals to 1. Figure 4.13(b) shows the weighting coefficient plots of the three detection beams from three zones. The yellow dashed line indicates the position from which the 1D beam intensity profiles were plotted. (b) Plots of the beam intensity profiles. The blue curve corresponds to the leftmost beam in (a), the red curve corresponds to the central beam in (a), and the black curve corresponds to the rightmost beam in (a).
beams. One can see that for non-overlapping areas the weighting coefficient is equal to 1, which suggests shear wave signal at these locations are from a single detection beam. For overlapping regions the weighting coefficients add up to be 1 at any spatial location.

![Weighting coefficients of the three beam intensity profiles shown in Fig. 4.12(b). (b) Weighting coefficient plots of the three detection beams.](image)

A pork belly/gelatin phantom study was conducted to compare the performance of shear wave detection with the multi-zone harmonic imaging detection method. Figure 4.14(a) shows the experiment setup. A pork belly was put in between the phased array P4-2 and the CIRS 3kPa phantom. The P4-2 was used for both shear wave generation and detection. Figure 4.14(b) shows...
the B-mode image of the pork belly and the phantom. The pork belly was about 32 mm thick, which produced a quite challenging shear wave imaging situation.

Three harmonic detection beams were tested: the single-zone harmonic detection with a wide diverging beam (the same one used in the phantom study in section 4.3.1); the sing-zone harmonic detection with a narrow diverging beam (the same one used in the ex vivo swine heart study and in vivo human heart study in sections 4.3.2 and 4.3.3); and the multi-zone harmonic detection with a wide beam as shown in Fig. 4.11. The push beam configuration was identical to the three types of detections. The results are shown in Fig. 4.15. It is clear that the single-zone harmonic detection with wide diverging beam struggled to detect discernible shear waves while the multi-zone harmonic detection was able to...
detect robust shear wave signals. This corroborates with the harmonic excitation results in Fig. 4.9 that the narrower the beam the better the harmonic excitation and shear wave detection.

![Image](image.png)

Figure 4.15 – (a) shear wave signal detected by single-zone harmonic detection with wide diverging beam. (b) shear wave signal detected by single-zone harmonic detection with narrow diverging beam. (c) shear wave signal detected by multi-zone harmonic detection with wide beam.

One potential limitation of the multi-zone harmonic detection technique is the reduced shear wave detection PRF. Given the setup in Fig. 4.11, the effective PRF is down by a factor of 6 (2 caused by pulse-inversion transmission and 3 caused by multi-zone sequential tracking) compared to the original scanning PRF. The sacrifice of PRF gains higher signal quality, but also increase the inaccuracy for shear wave speed measurement. For systole shear wave imaging, PRF has to be sufficient to account for the fast shear wave propagation speed which is typically on the order of 6 m/s \[112\]. One potential solution is to use the filter-based harmonic imaging sequence as discussed above, which can increase the effective PRF by a factor of 2 and thus brings the total PRF reduction factor to 3 (the number of zones). Optimization studies need to be conducted in the
future to systematically study the tradeoffs among tracking PRF, signal quality, and their impact on shear wave speed measurement.

4.5.2 2D quantitative mapping of myocardial stiffness

Given the substantially improved shear wave signal from closed-chest in vivo heart, it is possible to reconstruct 2D shear elasticity maps of the myocardium. A shear wave imaging user-interface was developed on the Verasonics system to enable real-time B-mode imaging, interactive selection of the focal point of the push beam, capturing the ECG-gated B-mode image as a reference, and executing the shear wave imaging sequence with a push beam and harmonic imaging detection. Figure 4.16 shows a flowchart of the imaging sequence.
Figure 4.17 shows an example of shear wave propagation on closed-chest *in vivo* human heart. One can see two shear waves propagating away from the push beam which was positioned in the middle of the FOV. The 2D shear wave speed calculation method proposed in the previous chapter was used to reconstruct the shear waves. The resulting 2D shear elasticity map was mapped onto the synchronized B-mode image, as shown in Fig. 4.17(e).
4.5.3 CUSE imaging of the heart

As demonstrated in Chapter 2, CUSE is the fastest shear wave imaging technique that can produce a 2D full FOV shear wave elasticity map with a single push-detect data acquisition. CUSE can capture tissue mechanical properties in as short as 25 milliseconds, which provides an ideal tool for cardiac shear wave elastography due to the fast moving nature of the heart. Due to the fast shear wave attenuation in the myocardium, it is beneficial to distribute multiple shear...
wave sources using CUSE along the shear wave propagation path on the heart wall so that a large portion of the heart tissue can be imaged with a single shot of push and detection. This idea is schematically presented in Fig. 4.18. M-CUSE can be used to quickly steer and march several push beams on the LV wall so that shear waves can fill the FOV. The standard CUSE processing algorithms can be implemented to remove shear wave interferences and reconstruct 2D shear elasticity maps of the myocardium.

An *ex vivo* porcine heart study was conducted to test the feasibility of implementing CUSE for cardiac SWE. Figure 4.19(a) shows the experiment setup. An excised porcine heart was emerged in saline and the left ventricular (LV) wall was located and imaged. An M-CUSE sequence with 2 teeth at different

![Figure 4.18 – Schematic plot of CUSE imaging of the heart. M-CUSE can be used to quickly steer and march multiple push beams on the LV wall. The resulting shear waves (yellow curves) can fill the FOV so that the entire LV wall can be imaged with a single shear wave push-detect data acquisition.](image-url)
steering angles was used. The duration of each beam was 400 μs. The time interval between push beam 1 and push beam 2 was 15 μs. The resulting shear waves are shown in Figs. 4.19 (c) – (d). One can see two waves were produced and propagating towards each other. The resulting 2D shear elasticity map is shown in Fig. 4.19(b). Future studies will be conducted on in vivo closed-chest porcine heart and human heart.
4.5.4 Phase aberration correction

Recall the eye analogy we made in the beginning of this chapter, it is also of great interests to see what happens to the light after passing through the
barricade. In other words, what happens to the ultrasound push beam and the resulting shear wave when transmitting through the pork belly or human chest wall? The same setup as shown in Fig. 4.4 was used with flipped transmission and detection: the P4-2 was used for push and the L7-4 was used for detection. A new piece of pork belly with thickness of about 32 mm was used. The goal was to use the L7-4 to see the quality of the shear wave produced by P4-2 through the pork belly. The L7-4 had direct contact with the phantom therefore there was no ultrasound noise contamination to the detection signal. Figure 4.20 shows the results. Surprisingly, the shear wave signal is very clean and with high motion amplitude (around 40 μm near the push beam), as shown in Fig. 4.20(a). Apparently the pork belly did not affect the push beam much in terms of defocusing and attenuating the acoustic radiation force. On the detection side, however, one can see from Fig. 4.20(b) that even using harmonic imaging detection, the same shear wave signal produced by the same push beam is with substantially worse quality and much lower motion amplitude as compared to the one shown in Fig. 4.20(a), which suggests that the pork belly affects the detection beam much more than the push beam. This interesting result corroborates with our previous findings and suggests that in situations where we cannot see shear waves, it may be the bad shear wave detection that causes it instead of the bad shear wave generation.
One possible reason that causes the dramatic difference between Fig. 4.20(a) and Fig. 4.20(b) is the phase aberration of the ultrasound detection beam [135, 136]. The shear wave motion calculation process [63] is vulnerable to variations of phase induced by variations of sound speed in tissue, therefore significant deterioration of shear wave motion signal may occur under the presence of the pork belly, chest wall or abdominal wall. Numerous efforts and attempts have been made to correct for phase aberration of tissue for ultrasound imaging, however it still remains as a challenging task at present [111, 135, 137-149].

Based on this study, a potential phase aberration correction approach can be proposed. Given that the acoustic radiation force-induced shear wave signal is with good quality through the chest wall or abdominal wall, one can iteratively and adaptively adjust the phase or ultrasound speed in the beamforming process for each spatial pixel location until the maximum shear wave motion amplitude or

Figure 4.20 – (a) Shear wave displacement signal detected by L7-4, which was directly touching the surface of the phantom. (b) Shear wave displacement signal detected by P4-2, which was generating and detecting shear waves through the pork belly.
the best quality shear wave signal can be obtained. A similar approach has been used in MRI to remove the blurring artifacts induced by motion [150]. Once the phase aberration profile is determined, one can apply the profile to the transmit beamformer to get better focused ultrasound push beams and better shear wave motion. Future work will investigate this approach as a potential phase aberration correction technique.
Chapter 5

Innovations in Shear Wave Elastography Implementation – Time Aligned Sequential Tracking (TAST)

5.1 Introduction

In chapters 2 to 4, we have introduced several novel techniques addressing many technical challenges that are currently existed in ultrasound shear wave elastography. Facilitating practical implementation of these techniques by making these techniques available to clinicians would greatly increase the impact of this thesis work. To realize this, we have to translate these shear wave elastography techniques that have been developed on the research platform Verasonics to much more popular clinical ultrasound scanners that are widely available in clinics.

The key difference between the Verasonics and a conventional clinically available scanner that matters for shear wave elastography is beamforming. Verasonics uses a software beamformer that can beamform the whole field-of-view (FOV) with a single pulse-echo insonification. As shown in Fig. 5.1(a), if using a plane wave for insonification and using all elements to receive, the software beamformer can reconstruct all the channel data from all the elements
at once [151, 152], which allows an ultrafast frame rate that is theoretically only limited by the round-trip time of ultrasound. This type of imaging technique is typically called “plane wave imaging”, “ultrafast imaging”, or “flash imaging”. The conventional scanners, on the other hand, typically use hardware beamformers which only allow beamforming a certain number of channels at a time and are only capable of imaging in a line-by-line scanning fashion. For example, as shown in Fig. 5.1 (b), only one imaging line can be beamformed by the hardware beamformer at a time, therefore multiple pulse-echo cycles are required in order to beamform the entire FOV. If the pulse-repetition-frequency (PRF) of the Verasonics is 15 kHz and the number of imaging lines is 60 (i.e. \( N = 60 \) in Fig. 5.1(b)), for example, then the conventional scanner PRF will be about 250 Hz (15 kHz divided by 60 pulse-echo cycles), which is far too low for shear wave tracking purposes. For transient shear waves produced by acoustic radiation force, the center frequency of the shear wave can be several hundreds of Hertz, and stiff tissues can produce even higher shear wave frequencies. So a high tracking PRF is required to provide a reliable shear wave speed estimate. Therefore it is necessary to increase the tracking PRF of conventional scanners before they can be used for shear wave elastography.
Thanks to the parallel beamforming technique that has been widely implemented on many commercial ultrasound scanners, the tracking PRF can be substantially improved [153, 154]. Parallel beamforming technique allows beamforming of multiple imaging lines at a time with a single pulse-echo cycle. If 4 lines can be beamformed at once, for example in Fig. 5.1(b), lines 1 through 4 can be beamformed together with one pulse-echo, lines 5 through 8 can be beamformed together with another pulse-echo, and only 15 pulse-echo cycles (60 divided by 4) will be needed to reconstruct the full FOV instead of 60, which

Figure 5.1 – Schematic plots of the scanning sequence of the Verasonics (a) and a conventional ultrasound scanner (b). The numbers indicate the indices of the pulse-echo cycle. The color of the numbers matches the color of the imaging lines. In (a), only one pulse-echo is needed to beamform the entire FOV. In (b), a total number of \( N \) pulse-echo cycles are needed to beamform the entire FOV.
is 4 times faster than before. This will bring the tracking $PRF$ to 4 times the original $PRF$ of 250 Hz to 1 kHz, which is sufficient to be used for shear wave tracking. To further increase $PRF$, one can break down the FOV into multiple zones. For example, one can track shear waves with lines 1 to 30 first, and then switch to lines 31 to 60 to continue the tracking. Such a two-zone tracking scheme will double the effective $PRF$ to 2 kHz. The effective shear wave tracking $PRF$ ($PRF_e$) is given by:

$$
PRF_e = \frac{PRF}{N / (PB \cdot Z)}
$$

where $PRF$ is the original pulse-repetition frequency, $N$ is the number of imaging lines, $PB$ is the number of imaging lines that can be parallel beamformed, and $Z$ is the number of zones. Increasing the number of parallel beamforming lines and increasing the number of zones can both increase the shear wave tracking $PRF$.

Motivated by the parallel beamforming capability of conventional scanners and the potentially sufficient tracking $PRF$, this chapter aims at developing a sequential shear wave tracking method that can take advantage of the parallel beamforming technique for implementation of shear wave elastography on a conventional ultrasound scanner. This chapter will first introduce the time aligned sequential tracking (TAST) approach including the sequential shear wave tracking method and the tracking delay compensation method. Then the chapter will show results of shear wave elastography from a conventional commercial scanner has been equipped with the TAST technique and the CUSE technique.
Both phantom results and in vivo case studies using TAST and CUSE will be presented. The chapter will end with discussion and conclusions.

5.2 Methods

Continuing from the setup introduced above, our target is to use the 60 imaging lines to track propagating shear waves. The conventional commercial scanner has a capability of parallel beamforming 4 imaging lines at a time, which brings the total number of pulse-echo transmissions to 15 (60/4 = 15). Figure 5.2 shows schematic plots of the sequential shear wave tracking sequence. In Fig. 5.2(a), a total number of 15 imaging vectors (V₁ to V₁₅) are used for shear wave tracking, with each imaging vector containing 4 parallel beamformed imaging lines. To track shear waves, the 15 imaging vectors are fired sequentially and iteratively: V₁ -> V₂ -> V₃ -> ... -> V₁₄ -> V₁₅ -> V₁ -> V₂ -> .... For each firing, 4 imaging lines are beamformed, from which the shear wave motion signal can be demodulated. For example, the first firing of V₁ will track a shear wave motion at time point 1, as shown by the solid square under vector V₁ in Fig. 5.2(b). The next firing of V₂ will track a shear wave signal at time point 2. Therefore the order of the tracked shear wave signal points is: 1 -> 2 -> 3 -> ... n -> n+1 -> n+2 -> nxm, as shown in Fig. 5.2(b). The time interval between consecutive tracking points (e.g. point n and point n+1) is 1/PRF. The time interval between consecutive tracking points on the same imaging vector (e.g. point 1 and point n+1) is 1/PREF, where PREF is given by Eq. (5.1). For actual shear wave...
imaging, this tracking sequence will be immediately initiated after the push beam sequence so that shear waves propagating inside the FOV can be tracked.

Such a sequential shear wave tracking method introduces a time delay to shear wave signals tracked by different imaging vectors, i.e. the starting point in time at $V_1$ is different from the starting point in time at $V_2$, as shown in Fig. 5.2(b).

Figure 5.2 – Schematic plots of sequential shear wave tracking sequence. (a) imaging FOV and the imaging vectors. Each imaging vector contains 4 imaging lines that can be parallel beamformed. (b) the sequential tracking sequence. The solid squares indicate the tracked shear wave data points. The hollow circles indicate the missed the data points.
This delay, if uncompensated for, can introduce error into the shear wave speed calculation. Two delay compensation approaches were designed to align the shear wave signals in time.

The first approach is shown in Fig. 5.3, which schematically shows shear wave signals tracked by 3 imaging vectors $V_1$, $V_2$, and $V_3$. The true starting time for all shear wave signals is time $t = 0$, as indicated by the vertical black solid line in Fig. 5.3. However because of the sequential tracking delay, the detected shear wave signals are aligned along a different starting time line, which is $t' = 0$ (indicated by the solid red oblique line). Therefore, to obtain the true time delay $\Delta T$ between shear wave signals tracked by vectors $V_1$ and $V_2$, the sequential tracking delay $\Delta t$ has to be added to the calculated delay $\Delta t'$, as shown in Fig. 5.3. The true shear wave propagation speed $c_j$ is given by:

$$ c_j = \frac{\Delta d}{\Delta T} = \frac{\Delta d}{\Delta t + \Delta t'} $$

(5.2)

where $\Delta d$ is the spatial distance between consecutive imaging vectors.
The second time alignment approach for tracking delay compensation is based on data interpolation, as shown in Fig. 5.4. An example of using 5 imaging vectors is shown. For each imaging vector, the original detected shear wave signal samples are interpolated along the time direction so that the points that were missed because of the sequential tracking can be retrieved. The interpolated data samples are indicated by the black circles in Fig. 5.4. By truncating the first 4 data points for \( V_1 \), first 3 data points and last data point for \( V_3 \), first 3 data points and last data point for \( V_3 \), first 3 data points and last data point for
$V_2$, first 2 data points and last 2 data points for $V_3$, first data point and last 3 data points for $V_4$, and the last 4 data points for $V_5$, one can obtain a data set without delay caused by sequential tracking, as indicated by the shaded area in blue in Fig. 5.4.

To generalize, given $N$ imaging vectors and $M$ data samples per imaging vector, this time alignment method includes the following steps:

1) Interpolate the original shear wave signal with $M$ data points by a factor of $N-1$. The interpolated data has a length of $(N-1) \times M - 1$. The interpolated data has a $PRF$ that is equal to the effective $PRF$ times $N$.

2) For vector $n$ ($n=1, 2, \ldots, N$), truncate the first $N-n$ data points and the last $n-1$ data points.

3) Align the truncated data. The aligned shear wave signal should have a dimension of $(M-1)(N-1)-1$ by $N$ (time by space).

This time alignment method regenerates shear wave data similar to the one tracked by a plane wave imager, i.e. the Verasonics. This method simplifies the shear wave calculation process because of the absence of the delay caused by sequential tracking. This can be a convenient method for dealing with a complex shear wave field with shear waves propagating at different directions, i.e. CUSE. One drawback of this method is that there is data loss. As shown in Fig. 5.4, the first vector and the last vector miss one raw data point while the rest of the vectors miss two. The truncated shear wave data starts $N-1$ times points late and ends $N-1$ time points early, which may cause some information loss at the starting and ending of shear wave propagation. For example, given a $PRF$ of 10 kHz and 10 imaging vectors ($N=10$), $N-1$ time points represent a time period of 0.9 ms, during which a shear wave with speed of 10 m/s can propagate 9 mm. Therefore truncating the first and last $N-1$ data points would cause a total loss of
18 mm of shear wave propagation, which is not negligible. One can address this issue by extending the tracking time on both starting and ending directions by $N-1$ time points. One may also choose to ignore the amount of shear wave propagation loss if the medium is soft (e.g. a 2 m/s shear wave will only cause a loss of 4 mm propagation) or the event of shear wave propagation only occurs in the middle portion of the time axis that is unaffected by data truncation.

The above introduced sequential shear wave tracking approach and the time alignment approaches are together named Time Aligned Sequential Tracking (TAST).

Figure 5.4 – Schematic plot of the second time alignment approach for tracking delay compensation.
5.3 Results

5.3.1 Validation study of TAST

TAST was implemented on a commercial scanner that has parallel beamforming ability of 4 (e.g. 4 imaging lines can be beamformed with one pulse-echo cycle). A method of producing out-of-plane planar shear waves as introduced in [155] was used to produce a shear wave for the commercial scanner. The experiment setup is shown in Fig. 5.5. The Verasonics system was used for push and the commercial system was positioned along the path of the resulting out-of-plane shear wave. The detected shear waves by TAST are shown in Fig. 5.6.

Figure 5.5 – Experiment set-up of out-of-plane shear wave generation for TAST tracking on the commercial scanner. The commercial scanner is positioned perpendicularly to the Verasonics L7-4 transducer.
Three CIRS homogeneous elasticity phantoms were tested in this study: CIRS phantom 1 (3 kPa Young's modulus), CIRS phantom 2 (6.75 kPa Young's modulus), and CIRS phantom 3 (12 kPa Young's modulus). The reconstructed shear wave speed maps using TAST and the commercial scanner are shown in Fig. 5.7. One can see that smooth shear wave speed maps could be obtained. There are some overestimation artifacts on the bottom right corner of phantom 1, lower left corner of phantom 2, and lower left corner of phantom 3. These are caused by the insufficient duration of shear wave tracking. These artifacts can be removed with extended tracking duration. Regions-of-interest (ROIs) as indicated by the red rectangle in Fig. 5.7 (a) were selected to measure the shear wave speeds of the three phantoms. The results are summarized in Fig. 5.8. Figure 5.8 also shows measurements with Magnetic Resonance Elastography (MRE) [87] and CUSE with Verasonics [74, 75] for phantom 2 and 3. The measurements

Figure 5.6 – Snapshots of the movie of out-of-plane shear wave propagation in phantom tracked by the commercial scanner. The white arrows with red outline indicate the shear wave front that propagates from the left to the right side of the FOV.
show good agreement between shear wave speed measurements among the three methods, which proves that the proposed TAST method worked well on a commercial scanner.

Figure 5.7 – Shear wave speed maps reconstructed from out-of-plane shear waves tracked by the commercial scanner. (a) phantom1, (b) phantom2, (c) phantom 3. The red box in (a) indicates the ROI selected for shear wave speed measurements. The same ROI was used for (b) and (c).
5.3.2 Implementing CUSE and TAST on the commercial system

The CUSE and TAST techniques have been implemented on a commercial ultrasound scanner for general radiology. The system realizes real-time CUSE imaging with a 2D shear elasticity map display. Figure 5.9 shows an example of CUSE shear wave propagation acquired from the commercial ultrasound system. The data was acquired on a homogeneous phantom. One can clearly resolve 4 shear waves produced by the 4-tooth focused comb-push. The reconstructed 2D shear wave speed map in real-time together with the B-mode image is shown in Fig. 5.10. The shear wave speed map is smooth and without artifact. The CUSE map quality control methods developed in Chapter 2 were built into the system in the form of a gain adjustment under shear wave mode. Both cross-correlation

Figure 5.8 – Summary of shear wave speed measurements by TAST using a commercial scanner, CUSE with Verasonics, and MRE. The MRE experiment was not performed on phantom1.
coefficient and shear wave energy are used in converting the quality of the shear wave speed calculation into gain. One can adjust the gain either online during the scan or offline on the saved shear wave images.
Figure 5.9 – Snapshots of the CUSE shear wave propagation movie at different time instants obtained from the commercial scanner. A 4-tooth focused comb-push was transmitted and the resulting shear waves were tracked by TAST.
Figure 5.11 shows an example of imaging an inclusion phantom (CIRS 049A) with the commercial ultrasound scanner. The type IV small lesion was imaged. One can see that a smooth 2D shear wave speed map with excellent contrast of the inclusion and background can be obtained from the system. Figure 5.12 shows another example of imaging a deep inclusion whose bottom is about 4 cm deep. Again the 2D shear wave speed map shows excellent contrast of the inclusion to the background. Figure 5.13 shows the same inclusion imaging with a curved array. The fast shear compounding method introduced in Chapter 3 was integrated in the system to account for oblique shear wave propagation. The curved array could image the inclusion well with good contrast. All inclusion images from Figs. 5.11, 5.12, and 5.13 have sharp boundaries.
Figure 5.11 – 2D shear wave speed map (right) of the inclusion phantom (CIRS 049 Type IV). The reference B-mode image is shown on the left. The color bar is in units of m/s.

Figure 5.12 – 2D shear wave speed map (right) of the inclusion phantom (CIRS 049A, Type IV). The reference B-mode image is shown on the left. The color bar is in units of m/s.
5.3.3 Phantom validation study

To validate the accuracy of shear wave imaging of the commercial system, a phantom study was conducted to compare the shear wave speed measurement of the commercial system to the Aixplorer scanner (SuperSonic Imagine, Aix-en-Provence, France) and the results from multiple ultrasound scanners equipped with shear wave elastography from 12 institutions worldwide conducted by the Quantitative Imaging Biomarkers Alliance (QIBA) [156]. Eleven pairs of CIRS homogeneous phantoms (these pairs of phantoms were identical) with different stiffness were tested by commercial shear wave elastography systems from Fibroscan, Philips, Siemens, and Supersonic Imagine, as well as several custom laboratory systems.

One pair of the phantoms was used in this study. The L10-2 probe and the C6-1 probe from the Aixplorer system (SSI) were compared with a matching linear array and a curved array from the commercial system equipped with CUSE and

![Figure 5.13 – 2D shear wave speed map (right) of the inclusion phantom (CIRS 049A, Type IV) obtained from a curved array. The reference B-mode image is shown on the left. The color bar is in units of m/s.](image-url)
TAST. Three data acquisitions were conducted at three different locations of the phantom for each probe of each machine. The mean and standard deviation values of the measurements are summarized in Fig. 5.14. Figure 5.14 also shows the approximate mean value of the phantom stiffness from the QIBA phantom study [156]. Figure 5.14 shows that Young’s modulus measurements for both phantoms from the commercial system equipped with CUSE and TAST are in good agreement with the Aixplorer measurements as well as the QIBA measurements.

Figure 5.14 – Summary of the phantom validation study. Two CIRS phantoms used in the QIBA study were tested. The linear array and curved array from the commercial system have similar center frequency and bandwidth to the SSI’s transducers.
5.3.4 *In vivo* case studies

A series of *in vivo* case studies on different organs were conducted with the commercial system equipped with CUSE and TAST. The ultrasound safety measurements were conducted by our industry collaborators. All shear wave imaging sequences are safe for human scanning.

Figure 5.15 shows a case study of imaging *in vivo* human biceps in flexed (upper graph) and extended (lower graph) positions. The same setup as in Fig. 2.27 was used. Smooth shear elasticity maps could be reconstructed by the system. ROIs were selected to measure muscle stiffness before (Young’s modulus = 16.5 kPa) and after the extension (Young’s modulus = 43.7 kPa). The biceps became more than twice as stiff at the full extension position than the flexed position.
Figure 5.16 shows a shear elasticity map of an *in vivo* human thyroid. The entire thyroid within the FOV could be imaged. The resulting 2D shear elasticity map is smooth. The Young’s modulus measured from the ROI is 18.6 kPa, which is 6.2 kPa after converting to shear modulus and is in good agreement to the literature value presented in Table 2.7.
Figure 5.17 shows a shear elasticity map of an *in vivo* human breast. The Young's modulus measured from the ROI is 14.93 kPa, which is about 4.98 kPa in shear modulus.

Figure 5.16 – 2D shear elasticity map of an *in vivo* human thyroid (right). The B-mode image is shown on the left.
Figure 5.17 – 2D shear elasticity map of an *in vivo* human breast (right). The B-mode image is shown on the left.

Figure 5.18 shows a shear elasticity map of an *in vivo* human liver scanned by a curved array. The measured Young's modulus from the selected ROI is 6.4 kPa, which is about 2.1 kPa in shear modulus and is in good agreement to the literature value presented in Table 2.7.
5.4 Discussion and Conclusions

This chapter introduced a key technique (TAST) that allows conventional ultrasound scanners without software beamforming functionality to realize shear wave imaging. TAST takes advantage of the parallel beamforming technique that is widely available on commercial ultrasound systems and uses a sequential tracking scheme and tracking delay compensation approach to realize shear wave detection. TAST bridges the gap between conventional ultrasound scanners and shear wave imaging. Without this technique, shear wave speed measurement is likely to be limited to a very small region (i.e. a point measurement) in a machine with parallel beamforming capability of 4. However, in this chapter, it was shown that TAST allowed reconstruction of 2D Full FOV
shear elasticity maps. TAST is a vital component of this thesis work in terms of facilitating the translation of the developed novel techniques such as CUSE and fast shear compounding from laboratory to clinic.

As shown in Eq. (5.1), the effective shear wave tracking \( PRF \) is inversely proportional to the number of imaging lines, which is directly related to the width of the tracking FOV. The width of the FOV needs to be sufficiently large to cover the whole event of shear wave propagation. For stiff materials where shear wave speed is fast, a wide FOV is demanded, otherwise the shear wave will be gone from the FOV within a very short time interval. Moreover, high shear wave speed also requires high tracking \( PRF \), which works against the desire of increasing FOV width. Under such circumstances, the only solution is to increase the number of zones for shear wave detection, i.e. increase the number of \( Z \) in Eq. (5.1). Increasing the number of detection zones means increasing the number of push-detect data acquisition cycles: if two zones are needed, then two push-detect data acquisitions will be needed to reconstruct the FOV. Such multi-zone detection will decrease shear wave imaging frame rate and may introduce motion artifacts. However, this is a sacrifice that has to be made in order to provide sufficient \( PRF \) for shear wave tracking. One can adjust the FOV size to increase the shear wave imaging frame rate. Breath hold will be preferred during shear wave imaging to avoid motion artifacts. In future work, with improvement of the parallel beamforming capability and possible realization of software beamforming
on conventional ultrasound scanners, more imaging lines can be beamformed simultaneously, which can substantially increase the detection PRF and relax the requirement on the number of detection zones. This can then take full advantage of the CUSE imaging method that can provide a full FOV shear elasticity map with a single push-detect data acquisition. Meanwhile with the faster shear wave imaging frame rate provided by CUSE, more frame averaging can be afforded and realized, which can markedly improve the quality and stability of shear wave imaging.

The CUSE and TAST techniques have been implemented on a popular commercial ultrasound system and will be made available to clinicians and researchers worldwide. The phantom studies showed that the commercial ultrasound system equipped with CUSE imaging and TAST tracking could provide robust and smooth 2D shear elasticity maps of homogeneous and inclusion phantoms with excellent contrast. The inclusions could be well imaged with sharp boundaries. The QIBA phantom study showed good agreement among the CUSE imaging on the commercial system, the SSI imaging on the Aixplorer system, and the average values from multiple institutions with various imaging systems and methods. The in vivo case studies demonstrated the feasibility of using the commercial system for real tissue imaging such as muscle, thyroid, breast, and liver. The measured tissue stiffness values are all in good agreement to literature values. These promising results indicate many possible
clinical applications of CUSE imaging such as diagnosis of breast cancer and thyroid cancer, staging of liver fibrosis and kidney fibrosis, evaluation of muscle stiffness for stroke patients and cerebral palsy patients, and assessment of myocardial stiffness for patients with cardiac conditions.
Chapter 6

Discussion and Summary of Thesis

6.1 Introduction

This chapter will discuss and summarize the work presented in this thesis. Brief summaries of the four main topics of the thesis and future directions of the developed techniques will be given first, followed by a discussion of the contributions and impact of this thesis work. Finally a list of academic contributions will be given in the end.

6.2 Summary of the Topics

6.2.1 Comb-push Ultrasound Shear Elastography (CUSE)

CUSE aims at providing full FOV shear elasticity imaging with a single push-detect data acquisition with improved shear wave signal SNR and absence of the push beam artifact. CUSE substantially improves shear wave imaging frame rate which minimizes motion artifacts and allows more frame averaging to improve image quality. CUSE distributes multiple shear wave sources along the shear wave propagation path and allows each imaging pixel to always have a shear wave source close by. CUSE sharpens the cross-correlation peak by using multiple shear waves which increases the robustness of local shear wave speed
recovery. Multiple versions of CUSE have been developed for different applications with different penetration and resolution requirements. These advantages make CUSE a promising and competitive technique for a wide spectrum of clinical applications. CUSE is also compatible with mainstream clinical ultrasound scanners and has been licensed and realized on a commercial ultrasound system. Clinical studies using CUSE with the commercial scanner will be conducted in applications such as breast cancer, thyroid cancer, and liver fibrosis staging.

The idea of CUSE has been generalized to a method that introduces multiple shear waves simultaneously into the tissue and solves for the complex shear wave field with the help of directional filtering and 2D shear wave speed calculation. The preliminary results of the rain-push technique are promising. Future work in this direction will be focused on optimizing the number and the position of the push beams to maximize the efficiency of shear wave generation so that the shear wave energy is evenly distributed throughout the FOV.

### 6.2.2 Fast shear compounding

The fast shear compounding technique takes advantage of the comb-push technique and realizes shear compounding with multiple differently angled shear waves within a single shear wave push-detect cycle, which preserves the shear wave imaging frame rate and minimizes motion artifacts. The fast shear compounding method uses a multi-directional filter to decompose the complex
shear wave field and uses a robust 2D shear wave speed calculation method to reconstruct and compound elasticity maps. Together with CUSE, the fast shear compounding technique has been implemented on the curved array shear wave imaging for a commercial ultrasound system.

Future work for the fast shear compounding technique will be toward two directions. The first is to systematically study the feasibility of push beam steering so that more flexible shear wave propagation angles can be obtained. This will allow better separation of the shear wave incident angles to the inclusion and achieve better compounding effect. The second is the use of mechanical vibrations to produce diffusive shear waves propagating at different directions for shear compounding [157]. Such a method is capable of producing certain angled shear waves that cannot be produced with acoustic radiation force, which can potentially achieve better shear compounding effect.

6.2.3 Shear wave detection with harmonic imaging

The shear wave detection with harmonic imaging technique was motivated by the challenging shear wave imaging situations in deep organs such as heart, liver, and kidney, and took advantage of the high B-mode imaging quality of the tissue harmonic imaging technique. Harmonic imaging shear wave detection showed substantial improvement of shear wave motion detection from ex vivo pig studies and in vivo human studies. The harmonic detection research demonstrated an important hypothesis that shear wave is actually being
produced in tissues and it is the poor shear wave detection that has been keeping us from seeing the shear wave. This part of the research makes us aware that shear wave detection is, if not more, at least equivalently important to shear wave generation.

Future research on harmonic imaging shear wave detection includes realization of harmonic imaging detection on curved array and linear array for shear wave detection. The detection beam configurations will be specifically optimized on each probe to achieve maximum harmonic excitation, maximum detection PRF, and maximum lateral range of the FOV. This research will benefit shear wave elastography applications that are being conducted on these types of probes. Second, the harmonic imaging detection will be improved and combined with the CUSE technique for cardiac shear wave elastography applications to realize in vivo quantitative mapping of myocardial stiffness throughout the cardiac cycle. This will provide a unique evaluation of cardiac functions that cannot be readily obtained from other echocardiography techniques.

6.2.4 Time Aligned Sequential Tracking (TAST)

TAST introduced an important concept of using conventional ultrasound scanners for shear wave elastography. TAST takes advantage of the parallel beamforming capability on most of the clinical scanners and realizes shear wave detection with sequential shear wave tracking and time alignment approaches. Combined with CUSE, TAST realized shear wave elastography on a commercial
ultrasound scanner. The QIBA (The Quantitative Imaging Biomarkers Alliance) phantom study showed that the commercial system provides accurate measure of the phantom stiffness compared to the results from multiple institutions using multiple imaging systems and methods. The in vivo case studies showed that the commercial system could provide robust 2D shear elasticity maps of different organs and the shear stiffness measurements were in good agreement to literature values.

Future work on TAST will be combined with future work on CUSE, and will be mainly focused on conducting clinical studies using the commercial system on a variety of applications such as breast cancer, thyroid cancer, and liver fibrosis staging.

6.3 Contributions and Impact

The main advances of this thesis research are significant contributions to the field of ultrasound shear wave elastography. This thesis identified challenges and technical difficulties that existed in current shear wave elastography techniques and managed to address these challenges by developing a series of novel techniques for shear wave generation, shear elasticity map reconstruction, shear wave detection, and shear wave elastography implementation, to fulfill the goal of providing faster and better shear wave elastography techniques that can be readily used by clinicians and researchers all over the world.
This thesis produced many firsts. CUSE imaging is the first to generate multiple shear waves simultaneously and provide full FOV 2D shear elasticity maps with a single push-detect data acquisition. Fast shear compounding is the first in realizing shear compounding with multiple differently angled shear waves with only a single cycle of push and detection. Harmonic shear wave detection is the first to use harmonic imaging for shear wave detection and provided in vivo assessment of human left ventricular wall stiffness in diastole. The clinical significance and impact of these firsts are finally reinforced by the TAST technique which provides a clear path to translating these techniques from laboratory to clinic. To the field of shear wave elastography, this thesis work exerts substantially positive impact in terms of facilitating faster and better techniques and broadening the spectrum of applications of shear wave elastography. This thesis brings shear wave elastography one step closer to the ultimate goal of providing a noninvasive and quantitative imaging biomarker for disease detection and diagnosis.

6.4 Academic Achievements

This thesis work has produced 7 published peer-reviewed articles, 7 conference proceedings and 5 conference abstracts on which I was an author, 4 pending patent applications, and various student awards. These accomplishments are listed below.
6.4.1 Peer-reviewed journal papers

The peer reviewed journal papers encompass the material presented in Chapters 2, 3, and 4:


Other peer reviewed papers:

6.4.2 Conference proceedings

I have authored or co-authored the following conference proceedings that are related to the thesis:


6.4.3 Conference abstracts

I have authored or co-authored the following conference abstracts that are related to the thesis:


6.4.4 Patent applications


speed from complicated wave fields," Disclosure date: May 23, 2013. (patent pending)

3) James F. Greenleaf, Armando Manduca, Pengfei Song, and Shigao Chen, "Comb-push ultrasound shear elastography (CUSE) with focused ultrasound push beams," Disclosure date: May 9, 2012. (patent pending)


6.4.5 Academic awards

The CUSE research has received the following awards:

1) IEEE UFFC Society 2012 student paper competition award presented at the 2012 IEEE International Ultrasonics Symposium, Dresden, Germany.

2) Student travel support, 2012 IEEE International Ultrasonics Symposium, Dresden, Germany.

The harmonic imaging shear wave detection work has been chosen as the finalist to the New Investigator Award Competition that will be held in Las Vegas in April.
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