Reconstruction and Analysis of Ultrasound Images for Transcranial Ultrasound Applications

Mehdi Hajian

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Reconstruction and Analysis of Ultrasound Images for Transcranial Ultrasound Applications

By

Mehdi Hajian

A Dissertation
Submitted to the Faculty of Graduate Studies through the Department of Mechanical, Automotive and Materials Engineering in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy at the University of Windsor

Windsor, Ontario, Canada

2016

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Reconstruction and Analysis of Ultrasound Images for Transcranial Ultrasound Applications

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ABSTRACT

Transcranial ultrasound phased array imaging through the thick human skull bone and outside of the temporal acoustic windows is investigated through the current study. The significant sound speed discrepancy between the skull bone and the brain tissue introduces phase aberration and refraction to the propagating wave fronts and consequently causes beam defocusing and image degradation. A non-invasive adaptive focusing technique is presented to compensate for the aberration effect of the skull bone in the transmission mode. For this purpose, it is necessary to extract the profiles of the skull bone through a preliminary step. The feasibility of 3-D skull profile extraction using an ultrasound matrix array is investigated for the first time. Two methods, multi-lag phase delay (MLPD) estimation and modified space alternating generalized expectation maximization (SAGE) are proposed to extract the map of the skull boundaries. Taking advantage of numerical modeling the method exploits multiple virtual acoustic sources embedded in the intended focal points behind the skull phantom and numerically tracks the propagating wave fronts through the heterogeneous medium in a finite difference framework. Using the computed arrival times at the coordinates of each element a new time delay set is generated and introduced to the transducer elements for focusing and steering through the skull bone. Numerical and experimental results show that the quality of focus is significantly improved through the presented procedure.

To characterize the distorting effects of the skull barrier on transcranial images the point spread function (PSF) of the imaging system is numerically modeled with and without the presence of skull. A method for refraction correction of transcranial passed array images is proposed. Exploiting the gradient information of the computed time-of-flights
over the interrogated area, the algorithm could successfully track the ray propagation paths from each focal point to the active aperture center. Dynamic focusing is then achieved along the estimated paths. The reconstructed images exhibit a 40% enhancement in contrast and a 38% increase in detection rate. Finally, a multiscale-based method is presented to suppress the speckle noise and detect the discontinuities and objects boundaries in ultrasound images, simultaneously.
DEDICATION

To my family.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Roman Gr. Maev for making this work possible. His valuable guidance and encouragement throughout the course of this work is highly appreciated. I would like to thank Dr. Robert Gaspar for his mentoring and constant support during my PhD program.

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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>CE</td>
<td>Coded Excitation</td>
</tr>
<tr>
<td>CFL</td>
<td>Courant–Friedrichs–Lewy</td>
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<tr>
<td>CNR</td>
<td>Contrast to Noise Ratio</td>
</tr>
<tr>
<td>CRLB</td>
<td>Cramer-Rao Lower Bound</td>
</tr>
<tr>
<td>CT</td>
<td>Computer Tomography</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>DFT</td>
<td>Discrete Fourier Transform</td>
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<tr>
<td>EM</td>
<td>Expectation Maximization</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FDTD</td>
<td>Finite Difference Time Domain</td>
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<td>FFT</td>
<td>Fast Fourier Transform</td>
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<tr>
<td>FIR</td>
<td>Finite Impulse Response</td>
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<td>FSM</td>
<td>Fast Sweeping Method</td>
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<td>GG</td>
<td>Generalized Gamma</td>
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<td>GN</td>
<td>Gauss-Newton</td>
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<tr>
<td>HIFU</td>
<td>High Intensity Focused Ultrasound</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>IQ</td>
<td>In-Phase/Quadrature</td>
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<tr>
<td>LNA</td>
<td>Low Noise Amplifier</td>
</tr>
<tr>
<td>LP</td>
<td>Low Pass</td>
</tr>
<tr>
<td>MAPD</td>
<td>Mean Absolute Percentage Deviation</td>
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<tr>
<td>MLPD</td>
<td>Multi-lag Phase Delay</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MSE</td>
<td>Mean Spectral Energy</td>
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<td>MSFM</td>
<td>Multi-Stencil Fast Marching</td>
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<tr>
<td>PDE</td>
<td>Partial Differential Equation</td>
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<td>PML</td>
<td>Perfectly Match Layer</td>
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<tr>
<td>PSF</td>
<td>Point Spread Function</td>
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<tr>
<td>RF</td>
<td>Radio Frequency</td>
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<tr>
<td>RMSD</td>
<td>Root Mean Square Deviation</td>
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<tr>
<td>SAGE</td>
<td>Space Alternating Generalized Expectation Maximization</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
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<tr>
<td>SOS</td>
<td>Speed of Sound</td>
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<tr>
<td>SRAD</td>
<td>Speckle Reducing Anisotropic Diffusion</td>
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<tr>
<td>SWT</td>
<td>Stationary Wavelet Transform</td>
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<tr>
<td>TGC</td>
<td>Time Gain Compensation</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>TIA</td>
<td>Transient Ischemic Attacks</td>
</tr>
<tr>
<td>TOA</td>
<td>Time of Arrival</td>
</tr>
<tr>
<td>TOF</td>
<td>Time of Flight</td>
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<tr>
<td>TBI</td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td>WGN</td>
<td>White Gaussian Noise</td>
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<td>WT</td>
<td>Wavelet Transform</td>
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Chapter 1:

Introduction

1.1 Background and motivation

Transmission of ultrasound through the intact human skull and without a craniotomy would provide an opportunity for various non-invasive therapeutic and diagnostic procedures. These potential clinical procedures include, but are not limited to, brain imaging [1], blood flow imaging [2], brain tumor hyperthermia [3], targeted drug delivery [4], and detection of foreign objects such as a bone fragment, bullet or shrapnel trapped inside the brain tissue [5].

The thick, multilayered structure of the human skull is considered a strict barrier in transcranial ultrasound applications. Due to the density and sound speed discrepancies between the skull bone and the brain tissue, focusing the ultrasound beams through the skull bone remains a challenging problem in the medical imaging field. Furthermore, strong scattering and attenuation induced by the skull bone distorts the ultrasound wave field.

In a typical ultrasound phased array system, focusing the ultrasound beams in a certain point in space can be achieved by exciting the transducer elements with a time delay
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pattern so that emitted waves arrive at that point simultaneously. In the receiving mode, reflected waves are collected on the aperture surface and then the signals delayed appropriately in order to coincide. For the homogenous medium, the time delay patterns for transmission and reception modes can be calculated using simple geometry and knowing the sound velocity in that medium. For an inhomogeneous medium such as the skull-brain that exhibits different sound velocities, the transducer becomes defocused because the travel time for each ray propagating through the skull differs with the variation in skull thickness. Therefore, the accuracy of focusing ultrasound through the skull is highly dependent on the estimation of skull thickness variations, i.e. the extraction of the skull bone profiles. The problem of accurate skull profile extraction has been addressed by using Magnetic Resonance Imaging (MRI) [6]–[9] and Computer Tomography (CT) [3], [10], [11] techniques presented in the literature. Despite the fact that MRI and CT modalities are able to accurately extract the profiles of the skull bone, these proposed methods are not suitable for transcranial ultrasound applications as they are rather complex and need a sophisticated technologist to interpret the data. MRI and CT techniques are relatively expensive and CT is not completely non-invasive as it generates ionizing radiation. Moreover, these techniques are only applicable in transcranial focusing of ultrasound for therapeutic purposes and cannot be applied in real-time transcranial ultrasound imaging. A primary motivation of the current study was to investigate the feasibility, accuracy, and precision of ultrasonic imaging of the skull bone using both linear and matrix array transducers and extract the three-dimensional (3-D) inner and outer profiles of the skull using a signal processing scheme.
Chapter 1: Introduction

The focus degradation, induced by the phase aberration of the acoustic wavefronts after passing through the skull decreases both the point resolution and the contrast resolution. In ultrasound images, the point resolution is an index for distinguishability between isolated scatter and the contrast resolution is an index for distinguishability between speckle patterns.

The quality of the ultrasound focus and consequently the quality of the transcranial images are improved by phase aberration compensation of the ultrasound beams in both transmission and reception modes. In recent years, several research studies have been carried out on phase aberration correction for real-time ultrasound imaging through the temporal bone acoustic windows [12]–[14]. The temporal bone acoustic windows are the thinnest areas of the skull, about 2 to 3 mm thick, and mostly composed of cortical bone, where the trabecular bone layer is either absent or very thin in these areas. Therefore, the attenuation in these acoustic windows is much less than other areas of the skull, i.e. 5.6 dB/cm compared with 50 to 140 dB/cm at 2MHz [11], making the transcranial imaging feasible through these windows. Recently, a least square cross correlation technique has been suggested [12] to estimate the phase delay profile induced by thickness variation of the skull bone in the temporal window for 3D phase aberration correction. The idea of using a temporal window as a thin, pores-free layer for transcranial ultrasound does not always hold, as this window does not necessarily exist in all patients. It has been reported that 8% to 29% of the general population may fail to have such a window [15]. The frequent occurrence of an insufficient temporal bone is considered the primary limitation of transcranial ultrasound. This prompted the author to investigate insonifying through the skull bone without using the temporal bone in this research.
Chapter 1: Introduction

Ultrasound imaging through the thick human skull bone still remains an extremely challenging task due to the severe aberration effects of the skull on the wavefronts. To the author’s knowledge, the phase aberration compensation along with the refraction correction of ultrasound beams through the thick, multilayered skull bone has not been fully addressed in experiment. The second part of this study, after extracting the skull phantom profiles, presents a new technique for focusing and steering the ultrasound beams through the thick skull bone. For this purpose, new time delay patterns are calculated by solving the wavefront evolution equation which is then applied to the transmit beamforming. Given the refraction effect of acoustic beams in the inhomogeneous medium it is necessary to determine the scan lines for each focal point. For this purpose, a gradient-based filter is proposed that can trace the ultrasound rays from the focal points to the center of the transducer’s active elements. For every scanning, new time delay patterns are calculated along the scan lines for dynamic receive focusing and applied to the receive beamformer. The image is finally reconstructed by adding the aligned signals in the Delay-and-sum beamforming step.

Edge detection of the reconstructed images can provide valuable information pertaining to the location, area, volume and geometric shape of the objects of interest. These objects can be foreign objects such as a bullet, shrapnel, or bone fragment trapped inside the brain tissue, an abnormality of brain tissue, or blood vessel stenosis diagnosed by transcranial imaging. The detection of the object boundaries can be performed manually but is time consuming and subject to inter- and intra-operator variability. Automatic detection of the object boundaries is desirable for the application in hand. However, the low signal to noise ratio of the acquired trans-skull images caused by the
attenuative and scattering effects of the skull, and the presence of the speckle noise limits
the effective applications of edge detection techniques. This issue prompted the author to
implement a new algorithm in ultrasound field to suppress the speckle noise and detect
the object boundaries simultaneously. The research structure flowchart is presented in
Figure 1.1 illustrating the steps taken in this study to acquire the desired results.

1.2 Objectives

The general objectives of this study were to:

• study the feasibility of ultrasound imaging of the human skull bone using
  linear and matrix array transducers and subsequently extract the inner and
  outer profiles of the bone. This is a preliminary step to accomplish the next
  two objectives.

• implement a phase aberration correction method to compensate for the
distortional effects of the human skull on ultrasound transmission and refocus
the beams behind the thick skull bone (correction in transmission).

• study the refraction phenomena introduced by the sound speed discrepancy
between the skull bone and brain tissue and correct the refractive effect in both
transmission and reception modes of beamforming in phased array transcranial
imaging. The proposed correction procedures are expected to improve the
quality of focus, reduce the beam steering error, and increase the axial and
lateral resolutions of the reconstructed images.
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Profile extraction

1. Estimate the arrival times via the modified SAGE algorithm
2. Select a speed of sound (SOS) value for the skull bone and extract the profiles
3. Estimate the SOS value through an adaptive procedure
4. Correct the location of inner profile according to the optimal SOS value

Beamforming

1. Construct the SOS map of the inhomogeneous medium
2. Solve the Eikonal equation in a finite difference framework using Multistencils Fast Marching
3. Calculate new Tx time delay patterns
4. Focusing and steering through the skull bone
5. Time Reversal Filtering
6. Beamformed image
7. Dynamic receive beamforming
8. Calculate new Rx time delay patterns along the traced rays

Post-processing

1. Low pass filtering
2. Time gain compensation
3. Demodulation
4. Scan conversion
5. Edge detection and despeckling by multiresolution processing
6. Automatic object detection

Figure 1.1 The research structure flowchart.
• further improve the important features such as edges in the reconstructed images by post-processing. Speckle noise reduction and automatic contour detection of the reconstructed images would be desired for image analysis.

1.3 Scope

The overall structure of this study takes the form of seven chapters, including the Introduction. In Chapter 2, the basics of transcranial ultrasound are introduced. Distortional effects of the human skull bone in terms of aberration and attenuation for therapeutic high intensity transcranial ultrasound and diagnostic transcranial ultrasound imaging are also discussed.

In Chapter 3, the problem of skull profile extraction using ultrasound is discussed. Two time of arrival (TOA) estimation algorithms, called multi-lag phase delay (MLPD) and modified space alternating generalized expectation maximization (SAGE), combined with an adaptive sound speed estimation procedure are presented to simultaneously extract the skull profiles and estimate the speed of sound (SOS) in the skull bone. The estimated thicknesses of the 2-D and 3-D skull phantoms via the proposed procedures are compared with the mechanical measurements. Statistical analysis is presented for further assessments.

In Chapter 4, focusing and steering of the ultrasound beams through the thick, multilayered skull bone is investigated. For this purpose, a finite difference scheme called Multi-Stencil Fast Marching Method (MSFMM) is utilized to model the propagation of the wavefronts though the inhomogeneous soft tissue-skull bone-soft tissue medium. From the numerical modeling the aberrated phases of the acoustic waves at the focal
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points for each active transducer element are obtained. Calculated phases are time-reversed to construct new time delay patterns for the transducer phase array. The new time delay patterns are fed into the nonlinear wave propagation simulator and the Ultrasound Advanced Open Platform (ULA-OP) and the quality of the focus is evaluated.

In Chapter 5, the study of dynamic focusing in the reception mode of beamforming is presented. A nonlinear ray tracing is applied to determine the scan lines and correct the refraction effect induced by the skull bone. The new time delay patterns are calculated along the scan lines and fed into the dynamic receiver beamformer. The reconstructed images are evaluated against the aberrated and the no-skull cases.

In Chapter 6, the reconstructed images are decomposed into detail images using a stationary discrete wavelet transform for further processing. Applying the implemented filter on the detail images suppresses the speckle noise and simultaneously improves the edges. A hybrid active contour model is subsequently applied on the processed images to automatically detect the objects boundaries.

Finally, Chapter 7 points out some future research directions in light of the presented work in this area.
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References


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Chapter 2:

A Review on Transcranial Ultrasound

2.1 Overview

In this chapter the significance of transcranial ultrasound for diagnostic brain imaging is reviewed. Traumatic brain injuries and ischemic stroke are the two primary potential clinical applications of transcranial ultrasound imaging that need to be diagnosed in a short time window after their occurrence. Phase aberration induced by the skull bone as the main contributing factor in transcranial ultrasound image degradation is briefly discussed. Next, a review on the existing phase aberration correction techniques proposed for the therapeutic transcranial ultrasound (correction in transmission mode only) and the diagnostic imaging (correction in transmission and reception modes) is presented. Finally, post-processing algorithms implemented for enhancing the quality of ultrasound images are reviewed.

2.2 Potential applications of transcranial ultrasound

2.2.1 Traumatic brain injuries

Traumatic head injury is considered a leading cause of morbidity and mortality, especially in children and elderly. In fact, among all kinds of injury around the world traumatic brain injury (TBI) is the most likely to cause death or permanent disability.
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According to the statistics provided by the Canadian Institute for Health Information [1], 16,811 cases were hospitalized for traumatic head injuries from 2003 to 2004. Traumatic brain injury was diagnosed for 91% of these cases. The mortality rate was 8% of the all head injury admissions as 1,368 cases were reported deceased in hospital. As Table 2.1 illustrates, the number of admissions and the disease rates vary significantly among gender and age groups. The majority of the admissions were male in each age group. Elderly with 59% death rate was the most vulnerable group.

Table 2.1 Head injury admissions in Canada from 2003 to 2004 [1].

<table>
<thead>
<tr>
<th>Age</th>
<th>0-19</th>
<th>20-39</th>
<th>40-59</th>
<th>60+</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number admitted</td>
<td>4,966</td>
<td>3,637</td>
<td>3,306</td>
<td>4,902</td>
<td>16,811</td>
</tr>
<tr>
<td>Male</td>
<td>3,318 (67%)</td>
<td>2,870 (79%)</td>
<td>2,403 (73%)</td>
<td>2,772 (57%)</td>
<td>11,363 (68%)</td>
</tr>
<tr>
<td>Death in hospital</td>
<td>120 (9%)</td>
<td>217 (16%)</td>
<td>222 (16%)</td>
<td>809 (59%)</td>
<td>1,368 (8%)</td>
</tr>
</tbody>
</table>

Traumatic brain injury from moderate to severe degree can significantly impair physical and cognitive functioning and therefore have important public health implications.

Penetrating head injuries and open head injuries are the two most common types of TBI that cause direct injuries to the brain. These usually result from the impact of any sharp objects such as knife or glass or a bullet that forces hair, skin, bones, and fragments into the brain, see Figure 2.1. For these cases, imaging through the different areas of the skull bone is a necessary clinical procedure to detect the possible bone fragments or foreign objects trapped inside the brain tissue.
Diagnosis within a short time window after incidents could increase the chance of recovery in patients. However, MRI and CT, the current standard clinical brain imaging modalities, are not fast and neither is portable enough to be used in emergency ambulances. This study investigates the feasibility and accuracy of the transcranial ultrasound imaging as an alternative modality.

2.2.2 Stroke

Stroke is a brain attack that occurs due to problems with blood supply to an area of brain. The hemorrhagic stroke is one of the two types of stroke and is caused by burst or leakage of a weakened blood vessel. The other type is ischemic stroke and it occurs when a blood vessel carrying blood to the brain is blocked or narrowed resulting in severely reduced blood flow (ischemia). These blockages occur when plasma proteins without adequate removal of fat and cholesterol from the macrophages progressively accumulate and form plaques in the arterial wall. Ischemic stroke accounts for about 85% of all
stroke cases [4], while the least common type of stroke, hemorrhagic, most often results in death.

2.2.2.1 Risk of Stroke

According to the latest statistics released by the American Heart Association (AHA) cardiovascular disease (CVD) is the first leading cause of death, accounting for 31.9% of all deaths, in the world [5]. Among the different types of CVD, stroke was the second leading cause of death (5.2%) in United States after coronary heart disease (15.4%) in 2010. Each year, about 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first attacks, and 185,000 are recurrent attacks.

Figure 2.2 presents the ten leading causes of death in United States where cerebrovascular disease (stroke) is the fifth cause after heart disease (32%), cancer (31%), lower respiratory disease (8%), accident (7%), with 7% of all deaths in 2013 [6].

The graph presented in Figure 2.3 shows the mortality rate caused by cerebrovascular disease from 1999 to 2013. As is shown the cerebrovascular related mortality rates have been declining continuously since 1999, in contrast to other causes of death such as Alzheimer’s disease. This reduction is the result of the recent advances in medical imaging and new therapeutic methods.

Stroke accounts for some non-modifiable risk factors such as age, gender and race and for some modifiable factors such as cigarette smoking, diet, physical inactivity, alcohol consumption, hypertension, cardiac disease, diabetes, hyperlipidemia, Postmenopausal hormone therapy, asymptomatic carotid stenosis, and transient ischemic attacks (TIA) [5].
2.2.2 Stroke diagnosis and treatment

An initial diagnosis is carried out immediately to confirm the impairment symptoms are caused by ischemic stroke and not by other systemic or neurological disorders. Furthermore, the initial evaluations are essential for further decisions about acute treatment with thrombolytic agents. Hence, the cause of the neurological impairments is sought by the physician in a preliminary diagnosis. Most stroke cases have a history of sudden or rapid onset of focal neurological symptoms. The stroke patients are usually alert, however those cases with major hemispheric infarctions, basilar artery occlusion, or
cerebellar strokes with edema causing brain stem compression experience a decrease level of consciousness [7].

Nonetheless, different conditions such as, brain tumor, subdural hematoma, syncope, toxic or metabolic disorders mimic stroke. The diagnostic accuracy of stroke referrals from ambulance staff, primary care, and emergency room (ER) physicians using the standard face arm speech test were compared in a study [8]. The best diagnostic accuracy was 79% (144 out of 183 stroke patients) obtained from the ambulance staff. Thus, 21% of stroke patients were misdiagnosed.

Brain imaging is applied after physical examination for more accurate diagnosis, where available. Non-contrast computed tomography (CT) is the most common technique applied to discriminate the intracranial hemorrhage and other non-vascular causes of
symptoms such as tumor from ischemic stroke [9]. Once hemorrhage and non-vascular causes are ruled out, vascular imaging modalities are applied to detect the intracranial and extracranial stenosis and occlusions. The current clinically-applied modalities are Transcranial Doppler ultrasound through the temporal window, magnetic resonance angiography, CT angiography and catheter angiography. Among the mentioned cerebrovascular imaging modalities, contrast-enhanced transcranial Doppler ultrasound imaging was recommended as a fast and reliable modality for intracranial imaging [10].

Tissue plasminogen activator (tPA, also known as IV rtPA) is the only FDA-approved treatment for ischemic stroke and improves blood flow to the part of the brain being deprived of blood by dissolving the clot. The thrombolytic tPA may improve the chances of recovering from a stroke only if it is administered within three hours after onset of the symptoms. The administration of tPA exacerbates any bleedings that could be caused by hemorrhage stroke or head trauma and therefore the chance of intracranial bleeding needs to be ruled out before proceeding with tPA administration. A significant number of stroke victims do not receive tPA within three hours as the patients are not diagnosed with the ischemic stroke fast enough.

Transcranial ultrasound imaging through the thick skull bone and without relying on the temporal bone could be an alternative solution. Being portable, transcranial ultrasound could be used in ambulances and emergency helicopters and may significantly reduce the diagnosis time. Moreover, ultrasound is cost effective and completely non-invasive compared to the other modalities.

Besides the diagnostic applications of transcranial ultrasound, several research projects have been dedicated to the investigation of focused ultrasound as an alternative means for
thrombolysis either alone or joined with tPA, and tPA-incorporating Echogenic liposomes (tPA-ELIP) [11]–[16]. However, due to the safety concerns related to the excessive amount of heating in skull and brain tissue, the accuracy of the focusing, and the size of the focal points, these attempts are in the study stage yet and have not been used clinically.

2.3 Phase aberration correction

2.3.1 Basic theory

When an acoustic wave encounters a boundary in an inhomogeneous medium, part of the energy is reflected while the rest of it is transmitted to the second environment. The amounts of reflected energy and energy transmitted to the second media are calculated based on the acoustic impedance mismatch between the two environments. In transcranial ultrasound, a substantial amount of the incident energy is reflected at the outer and inner surfaces of the skull bone due to the significant impedance mismatches in the skin-skull and the skull-duramater interfaces.

The acoustic pressure field can be stated as a function of distance, $r$, time, $t$, and wave number, $k$, as [17]

$$p(r,t,k) = Ae^{j(wt-kr)}$$  \hspace{1cm} (2-1)

where $A$ is the amplitude and $\omega$ is the angular frequency and the term $(\omega t - kr)$ is the phase. Using the theory of wave propagation in a multi-layered structure the pressure-reflection coefficient can be calculated as [17], [18]
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\[
R = \frac{j\left(\frac{z_b}{z_s} - \frac{z_s}{z_b}\right) \sin k_b d}{2 \cos k_b d + j\left(\frac{z_b}{z_s} + \frac{z_s}{z_b}\right) \sin k_b d}
\]

(2-2)

where \(d\) is the thickness of the skull bone, \(z_b\) and \(z_s\) are the acoustic impedances of bone and soft tissue, and \(k_b\) is the wave number in the bone. The transmission coefficient in the bone-soft tissue interface is stated as

\[
T = \frac{1}{1 + \frac{1}{4} \left(\frac{z_b}{z_s} - \frac{z_s}{z_b}\right) \sin k_b d}^2
\]

(2-3)

Considering the definition of the wave number, \(k = \omega/c\), the phase of the acoustic wave in soft tissue with the sound speed of \(c_s\) is obtained by

\[
\varphi_s = \omega \left( t - \frac{d}{c_s} \right)
\]

(2-4)

In clinical ultrasound phased array imaging systems the medium is considered homogenous and a constant value for the speed of sound (SOS) is set for soft tissue \((c_s \approx 1530 \text{ m/sec})\) in both transmission and reception modes. In transcranial imaging the media is no longer homogenous and the speed of sound in the skull bone is significantly higher than the brain tissue. The actual phase of the acoustic beam travelling through the bone with SOS of \(c_b\) is

\[
\varphi_b = \omega \left( t - \frac{d}{c_b} \right)
\]

(2-5)

Accordingly, the phase shift caused by the skull bone is

\[
\Delta \varphi = \omega d \left( \frac{1}{c_b} - \frac{1}{c_s} \right)
\]

(2-6)
The phase shifts induced by the skull cause focal displacement depending on the skull thickness at the insonified area. Furthermore, the thickness variation of the skull bone across the array elements, $\Delta d(x,y)$, induces different phase shifts for each element resulting in the phase aberrations of the beam stated as

$$
\Delta \phi(x,y) = \omega \Delta d(x,y) \left( \frac{1}{c_b} - \frac{1}{c_s} \right)
$$

The phase aberrations defocus the beams and significantly reduce the axial and lateral resolutions of the ultrasound images. Chapter 3 of this study focuses on the thickness estimation of the skull bone for phase aberration compensation purpose.

Figure 2.4 illustrates the structure of a Delay–and–sum beamformer in reception mode with a single scatterer in homogenous and inhomogeneous media. For the homogeneous case the time delays, $\tau_i$, are calculated based on the geometric distance between the scatterer and each element. For the inhomogeneous case, the skull bone with random curvature and unknown thickness degrades the ultrasound beams and therefore the calculations of the time delays, $\tau_i'$, would be a challenging task.

The above-mentioned discussion only addresses the phase shift without considering the refraction phenomena in the skull bone.
2.3.2 Phase correction techniques for therapeutic transcranial ultrasound

Focusing ultrasound beams through the human skull bone can also be applied for other therapeutic procedures such as the ablation of a tumor [11], [19] and targeted drug delivery [20]. Successful applications of these therapeutic methods are limited by the skull bone. A large discrepancy between the speeds of sound in the skull bone (around 2900 m/sec) and the brain tissue (1530 m/sec) combined with the strong scattering and attenuations of the acoustic field severely distort the ultrasound beams.

In early ultrasonic operations in the brain it was necessary to remove a piece of skull bone in a craniotomy procedure to be able to focus the beams inside the human head as
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the skull bone was considered impenetrable. In 1977, Fry investigated the transmission of an ultrasound beam through the skull bone using a single element transducer and reported a 2 to 3 mm focal displacement induced by the skull bone [21].

The recognition that skull bone distorts the acoustic fields and degrades the focus has led to studies of techniques for compensation of the phase aberration in ultrasonic array systems. The time reversal mirror (TRM) technique was proposed by Fink [22], [23] for focusing ultrasonic fields through an inhomogeneous medium. Using a hydrophone as a beacon embedded around the focal point, the focusing is accomplished by collecting the acoustic beams and then reemitting the time-reversed pressure field. The realization of a spatial-temporal matched filter to the propagation transfer function produces an optimum focus in time reversal focusing. Considering the aberration problem as a complex filtering operation the recent TRM technique is based on the decomposition of the transfer matrix [24]–[27].

A hemispherical phased array system with the purpose of maximizing the penetrated energy and minimizing the unwanted heating was proposed by Hynynen and his colleagues for ultrasound brain therapy, and its different therapeutic applications were extensively investigated [12], [28]–[32]. For the phase correction, Sun proposed to use MRI images to extract the inner and outer profiles of the skull and utilize this information in a theoretical model to estimate the aberrated phase [33], [34]. Later on based on a CT-derived skull thickness information, a three-dimensional finite difference numerical simulation of the complete wave equation was implemented to calculate the phase shifts induced by the skull and subsequently refocus the beams inside the skull [19].
Shear mode conversion is another transcranial technique that by taking advantage of the closer impedance match between the skull and brain in the shear mode (shear mode speed in the skull = 1500 ± 140 m/sec, longitudinal speed in the brain = 1530 m/sec) transmits more energy through the skull [35]–[37]. However, the energy attenuation in the skull bone is significantly higher in the shear mode when compared to the longitudinal mode (14 Np/m–70 Np/m in the longitudinal and 94 Np/m–213 Np/m in the shear modes at the frequency range of 0.2–0.9 MHz [36]), exacerbating the heating problem in the skull.

### 2.3.3 Phase correction techniques for diagnostic transcranial imaging

Unlike the extensive studies on the therapeutic transcranial ultrasound, limited research has been carried out on the imaging side. Using signals from random collections of scatterers and calculating the phase delays between neighboring elements by cross-correlation of the phase aberrations were determined for a general multi-layered medium [38]–[40]. Recently, a cross-correlation based phase aberration correction was suggested for real-time transcranial imaging by Ivancevich [41], [42]. In this study, temporal bone acoustic windows were used for insonification through the skull. Compensation of the phase aberrations improved the image qualities in terms of contrast to noise ration (CNR) and the number of detectable cysts. Results of the aberration correction of the blood flow images showed the merits of the cross-correlation method over the speckle brightness correction method [43].

In a numerical study, the phase aberrations induced by the skull were estimated and compensated by first obtaining the skull thickness through a dual focusing technique and
then computing the phase delays using a fast marching method [44]. This study showed the ultrasound-based phase correction method could improve the image quality and the obtained improvement is comparable with the ones from the CT-based correction method.

An ultrasound brain helmet was recently designed by Lindsey [45] in which multiple transducers were used to render a 3-D transcranial ultrasound volume. Taking advantage of the both temporal bone acoustic windows two matrix transducers were applied on both sides of the head in a pitch-catch mode where each transducer acts as a beacon for the opposing array [13], [46], [47]. This adaptive imaging technique assumes several isoplanatic patches for each transcranial imaging volume and updates the time delay patterns for each patch using cross-correlation technique [48].

2.4 Attenuation in the skull bone

Phase aberration is not the only factor that distorts the acoustic beams although it is the only one that could be compensated. The measured values of ultrasound attenuation in the human skull bone can be attributed to several physical phenomena occurring as ultrasound propagates through the bone. Reflection at the bone-soft tissue interfaces, absorption, scattering in the porous layer of the bone and mode conversion are the main factors that contribute to this energy loss. In a recent study, Pinton demonstrated that only a minor portion of the attenuation is due to absorption while the major portion is related to scattering, reflection and mode conversion [49]. The measured attenuation values reported in the literature have a broad range, which can be associated with the different porous layer thicknesses of the calvaria investigated in these studies. Considering attenuation as a growing function of porosity, Aubry [19] adjusted the power law model and formulated the attenuation based on the porosity map of the skull. The porosity map
can be directly related to the Hounsfield units of CT images. Using this model, the attenuation values at a center frequency of 1.5 MHz are as small as 2 dB/cm for the nonporous zone and as large as 80 dB/cm for the dipole layer. Considering the three-layer structure of the skull bone, an equivalent attenuation value of 41 dB/cm can be assumed for the areas with the porous layer having the same thickness as the compact layers. Fry and Barger [50] reported acoustic pressure attenuation of 24 dB/cm and 64 dB/cm for the dipole layer taken from two different calvarium samples. The significant difference in the attenuation values can be attributed to the different grain size of the dipole layer in these two calvaria.

2.5 Post-processing

2.5.1 Speckle noise

Medical ultrasound image quality is adversely affected by noise and artifacts originated from different sources during imaging. Speckle, an inherent property in all coherent imaging systems, is the primary factor that limits the contrast resolution of ultrasound images. The granular patterns called speckle appear as a result of diffuse scattering when an ultrasound wave interferes with small particles on a scale comparable to the acoustic wavelength. The speckle phenomenon is correlated to the roughness level of the surfaces scattering the incident waves.

Containing useful information about the imaging area speckle is not a noise per se, although it is a random process, and its information is used in certain applications such as ultrasound speckle tracking for blood flow imaging [51]. However, for the majority of applications speckle is perceived as a contaminating factor limiting the resolution of
diagnostic ultrasound images. Detection of small, low contrast lesions in the presence of speckle is often difficult for non-specialists. The multiplicative speckle noise masks fine details so that ultrasound specialists with insufficient experience may fail to extract the proper conclusions, resulting in a misdiagnosis.

Besides degrading the visual quality of ultrasound images speckle constrains the effective applications of computer-aided image analysis (automated object boundary detection and segmentation) and volume rendering in 3-D imaging. This effect is more severe in transcranial ultrasound cases where the contrast to noise ratio of the acquired images are extremely low due to the attenuative and scattering effects of the skull. To improve clinical diagnosis speckle removal is generally proposed with the goal of preserving important features and reducing the speckle level. The majority of despeckling filters are implemented for the purpose of visualization enhancement where the image texture is a desired feature and needs to be recovered [52], [53], in contrast to automated object boundary detection procedures where edges need to be recovered from the speckle and image textures should be removed to speed up the algorithms. In this study, automated detection of objects boundaries is desired as a final processing step. For this purpose, the speckle effects must be alleviated and edges need to be enhanced as a preliminary step to the contour detection.

2.5.2 Speckle in extracranial imaging of carotid artery

Speckle suppression has been found to be a necessary step for image analysis of the common carotid artery. Carotid atherosclerosis is considered to be the underlying cause of stroke and so it is crucial to be diagnosed. Atherosclerosis is a cardiovascular disease
in which the carotid artery starts to thicken due to the progressive accumulation of fatty substances, which results in plaque formation in the artery’s wall.

During the initial stage of atherosclerosis plaque formation causes enlargement of blood vessels without compression of the lumen. Therefore, measuring the stenosis from the blood flow images would not be helpful in the initial stage of the disease. Intima-media thickness (IMT) of common carotid artery has been considered to be an early indicator of cardiovascular disease and a good predictive value for stroke. Traditionally, IMT is measured from the acquired ultrasound images by a trained sonographer. The thickness is estimated from longitudinal projections of arteries. This manual measurement is subjective and time consuming and also dependent on the sonographer’s skills.

Automated detection of artery walls and subsequently IMT measurement from B-scan images have been investigated in the last decade not only to improve the detection accuracy of stenosis degree but also to provide the opportunity for computer-aided plaque characterization. In a recent work an automated IMT measurement technique has been proposed based on a combination of scale-space and statistical classification where the measurement accuracy improved to 94% [54]. A review on the state of the art ultrasound image processing techniques applied for the evaluation of stroke risk including despeckling, carotid artery segmentation, 2-D and 3-D carotid plaque segmentation and carotid plaque classification is presented in [55]. Reducing the speckle noise while preserving the edges, the useful feature for segmentation, is the main challenge in these procedures.
2.5.3 A brief review on despeckling filters

2.5.3.1 Adaptive filters:

Adaptive despeckling filters are the most commonly used techniques for speckle reduction of ultrasound and synthetic aperture radar (SAR) images. By applying a moving window these techniques estimate the central pixel intensity of the subregion based on the local statistics inside the window such as mean, variance, third and fourth moments, and entropy. The well-know despeckling Lee filter falls into this category and is designed based on minimum mean square error (MMSE) [53]. The denoised intensity is estimated from the mean value of intensities within the window, \( \bar{I} \), and its original value, \( I_{i,j} \), as

\[
\tilde{I}_{i,j} = \bar{I} + k_{i,j}(I_{i,j} - \bar{I})
\]  
(2-8)

The filter coefficients \( k_{i,j} \) are adaptively calculated based on the local statistics as follows

\[
k_{i,j} = 1 - \frac{C_u^2}{C_s^2}
\]  
(2-9)

where

\[
C_s^2 = \frac{1}{n} \sum_{i,j} (I_{i,j} - \bar{I})^2/(I_{i,j} - \bar{I})^2
\]  
(2-10)

and \( C_u^2 = \text{var}(I_{hom})/I_{hom}^2 \), a constant that is calculated over the homogeneous area of the image, \( I_{hom} \). The Kuan filter has a similar structure with a slight modification in calculation of filter coefficients \( k_{i,j} \) [56], [57]. Frost is another adaptive filter that applies exponentially damped convolution kernel based on the local statistics.
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2.5.3.2 Homogeneity filter

A homogeneity similarity-based despeckling filter estimates each pixel based on the most homogeneous neighborhood around the pixel [58]–[60]. Assuming the subregion is homogeneous, the filter takes into account only those pixels that belong in the processed neighborhood [61].

2.5.3.3 Median filter

The spatial median filter reduces the noise in a nonlinear procedure in which the central pixel intensity of the moving window is replaced by the median value of its neighborhood [62]. Adaptive median filters proposed in [63], [64] showed a better performance in preserving the important features of the image while reducing the speckle. However, they still seem to destroy the small features due to their low-pass filter characteristic.

The main drawback of window-based speckle reduction filters (Lee, Kuan, Frost, Homogeneity, Median) is that they are sensitive to the size and shape of the moving window. A filter with a large moving window can suppress the speckle but also it eliminates the subtle details and smoothes the edges. A filter with a small window can preserve the details but it is not efficient in suppressing the speckle noise. Nonetheless, Loizou et al. [60] reported that local statistics-based filters (Lee, Kuan, Frost) produced the best results by enhancing the visual quality of common carotid artery images and also by improving the accuracy of classification between symptomatic and asymptomatic plaques.
2.5.3.4 Homomorphic filter

Considering the multiplicative nature of the speckle noise homomorphic filters exploit a logarithmic transform to convert the speckle to an additive noise, yet a statistically independent process. The transformed image is filtered using a Wiener filter to suppress the noise and then exponentially transformed [65]. Homomorphic wavelet-based filtering proposed by Solbo showed its superiority over traditional window-based filtering [66], [67].

2.5.3.5 Anisotropic diffusion

Anisotropic diffusion is a despeckling approach, based on partial differential equations (PDE), that takes advantage of locality and anisotropy of certain differential equations. In contrast to linear homogeneous diffusion, that could filter the speckle successfully but also it blurs out the significant edges of the image, anisotropic diffusion techniques are capable of smoothing the speckle without crossing the edges between the homogeneous regions. Anisotropic diffusion technique, originally implemented by Perona and Malik [68], uses the following nonlinear PDE for smoothing the image

\[
\begin{cases}
\frac{\partial I}{\partial t} = div[c(|\nabla I|)\nabla I] \\
I(t = 0) = I_0
\end{cases}
\]  

(2-11)

where \(\nabla\) and \(div\) denote for gradient and divergence operators and \(I_0\) is the original image. Two diffusion operators were suggested as \(c(|\nabla I|) = 1/[1 + (|\nabla I|/k)^2]\) and \(c(|\nabla I|) = \exp \left[-\left(\frac{|\nabla I|}{k}\right)^2\right]\) where \(k\) is the diffusion or flow constant. A new diffusion derivation called SRAD, Speckle Reducing Anisotropic Diffusion, has been proposed by Yu and Acton in which adaptive Lee and Frost filters are cast in the partial differential
framework to develop the model for speckle filtering [69]. This technique enhances the edges while reducing the speckle by inhibiting diffusion across the edges and permitting diffusion on the homogeneous regions.

Employing nonlinear diffusion in the dyadic wavelet (NMWD) framework showed the merit in edge enhancement by utilizing normalized wavelet modulus and in speckle reduction by exploiting iterative multi-scale diffusion [70].

2.5.3.6 Multiscale processing

During the last decade wavelet based-speckle reduction methods have become popular. Denoising by soft thresholding, proposed by Donoho [71], is known as a platform for majority of wavelet-based noise filtering techniques. This technique based on a simple thresholding consisting of three steps. First, the data is transformed to an orthogonal domain using a discrete wavelet transform to obtain empirical wavelet coefficients. Then, a soft threshold is applied to the wavelet coefficients by \( \eta_t(y) = sgn(y)(|y|(y - t))_+ \) (the operator \((z)_+\) returns \(z\) if \(z\) is positive and zero otherwise) with the spatially chosen threshold \( t = \gamma_1 \cdot \sigma \cdot \sqrt{2\log(n)/n} \) where \( \gamma_1, \sigma, n \) are a constant coefficient, the standard deviation of the white noise, and the length of the input data, respectively. Next, the thresholded coefficients are inversely transformed to the space domain producing the denoised data.

Iterative shrinkage is an advance soft thresholding method that has been recently proposed for total-variation (TV)-based image restoration [72]. A summary of the discussed speckle reduction filters is presented in seven categories in Figure 2.5.
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In light of the existing methods mentioned here a multi-scale wavelet-based technique is presented in this study to suppress the speckle and also the textures of the simulation and experimental transcranial images. This method not only preserves edges but also enhances edges by exploiting the horizontal, vertical and diagonal details in a number of scales. This will be fully detailed in Chapter 5, and the results will be compared with the above-mentioned methods.
Figure 2.5 The existing despeckle filtering methods.
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3.1 Introduction

3.1.1 Overview

In this chapter, the feasibility, accuracy and precision of 3-D ultrasound imaging of the human skull bone for real-time profile extraction using a custom-designed matrix array transducer is investigated. Due to the attenuative, scattering properties of the human skull bone the backscattered echoes from the inner surface of the skull are severely degraded, attenuated, and at some points overlapped. Furthermore, the speed of sound (SOS) in the human skull varies significantly in different skull zones and even from case to case, introducing significant errors to the profile measurements if considered constant. The skull profile extraction is the first step of the proposed image reconstruction procedure. The results obtained in this chapter will be utilized for the adaptive phase aberration compensation in Chapter 4.
3.1.2 Background, significance and motivation

Non-invasive extraction of the three-dimensional profiles of the human skull bone is of great interest for various therapeutic and diagnostic procedures within the skull bone. These clinical procedures include, but are not limited to, robot-assisted brain surgery [1], skull bone harvesting [2], brain tumour hyperthermia [3]–[6], as well as transcranial ultrasound imaging [7]–[10]. In those procedures involving craniotomy, the knowledge of skull thickness is crucial for drilling in order to avoid the perforation of the Dura mater layer. Dura mater is a thick membrane right beneath the skull bone surrounding the brain.

However, the impetus for this study has been the increasing desire over the last decade for therapeutic and imaging applications of medical ultrasound on the human brain. The thick, multilayered structure of the human skull is considered a strict barrier in transcranial ultrasound applications. Skull bone with varying thickness across the array will cause phase aberration and consequently beam focus degradation; the travel time for each ray propagating through the skull differs with the variations of the skull thickness. Accurate extraction of the skull profiles would provide the opportunity to model the phase aberration and beam refraction induced by the skull and subsequently compensate them by a new time delay pattern for the array. Therefore, the accuracy of focusing ultrasound through the skull is highly dependent on the accuracy of the skull profile extraction.

The thickness and shape of the human skull bone as the main contributing factors to the phase aberration in transcranial ultrasound have been obtained by using modern imaging techniques in the literature. Magnetic resonance imaging (MRI) was applied to
extract the shape and thickness of skull by Hynynen [11], [12]. The skull profiles were manually delineated from MRI images and used in a mathematical model to calculate phase distribution for a phased array. Later on Clement et al. found Computer Tomography (CT) an accurate tool to extract the physical properties of the human skull bone including thickness, shape and density [13]. In that study, they investigated single-layer and three-layer models of the skull bone and examined the ultrasound phase dependency on the skull physical properties that can be obtained from CT scans. CT-scan imaging was evaluated for accurate modeling of the calvarium at different settings in [14]. The average accuracy of the model was reported as 0.4 mm with a slice thickness and slice distance of 1.5 to 2 mm and skull bone segmentation with a lower threshold of 300 or 400 Hounsfield units.

In spite of the fact that MRI and CT modalities are able to accurately estimate the thickness of the skull bone, these proposed methods are not suitable for transcranial imaging as they are rather complex and need a sophisticated technologist. MRI and CT techniques for this measurement are relatively expensive and not completely non-invasive, especially CT that generates ionizing radiation. More importantly, these techniques are not portable and cannot be used in pre-hospital emergency services.

Limited research has been carried out on thickness estimation of the skull bone using ultrasound. The human skull bone is composed of three layers. The sponge-like trabecular layer is sandwiched between two cortical layers; it highly attenuates and absorbs the energy of propagating sound waves. Consequently, the backscattered echoes from the inner surface of skull are very weak and usually buried in the speckle noise so that they cannot be easily detected without further processing. To overcome the above-
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mentioned problem, Tretbar et al. suggested a hand-piece, A-mode ultrasound system called SonoPointer that can measure skull bone thickness point by point using pulse-echo with direct coupling [15]. This system was integrated with coded excitation (CE) technique to improve the time-resolution of A-mode signals. By using this device, the results were significantly improved compared to the standard A-mode measurements. However, the suggested device is only designed for A-mode applications such as bone surface registration for robot or preplanned drilling procedures, and cannot be used for transcranial imaging. Double focusing is another, recently suggested technique for A-mode measurement of the skull bone thickness [16].

A methodology to extract the three-dimensional profiles of the skull bone using ultrasound is highly desirable. The present study investigates the feasibility, accuracy and precision of ultrasonic pulse-echo measurement of skull bone thickness using a custom-designed matrix array. In the first section, the problem of skull profile estimation is addressed in a time delay estimation framework and a multi-lag phase delay estimation (MLPD) is implemented to trace the inner and outer profiles from the ultrasound images. In the second part, a modified space alternating generalized expectation maximization (SAGE) is introduced to estimate the arrival times of ultrasonic echoes backscattered from the inner and outer surfaces of the skull. Having the arrival times obtained through the suggested methods the skull thickness can be simply calculated given the speed of sound (SOS) value in the skull bone. However, the actual SOS value in the skull bone is unknown. An adaptive sound speed estimation algorithm is proposed in this chapter to estimate the optimal SOS value and the skull bone thickness simultaneously.
3.2 Time of arrival estimation

3.2.1 Background

In ultrasound imaging the phase delay of an ultrasound backscattered echo at frequency, \( f_0 \), can be related to the time delay, \( t_d \), as

\[
\varphi = 2\pi f_0 t_d \quad (3-1)
\]

Therefore, the reference echo, \( y_r \), and the time-delayed echo, \( y_d \), are described by the following equations,

\[
y_r(t) = A(t) \cos(2\pi ft),
\]

\[
y_d(t) = \beta A(t - t_d) \cos(2\pi f(t - t_d) + \theta_c), \quad (3-2)
\]

where \( A(t) \) is the envelope of the echo, \( \beta \) is the attenuated amplitude, \( f \) is the carrier frequency, and \( \theta_c \) is the center frequency phase shift.

Normalized cross-correlation between two radio frequency (RF) signals has been suggested as a standard method to estimate the phase shift caused by the skull bone [17, 18]. The cross-correlation function is normalized by its standard deviation to prevent a bias in the phase, Eq. (3-3), which tends in the direction of bright or high-intensity areas.

\[
c_{NRF}(m) = \frac{\sum_{n=-M}^{M} (y_r(n) - \bar{y}_r)(y_d(n + m) - \bar{y}_d(m))}{\sqrt{\sum_{n=-M}^{M} (y_r(n) - \bar{y}_r)^2 \sum_{n=-M}^{M} (y_d(n + m) - \bar{y}_d(m))^2}} \quad (3-3)
\]
$\bar{y}_r$ is the mean of the reference signal over window size $M$ and $\bar{y}_d$ is the mean of the delayed signal over a window shifted by $m$ samples. The sample at which the cross-correlation is maximized indicates the delay between two signals.

### 3.2.2 Multi-lag phase delay estimation-method 1

In a phased array system, using demodulation and delay rather than RF time delay simplifies the requirements for a delay structure. Demodulation of the real-valued bandpass signals $y_r(t)$ and $y_d(t)$ can be accomplished by

$$bb_r(t) = y_r(t)e^{-j2\pi f_0 t} = A(t) e^{j2\pi(f-f_0)t},$$

$$bb_d(t) = \beta y_d(t)e^{-j2\pi f_0 t}$$

$$= \beta A(t - t_d) e^{j(2\pi(f-f_0)(t-t_d)+\theta_c)} e^{-j2\pi f_0 t_d}$$

where $bb_r(t)$ and $bb_d(t)$ are their complex, baseband counterparts. A block diagram of a baseband demodulation filter is illustrated in Figure 3.1. Since the demodulated signal is not smooth, a low pass filter is applied to eliminate the higher frequency variations and yield a smooth envelope. As it is seen, a baseband signal consists of in-phase, $I$, and quadrature phase, $Q$, components.

$$I_d(t) = \beta A(t - t_d)cos(2\pi(f-f_0)(t-t_d) + \theta_c - 2\pi f_0 t_d),$$

$$Q_d(t) = \beta A(t - t_d)sin(2\pi(f-f_0)(t-t_d) + \theta_c - 2\pi f_0 t_d).$$

In the following, using the baseband signal concept and Fourier theory the analytic cross-correlation function is presented in terms of time delay and center frequency phase shift.
In the spectral domain, a bandpass signal may be presented by frequency shifts of its baseband signal in the Fourier domain, as follows [20],

$$Y_r(f) = BB(f - f_c)/2 + BB^*(-f - f_c)/2,$$  \hspace{1cm} (3-6)

where $BB(f)$ is the Fourier counterpart of $bb_r(t)$. In addition, the frequency spectrum of the delayed signal $y_d(t)$ can be obtained in terms of the reference baseband signal by using Eqs. (3-4) and (3-6) as follows.

$$Y_d(f) = \frac{1}{2} \beta e^{-j(2\pi(f - f_0)t_d + \theta_c)} BB(f - f_c) + \frac{1}{2} \beta e^{j(2\pi(-f - f_0)t_d + \theta_c)} BB^*(-f - f_c)$$  \hspace{1cm} (3-7)

The time delay of the envelope, $t_d$, and the center frequency phase shift, $\theta_c$, can be calculated by computing the analytic cross-correlation function of baseband signals in the Fourier domain [20].

$$C_{y_r y_d}^a = \begin{cases} 2Y_d(f)Y_r^*(f) & \text{for } f > 0 \\ Y_d(0)Y_r^*(0) & \text{for } f = 0 \\ 0 & \text{for } f < 0, \end{cases}$$  \hspace{1cm} (3-8)
Substituting Eqns. (3-6) and (3-7) into the Eq. (3-8) yields the analytic cross-correlation function:

\[ c_{y_{r,y_{d}}}^a(f) = \frac{1}{2} \beta \exp \left[ -j(2\pi(f - f_0)t_d + \theta_c) \right] |BB(f - f_0)|^2 \]  

(3-9)

Now by defining the baseband autocorrelation as

\[ c_{bb}(t - t_d) = R_{bb}(t - t_d) \exp[j\phi_{bb}(t - t_d)], \]

and its Fourier transform \( C_{bb}(f - f_0) = |BB(f - f_0)|^2 \), the time domain analytic cross-correlation can be computed by an inverse Fourier transform of (3-9) as follows:

\[ c_{y_{r,y_{d}}}^a(t) = \beta R_{bb}(t - t_d) \exp \left[ -j(2\pi f (t - t_d) + \phi_{bb}(t - t_d) + \theta_c) \right]. \]  

(3-10)

where \( R_{bb} \) is the magnitude and \( \phi_{bb} \) is the phase of the baseband autocorrelation \( c_{bb} \).

Since the autocorrelation function is always maximum at time zero, \( R_{bb}(t - t_d) \) and consequently \( c_{y_{r,y_{d}}}^a(t) \) will have a peak at \( t = t_d \). Once the time delay is obtained, the center frequency phase shift can be estimated from the phase argument of (3-10) at the time lag \( t_d \).

\[ t_p = \tan^{-1} \left[ \text{Im}(c_{y_{r,y_{d}}}^a) / \text{Re}(c_{y_{r,y_{d}}}^a) \right] / 2\pi f_c, \]  

(3-11)

where \( t_p \) is the phase shift and \( f_c \) is the center frequency that is almost equal to the transducer’s center frequency.

Once the time delays between adjacent elements of the aperture have been estimated using the described method, the estimation of arrival times is needed in order to extract
the outer and inner skull bone profiles. A common technique for accomplishing that is to estimate the arrival time for a reference point and calculate other arrival times in the aperture with respect to the reference point by a simple summation. Since there are multiple paths between any two points, this method would not be accurate and summations along different paths produce inconsistent results due to the errors in the given arrival time differences.

Figure 3.2 An arbitrary cell structure from an $I$ by $J$ aperture showing the arrival times. Adjacent elements in vertical, horizontal and diagonal directions are connected to the central element indicating the available arrival time differences.

Nonetheless, by considering the arrival times as unknowns an over-determined system of equations can be assembled using the time delays between all signals within a specified spatial lag, expressed by [21]

$$ET = D$$  \hspace{1cm} (3-12)

For a two dimensional aperture of $I \times J = K$ elements, $T$ is a $K \times 1$ vector comprised of the arrival time vector, $D$ is the estimated time delays which is an $L \times 1$ vector, and $E$ is the $K \times L$ model matrix. When the time delays for all horizontal, vertical and diagonal neighbours are available, the total number of equations would be
Figure 3.2 demonstrates an arbitrary cell structure from an \( I \) by \( J \) aperture with the center element of \( m \) and its adjacent elements. Arrival time differences are obtained by subtracting the arrival time of each element from its adjacent elements, connected by an arrow in this figure.

The model matrix \( E \) is comprised of rows in which every element is zero except two elements that are either +1 or –1. Therefore, the columns of the matrix add up to a zero vector, implying that the rank of the matrix \( E \) is less than \( K \). Consequently, one of the arrival times cannot be determined using the available data and it needs to be estimated using a different procedure. To do this, one of the arrival times (the reference) is arbitrarily set to zero and the relative arrival time \( \hat{T} \) is calculated instead. The set of over-determined linear equations now can be solved by using the least mean square error (LMSE) method and the relative arrival times can be computed from

\[
\hat{T} = (E^T E)^{-1} E^T D,
\]

where \( E^T \) is the transpose of matrix \( E \) and \( (E^T E)^{-1} E^T \) is called the pseudo inverse of \( E \). The arrival times are obtained by adding the reference arrival time to the relative arrival matrix \( \hat{T} \).

The procedure of time of arrival estimation for the echoes backscattered from the outer and inner surfaces of the skull using the multi-lag phase delay (MLPD) algorithm can be summarized as follow,
Step 1. Demodulate the beamformed RF signals

Step 2. Select the area of interest by considering the maximum bone thickness as 13mm.

Step 3. Set the correlation’s kernel length to 30 samples, equivalent to 1.8 mm in the bone.

Step 4. Start with the horizontal direction; calculate the analytic cross-correlation for each element \((i, j)\) and its adjacent element \((i, j+1)\).

Step 5. Estimate the phase delays at the time lags \(t_d\) using

\[
t_p = \tan^{-1}\frac{\text{Im}(c_{y_d y_d}^a) / \text{Re}(c_{y_d y_d}^a))}{2\pi f_c},
\]

and construct the arrival time difference matrix \(D_1\).

Step 6. Repeat steps 2 and 3 for the vertical direction, between \((i, j)\) and \((i+1, j)\), and construct the \(D_2\).

Step 7. Repeat steps 2 and 3 for the diagonal directions, between \((i, j)\) and \((i+1, j+1)\), and also between \((i, j)\) and \((i+1, j-1)\), and construct \(D_3\) and \(D_4\).

Step 8. Construct the difference vector \(D = [D_1(:) D_2(:) D_3(:) D_4(:)]\) and the model matrix \(E\).

Step 9. Compute the relative arrival time \(T = (E^T E)^{-1} E^T D\).

Step 10. Select the reference signal; the envelope with biggest local maximum (excluding the global maximum) and estimate the time of arrival for the inner surface echo, \(TOA_{ref}\).

Step 11. The estimated arrival time would be \(T = T^* + TOA_{ref}\)
This procedure estimates the arrival times of the reflected echoes from the inner surface. The same procedure can be applied for the outer surface of the skull with the exception that, in step 10 \( TOA_{ref} \) is the arrival time for the first reflected echo.

The multi-lag phase delay (MLPD) algorithm is computationally efficient and easy to implement on the beamforming system, which makes it perfect for adaptive transcranial imaging. However, the accuracy and efficiency of this algorithm substantially decreases when the backscattered echoes are superimposed. In transcranial ultrasound, this might occur at some points where the bone layer is thin and the backscattered echo from the dipole layer is strong. Moreover, the time-resolution of the MLPD, as is every other cross-correlation-based algorithm, is limited to two times the sampling interval. In the next section a decomposition-based algorithm for arrival time estimation of the backscattered echoes from the skull bone will be discussed. This method solves the estimation problem in a maximum likelihood framework and can deal with the superimposed echoes by decomposing them to several Gaussian echoes.

### 3.2.3 Arrival time estimation by modified SAGE algorithm-method 2

The problem of the accurate profile extraction of the skull bone can be addressed in a high-resolution arrival time estimation scheme. In ultrasound imaging, the backscattered signals can be reconstructed from a number of Gaussian echo wavelets as,

\[
y(t) = \sum_{m=1}^{M} g(\theta_m; t) + n(t)
\]  

(3-15)

The idea of exploiting Gaussian model comes from the bandpass property of ultrasound echoes with Gaussian envelope [22]. A Gaussian echo wavelet is a nonlinear function of
a parameter set, $\theta_m$, and $n(t)$ denotes the measurement noise. This Gaussian modulated cosine echo can be represented by

$$g(\theta_m; t) = \beta_m e^{-\alpha_m (t - \tau_m)^2} \cos(2\pi f_{c,m}(t - \tau_m) + \varphi_m)$$  \hspace{1cm} (3-16)

with the parameter set $\theta_m = [\alpha_m, \tau_m, f_{c,m}, \varphi_m, \beta_m]$ for each signal component. This is a specific form of Eq. (3-2) in which the envelope, $A(t)$, is considered a Gaussian function.

The parameters of the model are bandwidth factor, $\alpha$, arrival time, $\tau$, center frequency, $f_c$, phase, $\varphi$, and amplitude, $\beta$, respectively. In order to evaluate the Gaussian assumption of the ultrasonic echoes, an ultrasonic pulse is sent by a linear array transducer immersed in a water tank, facing one of the walls, and the backscattered echo from the flat wall of the water tank is received by the same transducer as the reference transducer echo. The measured reference echo is then modeled using a single Gaussian echo.

The modeled wavelet in the time domain is depicted in Figure. 3.3 (a) superimposed with the measured wavelet and their frequency counterparts are presented in Figure 3.3 (b). The good agreement between the estimated and the measured echoes (mean absolute error of 0.031 between two echoes) validates the suitability of the Gaussian assumption.

It is worth noting that exploiting multi Gaussian echoes can model the fluctuation of the measured echo’s tail slightly better than using a single Gaussian echo, as it has been suggested for deconvolution purpose in the literature [22], [23]. However, modeling each reflected echo by multiple Gaussian echoes significantly increases the computational costs without offering any accuracy improvement such that it makes this method unsuitable for adaptive transcranial imaging, which is the purpose of this study. Furthermore, in a deconvolution problem each echo is considered as a time-shifted,
energy-attenuated replica of the reference wavelet, while this assumption is not valid for the echoes travelling through the skull bone due to the severe pulse distortion caused by the propagation path. Exploiting a single Gaussian echo model provides the opportunity to model the reflected echoes from the inner surface with completely new parameter sets than the ones from the outer surface. In other words, the center frequency phase shifts can also be taken into account for thickness calculation beside using the arrival time differences.

The objective of decomposing the measured signal into several Gaussian echoes, as represented in Eq. (3-15), is to estimate the parameter vectors $\theta_1, \theta_2, \ldots, \theta_M$ for the backscattered echoes. However, the reflected echoes from the inner, outer, and dipole layers of the skull bone are partially and sometimes severely superimposed, depending on the bone thickness and the location of the dipole layer at that area and also the transducer
bandwidth. This nonlinear parameter estimation problem can be addressed in a maximum likelihood estimation framework. Exploiting an iterative procedure for maximizing the joint likelihood, the expectation maximization (EM) algorithm has proven to be efficient in parameter estimation of superimposed signals [24], [25]. The idea of the expectation maximization algorithm is to decompose the observed signal, \( y(t) \), into its components and then to estimate the parameters of each signal component separately. The EM algorithm iterates back and forth to decompose the signal better using the updated parameter set and so to improve the subsequent parameter estimates.

In the E-step, the expectation of unobserved data is computed in terms of the received signal and the current estimate of the parameter vectors as follow [26]

\[
\hat{x}_m^{(k)}(t) = g(\theta_m^{(k)}; t) + \rho_m \left[ y(t) - \sum_{i=1}^{M} g(\theta_i^{(k)}; t) \right]
\]  

(3-17)

where \( \rho_m \) is any real-valued positive scalar satisfying \( \sum_{m=1}^{M} \rho_m = 1 \) and \( \hat{x}_m^{(k)}(t) \) is the expected signal at iteration \( k \). In the M-step, the likelihood of the expected signal from the E-step is maximized to obtain a new estimate of the parameter vector as

\[
\theta_m^{(k+1)} = \arg \min_{\theta_m} \int_{r_0}^{T_f} \left[ \hat{x}_m^{(k)}(t) - g(\theta_m; t) \right]^2 dt
\]

(3-18)

The M-step iterates the parameter estimation procedure to obtain an optimal value. The Gauss-Newton (GN) algorithm can be applied for the minimization in the M-step as it is computationally fast and also robust at the local maxima [26]. Taking advantage of the Gaussian echo model, the GN iteration formula for parameter estimation can be presented as
\[ \theta_m^{(k+1)} = \theta_m^{(k)} + \left( H^T \left( \frac{\partial}{\partial \theta_m} \theta_m^{(k)} \right) H \left( \frac{\partial}{\partial \theta_m} \theta_m^{(k)} \right) \right)^{-1} H \left( \frac{\partial}{\partial \theta_m} \theta_m^{(k)} \right) \left( \tilde{x}_m^{(k)} (t) - g \left( \theta_m^{(k)} ; t \right) \right) \] (3-19)

where \( H(\theta) \) denotes the gradients of the model with respect to parameters in the parameter vector \( \theta = [\alpha, \tau, f_c, \varphi, \beta] \). The gradient matrix is calculated analytically to speed up the computations.

The EM algorithm alternates between E-step and M-step iteratively to the point that the norm of the estimation error becomes less than a predefined tolerance. However, the EM algorithm has a slow convergence rate due to its computing structure at which all the parameters are updated simultaneously. The space alternating generalized EM (SAGE) algorithm has been suggested as a solution to speed up the convergence [26]. By updating the parameter sets sequentially, instead of simultaneously, and right after the M-step the SAGE algorithm yields a faster convergence than EM.

Unfortunately, this algorithm is still too slow to be used for 3-D skull profile extraction in real-time adaptive imaging; the computational time for running the standard SAGE on one frame of the skull phantom using a computer (Dual-core CPU 2.8 GHz with 4 Gigabytes of RAM) was several minutes. The following, proposed procedure alleviates the computational costs and speeds up the convergence time.

It is necessary to segment the acquired skull image and select the area of interest as a preliminary step before applying the algorithm. This can be done by first locating the outer surface of the skull from the global maximum of all the traces, as it is seen in Figure 3.4. Knowing the fact that the reported skull bone thickness for the thickest zone does not exceed 13 mm (the reported maximum skull thickness was 12 mm [27]) the area of interest would be determined.
Figure 3.4 The envelope signals of a 3-D frame of the skull phantom.

Through experimentation, it was found out that the SAGE algorithm is sensitive to the initial guesses so that an initial guess that is close to the actual parameter values significantly speeds up the convergence, while with a bad initial guess the algorithm fails to yield an accurate estimate of the parameters. By taking advantage of the demodulated signals, the amplitude and arrival time at the global maximum of each envelope are used as the initial guess for the outer surface echoes. However, the echoes backscattered from the inner surface are severely attenuated and degraded at some points that the initial guess cannot be obtained from those echoes. This can be related to the angle between the inner and outer surfaces at that location. The maximum energy is reflected where the two surfaces are locally parallel and also perpendicular to the ultrasound beam, and when the parallelism is violated at a location the energy is partially deflected away from the array and a very weak echo is captured. As a remedy to this condition, among $I*J$ signals received by the transducer aperture, the envelope signal $(i, j)$ with the biggest amplitude of the inner surface echo is selected. The initial guesses for the amplitude and arrival time of the outer and inner surface echoes are obtained by taking the first derivative of the
envelope and are input into the SAGE algorithm. Given the good initial guess the algorithm estimates the parameter vector $\theta(i, j)$ successfully.

The surface of the skull is physically continuous and so its thickness varies smoothly rather than abruptly. Furthermore, the distance between the adjacent elements on the matrix array is as small as 0.55 mm. Taking these two facts into account, the estimated $\theta$ for the element $(i, j)$ are employed as an accurate initial guess for its adjacent elements on the array such as $(i-1, j)$, $(i+1, j)$, $(i, j-1)$, and $(i, j+1)$. The flowchart of the algorithm is depicted in Figure 3.5.

As for the rest of the parameters, the transducer center frequency is taken as initial guess for the echoes center frequency. In addition, the estimated bandwidth for the reference wavelet would be taken as an initial guess for the bandwidth in this procedure.

The number of reflected echoes from the bone (the model order) varies from two to four at different regions depending on the presence of the dipole layer. For this specific problem the model order is initialized as two considering the inner and outer surface echoes. After the algorithm converges with this model order, the estimated echoes are subtracted from the measured signal to obtain the residual signal. The variance of the residual signal is then compared against the variance of measurement noise. The variance of noise was estimated from the signal-free part of the trace. If the variance of the residual signal is bigger than the variance of the noise by a factor of three ($\sigma_r^2 > 3\sigma_n^2$) the residual contains dipole layer echoes. The factor of three was found optimal throughout the experiments conducted in this study. Therefore, the model order increased and the peak of the residual signal is taken as initial guess for the amplitude and arrival time of
Figure 3.5 The flowchart of the modified space-alternating generalized EM algorithm.
the new echo. The algorithm iterates until the model order reaches to the optimal $M$.

The above-mentioned algorithm moves across the array to estimate the parameters for all signals received by the active elements. A summary of the algorithm is given in the following

Step 1. Demodulate the beamformed RF signals

Step 2. Select the envelope $(i, j)$ with the biggest inner surface echo.

Put model order as two $(M = 2)$.

Step 3. Make initial guesses from the envelope $(i, j)$ and form

$$\Theta^{(0)}(i, j) = [\theta_1^{(0)}; \theta_2^{(0)}; \ldots; \theta_M^{(0)}]$$

Set $k = 0$ (iteration number) and $m = 1$ (echo number).

Step 4. (E-step) Compute

$$\hat{x}_m^{(k)}(t) = g\left(\theta_m^{(k)}; t\right) + \frac{1}{M}\{y(t) - \sum_{i=1}^{M} g\left(\theta_i^{(k)}; t\right)\}$$

Step 5. (M-Step) Iterate the $m^{th}$ parameter vector using the Gauss-Newton algorithm

$$\theta_m^{(k+1)} = \theta_m^{(k)} + \left(H^T \left(\theta_m^{(k)}\right) H \left(\theta_m^{(k)}\right)\right)^{-1} H \left(\theta_m^{(k)}\right) \left(\hat{x}_m^{(k)}(t) - g\left(\theta_m^{(k)}; t\right)\right)$$

Set $\theta_m^{(k)} = \theta_m^{(k+1)}$

Step 6. Set $m \rightarrow m+1$ and go to Step 4 unless $m > M$.

Step 7. Check convergence criterion: if $\|\Theta^{(k+1)} - \Theta^{(k)}\| \leq$ tolerance, then go step 9.

Step 8. Set $m = 1, k \rightarrow k + 1$, and go to Step 4.
Step 9. Subtract the estimated echoes from the measured signal $y$, and calculate the variance of the residual $\sigma_r^2$.

Step 10. Compare the residual variance with the noise variance, if $\sigma_r^2 > 3\sigma_n^2$ set $M = M + 1$, make initial guess for the residual, set $m \to m + 1$ and go to step 4.

Step 11. The optimal model order is $M$; the estimated parameter vector is $\theta(i,j)$.

Step 12. Step forward or backward to the adjacent elements such as $(i+1, j)$ and take $\theta(i, j)$ as initial guess and go to step 4.

3.3 Simulation

Simulations were performed to evaluate the performance of the proposed algorithms for the skull bone thickness estimation and to compare these results with other methods. For this purpose, 1600 radio frequency (RF) signals are simulated with different phase delays for a 40 by 40 aperture. The base RF signals are generated using a Gaussian modulated cosine pulse, Eq. (3-16), where the bandwidth, $\alpha$, was 1 (MHz)$^2$ and the amplitude, $\beta$, and the center frequency $f_c$ were 1 and 2 MHz, respectively. The arrival times, $\tau$, at each element of the aperture are selected from a synthetic outer and inner skull profile. To account for the physical decorrelations in this simulation, the center frequency phase shift, $\theta$, is randomly chosen as a value between $-\pi/2$ to $\pi/2$ for every point. All of the simulated signals are contaminated with speckle noise. Nine datasets with different Signal to Noise Ratios (SNRs) of 0, 5, 10, 15, 20, 25, 30, 35, and 40 are synthetized to evaluate the performance of algorithms in different noise levels.
The arrival time profile is estimated using the two proposed methods multi-lag phase delay (MLPD) estimation, and the modified SAGE algorithm, as described in the previous section. The results are compared with those obtained from the two commonly used algorithms called normalized RF cross-correlation [17], [18] and baseband autocorrelation [28]–[30]. Figure 3.6 shows two cross sections of the original times of arrival (TOA) profile in solid lines. The actual TOAs are $\text{TOA} = \tau - \frac{\theta}{2\pi f_c}$, where $\theta$ is the unwrapped phase shift.

The TOAs estimated using NRF cross-correlation, Autocorrelation, modified SAGE and MLPD methods are plotted in this figure, superimposed with the original profile for evaluation. By visual comparison it can be clearly seen that the estimated profiles by the modified SAGE and MLPD have less deviation from the actual profile than ones by the other two techniques. The results will be quantitatively evaluated at the end of this section.

The time delay estimation is carried out using a finite length of speckle data that are contaminated by electronic noise and decorrelated by physical processes. These factors cause two types of errors in estimation process. The first type is called false peak error and is significant and the second type is called jitter that is smaller in magnitude. In this study, the false peak error is defined as any arrival time error bigger than a half cycle of the echo. A false peak occurs when a secondary peak has bigger amplitude than the primary peak due to the superimposing of echoes, noise, or signal decorrelation.
Figure 3.6 Arrival time estimation for a simulated 2-D profile, the cross sections along (a) elevation, and (b) lateral directions.

To be able to comprehensively compare the performance of the described methods, the estimation error and standard deviation of jitter error should be evaluated. Every estimator is subjected to the jitter error that degrades time delay estimations. This type of error is very small, yet cannot be eliminated. The Cramer-Rao Lower Bound (CRLB) theoretically can predict the minimum degree of the jitter error for unbiased estimators by [31]:

\[
\sigma(\tau - \hat{\tau}) \geq \frac{3}{\sqrt{2f_0^3 \pi^2 T (B^3 + 12B)}} \left( \frac{1}{\rho^2} \left(1 + \frac{1}{\text{SNR}^2}\right)^2 - 1 \right),
\]
which demonstrates how center frequency, $f_0$, kernel window length, $T$, fractional bandwidth, $B$, signal decorrelation, $\rho$, and SNR affect the standard deviation of the jitter error. Here $\tau$ is the true arrival time and $\hat{\tau}$ is the estimated arrival time. The signal to noise ratio is defined as the ratio of the root mean squared (RMS) amplitude of the signal to the root mean squared amplitude of the noise.

Figure 3.7 (a) depicts the theoretical bound obtained from the Eq. (3-20) versus different SNRs for the RF data. The standard deviations of errors (SDE) obtained from the MLPD, modified SAGE, Autocorrelation and NRF cross-correlation are plotted on the same figure for comparison. These SDE values are estimated by

$$\sigma(\tau - \hat{\tau}) = \sqrt{\frac{1}{1600} \sum_{i=1}^{1600} (\tau_i - \hat{\tau}_i)^2}. \quad (3-21)$$

It can be seen that the SDE for the proposed methods are very close to the theoretical limit for all SNRs. For the other two methods the amounts of SDE are somewhat close to the theoretical limit in higher SNR range (SNR >10 dB), though these amounts are much bigger than the ones obtained from the proposed methods in lower SNRs. For the SNRs lower than 10 dB, the amounts of SDEs obtained from the normalized cross-correlation method grow dramatically, comparing to the other three methods. Table 3.1 presents the values of SDE obtained from these methods.
Figure 3.7 Performance comparison of the algorithms for arrival time estimation, (a) standard deviation of the jitter error, the Cramer-Rao Lower Bound has been depicted in solid line as a theoretical limit, (b) the mean estimation error.

Figure 3.7 (b) depicts the mean estimation error versus SNR. The estimation error for the MLPD and modified SAGE are small and close to zero while this error is significant for the other two methods, especially in the lower SNR range. For instance, the estimation errors for SNR of 5 dB are 0.61 ns and 0.25 ns for MLPD and modified SAGE while these values are -73.22 ns and 194.74 ns for Autocorrelation and NRF cross-correlation respectively. The values of estimation error are tabulated in Tables 3.2.
Comparing the two proposed methods show that the modified SAGE algorithm can estimate the arrival times with a higher accuracy than the multi-lag phase delay (MLPD) algorithm for all SNRs, see Table 3.2.

The normalized radio frequency cross-correlation could accurately estimate the arrival times for less noisy signals (SNR>10) with error range between -9.63 ns and 0.45 ns. However, the substantial values of error and SDE at lower SNRs (-57.72 ns and 194.74 ns for SNRs of 0 dB and 5 dB) shows that the NRF cross-correlation falls into false peak detection in noisy signals. As it is expected the Autocorrelation is the least accurate method and this can be attributed to the fact that Autocorrelation only calculates the time delays between the envelopes without considering the phase shifts.

### Table 3.1 The Standard deviation of jitter error (Nanosec.) for the arrival time estimation from a synthetic profile.

<table>
<thead>
<tr>
<th>Method</th>
<th>SNR 0</th>
<th>SNR 5</th>
<th>SNR 10</th>
<th>SNR 15</th>
<th>SNR 20</th>
<th>SNR 25</th>
<th>SNR 30</th>
<th>SNR 35</th>
<th>SNR 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLPD</td>
<td>60.43</td>
<td>1.32</td>
<td>0.71</td>
<td>0.39</td>
<td>0.22</td>
<td>0.12</td>
<td>0.07</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Modified SAGE</td>
<td>206.96</td>
<td>64.12</td>
<td>2.62</td>
<td>0.38</td>
<td>0.21</td>
<td>0.12</td>
<td>0.06</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Auto corr.</td>
<td>86.04</td>
<td>40.62</td>
<td>38.56</td>
<td>37.91</td>
<td>38.35</td>
<td>33.84</td>
<td>32.59</td>
<td>30.98</td>
<td>32.38</td>
</tr>
<tr>
<td>NRF corr.</td>
<td>549.97</td>
<td>182.59</td>
<td>59.49</td>
<td>27.69</td>
<td>32.96</td>
<td>28.55</td>
<td>33.28</td>
<td>33.34</td>
<td>33.50</td>
</tr>
</tbody>
</table>

### Table 3.2 The obtained arrival time estimation error (Nanosec.) for a synthetic profile.

<table>
<thead>
<tr>
<th>Method</th>
<th>SNR 0</th>
<th>SNR 5</th>
<th>SNR 10</th>
<th>SNR 15</th>
<th>SNR 20</th>
<th>SNR 25</th>
<th>SNR 30</th>
<th>SNR 35</th>
<th>SNR 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLPD</td>
<td>-2.14</td>
<td>0.61</td>
<td>0.18</td>
<td>-0.09</td>
<td>0.05</td>
<td>-0.19</td>
<td>0.07</td>
<td>-0.04</td>
<td>-0.01</td>
</tr>
<tr>
<td>Modified SAGE</td>
<td>-0.95</td>
<td>0.25</td>
<td>-0.10</td>
<td>-0.01</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Auto corr.</td>
<td>-55.83</td>
<td>-73.22</td>
<td>-11.12</td>
<td>-33.43</td>
<td>-31.45</td>
<td>-12.77</td>
<td>-41.7</td>
<td>-33.5</td>
<td>-16.95</td>
</tr>
<tr>
<td>NRF corr.</td>
<td>-57.72</td>
<td>194.74</td>
<td>-22.91</td>
<td>0.45</td>
<td>-7.50</td>
<td>-5.97</td>
<td>-9.63</td>
<td>-8.03</td>
<td>-8.63</td>
</tr>
</tbody>
</table>
3.4 Adaptive sound speed estimation

Having the arrival times obtained through the suggested methods, the skull profiles can be simply calculated given the speed of sound (SOS) in the skull bone. However, the speed of sound in the human skull varies significantly in different zones and even from person to person depending on the race, age and gender. Tretbar [15], [32] reported the speed of sound in formaldehyde-preserved calvaria as 2921 ± 263 m/sec. Pejek [33] demonstrated that speed of sound varies from 2000 m/sec to 3100 m/sec depending on the density of the bone at the point of measurement. The variant sound speeds in one calvarium can be related to the inhomogeneous structure of the skull bone with two cortical bone layers and a layer of cancellous bone in the middle. The speed of sound in the cortical bone has been reported as 2900 m/sec while the reported SOS value for the cancellous bone (dipole layer) is only 2500 m/sec. The significant difference in the thickness of the dipole layer observed in the different zones of the skull, from 0 to 7.8 mm [36], is the main contributing factor in the sound speed variations within the skull bone.

Figure 3.8 Block diagram of the ultrasound imaging system in the reception mode.
In this section, a method is proposed to adaptively estimate the speed of sound in the different skull zones. This method is based on a real-time phase aberration correction that has been proposed by the author for transcranial adaptive imaging and implemented on our platform ultrasound machine.

An ultrasound imaging system with real-time aberration compensation in the reception mode is presented in Figure 3.8. The data acquired by the transducer is first amplified and sent to an analog to digital convertor before the beamforming. Using the pre-beamformed data the time delay patterns are estimated for each scan line and then fed into the digital beamformer to correct the phase aberration profile induced by the inhomogeneous media, i.e. the skull bone.

The calculation of the time delay patterns for the phase aberration compensation in the beamforming highly depends on the location of the boundaries of the inhomogeneity. These boundaries are in fact the skull profiles. Any deviation from the actual value of speed of sound in the bone would dislocate the boundary conditions and consequently change the time delay patterns.

Figure 3.9 illustrates the difference in the two time-delay patterns calculated by assuming the SOS value in the skull bone as 2950 m/sec in (a) and 2800 m/sec in (b), respectively. These time delay patterns are calculated for focusing the beams into the soft tissue (SOS=1540 m/sec) behind the skull bone at the depth of 20 mm.
Figure 3.9 Calculated time delay patterns for focusing and steering the beams into the soft tissue (SOS=1540 m/sec) behind the skull at the depth of 20 mm, from -22 to 22 degrees. The assumed SOS in the bone is (a) 2950 m/sec, (b) 2800 m/sec.

The idea is to estimate the optimal speed of sound value in the skull bone so using that the aberrated phase can be compensated the most in the beamforming procedure. An adaptive scheme can be adopted to search through a trial sound speed list and find the optimal value that maximizes the quality of beamformed images. For this purpose, a criterion needs to be defined for quality evaluation of the aberration-compensated images. A quality of focus factor based on the lateral image resolution was introduced in ref. [35]. The quality of focus was obtained by analyzing the lateral spatial frequency contents of the post-beamformed data and used for detecting an equivalent sound speed in the inhomogeneous soft tissues such as breast and abdominal tissues. In this study, the quality of focus factor is adopted for the purpose of evaluating the beamformed images. However, the assumption of considering an equivalent sound speed will no longer be valid for transcranial imaging due to the substantial discrepancy between the speeds of sound in the skull bone (about 3000 m/sec) and the brain tissue (about 1540 m/sec).

The proposed solution herein is based on a real-time phase aberration compensation procedure in which the medium is considered inhomogeneous, instead of homogeneous,
with two different sound speed values in the bone and the soft tissue. In this procedure, once the arrival times are calculated using the modified SAGE or MLPD algorithms, a trial SOS is selected from the list for the skull bone and from that the location of the inner and outer profiles are determined. The obtained profiles, the trial SOS value in the bone, and also the pre-known SOS value in the brain tissue are then used to construct a sound speed map of the medium. Having the sound speed map, the time delay patterns can be generated by solving the wave propagation equation via a finite difference method. The time delays are then fed into the dynamic receive beamformer to compensate for the aberrated phase of the B-scan image of the area of interest behind the skull. The pre-beamformed channel data are saved to be used for reprocessing of the same data multiple times for every trial sound speed.

The quality of the aberration-corrected image using the trial sound speed is then evaluated by analyzing the lateral spatial frequency contents of the image. For this analysis, a range of interest is determined from an echogenic area and magnitudes of the signals in this range are calculated. Subsequently, a lateral Fast Fourier Transform (FFT) is applied on each trace in this range. By averaging the spectrums over the range the mean spectrum is yielded. For comparison purpose the mean spectrum is normalized and then log-transformed. The mean spectrum is then integrated over the normalized spatial frequencies to obtain the mean spectral energy (MSE), i.e. a lateral resolution index used for comparing the quality of the images reconstructed by various trial sound speeds. This procedure is repeated until the MSE quantity is obtained for each sound speed in the trial list. The optimal speed of sound is the one yielding the biggest MSE value.
The proposed procedure is applied to estimate the speed of sound value in the skull bone phantom used for this study. Figure 3.10 illustrates the variations of the mean spectrums versus the normalized spatial frequency while each mean spectrum is obtained from the B-mode image reconstructed with different SOS values for the skull bone phantom. As it is seen, the mean spectrum magnitudes with the SOS of 2950 m/sec are bigger than the ones obtained with the SOS of 2850 m/sec and 3050 m/sec. After integrating the mean spectrums over the normalized frequencies the mean spectral energy values are obtained as an index of lateral resolution. The mean spectral energy values for different SOS plotted in Figure 3.11 have a peak at 2950 m/sec indicating the optimal SOS in the phantom.

Figure 3.10 The variations of the mean spectrums for different values of SOS in the skull bone.
Figure 3.11 The mean spectral energy vs. SOS.

The block diagram of the adaptive sound speed estimation algorithm is depicted in Figure 3.12. It is worth noting that in this adaptive procedure the speed of sound value within the brain tissue is assumed as a pre-knowledge (1540 m/sec) and does not change from case to case. This assumption is based on the fact that the variation of SOS within the brain tissue is not significant comparing to the SOS variation in the skull bone.
Figure 3.12 Simultaneous estimation of speed of sound in the skull bone and skull profiles using an adaptive algorithm.
3. 5. Experiments and results

3. 5. 1. Skull phantoms

The experiments have been done on the skull phantoms fabricated at the Institute for Diagnostic Imaging Research (IDIR). The physical and acoustical properties of the fabricated phantoms mimic those of a typical human skull bone [36]. Similar to the human skull bone these phantoms have a trabecular layer sandwiched between two compact layers. Two different types of phantom have been used in this study. The first phantom type has flat outer and undulating inner surfaces, Figure 3.13 (a). The second type of phantom has similar geometry and curvature as human calvarium. As it is seen in Figure 3.13 (b), the outer surface of this phantom is smooth while the inner surface is rough and has random curvatures. The phantom thickness varies from 3 mm to 12 mm in different areas.

The physical and acoustical properties of the first phantom type (2-D phantom), reported by the fabricator, are as follows: speed of sound = 2989 m/sec, acoustic impedance = 6.3 MRayl, density = 2.07 g/cm³, and attenuation =15.7 ± 0.7. For the second type (3-D phantom), the acoustical properties vary in different areas of the phantom as the density and thickness of the trabecular layer vary, similar to the human calvarium.
Figure 3.13 The fabricated skull bone phantoms used in this study, (a) 2-D phantom with (left) and without (right) porosity layer, (b) the 3-D phantom with porosity layer.

3.5.2 Data acquisition

A series of laboratory experiments were carried out to verify the proposed methods for profile extraction of the skull bone phantom. In these experiments the phantom has been immersed in a water tank and the measurements were taken in a pulse-echo mode. The transducer was mounted on a scanner with four degrees of freedom, as it is seen in Figure 3.14.
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Figure 3.14 The experimental setup.

The custom-designed transcranial transducer used in this study consists of a $16 \times 16 = 256$ element sparse matrix array operating at 2 MHz center frequency. The bandwidth of the transducer when attached to the system was determined by receiving the backscattered echo from the flat wall of the water tank and acquiring the radio frequency signal from the machine, shown in Figure 3.3 as a reference wavelet. The -6 dB fractional bandwidth was found to be 51%.

The transducer is connected to an ultrasound advanced-open platform (ULA-OP) system with 64 independent transmit-receive channels. Figure 3.15 shows the geometry of the matrix transducer in which the inactive elements are shown in gray color. Each element of the array is 45 mm by 45 mm with a 0.1 mm kerf.

For imaging the skull bone phantom, a $4 \times 4$ element cluster on the array transducer is excited to focus the beam behind the skull bone and the reflected echoes are received by
Figure 3.15 The matrix array with 256 elements and center frequency of 2 MHz used in our experiments. The gray color shows the inactive elements.

the same cluster. With each scan line the cluster is stepped across the aperture in either azimuth or elevation directions. The successive positions of the cluster are illustrated using solid and dashed boxes in Figure 3.15. This scanning procedure outputs 99 scan lines with 0.55 mm spacing on the matrix array face. The radio frequency analog signals go through a low noise amplifier (LNA) and programmable gain amplifier for time gain compensation. The amplified signals feed a bank of 8 ADS5281 (Texas Instrument,
Dallas, TX), each featuring 8 analog-to-digital convertors, operating at 50 Msps with 12-bit resolution. To increase the signal to noise ratio (SNR) 5 series of these 99 scan lines are captured and averaged. The data is then sent to the supervising computer for post processing.

The distance between the transducer and skull phantom is adjusted so that the transducer focuses behind the inner surface. The transducer is positioned perpendicular to the outer surface. Nonetheless, since the outer and inner layers of the skull are not necessarily parallel, the backscattered echoes are weak.

A three-dimensional ultrasound image of the skull phantom consisting of $11 \times 9 = 99$ beamformed signals is obtained using the demonstrated setup. Figure 3.16 shows the 3-D image in 9 B-scan frames with each frame consisting of 11 signals. The spacing between adjacent frames is 0.55 mm. The acquired image is fed into the proposed algorithms, MLPD and modified SAGE, to extract the inner and outer profiles of the skull phantom. The MLPD algorithm estimates the time shifts along horizontal, vertical and diagonal directions for the spatial lag of 2 in the first step. For the calculations of the time shifts the correlation’s kernel length is set to be 30 samples, equivalent to 1.8 mm in the bone. In the next step, a matrix model with 338 equations is constructed and subsequently, the arrival times for the inner and outer boundaries are obtained by solving the equations using the least mean squared error method. The 3-D image is also fed to the modified SAGE algorithm and the performances of the two algorithms are compared with each other. The computational time for estimating the echoes’ arrival times reflected from the boundaries of the skull phantom, shown in Figure 3.16, by the MLPD algorithm using
our computer (Dual-core CPU 2.8 GHz with 4 Gbytes) was 4.2 sec, while it took 8.58 sec for the modified SAGE algorithm to estimate the arrival times from the same image.

Subsequently, the obtained arrival times are used in the adaptive sound speed estimation algorithm to simultaneously estimate the optimal speed of sound in the bone and also the skull’s inner and outer profiles. The optimal speed of sound giving the biggest mean spectral energy value was found to be 2950 m/sec. The inner and outer profiles obtained from the modified SAGE and MLPD algorithm are plotted in solid and dashed lines, superimposed on the original image.

To assess the accuracy of the results, the thickness of skull phantom was measured mechanically using a micrometer caliper with 0-25 mm range and 0.01 mm accuracy.

The examiner measured the thickness of the skull phantom for the area facing to the active transducer aperture. In fact, this area is illuminated $11 \times 9 = 99$ times with 0.55 mm step size during imaging as the dataflow shows in Figure 3.15. Therefore, the area is limited to a $6.05 \text{ mm} \times 4.95 \text{ mm}$ rectangular. By considering the width of ultrasound beam this area is rounded to be $6 \text{ mm} \times 5 \text{ mm}$, and so the micrometer measurements were done at 30 points with 1 mm spacing between every two adjacent points. The measurements were repeated three times and the average thicknesses were calculated.

The mechanically measured thicknesses of the skull phantom are added to the outer surface profile to obtain the inner surface profile for comparison purpose. This $6 \times 5$ measured profile can be interpolated by two to be the same size of the ultrasonic measurements ($11 \times 9$). This profile is plotted for frames 1, 3, 5, 7, and 9 by dotted line in Figure 3.17 superimposed with the ones obtained from the MLPD and modified SAGE.
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Figure 3.16 The 3-D ultrasound image of the skull phantom with a porosity layer consisting of 9 B-scan frames. The lateral distance between each two successive frames is 0.55 mm, i.e. one element pitch. The inner and outer profiles of the skull phantom have been obtained by the proposed algorithms; modified SAGE (solid line), MLPD (dashed line).
Figure 3.17 Acquired profiles of the skull phantom using the mechanical measurement (dotted line), the modified SAGE algorithm (solid lines), and the MLPD algorithm (dashed line) after adaptive sound speed estimation in the bone phantom; The lateral distance between each two successive frames is 1.1 mm, i.e. two element pitches.

The skull bone profile estimation procedure is assessed based on the bone thickness obtained from the inner and outer profiles and comparing this thickness with the ones obtained from the mechanical measurements. For further comparison, the acquired 3-D
image of skull phantom is fed to the two commonly used algorithms, Autocorrelation and Normalized RF cross-correlation, to estimate the profiles and subsequently the phantom thickness. In the next section the obtained results, presented in Figures 3.16 and 3.17, are statistically evaluated.

3.5.3 Statistical data analysis

3.5.3.1 3-D phantom case

The accuracy of the thickness measurements is reported as the mean absolute percentage deviation (MAPD) of the skull phantom thickness determined with the ultrasonic methods, as compared with the reference thickness measured mechanically by the micrometer. The precision is estimated as the root mean square deviation (RMSD) between two measurement methods. The RMSD value represents the sample standard deviation of the differences between the estimated thickness by ultrasound and the measured thickness by the micrometer.

The accuracy of the proposed methods for bone thickness measurement combined with the adaptive SOS estimation was 7.93% for the MLPD and 4.21% for the modified SAGE method. The obtained accuracy for the Autocorrelation method was 14.44% while the corresponding value for the NRF cross-correlation was 10.75%. Comparison of the calculated accuracies shows that both methods of MLPD and modified SAGE perform better than the other two methods, while the modified SAGE yields the best accuracy.

The precision of the proposed methods in terms of root mean square deviation (RMSD) was 0.73 mm for the MLPD and 0.57 mm for the modified SAGE method. These values were 1.25 mm and 1.16 mm for the Autocorrelation and NRF cross-
correlation, respectively. For further assessment the coefficient of variation (CV), a unitless quantity, is obtained as the ratio of the root mean square deviation to the mean of all measurements. The values of CV for the bone thickness measurements using MLPD, modified SAGE, Autocorrelation and NRF cross-correlation were 9.28%, 7.17%, 15.89%, and 14.64%, respectively. The accuracy, precision, and CV values of the discussed methods are presented in Table 3.3.

**Table 3.3 Summary of the statistical results for the 3-D skull bone phantom thickness estimation.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy (MAPD)</th>
<th>Precision (RMSD)</th>
<th>Coefficient of variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autocorrelation</td>
<td>14.44%</td>
<td>1.25 mm</td>
<td>15.89%</td>
</tr>
<tr>
<td>NRF cross-correlation</td>
<td>10.75%</td>
<td>1.16 mm</td>
<td>14.64%</td>
</tr>
<tr>
<td>MLPD</td>
<td>7.93%</td>
<td>0.73 mm</td>
<td>9.28%</td>
</tr>
<tr>
<td>Modified SAGE</td>
<td>4.21%</td>
<td>0.57 mm</td>
<td>7.17%</td>
</tr>
</tbody>
</table>

For clinical applications the Bland-Altman method is used to compare two measurement techniques. This approach is an alternative to correlation coefficient and regression analysis methods which provide misleading analysis in measurement methods comparison data [37]. The Bland-Altman plots are used to further evaluate ultrasound thickness measurement techniques against the mechanical measurement. In the Bland-
Altman plots 95% limits of agreement tells us how far apart measurements by 2 methods are.

The mechanically measured thickness of the area of interest on the bone phantom was 7.89 mm on average ranging from 7.28 mm to 8.60 mm. Figure 3.18 presents the Bland-Altman plot for two repeated measurements by the micrometer. The vertical axis represents the difference in thickness for two measurements by the micrometer, and the horizontal axis is the mean for the two repeated measurements.

**Figure 3.18 Bland-Altman plot for two repeated micrometer measurements.**

The mean difference between two micrometer measurements was 0.06 mm, shown by the middle line, while the mean absolute difference was found to be 0.09 mm. The 95% limits of agreement for the repeated micrometer measurements were −0.14 mm and 0.25 mm.

The Bland-Altman plots between the micrometer measurements and the ultrasound (US) thickness estimation by Autocorrelation, NRF cross-correlation, MLPD and modified SAGE methods are presented in Figures 3.19 to 3.22, respectively. In these
plots, the vertical axis represents the difference in thickness measured by the micrometer and that estimated by ultrasonic methods while the horizontal axis is the mean for thickness measured by micrometer and estimated by ultrasonic methods.

The mean difference between the US Autocorrelation and mechanical measurements was -1.16 mm and the 95% limits of agreement for the mentioned method were -2.11 mm and -0.22 mm. The mean absolute difference was found to be 1.16 mm. For the NRF cross-correlation method, the mean difference value was reduced to -0.87 mm, comparing to Autocorrelation. The scatter of the data however increased as the limits of agreement increased to -2.38 mm and 0.64 mm.

The Bland-Altman plots for the two proposed skull profile estimation methods are presented in Figures 3.21 and 3.22. The mean difference of thickness obtained from the multi-lag phase delay method followed by the adaptive SOS estimation and the mechanical measurements was -0.64 mm. The same value obtained for the mean absolute difference as MLPD underestimated the thickness values for all points and therefore all difference values had the same signs. The 95% limits of agreement were -1.35 mm and 0.08 mm.

The mean difference and the mean absolute difference of thickness obtained from the modified SAGE followed by the adaptive SOS estimation and the mechanical measurements were -0.35 mm and 0.44 mm, respectively. The 95% limits of agreement for this method were found to be -1.24 mm and 0.53 mm. This means that it is possible to estimate the thickness with accuracy of less than 0.45 mm (1.96 × SD) with a confidence level of 95%.
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A simple inspection of the presented results, Figures 3.19-22, shows that the scatter of the data for Autocorrelation, NRF cross-correlation and MLPD are below the horizontal axis demonstrating the fact that these methods consistently underestimate the values of the skull bone phantom thickness. The plot for the modified SAGE shows the scatter of the data to both sides. This fact can also be observed in Figure 3.17 where the MLPD estimates smaller values for thickness than the modified SAGE.

Clinical judgment is required to determine the acceptance of the obtained agreement limits and it would depend on the application in hand. However, a comparison between the discussed methods show the limits of agreement for the proposed MLPD and SAGE were narrower than the ones for the conventional methods. It was found that the widest agreement interval is for the NRF cross-correlation with limits of $-2.38$ mm and $0.64$ mm while the largest mean absolute difference is for the Autocorrelation method ($1.16$ mm). Overall, the modified SAGE method combined with the adaptive SOS estimation outperforms the other methods and yields the best accuracy, $4.21\%$, and precision, $0.57$ mm, the smallest mean absolute difference of $0.44$ mm, and the narrowest limits of agreement, $-1.24$ mm and $0.53$ mm. Comparing to the two other conventional methods, the MLPD also yields satisfactory results.

As discussed earlier the computational time to run the modified SAGE is twice than the MLPD method. Therefore, the choice between these two proposed methods would be a trade off between the accuracy and the computational speed.
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Figure 3.19 Bland-Altman plot for comparison of Autocorrelation method with micrometer measurement.

Figure 3.20 Bland-Altman plot for comparison of Normalized RF cross-correlation method with micrometer measurement.

3.5.3.2 2–D phantom case

To further evaluate the performance of the discussed algorithms they were applied to extract the profiles of the 2-D skull bone phantom with flat outer and undulating inner surfaces, Figure 3.13 (a). The phantom has a thick inner porosity layer with large grains size, which makes the scattering high resembling the back zone of the human skull.
Figure 3.21 Bland-Altman plot for comparison of multi-lag phase delay estimation method with micrometer measurement.

Figure 3.22 Bland-Altman plot for comparison of modified SAGE method with micrometer measurement.

Due to the attenuated backscattered echoes the extraction of the inner profile would be a challenging task.

Figure 3.23 (a) shows the cross-section of the 2-D phantom with varying thickness. Thanks to the simple shape of the undulating phantom the actual profiles can be obtained from the picture of the phantom’s cross-section captured by a camera. An automatic
contour detection algorithm, developed by the author and discussed in Chapter 6, was applied to detect the actual profile of the phantom. This profile is depicted by dashed line in Figure 3.23 (c).

The cross-sectional B-scan of the phantom constructed of 512 A-lines is shown in Figure 3.24 (b). To acquire this image, the transducer moved along the phantom mechanically by the scanner to scan the whole width of the phantom. As it is seen the image is severely contaminated with the speckle noise so that the inner profile is not visible. By applying the MLPD and modified SAGE algorithms the profiles were estimated, while both Autocorrelation and NRF cross-correlation methods failed to estimate the profile with a reasonable error. A low pass filter (LPF) is then applied on the profile data to eliminate the sudden fluctuations and smooth the results. The profiles estimated by the MLPD and modified SAGE and followed by a LPF are drawn in Figure 3.24 (c)) in solid and dash-dot lines, respectively.

The performance of the profile extraction methods is evaluated based on the estimated thickness between the profiles and the results are compared against the actual phantom thickness. The accuracy of the proposed methods for the bone phantom thickness measurement was 12.30 % for the MLPD and 8.62 % for the modified SAGE methods.

The obtained precision was found to be 1.06 mm for the MLPD and 0.77 mm for the modified SAGE. The 95% limits of agreements were -2.23 mm and 1.85 mm for the MLPD and -0.69 mm and 1.02 mm for the modified SAGE, indicating a narrower interval obtained by the modified SAGE algorithm. The Bland–Altman plots for these results are depicted in Figures 3.24 and 3.25.
Figure 3.23 Profile extraction of the 2–D phantom with undulating inner surface, (a) image of the phantom’s cross-section, (b) cross-sectional B-scan of the phantom, (c) estimated profiles superimposed with actual profile.

From a clinical perspective a tolerance of 1.2 mm in skull bone thickness would be acceptable for certain procedures such as calvarial split bone harvesting and hearing device implantation [15]. However, for transcranial adaptive focusing, the purpose of this study, the clinical judgement is not concerned as the skull profiles are used only for the compensation of the phase aberration.
Figure 3.24 Bland-Altman plot for comparison of multi-lag phase delay estimation method with the actual data.

Figure 3.25 Bland-Altman plot for comparison of modified SAGE method with the actual data.

3.6 Summary

In this chapter, the feasibility of the 3-D ultrasound imaging of the skull bone using a 2-D matrix array transducer is studied for the first time. Due to the thick, highly attenuative, multilayered structure of the skull bone the profile extraction of skull is a
Chapter 3: 3-D Profiles Extraction of Skull Bone using an Ultrasonic Matrix Array

challenging task. Furthermore, the actual speed of sound value in the skull is unknown as this value can vary in different skull zones, between genders and races and during aging due to the changes in the elastic properties of bone. For this purpose, a new method is proposed to estimate the thickness of the skull bone and the speed of sound within the skull bone, simultaneously. The proposed method is a two-folded procedure; in the first step the arrival times of the backscattered echoes from the skull bone are estimated using the multi-lag phase delay and modified SAGE algorithms. The performance of the arrival times estimation algorithms was evaluated in a synthetic profile estimation procedure in terms of estimation error and jitter and the results were compared with the ones from Autocorrelation and Normalized RF cross-correlation methods. In the second step, the estimated arrival times are fed into an adaptive sound speed estimation algorithm to estimate the optimal SOS value at the point of interest. For the purpose of quantitative evaluation, the estimated bone phantom thicknesses are compared with the mechanical measurements. The modified SAGE combined with the adaptive sound speed estimation method yields the smallest mean absolute difference of 0.44 mm for the 3-D phantom. This is comparable to the 0.4 mm value obtained from computer tomography (CT) by Eggers [14] and 0.5 mm value obtained from SonoPointer by Tretbar [15]. However, the proposed method is radiation free, non-invasive, and can be used in real time transcranial imaging, and unlike the SonoPointer it is able to extract the 3-D profiles of the skull. The proposed procedure is a promising method that may improve the clinical applications of transcranial ultrasound.
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References


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Chapter 4:

Adaptive focusing of ultrasound beams through the skull bone

4.1 Overview

This chapter focuses on non-invasive adaptive focusing of ultrasound beams through thick human skull bone without using the temporal bone acoustic windows. To compensate for the heterogeneity of the propagation medium, a preliminary B-scan of the skull bone is acquired through a custom beamforming. The propagation medium is modeled as a gridded sound speed field where the inhomogeneity boundaries are the skull bone profiles obtained through the modified SAGE algorithm. For each point on the gridded field a time-of-flight (TOF) at which the acoustic wave traverses the point is computed by using a finite difference numerical modeling. The computed TOFs are then used to generate a new time delay pattern for the adaptive beamforming.

4.2 Focusing

Focusing and steering the ultrasound beams can be done by electronic excitation of each array element with a proper phase delay. To focus the beam at a point \((x_f,y_f,z)\) the phase delays are applied to the aperture so that the wave amplitudes add constructively at the intended focal point. Using the Rayleigh Sommerfeld diffraction formula [1] in the
frequency domain for a harmonic vibration of the form $e^{-j\omega t}$, the complex amplitude at the focal point can be expressed as

$$U_f(x_f, y_f, z) = \frac{1}{j\lambda z} \iint_{\Sigma} U_a(x, y, 0) \exp \left\{ jk \left( (x_f - x)^2 + (y_f - y)^2 + z^2 - \sqrt{x_f^2 + y_f^2 + z^2} \right) \right\} dx dy$$

(4-1)

where $U_a(x, y, 0)$ denotes the unshifted complex amplitude over the aperture $\Sigma$ radiated from the transducer element with coordinate $(x, y)$. Also, $k$ is the wave number and $\lambda$ is the wavelength. Two assumptions have been used in this formula. First, the amplitude on the transducer plane is zero beyond the aperture $\Sigma$, which is true in ultrasound transducers. Second, the focal point is in the far field so that the distance between the element and the focal point is approximated by the axial distance, $z$, in the equation denominator. Considering that the beamforming technique used in this study is a Delay-and-sum that works with the time delays, the time domain form of the diffraction formula for a general 3-D case is expressed as [2]

$$u_f(x_f, y_f, t) = \frac{1}{2\pi cz} \iint_{\Sigma} \frac{\partial}{\partial t} u[x, y, t - \tau(x, y, x_f, y_f)] dx dy$$

(4-2)

where $c$ is the longitudinal speed of sound in the propagation medium and $\tau$ is the time delay for each active element at each focal point. It demonstrates that the signal at the focal point is obtained by appropriately time-shifting the temporal derivative of the aperture signals $u(x, y, t)$ and adding the delayed signals.
In conventional phased array imaging, time delays are calculated based on the geometrical path lengths between active elements of the array transducer and the focal points. The delays are fed to the transmit and receive beamformer to construct multiple foci within the tissue and subsequently to form the image. Assuming the medium homogeneous the geometrical paths are considered straight lines. Accordingly, the required time delays for each element to focus the beam using a linear transducer with \( N \) active elements can be calculated as

\[
\tau_{\text{conventional}}(y, y_f, z) = \frac{1}{c} \left[ \sqrt{(y_f - y)^2 + z^2} - \sqrt{y_f^2 + z^2} \right] \quad (4-3)
\]

The position of each element is related to the element number, \( n \), by \( y = np \) where \( p \) is the element pitch on the array transducer as shown in Figure 4.1.

![Figure 4.1 Using geometrical path lengths for calculation of conventional beamforming delay sets. The array transducer is linear with element pitch of \( p \), and the desired focal point is in the transducer plane with the coordinate \( F(0, y_f, z) \).](image-url)
Then, the time delays can be expressed in terms of the range, $R$, and the steering angle, $\theta$, and element number, $n$ (where $-\frac{N-1}{2} \leq n \leq \frac{N-1}{2}$), as

$$\tau_{\text{conventional}}(R, \theta, n) = \frac{1}{c} \left[ \sqrt{(R \sin \theta - np)^2 + (R \cos \theta)^2} - R \right]$$

The above equation uses a spatially constant speed of sound, $c$, in the propagation medium ($c_{\text{soft tissue}} \approx 1540 \text{ m/sec}$) to calculate the time delays for the beamforming. Without taking into account the distorting effects of the inhomogeneous medium, several attempts have been dedicated to estimation and correction of sound speed in human organs [3], [4]. An automatic sound speed estimation method has been proposed by Napalitano for Zonar’s medical ultrasound systems [5] in which an equivalent sound speed value is computed for the inhomogeneous path and used in the beamforming to reconstruct the B-mode images. Using an equivalent sound speed could improve the quality of focusing in the presence of a fatty tissue aberrator such as in abdominal or breast imaging ($c_{\text{fatty}} \approx 1452 \text{ m/sec}$ [6]); However, it cannot be employed for transcranial cases due to the large sound speed discrepancy ($c_{\text{bone}} \approx 2950 \text{ m/sec}$) in the medium.

In addition to the constant sound speed assumption the conventional beamforming technique, Eq. (4-4), uses straight ray approximation to calculate the time delay sets. These assumptions introduce significant errors to the time delay calculations and result in defocusing the beams, as the acoustic rays are significantly refracted at the skull bone interfaces.

The idea of the present study is to exploit virtual acoustic sources embedded in the desired foci in the brain tissue as beacons. This provides the opportunity for non-invasive
time reversal focusing by eliminating the need of using an actual hydrophone in the brain tissue which is the basis of time reversal mirror techniques [7]. The radiated waves from the virtual sources are numerically propagated through the heterogeneous medium using finite difference numerical modeling and recorded by the active receiving elements at the array transducer surface. The phase shifts induced by the skull bone can be estimated from the recorded signals and be compensated by introducing the delays to the beamformer in the transmission and reception modes of imaging.

The most accurate way to estimate the distortions caused by the skull is to simulate the full-wave propagation equation for the heterogeneous medium. However, solving the full-wave equation is computationally extremely expensive for such a multi-dimensional problem as discretization of 5-20 nodes per wavelength is required. Simulation of the full-wave equation for the heterogeneous absorbing medium of skull-brain was presented in the seminal work of Aubry et al. [8]. In that study it was reported that 20-hour computational time is required for 3-D simulation of ultrasonic wave for a 70 mm × 10 mm ×30 mm volume at a 1.5 MHz central frequency with 500 MHz computer. This computational cost makes the full-wave equation-based method impractical for transcranial imaging applications, although it can be reasonable for high intensity focused ultrasound (HIFU) therapy applications. Born and Rytov approximations can be used to somewhat alleviate the computational cost, as they are commonly used in ultrasound computer tomography [9]–[11]. They are first-order scattering approximations and could be applied when the multiple reflections can be omitted.

Shooting and bending methods of ray tracing could be potentially used for the challenging problem in hand. These methods are well established in other areas of
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sciences including seismology, ocean tomography, and atmospheric physics [12]–[15].

In the bending method of ray tracing the initial arbitrary path joining the acoustic source and the receiver is updated through an iterative procedure until it satisfies all boundary conditions based on Fermat’s principle. In a recent work the iterative ray tracing method was adopted for the transcranial ultrasound problem by Shapoori et al. in 2015 [16], where the time shifts induced by the skull were estimated based on the new ray paths and were used for transcranial focus reconstruction.

Shooting methods formulate the first order ray differential equations given the initial ray path and the source location, and subsequently ray trajectories are estimated by solving these differential equations. Ray tracing techniques are computationally more efficient than full-wave modeling approach as they neglect the diffraction and only take into account the direction and phase of the propagating wave. However, when a large number of focal points (virtual sources) and active transducer elements (receivers) are involved in the modeling or when the medium is 3D ray tracing converges slowly and becomes inefficient. Furthermore, in a complicated medium they might fail to converge on true two-point ray paths as they are easily trapped into local minima.

Since refraction is the dominant cause of beam distortion in transcranial ultrasound, rather than other physical mechanisms such as scattering, and is the only one that can be compensated through the beamforming this study investigates tracking the wave fronts through the skull-brain medium based on the bent rays. For this purpose, the medium is modeled by a gridded sound speed field in which the boundaries are determined from the estimated profiles of the skull bone presented in Chapter 3. The arrival times at each grid point are estimated by using a highly accurate finite difference scheme.
4.3 Finite difference modeling

4.3.1 Wave propagation

To be able to estimate the arrival times at each receiving element it is necessary to track the wave propagation from the virtual sources to the receivers. To be able to accurately model the refraction effects of the skull a nonlinear ray tracing technique is implemented that does not have the above-mentioned limitations of conventional ray tracing methods.

The acoustic wave propagation equation in a three-dimensional heterogeneous medium may be stated as

\[ \nabla^2 p - \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} = 0 \]  \hspace{1cm} (4-5)

where \( p \) stands for the pressure of the acoustic wave and \( c \) represents the speed of sound in the medium and \( \nabla^2 \) is the Laplace operator. By separation of variables a harmonic solution with amplitude function of \( A \) and angular frequency of \( \omega \) can be assumed as

\[ p(r, t, k) = A\exp(\pm ikr) \]  \hspace{1cm} (4-6)

where \( k = \omega/c \) is the wave number and \( r \) is the distance. The time of flight (TOF) of the wave traveling from the source to the current coordinate can be expressed as \( T = kr/\omega \).

The surfaces with the constant phases \( \omega T \) are defined as wave fronts. By substituting Eq. (4-6) into Eq. (4-5) and taking the real part, the wave equation can be written as

\[ |\nabla T|^2 - \frac{\nabla^2 A}{A\omega^2} = \frac{1}{c^2} \]  \hspace{1cm} (4-7)
The high frequency approximation is then applied where the normalized Laplacian of the amplitude is assumed negligible compared to the angular frequency, \( \frac{\nabla^2 A}{A} \ll \omega^2 \), simplifying the equation to

\[
|\nabla T|^2 = \frac{1}{c^2}
\]  

(4-8)

This is a first order nonlinear partial differential equation (PDE) known as Eikonal equation. Eikonal is a particular class of Hamilton-Jacobi equation, which is widely used in seismology and computer vision applications [17], [18]. Based on this equation, the magnitude of the arrival time gradient at each point on the propagation path is equal to the inverse of the speed of sound value at that point.

In general, the Eikonal equation describes the kinematic propagation of high frequency waves. Due to the high frequency assumption in the model the detectability is limited to the half of the wavelength (0.5\( \lambda \)) and so the length of the reflectors should be equal or bigger than that value. Considering the transducer used in this study with 2 MHz center frequency and the soft tissue with \( c \approx 1540 \text{ m/sec} \) as the medium half of wavelength is a small value, 0.375 mm, and so the assumption is valid for the transcranial ultrasound application as it will be shown through the experiments in this study.

By solving the Eikonal equation the travel times from each emitter to any point on the defined grid system are estimated, given the gridded sound speed field. Various finite difference numerical schemes have been implemented to solve this equation to track the evolution of the front in different fields of studies, including fast sweeping method (FSM), and fast marching method (FMM) [17], [19]–[23]. Combining unconditional stability with fast computation makes the FMM an attractive technique that is more efficient than
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the other schemes. FMM is a grid-based numerical technique that can track a monotonically advancing wave front and update the points on the front using upwind entropy satisfying finite difference approximations to the gradient conditions. The FMM computes the arrival time at each point based on only those neighbor points that have smaller arrival times.

Through the initial numerical experiments of this study it was found that the estimated arrival times by the FMM are not very accurate, especially along the diagonal directions. This could be related to the irregular shape and random curvatures of the inner skull surface, making the propagation medium complex for ray tracing. In this study, a multi-stencil fast marching (MSFM) method, originally derived by Hassouna [24], is employed that unlike the FMM can take into account the information provided by the diagonal points around each grid point.

4.3.2 Tracking of wave fronts evolution

Entropy satisfying viscosity weak solutions may be obtained by applying the upwind gradient operators to the Eikonal equation in a fashion that considers the wave front propagation. The grid points lying downwind of the wave front are updated based on the arrival times of the neighboring points in the upwind side. The upwind scheme for the 2-D case may be expressed as

\[ \max (D_{ij}^{-x} T, -D_{ij}^{+x} T, 0)^2 + \max (D_{ij}^{-y} T, -D_{ij}^{+y} T, 0)^2 = \frac{1}{c^2(x)} \] (4-9)

where \( T \) is the arrival time and \( D_{ij}^{-x} \) and \( D_{ij}^{+x} \) are standard backward and forward finite difference schemes, and \( c(x) \) is the propagation speed at the point \( x \). Successful
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implementation of Eq. (4-9) requires separation of the grid points with known arrival times from the unknown ones so that the order of updating points be consistent with the propagation direction. To achieve this, the MSFM employs a Narrow-band in which the grid points have trial values. The algorithm begins with taking all boundary points, the sources, as Frozen. The adjacent grid points connected to the sources are then put into the Narrow band. As the wave front reaches a point on this band the arrival time is computed by MSFM and among the narrow-band points the one with the minimum arrival time is selected. This point is tagged as Frozen and its adjacent points are put into the narrow-band. The wave front expands over the gridded field and the arrival times are computed for any grid points. The output is a time of flight (TOF) matrix for every source, representing travel times from that single source to the grid points. For instance, the number of active transmitting elements of the transducer was 32 in this study; therefore, 32 TOF matrixes were computed for the beamforming purpose.

The concept of upwind finite difference scheme is illustrated in Figure 4.2; the Frozen grid points have known arrival time values, the Narrow-band points have trial values which can be changed later, and the Far points have no values computed.

By applying two stencils for a 2-D case all adjacent grid points of a point $x$ can be covered. The first type stencil, $S_1$, is parallel to the original coordinate system, as presented in Figure 4.3 (a). The second type stencil, $S_2$, is aligned with the diagonal adjacent points, as shown in Figure 4.3 (b). Both stencils are centered at the current point $x$. The first order finite difference approximation of arrival time, $T(x)$, at the point $x$ for the stencil $S_1$ can be obtained by solving
Figure 4.2 Upwind wave front evolution scheme; Given the location of the source indicated by a star, the horizontal, vertical and diagonal adjacent points to the grid points with known arrival times are first put into a narrow-band. The arrival times is then computed using MSFM and the algorithm marches toward the far point till the arrival times for the entire gridded field is computed.

Figure 4.3 (a) The stencil $S_1$, parallel to the original coordinate axis, (b) the stencil, $S_2$, aligned with the diagonal points.
where \( T_1 \) and \( T_2 \) are the minimum arrival times at the adjacent points as follow:

\[
\begin{align*}
T_1 &= \min(T_{i-1,j}, T_{i+1,j}) \\
T_2 &= \min(T_{i,j-1}, T_{i,j+1})
\end{align*}
\]  

(4-11)

Here the grid spacing along both directions are considered equal, \( \Delta = \Delta_x = \Delta_y \). For higher accuracy in computation of arrival times using MSFM a second order finite difference approximation can be applied. For the stencil \( S_1 \) this can be obtained as [24]

\[
\sum_{\varphi=1}^{2} \max \left[ \frac{T(x) - T_{\varphi}}{\Delta}, 0 \right]^2 = \frac{1}{c^2(x)}
\]  

(4-12)

where \( T_1 \) and \( T_2 \) are:

\[
\begin{align*}
T_1 &= \min \left( \frac{4T_{i-1,j} - T_{i-2,j} + 4T_{i+1,j} - T_{i+2,j}}{3}, \frac{4T_{i+1,j} - T_{i-2,j} + 4T_{i,j+1} - T_{i,j+2}}{3} \right) \\
T_2 &= \min \left( \frac{4T_{i,j-1} - T_{i-2,j} + 4T_{i,j+1} - T_{i,j+2}}{3}, \frac{4T_{i,j-1} - T_{i,j-2} + 4T_{i,j+1} - T_{i,j+2}}{3} \right)
\end{align*}
\]  

(4-13)

The second order approximation is used only when the upwind arrival times are available. If the casualty does not allow using that order, the algorithm reverts to the first order scheme. For instance, if \( T_{i-1,j} \) and \( T_{i-2,j} \) are both available and \( T_{i-1,j} > T_{i-2,j} \) a second order approximation is permitted, while if \( T_{i-1,j} < T_{i-2,j} \) the first order gradient is taken into account.

For the stencil \( S_2 \) the directional derivative is taken along the diagonal, and the first and second order approximations are respectively obtained by solving [24]:

\[
\sum_{\varphi=1}^{2} \max \left[ \frac{T(x) - T_{\varphi}}{\Delta}, 0 \right]^2 = \frac{1}{c^2(x)}
\]  

(4-10)
The computed arrival time $T(x)$ is a trial value and should be checked to see if it satisfies the upwind condition. The computed value is accepted and tagged as frozen if it is larger than the arrival times of the adjacent points contributed to the computation.

4.4 Non-invasive time reversal focusing

In order to estimate the arrival times of the wave fronts on the transducer aperture the knowledge of the skull bone boundaries is crucial and needs to be determined beforehand. In the proposed method, a B-scan of the skull bone at the area of interest is captured by using the same interrogating transducer. To receive better reflections from the skull interfaces and consequently to acquire a B-scan with higher SNR seven elements of the transducer are set to contribute to the transmit beamforming at each time, focusing the ultrasound beams at 12 mm depth, beyond the skull bone thickness. The same elements are set to be active for the reception mode of the beamforming. This aperture is stepped across the entire transducer with a single element pace. This results in 128 RF traces sampled at 0.17 mm spacing on the transducer aperture. A B-scan image of the skull bone phantom is presented in Figure 4.4.

Subsequently, by applying the proposed skull profiles estimation procedure, presented in detail in Chapter 3 of this study, the accurate inner and outer profiles of the skull bone

\[
\sum_{\theta=1}^{2} \max \left[ \frac{T(x) - T_\theta}{\sqrt{2} \Delta}, 0 \right]^2 = \frac{1}{c^2(x)} \tag{4-14}
\]

\[
\sum_{\theta=1}^{2} \max \left[ \frac{3(T(x) - T_\theta)}{2 \sqrt{2} \Delta}, 0 \right]^2 = \frac{1}{c^2(x)} \tag{4-15}
\]
are extracted from the ultrasound image. The acquired profiles are then automatically fed to the code for time delay computation.

**Figure 4.4 A B-scan of the skull bone phantom acquired by a 1D transducer.**

The phase aberration induced by the skull bone is then compensated through beamforming using a time reversal technique. The theory of the time reversal describes that if the emitted waves from a point-like source is collected at the receiver transducer, time-reversed and then re-emitted the point source can be reconstructed. Taking advantage of numerical simulation, virtual acoustic sources are placed at the desired focal points and the emitted wave fronts are numerically propagated through the medium. The Multi-stencil fast marching (MSFM) algorithm estimates for each grid point the time at which the propagating wave radiated from a specific virtual source has traversed it. This computation produces $N$ time of flight (TOF) matrixes, where $N$ is the number of emitters. It is worth noting that travel time from a particular emitter to a receiver will be equal if the positions of the emitter and receiver are exchanged. Hence, to keep the computational costs low in the finite difference modeling the number of virtual sources are selected.
between the number of focal points and the number of active transducer element, whichever is the smaller. For instance, if \( N \) active elements participate in focusing the ultrasound beams on \( M \) focal points where \( N > M \), \( M \) sources are embedded in the focal points locations and subsequently \( M \) time of flight matrixes are computed.

Figure 4.5 presents the computed TOFs of the wave fronts radiated from the first (a), middle (b), and the last (c) elements of the active aperture of a one-dimensional transducer, and propagated through a three-layered soft tissue/skull bone/soft tissue medium. The gridded velocity field contains 2900 by 685 grid points. The boundaries of the skull bone phantom are obtained from the acquired B-scan, presented in Figure 4.4, using the modified SAGE algorithm and are shown in the gridded field by solid lines.

For a better visual perception, the computed TOF for the case of first element being the source is plotted using contours in Figure 4.6, where the time difference between isolines is 0.35 microseconds. The effect of refraction on the skull bone interfaces can be easily observed in this figure.

The location of the transducer elements in the finite difference gridded field is of great importance during time delay computation. It is crucial to accurately place the transducer on the grid points with the exact coordinates as in the experiment, since a small deviation from the actual transducer position would introduce errors in all TOF computations. To avoid such errors, the grid spacing along \( x \) and \( y \) directions are selected to be an exact fraction of the transducer element pitch (in this study, it is one tenth of the element pitch).
Figure 4.5 Examples for the computed time of flight (TOF) of the wave fronts propagating through the heterogeneous medium, where the source is (a) the first \((n=1)\), (b) the middle \((n=32)\), and (c) the last \((n=64)\) active elements of a 128-element transducer.

Once the times of flight between any transducer elements and focal points are computed they are time-reversed and shifted to produce the coherent beamforming time delays. The element with the biggest calculated TOF is excited with no delay in the beamformer and the element with the smallest TOF is excited the last, making the waves emitted from the all active elements arrive at the focal point, coincidently.

The computed TOFs, i.e. the arrival times, using the proposed method for focusing the ultrasound beams at 60 different focal points are presented in Figure 4.7 (a). The focal points lie at the range of 80 mm with the steering angles from -20 to +20 degrees. The beamforming time delay set calculated from the arrival times is shown in Figure (b).
Figure 4.6 Representation of the computed TOF using contours with 0.35 microsec time difference between isolines. The acoustic source is shown by a diamond and the skull bone profiles are depicted with solid black lines.

To show the significant influence of inner skull profile curvature on the beam refraction and consequently on the arrival times, a planar skull model is investigated in Figures (c) and (d) in which the thickness of skull bone in contact with the transducer is considered constant similar to the recent study [25]. The computed arrival times for planar skull profiles having an equivalent thickness of 7.78 mm, the average of the actual skull thicknesses, are plotted in Figure 4.7 (c) and its corresponding time delay set is presented in Figure (d). The TOF and the time delay set obtained based on the planar skull model are superimposed with the ones obtained based on the actual skull bone phantom profile for comparison in this figure. Significant time differences at a glance are observed indicating the fact that the quality of focus is expected to improve when the geometry of inner profile is taken into account in beamforming time delay computation.
Figure 4.7 Time of flight (a) and time delay (b) patterns for adaptive focusing of ultrasound through the skull bone phantom using a linear array with 64 active elements. The profiles of the skull phantom are extracted from the pre B-scan image and fed into the code for adaptive phase compensation in (a) and (b). A planar skull model with the equivalent thickness of 7.78 mm is assumed in the time delay computation in (c) and (d).

4.5 Numerical and experimental verification and discussion

4.5.1 Simulation

To verify the proposed non-invasive adaptive focusing method, numerical modeling was employed to simulate the ultrasound wave propagation through skull/brain tissues.
The simulation was done by using a k-space pseudospectral method proposed by Treeby for modeling of nonlinear ultrasound propagation through tissue realistic media [26]. The governing equations of this method were derived from the momentum and mass conversion equations under the assumption that the effect of heterogeneities on the ultrasound field is considered as second order, and any higher order heterogeneity terms are neglected. In this method the nonlinear equation for heterogeneous media with power law absorption is stated as [26]

\[
\nabla^2 p - \frac{1}{c_0^2} \frac{\partial^2 p}{\partial t^2} - \frac{1}{\rho_0} \nabla \rho_0 \cdot \nabla p + \frac{\beta}{\rho_0 c_0^4} \frac{\partial^2 p^2}{\partial t^2} - L \nabla^2 p = 0
\]

which is a modified form of the Westervelt equation. In this equation \( p \) is the acoustic pressure, \( \rho_0 \) is the ambient density and \( \beta \) is the coefficient of nonlinearity. The term \( L \) denotes a general loss operator and can be related to the absorption and dispersion proportionality coefficients, \( \tau \) and \( \eta \), as follow

\[
L = \tau \frac{\partial}{\partial t} (-\nabla^2)^{y/2-1} + \eta (-\nabla^2)^{(y+1)/2-1}
\]

where \( \tau = -2\alpha_0 c_0^{y-1} \) and \( \eta = -2\alpha_0 c_0^y \tan (\pi y/2) \), \( \alpha_0 \) is the power law prefactor and \( y \) is the power law exponent. As opposed to standard finite difference methods in which the spatial gradients are calculated based on the adjacent grid point values, the spectral method computes the spatial gradients globally by taking the fast Fourier transform (FFT) across the whole domain. The finite difference computation of the temporal gradients produces unwanted numerical dispersion, which is reduced by the k-space operator. In an iterative procedure the discrete nonlinear equations, derived from Eq. 4-16, are solved using a time step that is conditioned by the Courant–Friedrichs–Lewy (CFL) number.
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The details about discretizing the coupled governing equation by the k-space pseudospectral method are avoided here as they can be found in [26], [27].

In the simulations presented here the ultrasound beam patterns emitted from a one-dimensional phase array probe with 128 rectangular elements and 0.17 mm element pitch were investigated. The properties of the transducer in these simulations were the same as the one used in the experiment. The 64 elements positioned around the transducer center were active in the beamforming.

The grid point spacing was set to be 0.17 mm. This corresponds to 8.82 grid points per wavelength in the skull bone and 4.41 grid points per wavelength in the brain tissue for a center frequency of 2 MHz, given the speed of sound in the skull bone and brain. The size of the computational grid field varies proportional to the desired depth; For instance, the computational grid size for a 120 mm depth was $705 \times 864 \times 10 = 6,091,200$. The memory used to model ultrasound waves for such a grid size was 1.2 GB. For absorbing ultrasound waves at the boundaries of the computational domain a perfectly match layer (PML) of $20 \times 10 \times 10$ points was defined in the grid system. Each transducer element was modeled by a single grid point in the azimuth direction and ten grid points in the elevation direction.

The transducer elements were excited by a Gaussian modulated sinusoidal pulse with 2 MHz center frequency and digitized at the sampling frequency of 50 MHz. Each grid point of the transducer elements was introduced with a sound pressure of 1 MPa. The Courant number (CFL) was set to 0.25 that yields the algorithm time step of 14.2 Nanosec, considering the maximum speed of sound in the medium as 3000 m/sec ($CFL = c_{max}\Delta t/\Delta x$).
The propagation medium was modeled as inhomogeneous comprising three layers of soft tissue (skin layer with 2-3 mm thickness), skull bone, and soft tissue (brain). For the soft tissue the properties were set to those of brain tissue, where the speed of sound and the density are 1540 m/sec and 1030 kg/m$^3$, respectively. The skull bone was modeled as homogeneous medium with equivalent values of 3,000 m/sec for the speed of sound and 2,070 kg/m$^3$ for the density. It is worth noting that the density of skull bone varies significantly in different skull zones, depending on the thickness of the trabecular layer, and the speed of sound value changes accordingly. The coefficient of nonlinearity, $\beta$, describes the relative contribution of finite amplitude to the speed of sound and was fixed at 4 (B/A=6).

The attenuation coefficients, $\alpha_0$, for the soft tissue and skull bone were set to 0.8 and 6 dB.MHz$^y$/cm and the power law exponent, $y$, was fixed at 1.5 giving the attenuations of 2.12 dB/cm in the soft tissue and 17 dB/cm in the skull bone at 2 MHz frequency based on the power law absorption model ($\alpha = \alpha_0 \omega^y$ [28]).

In the first two simulations presented here, Figures 4.8 and 4.9, the boundaries of the skull layer were simulated in MATLAB and used in the finite difference wave propagation modeling. The Figures 4.8 and 4.9 (a) present the ultrasound beam patterns propagated through the homogenous soft tissue medium (the control case) with the desired focal points of (25 mm, 0$^\circ$) and (25 mm, +20$^\circ$), respectively. The horizontal axis represents the lateral position and the vertical axis represents the range. The plane of interest is covered using a binary sensor mask and the maximum of recorded pressure at each sensor position is selected to produce the beam profile map.
In the presence of the simulated skull layer the ultrasound beams were severely deviated from the desired focal points, indicated by a white cross, as shown in the figures (b). A new time delay pattern for every focal point was estimated using the proposed method and the delays were introduced to the transducer elements for adaptive beamforming. The aberration-corrected beam patterns, presented in figures 4.8 and 4.9 (c), show that the defocusing effect of the skull was compensated by using the corrected time delays and the beams were brought back to the desired focal points. For a better comparison the beam profiles at the focal plane for the no skull (control), aberrated and phase corrected cases are depicted in Figures (d). The acoustic pressure of the wave is severely reduced after travelling through the skull due to the reflection in the interfaces, attenuation and scattering in skull bone, as shown in Figure 4.10. Hence, for better assessments, the beam profile amplitudes of the no skull cases were scaled down to the maximum beam profile amplitudes of the phase corrected case in Figures 4.8 and 4.9 (d). The focal displacement errors for the focusing without steering and for the focusing with $+20^\circ$ steering simulations were 3.24 mm and 5.45 mm, respectively. After phase aberration compensation using the proposed method these errors were significantly reduced to 0.51 mm and 0.34 mm, respectively. Also, the peak acoustic pressure at the desired focal point increased from 40 kPa at the aberrated beam profile to 45 kPa at the corrected one.

Further simulations were carried out to assess the adaptive focusing through a custom-designed skull bone phantom fabricated in the lab. For this purpose, a B-scan of the skull phantom was captured and consequently the profiles of the skull phantom were estimated with high accuracy using the modified SAGE method, proposed in Chapter 3. The
estimated profiles were automatically fed into the phase aberration compensation algorithm to produce a new time delay set. The results of focusing at a near focal point (20 mm, -15°) and a reasonably far point (100 mm, -20°) are presented in Figures 4.11 and 12. At the near point, the focal displacement error of the aberrated beam was 4.43 mm, while this error was entirely eliminated for the corrected beam. At the far point, the focal displacement error of the aberrated beam was as big as 8.35 mm. After the phase aberration compensation this error reduced to 0.33 mm. Furthermore, the peak acoustic pressure at the focal point increased from 26.0 kPa in the aberrated beam to 29.6 kPa in the corrected beam. The summary of focal displacement error induced by the skull bone for four different focal coordinates is presented in Table 4.1.

<table>
<thead>
<tr>
<th>Focal coordinates</th>
<th>Aberrated beam</th>
<th>Corrected beam</th>
</tr>
</thead>
<tbody>
<tr>
<td>(25 mm, 0°)</td>
<td>3.24 mm</td>
<td>0.51 mm</td>
</tr>
<tr>
<td>(25 mm, 20°)</td>
<td>5.45 mm</td>
<td>0.34 mm</td>
</tr>
<tr>
<td>(20 mm, -15°)</td>
<td>4.43 mm</td>
<td>0.00 mm</td>
</tr>
<tr>
<td>(100 mm, -20°)</td>
<td>8.35 mm</td>
<td>0.33 mm</td>
</tr>
</tbody>
</table>
Chapter 4: Adaptive focusing of ultrasound beams through the skull bone

Figure 4.8 Nonlinear beam patterns generated by a 1D array using the k-space method focusing at (25 mm, 0°), (a) homogeneous medium with no skull (control case), (b) with the presence of the simulated skull but without any correction, (c) with the presence of the simulated skull and after phase aberration correction, (d) The beam profiles at the focal plane.
Figure 4.9 Nonlinear beam patterns for focusing at 25 mm and steering at +20°. (a) homogeneous medium with no skull (control case), (b) with the presence of the simulated skull without any correction, (c) with the presence of the simulated skull and after phase aberration correction, (d) The beam profiles at the focal plane.
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Figure 4.10 Comparison of beam patterns before (top) and after (bottom) insertion of the skull bone in front of the transducer. The effects of reflection at the skull interfaces, scattering and attenuation can be observed.
Figure 4.11 Nonlinear beam pattern results for focusing at a point close to the inner skull interface, (20 mm, -15°). The boundaries of the skull bone phantom were extracted and used in the modeling. (a) no skull, (b) aberrated, (c) corrected beam patterns, (d) The beam profiles at the focal plane.
Figure 4.12 Nonlinear beam patterns for focusing at a far point, $(100 \text{ mm}, -20^\circ)$. The boundaries of the skull bone phantom were extracted and used in the modeling. (a) no skull, (b) aberrated, (c) corrected beam patterns, (d) The beam profiles at the focal plane.
4.5.2 Experiments

Several experiments were carried out on a custom-designed skull bone phantom to further evaluate the proposed adaptive focusing method. For these experiments, the algorithms were implemented on an ultrasound advanced-open platform (ULA-OP) connected to a one-dimensional cranial array transducer (PA230-Esaote) with 128 elements operating at 2 MHz central frequency. Each element of the array transducer is 14 mm long in the azimuth direction, 0.1 mm wide in elevation with 0.17 mm pitch.

During the transmission mode 64 independent arbitrary waveforms are generated in TX section of the machine and sent to the linear power amplifier. Using a programmable multiplexer matrix these waveforms are simultaneously mapped to 64 arbitrarily designated elements on the array. For this experiment only the 64 elements symmetrically aligned around the probe center are powered.

The skull bone phantom used in this experiment was composed of two compact layers with a porous layer in the middle and was fabricated in the lab. The phantom has a flat surface on one side and an undulating surface on other side to resemble a skull bone piece with a thickness range of 5.2 mm–10.0 mm. The acoustical properties of the skull bone phantom are in the range of the reported acoustical properties of the real human skull. The speed of sound in this phantom is 2980 m/sec, and the attenuation is 13.2 dB/cm at 2 MHz frequency and the density is 2070 kg/m³.

Measurements of acoustic pressure field were conducted in immersion mode in a tank filled with water in 25°C temperature. It is worth noting that the speed of sound and density values in water are close the ones in the brain tissue \( c_w = 1480 \text{ m/s} \),
\( \rho_w = 1000 \text{ kg/m}^3 \) and \( c_b = 1540 \text{ m/s} \), \( \rho_b = 1030 \text{ kg/m}^3 \) making the water a suitable medium for this experiment. An acoustic hydrophone (Pinducer, Valpey-Fisher) was mounted on a 4D scanner to collect the acoustic pressure field in the elevation plane of the transducer. The hydrophone scanned the area with 0.5 mm step size while its positions were controlled by the computer. At each hydrophone position the recorded signal was sent to the pulser-receiver (Utex) for amplification and the resulting RF signal was digitized and saved in the computer for further processing. Figure 4.13 shows the schematic of the experimental setup.

**Figure 4.13** A schematic of the experimental setup for ultrasound field measurements.
The results of 2D mapping of acoustic pressure fields using the illustrated setup are presented in Figure 4.1. The array elements were excited to focus the ultrasound beam at 35 mm depth with the steering angle of -5°. Minimum beam distortion is expected in this experiment as the beam is close to the normal. For this mapping the hydrophone scanned an area of 20 mm × 42 mm around the desired focal coordinate in the axial-lateral plane. Figure 4.1 (a) shows the measured beam pattern for focusing in water without the presence of the skull phantom. The black cross indicates the intended focal coordinate. Figure 4.1 (b) presents the beam pattern measured after interposing the skull phantom between the array and the focal point. The phantom is positioned in front of the transducer and normal to the transducer axis with 4 mm distance representing the skin layer. The beam patterns presented in Figures (a) and (b) were obtained by using conventional beamforming. Figure 4.1 (c) shows the measured beam profile with the presence of skull when the phase aberration correction was applied. At the first glance it can be observed that the acoustic pressures were attenuated in the aberrated and corrected beams compared to the no skull beam.

For better evaluation the beam profiles at the focal plane are presented in Figure (d). A close inspection of the beam profiles reveals that the beam in presence of the phantom and without any correction is deviated from the focus for 1 mm. The phase aberration compensation brought back the beam to its intended direction with no focal displacement error, as shown in the beam profile plot. To assess the quality of focus the full width at half maximum (FWHM) parameter was calculated along the lateral direction for the no skull, aberrated, and corrected beam profiles. The beam width was 6.75 mm for the no skull beam profile. The aberrated beam profile showed a 130% increase in FWHM
comparing to its corresponding value in the no skull case. The phase aberration compensation alleviated the beam widening effect of the skull phantom where the FWHM value for the corrected beam was only 22% greater than the one for the no skull case.

Figure 4.14 The measured ultrasound beam patterns in water (a), through the skull phantom with conventional beamforming (b), through the skull phantom with phase aberration compensation (c). The black cross indicates the intended focal point. The beam profiles at the focal plane along the lateral direction (d).
Furthermore, the clutter pressure around the main lobe was reduced by approximately 5 dB, as seen in Figure (d).

The experimental results presented here verified the results obtained through the numerical modeling. These results showed the effectiveness of the proposed algorithm in focusing and steering the ultrasound beams through the thick human skull bone for transcranial ultrasound applications.

4.4.3 Comparison and conclusion

The phase aberration induced by the skull barrier is compensated through the Delay-and-sum beamforming process by applying a corrected time delay set, which is obtained based on the estimated time-of-flight (TOF) between each element and the desired focal points. Hence, in this section a setup is configured to evaluate TOF estimation using the presented method in this study against the ones obtained from solving the full-wave propagation equation. To recall, the TOF estimation procedure was based on solving the Eikonal equation in a multi-stencil fast marching (MSFM) framework. Comparing to the full-wave equation Eikonal is a simplified equation by the high frequency approximation, which makes it computationally affordable to solve.

In this testing each element on the active aperture is individually excited to transmit the pulse through the skull barrier. On the other side of the skull barrier the receiving sensor is positioned at the designated focal points to record the propagated pulse.

To model the full-wave propagation through the skull-brain medium a k-space pseudospectral method, recently proposed for transcranial ultrasound focusing [29], was implemented. The k-space method has been proven to be a computationally more
efficient method than the finite difference time-domain technique, which was used by Aubry for time reversal focusing [8].

Numerical modeling of ultrasound waves using k-space, as a reference method, as well as tracking the wave front using MSFM, the proposed method, are repeated for each active element of the array. Here, 64 elements of the array are designated as transmitters. The reception is done at six different focal points behind the barrier. The first set of the foci is laid at 30 mm axial distance ($z = 30$ mm, see Figure 4.1) from the transducer surface with the steering angles of $-20^\circ$, $0^\circ$, and $+20^\circ$. The second set of the foci is laid at 45 mm axial distance with the same steering angles. The corresponding coordinates of these points can be summarized as $(z_i, \theta_i) = \{(30 \text{ mm, } -20^\circ), (30 \text{ mm, } 0^\circ), (30 \text{ mm, } +20^\circ), (45 \text{ mm, } -20^\circ), (45 \text{ mm, } 0^\circ), (45 \text{ mm, } +20^\circ)\}$.

In the k-space method the transducer elements are excited one by one and for each excitement the pulse is recorded for all focal points using a sensor binary mask. To compute the arrival time, i.e. TOF, at each focal point the analytic cross-correlation between each recorded RF echo and a reference echo was calculated. The estimated TOF through the k-space pseudospectral method for six different focal coordinates are depicted in dash lines in Figure 4.15.

The presented MSFM method tracks the advancing of the wave fronts that has been emitted from a single element through the medium. This procedure produces 64 TOF matrixes with the size of the gridded field where each matrix corresponds to an active element on the aperture. Having the coordinates of the focal points the times-of-flight between each element and the foci are obtained. The computed TOF values are plotted in solid line in Figure 4.15.
A visual inspection of the graphs reveals that the computed TOFs by solving the wave fronts using MSFM have a good agreement with TOFs obtained by solving the nonlinear full-wave equation using the k-space method. For quantitative evaluation the mean absolute deviation (MAD) of the TOFs for all six focal points was computed to be 38 ns and the standard deviation was 47 ns. The mean absolute deviations for each point in order were 17 ns, 27 ns, 59 ns, 21 ns, 28 ns, and 57 ns. The outlier with maximum deviation of 79 ns was observed. Considering the pulse duration, 5.57 µs, the mean absolute deviation of all six points is only 0.7% of the pulse duration.

The computational time to calculate the TOF matrices by solving the wave front evolution using the MSFM method for 64 active elements was 10 min and 42 s. This corresponds to a $60 \times 80 \text{ mm}^2$ medium gridded with 0.017 mm intervals. The computation was done by using a desktop computer with 24-core CPU and 30 Gigabytes of RAM. This computational time increased to 10 h and 8 min when using the full-wave k-space method, while the grid interval was chosen ten times courser (0.17 mm). For the same fine grid size, it takes 56 days and 12 h to compute the TOFs using the full-wave method, which makes it practically infeasible for any imaging or therapeutic applications. A close inspection of the graphs for focal points 2 and 5 shows that the full-wave modeling method failed to estimate the TOF accurately and computed the same value for the adjacent elements (see the arrival times for elements 40 to 60) due to its coarse grid size. From this comparison it can be concluded that solving Eikonal equation using a multi-stencil upwind finite difference method can produce comparable results as the nonlinear full-wave modeling of ultrasound. However, thanks to its low computational cost, the MSFM method can track the wave fronts very accurately by choosing fine grid
points without substantially increasing the processing time, while this cannot be done in
full-wave modeling method. It is worth noting that solving the Eikonal provides the phase
of the propagating wave at each grid point without other information; therefore, it can
only be used for phase aberration correction, which is the primary concern in transcranial
ultrasound, and not for amplitude correction.
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Figure 4.15 Estimation of time-of-flights between 64 active elements and 6 different foci in the presence of the skull using MSFM and full-wave k-space methods.
References


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Chapter 4: Adaptive focusing of ultrasound beams through the skull bone


Chapter 5:

**Refraction correction in transcranial phased array imaging**

5.1 Overview

This chapter focuses on the compensation of the distortion effect induced by the skull in the reception mode of phased array imaging. First, the degradation of the imaging system’s point spread function (PSF) is studied through numerical modeling. Then, a new method is proposed for refraction correction of transcranial images.

5.2 Point spread function

To characterize the distortion effects of the skull on transcranial ultrasound images the point spread function (PSF) of the imaging system is modeled. For this purpose, the propagation of ultrasonic waves through the modeled representation of the human head is simulated using a finite difference time domain (FDTD) scheme. The simulation method numerically models the wave propagation from a transducer that has the same characteristics as a commercial diagnostic transducer. To obtain the PSF a point scatterer with 0.128 mm diameter is embedded in the propagation medium at the depth of 10 mm. In order to receive appreciable backscatter from the point target the value of sound speed for the target was selected 30% higher than its surrounding medium.
Chapter 5: Refraction correction in transcranial phased array imaging

A three-dimensional heterogeneous tissue representation model is deployed as a model for the human head. The acoustical properties of the model are presented in Table 5.1. The tissue model is constructed based on the boundaries of the skull bone, which is obtained through a preliminary imaging of the skull layers in linear mode. The procedure of skull profile extraction was presented in detail in Chapter 3.

To simulate a scattering propagation medium points scatterers with random speed of sound values and positions were added to the tissue representation model. The mean variation of the sound speed for the scatterers were 60 m/sec, which is about 4% of the average sound speed value in the soft tissue medium (1540 m/sec).

Table 5.1 Acoustical properties of the tissue representation model.

<table>
<thead>
<tr>
<th></th>
<th>$c$ (m/sec)</th>
<th>$\rho_0$ (kg/m$^3$)</th>
<th>$\alpha_0$ (dB.MHz$^2$/cm)</th>
<th>B/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>1730</td>
<td>1150</td>
<td>0.8</td>
<td>6</td>
</tr>
<tr>
<td>Cortical bone</td>
<td>2600</td>
<td>2070</td>
<td>6.0</td>
<td>6</td>
</tr>
<tr>
<td>Brain</td>
<td>1540</td>
<td>1030</td>
<td>0.8</td>
<td>6</td>
</tr>
</tbody>
</table>

To investigate the degrading effects of the inhomogeneous path the point spread function (PSF) of the imaging system was simulated in different conditions. The system PSF was obtained from a homogenous propagation medium with no random scatterers as a control by using the K-wave [1] demonstrated in the previous chapter. The RF representation of the acquired 2-D PSF is plotted in Figure 5.1 (a).
Figure 5.1 Point spread functions (PSFs) of the imaging system, (a) homogeneous medium, (b) heterogeneous tissue representation model with random scatterers, (c) heterogeneous with phase aberration compensation.
Propagation of ultrasound through the inhomogeneous composite of the tissue structure can cause several degradation effects on the PSF, which leads to severe reduction of spatial resolution in the beamformed images. The phase and amplitude aberration induced by the skull is expected to primarily cause PSF degradation in the lateral direction. In the reception mode uncorrected phase errors would result in increasing the length of the received echo and affecting the axial resolution.

Reverberation of the transmitted pulse in each of the tentative three bone tables and then transmitting to a deeper area would lengthen the transmitted pulse. This can be seen as a low amplitude noise tailing the system PSF.

Figure 5.1 (b) presents the system PSF when the scalp/skull/brain model is taken as the propagation medium. Interaction of the ultrasound waves with the scatterers produces speckle patterns, which are seen with random amplitudes in this RF representation. Comparing to the control PSF, the PSF of the heterogeneous medium suffers a substantial amount of degradation, as seen in the figure. The presence of the skull aberrator leads to a significant peak amplitude drop from 6.7 dB to 0.4 dB.

For quantitative evaluation the fundamental image was obtained by removing the carrier signal from the radio frequency signals. Also, the harmonic image was generated by filtering the carrier signal from the RF signals by using a band-pass filter centered at the second harmonic frequency, i.e. 4MHz. The fundamental and harmonic images are displayed at Figure 5.2. From the fundamental PSF the full width at half maximum (FWHM) of the PSF was computed along the lateral direction. The aberrated PSF exhibited an increase of 11% in FWHM along the lateral direction relative to the corresponding value for the control PSF, which would be the main source of lateral
resolution degradation in ultrasound images. In the axial direction and along the maximum peak of the PSF, the length of the pulse has increased by 33% comparing to the control. By comparing the aberrated PSF with the control PSF in Figure 5.2 it can be seen that several clutters have appeared in both fundamental and harmonic aberrated PSF, which can be attributed to the distortion effect of the skull barrier.

The PSF of the imaging system was obtained using the same inhomogeneous medium representation model but the distortion effect of skull barrier was compensated by applying the proposed adaptive phase aberration correction method. Figure 5.1 and 5.2 (c) display the radio frequency, fundamental and harmonic representations of the corresponding PSF. At a glance it is notable that the phase corrected PSF exhibits the same sharpness and axial and lateral width as the control PSF. Compared to the PSF with no correction the phase corrected PSF exhibited a 10% reduction in the lateral width and 33% reduction in the pulse length. Also, an increase of 0.43 dB in the peak amplitude of the phase corrected PSF was observed.

Due to the refraction effect of the barrier and also the gross sound speed error the point target in the aberrated image appeared with 0.76 mm displacement error in lateral direction and 0.94 mm displacement error toward the transducer aperture. The phase correction procedure brought back the point target to its actual location with no displacement error.
Chapter 5: Refraction correction in transcranial phased array imaging

5.3 Phased array imaging

Ultrasound phased array imaging, a widely used modality for imaging the deep tissues, is obtained by focusing and steering the beams along multiple directions in transmission and reception modes. Electronic focusing and steering can be accomplished through a Delay-and-sum beamforming, which works based on the time-of-flight computations.
from a particular point to the transducer aperture. For each point the signals are appropriately delayed and summed to focus at that point in both transmission and reception modes.

In commercial ultrasound machines the access to the pre-beamformed data is limited and the beamforming is done based on a constant speed of sound value for the propagation medium. Therefore, echoes coming from a coherent source and traveling through the heterogeneous brain/skull bone/ scalp medium are summed out of phase, producing diagnostic images with low contrast and SNR, and poor spatial resolution. It is worth noting that spatial resolution is an index showing the ability of a particular ultrasound system to distinguish closely spaced reflectors, and can be defined in axial, lateral or elevation directions.

Assumption of homogeneous medium with constant sound speed in the beamforming of transcranial imaging introduces significant image degradation. In this study, phase aberration, as the main source of image degradation, is divided into two categories as:

- Underestimation of the sound speed value by pre-assuming the skull as homogeneous soft tissue in the ultrasound beamforming software (1540 m/sec)
- Beam refraction due to the substantial sound speed discrepancy between the bone and the brain tissue

Majority of the phase aberration compensation methods presented in the literature address the first type of aberration induced by the skull and correct the phase shift. However, compensation of the refraction effect requires the geometry of the aberrator to trace the refracted rays. In one of the most recent works, presented by Lindsey [2], the
refraction correction of the skull bone is addressed by iterative tracing of propagation paths based on the Snell law. In this refraction correction procedure, a planar tissue model was used without considering the inner curvature of the skull.

The adaptive phase aberration correction method presented in the current study inherently compensates for both types of aberrations by modeling the wavefronts propagation through a three-layer inhomogeneous tissue model. This model is constructed based on the thickness and geometry of the skull bone that is obtained through a preliminary process at the area of interest.

5.3.1 Dynamic receive beamforming

Real-time receive beamforming of the backscattered echoes is conducted along different paths based on the time-of-flight (TOF) data computed for the interrogated area. Minimum and maximum ranges of receive beamforming can be taken as input to the phase correction code, along with the steering angles and focal coordinates. Similar to the transmission mode time-of-flights computation is done using a second-order finite-difference scheme. The TOFs at a particular grid point \( x, T(x) \), are computed by solving the following differential equations for the first type stencil with parallel elements to the original coordinate axis

\[
\sum_{\phi=1}^{2} \max \left[ \frac{3(T(x) - T_\phi)}{2\Delta}, 0 \right]^2 = \frac{1}{c^2(x)} \quad \text{(5-1)}
\]

and for the second type stencil with elements perpendicular to the coordinate axis

\[
\sum_{\phi=1}^{2} \max \left[ \frac{3(T(x) - T_\phi)}{2\sqrt{2}\Delta}, 0 \right]^2 = \frac{1}{c^2(x)} \quad \text{(5-2)}
\]
where $T_1$ and $T_2$ are the minimum arrival times between the adjacent points along the lateral and axial directions, respectively. Also, $\Delta$ is the grid spacing and $c(x)$ is the speed of sound at that particular grid point.

The computation of time-of-flights over the area of imaging is done only once considering the travel times in the transmission and reception modes are equal. However, an ultrasound phased array system is supposed to capture both close-in reflections in the near field as well as reflections in the far field. The implementation challenge for receive beamforming is to dynamically change time delay patterns of the aperture to move the focal zone from the near field to the far field in every scanning. To be able to do so, the propagation paths of acoustic rays between the transducer aperture and the focal points are required to be determined. Unlike the conventional ray tracing techniques, the proposed time-of-flight estimation method computes the arrival times at which the waves transverse the grid point without determining the ray path. Hence, in this section a novel method is implemented to trace the propagation paths, i.e. the scan lines, from the focal points to the center of the active aperture. The idea is to take advantage of the gradient properties of the time-of-flight matrix computed for the central element of the aperture. The algorithm starts from a focal point and put 5 by 5 neighboring grid points in a narrow band. The grid point with a maximum absolute time difference and a negative sign is taken and saved as a point on the scan line. The five by five gradients kernel is displayed in Figure 5.3 where $\Delta T(i,j)$ is the time-difference of flight between the adjacent grid point $(i,j)$ and central grid point of the kernel. The gradient kernel is then moved to the new point and the procedure is repeated until scan line reaches to the source.
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<table>
<thead>
<tr>
<th>$\Delta T(i,j)/\sqrt{8}$</th>
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Figure 5.3 A $5\times5$ moving gradient kernel for tracing the scan lines from the foci to the acoustic source.

Figure 5.4 Tracking the scan lines (ray) from the focal points to the central element of the active aperture.

The process of tracking the scan line from the focal point to the central element is repeated for all focal points that are predetermined by the focal depth and steering angles during phased array imaging. Figure 5.4 presents the scan lines for 23 times transmitting through the skull bone phantom. The scan lines are superimposed with the time-of-flight.
image and the boundaries of the skull phantom are depicted in solid black lines. Starting from the focal points all of the lines successfully reached to the exact coordinate of the acoustic source. The tracked lines explain the beam refraction at the first and second interfaces of the skull bones, and the incident and transmitted angles have a good agreement with the Snell’s law of refraction.

5.4 Results and discussion

5.4.1 Refraction correction

This section presents the results for refraction correction of phased array images in transcranial ultrasound imaging. A 2-D skull bone phantom with no porosity layer, resembling cortical bone, was used where the inner and outer profiles of the phantom were obtained by applying the modified space-alternating generalized expectation maximization (SAGE) algorithm to the B-scan image of the phantom. The acquired information about the position and thickness of the skull bone is then fed into the adaptive phase aberration compensation algorithm and a new time delay pattern, called Tx file, is generated for each transmission time. The transducer scans the area of interest by multiple transmissions, each time with different steering angles. The generated Tx file is read by the transmit beamformer and the delays are introduced to the excitation pulses for adaptive focusing and steering through the aberrator. The acoustical properties of the tissue representation model used here are presented in Table 5.1, similar to the ones used in section 5.2. For the skull bone without porosity layer, the speed of sound and density were considered 2600 m/sec and 2070 kg/m$^3$. The attenuation prefactor in the bone was 6.0 (dB. MHz$^2$/cm) which imposes 17 dB/cm of attenuation at 2 MHz frequency.
To assess the performance of the adaptive refraction correction algorithm in enhancing ultrasound image quality a numerical wire phantom was employed. Distinguishability of the closely-spaced wires determines the axial and lateral resolutions of the acquired images. The wires have 0.5 mm diameter with 8050 kg/m$^3$ density and sound speed of 1790 m/sec. The wires are laid along the transducer elevation, perpendicular to the imaging plane, at four different rows with 18 mm, 23 mm, 25.5 mm and 28 mm distance from the transducer aperture. Figure 5.6 (a) displays the positions of the wires and the skull bone phantom in a cross-sectional image.

The transducer elements were excited by four-cycle tone burst signals with 2 MHz frequency and digitized at the sampling frequency of 50 MHz. The transducer was a one-dimensional array with 128 elements and 0.17 mm element pitch. The probe scanned the area of interest by multiple focusing and steering with 2° step size. During transmission and reception only the 32 elements positioned around the transducer center were active.

In order to achieve successful implementation of a dynamic receive beamforming, the propagation paths of the ultrasonic rays were tracked from all intended foci to the aperture using the proposed method. Having the ray path coherent beamforming time delays were computed by taking those time-of-flights that were laid on the ray paths and then time-reversing and subsequently shifting them by an offset. The generated time delays are saved in an Rx file and fed into the beamforming for dynamic receive focusing.

The beamformed RF data is then required to go through several processing steps before display. Figure 5.5 shows the block diagram of these processing steps. A time gain compensation (TGC) is applied to the data to compensate for the attenuation (absorption
and scattering) of the propagation medium. The correction factor is exponentially increased by depth \( r \), \( TGC = \exp (\mu f_0 (100r)) \), to amplify the backscattered echoes from the deep tissue. Here, the TGC prefactor \( \mu \) was set as 0.4 (dB/(MHz.cm)).

To suppress the noise outside of the bandwidth the recorded signals are then filtered using a low pass FIR Gaussian filter centered at the transducer center frequency. A demodulation filter is then applied on the RF signals to remove the carrier signal and generate the IQ data. Due to the large amplitude variations of ultrasound data, the presence of a few high intensity pixels overshadows many important tissue structures. Hence the data is log-compressed to reduce the dynamic range. The compression rate used for the images presented here was 3. The log-compressed envelope data are then interpolated and remapped into a display grid generating a geometrically correct sector image through the scan conversion.

![A block diagram of processing steps on the raw RF data.](image)

Figure 5.6 (b) displays a processed sector image of the closely-spaced wires obtained through the conventional beamforming, with no phase correction. In this case, the transducer focused the beam at 23 mm depth, which is approximately the center of the
area of interest, and the dynamic range in the reception mode was between 5 to 30 mm. In the second case, the time delays generated by the adaptive phase aberration compensation code was introduced to the beamformer in both transmission and reception modes. The image was reconstructed for a fixed focus at 23 mm through the receive beamforming, due to the unknown propagation paths of rays. The phase corrected sector image is displayed in Figure 5.6 (c). For the third case, the adaptive phase aberration compensation was applied and the image was reconstructed by dynamic receive beamforming along the estimated propagation paths of rays for each scan line. The reconstructed image is displayed in Figure 5.6 (d). In all these images, the inner boundary of the skull and also the shadow of the inner boundary caused by the reverberation are visible.

For a better visual assessment, the acquired phased array images were cropped at the region of interest and displayed at Figure 5.7. At the first glance, it is noticeable that the locations of the wires in the original image with no correction (a) have substantial displacement error both in depth and lateral directions. The average displacement errors of the wires are about 3 mm in axial and 1 mm in lateral directions. This displacement is attributed to underestimation of sound speed in the bone, by assuming the medium is a homogenous soft tissue with 1540 m/sec sound speed, which causes focal displacement and also makes the objects appear closer to the transducer aperture in the image (first type aberration). The phased array image obtained based on the corrected phase presents the wires in their original positions, Figure (b). Furthermore, the phase corrected image exhibits some improvements in the contrast and lateral resolution, compared with the original image. Employing dynamic focusing along the tracked ray paths significantly
improves the contrast and resolution as it is seen in Figure (c). To quantitatively assess the performance of the proposed procedure two metrics were used. These metrics are number of detected wires and contrast to noise ratio (CNR) defined as:

\[
CNR = \frac{\langle S_{wire} \rangle - \langle S_{speckle} \rangle}{\sqrt{\sigma_{speckle}^2}} \tag{5-3}
\]

where \( \langle S_{wire} \rangle \) and \( \langle S_{speckle} \rangle \) respectively are the mean of the signal amplitudes at all thirteen wires and an adjacent area of speckle, and \( \sigma_{speckle}^2 \) denotes for the variance of speckle. The average numbers of detected wires, judged by two independent observers, were 8 in the original image (no correction), 11 in the phase corrected with a fixed focus, and 13 out of 13 in the phase corrected image with dynamic focusing. The CNR estimated for all objects that were detected by the observers was 14.15 in the aberrated image and 19.77 in the dynamically phase corrected image. The results show the proposed algorithm improves the image contrast by 39.7%.
Figure 5.6 Refraction correction in transcranial phased array imaging.
5.4.2 Head phantom with inclusions

To further investigate the refraction and phase correction in transcranial images a head phantom was used. The phantom is constructed from a 2D skull bone phantom with a porosity layer and a brain mimicking gel with similar acoustical properties as human brain. Several inclusions with random positions have been embedded in the gel mimicking the penetrating head injuries where objects such as bullet, shrapnel or bone fragment are trapped in the brain tissue.

The ultrasound advanced-open platform (ULA-OP) machine empowered 64 elements of the 1D transducer with 128 elements operating at 2 MHz central frequency.

Figure 5.7 Log-envelope images of the 13 closely-spaced wires after conventional beamforming (original) (a), phase correction in both transmission and reception for a fixed focus (f=23 mm) (b), phase correction with dynamic receive beamforming (the proposed method) (c).
To acquire a sector image of the phantom the array transducer scanned the area with 0.5-degree step size. This step size has been chosen to meet the Nyquist criteria in lateral direction. The field of view (FOV) is set from -31.75 to 31.75 degrees to avoid critical angle in the bone interfaces. In each transmission the aperture focused the beam at 50 mm range. The backscattered echoes were beamformed for the 5mm to 80mm dynamic range with 50 mm focal depth. A dynamic apodization was applied to the receiving elements using a Hamming window. Figure 5.9 (a) shows the measured phased array image of the phantom using the conventional beamforming, i.e. the machine’s default. Without moving the transducer on the bone phantom new time delay files, Tx and Rx, were generated for the bone geometry at the current location and fed into the transmit and receive beamforming. The output is the refraction-corrected image, presented in Figure (b). The positions of the reflectors appeared about 3.3 mm further from the aperture in the corrected image as a result of sound speed correction in the bone phantom. Similar to the previous section the number of detected objects and the contrast to noise ratio (CNR) were used as metrics for quantitative evaluation. From the original image, two objects were detected with certainty, while the number of detected objects increased to 4 in the corrected image.
Figure 5.9 Log-envelope phased array images of the head phantom, (a) original image, (b) refraction-corrected image.
Chapter 5: Refraction correction in transcranial phased array imaging

The CNRs calculated for the detected inclusions were 5.62 in the original image and 7.38 in the corrected image, exhibiting 31% enhancement in the image contrast.

5.5 Summary

In this chapter, the challenges in ultrasound phased array imaging through the thick skull bone were investigated. In the first step, the point spread function (PSF) of the imaging system was modeled under different conditions to characterize the distortion effects of the skull barrier on the backscattered signals. For this purpose, a point scatterer was embedded in a heterogeneous tissue representation model and the PSF was modeled for a homogeneous medium, heterogeneous medium, and heterogeneous medium with corrected phase. The results from the fundamental and harmonic PSFs showed the lengthening effect of the aberrator on the PSF. In the second part, a new method was proposed for the refraction correction of transcranial images. The proposed method takes advantage of the gradient properties of the time-of-flight, which was already computed in a finite difference framework for the interrogated field, and tracks the propagation paths of rays from the foci to the aperture. The challenging problem of dynamic focusing was addressed by time delay computation along the estimated paths. Comparison of the results showed that significant enhancements in spatial resolution and contrast to noise ratio were achieved through the proposed method.
References


Chapter 6:

Post-processing and automated contour detection in ultrasound images

6.1 Overview

In this chapter, automated detection of object boundaries in the presence of speckle noise is addressed within a multiscale framework. The ultrasound image is taken as an input and passed through a preliminary processing step to reduce the correlation between the data samples. The filtered image is subsequently fed into an algorithm to detect the discontinuities and edges.

6.2 Objective

Although aberration induced by the inhomogeneity of the propagation medium is the primary factor that degrades ultrasound image qualities speckle is another major factor that severely limits the image resolution. Speckle, an inherent characteristic of ultrasound imaging, is a result of diffuse scattering after an ultrasound wave interferes with small particles on a scale comparable to its wavelength. Successful implementation of automated object boundary detection algorithms is constrained in the presence of speckle as it masks important features such as the edges. A review on the state of the art ultrasound image despeckling techniques was presented in Chapter 2 of this study. In this
Chapter 6: Post-processing and automated contour detection in ultrasound images

section, a new method is presented that can simultaneously suppress the speckle noise and detect the object boundaries in ultrasound images.

6.3 Multiscale wavelet-based edge detection

In the presented method, detection of discontinuities and edges of ultrasound images in presence of speckle is addressed within a multiscale wavelet transform. Mallat and Zhong [1] originally related the multiscale edge detection problem to the wavelet transform (WT) for the characterization of signals and images. A continuous wavelet transform of a function \( f(x) \) can be defined by:

\[
W_{a,b}f(x) = \langle f, \psi_{a,b} \rangle = \int_{-\infty}^{+\infty} f(x) \frac{1}{a} \psi \left( \frac{x - b}{a} \right) dx
\]  

(6-1)

where \( W_{a,b} \) is the wavelet coefficients and \( \psi_{a,b} \) is the dilated form of the wavelet function \( \psi(x) \), \( \psi_{a,b} = \psi((x - b)/a) \), by a scaling factor of \( a \) and a translation parameter of \( b \). For the purpose of local sharp detection in the tissue structure the wavelet function is defined here as a first-order derivative of a smoothing function \( \theta(x) \)

\[
\psi(x) = \frac{\partial \theta(x)}{\partial x}
\]  

(6-2)

The smoothing function can be chosen to be any function whose integral is equal to 1 and converges to 0 at infinity. For a 2-D case, which is the case here, the wavelet functions can be defined by the derivative of the smoothing function along horizontal and vertical directions as

\[
\psi^1(x, y) = \frac{\partial \theta(x, y)}{\partial x}
\]  

(6-3)
Therefore, the dyadic wavelet transform is proportional to the first (or any higher) derivative of the image \( f \) smoothed at the scale \( a \) (or level \( j, a = 2^j \)). The details, \( W^d_j \), can be obtained by convolving the image with the wavelet function as

\[
\begin{align*}
\begin{pmatrix}
W^1_j f(x, y) \\
W^2_j f(x, y)
\end{pmatrix}
= f(x, y) * \psi^{d}_{a,b}(x, y) = 2^j \nabla(f * \theta_j)(x, y)
\end{align*}
\]  

(6-4)

The coarse approximation of the image may be obtained by a scaling function at each level. The finite-level discrete dyadic wavelet transform of a 2-D discrete function \( f(m, n) \) can be represented as

\[
W[f(m, n)] = \{(W^d_j f(m, n))_{d=1,2,3,1 \leq j \leq J}, S_j(f(m, n))\}
\]  

(6-5)

where \( S_j(f(m, n)) \) is the coarse approximation of \( f \) at the final level \( J \). For the purpose of this study three directional wavelet transforms along the horizontal, vertical and diagonal directions, \( W^1_j, W^2_j, W^3_j \), are computed for each level \( j, 1 \leq j \leq J \).

Due to the multiplicative characteristic of speckle sharp variations with high intensities appear in ultrasound images, while these variations do not represent actual edges. This makes the original wavelet-based edge detection, which is based on the local maxima of the modulus \( [2] \) defined by \( M_j = \sqrt{|(W^1_j f(m,n))|^2 + |(W^2_j f(m,n))|^2} \), inefficient to detect the actual edges in the presence of speckle. Successful implementation of an edge detection algorithm requires an accurate and reliable model of speckle noise. A general model of speckle can be presented as \( [3] \):

\[
f(m, n) = g(m, n)\eta_s(m, n) + \eta_a(m, n)
\]  

(6-6)
where \( f(m, n) \) is a noisy discrete function and \( g(m, n) \) is a noise-free desired function. The terms \( \eta_s \) and \( \eta_a \) denote for speckle and additive noise, respectively. Whereas speckle is the dominant noise in ultrasound images the additive noise can be neglected in the above model. It is desired to separate the speckle noise from the noise-free image through a logarithmic transform as

\[
f^l(m, n) = g^l(m, n) + \eta_s^l \tag{6-7}
\]

The upper index \( l \) denotes for the logarithm. By this transform the speckle can be treated as an additive noise while its statistical distribution is approximated as Gaussian. Taking discrete wavelet transform from both sides of the above equation yields:

\[
W[f^l(m, n)] = W[g^l(m, n)] + W[\eta_s^l] \tag{6-8}
\]

In this transform choosing of a wavelet function suitable for the task is of great importance. In this application it is desired to reduce the speckle while preserving the accurate location of the edges. Therefore, a wavelet with short spatial support would be desired. On the other hand, the presented method relies on the persistence of edges in different scales. Hence, for the effective implementation of the algorithm the wavelet is required to be a linear phase and with a small number of coefficients. The Haar wavelet with 1 vanishing moment and 2 coefficients is chosen to serve here,

\[
\psi(x) = \begin{cases} 
1 & 0 \leq x < \frac{1}{2} \\
-1 & \frac{1}{2} \leq x < 1 \\
0 & \text{otherwise}
\end{cases} \tag{6-9}
\]

When sharp variation of intensity is present in the function interval the wavelet coefficients produce a local maximum, showing the location of the edges. However,
when no discontinuity is in the interval the transform simply subtracts the summation of the log-speckle over the two adjacent intervals [4]. This can be stated as follow, which has been obtained by substituting the Eq. 6-9 in the wavelet transform formula:

\[ W[\eta^{L}_S] = \int_{b}^{b+a/2} \eta^{L}_S dx - \int_{b+a/2}^{b+a} \eta^{L}_S dx \]  

(6-10)

With the assumption of white Gaussian distribution for the log-speckle the above equation can be approximated as zero. Therefore, by filtering the image through this procedure the speckle level in the homogeneous regions is reduced and the boundaries between the regions are detected along the direction of the wavelet.

6.4 A preliminary processing step

In this section, the common assumption, also used in the previous section, that the multiplicative speckle noise is converted to an additive noise through a log-transform, and therefore can be dealt with as such is examined. In several studies [2]–[6] the despeckling filters have been implemented based on this general assumption that the samples of the noise after log-transform are mutually uncorrelated and follow a Gaussian distribution.

The statistical properties of speckle noise have been examined in multiple studies and it was found that the intensities of speckle images obey a Rayleigh distribution where a large number of scatterers are laid in each resolution cell. While, the statistics deviates from Rayleigh distribution where the number of scatterers is low. Different types of distributions have been proposed for the weak scattering medium case including Weibull distribution, Nakagami distribution, and K-distribution. A Generalized Gamma (GG)
distribution was proposed in [7] as the other mentioned distributions can be considered as special cases for GG. For experimental examination a region of the B-scan image of the head phantom that does not contain any embedded reflectors was selected as speckle and displayed in Figure 6.1 (a). The statistical distribution of the speckle samples is depicted in Figure (b), resembling a GG distribution.

![Figure 6.1](image)

**Figure 6.1** (a) Speckle image obtained from the head phantom, (b) its statistical distribution.

To be able to understand the correlation between the samples of the acquired data, a mathematical model that can represent the physical interactions between the ultrasound waves and the interrogated tissue is required. Assuming linear wave propagation and weak scattering in the tissue, a convolution model can represent the relationship between the acquired RF image and the tissue reflectivity function, which can be defined in spatial domain by [8]:

\[
f(m, n) = r(m, n) * h(m, n) + \eta_a(m, n) \quad (6-11)
\]

In this general well-known model \( f(m, n), r(m, n), h(m, n) \) and \( \eta_a(m, n) \) respectively denote for the RF image, the reflectivity function, the point spread function, and the additive noise. Figure 6.2 displays a schematic of image formation process based on the
Figure 6.2 Schematic implementation of image formation model.
convolution model in ultrasound imaging. The reflectivity function, \( r(m, n) \), represents the echogenicity of the tissue structures multiplied with a random white noise to model the tissue scattering. Knowing the fact that the convolution can be replaced with multiplication in frequency domain, the power spectral density of the image \( f(m, n) \) can be stated as

\[
P_{ff}(f_1, f_2) = P_{rr}(f_1, f_2) |H(f_1, f_2)|^2 + P_{a\eta_a}(f_1, f_2)
\]

(6-12)

Where \( P_{ff}(f_1, f_2) \), \( P_{rr}(f_1, f_2) \) and \( P_{a\eta_a}(f_1, f_2) \) respectively denote for the power spectral densities of the acquired RF image, the reflectivity function, and the additive noise. The term \( |H((f_1, f_2))| \) stands for the magnitude of the PSF in the frequency domain. It is worth noting that power spectrum density is the frequency counterpart of autocorrelation function of any given data.

Without loss of generality the reflectivity function can be assumed a white process considering the fact that tissue heterogeneity is generally formed by numerous small independent structures [7]. White noise is defined as an uncorrelated stochastic process that has a flat spectrum and equal power spectral density over the frequency bandwidth of the imaging system. Therefore, the power spectral density of the reflectivity is equal to the variance of the samples denoted by \( \sigma_r^2 \). On the other hand, the samples of the additive noise can be reasonably assumed as white Gaussian noise (WGN), and subsequently its power spectral density \( P_{a\eta_a}(f_1, f_2) \) is constant and can be estimated by the noise variance, \( \sigma_{\eta_a}^2 \). With those being stated the power spectrum of the RF image is directly proportional to the PSF spectrum plus noise variance, proving the fact that the samples of speckle are indeed correlated.
To decorrelate the samples of image \( f(m, n) \) one should eliminate the effect of the PSF of the imaging system from the image. Here, a deconvolution Wiener filter, a well-known pseudo-inverse filter, is employed as it is efficient and easy to implement. Denoted by \( f^p(m, n) \) the filtered image is obtained by:

\[
f^p(m, n) = DFT^{-1} \left\{ \frac{\sigma_r^2 H^*(f_1, f_2)}{\sigma_r^2 |H(f_1, f_2)|^2 + \sigma_{QA}^2} F(f_1, f_2) \right\}
\]

(6-13)

where \( DFT^{-1} \) is the inverse discrete Fourier transform operator and \( F(f_1, f_2) \) is the spectrum counterpart of the ultrasound image. Implementation of the above filter requires the variance of noise to the variance of reflectivity ratio, which is not available in practice. Here in this study a constant value obtained empirically is used to tune the filter. This value is equal to 0.01 \( |H(f_1, f_2)|_{\text{max}}^2 \) and has been used in several studies [9]–[11]. The point spread function was a \textit{priori} knowledge to this implementation, as it can be practically obtained through measurement. The problem of PSF estimation from the acquired ultrasound image at different depth of imaging, when considering spatial variability of the PSF, is out of the context of this study and one can find recent developments in this area in [12], [13].

According to the work presented in [14], the speckle cell size can be related to the resolution cell size, where in the axial direction the speckle cell size is proportional to the PSF length and in the lateral direction it is comparable with the transducer beam width (PSF width).

Due to the finite bandwidth of ultrasound transducers the PSF of the imaging system exhibits bandpass characteristic and filters the out-of-band contents of the reflectivity spectrum. To estimate the lost content of the reflectivity spectrum and consequently to
decorrelate speckle samples further, an Autoregressive spectral extrapolation algorithm was applied on the deconvolved spectrum. For this purpose, a portion of the estimated spectrum that has high SNR, is optimally selected. Subsequently, the Autoregressive coefficients are computed using the Burg method. The method is based on the minimization of the sum of forward and backward squared prediction errors while constraining the coefficients to satisfy Levinson-Durbin recursion [15]. Based on this selected portion, the rest of the spectrum is extrapolated in both directions using the following equations

\[
\begin{align*}
F_p^v & = - \sum_{i=1}^{k} a_i^* F_{v+i} \quad v = 1, 2, \ldots, m - 1 \\
F_p^w & = - \sum_{i=1}^{k} a_i^* F_{w-i} \quad w = n + 1, \ldots, N
\end{align*}
\]

where \(F_p\) is an extrapolated value of the spectrum, \(N\) is the Nyquist frequency, and \(a_i\) and \(a_i^*\) are Autoregressive coefficients and their complex conjugates, respectively.

The top left column of the Figure 6.3 displays the log-envelope image of carotid artery synthetized through the image formation process, presented in Figure 6.2. The right column of this figure presents the log-envelope of the same image that has been processed by the filtering techniques presented in this section. At the first glance the processed image presents the same information as the original image. However, the granular pattern of speckle is substantially finer in the processed image, indicating the correlations between the samples have been reduced. Furthermore, the speckle has been suppressed, particularly at the echolucent region of the image.
Figure 6.3 Top: Log-envelope image of the synthesized carotid artery before (left) and after processing (right). Middle: Autocorrelations of the original (left) and processed (right) image. Bottom: Cross-sections of the autocorrelations along the lateral (left) and axial (right) directions. Applying the processing step substantially reduces the correlation between the samples.
For further evaluation of the images the autocorrelation of the original and processed images are plotted in the middle row of the figure. Their cross sections along axial and lateral directions and through the center point \((0, 0, 0)\) are also presented in the bottom row. A simple inspection of the autocorrelation functions shows that the autocorrelation of the processed image is spiky with narrow support while the autocorrelation of the original image exhibits a wide support, confirming loss of correlation and enhancement of resolution after applying the processing steps.

### 6.5 The filtering method

The proposed method for automated detection of discontinuities of ultrasound images in the presence of speckle is comprised of four steps, which are preprocessing, modulus construction, inter-scale multiplication, and active contour detection.

1) **Preprocessing:** The RF data collected by the ultrasound scanner is taken as input. Following the procedure presented in section 5.5.3, the RF image is passed through a deconvolution Wiener filter and Autoregressive spectral extrapolation step in order to reduce the correlation between speckle samples and also to enhance spatial resolution of the image. Through a Hilbert transform, the envelope of all traces are detected and the envelope-detected image is constructed. The processed image is subsequently log-transformed to convert the multiplicative noise to additive noise. At this stage the effect of noise can be reduced by using homomorphic filtering at the expense of smoothing the edges.

2) **Modulus image construction:** Taking the processed image, the wavelet coefficients are then computed along the horizontal, vertical and diagonal directions using a 2-D
stationary wavelet transform (SWT) with Haar being the wavelet function. The SWT is a redundant scheme that output image at any level of decomposition has the same size as the input. After magnitude detection and normalization of each sub-band, the edge modulus is constructed at level $j$ by finding the local maxima along the gradient direction:

$$M_j(m, n) = \max\{\|W_j^1 f^{lp}(m, n)\|, \|W_j^2 f^{lp}(m, n)\|, \|W_j^3 f^{lp}(m, n)\|\} \quad (6-15)$$

The term $f^{lp}(m, n)$ denotes for the log-envelope of the processed image.

3) **Inter-scale multiplication:** From the previous step multiple modulus images can be constructed at different scales, $1 \leq s \leq 2^j$. However, the detected edges at different scales do not share the same quality. This can be explained by the fact that the interval size at a wavelet function is directly determined by the scale at which the decomposition is done. At higher scales, the function interval is wider and therefore the transform performs better in smoothing the speckles. However, this comes with the drawback of lower precision in the estimation of the actual location of the edges. Furthermore, smoothing at higher scales smear the sharps with small amplitudes. Detection of the small variations would be possible by using a lower scale, however this can result in misdetection of speckles as edges. For better illustration the modulus images of the synthesized carotid artery were computed for scales $2^2$, $2^3$, and $2^4$ and displayed in figure 6.4.
Figure 6.4 Edge modulus image, $M_j(m, n)$, of the synthesized artery image at three different levels.

One can see the persistence of edges through the different scales while the speckle is cancelled better at the higher scale. To take advantage of the good performance in smoothing the speckle noise at higher scales, and high sensitivity in detection of and high accuracy in localization of the edge at lower scales simultaneously the proposed method exploits multiple levels of gradient smoothing. The combination of multiple modulus images, obtained from the previous step, is done through an inter-scale multiplication procedure as

$$E(m, n) = \prod_{j=1}^{J} M_j(m, n)$$  \hspace{1cm} (6-16)

where maximum number of levels is determined beforehand, depending on the discontinuities in the image and the level of speckle noise. Detection of impulses and steps using multiscale products were characterized in [16] where the noise level was so low that did not affect the steps. The number of scales was suggested to be odd in order to preserve the edge polarity information. For the results presented in the current work this number was set to 5.
4) **Contour detection via a Hybrid level-set model:** Realization of an automated boundary detection procedure requires a decision making to detect the actual edges once the multiscale modulus image was computed. Among the numerous techniques presented in the literature the geometric active contour method [17], which is a boundary-based segmentation technique, has been extensively used before and could be a good candidate for this application. Through the initial experiments, it was found out that this technique suffers from the leakage when the evolving contours encounter broken edges, and therefore failed to detect the actual boundaries. A region-based contour evolution model, also known as Chan-Vese model [18], exhibits more robust performance when encountering weak or broken edges by using only the region information. To take advantage of the detected edges obtained by the proposed method and also to overcome the leakage problem a hybrid model, originally developed by Zhang [19], is employed that uses both edges and region information.

A level set framework has been used for the problem of contour evolution where a curve \( C \) is represented implicitly using a Lipschitz function \( \varphi \) by \( C = \{(x, y)|\varphi(x, y) = 0\} \). The points inside and outside the contour have positive and negative \( \varphi \) values respectively, as shown in Figure 6.5. The positive direction of the curve normal vector is defined to be outward. The original geodesic active contour in a level-set formulation can be given by [17]:

\[
\begin{aligned}
\left\{ \frac{\partial \varphi}{\partial t} = |\nabla \varphi| \left[ \text{div} \left( g(|\nabla u_0|) \frac{\nabla \varphi}{|\nabla \varphi|} \right) + v g(|\nabla u_0|) \right] \right. \\
\varphi(0, x, y) = \varphi_0(x, y) 
\end{aligned}
\]

(6-17)
The model evolves to find the curve with minimum geodesic length. The term $g$ is a decreasing function of the image gradient, given by:

$$g(\nabla f(x,y)) = \frac{1}{1 + |\nabla \theta(x,y) \ast f(x,y)|^p}$$  (6-18)

which in fact was computed via the proposed method in previous steps. The hybrid model integrates the region information to the geodesic contour model by [19]:

$$\frac{\partial \phi}{\partial t} = |\nabla \phi| \left[ \alpha (f - \mu) + \beta \text{div} \left( g(|\nabla u_0|) \frac{\nabla \phi}{|\nabla \phi|} \right) \right]$$  (6-19)

where $f$ is the envelope-detected (original) image and $\alpha$ and $\beta$ are predefined weights to balance their corresponding terms. The term $\mu$ indicates for the lower band grey-scale of the object, which can be set by average value of the image intensity assuming the desired objects have high gray-scale values. The first term of the above model forces the contour to enclose the regions with intensities greater than $\mu$, while the second term encourage the contour toward the highest gradient value, which would be the boundary of the object.

![Figure 6.5 Curve propagation in level-set framework.](image)

Figure 6.5 Curve propagation in level-set framework.
Figure 6.6 presents the block diagram of the proposed method for speckle suppression and automated detection of object boundaries in ultrasound images. The algorithm receives scanner RF data as input and applies the presented four-step procedure to extract object boundaries and image discontinuities. The terms G and H, used in the multiscale edge detection step, respectively denote for high pass and low pass filters.

\[
\begin{align*}
L & = t r a n s f o r m \text{ for } H \quad W_{j+1}^H \\
G & = s i z e o f \text{ for } G \quad W_{j+1}^G \\
H & = s i z e o f \text{ for } H \quad S_{j+1} \\
& \text{Yes } \quad j = j + 1 \\
\text{Normaliz} & \text{ation} \\
\text{Modulus} & \text{ image} \\
\text{construction} \\
\end{align*}
\]

Figure 6.6 A block diagram of the proposed method for speckle suppression and automated detection of object boundaries in ultrasound images.

6.6 Results

In this section, the performance of the presented method in detection of object boundaries and discontinuities when the ultrasound image is degraded by speckle noise is evaluated. Simulation studies are of great importance in verification of an edge detection algorithm, since the original echogenicity map is provided. In the current study, a two-dimensional (2-D) ultrasound RF image of the carotid artery was simulated according to the convolution model, Eq. (6-11). The Carotid artery was chosen here since the segmentation of the carotid artery ultrasound images provides substantial information,
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including intima-media thickness of the artery, which are used for the risk-of-stroke analysis, and therefore may be considered as a complimentary test to the transcranial imaging.

For this simulation, the tissue reflectivity function was generated as a product of the tissue echogenicity map with 2-D white Gaussian noise field. The RF image was obtained through the convolution of the reflectivity with a simulated PSF. Assuming the PSF is separable along the axial and lateral directions, i.e. \( h(x, y) = h(x)h(y) \), the \( h(x) \) was modeled by a Gaussian-modulated sinusoidal echo as

\[
h(\theta; x) = \beta \exp \left(-\alpha (x)^2\right) \cos(2\pi f_c x/c + \varphi)
\]  

(6-20)

where \( \theta = [\beta, \alpha, f_c, \varphi] \) is the parameter set of the Gaussian echo denoting for amplitude, bandwidth, center frequency, and phase, respectively. The center frequency was set to 2 MHz. Along the lateral direction the \( h(y) \) was modeled by

\[
h(y) = \exp \left(-\frac{y^2}{\sigma_y^2}\right)
\]  

(6-21)

where \( \sigma_y^2 \) represents the beam-width of the transmitting pulse, which was set to 1.5 in this simulation. The acquired RF data is then passed through a demodulation filter generating and envelope image. A schematic of the image formation process was presented earlier in Figure 6.2. The most left window of Figure 6.7 (a) displays the simulated envelope image. For comparison three speckle reduction filters were employed. Lee filter and adaptive Wiener filter are two well-known classical filters while the Speckle reduction anisotropic diffusion (SRAD) is a state-of-the-art technique, which has been excessively used thanks to its great performance in speckle suppression.
Figure 6.7 Synthetized carotid artery image, left column: (a) original image, (b) Lee filter, (c) Adaptive Wiener filter, middle column: Canny edge detection of the corresponding image in the left column, right column: a lateral cross-section of the left column’s image.
Figure 6.7 (continued): (d) left: SRAD filter, middle: SRAD+ Canny, right: a lateral cross-section, (e) left: Multiscale edge detection and speckle suppression, middle: Multiscale edge detection followed by hybrid contour detection, right: a lateral cross-section.

When applying the Lee and SRAD, the input image was intensity but applying the adaptive Wiener the image was log-transformed. The Window size is set to 7×7 pixels for the adaptive Wiener and Lee. The results of filtering are displayed in the left column of Figure 6.7 (b)-(d). Canny edge detector was employed to detect the discontinuities of the filtered images. Similar to the presented method, Canny utilizes the gradient of the image that has been smoothed by a Gaussian filter. The standard deviation of the filter, the low and high threshold values were empirically determined for each case. The results of Canny edge detection are presented in the middle column of the Figure 6.7 (a)-(d).
By applying the presented method, the original image was first decorrelated to reduce the correlation between the image samples (step 1). In the decorrelation step, a constant value of $0.01 |H(f_1, f_2)|_{max}^2$ was set for tuning the filter. The spectral window borders were determined at the range of 3 dB to 10 dB drops of the spectrum peak and the spectrum was extrapolated for all selected windows and finally averaged. The order of autoregressive extrapolation was set to 20, considering the complexity of the data.

Subsequently, the processed image was passed through the multiscale wavelet-based edge detection process (steps 2 and 3 in the previous section). The decomposition was conducted for 5 levels, $j = 5$. The results have been displayed in the left window of the Figure (e). As a complementary step the hybrid contour detection was employed to detect the final edges (step 4). The detected contours are depicted in the center window of Figure (e).

For further visual assessments the lateral cross-section of the images in the left column at one fifth of the depth are plotted in the right column of the Figure 6.7. A simple visual inspection of the results in the middle column reveals the outperformance of the presented method along with the SRAD over the other two filters. The multiscale-hybrid contour method could successfully detect the boundaries between the blood, vessel wall and the muscle/fat tissue regions in the simulated image. The actual locations of discontinuities are depicted in red dashed lines in the cross-sectional plot (e) showing the localization accuracy of the detected edges.

Finally, the algorithm is applied to the transcranial phased array images, presented in the previous chapter, to detect the boundaries of the wires without any supervision. The arbitrary parameters of the multiscale edge detection method were set the same as the
Figure 6.8 Automated detection of object boundaries in transcranial ultrasound images, (a) Original image, (b) Refraction-corrected image.

previous example. Figure 6.8 displays the envelope-detected images of the wires before (a) and after refraction correction (b). The detected contours via the presented method are plotted in this figure, superimposed with the original envelope images. The results show the automated detection rate of objects in transcranial images increased from 61% (8 out of 13 wires) to 92% (12 out of 13 wires) after applying the refraction correction procedure.

6.7 Summary

In this chapter, a new method for automated detection of discontinuities and object boundaries in ultrasound images is proposed. The presented method is consisted of three
primary steps. The first step tends to reduce the correlation between speckle samples, while improving the sharpness of the edges. A deconvolution Wiener filter followed by an autoregressive spectral extrapolation was employed for this purpose. Taking advantages of the multiscale properties of the processed image the presence of discontinuities and edges are detected through a nonlinear processing in the second step. At the final step, a hybrid contour detection technique is employed in level-set framework to detect the final boundaries and edges. The algorithm was tested on a synthesized carotid artery image and transcranial phased array images of the numerical wire phantom. The capability of the presented algorithm in detection of the actual edges and suppression of the speckle amplitude variations was compared against other well-known methods.
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Chapter 7:

Conclusion and future work

7.1 Conclusion

In this study, a new procedure for transcranial ultrasound imaging through the thick human skull bone and without the use of temporal bone acoustic windows is introduced. The proposed procedure consists of four major steps that in each step a specific challenge of transcranial ultrasound is addressed.

The human skull bone with thick, multilayered structure is considered a strict barrier in transcranial ultrasound applications. The thickness and shape of the human skull bone as the main contributing factors to the phase aberration in transcranial ultrasound have been obtained by using MRI and CT in the literature. In this study, for the first time the feasibility, accuracy and precision of the 3-D skull bone profile extraction using a 2-D ultrasound matrix array transducer is investigated. Two methods called modified space alternating generalized expectation maximization (SAGE) and multi-lag phase delay estimation (MLPD) are presented to estimate the arrival times of the backscattered echo from the first and second interfaces of the skull phantom and subsequently to extract the geometry of the bone under interrogation. A minimum absolute error of 0.44 mm was
yielded by the modified SAGE technique through the thickness estimation of the 3-D skull bone phantom. This is comparable to the 0.4 mm value obtained from the computer tomography (CT) of human skull by Egger [1].

In the second step, non-invasive adaptive focusing of the ultrasound beams through the heterogeneous medium is investigated. The acquired boundaries of the skull bone are fed into the code to construct a heterogeneous gridded sound speed field. The idea is to exploit virtual acoustic sources embedded in the desired foci in the brain tissue as beacons. The radiated waves from the virtual sources are numerically propagated through the heterogeneous medium using finite difference numerical modeling and recorded by the active receiving elements at the array transducer surface. To reduce the complexity of full-wave propagation modeling and to increase the computation speed a multi-stencil fast marching method is employed that tracks the advancing of the wave fronts from the emitter to the receiving aperture. The phase shifts induced by the skull bone are estimated from the computed time-of-flights (TOFs). Accordingly, a new time delay set is introduced to the beamformer to compensate the distortion effect of the skull. The code was implemented on an ultrasound advanced-open platform (UAL-OP) for experimental verification. The numerical and experimental results show that the proposed adaptive focusing method can correct up to 8 mm focal displacement error at 100 mm depth.

The third step deals with the refraction correction of transcranial ultrasound phased array images in the reception mode of the beamforming. Taking advantage of the gradient information of the time-of-flight matrix, which was already computed for the transmission mode, the presented method could successfully track the ray propagation path between foci and the aperture center. As a result, dynamic focusing along the
estimated propagation path is achieved, given the computed time-of-flights for the gridded field. The experimental results show the refraction correction enhances the image contrast to noise ratio by approximately 40%.

Once the ultrasound image is reconstructed some post-processing steps would be desired for further image analysis. As a final step, automated detection of discontinuities and object boundaries is addressed in a multiscale framework. These can be foreign objects such as a bullet, shrapnel, or bone fragment trapped inside the brain tissue, an abnormality of brain tissue, or blood vessel stenosis diagnosed by transcranial imaging. The presented results show that the algorithm could successfully detect the boundaries and simultaneously suppress the speckle noise in ultrasound images.

### 7.2 Future work

In this section the potential areas for future investigation illuminated by the presented work are discussed. In the current method refraction-corrected phased array imaging through the skull bone phantom has been accomplished by using a 1-D array transducer. Taking into account the fact that refraction is a physical phenomenon that occurs in a three-dimensional environment, implementation of the current method for 3-D imaging would provide the opportunity to also correct the out-of-plane refractions and consequently to further improve the resolution and CNR of the reconstructed images. However, the clinical application of matrix arrays in transcranial imaging is still undetermined due to the existing challenges in interconnect technology which also makes the matrix array costly to manufacture. The programming code developed for this study is compatible to be used for 3-D imaging; nevertheless, implementation of the code on the ULA-OP for the 2-D array transducer demands some work.
The current method takes about 2 minutes to compute the transmission and reception time delay sets for a high-resolution mode. Although it is satisfying when compared with the other methods, it is necessary to reduce the computational time to at least one fourth of the current one to be able to use the current method for clinical applications. One suggestion is to increase the grid size of the finite difference model and instead employ a spline-based algorithm [2], [3] for sub-sample interpolation.
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References


# VITA AUCTORIS

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