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Ultrasound Image guidance and Therapy with Random Phased Arrays

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Abstract

The dream of replacing surgeons' knife with a non-invasive procedure to treat cancer and other major ailments is no more a fantasy. Ultrasound is a leading technology behind non-invasive therapy. High intensity focused ultrasound (HIFU) has been proposed for treatment of various ailments. HIFU transducers produce high intensity levels needed for ablative therapy or mechanical destruction of tissue. With the use of advanced imaging modalities such as MRI, CT scan and diagnostic ultrasound, it has got widespread recognition. Each one of them has its own advantages and shortcomings. These modalities, when integrated with HIFU, not only increase the cost and complexity of the system but also suffer from low frame rate, difficulty in alignment, image registration problems and low spatial resolution and thus cause hindrance in the clinical use of HIFU. Imaging with the therapeutic transducer is a natural solution due to the intrinsic ability of the imaging transducer to have same coordinates as the therapy transducer and thus can benefit from the inherent registration between the imaging and therapeutic frames of reference. Furthermore, the operating bandwidth of these transducers is wide enough to offer image quality suitable for planning and monitoring the treatment procedure. However, therapeutic arrays are optimized for therapy only with large, directional elements operating at low MHz frequency, conventional beamforming techniques are thus not useful to produce adequate images with such an array. The objective of this thesis was to investigate the feasibility of using synthetic aperture imaging techniques with a therapeutic random phased array. Various synthetic aperture techniques were implemented, in simulation and experiments, with the random phased array and its potential to accurately image the target was demonstrated for the first time.

One of the difficulties that currently hinders the clinical application of HIFU to

treat liver tumours is the transmission of sufficient energy to cause tissue necrosis while avoiding the ribs from being heated. The rib bones not only absorb and reflect ultrasonic energy causing overheating of the surrounding tissue but also distort the focus and create secondary maxima. The occurrence of secondary maxima leads to tissue heating in undesired areas. Thus it is important to devise techniques to prevent heating on the ribs while performing tissue ablation intercostally. Various techniques have been proposed to avoid thermal damage to the ribs but they either rely on MR/CT images, the physical existence of a point target at the focus or operate on pulses. Imaging with the therapeutic transducer not only eliminates the cost of an external imaging modality such as MRI but also offers the opportunity to detect strong scattering objects such as ribs during or before the therapy procedure. In this work, a binarized apodization model based on geometric ray tracing was used to minimize heating of the ribs while maintaining sufficient intensity at the focus. This model rely on simple shadowing technique overcoming the computational challenges for large domain dimensions at 1 MHz frequency. Focusing through the ribs was investigated in detail and intensity distributions were calculated both in the presence of idealized ribs and anatomically correct rib structures. Various practical situations that can arise during HIFU therapy were taken into consideration and focus quality was analyzed in terms of various practically relevant parameters. A model capable of predicting 3D intensity distribution in the focal plane and in the plane of the ribs was thus developed which is helpful in devising treatment planning strategy for HIFU therapy of liver tumour behind the ribs.

The final achievement of this work was to design and model an improved random phased array by modifying the existing 256-element array. This overcame the limitation of reduced intensity at the focus due to a central aperture hole for imaging and the turning off of some elements in the existing transducer to spare the ribs. Since very high peak output power of the array is required for transcostal therapy, the improved design had an increased gain resulting in higher intensity at the focus as well as an extended steering range with out any increase in the grating lobes away from the focus. Moreover, the sidelobes were significantly reduced which helped in improving the imaging resolution of the system.

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To my parents

The greatest challenge to any thinker is stating the problem in a way that will allow a solution.

Bertrand Russell

Failure is not fatal until we surrender
trying again is the key of a glorious victory.

Allama Mohammad Iqbal

Statement of Originality

I declare that this thesis is the result of my own work. The information and ideas derived from others' work have been acknowledged in the text and references are provided in the bibliography. The material in this thesis is original and has not been submitted for a degree or diploma at any other university.

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Acronyms

BEM Boundary Element Method.

CT Computed Tomography.

CUDA Compute Unified Device Architecture.

DAS Delay And Sum.

DORT Decomposition of the Time-reversal Operator.

FDA Food and Drug Administration.

FFT Fast Fourier Transform.

FPGA Field Programmable Gate Array.

FWHM Full Width Half Maximum.

GPU Graphical Processing Unit.

HIFU High Intensity Focused Ultrasound.

HRI High Resolution Image.

IR Infra-Red.

LIFU Low Intensity Focused Ultrasound.

LRI Low Resolution Image.

M-SAF Multielement Synthetic Aperture Focusing.

MRI Magnetic Resonance Imaging.

RF Radio Frequency.

SAF Synthetic Aperture Focusing.

SAI Synthetic Aperture Imaging.

SIMT Single Instruction Multiple Threads.

SNR Signal to Noise Ratio.

STA Synthetic Transmit Aperture.

STL Stereolithography.

SVD Singular Value Decomposition.

VHDL VHSIC Hardware Description Language.

VHSIC Very High Speed Integrated Circuit.

VTFS Voronoi-Tessellated Fermat Spiral.

ZIF Zero Insertion Force.

List of Publications

Following is the list of publications and conference presentations that were produced from the material in this thesis:

- Muhammad Zubair, R. J. Dickinson, "3D Synthetic Aperture Imaging with a Therapeutic Random Phased Array" (In Preparation).
- Muhammad Zubair, R. J. Dickinson, "Focusing ultrasound through the ribcage with a therapeutic random phased array" (In Preparation).
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- Muhammad Zubair, Sevan Harput, R. J. Dickinson, "3D Ultrasound Image guidance and Therapy through the Rib Cage with Therapeutic Random Phased Array", *in proceedings IEEE Ultrasonic Symposium, Kobe, Japan, Oct. 2018*
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Chapter 1

Introduction

1.1 Project Objectives

The overall goal of this thesis is to investigate the use of a therapeutic random phased array for image guidance and therapy. The hypothesis that underpins the work in this thesis is that a therapeutic random phased array can operate both as an imaging and a therapy transducer and that synthetic aperture beamforming techniques have the potential to image with such an array thus providing an image-based feedback for focusing in the presence of strongly attenuating and scattering objects such as ribs. The hypothesis thus motivated the following goals that were investigated during this work:

- To demonstrate that a therapeutic random phased array can be used both for image guidance and therapy.
- To evaluate the potential of different synthetic aperture techniques to image with a therapeutic random phased array.
- To program the ultrasound scanner to obtain pulse-echo signals that can be reconstructed using a synthetic aperture algorithm to locate and image obstacles such as ribs.

- To investigate the effect of the ribcage on focus quality during HIFU therapy procedure.

1.2 Thesis Contribution

The aim of this thesis was to enable and use a therapeutic random phased array for image guidance. However, the random phased array used in this work is optimized for therapy with large, directional elements and so conventional delay and sum beamforming was not suitable for imaging with this array. Different synthetic aperture techniques were thus reviewed and evaluated. These techniques were implemented both in simulation and experiment to single out the best technique for imaging with the random array. It was shown that the random phased array is capable of imaging the intervening tissue along with the delivery of high energy in to the tissue for therapy. This leads us to image-guided surgery with HIFU for monitoring, control and imaging the therapeutic procedure with the same array due to the fact that the coordinates of both the imaging and therapeutic transducers are inherently registered. The random phased array was integrated with state-of-the-art research ultrasound scanner, Vantage256 (Verasonics, Kirkland, WA), via custom-built connectors to obtain pulse-echo data which was then used in beamforming algorithms to image the field of interest.

A major contribution of this work was to enable the therapeutic array to image strongly scattering objects such as bones. This is of particular importance during HIFU therapy of liver where the ribcage not only gets heated leading to skin burns but also distorts focus quality. It is thus of paramount importance to prevent the ribs from heating. It was hypothesized and later shown in experiments that therapeutic random array is capable of imaging bones. The ribs can thus be detected in real time and spared from being heated during therapy.

Focus quality of the HIFU system in the presence of idealistic planar rib phantoms has been the subject of previous studies which were validated both in simulation and

experiment. This work was then extended to model the effect of anatomically correct realistic human ribcage model and recommendations were made for treatment in the presence of a ribcage.

Since the presence of ribcage reduces intensity at the focus by shadowing some array elements, modifications were made to the existing array by introducing more elements positioned randomly in the unused surface. The modified array offer an increased transducer gain thus allowing to deliver more energy into the target tissue. The modification also improved the imaging performance of the system.

1.3 Thesis Overview

The major novel contribution of this thesis is the investigation and assessment of different imaging algorithms with a therapeutic random phased array. It has been shown that therapeutic random phased arrays, despite of their limitations, are not only capable of detecting scatterers in the HIFU beam path but can also perform imaging. This proves the concept that if the transducers are optimized both for therapy and imaging, both the operations can be performed simultaneously without any external imaging modality and in real time.

The thesis breakdown is as follows:

- Chapter 2 explain the basics of ultrasound, characteristics of the medium, transducer properties and numerical modeling of acoustic waves.
- Chapter 3 gives a detailed literature review of ultrasound with a focus on therapeutic ultrasound and the advancements achieved in designing the phased arrays and state-of-the-art in image guided high intensity focused ultrasound.
- Chapter 4 reviews synthetic aperture imaging techniques. Different techniques are analyzed in simulation with a linear array and the results are applied to a random phased array.

- Chapter 5 presents the experimental implementation of synthetic aperture imaging with both linear and the random phased array. The materials used in this work are also briefly described.
- In chapter 6, acoustic modeling through the rib cage is discussed in detail. Intensity distribution is calculated in the focal and ribs plane and the effect of ribs on the focal quality is analyzed.
- In chapter 7, a modified random phased array is proposed and the improvements in its imaging and therapeutic capabilities over the existing array are highlighted.
- The final chapter presents the conclusion and future work.

Chapter 2

Ultrasound Basics

This chapter discusses some basics of ultrasound physics including characteristics of acoustic medium, acoustic wave properties, transducer materials, construction of a simple transducer, focusing of ultrasound waves, interaction of ultrasound with tissues and bioeffects of ultrasound and modeling of acoustic waves.

2.1 Ultrasound wave propagation

Ultrasonic waves are mechanical waves with frequency above the human hearing and are caused by the displacement of a small part or particle of the material. There are two main of ultrasonic waves, transverse and longitudinal. The particle displacement is perpendicular to the direction of propagation in the former type and parallel in the later. They are also referred to as shear and compressional waves, where shear waves only propagate in solids, compressional waves can propagate in any medium. There is another type of wave called surface waves which may propagate at the boundary of a liquid and a solid. Acoustic waves are further classified into planar and spherical waves based on the shape of their wavefront. Planar waves has a wavefront located on a plane propagating through the space while spherical waves propagate symmetrically around a reference point.

2.2 Characteristics of Acoustic medium

2.2.1 Speed of sound

The speed at which the acoustic wave propagate through the medium is the medium's speed of sound. It is measured in m/s. It is calculate in terms of frequency f and wavelength λ as

$$c = \lambda f \quad (2.1a)$$

$$c = \lambda/T \quad (2.1b)$$

where T is the time period.

The speed of sound of a medium can be calculated with its elastic bulk modulus B (pa) or compressibility β (m^2/N) and density ρ as follows

$$c = \sqrt{\frac{1}{\beta\rho}} \quad (2.2a)$$

$$c = \sqrt{B/\rho} \quad (2.2b)$$

where $B = 1/\beta$.

In human tissue, sound speed is around 1500 m/s and varies from 1450 m/s to 1700 m/s depending on the tissue type. Typical values of c in bone are in the order of 1800 - 3700 m/s.

2.2.2 Density

Density of a medium is the ratio of its mass per unit volume and its unit is kg/m^3 . Density effects the characteristic impedance of the medium and is thus an important parameter in determining the behaviour of acoustic waves in any medium. Typical

density value for soft tissue in human body is 1000 kg/m^3 and approximately 1900 kg/m^3 .

2.2.3 Acoustic Impedance

Characteristic acoustic impedance is an inherent property of a medium and is calculated by the product of its density and speed of sound. It is denoted by Z and is given by

$$Z = \rho c \quad (2.3)$$

It is measured in Rayls or $\text{kg/m}^2/\text{sec}$. Characteristic impedance of soft tissue, air and bone are of the order of 1.5 MRayls, 0.5 MRayls and 3 - 5 MRayls, respectively.

The difference in impedance between different tissues and air forms basis for ultrasound imaging. The sound reflects from the borders/boundaries between two materials due to the difference in their acoustic impedance. The strength of the reflected echoes depend on the difference in the impedance of the two mediums. The difference in the impedance of two mediums is termed as impedance mismatch. The greater the quantity, the greater will be the reflected acoustic energy from the boundary interface of two mediums.

When the acoustic wave hits the boundary of another medium while propagating in one medium, a portion of its energy is reflected back while the remaining energy is transmitted through the second medium. The ratio of the reflected pressure to the incident pressure is calculated with reflection coefficient R and that of the transmitted pressure with incident pressure is calculated with transmission coefficient T . The reflection coefficient for sound propagation from tissue with impedance Z_1 to tissue with impedance Z_2 is given by

$$R_p = \frac{P_r}{P_i} = \frac{Z_2 \cos \theta_i - z_1 \cos \theta_t}{Z_2 \cos \theta_i + z_1 \cos \theta_t} \quad (2.4)$$

where P_i and P_r are incident and reflected pressures, θ_i and θ_t are angles of incidence and transmission, respectively. Transmission and incident angles are related according to snell's law as

$$\frac{c_1}{c_2} = \frac{\sin\theta_t}{\sin\theta_i} \quad (2.5)$$

The transmitted pressure is given by

$$T_p = \frac{P_t}{P_i} = \frac{2Z_2\cos\theta_i}{Z_2\cos\theta_i + Z_1\cos\theta_t} \quad (2.6)$$

where $\theta_i = \theta_t$, i.e. the incident wave is perpendicular to the interface, then

$$R_p = \frac{P_r}{P_i} = \frac{Z_2 - Z_1}{Z_2 + Z_1} \quad (2.7a)$$

$$T_p = \frac{P_t}{P_i} = \frac{2Z_2}{Z_2 + Z_1} \quad (2.7b)$$

2.3 Acoustic wave properties

2.3.1 Acoustic Intensity

The kinetic energy carried by an acoustic wave as it propagates through the medium can be described in terms of intensity which is the amount of energy per unit volume (i.e. energy density). Acoustic intensity is thus defined as the energy propagating through a unit area per unit time. Acoustic intensity is measured in W/m^2 and is calculated as

$$I = \frac{P^2}{2Z} \quad (2.8)$$

$$= \frac{P^2}{2\rho c} \quad (2.9)$$

where P is the absolute amplitude of acoustic pressure in pascals, Z is the characteristic impedance in Rayls, c is the speed of sound in the medium in m/s, ρ is density of the medium in kg/m^3 .

2.3.2 Attenuation

When an ultrasonic wave propagates through the medium, energy is lost from the beam either by absorption or reflection. A plane wave with initial amplitude A_0 will have an amplitude $A(x)$ after travelling a distance x

$$A(x) = A_0 \exp(-\mu x) \quad (2.10)$$

where μ is given by

$$\mu = \frac{1}{x} \log_e \frac{A_0}{A(x)} \quad (2.11)$$

and is expressed in nepers per metre.

The attenuation coefficient is expressed in decibels per metre and is given by

$$\alpha = 20(\log_{10} e)\mu = 8.686\mu \quad (2.12)$$

In homogeneous medium with no scattering such as fluids, the attenuation coefficient can simply be referred as absorption coefficient. The attenuation loss is different

for different materials and always increases with frequency. Some typical values for attenuation coefficient are given in table 2.1

Table 2.1: Typical values of attenuation coefficient (Np/m) at 1 MHz and 20 °C

Material	Attenuation Coefficient
Water	0.025
Castor oil	10.9
Fat	7.0
Blood	1.7
Brain	8.6
Liver	14.0
Skull bone	164
Muscle	11.0 - 16.0

2.4 Transduction

2.4.1 Piezoelectric Materials

Piezoelectric effect is the main technique to generate ultrasonic wave, which involves the conversion of electrical and mechanical energy into one another. The materials in which this effect takes place are called piezoelectric materials. These materials can be found naturally such as quartz but they have weak piezoelectric properties and are rarely used in medical ultrasonic applications. Ceramic materials such as lead zirconate titanate (PZT) were employed in late 1950s and plastic materials such as polyvinylidene difluoride (pvdf) in the late 1970s. Their main characteristics are summarized in table 2.2

By applying voltage, particle displacement is produced in the material which is determined by transmitting constant d . The receiving constant is denoted by g . A high value of g ensures that the device is sensitive to receive small echoes. The product of d and g is one factor to determine pulse-echo efficiency of the device. Clearly PZT is better than quartz and PVDF, however, PVDF has a high receiving constant thus a lower exposure would suffice for a given level of received signal. Moreover, the characteristic acoustic impedance of PVDF is closer to water/tissue as

Table 2.2: Characteristics of different piezoelectric materials

	Quartz	PZT5A	Pvdf
d (m/v)	2.31×10^{-12}	374×10^{-12}	20×10^{-12}
g (v m/N)	5.78×10^{-2}	2.48×10^{-2}	17.4×10^{-2}
$\rho(kg/m^3)$	2650	7750	1780
c (m/s)	5740	3780	3000
Z (kb/m ² /s)	15.21×10^6	29.29×10^6	5.34×10^6
T _c (°C)	573	365	80
k	0.095	0.705	0.10

compared to PZT, thus ultrasound can be efficiently transferred between transducer and the medium. PZT materials have a higher operating temperature than PVDF.

2.4.2 Transducer construction

An ultrasound transducer is a device that converts electrical energy to acoustic and vice-versa. Majority of transducers are made with piezoelectric ceramics which can be mould into various sizes and shapes. When a piezoelectric material is deformed, it generates an electric charge and this is known as piezoelectric effect. Conversely, when an electric field is applied to the piezoelectric material, deformation occurs which is known as inverse piezoelectric effect.

In a transducer made of PZT, the element resonates mechanically in a thickness mode at a given frequency. The thickness is chosen to be half a wavelength. When the electrodes are attached, the element is placed in a holder and protected with a protective layer. The characteristic impedance of the protective layer is chosen to be between the element material and the tissue. The thickness of the protective layer is normally chosen to be $\lambda/4$ and is a factor in optimizing the transmission and reception at a particular frequency. No backing material is commonly attached for continuous wave operation.

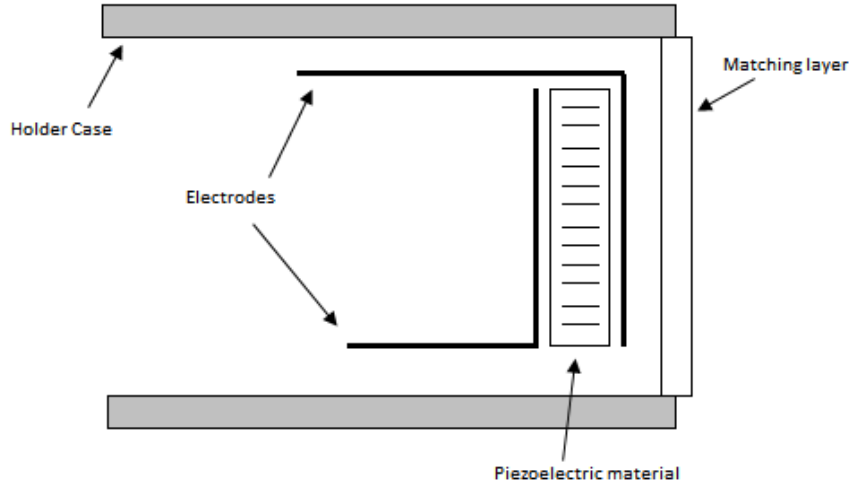


Figure 2.1: Schematic of construction of a single element air backed transducer

2.4.3 Ultrasound Field generation

A simple case of ultrasound generation is shown in fig. 2.1, in which metal electrodes are connected to the front and back surface of a piezoelectric plate. A time-varying voltage is applied to the electrodes via the radio frequency driving-line connected to them. Due to the voltage applied, the piezoelectric material expands and contracts and produces a disturbance in the medium in contact with its surface. A sinusoidal signal is generated by a signal source at the resonance frequency of the transducer, which is amplified and propagated through a tuning network. The tuning network matches the transducer's impedance to the output impedance of the amplifier. In case of phased array, each array element is driven with its own RF-driving line independently.

When the thickness of the plate is half the wavelength in the piezoelectric material, the transducer can be driven at a resonance frequency and maximum acoustic output can be achieved. The transducer can also be driven at odd-integer multiple of resonance frequency but it would severely degrade the electric and acoustic power conversion efficiency.

Transducers for therapy are usually air-backed so that total reflection occurs at the back surface and majority of energy is transmitted through the front surface.

Matching layers are used to improve the transmission of energy from material to tissue due to very high acoustic impedance of the transducer material as compared to the tissue.

2.4.4 Focusing of Ultrasound waves

Ultrasound beams are focused in order to account for the losses encountered by the signal while propagating in the tissue. Focusing can be achieved by using a spherical bowl transducer [5], using a lens [6] or using a multielement transducer in which the relative phases of the elements are changed in transmission, reception or both. The ultrasound field can be focused on a single spot using large transducer. The size of a focal spot is of the order of a wavelength. The size and location of the focus can be varied by varying the geometry and frequency of the transducer. The focal spot can be steered in axial, lateral or both directions depending on the geometry of the transducer. For a spherically curved transducer, the focal spot is elliptical in shape and can be approximated using

$$P(r, \theta) = \frac{2J_1(kas\sin\theta)}{kas\sin\theta} \quad (2.13)$$

where J_1 is the first order bessel function. The full width half maximum (FWHM) is often used to measure the focal spot size.

$$FWHM = 0.71\lambda \frac{F}{a} = 0.71 \frac{cF}{fa} \quad (2.14)$$

where λ is the wavelength, F is the focal length, f is frequency and a is radius of the bowl.

The intensity full width half maximum can also be estimated by $1.0\lambda \times f - number$, and the depth of field in axial direction by $7.2\lambda \times f - number^2$. The $f - number$

is defined as the ratio of focal length (F) to the effective diameter of the aperture (D), $f - number = F/D$. The energy deposition in near and far-fields is usually low in highly focused transducers.

2.4.5 Ultrasound propagation through tissue

An ultrasound wave travels through multiple tissues prior to reaching its target and thus induce a variety of biological effects while traveling from one tissue to another, a part of the energy will be reflected by the tissue interface while the rest of energy is transmitted depending on the difference in the acoustic impedance of the two mediums. Furthermore, the pressure fluctuations induced due to ultrasound propagation through a tissue results in frictional heating of the tissue by converting mechanical energy carried by the wave into heat. This leads to a mechanism called hyperthermia, in which the tissue is exposed to ultrasound waves to maintain mild temperatures ($40-45^{\circ}C$) for long time or few minutes to few hours [7]. Hyperthermia can be directly cytotoxic or can be used in coordination with other therapies [8].

Other forms of ultrasound induced therapies can be categorized into thermal ablation and mechanical effects. In thermal ablation, absolute temperature of the tissue is raised to about $60^{\circ}C$ with high power ultrasound exposure for a short duration. The ultrasound exposure which lasts for few seconds to minutes leads to rapid cell death thus causing coagulation necrosis [4]. Non-thermal or mechanical effects are achieved by exposing tissue to repeated short-duration pulses of high intensity ultrasound. The tissue is thus mechanically disrupted. Mechanical disruption of tissue is caused by different methods depending on the variation of parameters such as intensity, duty cycle, duration and number of pulses. These effects are termed as histotripsy, boiling histotripsy and millisecond boiling in the literature [9, 10, 11, 12, 13, 14, 15, 16].

Different bioeffects can be induced in the tissue depending on the ultrasound intensity. Small biological changes are caused with ultrasound techniques with intensity less than $1KW/cm^2$ [14, 17]. Cell apoptosis [18] can be induced with higher in-

tensities ($1 - 10KW/cm^2$). These higher intensities can also result in an increase in permeability of blood vessels which can in turn enhance drug delivery [14, 18]. Focused ultrasound with extremely high intensities (greater than $10KW/cm^2$) can lead to complete destruction and fractionation of the tissue. These techniques are called histotripsy and bioling histotripsy [19, 20, 9]. An advantage of pure mechanical destruction over thermal ablation is the avoidance of damage to surrounding healthy tissue due to precise demarcation of the treated area. Another advantage is the fragmentation of tissue that results in debris which can either be absorbed or removed from the body. However, the mechanical bioeffect of ultrasound waves are not fully understood.

2.5 Modeling of Acoustic waves

Propagation of acoustic waves can be described with mathematical models that can be categorized into two broad categories. Simple acoustic numerical models which are simple, easy to implement and computationally efficient; and Full wave models which accounts for complex inhomogeneous media and offer more realistic modeling of acoustic wave propagation in human tissue. They are complex and more computationally expensive, however. Both types of models are briefly described in the following paragraphs.

2.5.1 Simple Acoustic models

These models provide an approximation of acoustic wave propagation in a homogeneous medium. They are easy to implement numerically, hence they are commonly used. Two popular types of such techniques are *Rayleigh Sommerfield integral* and *Angular Spectrum method*.

2.5.1.1 Rayleigh Sommerfield integral

Rayleigh Sommerfield (RS) integral is the most widely used model and is based on two assumptions. First, the vibrating element is flat and part of an infinite rigid

baffle. Secondly, the generated wave propagates in an infinite, homogeneous, linear medium.

To calculate RS integral, the surface of the transducer is divided into finite number of small elements and the medium is also sampled into a finite number of field points. The contribution of each point source at each of the observation point is then calculated. The total acoustic pressure at each field point is the sum of all the contributions from all the source points. For planar piston ultrasonic transducer radiating acoustic beam directly into the medium, the pressure at a point x is calculated using the RS integral as

$$p(x, \omega) = \frac{-i\omega\rho v_0}{2\pi} \int_s \frac{\exp(ikr)}{r} ds \quad (2.15)$$

where p is complex acoustic pressure at point x , ω is angular frequency of ultrasound wave, r is distance between point source and the field point, v_0 is velocity of sound wave. Absorption coefficient can be incorporated to account for the absorption in the medium by replacing $\exp(ikr)$ with $\exp((ik - \alpha)r)$.

The RS integral is simple to calculate and implement however, the computation time increases when both the medium and source are finely discretized to increase the accuracy. The model also suffers from limited accuracy in the near field. The assumption of infinite baffle does not take into account the diffraction effects at the transducer edges. The medium is also assumed to be infinite and homogeneous. There have been some extensions to the original model to account for these limitations. These include *Tupholme-Stepanishen Impulse Response model* [21, 22, 23] to account for diffraction effects at the edges of the transducer and *fast near-field method* [24] to account for inaccuracy in the near field.

2.5.1.2 Angular Spectrum Approach

The Angular Spectrum Approach (ASA) was first used in optics for field propagation from source to destination plane [25]. It has been widely used in ultrasonics due

to its fast computation time. In this technique, a pressure distribution on a plane surface is decomposed into its equivalent two-dimensional spectrum of waves [26]. Propagation of the wave from one plane to another is computed by multiplying each spectral component by appropriate phase factor. The model provides high computational efficiency. The model is capable of forward propagation from source plane to receive plane and backward propagation from receive plane to source plane.

Assume a continuous wave field propagating in the z -direction. The complex pressure field $P(x, y, z_0)$ at a source plane at z_0 is decomposed into two-dimensional angular spectrum of component plane waves, each propagating in different direction. By taking two-dimensional fast fourier transform (FFT) of the source-plane pressure wave, the angular spectrum denoted by $P(f_x, f_y, z_0)$ is obtained as follows [27]

$$P(f_x, f_y, z_0) = \int \int_{-\alpha}^{\alpha} P(x, y, z_0) e^{-i2\pi(f_x x + f_y y)} dx dy \quad (2.16)$$

where f_x and f_y are spatial frequencies in xy directions, respectively. The pressure field at a plane parallel to the source plane can be calculated by multiplying the phase factor with the components of the angular spectrum of the source plane. the phase factor is [27]

$$\begin{aligned} G(f_x, f_y, z_0, z_1) &= e^{j2\pi \frac{z_0 - z_1}{\lambda}} \sqrt{1 - (\lambda f_x)^2 - (\lambda f_y)^2} \\ &= e^{j(z_0 - z_1)} \sqrt{k^2 - (\omega_x)^2 - (\omega_y)^2} \end{aligned} \quad (2.17)$$

where λ is the wavelength, k is the wavenumber, ω_x and ω_y are angular frequencies in xy directions, respectively.

The pressure field distribution on the target plane can be calculated by an inverse FFT of the angular spectrum of the target plane as

$$p(x, y, z_1) = \int \int_{-\alpha}^{\alpha} P(f_x, f_y, z_1) \cdot e^{j2\pi(f_x x + f_y y)} df_x df_y \quad (2.18)$$

The acoustic pressure field is thus calculated for all the plane parallel to the previous planes. This technique is not only computationally efficient but can also reconstruct the source distribution from the measurement of the radiated field due to its backward propagation. However, the model is not capable of modeling wave propagation in inhomogeneous media and can not account for attenuation, reflection and refraction. It is also not capable of modeling non-harmonic waves such as pulses and does not model non-linear propagation. Moreover, the source field distributions are limited to planar sources in simulation.

Various techniques have been employed to account for these limitations such as modeling of inhomogenities in a layer-based approach along the axis of propagation. Different speeds of sound are assigned for each plane of the wave in different media while calculating the phase factor which is a function of the speed of sound and frequency in the medium [26, 27, 28, 29]. Non-harmonic excitation such as broadband pulses are also simulated with this approach by transforming the excitation signal from time-domain to frequency-domain and simulating each spectral component separately. Total pressure field resulting from the non-harmonic signal is then calculated by summing each of the acoustic pressure field simulated separately [26]. To account for attenuation and absorption, the real-valued wave number is replaced by a complex number and the energy loss due to propagation in a lossy media can thus be measured.

2.5.2 Acoustic Full Wave models

Simple acoustic beam models simplify numerical modeling of wave propagation using approximation and thus do not take reflection, refraction and medium absorption

into account. On the other hand, full wave models provide more realistic representation of wave propagation in a complex, inhomogeneous medium. The most prominent of these models are *Westervelt equation* and *Khoklov-Zabolotskaya-Kuznetsov (KZK) equation*.

2.5.2.1 Westervelt equation

Westervelt equation is very famous for ultrasound modeling and provides high accuracy in inhomogeneous media. The generalized form of *Westervelt equation* is [30, 31, 32]

$$\rho \nabla \cdot \left(\frac{1}{\rho} \nabla \rho \right) - \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} + \frac{\delta}{c^4} \frac{\partial^3 \rho}{\partial t^3} + \frac{\beta}{\rho c^4} \frac{\partial^2 p^2}{\partial t^2} = 0 \quad (2.19)$$

where p is sound pressure, δ is sound diffusivity, β is nonlinearity coefficient, c is sound speed and ρ is density of the medium. The first and third term accounts for diffraction and attenuation, respectively. This equation takes medium heterogeneity in account. A simplified version for homogeneous media will be [33]

$$\nabla^2 p - \frac{1}{c_0^2} \frac{\nabla^2 p}{\nabla t^2} + \frac{\delta_0}{c_0^4} \frac{\nabla^3 p}{\nabla t^3} + \frac{\beta_0}{\rho_0 c_0^4} \frac{\nabla^2 p^2}{\nabla t^2} = 0 \quad (2.20)$$

where c_0 is the sound speed, δ_0 is the diffusivity, ρ_0 is density of the given medium. By setting the nonlinearity coefficient to 0, linear acoustic wave equation can be derived as

$$\nabla^2 p - \frac{1}{c_0^2} \frac{\partial^2 p}{\partial t^2} + \frac{\delta_0}{c_0^4} \frac{\nabla^3 p}{\nabla t^3} = 0 \quad (2.21)$$

Equations 2.20 & 2.21 can be used to approximate wave propagation in weakly heterogeneous tissues. The nonlinear wave equation 2.19 can be used in HIFU modeling through the ribcage or skull. Because of the presence of high harmonics in the HIFU field, spatial and temporal resolution should be refined, which considerably

increases the computation time. It has been suggested that *Westervelt equation* is accurate for highly focused transducers [30, 33]. This equation can model all propagation phenomena except propagation of shear waves, thus has limited accuracy in modeling propagation through solids.

2.5.2.2 Khoklov-Zabolotskaya-Kuznetsov equation

The *Khoklov-Zabolotskaya-Kuznetsov (KZK) equation* has been widely used for numerical modeling of ultrasound. It accounts for diffraction, absorption, energy losses and nonlinear effects. It is a parabolic approximation of *Westervelt equation* and therefore less accurate in the near-field as well as away from the main axis. Thus steered beams can not be modeled accurately with *KZK equation*. In case of focused transducers, *KZK equation* can model wave traveling within 16° of the beam axis compared to *Westervelt equation* which can model up to 80° of the beam axis, *KZK equation* is this not accurate for highly focused transducers [31].

The *KZK equation* for homogeneous media is written as [32]

$$\frac{\partial^2 p}{\partial z \partial t'} - \frac{c_0}{2} \nabla_{\perp}^2 p - \frac{\delta_0}{2c_0^3} \frac{\partial^3 p}{\partial t'^3} - \frac{\beta_0}{2\rho_0 c_0^3} \frac{\partial^2 p^2}{\partial t'^2} = 0 \quad (2.22)$$

where t' is retarded time i.e. $t' = t - \frac{z}{c_0}$ and $\nabla_{\perp} = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}$ is the transverse laplacian.

The major advantage of *KZK equation* is modeling nonlinear acoustic wave propagation. Inability to model solid media accurately and the paraxial approximation are its main limitations. The paraxial approximation cause errors in the near-field and away from the axis. Thus this model is not appropriate for highly focused ultrasound.

2.6 Summary

In this chapter, some basics of ultrasound including acoustic wave properties, characteristics of the medium, transducer properties, focusing of ultrasound waves, propagation of ultrasound through tissue and modeling of acoustic waves, are briefly described. In the next chapter, a detailed overview of the therapeutic ultrasound and the recent advances in the transducer design and image guidance is given.

Chapter 3

Background and Literature Review

This chapter starts with an introduction to High Intensity Focused Ultrasound (HIFU) and the technique to use HIFU for tissue ablation. It then gives a historical overview of the evolution of ultrasound into the present therapeutic ultrasound with a brief review of the diagnostic ultrasound in the beginning. Therapeutic ultrasound, its mechanism of action, various types of therapeutic transducers are discussed in detail with an emphasis on how attempts are being made to perform HIFU therapy behind the ribcage. Treatment planning and monitoring of HIFU therapy are discussed and an overview of the current imaging modalities used for HIFU is given and the need of imaging with therapeutic arrays is highlighted.

3.1 High Intensity Focused Ultrasound

Medical ultrasonics applications fall into two categories: diagnostic ultrasound and therapeutic ultrasound. The focus of this chapter is on therapeutic ultrasound. Ultrasound has the ability to penetrate deep into the soft tissue at millimetric wavelengths which makes it an ideal method for completely non-invasive interventions. Therapeutic ultrasound offers a noninvasive way of treatment of various ailments in

human body with reduced recovery time and reduced risk of infections [34]. Different physical effects are induced by the interaction of ultrasonic waves with the tissue. Therapeutic ultrasound or focused ultrasound can be categorized into two categories depending on the amount of energy being delivered to the body, Low intensity focused ultrasound (LIFU) and High Intensity Focused Ultrasound (HIFU). LIFU uses frequency between $0.2 - 2$ MHz and produces pressure on the order of a few MPa. Short bursts of ultrasound pulses are used in LIFU to induce cavitation without any significant thermal effects and is commonly used in sonoporation, opening of the blood brain barrier, thrombolysis and neuromodulation. HIFU, on the other hand, apply ultrasonic waves with pressure on the order of tens of MPa and intensities of $5000 - 10000$ W/cm^2 . The frequency of operation is normally $0.5 - 3$ MHz with continuous wave sonication that may last few seconds.

3.2 Technique of HIFU ablation

HIFU ablation is performed typically with a piezoelectric transducer at low MHz frequencies. The ultrasound field is focused into the body at the desired target, which is absorbed by human tissue when the ultrasound wave propagates through it. The absorbed acoustic energy is transformed into heat. At the focus point, the increase in temperature exceeds $60^\circ C$ and causes coagulation necrosis. In addition to increase in temperature, inertial cavitation is induced which leads to extremely high local temperatures and mechanical stresses resulting in cell death and the targeted tissue region is thus destroyed. The surrounding tissue and the tissue in the path of HIFU beam remain unaffected due to the low ultrasound energy density. A sonication may last up to a few seconds and a gap is needed between adjacent sonications to cool down the intervening tissue in order to avoid thermal damage. This may increase the total duration of HIFU treatment. Treatment time can be reduced by generating multiple HIFU beams.

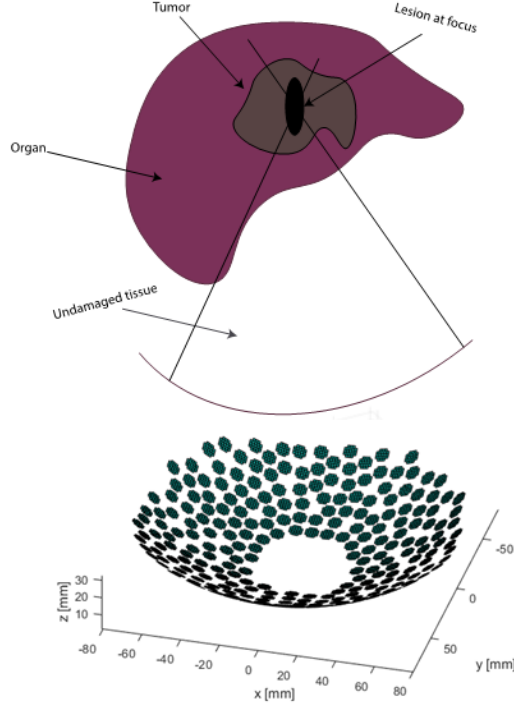


Figure 3.1: Diagram showing HIFU ablation by a therapeutic random phased array.

3.2.1 Steering of single Focus

The simplest and most widely used technique to ablate a larger tumour is to scan the HIFU beam. Scanning provides increased spatial coverage granting access of the HIFU beam to entire tumour. Scanning can either be done using mechanical scanning (fixed single element transducer), electronic scanning (phased arrays) or both.

3.2.2 Generation and Steering of Multiple Foci

Multiple foci can be generated by adjusting the phases and amplitudes of the elements in a phased array. Multiple foci may decrease the treatment time by performing volumetric ablation. Ebbini *et al.* were the first to show the ability of phased array to generate multiple simultaneous foci [35]. The synthesis of multiple simultaneous foci by phased arrays was studied in many other studies. This feature of phased arrays is of considerable importance in applications when the tumor is deep located in tissue and treatment time needs to be shortened. Generation of multiple

foci has the advantage of reduced peak pressure in each of the focus as it would avoid inertial cavitation. However, to obtain optimum pressure levels at each of the foci, input acoustic power has to be increased which may lead to near-field heating.

3.3 Historical Overview

3.3.1 Diagnostic Ultrasound

The study of ultrasound dates back to at least few centuries when physiologist Lazzaro Spallanzani studied echolocation among bats in 1790 which formed the basis for ultrasound physics [36]. In 1822, a Swiss physicist Jean Daniel Colladen calculated the speed of sound in water by using underwater bell in Lake Geneva [37]. Experiments with ultrasound began with the discovery of piezo-electric effect by Pierre Curie and his brother Jacques Curie in 1880 in Paris [38]. With the advancement in electronics, French physicist Paul Langevin and Russian scientist Constantin Chilowsky developed powerful high frequency echo-sounding device that was used in world war I [39]. In 1940s, Karl Theo Dussik, a neurologist at University of Vienna measured the transmission of ultrasound beam through the skull in an attempt to locate a brain tumour [40]. Ultrasound as a diagnostic tool was properly analysed by George Ludwig in Maryland, United States in late 1940s [41]. He used pulse-echo technique similar to RADAR to detect foreign objects in animal tissues first and then the detection of gall stones in human body. The first real time ultrasound images were produced in early 1950s by John Wild and John Reid in Minnesota when they produced images of cancerous growth of the breast [42]. Douglas Howry at the University of Colorado did some pioneering work in developing B-mode equipment. Together with other colleagues including Joseph Holmes, he obtained interpretable 2-D images of internal organ structures. The first handheld compound B-mode scanner designed by Holmes and colleagues was commercially launched in the United States in 1963 [43]. In 1970s, continuous wave Doppler and color Doppler ultrasound instruments were developed. Kazunori Baba from Univer-

sity of Tokyo developed 3D ultrasound and captured 3D images of a fetus in 1989 [44]. Since 1990s, ultrasound imaging is getting more sophisticated and the image quality is improving along with the adoption of 3D and 4D capabilities.

3.3.2 Therapeutic Ultrasound

While ultrasound is widely known for its imaging capabilities, its use in medicine started initially as a therapeutic modality rather than diagnosis in 1920s when Langevin and then Wood and Loomis saw a surprising effect of using sound waves of high frequency and intensity killed fish and frogs with an exposure of up to two minutes when they swam in the ultrasound beam, whereas the bacteria survived. The cause of death was thought to be due to the internal heating as dropping ice into the water around the fishes did not prevent them from getting heated and being killed [45]. While high intensity ultrasound was thought to be a destructive tool, the first thought of therapeutic use of ultrasound was by H. Freundlich and colleagues who suggested that it can be used to heat tissue [46]. The first animal testing was performed by John G. Lynn in 1942 who was able to produce lesion deep in the bovine liver without damaging the surrounding tissue [36]. William Fry and Francis Fry were the first to develop a focused ultrasound device by mechanically aligning four ultrasound generators (fig. 3.2) to produce a lesion in a single point without damaging the surrounding tissue [1, 47]. They conducted animal and human studies in 1950s and showed that high powered ultrasound can be focused to target a small part of the body and create a localized lesion. In 1964, M. Oka successfully used focused ultrasound to treat thyroid and breast cancers [48]. These and other initial experiments with high intensity focused ultrasound (HIFU) showed great promise in 50s and 60s and many patients were treated for diseases such as Parkinson's and Essential Tremor [49, 50]. By 1970s, the use of therapeutic ultrasound was established for physiotherapy and research was continued for use in other difficult applications such as neurosurgery and cancer treatment [51, 52]. The major difficulty with these initial experiments with HIFU were their long treatment time,

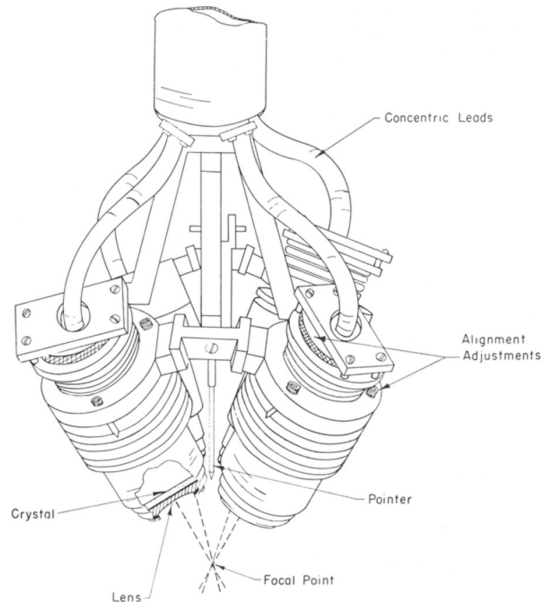


Figure 3.2: Schematic of the therapeutic transducer system consisting of four individual transducers to create a high-intensity localized focus [1]

lack of suitable imaging modalities and the invasive nature e.g. removal of the skull.

3.3.2.1 Single element Transducers

In 1990s, HIFU saw a renaissance due to the advancement in high quality imaging and monitoring techniques. Much of the work done so far involved a single or few transducers with curved surfaces [50, 53, 54, 55]. Later, small sized single element transducers were used for a widely used application of the treatment of prostate cancer. The transducer would be moved mechanically within the rectum to transversely target the prostate. Sonablate (Focus Surgery, Indianapolis, IN, USA) was a USA based such device [56, 57, 58], consisting of two single focused transducers with different focal distances which were mounted back to back and could be moved mechanically inside the rectum and irradiate the prostate. Another commercial device is Ablatherm (EDAP-TMS SA, Vaulx-en-Velin, France) comprising a treatment transducer driven at 3 MHz and an imaging transducer at 7.5 MHz [59, 60]. Both these transducers suffered from fixed focal lengths so for treating a different depth, a transducer with different focal distance was needed. Thus the use of phased array was needed to steer the focus.

3.3.2.2 1D Arrays

The improvement in piezo technology allowed the construction of high-powered phased arrays for therapeutic applications [61], capable of creating sharp single and multiple foci and able to treat the diseased site while avoiding critical structures [35]. Linear arrays were widely adopted for the treatment of prostate cancer. Diederich and Hynynen used a 0.5 MHz cylindrical array for intracavitary hyperthermia of prostate and showed experimentally that at a depth of 20 – 50mm of the tissue, hyperthermia temperatures could be achieved [8]. Hand *et al.* suggested an intracavitary linear phased array to achieve high temperatures for the treatment of prostate [62]. This was followed by implementation of linear phased arrays for treatment of prostate mainly by Hynynen and his colleagues [63, 64] and Gavrilov and Hand [65, 66]. It was soon realized that phased arrays suffer from generation of secondary intensity maxima also called grating lobes away from the main focus, if the Nyquist criteria is not fulfilled. Appearance of such unwanted intensity maxima give rise to a considerable risk of thermal damage to the healthy tissue. To decrease the level of grating lobes, the spacing between the array elements should be less than $\lambda/2$, where λ is the wavelength. However, this necessitates the use of small elements giving rise to a large number of elements and number of channels thus complicating the system and increasing its cost.

Several methods were used to reduce the level of grating lobes of a linear array. In one method, the central part of the array was excited with higher amplitude and the periphery with lower [67], however, this led to lower acoustic power at the target. Another technique was to use elements with unequal sizes as was suggested in [63, 64]. They used a linear phased array consisting of 57 elements of equal lengths but different widths and hence different center-to-center spacing and the reduction of grating lobes was predicted to be less than 40% [64]. It was also observed that the average element width can be increased by 20 - 35 % in aperiodic arrays while maintaining the same level of grating lobes as periodic arrays. In another

approach, Gavrilov and Hand deactivated several elements in the array to suppress grating lobes [66]. They showed that using subsets of active elements resulted in significant decrease in intensity of the grating lobes compared to when all elements are activated. A linear phased array for endocavitary treatment of prostate cancer consisting of 70 elements 1 mm wide, 15 mm long and 1.73 mm thick and operating at 1 MHz was presented in [65]. The length of the array was 77 mm and inter-element spacing was 0.73. The method of activating a subset of elements was used and a reduction in the magnitude of grating lobes was observed. Hutchinson and Hynynen showed *in vivo* results in a rabbit thigh muscles using a linear phased array [64]. An improved design was presented by Hynynen in a later work in which the array was rotated mechanically using an ultrasonic motor, hence the focus could be moved both in axial and transverse directions [68]. The commercially available devices for prostate surgery (Focus Surgery, USA and EDAP-TMS, France) are based on single transducers with fixed focal length, efforts were made to replace the fixed focus single element transducers with steerable phased array transducers. Tan *et al.* [69, 70] at Focus Surgery Inc. (IN, USA) studied the ability of a cylindrical concave array to move the focus along the depth. Curiel *et al.* [71] at EDAP-TMS (Lyon, France) proposed and simulated two different 1.5-dimensional array operating at 2.5 MHz for the treatment of localized prostate cancer. Seip *et al.* [72] at Focus Surgery presented *in vitro* and *in vivo* results of two array designs in 4th International Symposium on Therapeutic Ultrasound. One design consisted of a 20-channel annular array capable of focusing in depth from 25 mm to 50 mm and operating at 4 MHz. The other design was a 422-elements cylindrical array, capable of focusing in depth from 25 mm to 50 mm and steering laterally over a range of ± 20 mm. There were some other efforts in designing linear arrays for treating prostate cancer including those proposed by Held *et al.* [73] and Chen *et al.* [74]. Many applications benefit from 2D arrays, however.

3.3.2.3 2D Arrays

The advantage of using linear arrays for HIFU therapy is that they are thin and can be inserted into the body cavity to perform tissue ablation. With linear arrays, the focus can be steered in both lateral and axial directions but electronic steering of the focus in third direction is not possible. Two-dimensional phased arrays not only offer electronic steering of focus in all three directions but are also able to generate patterns of multiple foci, thus increasing the necrosed tissue volume and reducing the treatment time. Research in phased arrays for hyperthermia and surgery started in the second half of 1980s. Ocheltree presented a phased array device by stacking five linear phased arrays [75]. Cain and Umemura were the first to propose a sector-vortex array, which was able to create an annular focus at the geometric center of the array [76, 77].

Ebbini and Cain were the first to propose a spherical section array in which elements were mounted on a spherical shell [78]. The array not only produced sharp focus at the target but was also able to steer the beam both laterally and axially with lower grating lobe level than a planar array. Hynynen came up with array designs including a simple spherical two-dimensional array comprised of 16 elements while leading a research group at Boston [79]. In vivo experiments were performed by Hynynen and his team [80] with another spherical array consisting of 256 elements and operating at 1.1 MHz. Lesions with an area of $10 \times 10 \text{ mm}^2$ were created at a depth of 70 mm inside the tissue. Maximum acoustic power was 350 W and side-lobe levels did not exceed 10% of the main beam. Clement *et al.* [81] investigated a hemispherical array with 64 equally sized elements operating at 0.665 MHz. The array was designed for trans-skull ultrasound therapy non-invasively. The aim was to correct the distortion of the beam through the skull and minimize heating of the skull bone. They exposed a sample of rabbit muscle tissue through a human skull with a maximum power of 2624 W for 8 seconds, and ablated the tissue. Heating on the skull was noted, with an increase in temperature ranging from 12 °C to 18

°C. They further calculated pressure at the geometric centers of arrays with various number of elements, and compared the results with the original 64-element array and found that performance of the array was significantly better than the 8- and 16-element arrays but wasn't much inferior to the 228- and 501-element array. It was thus concluded that a 64-element array is the optimum in terms of cost and complexity of the system for the given performance [82]. Trans-skull brain-tissue ablation was further investigated by Clement *et al.* [83, 84] using a two-dimensional 500-element array operating at 0.74 MHz. It was claimed that use of the array is feasible for a complete non-invasive therapy through the intact skull. An annular array was developed for transcranial applications by White *et. al* [85] comprising 448 elements with a diameter of 120 mm and a radius of curvature of 120 mm, operating at 1.1 MHz. The elements were distributed regularly within 12 rings. The array was driven in two steps. First, elements from 1 to 256 were driven and then the rest and the results were superimposed for a composite scan. The first Magnetic Resonance Image guided (MRI-guided) clinical device for treatment of Uterine Fibroids was based on the designs discussed above [86]. Commercially, Insightec (Haifa, Israel) has been developing MR-guided phased array devices, namely ExAblate 2000, ExAblate 3000 and ExAblate 4000. ExAblate 3000 is a hemispherical ultrasound array system with 512 elements. The radius of curvature of the array is 15 cm and the frequency of operation is 670 KHz. The ExAblate 4000 has 1024 elements and has two variants, one operating at 220-230 KHz and the other at 650-660 KHz. Both these devices are for transcranial applications. Hynynen and colleagues thoroughly investigated the low frequency device and pointed out the danger of skull heating, and suggested safety limits for treatment through the skull [87].

3.3.2.4 Sparse Random Phased Arrays

Two dimensional phased arrays provide the flexibility to steer the focus in three orthogonal directions and thus can ablate a tissue volume. Size of the elements need to be reduced in order to increase the extent of volume to be treated. The active area of the array should not be less than 50 cm² to deliver enough energy to ablate

the tumour, however [88]. It is also important that the intensity in the secondary maxima must be kept low to avoid thermal damage. In order to eliminate the grating lobes, spacing between the centers of the array elements must be less than $\lambda/2$ [67]. This necessitates a large number of elements and channels and thus increases the cost and complexity of the system. The phased arrays discussed in the previous section suffered from undesired grating lobes and other secondary intensity maxima to some extent. The regularity in the grating lobes in the acoustic field is due to the spatial regularity of the array structure which can be diminished by randomly distributing array elements on the surface of the array. Formation of regular grating lobes is mitigated by the randomness of the array elements. Goss *et al.* [89] used a 108-elements spherical array with diameter of 100 mm and radius of curvature 102 mm to experimentally demonstrate the effect of randomness in therapeutic applications. The size of each element was 8 mm, which was approximately eleven times the wavelength, and the operating frequency was 2.1 MHz. They activated only 64 elements, randomly selected from the set of 108 regular elements; however, six grating lobes were observed. They concluded that randomly selecting elements from a regular structure does not help in mitigating grating lobes. Rather, the elements should be randomly distributed on the array surface. Gavrilov *et al.* [90, 91] developed an approach to randomize the elements over the surface of the array and suggested that the diameter of each element must not exceed five wavelengths. Furthermore, the sparseness of the elements must not be too much, at least 40% of the array surface must be covered to deliver enough acoustic energy at the target. It was thus shown that random phased arrays improve the quality of intensity distribution and reduce the grating lobes [92].

An MRI-guided random phased array device for clinical uterine fibroid treatments was designed by Hand *et al.* [4]. The array consisted of 254 elements randomly positioned on a spherical shell of diameter 170 mm and radius of curvature 130 mm. The diameter of each circular element was 7 mm and the inter-element spacing varied from 7.9 mm to 9.4 mm. The frequency of operation was 0.8 – 1.2 MHz and

active area of array was approximately 100 cm^2 . A sparse quasi-random array was fabricated at Université Paris consisting of 200 piezocomposite transducers each 8 mm in diameter and mounted on a spherical surface. The diameter of the array was 180 mm and radius of curvature was 120 mm. The frequency of operation was 0.9 MHz and the maximum intensity at the transducer surface was 20 W/cm^2 . Gelat *et al.* [93] investigated and optimized theoretically the acoustic field of a 1 MHz random phased array consisting of 256 elements mounted on a spherical shell with radius of curvature 18 cm and diameter 16 cm. The diameter of each element was 6 mm. Some other random phased arrays that were used and evaluated with improved performance were developed in [94, 95, 96, 97]. In these arrays, the elements were distributed aperiodically which reduced the secondary hotspots while maintaining sufficient intensity at the focus.

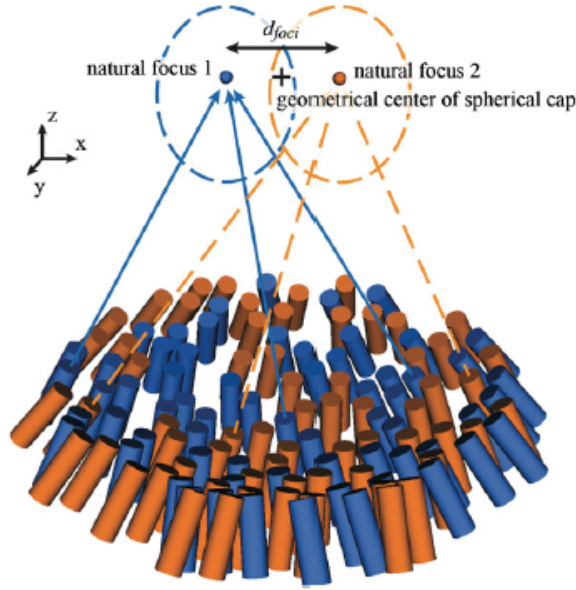


Figure 3.3: Design principle of the random phased array with two natural foci, defined as the points of intersection of the normal direction of elements of the corresponding sub-array. d_{foci} is the distance between the two foci. Image taken from Auboiroux *et al.* [2]

3.3.2.5 Dense Random Phased Arrays

Despite their advantages, sparse random arrays have shortcomings. Though the aperiodic distribution of elements leads to incoherent distribution of energy in the treatment volume, avoiding the formation of secondary hot spots, this comes at

the expense of reduction in the focal intensity due to the unused surface of the array. More input power is thus required to achieve the desired focal intensity equivalent to a fully populated array. This results in transmitting extra energy through the underlying tissues increasing its temperature leading to a reduction in the rate of ablation [98]. Moreover, due to the high directional elements, the steering range of the array is small and steering beyond a distance of the order of 1 cm results in reduced focal intensity and increased secondary hotspots. For efficient energy delivery, there is need of a large aperture with high gain. Large spherical aperture however limits the steerability of the acoustic energy. Large aperture also dictates the need to increase the number of elements which increase the number of channels and interconnects. It is thus desirable to build a high power array with maximum steerability without any grating lobes and minimum number of elements. Ultrasound field simulations should be performed to optimize the number and positions of elements to maximize the array performance [7].

In addition to breaking periodicity of the array by randomizing the element distribution, a very high peak power of the array is required for ablation in applications such as abdominal treatments and transcostal treatments through skull or ribcage. Increasing the input power would increase intensity at the surface of the elements and may exceed the maximum permissible value of $\sim 40 \text{ W/cm}^2$ [99, 100]. One way to increase the acoustic power is to increase the active radiating surface or the filling factor of the array. Densely packed arrays with filling factor close to 100% are best for obtaining high intensity fields at the geometric focus without overheating the nearfield tissue.

In order to study the effect of increasing the array filling factor on intensity at the focus and sidelobe reduction, various geometries have been proposed recently. Auboiroux *et al.* [2] proposed and tested a random phased array architecture with increased capability of electronic steering without reducing the size of each element. They divided the array into two sub-arrays such that each element in a subarray pointed to a distinct focus point. Each subarray was capable of steering the focus

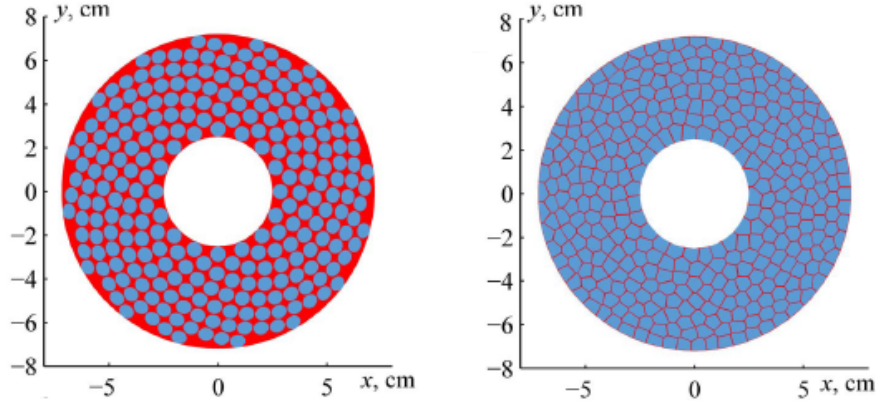


Figure 3.4: Front view of a 256 circular elements phased array with a compact 16-spirals layout (left), capacity-constrained tessellation array with 364 elements with elements shaped as spherical polygons [3]

of up to 1 cm surrounding its natural focus. The resulting steering range was thus larger than that achieved by a usual random phased array. The array was claimed to benefit medical applications in which large tumours in moving organs need to be operated. Raju *et al.* [101] from Philips research (NY, USA) designed two 2D therapeutic arrays with 128 elements each distributed on a spherical shell. Both arrays were based on two types of tessellation patterns, one based on the two-shape aperiodic Penrose tiling and the other based on a single rectangular shape non-periodic tiling. The performance of both arrays was compared with a spherical random array with circular elements and a spherical regular array with square elements. Off-axis steering capability and intensity gain of both tessellated arrays was assessed and compared with the other two arrays. It was shown that space-filling non-periodic arrays (Penrose and Rectangular array) and spherical arrays with circular elements produced grating lobes less than -10 dB when steered 8 mm off axis and the energy was concentrated in the main beam. It was further shown that the rectangular aperiodic array generated two and half times more power compared to the random array with circular elements. The computed acoustic pressure at input acoustic power of $1W/cm^2$ was, 3.91 MPa for Penrose array, 4.11 MPa for rectangular array, 2.64 for array with random circles and 3.74 MPa for periodic array.

Rosnitskiy *et al.* [102] studied the possibility of designing densely packed arrays in

which elements are distributed in spiral shape. The benefits of such arrays were claimed to be twofold: one, the elements are positioned aperiodically on the array surface, thus the periodicity is broken and secondary hot spots are avoided. Secondly, the filling factor is increased and is much larger than usual phased array. Two spiral arrays with 512 elements and operating at 1 MHz were proposed and compared with random phased array. The first array was composed of disk elements with diameter of 6 mm, whereas, the second array had square elements with sizes of 6×6 mm. They concluded that with the spiral arrays more gain in the intensity at the focus can be obtained. The scanning area of such arrays is smaller than the random arrays which can be widened if square elements are used instead of disks in spiral arrangement. Four novel transducers based on Fermat's spirals, two of which were Voronoi-tessellated were proposed and evaluated numerically [103, 104]. One of the designs based on Voronoi-tessellation, was examined experimentally. It was concluded that such designs provide a high degree of focusing, making them relevant for HIFU thermal ablation, histotripsy and shock-wave enhanced heating while maintaining the possibility of beam steering. A fully populated random array with equal area polygonal elements and 100% filling factor (if no gaps are introduced between elements) was proposed. Capacity constrained tessellation was used to partition the surface of the array. The array was compared with an existing 256-element spiral array and the peak intensity at focus was shown to be twice as high. They also suggested that with the given technique, it is possible to design arrays with different shapes to suite different HIFU applications [3].

3.4 HIFU therapy behind the ribcage

One major limitation in the use of HIFU for tumour ablation is the presence of strong scattering and absorbing obstacles such as ribcage. Planning for the HIFU treatment of the liver is severely affected by the presence of ribcage due to the fact that ribcage acts as an aberrator which decreases the focus quality and also the bones get heated due to the high absorption coefficient of the bone [105]. Heat

is thus dissipated to the surrounding tissues [106]. Due to heating of the ribcage and the risk of skin burns, HIFU treatment of the organs behind the ribs is very difficult. Several studies have been undertaken to determine the effect of ribs on focus quality and quantify the energy delivery and heating at the ribs surface. A theoretical feasibility study for treating liver tumors through the rib cage with a phased array was performed by Botros *et al.* but was not experimentally evaluated [107]. In clinical applications, partial surgical removal of the ribs above the tumour was performed to make an acoustic window for the HIFU procedure but this did not satisfy the non-invasive nature of HIFU operation [108]. A linearly-segmented single element focused ultrasound system for treatment of liver tumors was developed by Civale *et al.* [109]. The device was positioned behind the ribs and close to the bottom of the rib cage such that the segment lying over the ribcage could be switched off to protect the ribs from overheating.

More numerical and experimental studies were performed to study the HIFU field in the presence of ribs. Liu *et al.* [110] theoretically investigated the feasibility of transrib focusing by exploiting CT images of the ribs from patients to perform modelling of propagation in liver and through ribcage. They deactivated a number of elements whose normal vectors crossed the ribs and studied the effect on acoustic pressure at the focus and temperature increase on the ribs. The method proposed by Liu *et al.* [110] was applied by Quesson *et al.* [111] to provide a proof of concept of the method. Anatomical MRI data of the patients was analysed and its effect on temperature distribution was evaluated both *ex vivo* and *in vivo*. Those transducer elements whose 50% surface was covered by the shadow of the bones were deactivated and concluded that this technique reduces the risk of excessive near-field heating and skin burns. Two approaches were proposed by Bobkova *et al.* [99] to determine the optimal amplitude-phase distribution of the acoustic field at the radiator surface to minimize the field on the ribs. In the first approach, the velocity amplitude at the elements shadowed by the ribs is set to zero. In the second approach, diffraction effects are included to improve focusing and protect the ribs. Splitting of the focus

into three foci was observed both in simulation and experimentally [99]. Theoretical investigation of the effect of focus splitting after propagation of focused ultrasound through a phantom of parallel strips was studied by Khokhlova *et al.* [112]. Splitting parameters such as number of foci, their diameter, amplitudes and distance between them were analytically estimated. A time-correction method was used by Aubry *et al.* [105] to correct phase aberrations to maximize the ratio between energy deposition at the focus and the total emitted energy in the presence of ribs. It was shown that the temperature elevation on the ribs was reduced by 83% using this method compared to non-corrected spherical wavefront. However, this technique required a transducer to be placed at the desired focal point, which makes it an invasive procedure. The study was followed by a noninvasive solution by proposing a method to focus an acoustic field on a target while sparing ribs using the so-called decomposition of time reversal operator (DORT) method [113]. Three human ribs were immersed in water and a linear array was used to measure the set of singular vectors. Backscattered echoes were recorded on a transmit-receive array to find the invariants of the time-reversal process. The invariants defined the medium and were used to send energy back on the reflectors.

Gelat *et al.* [114, 93, 115] proposed a boundary element method (BEM) to model the scattering of HIFU field by human ribs in 3D. The model was reformulated as an inverse model in subsequent papers where normal velocities on element surfaces was optimized such that the acoustic pressure on the surface of the ribs remained below a specific threshold. An MR-guided HIFU system was used to study the focus quality through the ribcage in the University of Dundee, UK [116, 117, 118]. A rib phantom was used and elements shadowed by ribs were de-activated. Temperature rise near the ribs was observed to be reduced; however, the temperature rise in the focus was also low. Qiao *et al.* [119] proposed a modified geometric correction method in which the outputs of elements are adjusted based on their relative area being shadowed by the ribs. The ultrasound propagation through the ribs was then computed using a hybrid method including the Rayleigh-sommerfield integral, k-space method and

angular spectrum method.

A numerical study was conducted by Ramaekers *et al.* [103] to evaluate a Voronoi tessellated Fermat spiral shaped transducer for intercostal HIFU ablation using the binarized apodization approach [110, 111]. Energy density in prefocal tissues and energy incident on the ribs was evaluated for different tissue depths in simulation. It was shown that VTFS array provides low-intensity levels in the ribs plane and high intensity in the focal plane due to the increased active surface.

3.5 Image guidance and monitoring

Due to the non-invasive nature of HIFU, an integrated visualization method is required to accurately target the diseased tissue, precisely monitor the therapeutic procedure and avoid unnecessary thermal damage to healthy tissues. X-Ray CT, ultrasound and MRI have been used for image guidance and monitoring. MRI offers excellent soft-tissue contrast and allows accurate boundary mapping of the target region. MRI also provides information about the temperature rise of the tissue such that the temperature elevation at the focus point can be detected and localized. Current systems used clinically for targeting uterine fibroids use MR for guidance and monitoring and is the only guidance method approved by U.S. Food and Drug Administration (FDA) for treatment of uterine fibroids. However, MR suffer from some limitations that prevent its use in imaging the HIFU procedure in some tissues. It can take several seconds to acquire an MR image which results in long HIFU procedure times. The overall cost of the MR system including purchasing and maintenance cost and long acquisition times are its main limitations. Ultrasound, on the other hand, is a proven imaging modality. Though it does not offer the same level of soft tissue image contrast as MR, the low cost, compact size and the ability to image in real time makes it more attractive. It is the most widely used modality for guiding HIFU therapy. Though it does not offer reliable temperature mapping like MRI, research is being undertaken to develop techniques that can estimate cavitation activity, temperature rise and viscoelastic properties of tissue

[120, 121, 122, 123, 124].

In Ultrasound imaging of HIFU treatment, two different ultrasound systems are used. One for therapy whereas the other one for imaging. This technique poses some difficulties, mainly the limited field of view and low resolution of the imaging array due to its size, the alignment difficulties in the two arrays and the reverberations caused by the water stand-off required for therapy array. Moreover, HIFU has large aperture and long focal distance requiring the imaging transducer to image with a long stand-off distance. The imaging transducer needs to be fit mechanically within the area subtracted from the active area of the therapy transducer which necessitates a reduction in the size of the imaging transducer and effects the imaging quality.

An alternative is to image with the therapeutic array, which has an added advantage of inherent registration between the therapeutic and imaging frames of reference so strong scattering objects in the path of HIFU beam are also in the path of imaging beam. Hence the HIFU beam can be adjusted accordingly [125]. Typical HIFU systems are not optimized for imaging though, because they have highly focused large elements and the system has low spatial resolution away from the focus. Moreover, random phased arrays, such as the one used in this work, have elements that are larger in size, randomly distributed with inter-element spacing much more than the required half a wavelength, highly directional and operates in low MHz frequency, thus offering poor resolution and has limited field of view away from the geometric focus. HIFU arrays are normally narrowband for efficiency. Conventional beamforming is thus not suitable to image with such an array. Synthetic aperture imaging techniques have the potential to improve the spatial resolution of a therapeutic random phased array however, and is the technique used for the beamforming and imaging in this work. Imaging with the therapeutic array provides an opportunity to detect strongly scattering objects such as ribs which can then be avoided from being damaged during the HIFU treatment. The dual nature (imaging and therapy) of therapeutic arrays has been explained and presented in detail previously by Ebbini *et. al* [125, 126], however, their work is limited to convex, linear, regular phased

arrays and random phased arrays are not discussed. Moreover, detailed comparison of different synthetic aperture techniques with a therapeutic array has not been presented previously. It was thus important to determine the imaging potential of a therapeutic random phased array by analyzing and comparing variants of synthetic aperture imaging techniques and establish the benefit of using the array both for image guidance and therapy.

3.6 Summary

A chronological overview of High Intensity Focused Ultrasound is presented. Different types of ultrasound phased array for therapy are discussed. HIFU Therapy of the liver tumor behind the ribcage is explained and a summary of the previous efforts to ablate the tumor without damaging the ribcage is given. The significance and need for imaging with the therapeutic array is highlighted. In the following chapters, synthetic aperture imaging techniques will be implemented with the available random phased array both in simulation and experiment. Imaging with the therapeutic array enables us to find exact location of the ribs and the information is then used for image-based refocusing of the phased array to avoid heating the ribs. The effect of presence of ribs in the HIFU beam path are discussed in detail in the coming chapters.

Chapter 4

Synthetic Aperture Imaging - Simulation Results

The purpose of this chapter is to conduct simulations to select the focusing method that would subsequently be studied experimentally using the existing random phased array in the later chapter. Synthetic Aperture Imaging is described and the performances of different types of synthetic aperture imaging techniques are compared. Previously, synthetic aperture imaging techniques have been used only with the diagnostic transducers or with a dual mode convex, linear array as mentioned in the previous chapter. It was thus important to assess the performance of these imaging techniques with the random phased array. Simulations were first performed for a 128-element linear array to reconstruct images of wire phantoms followed by simulations with the existing 256-element therapeutic random phased array. The performances of these imaging techniques were compared and the best algorithm to image with the therapeutic array was singled out.

4.1 Conventional Delay and Sum beamforming

Beamforming is one of the most important processes of ultrasound image formation. In basic beamforming technique, an ultrasound waveform is generated by exciting

a transducer element with an electrical signal which would transmit a sound beam that propagates through the tissue. Beamforming is thus the process of combining signals to and from transducer elements. Various mechanisms take place at tissue interface such as scattering, diffraction, reflection and attenuation. Signals at particular angles experience constructive interference while others experience destructive interference. The transducer receive the reflected and scattered echoes generated by tissue inhomogenities and convert them back to the electrical signal. The received signals are then processed to form an image.

The most basic and widely used beamforming technique is delay and sum (DAS) beamforming. In DAS beamforming, a point source located at (x, y, z) is assumed to emit a short pulse at $t = 0$, denoted by S_t which is recorded by all elements. Signals recorded at elements positioned at coordinates (x_e, y_e, z_e) are scaled and time delayed according to distance r .

At every element (x_e, y_e, z_e) , signals are time reversed and emitted back. The time reversed signal is $S^*(t, x, y, z)$. At field point (x, y, z) , the wavefield is given by the superposition of the wave emitted from all elements,

$$P(t, x, y, z) = \int \frac{S^*(t - \frac{r}{c}, x_e, y_e, z_e)}{r} dx \quad (4.1)$$

$$P(t, x, y, z) = \int \frac{S(\frac{r}{c} - t, x_e, y_e, z_e)}{r} dx \quad (4.2)$$

where $S^*(t) = S(-t)$, P is the pressure field and r is the distance from the source to field point.

Replacing $\frac{1}{r}$ with general apodization weight $\alpha(x)$, the focused image pixel value at (x_0, y_0, z_0) is given by

$$I_p(x, y, z) = \int \alpha(x) \cdot S\left(\frac{r}{c}, x_e, y_e, z_e\right) dx \quad (4.3)$$

Thus, the formation of a single pixel corresponds to an integration along the hyperbola $t = \frac{r}{c}$ in the $t - x$ domain, weighted with the apodization factor α . This approach is called Delay and Sum (DAS) as the integration corresponds to summation of recorded signals with different time delays applied. Since the shape and location of the scatterer is not known, so the imaging procedure given by eq. 4.3 must be repeated for all points of interest to image the entire plane.

While transmitting, the directionality of the array can be changed by controlling the phase and relative amplitude of the signals at each element. Each ultrasound element has its own directivity pattern, also known as beam pattern or radiation pattern. When the element size is comparable to the wavelength, the influence of element directivity on wavefield generation and reception become significant and will produce errors in the resulting image if ignored, ensuring that the maximum response occurs at a given direction.

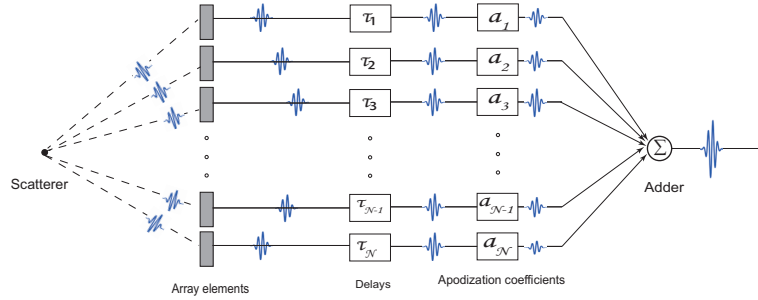


Figure 4.1: Delay and sum beamforming

In conventional beamforming, all elements in the aperture are used to transmit and receive and the beam is steered by introducing phase delays between the elements. Dynamic focusing is used in the receive mode by varying delays of the elements of transducer as a function of distance to the focus point. Lateral resolution, which is highest at the focus point and degrades away from it, can be improved by transmitting several beams focused at different points, however, this will decrease the

acquisition time. The frame rate is low because one image line is acquired at a time. The acquisition rate depends on the speed of sound and the maximum frame rate for a depth D and number of lines N_l is [127]

$$FR_{PA} = \frac{c}{2DN_l} \quad (4.4)$$

which in terms of pulse repetition frequency is:

$$FR_{PA} = \frac{prf}{N_l} \quad (4.5)$$

Number of lines N_l is determined by the lateral resolution of the system [128]. $N_l \geq 2N$ can be a good approximation for phased array systems [129], where N is the number of elements in the array. Frame rate for phased array system becomes

$$FR_{PA} = \frac{prf}{2N} \quad (4.6)$$

The frame rate gets lower for increasing number of lines and for large depths. Phased array imaging is also limited to a single focal depth in transmit. We can have more than one transmit focus points but at the expense of frame rate. There is thus a need to develop alternative technique to solve the problem of frame rate and single transmit focusing. Synthetic aperture imaging has the potential to address these problems but has several associated problems that should be addressed as well.

There are other advanced beamforming techniques such as parallel receive beamforming, spatial compounding, adaptive beamforming, passive acoustic mapping and robust capon beamforming [130, 131, 132, 133, 134] but only synthetic aperture imaging techniques are discussed in this thesis.

4.2 Image Resolution

The resolution of ultrasound imaging system is determined by its Point Spread Function (PSF) which is the response of the imaging system to a point source and is a powerful tool to assess the image quality. PSF is used to measure the spatial imaging resolution and is the image of a point in the space by the given imaging system. Resolution depends on the size of the PSF, the smaller the PSF, the better the image resolution would be.

Spatial resolution is the smallest distance between two targets or scatterers that can be resolved by the imaging system. Image resolution in the lateral direction is proportional to the width of the beam and is given by:

$$\Delta x = \frac{F\lambda}{a} \quad (4.7)$$

where F is focal distance, λ is the wavelength and a is the width of the aperture, whereas, axial resolution depends on the length of the pulse and is given by

$$\Delta z = \frac{c \cdot T_{pulse}}{2} \quad (4.8)$$

where c is the speed of sound, T_{pulse} is the pulse length.

Contrast resolution also defines the image quality and is a measure of how well the imaging system can differentiate between two regimes with different scattering properties. Contrast resolution is improved by lowering the sidelobe level of the PSF. Contrast resolution is also affected by the appearance of grating lobes which occur when the pitch is too large compared to the wavelength and the element distribution does not fulfill the Nyquist criterion.

4.3 Synthetic Aperture Imaging

In conventional phased array imaging system, all elements of transducer are used during both Transmit and Receive in each excitation cycle. Delay between the elements is introduced to steer the beam and scan a 2D plane or 3D volume. Dynamic focusing is used in the receive mode by adjusting delays of transducer elements as a function of range at which focusing is desired. At the focal point, the lateral beamwidth is smallest thus best lateral resolution is obtained, whereas it increases away from the focus point. The spatial resolution of ultrasound can be improved by using several beams transmitted during each scan, each focusing at different points. However, acquisition time decreases as the number of foci increases.

Synthetic aperture techniques can be used to obtain appropriate spatial resolution without decrease in acquisition time. In synthetic aperture imaging, data are acquired simultaneously from all directions over a number of emissions and these data are used to reconstruct the image. Due to the availability of the complete data set, focusing is possible in both transmit and receive at every field point. A single element or group of elements in transducer aperture transmits an unfocused wave with limited directivity, unlike conventional DAS beamforming in which focused waves are transmitted. The received signal is sampled for each transmission and for each element and the data is stored which is later used for reconstructing a low resolution image focused in the receive since the transmitted signal was unfocused. The focus point can be determined by summing the difference of the distances between transmitting element and imaging point and from imaging point back to receiving element. The time taken by the signal to travel from one transmitting element to focus point and back to receiver is obtained by dividing this distance by sound speed. For an image point r_p , the time is [127]

$$t_p(m, n) = \frac{|r_p - r_t(m)| + |r_p - r_r(n)|}{c} \quad (4.9)$$

where $r_t(m)$ is position of m th transmitting element and $r_r(n)$ is the n th receiving element. This is calculated for every point to yield a low-resolution image. A high resolution image is obtained by combining the low resolution images. The final focused signal is [127]

$$S_f(r_p) = \sum_{n=1}^N \sum_{m=1}^M a(t_p(m, n), m, n) S_r(t_p(m, n), m, n) \quad (4.10)$$

where $S_r(t_p, m, n)$ is the received signal for m^{th} emission on n^{th} element, $a(t_p(m, n), m, n)$ is the apodization applied on this signal, N and M are the number of transducer elements and emissions, respectively. The low resolution images are summed coherently to synthesize the transmit focusing which is dynamic for all points in the image. Thus, a dynamic focus is obtained both in transmit and receive with very good resolution everywhere in the image.

Several methods can be used to form synthetic aperture for ultrasound imaging, depending on which elements are being chosen for transmit and receive. These include Synthetic Aperture Focusing [135, 136, 137], Synthetic Receive Aperture [138] and Synthetic Transmit Aperture [139]. Each one is discussed briefly in the following sections.

4.3.1 Synthetic Aperture Focusing (SAF)

The concept of SAF is being used since 1950s in Radar and was used by Thomson *et al.* [135] in 1980s to digitize ultrasonic signals and O'Donnell *et al.* [136] to reduce cost and size of the imaging systems. In SAF only one element acts as an active transmitter and receiver at a time. The active element transmits a short pulse, which is received by the same element upon reflection and is stored. This process is repeated for all N -elements thus synthesizing an N -element array. The A-scan signal for each image point (r, θ) is

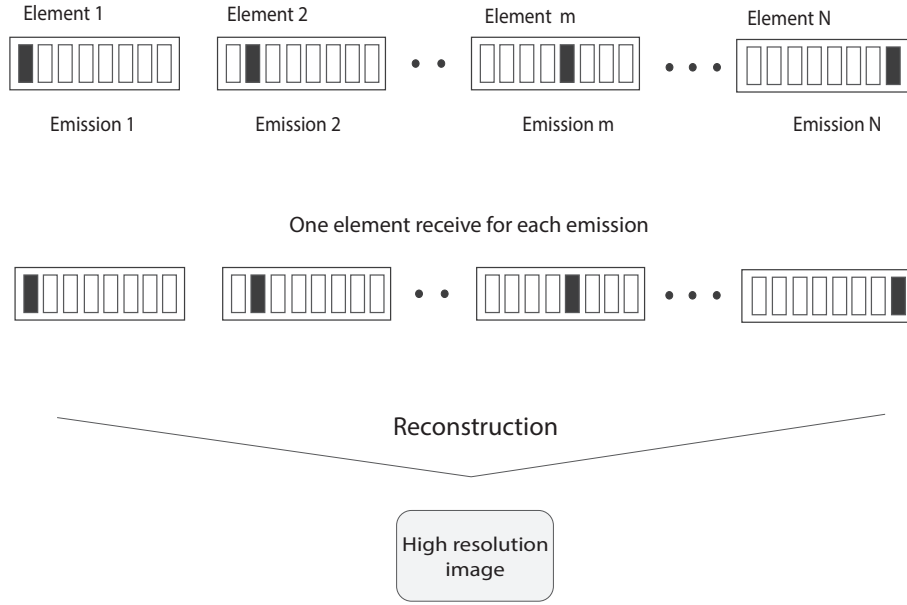


Figure 4.2: Transmitting and Receiving elements in SAF

$$A(r, \theta) = \sum_i^N S_i(t - \tau_i) \quad (4.11)$$

where $S_i(t)$ and τ_i are the echo signal and beamforming delay for the i_{th} element, respectively.

Due to one element in transmit and receive, complex electronics are avoided. Moreover, due to full dynamic focusing on both transmit and receive, high spatial resolution is possible. However, there are some disadvantages including: a) low SNR due to transmit with one element b) higher side lobes resulting in poor contrast resolution, c) grating lobes due to spatial under sampling.

Frame rate in synthetic aperture focusing is given by

$$FR_{SAF} = \frac{prf}{N_{emissions}} \quad (4.12)$$

where $N_{emissions}$ is the number of emissions being used to acquire the data for a single frame. Since all the transducer elements are normally used one after the other in the transmission, the number of emissions is equal to the total number of elements in the array, i.e. $N_{emissions} = N$. Frame rate is then

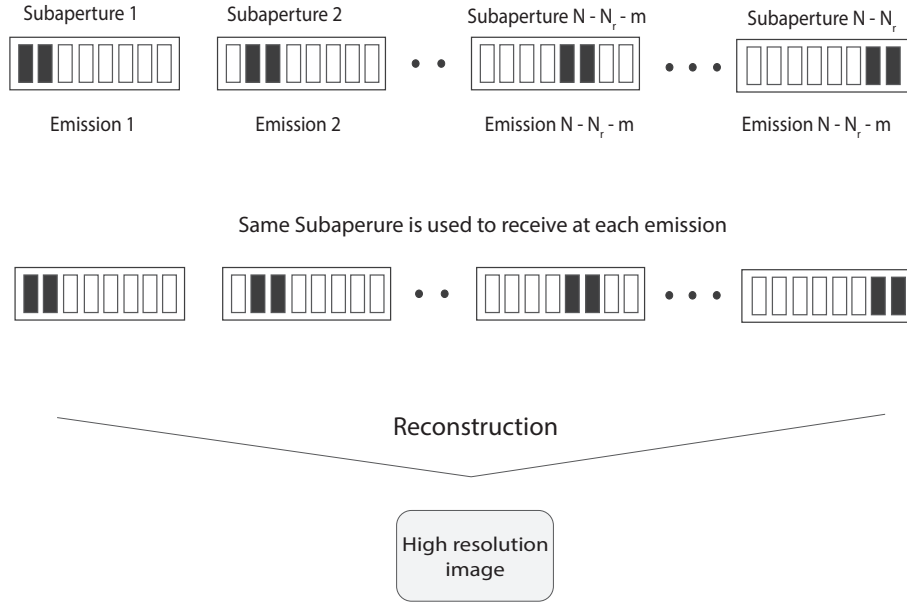


Figure 4.3: Transmitting and Receiving elements in MSAF

$$FR_{SAF} = \frac{prf}{N} \quad (4.13)$$

By comparing the frame rates for both conventional phased array imaging and synthetic aperture focusing, it is noticed that synthetic aperture focusing has higher frame rate than phased array imaging.

$$\frac{FR_{SAF}}{FR_{PA}} \geq 2 \quad (4.14)$$

The advantage of SAF is that circuitry for only one transmitting and receiving element is needed, reducing the cost of circuitry. Full dynamic focusing is performed in both transmit and receive, higher spatial resolution is thus possible. However, it suffers from low SNR since only one element is used in transmission. Moreover, the contrast resolution is low due to higher side and grating lobes. The grating lobes can be completely removed if the Nyquist criterion of $\lambda/2$ element spacing is employed.

In SAF, since only one element transmits an acoustic pulse, the acoustic power delivered to the medium is very small. To increase the signal to noise ratio, Multi-element Synthetic Aperture Focusing (M-SAF) technique can be used, in which

multiple elements are fired simultaneously thus improving the SNR. In M-SAF, an N_t - element transmit subapertures transmits and the echo is received by an N_r - element receive subaperture after the reflection [129]. One element is dropped and a new element is added to both transmit and receive subapertures in the next acquisition. All elements in the transmit subaperture are fired simultaneously and thus emulates a single high-power transducer element. The transmit beam is similar to that of a single element, a defocusing lens on the transmit subaperture is thus used. M-SAF has the advantage of increasing acoustic power in comparison to SAF [137].

Frame rate for Multi-SAF is given by

$$FR_{MSAF} = \frac{prf}{N_{SubAper}} \quad (4.15)$$

$N_{SubAper}$ is the number of transmit subapertures. The more the number of elements in a subaperture, the higher the frame rate will be.

4.3.2 Synthetic Receive Aperture (SRA)

Resolution of a phased array Ultrasound Imaging system can be improved by enlarging the transducer which requires increasing the number of transmitting and receiving elements to fully populate the array while maintaining the spatial Nyquist criteria. It is easy to increase the number of transmit channels but increasing the number of parallel receive channels increases cost, complexity and power consumption. There are other limitations associated with increasing the physical dimension including availability of the acoustic window and the diffraction limited resolution as described in [138].

Trahey *et. al* [138] proposed SRA method suggesting that number of active receive elements can be increased without an increase in receive channels thus obtaining a large receive aperture. The receive sub-aperture is divided into many subapertures

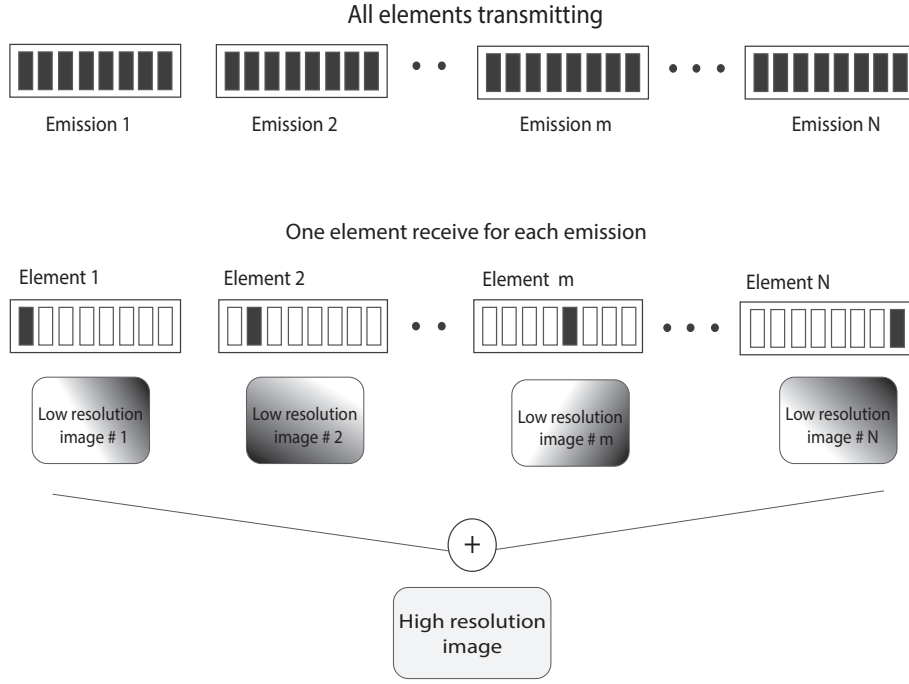


Figure 4.4: Transmitting and Receiving elements in SRA

and transmitter is fired once for each receive sub-aperture to form one image line of data. A single pulse is transmitted by all transmit pulses and the RF sum for each receive subapertures for that pulse is formed. A second pulse for the second subaperture is transmitted in the same direction and RF sum for this sub-aperture is obtained and stored. All the RF sums from all the receive subapertures are then coherently added. A large transmit subaperture is used and a large receive aperture is thus synthesized. Since in SRA, all elements transmit simultaneously unlike SAF where only one element transmits at a time, the received echo is supposed to be much stronger in comparison to the noise, whereas, in case of single transmission, the received echo is weaker and likely to be degraded by the noise.

4.3.3 Synthetic Transmit Aperture (STA)

Synthetic Transmit Aperture (STA) is an alternative method of improving the spatial resolution, in which images are generated with dynamic focusing [139]. In conventional STA imaging, a single element transmits which covers the entire region of interest and all elements receive the echo coming from all imaging directions, which are recorded and stored in computer memory. The stored echoes are then

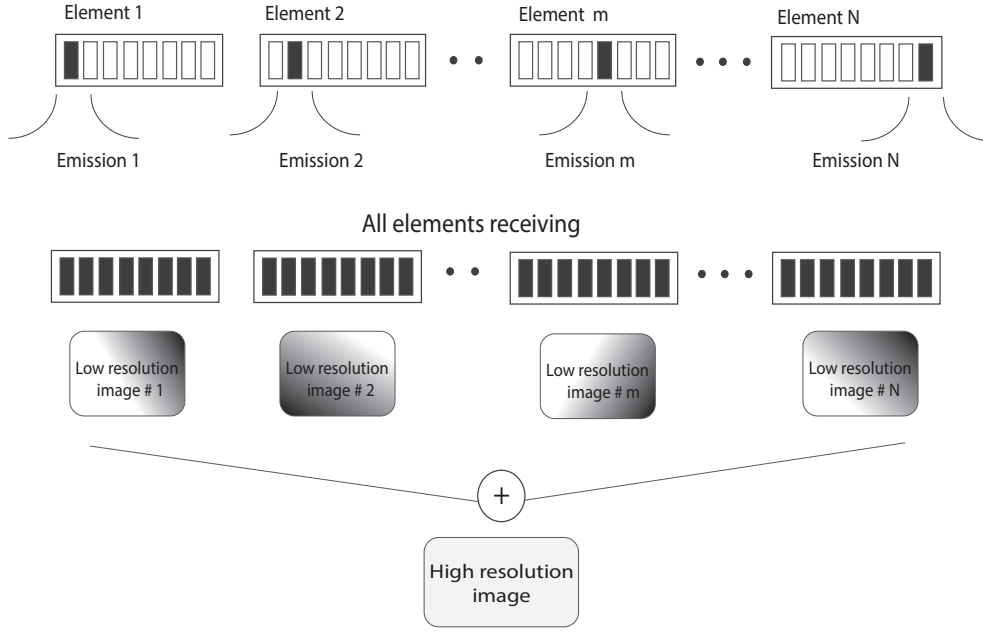


Figure 4.5: Transmitting and Receiving elements in STA [30]

synthetically focused using algorithms.

Focusing can be performed by determining the geometric distance from transmit element to the imaging point and back to the receiving element and adding the corresponding delays. The system is thus in focus at every pixel of the image. Element m transmits a short pulse that is received by element n , the round trip delay is then

$$\tau_{m,n} = \frac{1}{c} \left(\sqrt{(x_p - x_m)^2 + (y_p - y_m)^2 + (z_p - z_m)^2} + \sqrt{(x_p - x_n)^2 + (y_p - y_n)^2 + (z_p - z_n)^2} \right) \quad (4.16)$$

where (x_p, y_p, z_p) are coordinates of the image pixel, (x_m, y_m, z_m) are coordinates of transmitting element and (x_n, y_n, z_n) are coordinates of the receiving element. c is speed of sound.

For an N -element array, the image pixel at (x_p, y_p, z_p) is thus computed by

$$I(x_p, y_p, z_p) = \sum_{m=1}^N \sum_{n=1}^N W_{m,n} S_{m,n} \left(\frac{2r}{c} - \tau_{m,n} \right) \quad (4.17)$$

where S_{mn} is the echo signal, $\tau_{m,n}$ is the beamforming delay and $W_{m,n}$ is the apodization factor for the (m, n) transmit-receive combination. The first and second summation corresponds to the transmit and receive beamforming.

The number of emissions to scan an image is

$$N_{emissions} = N \quad (4.18)$$

and frame rate is

$$FR_{STA} = \frac{prf}{N} \quad (4.19)$$

STA offers much faster imaging especially when some but not all of the elements are used for transmit, in which case the frame rate would be

$$FR_{STA} = \frac{prf}{N_{act}} \quad (4.20)$$

where N_{act} are the active transmitting elements. However, signal to noise ratio (SNR) and penetration depth are reduced with fewer transmitting elements. Different means of increasing the transmit power are suggested in literature including firing with multiple elements simultaneously, use of virtual ultrasound sources and spatial and temporal encoding [137].

One disadvantage of STA is large amount of data used for image reconstruction. For N -element array, N echo recordings are required for image reconstruction in conventional phased array system, whereas, $N \times N$ echo recordings are required to synthesize STA image. Since only one element is used to transmit, STA has low

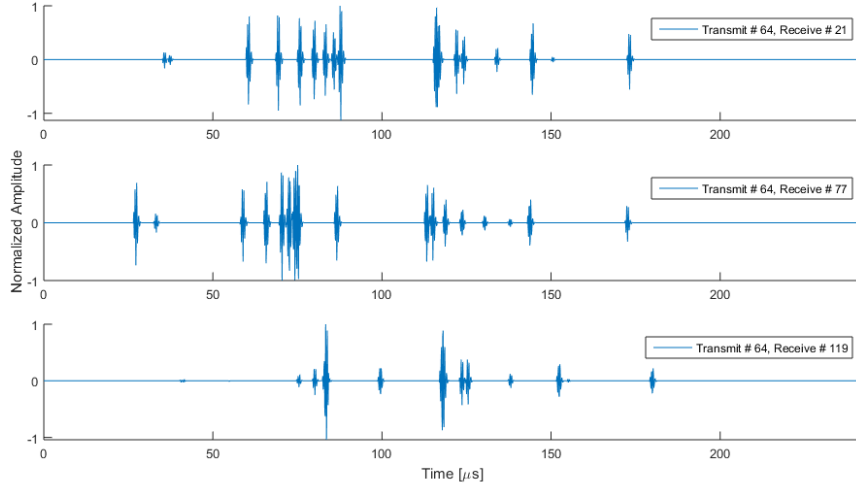


Figure 4.6: An example of simulated RF echo signals obtained while transmitting with element # 64 and receiving with element # 21 (top), element # 77 (middle) and element # 119 (bottom)

SNR and low penetration depth which is the main shortcoming of this technique. Various techniques have been proposed to increase SNR. One approach is to use Transmit Sub-Aperture composed of multiple elements creating a spherical wave and improving SNR as a function of number of elements in the Transmit Sub-Aperture [140].

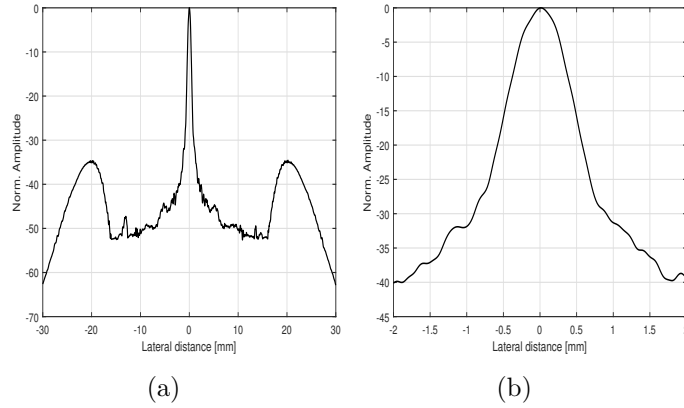


Figure 4.7: Normalized cross-section of the beamprofile for SAF, with a 128-element linear array with inter-element spacing 0.3 mm and operating at 6.25 MHz, corresponding to a scatterer located at 40mm axial distance, and for (a) lateral distance ± 30 mm, (b) zoomed to ± 2 mm

4.4 Simulated Imaging Results

4.4.1 Imaging with Linear array

A 128-elements linear array transducer was used in simulation to assess the performance of the beamforming schemes discussed in the previous section. Simulations were performed in MATLAB with a linear probe consisting of 128 elements operating at 6.25 MHz. The inter-element spacing is 0.3 mm. All the elements can be used for both transmit and receive depending on the synthetic aperture imaging technique being used. Three of the simulated RF echo signals are shown in fig. 4.6. All RF echo signals are different depending on the position of the transmitting and receiving elements as well as the distance to the targets. The echo data was simulated using Verasonics system and was fed into our image reconstruction algorithms to obtain simulated images of different wire phantoms.

The synthetic aperture imaging techniques discussed above were used in simulation to image a wire phantom. Simulated synthetic aperture data of point reflectors was used in MATLAB and input to the Synthetic Aperture algorithm to produce 2D B-mode ultrasound images. Beamprofile for SAF is shown in fig. 4.7, the grating lobes appear at 20 mm off the axis. The reason for appearance of the grating lobes is the inter-element spacing which is of the order of a wavelength. Beamprofile for SRA is shown in fig. 4.8. The grating lobes which were present in SAF are disappeared and the width of the main lobe is reduced, however, sidelobes with amplitude of -14 dB appear at 0.6 mm off the main axis. Since it is easy to enlarge the transmit aperture but very expensive to build a large receive aperture, this method synthesizes a large receive aperture without physically increasing the number of receive channels. Beamprofile for STA is shown in fig. 4.9. The side and grating lobes present in the above two techniques are significantly reduced down to -29 dB and -49 dB, respectively.

Comparison of the lateral beamprofile of a point target at an axial distance of 40

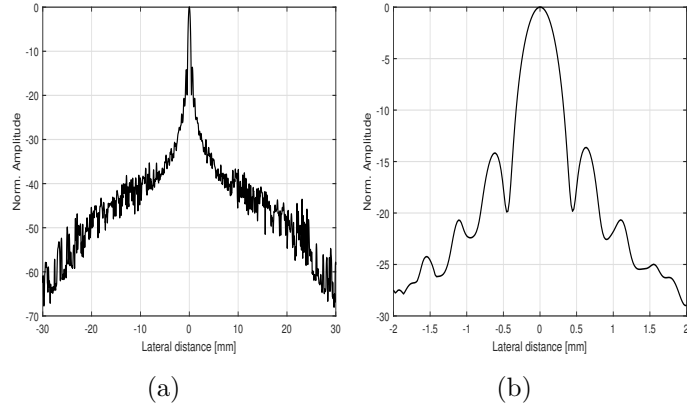


Figure 4.8: Normalized cross-section of the beamprofile for SRA with a 128-element linear array with inter-element spacing 0.3 mm and operating at 6.25 MHz, corresponding to a scatterer located at 40mm axial distance, and for (a) lateral distance ± 30 mm, (b) zoomed to ± 2 mm

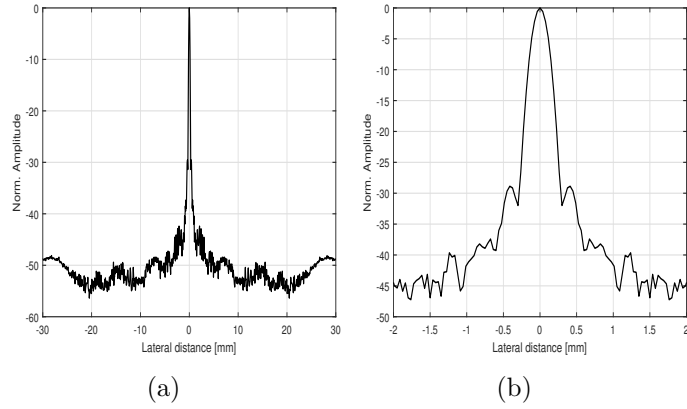


Figure 4.9: Normalized cross-section of the beamprofile for STA with a 128-element linear array with inter-element spacing 0.3 mm and operating at 6.25 MHz, corresponding to a scatterer located at 40mm axial distance, and for (a) lateral distance ± 30 mm, (b) zoomed to ± 2 mm

mm from the source shows that STA performs the best in terms of low side and grating lobes and narrower beam width (fig. 4.10). The side and grating lobes were less than -45 dB which is a considerable improvement than in SAF in which grating lobes appear at 15 mm either side of the main beam with a magnitude of -23 dB. STA was thus used for further imaging the wire phantoms.

In STA, Only a single element transmits and all elements receive the echoes giving a total of 128×128 possible RF A-scans. Each A-scan is sampled at 25 MHz and has 2048 samples. A low resolution image is first obtained by transmitting on a single element and then all low resolution images are summed coherently to obtain the

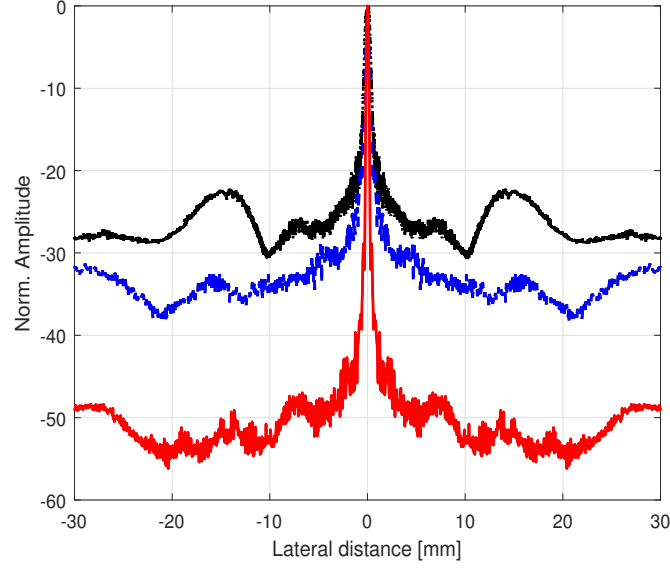


Figure 4.10: Lateral resolution of SAF (black dotted line), SRA (blue dashed line) and STA (red solid line). STA clearly has lowest sidelobes and narrowest main lobe.

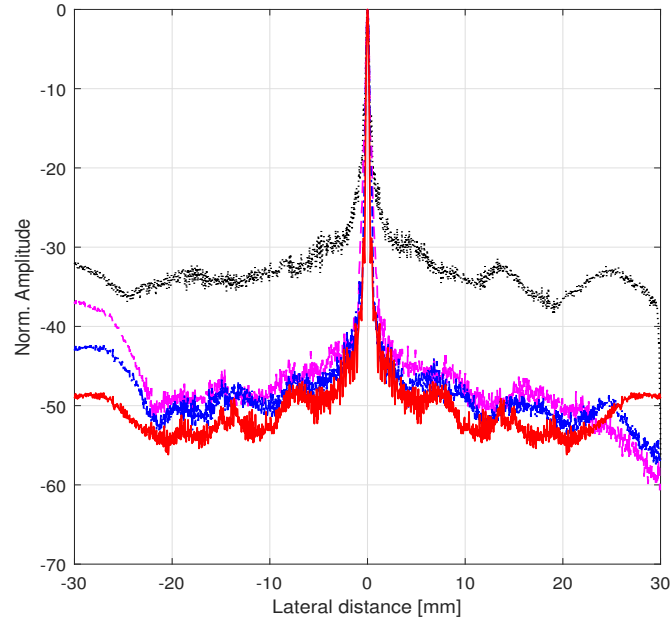


Figure 4.11: Effect of number of emissions on beamprofile in STA imaging, 1 emission (black dotted line), 32 emissions (magenta dashed line), 64 emissions (blue dashed line), 128 emissions (red solid line)

high resolution image. Comparison of the beamprofiles for different emissions using STA is shown in fig. 4.11. High side lobes can be observed in one emission, whereas, the sidelobes get lower and the beam gets narrower with the increased number of emissions.

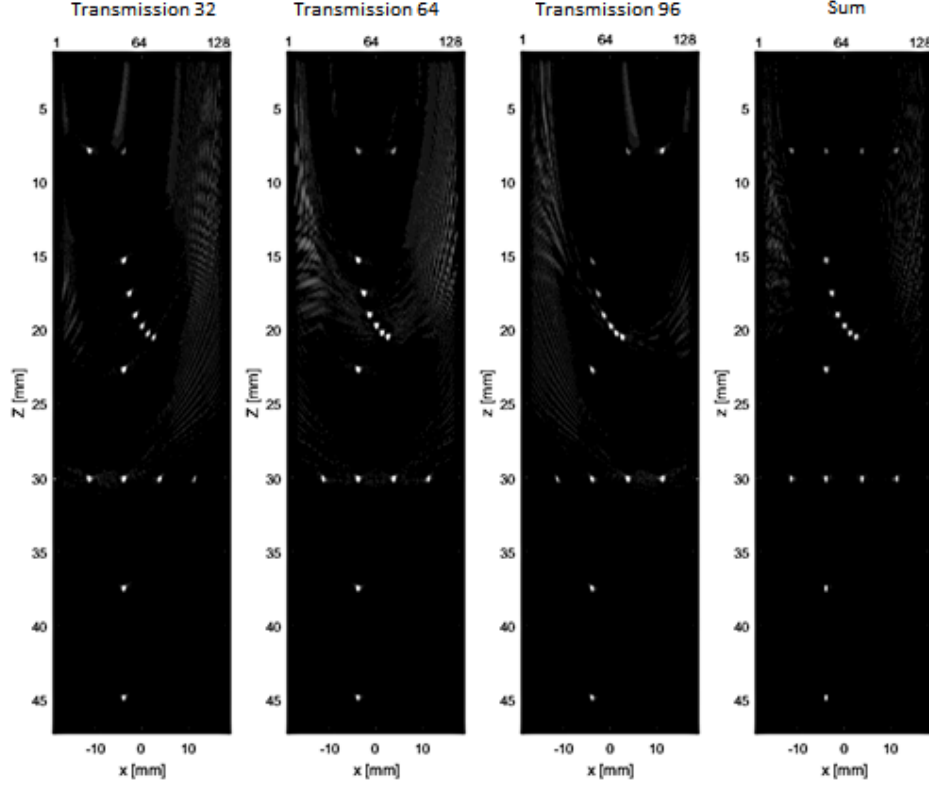


Figure 4.12: Illustration of the effect of number of emissions on image quality. All three low resolution images on the left are obtained with single emission from different elements and suffer from limited visibility and cumulative grating lobes, a high resolution image with multiple emissions reduce the side and grating lobes and improves the imaging resolution (right)

Images produced with STA are shown in fig. 4.12. High side- and grating lobes are observed in all low resolution images which are diminished in the combined high resolution image. Moreover, the targets close to the transducer are more clearly visible in the combined image.

A wire target phantom was used in simulation to compare the above three synthetic aperture techniques. Five wires were positioned with a spacing of 3 mm both in lateral and axial directions such that the closest wire was 15 mm and the farthest wire was 27 mm deep axially. B-mode images of the wire phantom are shown in fig. 4.13. As expected, SAF suffered from grating lobes and with SRA there were some sidelobes, whereas, images reconstructed with STA has best resolution with no side/grating lobes.



Figure 4.13: Beamformed images of the wire phantom formed using SAF (left), SRA (middle) and STA(right), displayed over 40 dB dynamic range. Five wires are placed at $(x,z) = (-6,15)$, $(-3,18)$, $(0,21)$, $(3,24)$ and $(6,27)$ mm. Side and grating lobes are visible in the images produced with SAF and SRA which are completely removed in the image produced with STA

4.4.2 Imaging with Random Phased Array

One of the aims of this thesis was to image with an existing therapeutic random phased array. Simulations were thus conducted to use the beamforming technique to reconstruct images with the random phased array. The array is a spherical bowl with 256 elements and radius of curvature 130 mm. The elements are randomly distributed on its spherical shell with inter-element spacing of 7.9 - 9.4 mm and element size of 7 mm. One single element in the transducer aperture was used for transmitting a wave which is focused at the geometric centre of the array due to the geometry of the array transducer and all 256 elements receive the echo. The received signal for all the elements in the aperture is sampled during each transmission. The transmit and receive elements combination gives a total of 256×256 possible RF A-lines. All these A-line echo signals are sampled at 4 MHz. The transmitting frequency used is 1 MHz. Focusing is performed by finding the geometric distance between the transmitting and receiving elements and the imaging point. Geometric relation between transmit and receive element combination is shown in fig. 4.14.

Simulations were performed to verify the performance of STA algorithm. Point reflectors were placed 5 mm apart laterally and 10 mm apart axially to determine the lateral and axial resolution as well as the imaging depth. The point reflectors

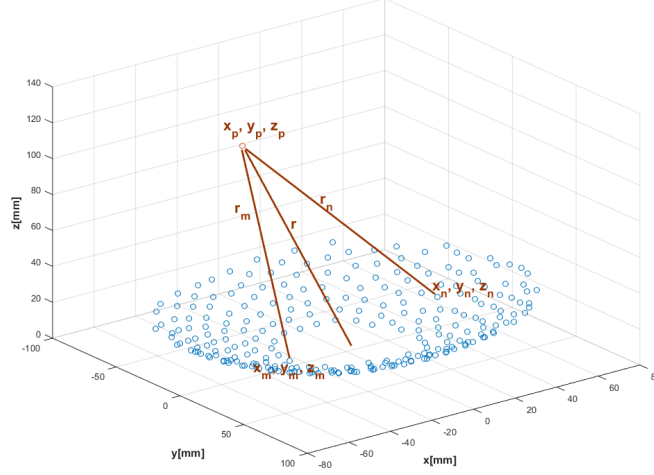
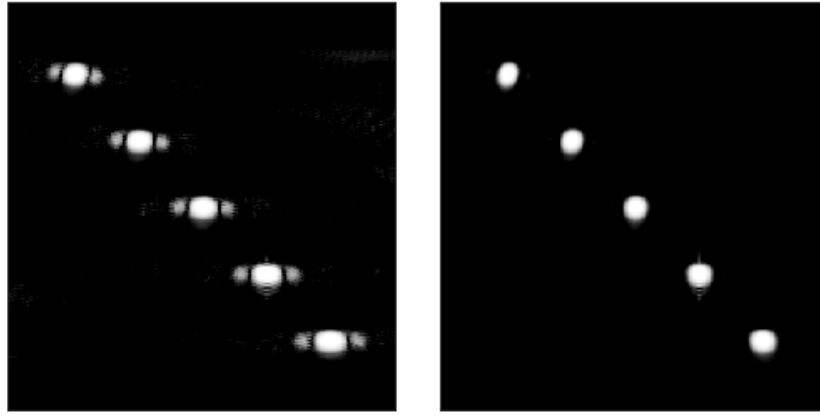


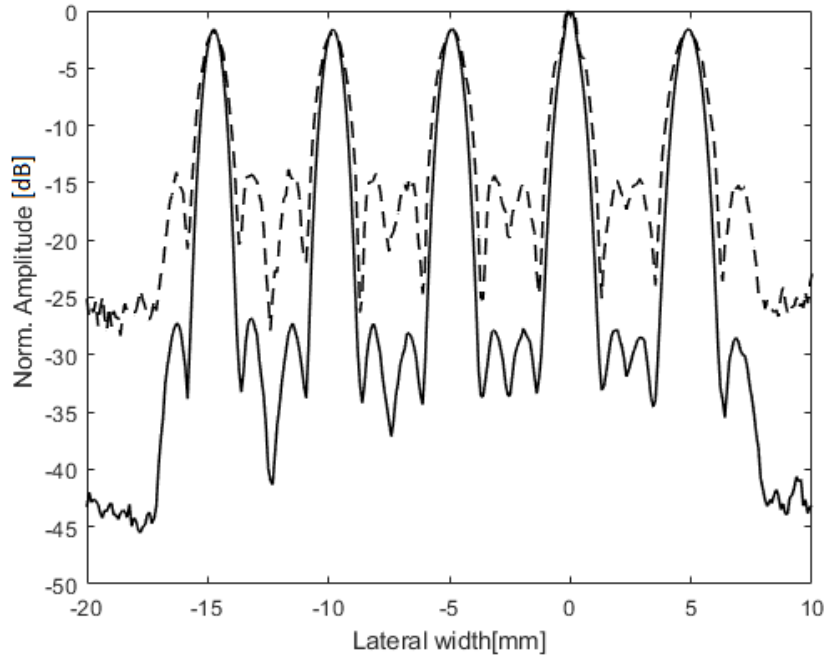
Figure 4.14: Point source located at (x_p, y_p, z_p) . r_m and r_n are the distances of transmitting and receiving elements to the point and r is the distance from the centre of the array to the point

were positioned from depth of 100 mm to 140 mm such that the top point reflector was at 100 mm and the bottom one at 140 mm depth. One of the point reflectors was at the geometric center of the array. A low resolution image (LRI) is obtained while transmitting at a single element and sampling the received signal for each transmission. The LRI is focused only in receive. Dynamic focusing is performed by finding the geometric distance between the transmitting and receiving elements and the image point. The low resolution images are then added coherently to form a high resolution image (HRI). The image is hence focused in all the image points [141]. The resulting images of the point reflectors are shown in fig. 4.15(a).

Improvement in image quality can be observed by increasing the number of transmissions. The sidelobes are clearly visible in the low resolution image which are significantly removed in the high resolution image. The reduction in side lobes can further be seen in fig. 4.15(b), where the lateral cross-section of the point reflectors is shown. As can be seen, the side lobes for all the point reflectors have magnitude of only -14.04 dB for a single emission which are reduced to around -29 dB for all 256 emissions. Lateral cross-section of the echoes of a point scatterer is shown in fig. 4.16, which confirms the reduction in the level of side lobe. Furthermore, grating



(a)



(b)

Figure 4.15: (a) Comparison of a low resolution image with 1 emission (left) and high resolution image with 256 emissions (right), displayed over 30 dB dynamic range, (b) Lateral cross-section in logarithmic scale for 1 emission (dashed line) and 256 emissions (solid line), showing the effect of number of emissions on side lobe level

lobes seem to appear at a lateral distance of 5 mm and 10 mm from the main beam with a magnitude of -30 dB and -40 dB for a single emission which are suppressed to below -55 dB and -65 dB for all 256 emissions, respectively. The beam gets narrower when all elements emit thus improving the lateral resolution.

Further simulations were performed to evaluate and compare the imaging performance of Synthetic Transmit Aperture Imaging (STA) with Synthetic Receive Aper-

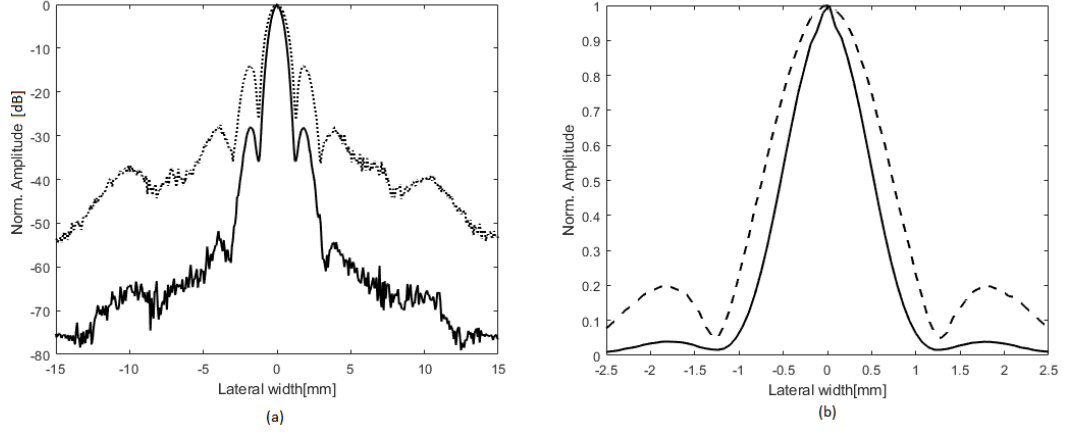


Figure 4.16: Normalized lateral cross-section of the beamprofile corresponding to a scatterer located at the geometric focus at a depth of 130mm for 1 emission (dashed line) and 256 emissions (solid line), and for (a) lateral distance ± 15 mm, (b) zoomed to ± 2.5 mm

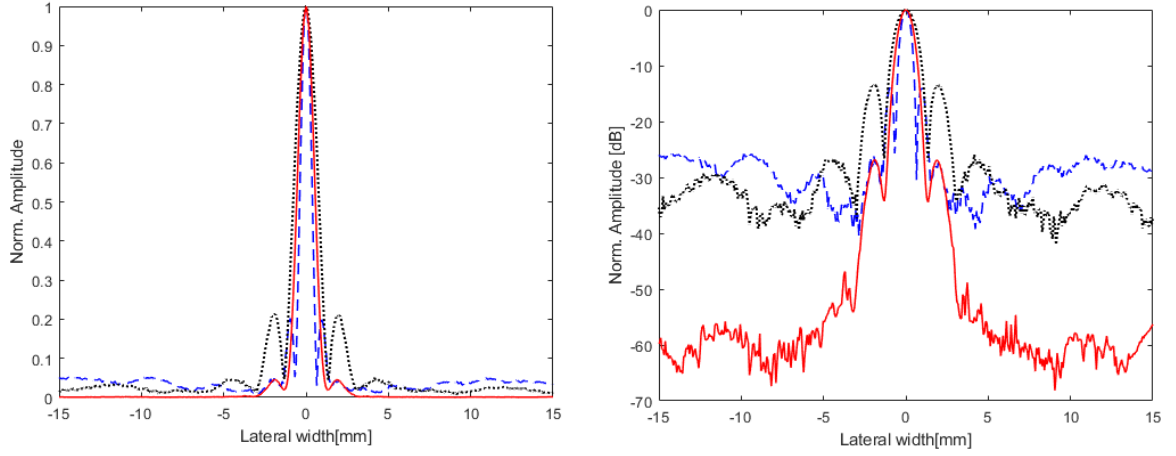


Figure 4.17: Comparison of the normalized cross-section of beamprofile of different synthetic aperture techniques corresponding to a scatterer located at geometric focus in linear (left) and logarithmic (right) scales for SRA (black dotted line), SAF (blue dashed line) and STA (red solid line)

ture (SRA) and Synthetic Aperture Focusing techniques (SAF). Lateral cross-section of the normalized beamprofile of a point scatterer are shown in fig. 4.17. As expected, STA performs the best with lowest side lobes. Both SRA and SAF have high sidelobes with magnitudes -12 dB and -13 dB, respectively, whereas, the sidelobes in STA are only -29 dB in magnitude. Though SAF offers narrower beam but suffers from higher side and grating lobes. STA thus outperforms the other two imaging techniques.

Images of the wire phantom discussed above were simulated with all three tech-

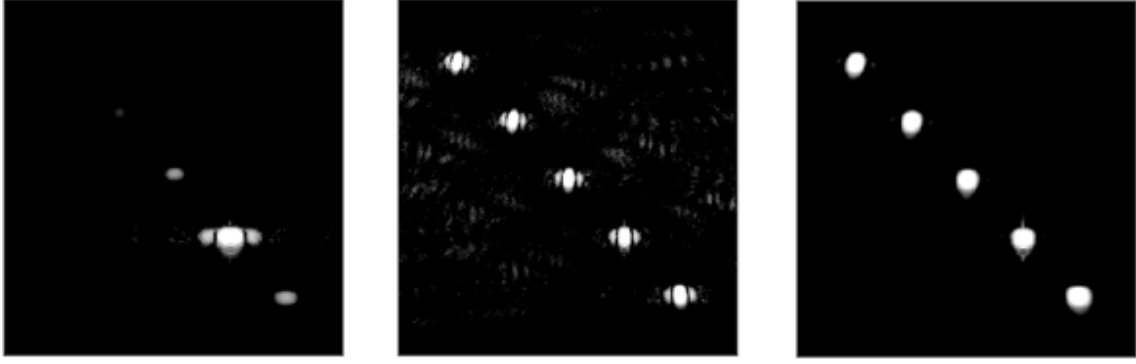


Figure 4.18: B-scan images of the wire phantom, displayed over a dynamic range of 30dB, reconstructed with SRA (left), SAF (middle) and STA (right). Sidelobes and grating lobes are removed with STA.

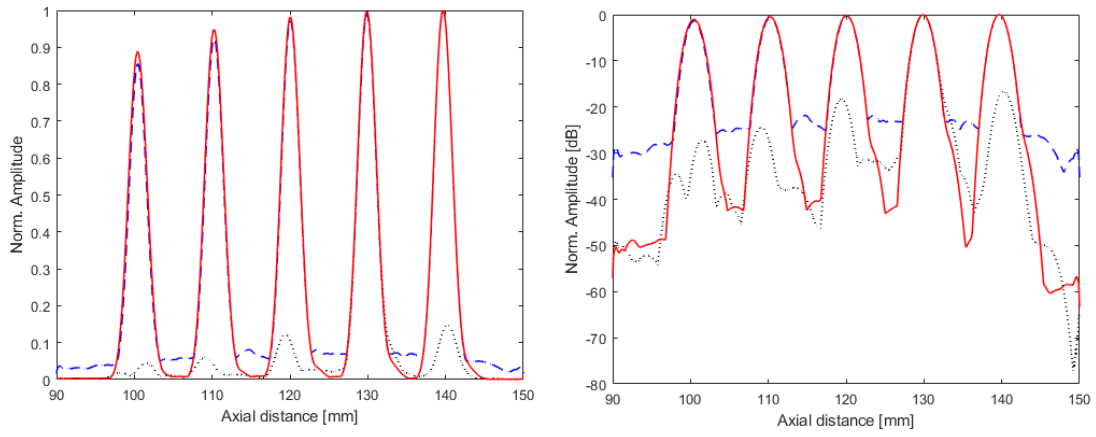


Figure 4.19: Comparison of the normalized cross-section of axial beamprofile of SRA (black dotted line), SAF (blue dashed line) and STA (red solid line) corresponding to the wire phantom in linear (left) and logarithmic (right) scales. Significantly reduced sidelobes and maximum amplitude can be observed in case of STA

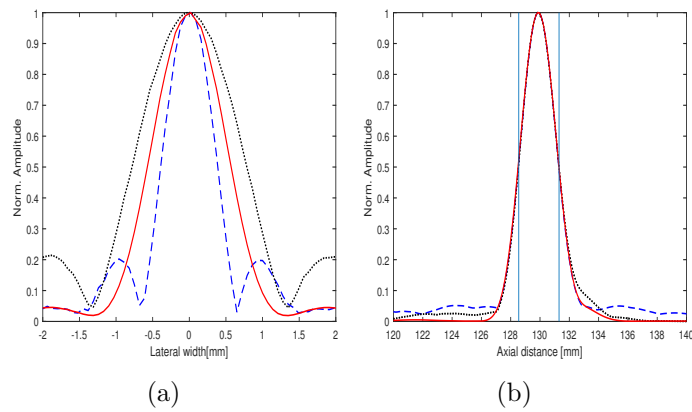


Figure 4.20: Comparison of (a) lateral and (b) axial Full Width Half Maximum (FWHM) for all three synthetic aperture techniques corresponding to a scatterer located at the geometric focus. Lateral FWHM are 1.57mm, 0.78mm and 1.15mm for SRA, SAF and STA, respectively. Axial FWHM is 2.75mm for all three techniques

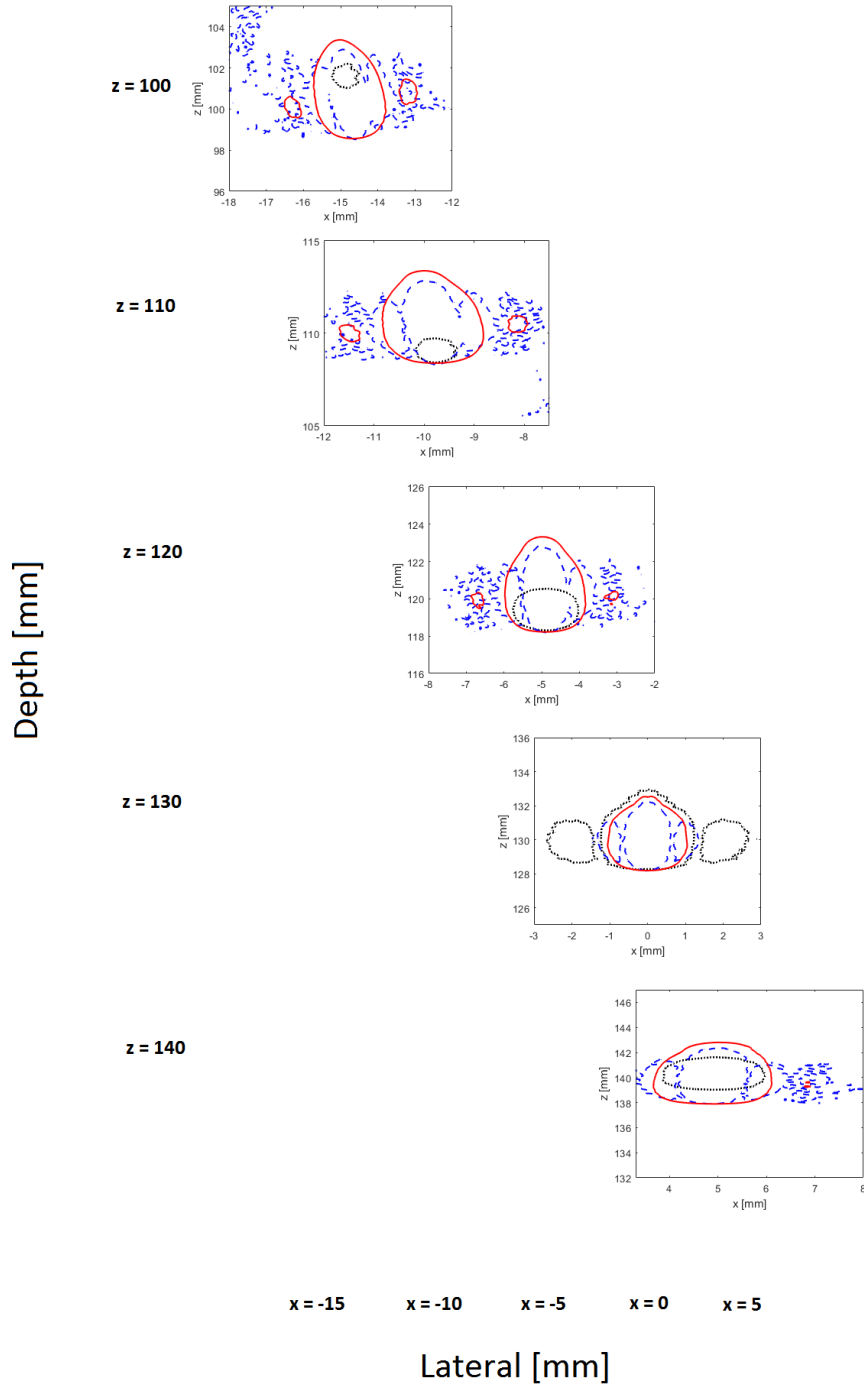


Figure 4.21: Contour plots of -30 dB amplitudes of the wire target at different positions for SRA (black dotted line), SAF (blue dashed line) and STA (red solid line). x -axis is the lateral position and y -axis is depth in mm. STA offers lowest side lobes at all depths compared to the other two techniques.

niques. Only three wires are visible in the image reconstructed with SRA, whereas high side lobes are observed and grating lobe artefacts are present in the image reconstructed with SAF, which are completely removed in image with STA (fig. 4.18). Furthermore, the SNR is higher in the STA imaging and all the wires are clearly

Table 4.1: Comparison of Lateral and Axial FWHM for all three imaging techniques

FWHM	SRA	SAF	STA
Lateral [mm]	1.57	0.78	1.15
Axial [mm]	2.75	2.75	2.75

visible in the B-scan image. The SAF has a slightly reduced sidelobe level compared to SRA but suffer with higher side lobes. The normalized cross-section of the axial beamprofile is shown in fig. 4.19. The Full Width Half Maximum (FWHM) of all three techniques are shown in fig. 4.20. As can be seen that axial FWHM is same for all techniques and is 2.75 mm, the lateral FWHM varies significantly. For SRA, the FWHM is 1.57 mm, for STA it is 1.15 mm, whereas in case of SAF, the FWHM is 0.78 mm. SAF thus offers smallest beamwidth but suffers from high sidelobes.

For a more detailed comparison, -30 dB contour plots of the wire targets are plotted (fig. 4.21). Amplitude of each point target is plotted separately with all three imaging techniques. It is confirmed that SAF has smaller beamwidth but suffers from high sidelobes, SRA suffers from high grating lobes at the geometric focus, however at other depths it has no side lobes and narrower beam, where as STA is best in terms of beamwidth, resolution and sidelobes.

4.5 Summary

The aim of this chapter was to review and investigate various available synthetic aperture imaging techniques and conduct simulations with a linear array to reconstruct images with these techniques. Simulations with linear array were performed to ascertain the best imaging techniques and then reciprocate the simulations with the therapeutic array to select the method that would be used for imaging in experiments using a pre-existing therapeutic phased array. This was the first time that various synthetic aperture imaging techniques were simulated with a therapeutic random phased array. It was shown that Synthetic Transmit Aperture (STA) imaging technique performs the best in terms of image resolution, has narrow beam width

and lowest side lobes. In the next chapter, this imaging technique will thus be used to reconstruct images with the therapeutic random phased array in experiments.

Chapter 5

Synthetic Aperture Imaging - Experimental Implementation

This chapter presents the experimental implementation of the STA technique described in the previous chapter. Preliminary experiments are performed with various phantoms and ex-vivo tissue. Equipment used in the experiments are briefly explained. Synthetic Transmit Aperture Imaging technique discussed in previous chapter is implemented first with a linear array and then with the therapeutic random phased array in experiments. The phased array is integrated with a research ultrasound scanner via a custom designed interface to acquire RF data for a variety of phantoms and ex-vivo tissue. Synthetic aperture technique is then used to reconstruct images of the field of interest. It is shown that the therapeutic phased array is suitable for image guidance and can detect obstruction such as ribs.

5.1 Materials and Methods

5.1.1 Linear Array Transducer

To test the validity of our methods and the software, the technique was implemented first with a linear array. The linear array transducer named L11-4v designed by Vera-

sonics operating at 6.25 MHz and 0.3 mm pitch was used to implement and validate the simulation results of Synthetic Transmit Aperture imaging technique. The linear array was used to acquire backscattered raw data from a Gammex Ultrasound phantom 403GS LE. The resolution patterns and horizontal and vertical targets are constructed of 0.1mm nylon fibers for better detail definition and spatial resolution.

5.1.2 Random Phased Array Transducer and RF System

The random phased array transducer used in this project for imaging and therapy was already installed in our lab and was identical to the one described by Hand et al. [4], consisting of 256 elements, each 7 mm in diameter and positioned randomly on a spherical shell with diameter 170 mm and radius of curvature 130 mm. The spacing between elements vary from 7.9 mm to 9.4 mm. The device was designed in accordance with the criteria described by Gavrilov and Hand [92, 65] and was constructed using a composite material by Imasonic (Voray sur l'Ognon, France). A central hole of 38 mm in diameter is provided for insertion of imaging transducer. The range of frequency of operation is 0.8 - 1.2 MHz. A commercially available system (Model 500-013, Advanced Surgical Systems Inc., Tucson, AZ) is used to generate and control the RF signals.

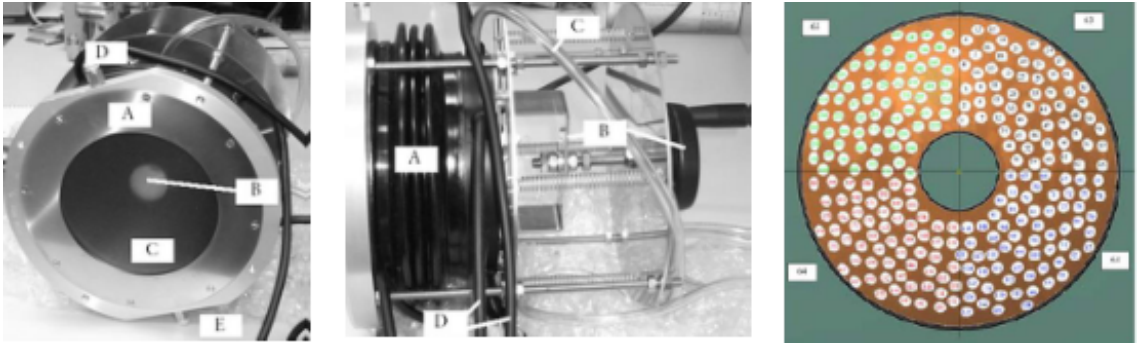


Figure 5.1: Front view of the array and positioning mechanism [4]

RF signals are fed through miniature coaxial cables bundled into four groups for each quadrant of the array. The 256-channel system has a power capability of up to 60 W/channel constrained within a total power of 1800 W. Four RF outputs via multi-pin connectors (ITT/Cannon type DL 156) is used to provide power to the

four quadrants of the array. Fig. 5.1 shows the front view of the array with element distribution and the positioning mechanism.

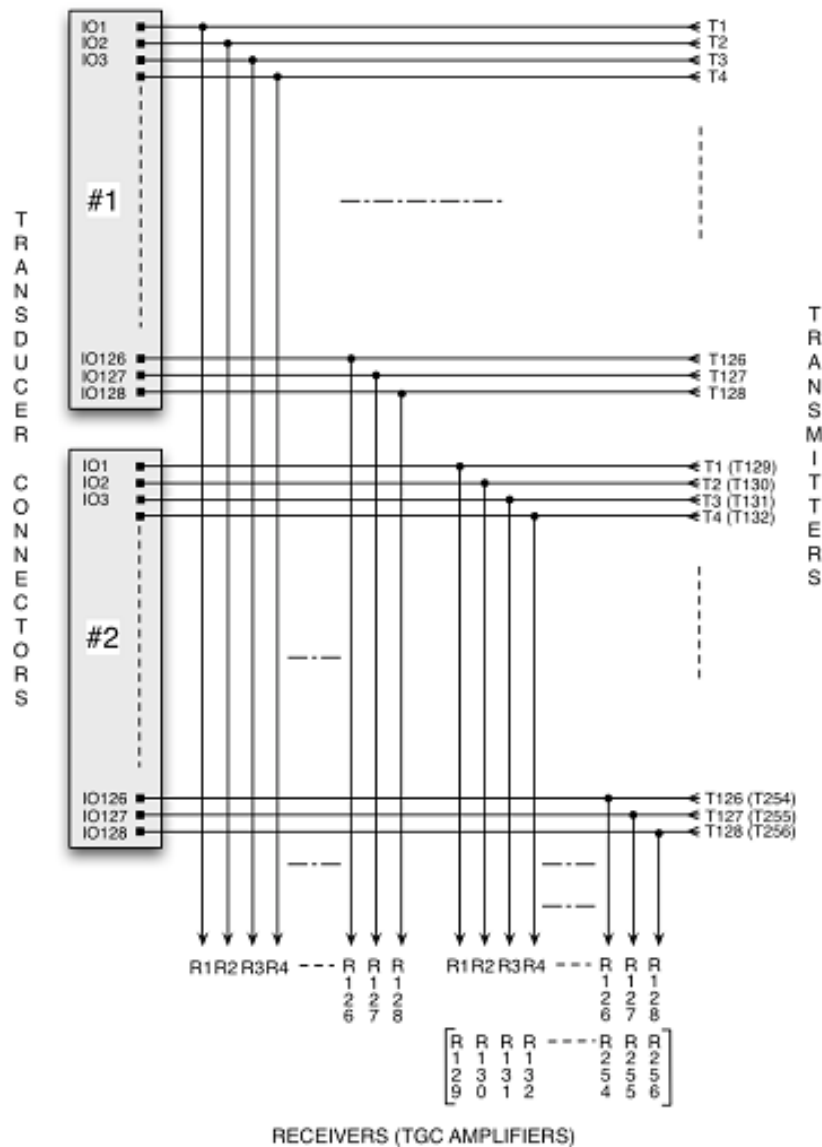


Figure 5.2: Front end connections of 256 Vantage system [Courtesy Verasonics User's manual]

The maximum acoustic power that could be delivered by each element is 2.3 W. Air cooling is provided to the array to avoid overheating. 256 customized L-C impedance matching networks are inserted in four groups of 64 each between the four outputs of the generator and each of the quadrants of the array. The generator is controlled by a laptop computer through an RS-232 link. The operating frequency, active elements and relative phases are set with a proprietary software (Large Array

Interface v1.2.0.0, Advanced Surgical Systems Inc., Tucson, AZ). Phases for each of the 256 channels to produce and steer a single focus and patterns of multiple foci were generated using MATLAB code based on the theory described by Gavrilov and Hand [92].



Figure 5.3: DL-156P connector (left), DL5-260P connector (right)



Figure 5.4: Solid Bump crimp (left), Solid flat crimp (right)

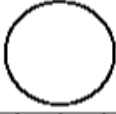
5.1.3 The Verasonics System

The Verasonics Vantage system (Verasonics, Inc., Kirkland, USA) is a flexible tool for transmitting, receiving and processing ultrasound signals and includes all essential features of a modern commercial ultrasound system. It is fully controllable by the user and new methods of ultrasound acquisition and processing can be created and implemented with this system. It consists of the Verasonics Data Acquisition Hardware connected to a Host Controller Computer. The Acquisition Hardware contains electronic modules that are responsible for multi-channel transmit waveform generation, receive signal amplification and filtering. The host computer has the software modules implemented in Matlab to allow the user to program and run the sequences of actions. The Verasonics system comes with its own transducers but

it is possible to integrate a custom probe. For connecting a custom probe with the system, a transducer mating connector is used. The probe elements are connected to the appropriate IO pins on the connector. In the Vantage256 system, there are 256 transmit and receive channels connected to two scanhead connectors as shown in fig. 5.2. A custom probe of up to 256 elements can use the two connectors in the verasonics system by connecting 128 elements to each connector.

RF Connector Pinout

ITT/Cannon P/N DL1-156P
SH = Coax Shield
P = Center Conductor

	1	2	3	4	5	6
A	P1	SH2	P3	SH4	P5	SH6
B	SH1	P2	SH3	P4	SH5	P6
C	P7	SH8	P9	SH10	P11	SH12
D	SH7	P8	SH9	P10	SH11	P12
E	P13	SH14	P15	SH16	P17	SH18
F	SH13	P14	SH15	P16	SH17	P18
G	P19	SH20	P21	SH22	P23	SH24
H	SH19	P20	SH21	P22	SH23	P24
J	P25	SH26	P27	SH28	P29	SH30
K	SH25	P26	SH27	P28	SH29	P30
L	P31	SH32				
M	SH31	P32				
N						
						
P						
R					P33	SH34
S					SH33	P34
T	P35	SH36	P37	SH38	P39	SH40
U	SH35	P36	SH37	P38	SH39	P40
V	P41	SH42	P43	SH44	P45	SH46
W	SH41	P42	SH43	P44	SH45	P46
X	P47	SH48	P49	SH50	P51	SH52
Y	SH47	P48	SH49	P50	SH51	P52
Z	P53	SH54	P55	SH56	P57	SH58
a	SH53	P54	SH55	P56	SH57	P58
b	P59	SH60	P61	SH62	P63	SH64
c	SH59	P60	SH61	P62	SH63	P64

Top View

Figure 5.5: RF connector pinout of DL-156P connector

5.1.4 RF Connectors

The Random phased array was initially designed for therapy and thus had no receiver circuitry, integrating it with Verasonics system was thus required to acquire RF data for image reconstruction. The phased array is divided into four quadrants with 64 channels each. Each quadrant is connected via a single *Cannon 156P* connector,

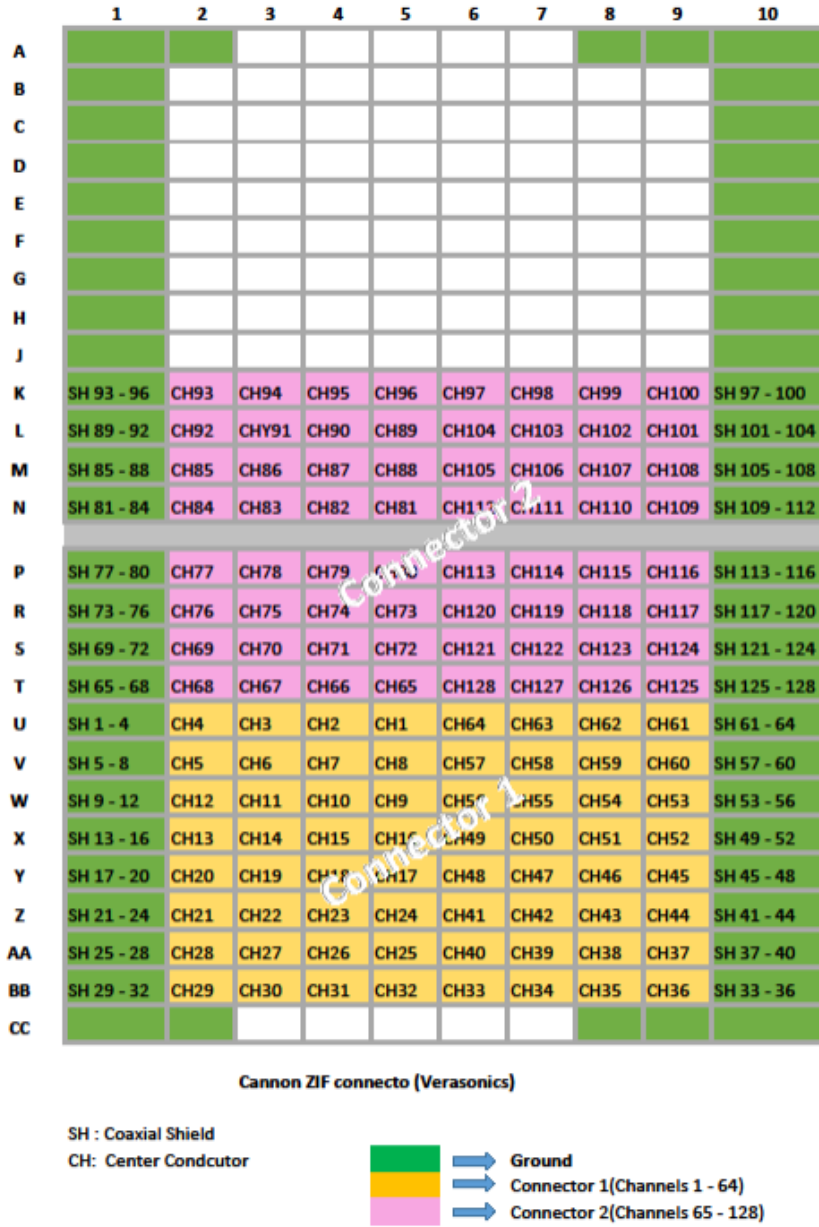


Figure 5.6: Pin layout of ZIF260 connector

which is a 156-way heavy duty female plug with a termination type *Flat crimp*, which is used to wire 64 channels. The connector that Vantage256 can host is of different model (ITT Cannon DL5-260P or 260-pin ZIF in short), which is a 260-way plug with a termination type *Bump crimp*. Vantage256 can house only two such connectors with 128 channels each. It was thus essential to wire the four 156P connectors to the two 260-pin ZIF connectors using a custom-made adaptor cable. The crimps used were ITT Cannon MS Series Male crimps as shown in fig. 5.4. A

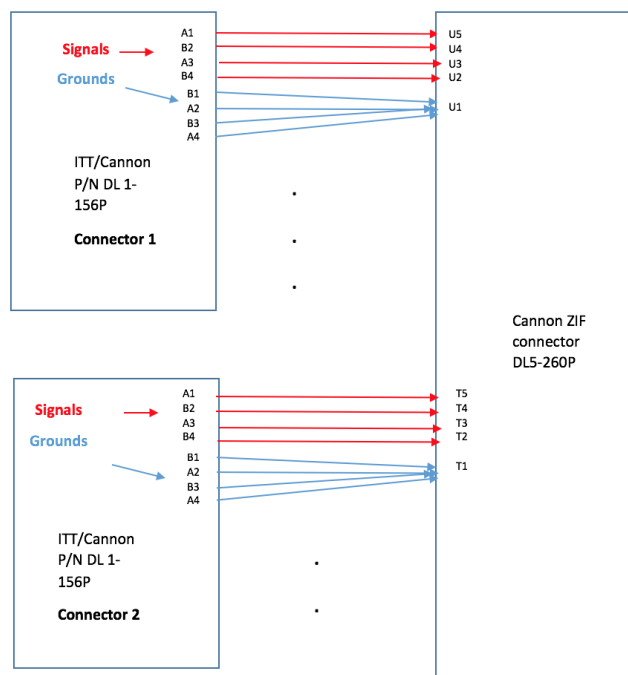


Figure 5.7: Schematic of connections between two 156P and one 260P connectors



Figure 5.8: The RF connectors

standard equipment red wire was used to connect the connectors. A single 156P connector allowed us to use only up to 64 channels and therefore we needed to use two such connectors to utilize 128 channels which was the maximum number of channels the DL5-260P connector could support. The pin layouts of both types of connectors are shown in fig. 5.5 and 5.6, respectively. The signals and grounds are numbered in fig. 5.7. Since there were not as many holes for grounds as the number of signals/channels, we needed to group the grounds for four channels and insert them in one hole assigned for ground (coloured in green). Therefore, four blue cables were crimped in a single bumped crimp on one side and inserted in the 260-pin ZIF connector, and all the four blue wires were twisted with the red wires. A group of 5 bumped crimps were inserted into the ZIF260 connector and 8 flat crimps went in one of the 156P connectors. Block diagram of connections between two 156P connectors connected to a single 260-pin ZIF connector is shown in fig. 5.7. Image of the final connectors can be seen in fig. 5.8. No impedance matching was taken into account. These connectors are fully custom made and their design, wiring, connections and implementation was done by the author.

5.1.5 The Data Acquisition System

The array was integrated with a programmable PC-based imaging system (Verasonics system) to acquire data for synthetic aperture beamforming with random phased array. A custom designed interface provided connection between the Verasonics system and the phased array. The RF data collected by Verasonics data acquisition system is transferred via PCI-Express interface to a PC. The PC runs image reconstruction algorithm to construct the image. For an imaging depth of 170 mm and sampling rate of 4 MHz, the system acquires 1024 samples per A-scan. Each data sample is stored as 16-bits unsigned integer, 134 Mb raw data is thus obtained per frame from 256 transmit and 256 receive events. The architecture of the imaging system is shown in figure 5.9.

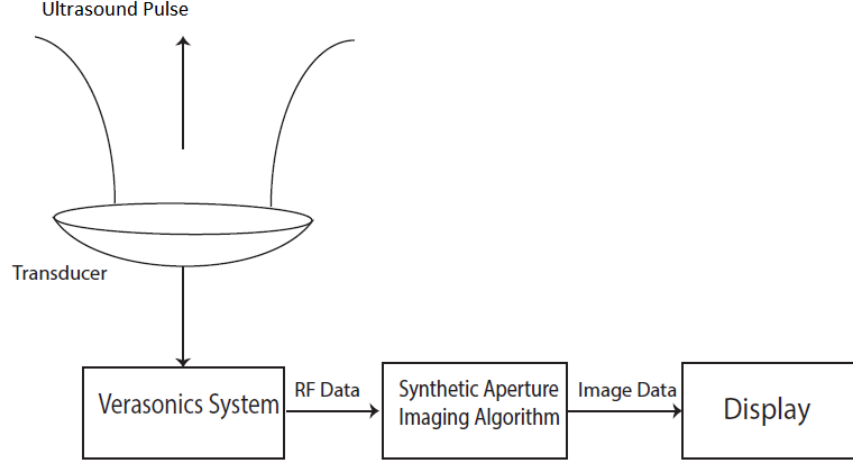


Figure 5.9: Block diagram of a Synthetic Aperture Ultrasound Imaging System

5.1.6 Phantoms

Experiments were performed with different targets to illustrate the imaging capabilities and assess the performance of random phased array. These included wire phantom, metallic balls, rib cage phantom and *exvivo* ribs.

5.1.6.1 Wire Phantom

The wire phantom consisted of five thin metallic cylinders with diameter 2 mm tightened in a frame such that the wires were placed from -10 to 10 mm along lateral direction and 100 to 140 mm in axial direction. The wires were positioned with a separation distance of 10 mm axially and 5 mm laterally. The phantom was placed in the water bath such that one of the wires passed through the geometric center of the array (fig. 5.10).

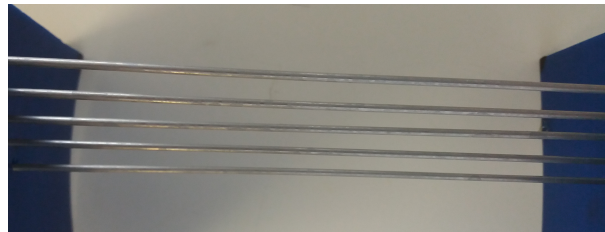


Figure 5.10: Experimental setup for imaging wire phantom with five wires of diameter 2 mm positioned 10 mm apart axially and 5 mm apart laterally at axial depths of 100 mm to 140 mm from the center of the array.

5.1.6.2 Metallic Ball Phantom

A ball phantom consisting of three metallic balls was used to determine the image resolution of the array near its geometric center. The diameter of each ball was 7 mm and they were arranged in a triangular shape such that the spacing between each pair was 10 mm. The arrangement of the phantom is shown in fig. 5.11.

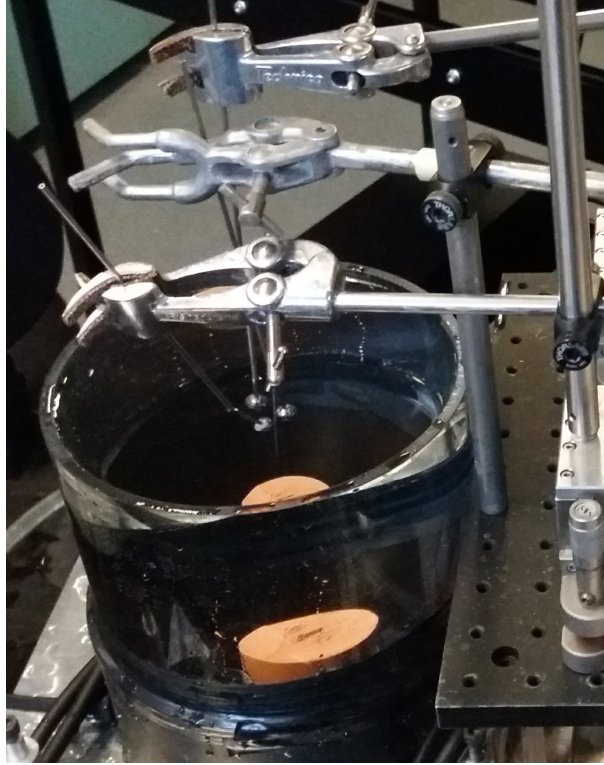


Figure 5.11: Experimental setup for imaging metallic balls phantom with three balls of diameter 7 mm positioned at a depth of 12 cm and 13 cm. The spacing between each pair of ball is 10 mm

5.1.6.3 Rib Phantom

To understand the capability of the random phased array to image the ribs, experiments were conducted with rib phantom which consisted of two metallic cylindrical bars with 10 mm diameter and 100 mm length (fig. 5.12). The phantom was adjusted in different configurations and spacing between them.

5.1.6.4 Ex-Vivo Ribs

To illustrate that the random phased array is capable of imaging bone, ovine ribs were purchased from a local butcher. Two ribs were detached from the spine and

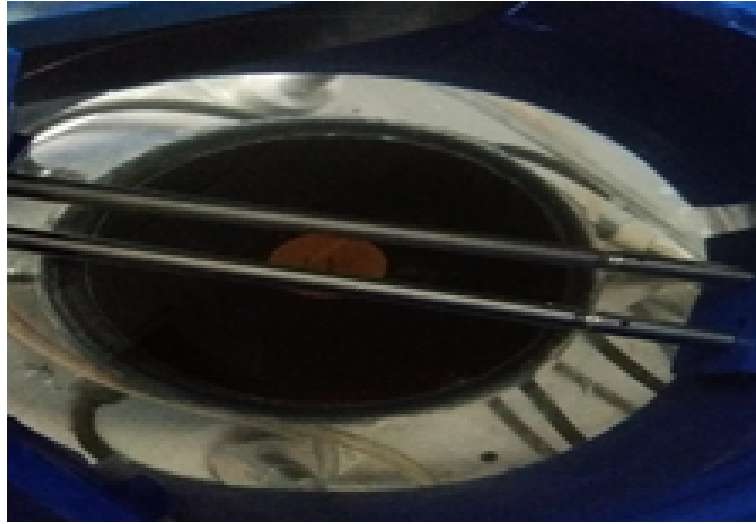


Figure 5.12: Experimental setup for imaging two metallic cylindrical bars with diameter 10mm and spacing 20 mm positioned at a depth of 10 cm from the centre of the array

from the rest of the cage and immersed in degassed water as shown in 5.13.

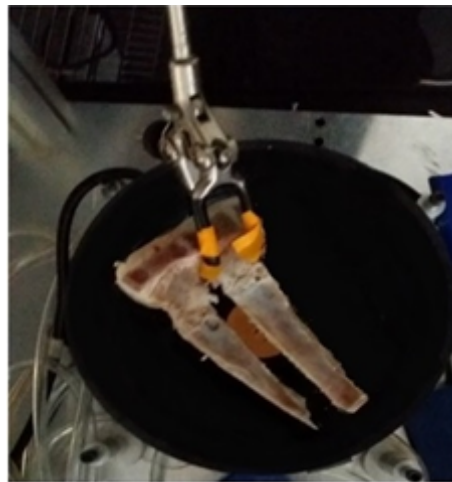


Figure 5.13: Two ovine ribs detached from a rib cage positioned in degassed water near the geometric center of the array

5.1.7 Infrared camera

To find the field distribution in the ribs plane, hydrophone scanning would be slow and time consuming whereas thermocouples would be limited to determine the temperature rise at certain location, an infrared (IR) camera was therefore used to provide a fast assessment of the field distribution in the ribs plane. The camera was Optris PI200 IR camera which allows recording of real-time and thermographic videos and images. The camera operates in the band 7.5 - 13 μ m providing an optical

resolution of 160×120 pixels at a pitch of 25 μ m with a frame rate of 128 Hz. The temperature range for the camera is -20 to 900 $^{\circ}$ C and the thermal resolution is 40 mK. The accompanying software provided a user-friendly interface to acquire, view and store IR images through an RS422 link. The ultrasound beam was directed upward onto a 10 mm thick ultrasonic absorber sheet (Aptflex F48, Precision Acoustics, Dorchester, UK). The distance between the transducer and the absorber was adjusted and the other side of the sheet was air backed such that there was no other medium between the IR camera and the absorber. The absorber was placed at a height of 45 mm from the center of the array and the distance between the camera and the absorber was set to 30 cm.

5.2 Experimental Imaging Results

Experiment was performed with the linear array to validate the simulation results of the STA imaging technique. Raw data was acquired for all 128 channels first by transmitting only on one central element, then by transmitting with central 3 elements one after another and finally by transmitting with all elements in turn. The received signals for all the elements were beamformed retrospectively using STA technique to obtain low resolution images (fig. 5.14), which are focused only in receive due to unfocused transmission. Focusing is done by calculating distance from all the pixels in the imaging field of view to the transmitting element and then back to the receiving element as in eq 4.3. The artefacts near the transducer surface can be seen in the low resolution images due to small number of transmissions (see fig. 5.14 (a,b)), which are completely removed when all the elements are used for transmission, thus 128 low resolution images are obtained which are added coherently to obtain the high resolution image (see fig. 5.14 (c)). No further experiments were conducted with the linear array.

The random phased array was then used for imaging with a variety of phantoms to demonstrate its excellent imaging capabilities and its potential to detect and image strong scattering objects such as ribs. With a synthetic aperture imaging

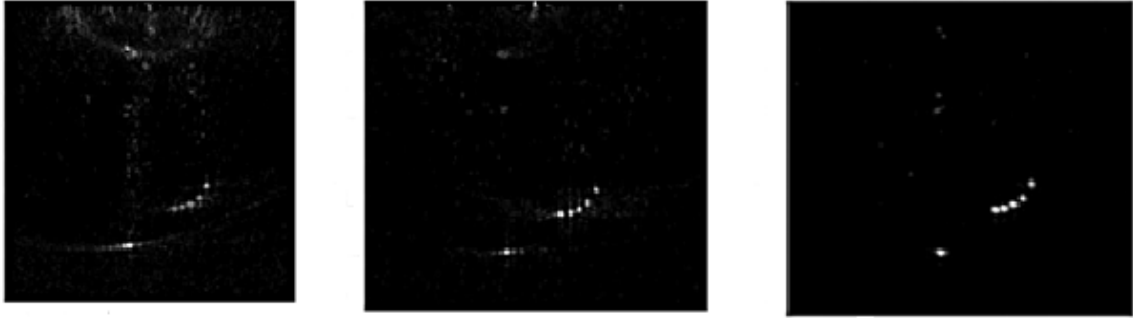


Figure 5.14: Image reconstructed with the acquired RF data from the Gammex Ultrasound phantom with 6.25 MHz 128-element transducer array with 0.3mm pitch and $N_t = 1$, (left), $N_t = 3$ (middle), and $N_t = 128$ (right). The width of the image is 30 mm and the depth is 45 mm

system as shown in 5.9, RF data was collected for all 256 elements. Unlike the conventional Ultrasound system, the data was stored for all receiving elements and for all emissions. Thus 65536 (256×256) RF lines were obtained for all 256 elements. All these A-line echoes were sampled at a sampling frequency of 4 MHz and stored which were then processed with Synthetic Aperture Imaging algorithm.

The wire phantom was used to illustrate the spatial resolution of the system and find the range of imaging field of view (IxFOV). SA image data from the wire target was collected experimentally using the setup described in section 5.1. Both 2D and 3D images are reconstructed and shown in fig. 5.15.

Similarly metallic balls were used to determine the imaging resolution of the array near its geometric center. The ball phantom discussed in section 5.1.6.2 was immersed in degassed water bath. Both 2D (fig. 5.16) and 3D (fig. 5.17) images are shown below. The balls are clearly visible in both the images.

To understand the capability of the phased array to image the ribs, two further experiments were conducted. First a rib phantom consisting of two acrylic and metallic cylindrical bars with 10 mm diameter and spacing 20 mm were positioned in water bath. Raw data was collected and beamformed using STA approach. The rib phantom was modified and spacing between the ribs as well as the geometric position of the rib phantom was varied to determine the imaging field of view (IxFOV) and the capability of the phased array to image the phantoms with different orientations.

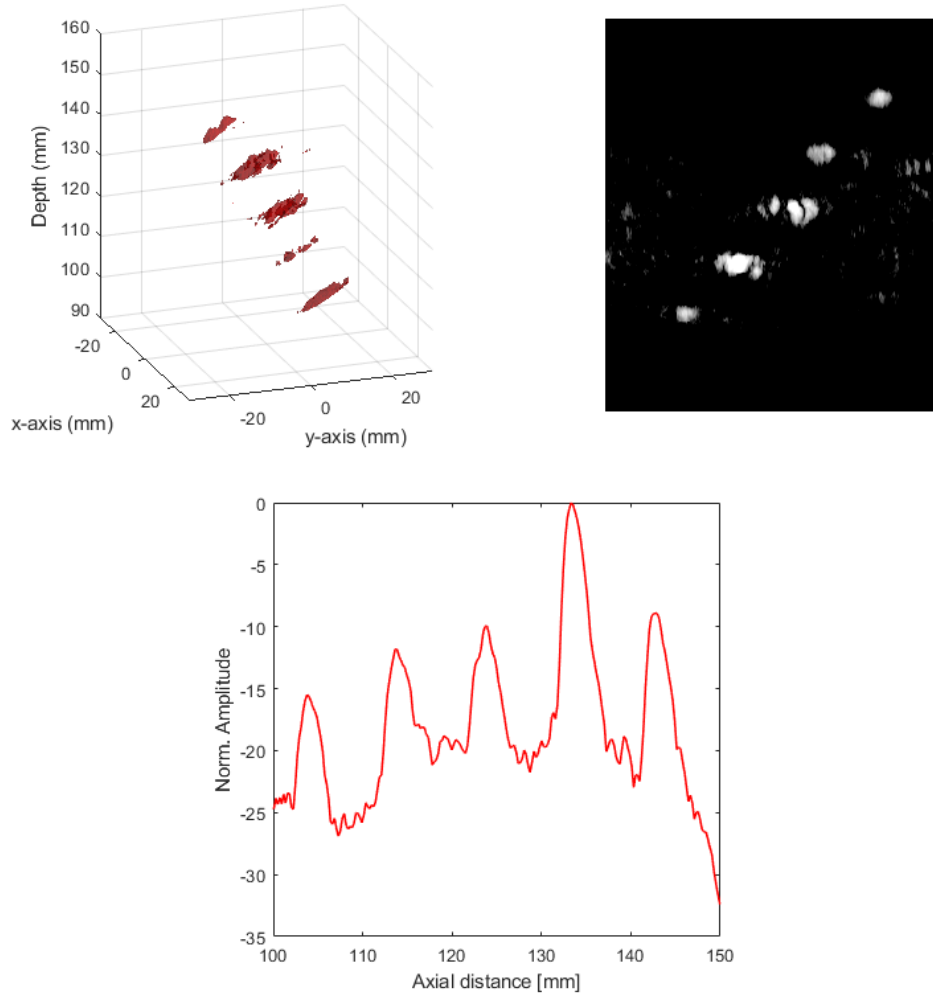


Figure 5.15: 3D image of a wire phantom comprising of 5 wires each with 2mm diameter and spaced 10 mm apart (top left), corresponding Bmode image, displayed over a dynamic range of 20 dB (top right), normalized cross-section of the lateral beamprofile (bottom)

It was observed that the ribs can be imaged if the distance of the ribs from the array center is 70 mm which is 30 mm from the surface membrane of the array. The IxFOV was thus observed to extend from 70 mm to 150 mm from the array center in axial direction. 2D and 3D images of one of the phantoms when it is positioned at 90 mm from the array center are shown in figs. 5.18 and 5.19, respectively. This would resemble to a treatment scenario when the focus is 4 cm deep in the body. Both the ribs in the phantom can be clearly seen in these images. Furthermore, ovine ribs (fig. 5.13) were obtained from a local butcher, detached from the spine and immersed in degassed water to image with the array. Raw data was collected with the Verasonics system and 3D image was reconstructed with the STA approach to

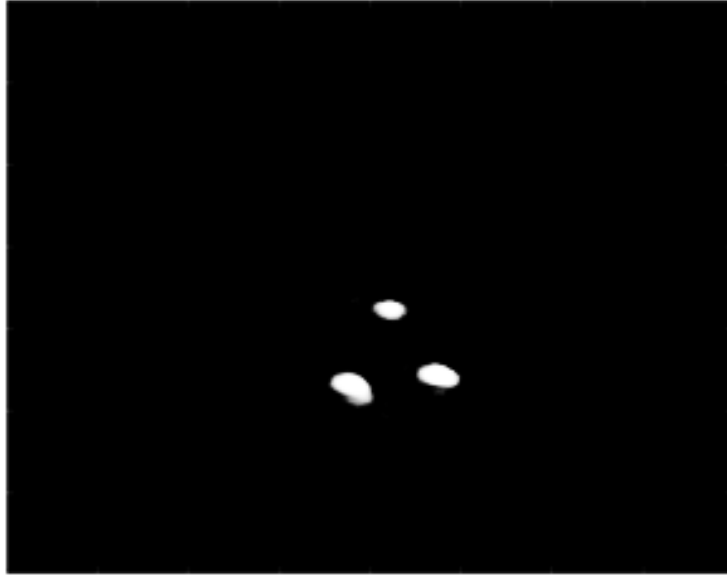


Figure 5.16: Gray-scale image of the ball phantom displayed over a dynamic range of 20 dB

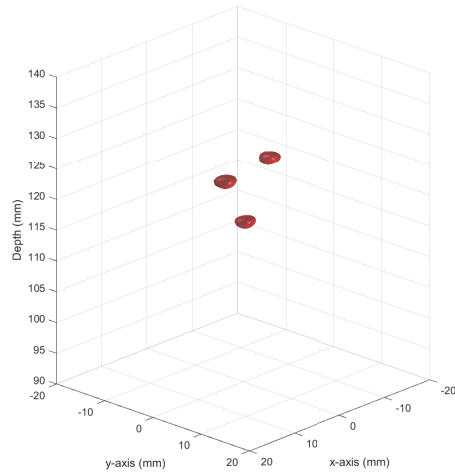


Figure 5.17: 3D image of the ball phantom displayed over a dynamic range of 20 dB

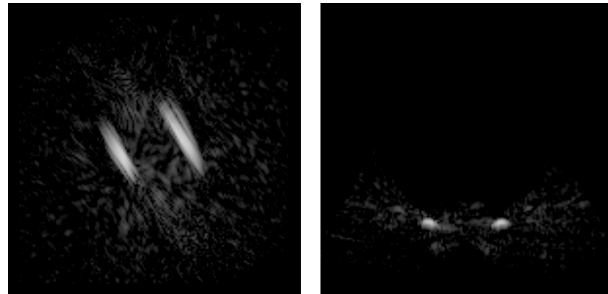


Figure 5.18: Bmode image of the cylinder bars displayed over a dynamic range of 30 dB in xy (left) and xz (right) plane

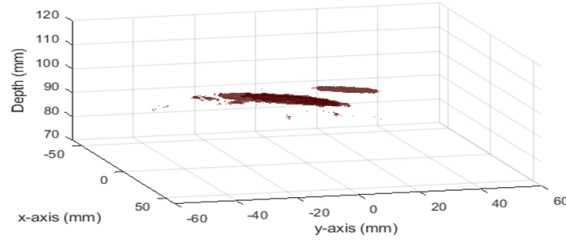


Figure 5.19: 3D image of the parallel cylinders

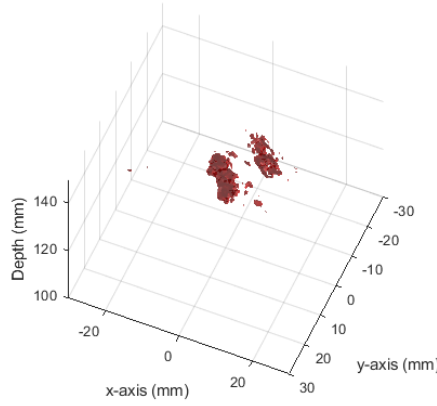


Figure 5.20: 3D image of the ovine ribs

illustrate the capability of the phased array to image bones. Both the ribs in the image were clearly visible and distinguishable from one another (fig. 5.20).

5.3 Summary

In the work reported in this chapter, the random phased array was integrated with state-of-the-art research ultrasound scanner, *Verasonics*, via custom-built connectors. The scanner was programmed to obtain pulse-echo signals that were reconstructed using synthetic aperture imaging algorithm to obtain images of different phantoms. The position, shape and orientation of the phantoms were varied to ascertain that the phased array can image structures of various shapes. Images of rib phantoms and ex-vivo ribs were reconstructed and it was shown that the random phased array is capable of imaging and locating obstacles such as ribs so that they can be avoided from damage during the therapy. In the next chapter, a technique

for sparing the ribs in HIFU therapy and the effect of human ribs on focus quality will be discussed in detail.

Chapter 6

Therapy through the Rib cage

This chapter discusses the effect on focus quality after the HIFU beam propagates through the rib cage. A technique to minimize heating on the ribs while maintaining high intensity at the focus is discussed and implemented in simulation and experimentally. Both idealized parallel strips and anatomically correct ribs are used to show that adequate focusing through the ribs can be achieved without overheating the intervening tissue. Parameters of focus splitting are analyzed in detail and suggestions for the improvement of focus quality in the presence of human rib cage are made.

One of the big challenges of using HIFU for treating deeply positioned tissues is the presence of structures that strongly reflect or absorb acoustic energy. One of such obstacles is the rib cage which does not allow the acoustic energy to be passed without being damaged due to its high absorbing capabilities of the ultrasound [108, 110], which may dissipate heat into the surrounding tissues and result in skin burns . Moreover, the shadowing of the phased array due to the rib cage leads to lower intensity levels than required for the ablation of tumor in the liver. The ribs also act as diffractors and cause focus distortion. Thus the major difficulty in its clinical use for ablating liver tumours is the transmission of sufficient energy through the ribs to induce tissue necrosis while minimizing the energy in side-lobes. It is

therefore of paramount importance to calculate the acoustic intensity distribution near the ribs to determine the efficacy of the system in terms of peak intensity levels in the focal plane and low intensity levels in the rib plane. A thorough understanding of the effect of rib cage on ultrasonic pressure field of the HIFU array is required as part of the treatment planning strategy.

Three problems are associated with the presence of ribcage in the HIFU beam path. First, absorption of acoustic energy by the ribs and reflections inducing high pressure spots that causes ribs heating and skin burns. Secondly, reduction in the intensity at the focal spot due to the shadowing of elements by the ribs and finally, focus deterioration due to the periodic structure of the ribs. Several research groups have tried to minimize heating of the ribs while preserving high intensity at the focus in the presence of ribcage [93, 96, 99, 105, 107, 109, 110, 111, 113]. The parameters of focus splitting were quantified and it was determined that the rib cage acts as a diffractor [99]. In all these studies, the authors showed the effect of focus splitting and variation in the intensity distributions when the ultrasound beam passed through the rib cage. Some studies discussed the effect of focus splitting in detail including [99] and [112] but their study was limited to idealized rib phantoms and the effects of human rib cage on focus quality was not taken into account.

The aim of this chapter is to understand the effect of human ribcage on the intensity distribution of a random phased array and analyze focus splitting for various different parameters and scenarios. Simulations are thus performed to calculate intensity distribution of the phased array in presence of rib phantoms. A binarized apodization technique based on geometric ray tracing approach [110, 111] was used to minimize the effect of HIFU on the ribs. The advantage of using this technique is its simplicity as well as its non-invasive nature. Furthermore, the technique has potential to detect ribs and minimize its heating and does not suffer from registration problems when used in conjunction with the imaging with the therapeutic transducer. In this approach, the focus point is connected with the center of each

element. If the ray connecting the element with the target passes through any of the ribs, the element is being blocked by the rib, the velocity distribution at that element is set to zero and the element is deactivated. If the ray connecting the element to the focus passes through the intercostal space, the velocity amplitude is set to maximum and the element is activated.

6.1 Acoustic Field Modeling

The far-field pressure of the phased array is calculated by summing the contribution from each circular element which is calculated analytically at a point in the field with coordinates (x, y, z) , which is at a distance r from the centre of the element and at an angle θ from the line joining the centre of the element with the geometric focus [142]:

$$P(x, y, z) = \sum_j \frac{ip_0 Z_R e^{i(kr + \phi_j)}}{r} \frac{2J_1(ka \sin \theta)}{ka \sin \theta} \quad (6.1)$$

where p_0 is the pressure on elements surface and its value is equal to ρcv , where ρ is the density of the medium in kg/m^3 , c is the speed of sound and v is the vibration velocity at the surface of the transducer, a is radius of the element, k is the wave number, $Z_R = \frac{ka^2}{2}$ is the Rayleigh length, r is the distance from the element center to the field point, ϕ is the phase angle calculated using the pseudo-inverse method discussed later and J_1 is the first order Bessel function.

The phase and amplitude of each element of the array can be adjusted independently for a given focus point. The initial phase can be adjusted to a constant value to focus at the geometric center of the array and the phases can then be varied for an electronic steering of the focus. For a particular focus configuration, the distribution of phases and velocity for each element is calculated using the pseudoinverse method

[61]:

$$u = H^{*t}(HH^{*t})^{-1}p \quad (6.2)$$

where $\mathbf{u} = [u_1, u_2, \dots, u_n, \dots, u_N]$, $\mathbf{p} = [p_1, p_2, \dots, p_m, \dots, p_M]^t$ and $\mathbf{H}$ is the $M * N$ matrix with elements $\mathbf{h}_{mn} = \frac{\mathbf{ip}_0 \mathbf{Z}_R \mathbf{e}^{i(\mathbf{k}r_{mn} + \phi_n)}}{r_{mn}} \frac{2\mathbf{J}_1(\mathbf{k}a \sin \theta)}{\mathbf{k}a \sin \theta}$, where m and n are number of control points and elements, S is area of an element, ϕ_n is the excitation phase for each element. Eq. 6.2 is a minimum norm solution for an undetermined system of equations, $Hu = p$. A minimum-norm least square estimate of $\mathbf{u}$ is given by

$$\hat{u} = H^+ p$$

Where H^+ is the pseudoinverse of H . This operator can be calculated by spectral value decomposition (SVD) of the matrix $\mathbf{H}$ or some efficient iterative algorithm that converges to minimum norm least-square solution. However, this is not useful in many practical situations when $M < N$ and the above equation becomes an undetermined system of equations. When H is full rank then eq. 6.2 is the minimum norm solution, where H^{*t} is the conjugate transpose of H . To determine $u_n (n = 1, 2, \dots, N)$, phases and amplitudes of $p_m (m = 1, 2, \dots, M)$ are selected. A matrix of contributions of transducer elements to the focus points pressures $p(x, y, z)$ are first obtained, this is called forward propagation operator $\mathbf{H}$. Then the matrix $(HH^{*t})^{-1}p$, which is a pre-emphasis vector is calculated to transform vector p into $p_w = (HH^{*t})^{-1}p$ that has same dimensions as H . The backward propagation operator is then applied to p_w to obtain $\hat{u}$ that is now orthogonal to H , thus giving the minimum norm solution. The phases of each element are then calculated to produce patterns of multiple foci. The intensity distribution was calculated both in the lateral and axial planes from the pressure distribution as

$$I(x, y, z) = p^2/2\rho c \quad (6.3)$$

Where p is the pressure amplitude, ρ and c are the density and speed of sound of the medium, respectively.

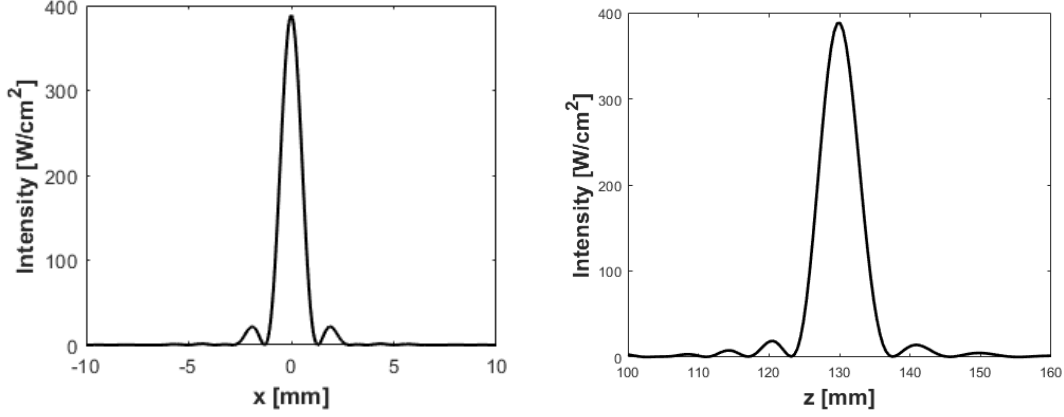


Figure 6.1: Lateral and axial Intensity profiles for a single focus targeted at $(x,y,z) = (0,0,130)$

6.2 Ultrasound Intensity distribution in absence of Ribs

Intensity distributions for a single and set of multiple foci were calculated in the focal plane. The work presented by Hand *et al.* [4] was repeated and extended to the generation of a single focus steered both laterally and axially and calculating the intensity distribution in various planes for the steered focus. Moreover, sets of four and five foci were generated and steered and the effect on intensity distribution was calculated.

6.2.1 Single focus on- and off-axis

Field distribution was modeled at a minimal total acoustic power of 15 W which produced an average intensity of 0.152 W/cm^2 at each of the 256 elements. Simulations were performed in MATLAB on a computer with Intel Core i7-4790 processor

running at 3.60 GHz using 16 GB of RAM and running Windows 10.

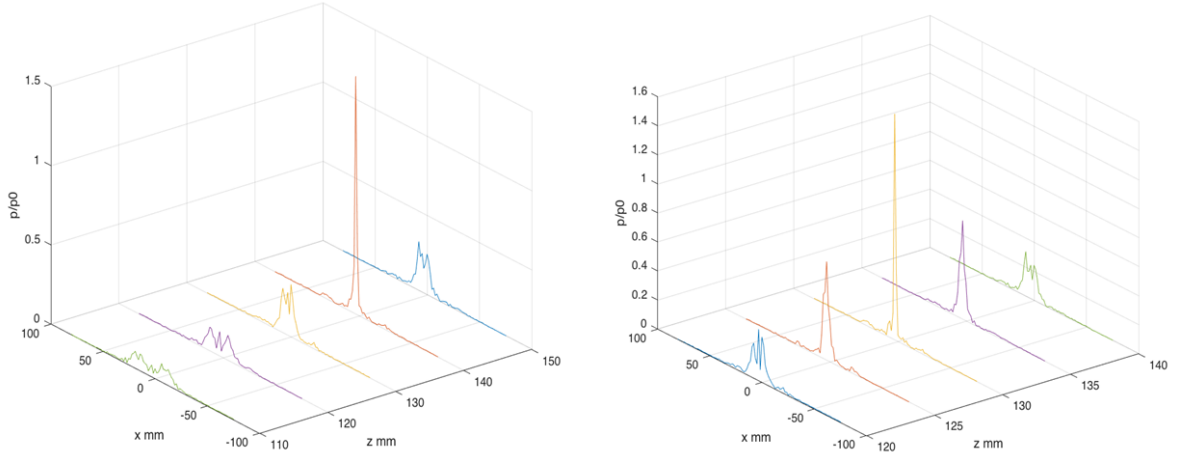


Figure 6.2: Spatial distribution of the relative intensity of the array field: for focusing at $(0,0,140)$ mm (left) and $(0,0,130)$ mm (right).

A single focus targeted at the centre of the curvature of the array has 1.2mm -6dB full width. The maximum intensity predicted in the focal plane was 388 W/cm^2 and the corresponding maximum pressure amplitude is 3.4 MPa . Lateral and axial intensity profiles for a single focus centered at the geometric focus of the array are shown in fig. 6.1. The axial distribution of relative intensity in array field is shown in fig. 6.2. The intensity at 5 mm from the focus is approx. $0.2I_{max}$ and is $0.1I_{max}$ at 10 mm. Peak intensity at the focus is reduced to 201 W/cm^2 when it is steered 15 mm off the axis in x or y directions but no secondary hotspots are observed (fig. 6.3). When the focus is steered 15 mm off both the x- and y-axes (equivalent to 21 mm away from geometric focus), local hotspots start to appear away from the focus. The peak intensity reduces to 97.4 W/cm^2 and intensity in the hotspots is upto $0.13I_{max}$. It is thus concluded that the focus can be steered 1.5 cm either side of the axis.

The focus can also be steered along the axis. Predicted intensity distributions in $x - y$ planes are shown in fig. 6.4 for a single focus on axis and centered at $z = 140$ mm, $z = 130$ mm and $z = 120$ mm. It is observed that for a single focus on axis centered at $z = 140$ mm, the peak intensity would drop to less than 25% at 5 mm

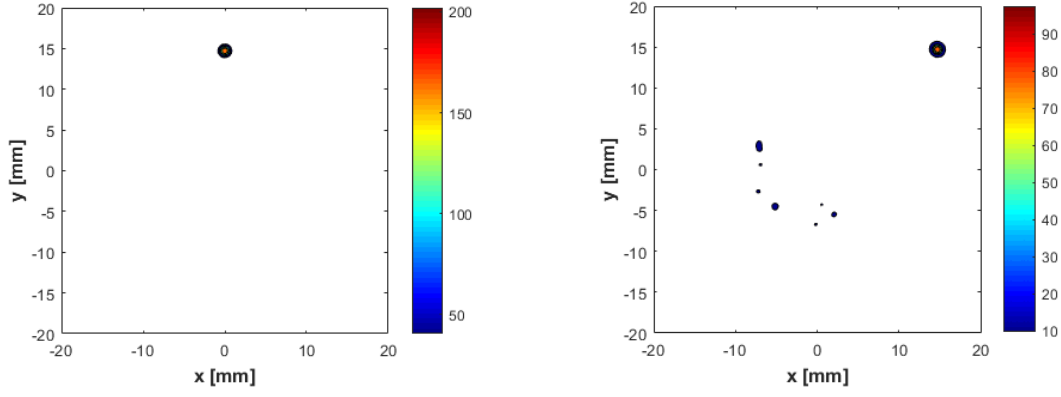


Figure 6.3: Predicted intensity distribution for a single focus steered to $(x,y,z) = (0,15,130)$ mm (left), $(15,15,130)$ mm (right), colorbar indicates intensity in W/cm^2 . Grating lobes appear when the focus is steered beyond 15 mm. Intensity in the grating lobes is less than $0.15I_{max}$

away from the focus axially and less than 5% at a distance of 10 mm. For a single focus centered at geometric focus $z = 130$ mm, peak intensity would drop to less than 15% at 5 mm and less than 5% at 10 mm. For a single focus on axis steered at $z = 120$ mm, peak intensity in the beam would drop to less than 10% at 5 mm distance and less than 4% at 10 mm. Thus there is a sharp decline in the intensity level off the focus. The beam is narrow only at the focus point and gets wider away from it. When a single focus was targeted at $z = 120$ mm, the predicted -6dB full width and full length were 1 mm and 5.7 mm, respectively. At $z = 140$ mm, -6dB full width and full length were 1.2 mm and 7.1 mm, respectively.

Table 6.1: Peak Intensity at the target generated by the random phased array when a single focus is targeted at three different depths

Single focus targeted at	Peak Intensity (W/cm^2) in $x - y$ plane at				
	120mm	125mm	130mm	135mm	140mm
(0,0,120)mm	400	45	17	6	5
(0,0,130)mm	18	45	380	60	14
(0,0,140)mm	5.5	6.5	14	82	330
(10,0,120)mm	300	30	12	7	8
(10,0,130)mm	14	30	280	45	9
(10,0,140)mm	8	7	10	63	248

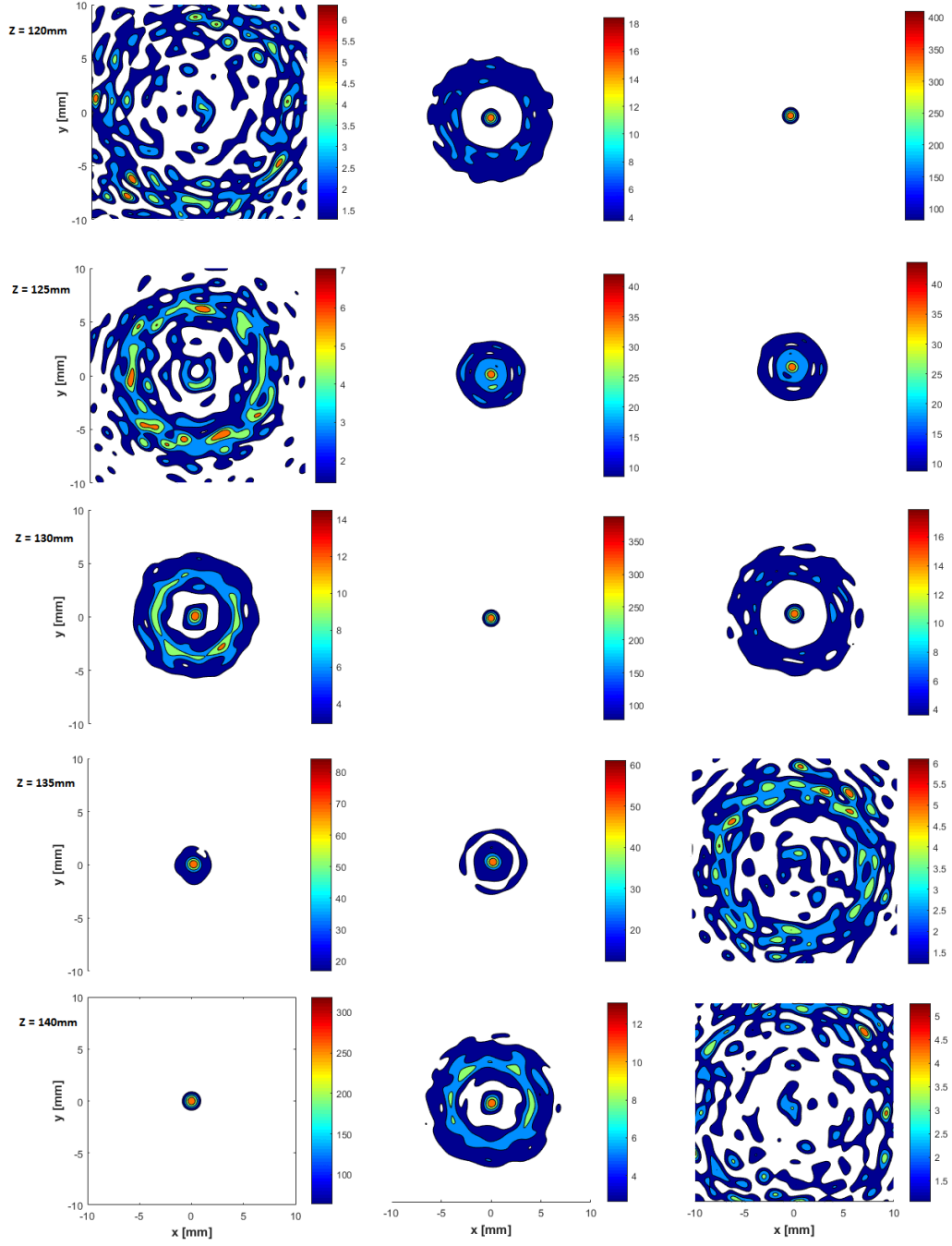


Figure 6.4: Predicted intensity distributions in $x - y$ planes at $z = 120, 125, 130, 135$ and 140 mm for a single focus on axis and focused at $z = 140$ mm (left column), $z = 130$ mm (middle column) and $z = 120$ mm (right column). Energy is focused at the intended target and spreads elsewhere with low intensity. Colorbar indicates intensity in W/cm^2

(10,0,120) mm, peak intensity in a plane 5 mm away from the focal plane was only 10% of the focus point and only 4.3% in a plane 10 mm away. This indicates that energy is mostly concentrated at the focus point and low level of energy is deposited elsewhere. The intensity values are shown in table 6.1.

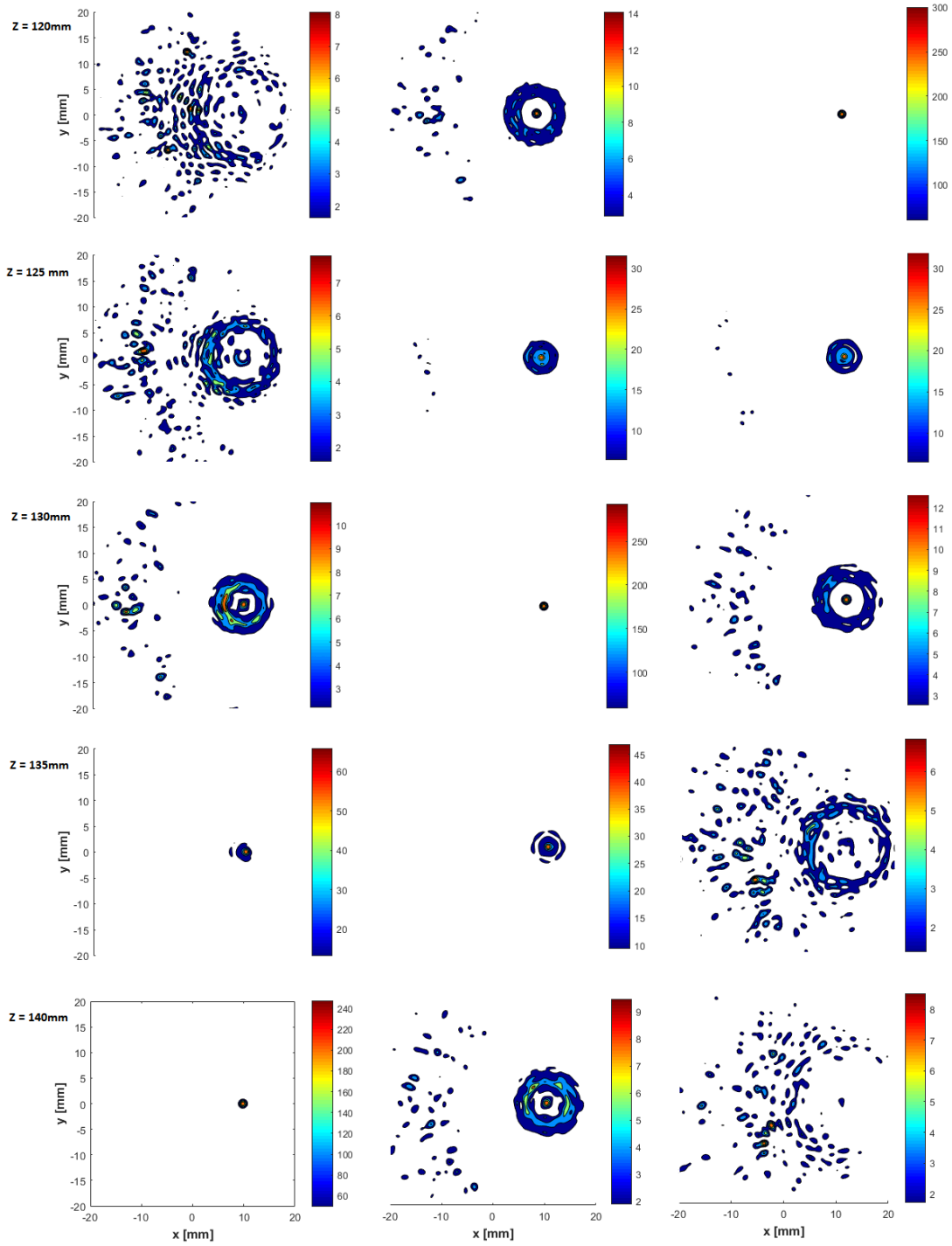


Figure 6.5: Predicted intensity distributions in $x - y$ planes at depths $z = 120, 125, 130, 135$ and 140 mm for a single focus 10 mm off axis and focused at $z = 140$ mm (left column), $z = 130$ mm (middle column) and $z = 120$ mm (right column). Energy is focused at the intended target and spreads elsewhere with lower intensity. Colorbar indicates intensity in W/cm^2

6.2.2 Multiple simultaneous foci

Phases are calculated for all elements using eq. 6.3 to generate multiple foci. Sets of two, three, four and five foci were generated and steered. In the case of pattern

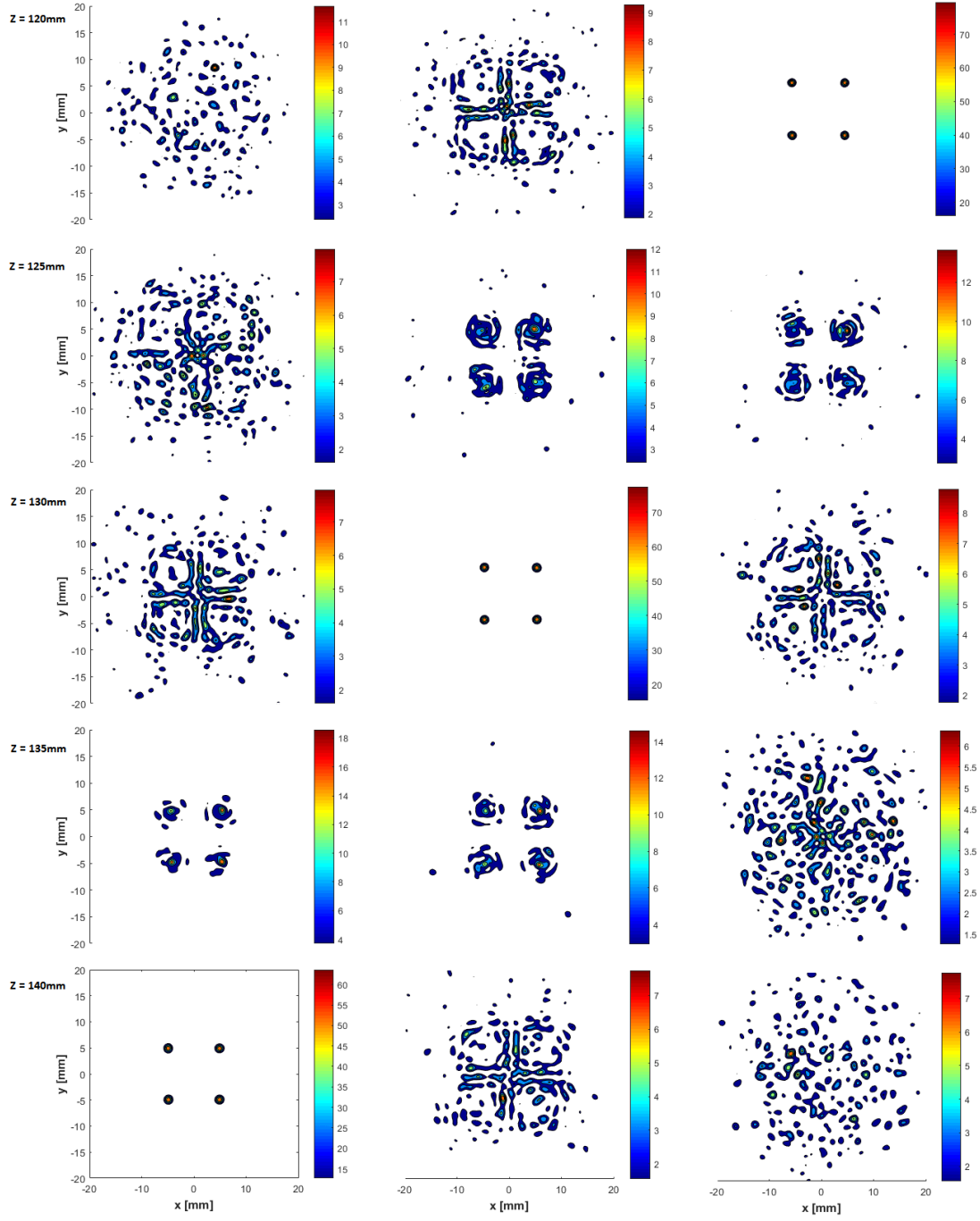


Figure 6.6: Predicted intensity distributions in $x - y$ planes at depths $z = 120, 125, 130, 135$ and 140 mm for a set of four foci on axis and focused at $z = 140$ mm (left column), $z = 130$ mm (middle column) and $z = 120$ mm (right column). Four sharp foci are visible at the intended depth and the energy spreads with decreased intensity as the axial distance from the focal plane increases. Colorbar indicates intensity in W/cm^2

for four foci, the foci were targeted at $(x,y) = (4,4), (-4,4), (-4,-4)$ and $(4,-4)$ mm and $z = 120, 130$ and 140 mm. It was observed that the peak intensity in the four foci is significantly less than the single focus due to the distribution of energy in

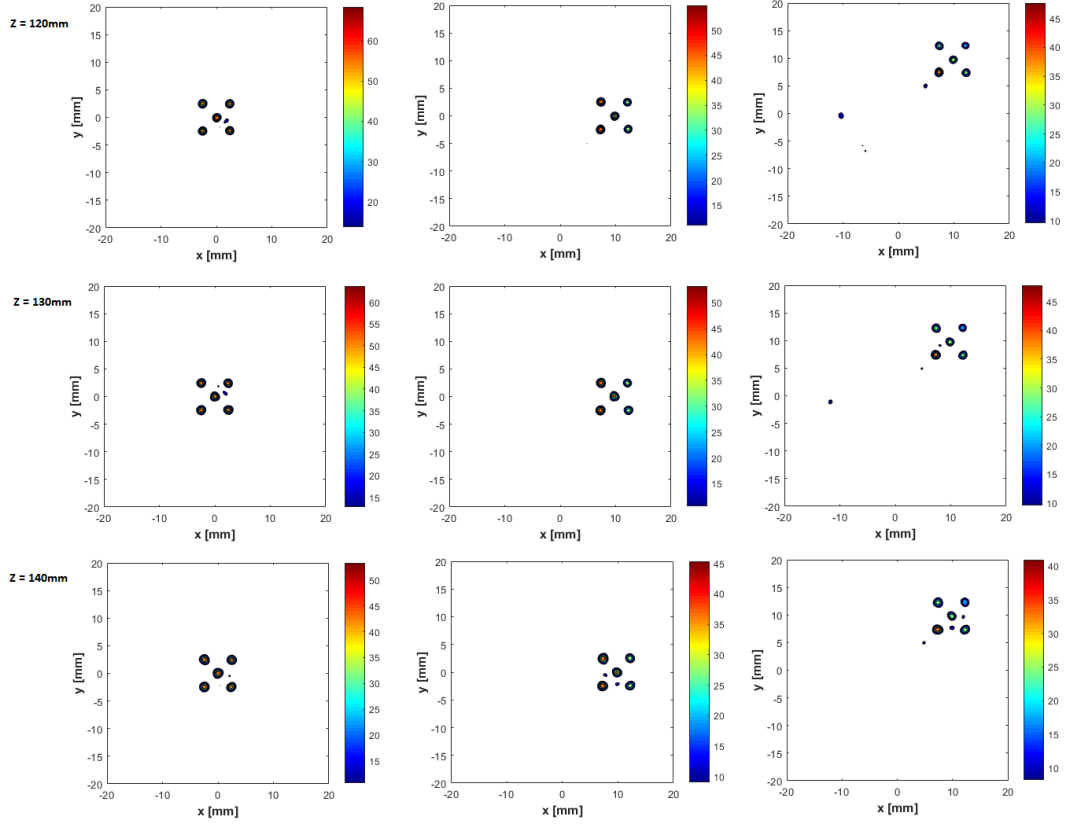


Figure 6.7: Predicted intensity distributions in $x - y$ planes at $z = 120$ mm (top row), $z = 130$ mm (middle row) and $z = 140$ mm (bottom row) for a set of five foci on axis and steered at $(x,y) = (0,0)$ mm (left column), $(x,y) = (10,0)$ mm (middle column) and $(x,y) = (10,10)$ mm (right column). Negligible grating lobes appear when the set of foci is steered inside the therapeutic operating field (ThxOF). Colorbar indicates intensity in W/cm^2

multiple foci and thus more input power would be required to achieve the same level of heating. The peak intensity was $77 W/cm^2$ when the set of foci was targeted at $z = 130$ mm, and the peak intensity in the planes 5 mm and 10 mm away from the focal plane was 15% and 10% of peak intensity in the focal plane, respectively. The set of four foci was also steered along the axis as shown in fig. 6.6.

Patterns of five foci were generated in circles of 5 cm, 8 cm and 16 cm in the plane at $z = 130$ mm with coordinates $(0,0,130), (2.5,2.5,130), (-2.5,2.5,130), (-2.5,-2.5,130)$ and $(2.5,-2.5,130)$ mm. The pattern was steered both in lateral and axial directions as shown in fig. 6.7. The foci are generated in $z = 120, 130$ and 140 mm planes and steered at $x = 10$ mm and $x = 10, y = 10$ mm. No significant side lobes are observed

and all grating lobes are well below 20% of the peak intensity. The foci were 2.5 mm apart from each other. It was observed that the maximum intensity for the given acoustic power is $90.5W/cm^2$, $82.5W/cm^2$ and $67.75W/cm^2$ when the spacing between the focus points is 2.5, 4 and 8 mm, respectively. The set of multiple foci was also steered in the focal plane and the secondary intensity maxima were below 20% of the peak value. It was possible to steer the pattern of foci upto 15 mm off axis for ranges between 90 mm to 140 mm with an acceptable level of secondary lobes.

6.3 Ultrasound Intensity distribution in the presence of Ribs

Simulations were performed to demonstrate the effect of ribs on ultrasound focusing and calculate intensity distribution in the rib and focus planes. It is important to analyze the intensity field in the focal plane for different geometries of the rib cage. Intensity in the focal plane is dependent on the the ratio of beam width in the ribs plane and width of the ribs, the position of beam axis relative to the ribs, position of ribs relative to the transducer, width of the ribs, width of intercostal space and number of ribs. The estimate of decrease in the HIFU intensity in focal plane and increase of intensity in secondary maxima due to the presence of ribs is important for practical applications. The spacing between ribs and the depth of sonication are important parameters and have impact on the focal quality and thus the patient safety and should be studied in detail. First the intensity in the presence of idealized rib phantom was studied to validate the previous work [99, 112], which was then extended to include the anatomically correct human rib cage.

6.3.1 Parallel strips

Five idealized rib geometries were studied. These geometries consisted of parallel strips of different width and spacing between them. These strips were 6 mm, 10 mm, 16 mm, 20 mm and 18 mm wide and the spacing between them was 18 mm, 20 mm, 18 mm, 10 mm and 6 mm, respectively. Moreover, these strips were positioned in such a way that the focal point was 90 mm, 60 mm and 30 mm behind the ribs i.e. the strips were placed at depths of 40 mm, 70 mm and 100 mm from center of the array. For each of these configurations, two scenarios were further investigated: when the array axis passes through the middle of one of the ribs and when it passes through the center of an intercostal space.

The geometric configurations can be summarized as:

Geometries:

- Width = $[1/3d, 1/2d, d, 2d, 3d] \times$
- Depth = $[40 \text{ mm}, 70 \text{ mm}, 100 \text{ mm}] \times$
- Beam axis through = $[\text{Ribs}, \text{Intercostal space}]$

where d is the spacing between the strips.

For all these geometric configurations, acoustic intensity distribution was calculated in simulation and the focus quality was determined in terms of peak intensity at the focus point, focus splitting, distance between sidelobes and main lobe and the sidelobe level.

The results of only one of the above geometries (i.e. Width $\approx$ Depth) will be discussed in the following paragraphs. The effect of other geometries are summarised

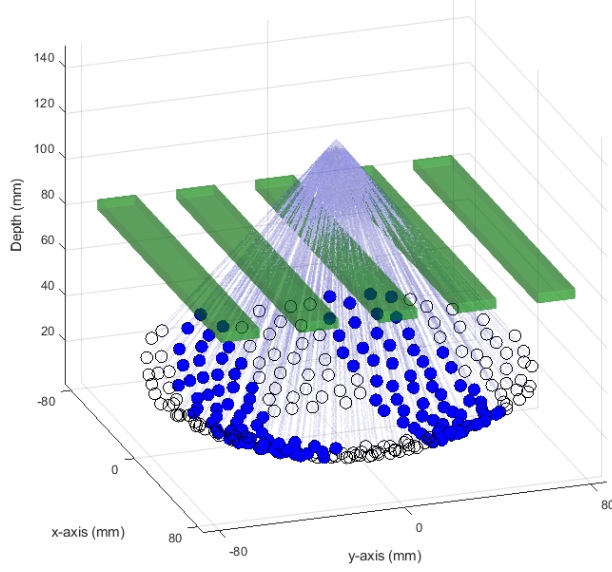


Figure 6.8: Geometry of the Rib phantom consisting of parallel strips, each 16 mm wide and 4mm thick. The spacing between the strips is 18mm. Geometric Ray Tracing approach indicated with blue lines, the elements whose normal cross the intercostal space are turned ON (blue)

in tables 6.2 & 6.3 and figs. 6.14 - 6.18. The ribcage model discussed below consists of five parallel strips, each having width of 16 mm and spacing between edges of two strips was 18 mm. The thickness of each strip was 4 mm. The middle strip was right above the geometric centre of the array hence the array axis passed through the strip. The model was positioned at various heights from the center of the array and geometric ray tracing was performed to determine the elements being blocked by the strips while focusing at the geometric center of the array, as illustrated in fig. 6.8. The elements whose normal was crossing any of these strips was deactivated and acoustic field was calculated with the remaining elements. For multiple simultaneous foci, the normals from all elements to each focus was used to find the blocked elements.

The acoustic power of the phased array was arbitrarily set to $W_0 = 15W$. When all the elements are active with uniform distribution, the maximum intensity in the focal plane in water is 387.6 W/cm^2 . When the ribs were placed at 40 mm from the array center, only 128 elements were activated and the peak intensity was reduced

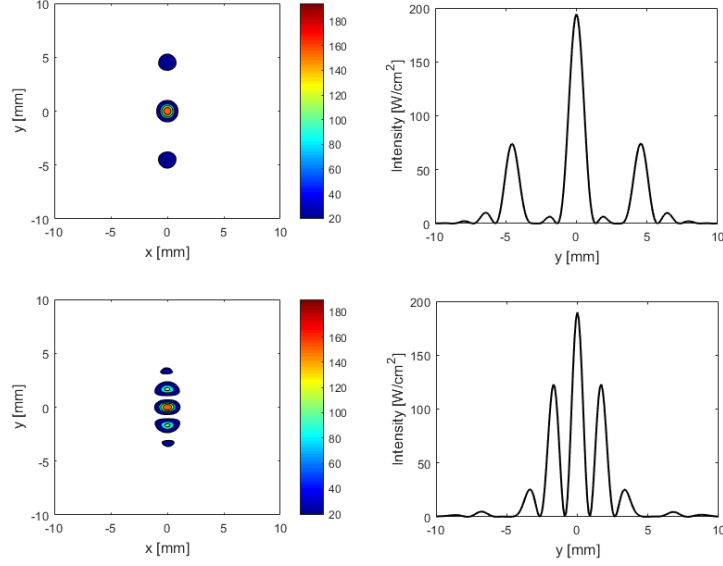


Figure 6.9: Focus splitting effect when the rib phantom is positioned at 40 mm from the center of the array (top row) and 100 mm (bottom row). Focus is split into three and five, respectively.

to 194.2 W/cm^2 . The beampower within -6dB of the focal peak is 53.5% of the initial power. The intensity in the focal plane is reduced to 46.2% of the intensity without any rib cage. When the rib phantom was positioned at a depth of 100 mm from the transducer, the number of active elements was changed to 132 and the peak intensity at the focus plane was slightly increased to 198.8 W/cm^2 . Moreover, the intensity in the rib plane near the ribs was increased more than threefold due to its distance close to the geometric focus.

6.3.1.1 Intensity distribution in the Ribs plane

Simulations and experiments were conducted to determine the intensity distribution and effect of ultrasound heating in the ribs plane. Elements which were shadowed by the ribs were deactivated to avoid hitting the ribs and transfer acoustic energy intercostally. Fig. 6.10 shows the active elements and the resulting simulated intensity distribution in the plane of the ribs, when the ribs phantom was placed at 45 mm from the center of the transducer. The dashed lines show the edges of the spacing between the strips. Striped acoustic field distribution is observed and no

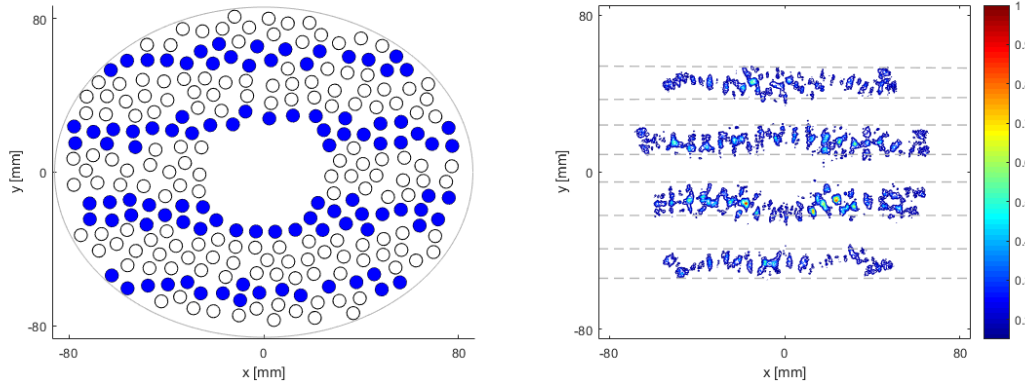


Figure 6.10: Normalized intensity distribution when the ribs are located at 40 mm. Active element are shown in blue (left), intercostal intensity distribution in simulation (right). The white space in the image in right is the position of the strips and determines the absence of any acoustic energy on its surface.

hotspots are observed on the ribs as evident in the figure.

Experiment was conducted with the random phased array and an infrared camera to validate the simulation results. The distribution of temperature rise was obtained with an IR camera described in section 5.1.7. An ultrasonic absorber (Aptflex F48, Precision Acoustics, Dorchester, UK) was positioned in-front of the transducer in a water bath at a distance of 45 mm. The ultrasound beam was directly upward onto the ultrasonic absorber sheet. The distance between the transducer and the absorber was adjusted. The other side of the sheet was air backed such that there was no other medium between the IR camera and the absorber. The distance between the absorber and the IR camera was set to 30 cm.

Active elements were determined in MATLAB and the relative phases and amplitudes were then used to excite the elements of the random phased array. Video of the increased heating of the absorber sheet was recorded and striped heating pattern in the ribs plane was observed as can be seen in fig. 6.11. IR image of the top surface of the absorbing material shows white stripes that indicate maximum temperature, whereas, pink indicates room temperature. The striped heating pattern delineates the effect of shadowing method to transmit intercostal acoustic energy and avoid heating the ribs.

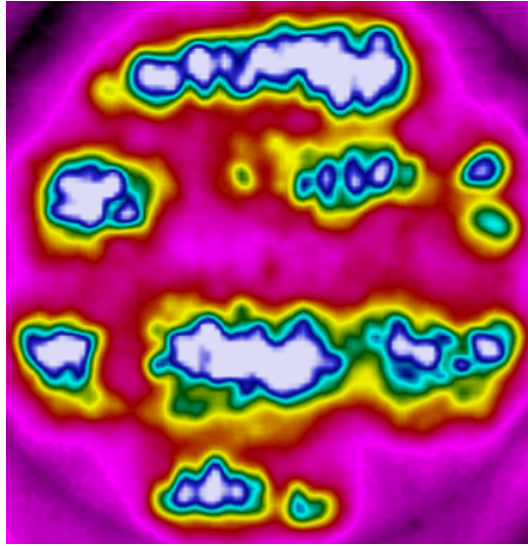


Figure 6.11: Image of temperature rise on an ultrasonic absorber obtained with an IR camera. The absorber was positioned in water bath at 45 mm from the center of the transducer and was air backed. The distance between the camera and the absorber was 30 cm. White indicates maximum normalized temperature and pink indicates room temperature. The striped shape confirms the absence of any heating on the ribs.

6.3.1.2 Focus Splitting

Another phenomenon which is also discussed by Bobkova *et al.* [99] and Khokhlova *et al.* [112], is focus splitting due to periodic spatial structure of the rib phantom. It was observed that by turning off selective elements to avoid hitting the ribs, focus is split into three as can be seen in fig. 6.9. When the rib phantom was positioned at 40 mm depth, the secondary lobes appeared on either side of the main lobe at a lateral distance of 4.5 mm. Secondary lobe level was 38% of the main lobe, whereas half power beam width of the main and side lobes was 1.2 mm and 1.1 mm, respectively. When the rib phantom was positioned at 100 mm, the secondary lobes appeared closer to the main lobe at a distance of 1.7 mm. The level of secondary lobe increased to 62% of the main lobe, whereas -6dB width of the main lobe and secondary lobes was 0.8 mm each. We can conclude that distance between the main beam and side lobes depend on the position of the ribs, the closer the ribs to the transducer, the larger will be the separation distance. However, the level of the secondary lobes is smaller, if the ribs are closer to the transducer.

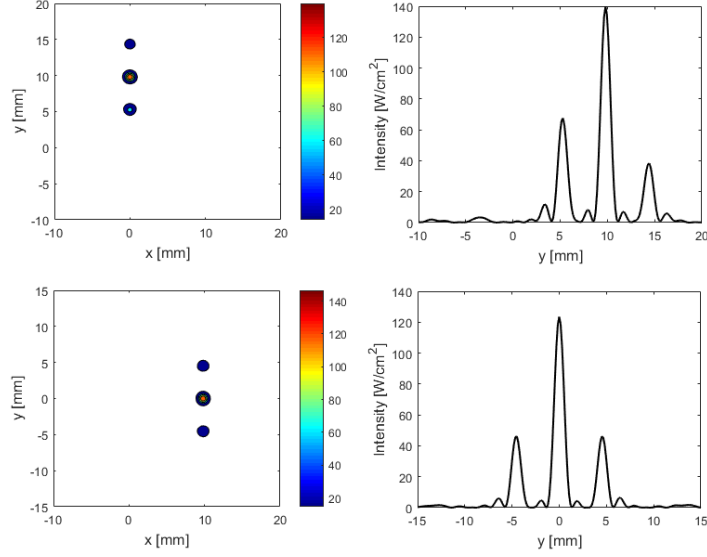


Figure 6.12: Focus splitting in the focal plane when beam is steered at $[0, 10, 130]$ mm (top row) and $[10, 0, 130]$ mm (bottom row) in the presence of rib phantom positioned at depth of 40 mm. Focus is split into three and five, respectively.

6.3.1.3 Focus steering in presence of ribs

One of the benefits of the phased array is its capability of steering the focus within the therapeutic field of interest. It has been shown in this work and previously by

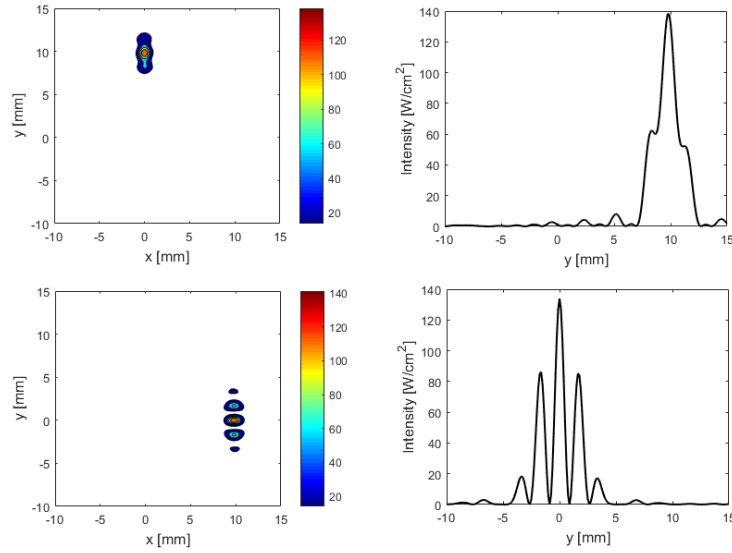


Figure 6.13: Effect on focus splitting in the focal plane when focus is steered at $[0, 10, 130]$ mm (top row) and $[10, 0, 130]$ mm (bottom row) in the presence of rib phantom positioned at depth of 100 mm. The secondary maxima gets unified with main beam increasing its width in the top row.

Hand *et. al* [4] that the random phased array is capable of steering single and set of multiple foci up to 15 mm either side of the geometric focus without any significant grating lobes. However, the effect of ribs on the steering of focus and its splitting was not studied. The effect on focal quality was thus determined for steering the focus in lateral direction when the ribs geometry is positioned at different depths. When positioned at a depth of 40 mm, the focus is steered 10 mm off the geometric focus along y-axis, a spacing of 4.5 mm between main and secondary lobes is observed but the level of secondary lobes is not uniform. The secondary maxima away from the geometric focus is only 26.5% of the main lobe whereas the one closer to the geometric focus is 51% of the main lobe (fig. 6.12). Width of main lobe is increased to 1.38 mm, whereas the width of the secondary lobes is 1.2 mm. When the focus was steered 10 mm along x-axis i.e. along the strip, the levels of secondary lobes kept uniform to 38% of the main lobe. The width of the main lobe and the secondary lobes are almost equal to 1.125 mm. We can thus conclude that steering the focus along the direction/length of the ribs has no significant effect on the levels and width of the secondary lobes. When the ribs phantom is positioned at a depth of 100 mm from the transducer and the focus is steered 10 mm along y-axis, it is observed that the secondary lobes get unified with the main lobe increasing its width to 2.63 mm at -6dB level (6.12). Conversely, when the focus was steered along x-axis, large sidelobes started to appear with amplitude as much as 64.5% of the main focus.

Simulations were also performed for the second scenario when the array axis passes through the spacing between the middle two strips for all the configurations discussed earlier. The results are not discussed here and presented in fig. 6.18 at the end of this section. Table 6.2 and 6.3 summarize the intensity distribution and focal quality for all the configurations when the array axis passes through the middle strip and through the spacing between the strips, respectively. These are elaborated and further discussed in the following sections.

Table 6.2: Intensity distribution and focal quality for different ribs geometry configuration, when the array axis passes through the middle of one of the ribs. Strips width is the width of the strips in terms of the intercostal spacing d . The results shown are for a single focus targeted at the geometric center of the array

Depth [mm]	Strips width	I_{peak} [W/cm ²]	No. of foci	Distance to secondary foci [mm]	Secondary foci level [%]	No. of active elements
40	1/3d	264.15	3	6.5	9.5	174
	1/2d	226.20	3	5	20	149
	d	195.83	3	4.5	38	129
	2d	92.6	5	5 & 10	67 & 18	61
	3d	60.72	5	6.6 & 12.9	60 & 14	40
	–	–	–	–	–	–
70	1/3d	271.75	3	4.3	9.5	174
	1/2d	247.45	3	3.5	20	149
	d	179.13	3	2.7	38	129
	2d	113.86	7	3.4 & 5.7 & 9	67 & 18	61
	3d	72.87	5	4.2 & 8.6	74 & 30	48
	–	–	–	–	–	–
100	1/3d	308.18	3	4.1	15.8	147
	1/2d	274.78	3	1.8	38.5	181
	d	192.80	5	1.7 & 3.3	64 & 13.2	127
	2d	113.86	7	1.7 & 3.3 & 5	97.3 & 60 & 25	75
	3d	78.94	9	2.1 & 4.1 & 6.1 & 8.2	89 & 65 & 36.5 & 14.8	52
	–	–	–	–	–	–

Table 6.3: Intensity distribution and focal quality for different ribs geometry configuration, when the array axis passes through the intercostal space. Strips width is the width of the strips in terms of the intercostal spacing d . The results shown are for a single focus targeted at the geometric focus of the array

Depth [mm]	Strips width –	I_{peak} [W/cm ²]	No. of foci –	Distance to secondary foci [mm]	Secondary foci level [%]	No. of active elements
40	1/3d	259.6	3	6.3	12.8	171
	1/2d	236.82	3	5.3	20.5	156
	d	176.10	3	4.6	33.7	116
	2d	110.82	3	5.1	50	74
	3d	65.28	5	6.4 & 12.7	60 & 13	43
70	1/3d	253.52	3	4.3	10.5	167
	1/2d	236.82	3	3.5	10	137
	d	186.73	3	3.1	43	123
	2d	112.34	5	3.4 & 6.8	70.5 & 22.2	74
	3d	51	7	4.1 & 8.3 & 12.4	78 & 37 & 10.7	33
100	1/3d	226.2	3	4.1	15.8	147
	1/2d	208	3	3.5	10	137
	d	171.54	3	4	8	113
	2d	88.05	1	0	0	58
	3d	44	1	0	0	29

6.3.1.4 Influence of width of the strips

The width of the strips has two major effects on the focal quality. First, the wider strips would shadow more elements and less number of elements would be available for the therapeutic operation thus the peak intensity at the focus would be lower for a given input acoustic power as can be seen in fig. 5.14. Secondly, the number and level of secondary foci increases with the increase in width of the strips. By comparing both tables 5.2 & 5.3, it is seen that intensity at the focus and level of secondary foci changes when the array axis passes through the rib and the intercostal space. As shown in figs. 5.15 & 5.16, the amplitude of secondary foci is smaller for narrower strips and is increased for wider strips. For strips with width w twice as the spacing d , the level of the secondary maxima is more than 60%, and the secondary foci appear as far as 10 mm from the intended main focus, which may not be acceptable in practical applications.

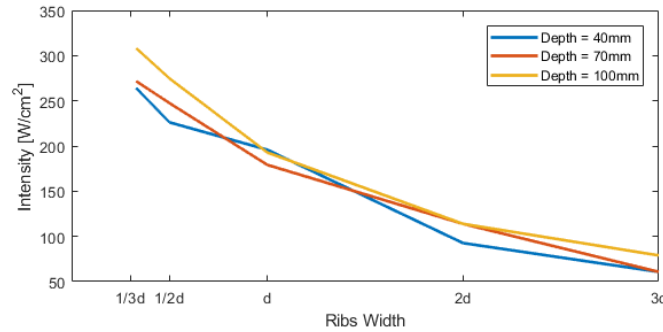


Figure 6.14: Effect of the width of the strips in the rib phantom on intensity distribution in the focal plane when the phantom is positioned at depth of 40 mm, 70 mm and 100 mm. Peak intensity in the focus is reduced when the width of the ribs is increased.

6.3.1.5 Effect of depth of the rib plane

The depth of the ribs plane influences the strength of intensity in the focus as it determines the number or spatial period of the ribs that would come across the beam aperture. From fig. 6.14, it is observed that the intensity at the focus is highest

when the rib plane is at a depth of 100 mm from the array due to the fact that fewer ribs come in the way of beam path. Conversely, for the ribs plane closer to the transducer, more ribs come across the beam path resulting in a decrease in the intensity at the focus.

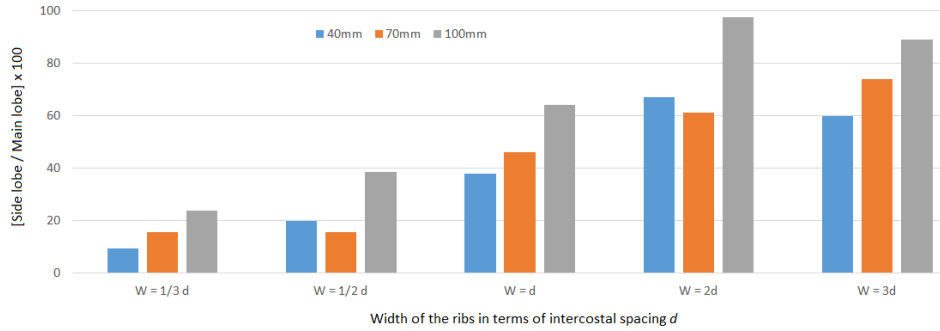


Figure 6.15: Effect of the width of the strips on side lobe level in the focal plane when the phantom is positioned at depth of 40 mm, 70 mm and 100 mm and the array axis passes through middle of a rib. x -axis is width of the strips in terms of edge-edge spacing ' d ' and y -axis is the side lobe to main lobe ratio. Side lobes are increased in magnitude with an increase in the width of the strips and when the ribs are closer to the focus point.

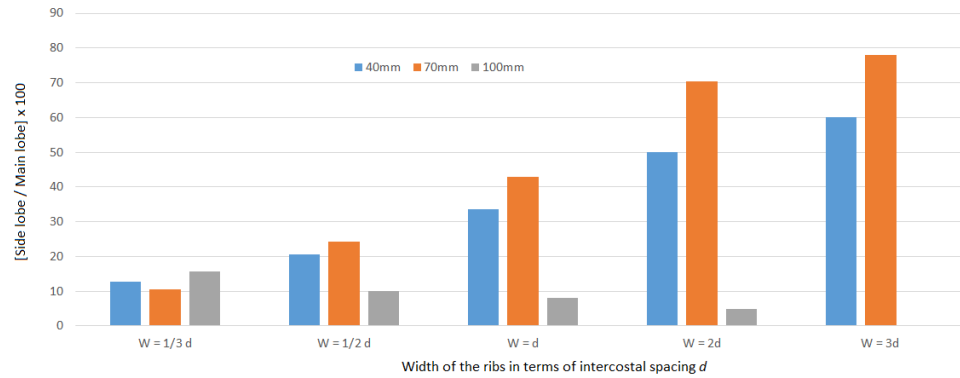


Figure 6.16: Effect of the width of the strips on side lobe level in the focal plane when the phantom is positioned at depth of 40 mm, 70 mm and 100 mm and the array axis passes through intercostal spacing. x -axis is width of the strips in terms of edge-edge spacing ' d ' and y -axis is the side lobe to main lobe ratio. Side lobes are increased in magnitude with an increase in the width of the strips and when the ribs are positioned at 70 mm from the array center.

6.3.1.6 Effect of spatial position of rib geometry

The alignment of the ribs also has an effect on the focus quality. Fewer secondary maxima with lower amplitude appear when the beam axis passes through the intercostal space as evident from tables 6.2 & 6.3. As can be seen in fig. 6.17, the level of secondary foci is reduced significantly when the beam axis crosses at the

middle of intercostal space, however, this comes at the expense of an increase in the diameter/width of main focus and a slight decrease in the peak intensity at the focus point. Focal quality of the three different geometries at a depth of 100 mm is compared in fig. 6.17. It is seen that the higher the width of the strips, the greater the number of secondary foci with higher amplitude will be. The secondary foci can be eliminated if the beam axis passes through the intercostal space and avoid hitting the ribs. However, when the array axis passes through the intercostal space, the main lobe gets wider. The main lobe also gets wider with wider strips (fig. 6.17).

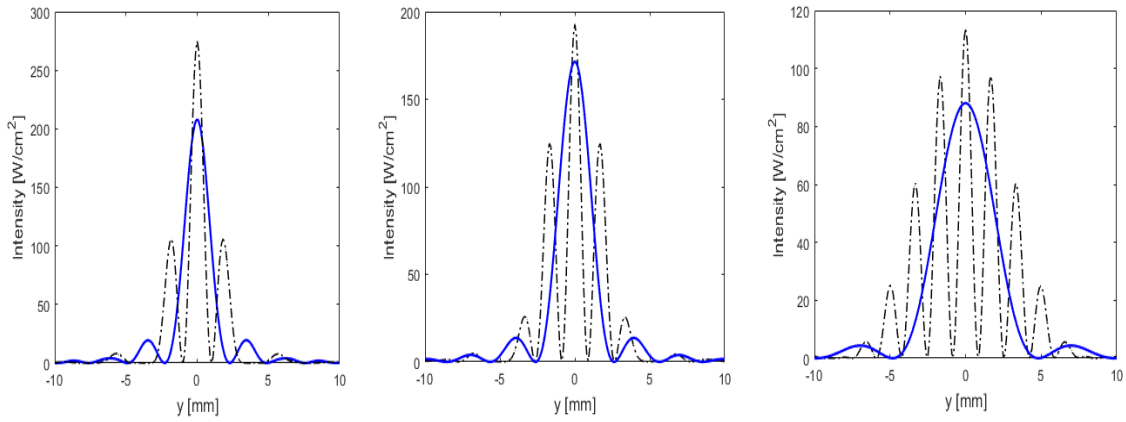


Figure 6.17: Intensity distribution in the focal plane when the array axis crosses: center of a rib (thin dashed line) and center of intercostal space (thick solid line), when $w = 1/2d$ (left), $w = d$ (middle), $w = 2d$ (right). The phantoms are positioned at 100 mm from the center of array. Peak intensity at the focus is maximum for thin ribs and reduces for wider ribs. Intensity in the side lobes increase when the beam axis passes through one of the ribs. Side lobes are reduced when the beam passes through the spacing but results in wider main beam.

Intensity distributions of all the geometries discussed above are shown in fig. 6.18, which shows the influence of the variation of different parameters of the ribs geometry on the quality of the focus. As expected, increased side lobe to main lobe ratio is observed for wider strips. When the beam passes through one of the strips and the rib plane is closer to the focus point, higher secondary maxima are observed than when the rib plane is farther from the focus plane. Conversely, when the beam axis passes through the spacing, lower secondary lobes appear when the plane of the ribs is closer to the focal plane.

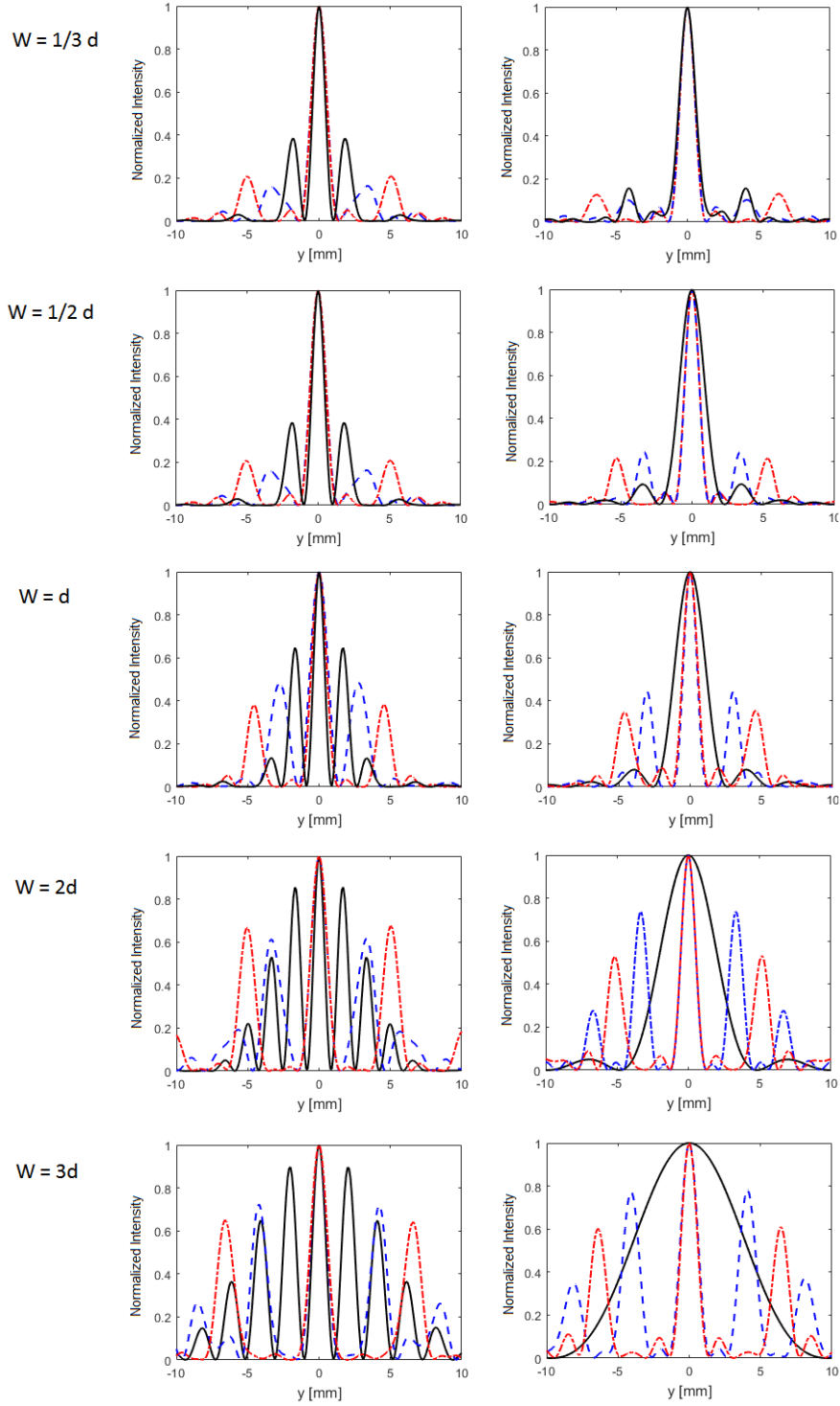


Figure 6.18: Intensity distribution in the focal plane for different rib phantoms when the phantoms are positioned at a depth of 40 mm (red dotted line), 70 mm (blue dashed line) and 100 mm (black solid line), and when the beam axis passes through one of the rib (left column) and intercostal space (right column). Side lobe to main lobe ratio increases for wider ribs. Distance between main beam and secondary lobes decreases when the transducer is placed away from the ribs. Intensity in the secondary lobes is significantly reduced when the beam passes through the intercostal space and when the ribs are positioned at 100 mm but leads to a wider main beam.

6.3.2 Anatomically Correct Ribs

To better understand the effect of ribs on HIFU intensity distribution and delivery of energy at focal point, simulations were performed using anatomically realistic 3D ribs. A rib topology that was obtained in STL (stereolithography) format from an anatomically correct rib phantom was downloaded from an online repository called *embodi* [143]. Ribs 7 to 12 of the left side of the rib cage (fig. 6.19) were used in simulation after truncating them from the spine. A MATLAB function using a ray intersection method similar to the one described by Patil *et al.* [144] was used to voxelize the phantom [145].

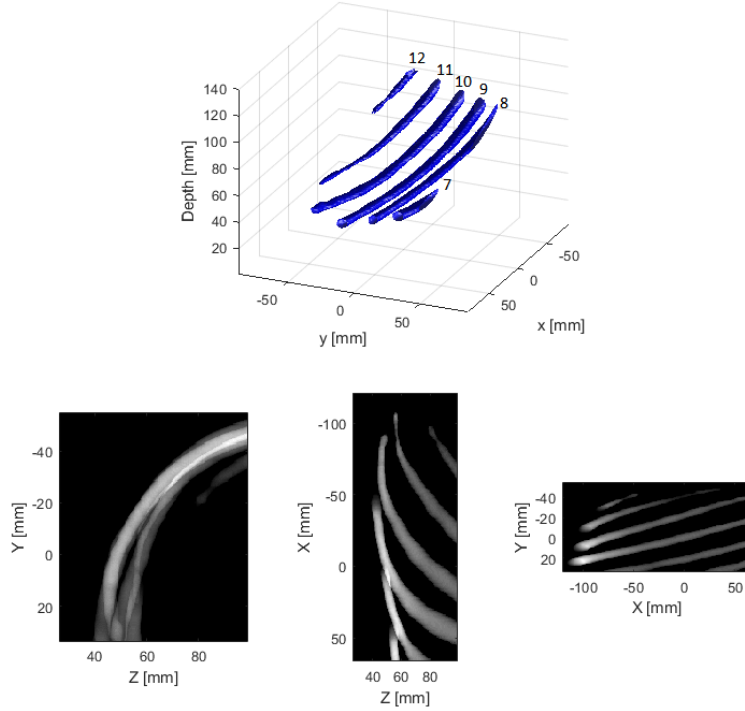


Figure 6.19: Geometry of the ribcage. Ribs 7 - 12 of left side of the ribcage of an adult human are truncated from the spine and shown in 3D and 2D slices

The spatial position of the ribcage was changed to assess the focus quality. The ribs were initially positioned so that the rib plane was 40 mm away from the array and the array axis crossed the middle of rib number 9. Only one focus was observed in the focal plane with the secondary foci having intensity less than 10% of that in the main focus, which is insignificant. The ribs were then positioned at 70 mm

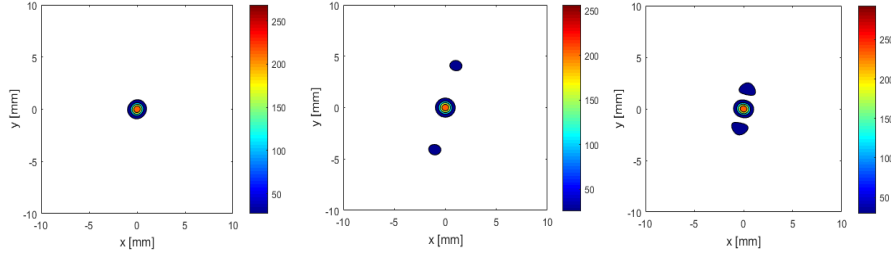


Figure 6.20: Intensity distribution for anatomically correct ribs left side, ribs 8 - 12, when the array axis crosses rib 9 and rib 9 is at 40 mm (left), 70 mm (middle) and 100 mm (right) from center of the array

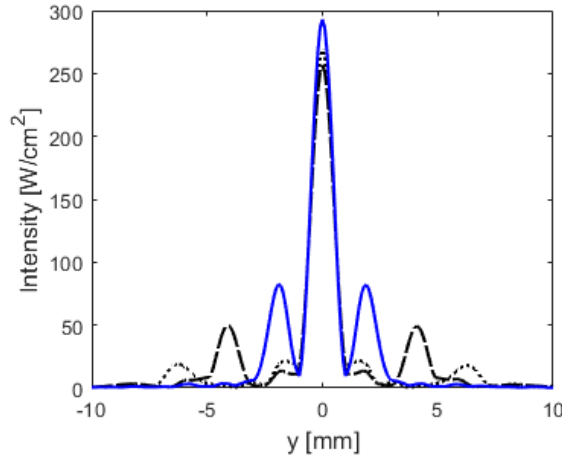


Figure 6.21: Intensity distribution when the ribs are at 40 mm depth (dotted line), 70 mm (dashed line) and 100 mm (solid line) and the array axis passes center of a rib

depth such that the target was 60 mm deep inside the ribs, it was observed that the number of active elements was reduced and so was the intensity in the focus, whereas, the level of secondary foci increased to $\sim 20\%$. When the ribcage was moved to a distance of 100 mm such that the target was 30 mm inside the ribs, the intensity at the focus point increased but the level of side lobes also increased to 28%. The intensity distribution in the main focus and secondary maxima can be seen in fig. 6.20 & fig. 6.21.

Table 6.4: Intensity distribution and focal quality for anatomical ribs, when the array axis passes through the ribs and the intercostal space. The results shown are for a single focus targeted at the geometric focus of the array

Position Axis through:	Depth [mm]	I_{peak} [W/cm ²]	No. of foci —	Dist. to sec. foci [mm]	Sec. foci level [%]	No. of active elements
Ribs	40	268.70	3	6.3	7	177
	70	256.56	3	4.1	19.45	169
	100	293	3	1.9	28.18	193
	115	189.76	5	1.6 & 3.2	64 & 13.1	125
Intercostal space	40	282.37	3	5.7	8.8	186
	70	255.04	3	4	10.6	168
	100	211.02	5	2.5 & 4.1	16 & 3.5	139
	115	273.26	-	-	-	180

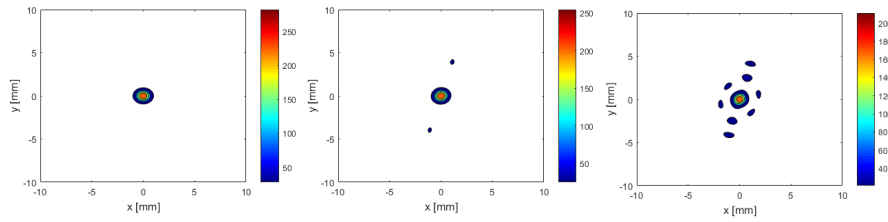


Figure 6.22: Intensity distribution for anatomically correct ribs left side, ribs 7 - 12, when the array axis crosses middle of the spacing between ribs 9 and 10 and the rib cage is at 40 mm (left), 70 mm (middle) and 100 mm (right) from center of the array

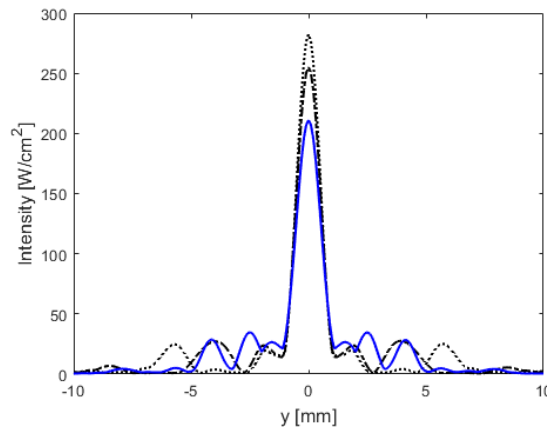


Figure 6.23: Intensity distribution when the ribs are at 40 mm depth (dotted line), 70 mm(dashed line) and 100 mm(solid line) and the array axis crosses the intercostal space

The ribcage was re-positioned and the array axis now crossed the intercostal spacing between ribs 9 and 10. The ribcage was positioned again at 40 mm, 70 mm and 100 mm depth and the intensity distribution was calculated. When at 40 mm, not much difference in the intensities and level of secondary lobes was observed from the previous case. At 70 mm, the peak intensity is same for both geometries, however, the level of secondary maxima drops to half (fig. 6.22 & 6.23). At 100 mm, the intensity at focal point drops but the level of secondary lobes also drop significantly, however, the focus is split into many foci that would surround the main focus in a circle of around 5 mm (fig. 6.22).

Further spatial positions were considered for the ribs geometry. Higher levels of secondary foci are observed when the array axis crosses the middle of a rib. The results for different heights of the ribs plane are summarized in table 6.4. The effect on sidelobe level is more pronounced at higher depths, e.g. at 100 mm, the level of secondary foci is 28% of the main focus, when the array axis crosses the center of

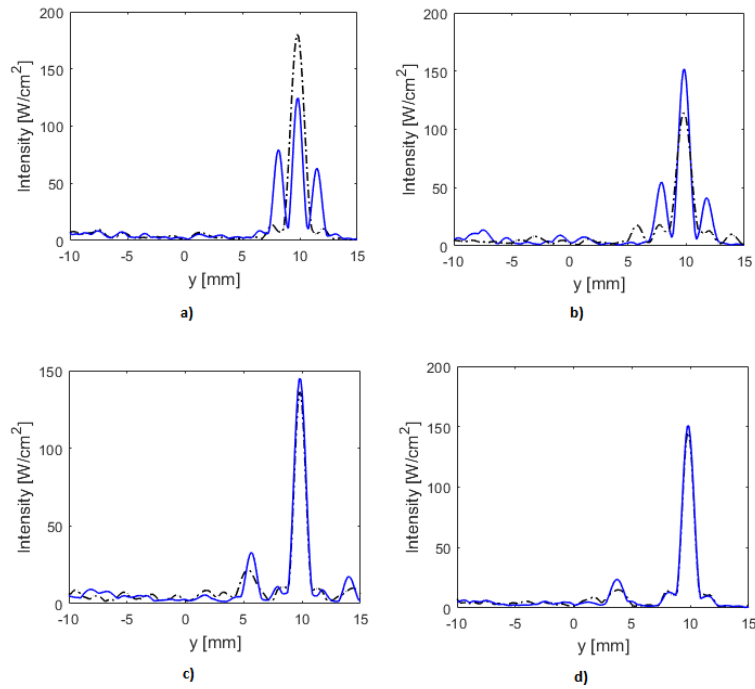


Figure 6.24: Intensity distribution for a single focus targeted at $(x,y,z) = (10,10,130)$ mm, when the ribs are located at a) 115 mm, b) 100 mm, c) 70 mm, d) 40 mm and the array axis crosses middle of the rib (dashed line), and middle of intercostal space (solid line)

a rib and is only 16% when it crosses the middle of intercostal space. At 115 mm, the sidelobe level is increased to 64% in the first case and no secondary maxima was observed in the second case. The intensity in the main focus was 70% more than the first case. Thus, for depths around 100 mm, it is better to align the array axis at the intercostal space to avoid formation of secondary maxima and maximize the intensity in the main focus point.

For a steered focus at $(x, y, z) = (10, 10, 130)$ mm, the effect of ribs at different heights was determined. It is seen that when the focus point is close to the ribs and above the intercostal space, the focus is not distorted and the intensity in the focus is high as compared to the focus above one of the ribs where high sidelobes would

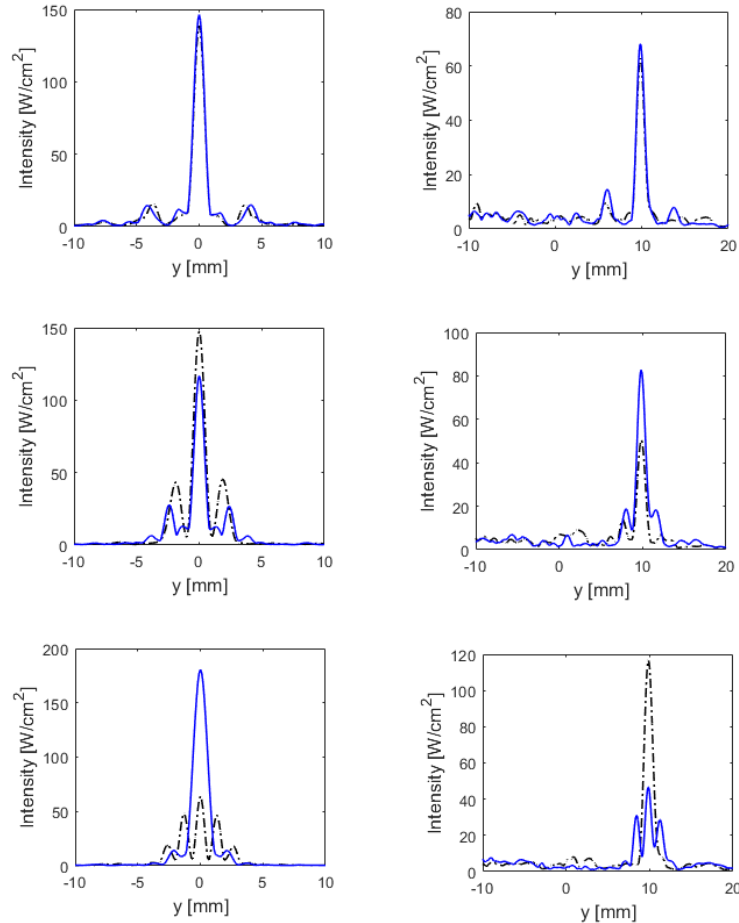


Figure 6.25: 1D Intensity distribution for a single focus targeted at $(x,y,z) = (0,0,100)$ mm (left) and $(x,y,z) = (10,10,100)$ mm (right), when the ribs are located at 40 mm (left), 70 mm (middle), 85 mm (right) and the array axis crosses middle of the rib (dashed line), and middle of intercostal space (solid line)

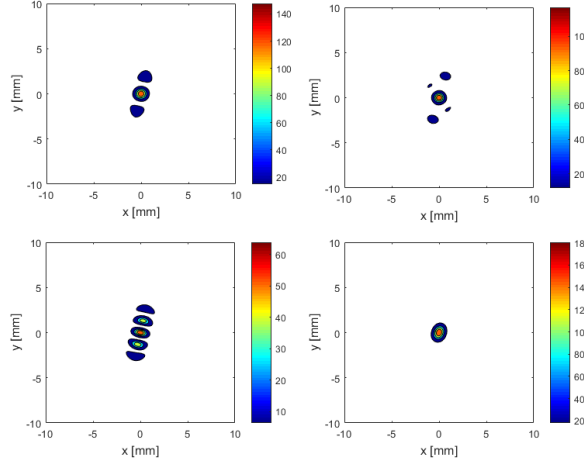


Figure 6.26: 2D Intensity distribution for a single focus targeted at $(x,y,z) = (0,0,100)$ mm, when the ribs are located at 70 mm (top), 85 mm (bottom) and the array axis crosses middle of the rib (left), and middle of intercostal space (right)

appear. However, when the distance between the focus point and the ribs is large, no significant difference in the focal quality is observed in both cases (fig. 6.24).

When the focus is steered axially at $(x,y,z) = (0,0,100)$ mm, then the ribs at 40 mm and 70 mm yield almost similar effect on the intensity level and secondary foci whether the array axis passes through the rib or the intercostal space, however, when the ribs are at 85 mm, the focus is deteriorated if the array axis passes through the rib. The focus is split into five with 75% intensity in the secondary maxima and a very low intensity of $63.9W/cm^2$ in the main beam. When the array axis is moved to the space between the ribs, the intensity in the main focus increases three folds and secondary maxima disappears (fig. 6.26 & 6.25). This is also depicted in fig. 6.25 (right column) for a focus steered in both lateral and axial directions at $(x,y,z) = (10,10,100)$ mm. The intensity in the main focus decreases when the focus is targeted behind one of the ribs. This suggests that for a target less than 3 cm close to the rib cage, the array and/or beam axis should pass through the intercostal space to avoid focus splitting and get maximum energy in the main focus.

6.3.2.1 Effect of Axial steering on Intensity distribution in focal plane

The transcostal performance of the phased array was analyzed by steering the focus in the therapeutic field from a depth of 110 mm to 150 mm along the array axis. Simulations of the acoustic wave propagation were performed by varying the focal length to assess the best geometric configuration of the ribcage relative to the phased array in terms of peak intensity and energy in the secondary foci. The ribcage was positioned at three different heights from the center of the phased array i.e. 40 mm, 70 mm and 100 mm and was aligned such that the array axis passed through the center of the rib, middle of intercostal spacing, edge of a rib and edge of the intercostal spacing. The focus point was steered from 110 mm to 150 mm with a step of 10 mm. No transverse steering was performed.

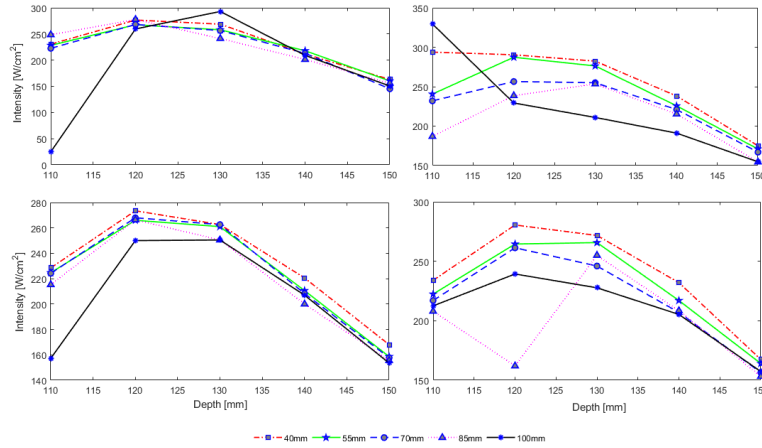


Figure 6.27: Change in the peak focal intensity with varying focal depths for ribcage positioned at 40 mm, 55 mm, 70 mm, 85 mm, 100 mm and when the array axis crosses center of the rib (top left), center of intercostal spacing (top right), edge of the rib (bottom left), edge of the spacing (bottom right).

The effect of changing the focal depth as well as the height of the ribcage is shown in fig. 6.27. It is observed that intensity tends to be maximum at and near the geometric focus irrespective of the position of the ribcage. The ribcage was moved both in axial and transverse directions to see the effect on peak intensity at the focus. A steady response was observed when the ribcage was closer to the transducer i.e. peak intensity slightly increases when the focus point is moved towards the geometric focus and decrease by moving it further away in axial direction. However, when the

ribcage is positioned at a depth of 100 mm i.e. closer to the geometric focus then there was a high dependency on the transverse position of the ribcage. If the array axis passes through the middle of a rib and the focus point is only 10 mm behind, minimum peak focal intensity can be achieved, whereas, maximum focal intensity is observed for the same focal depth when the array axis passes through the middle of the intercostal space. High secondary foci will appear if the focus point is close to the ribcage and the array axis crosses a rib.

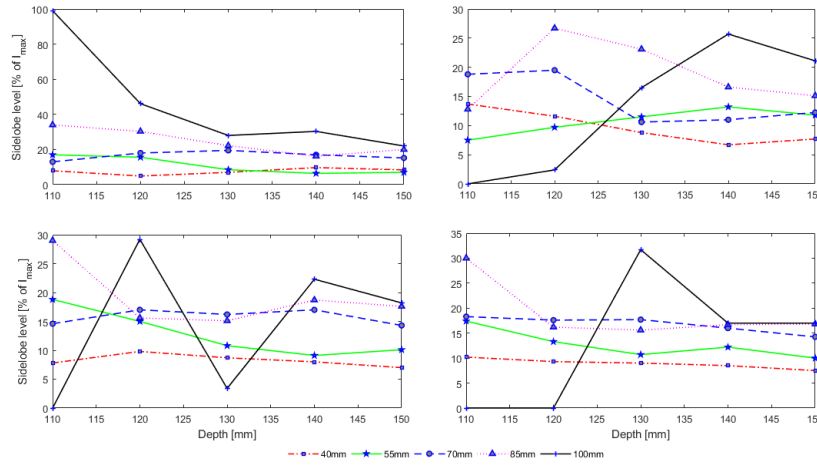


Figure 6.28: Change in the magnitude of secondary foci with varying focal depths for ribcage positioned at 40 mm, 55 mm, 70 mm, 85 mm, 100 mm and when the array axis crosses center of the rib (top left), center of intercostal spacing (top right), edge of the rib (bottom left), edge of the spacing (bottom right)

As can be seen in fig. 6.28, the amplitude of the peak intensity in secondary focus is equal to that in the main focus at a focal depth of 110 mm when the ribcage is positioned at 100 mm depth and the array axis passes through the rib. The intensity in secondary foci decreases by increasing the distance between the focus point and the ribcage. Almost opposite phenomena is seen when the array axis passes through the middle of intercostal spacing i.e. the closer the ribcage to the focus point, the smaller is the amplitude of the secondary focus. The spacing between main focus and the secondary foci varies linearly with the position of the ribcage. The larger the distance between the focal point and the ribcage, the more will be the spacing between the main focus and secondary foci.

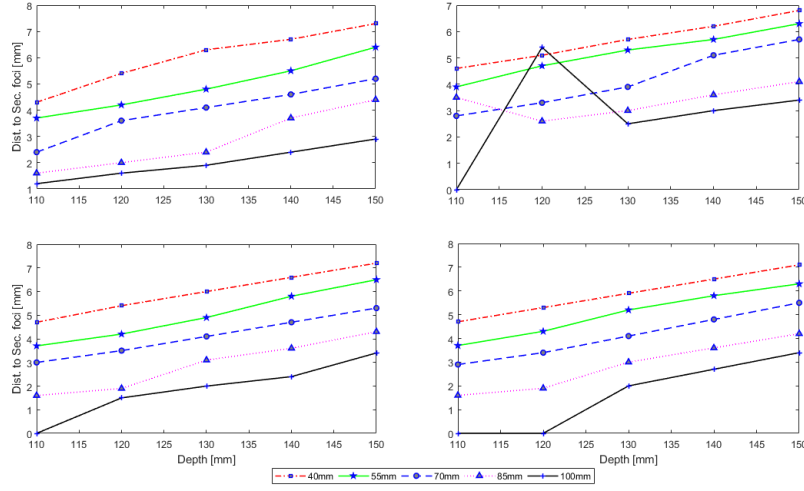


Figure 6.29: Distance to the secondary foci from the main focus with varying focal depths for ribcage positioned at 40 mm, 55 mm, 70 mm, 85 mm, 100 mm and when the array axis crosses center of the rib (top left), center of intercostal spacing (top right), edge of the rib (bottom left), edge of the spacing (bottom right)

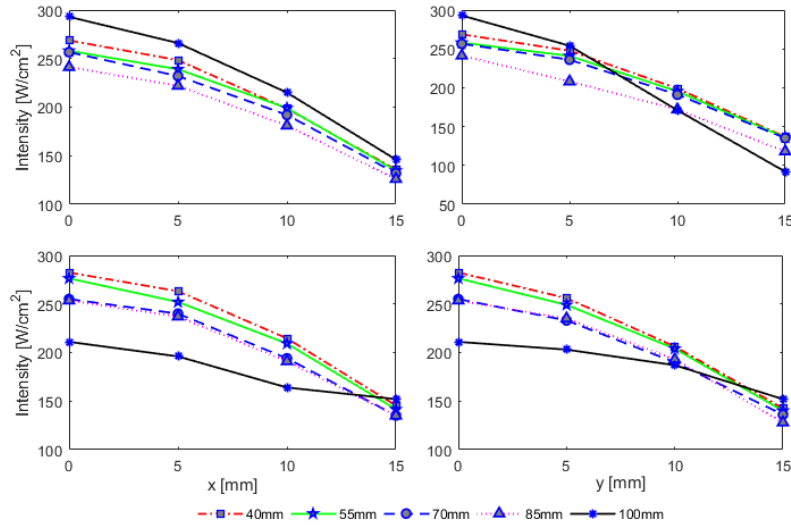


Figure 6.30: Change in the peak focal intensity with transverse steering for ribcage positioned at 40 mm, 55 mm, 70 mm, 85 mm, 100 mm and when the array axis crosses center of the rib (top row), intercostal space (bottom row), steered in x -direction (left column), y -direction (right column)

6.3.2.2 Effect of Transverse steering on Intensity distribution in focal plane

The focal quality was assessed by steering the focus point in both transverse directions in the focal plane from geometric focus to 15 mm with a step size of 5 mm.

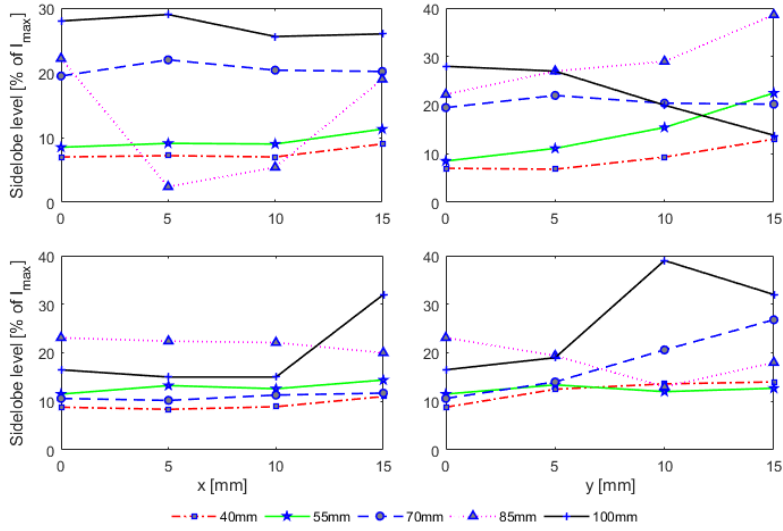


Figure 6.31: Change in the magnitude of secondary foci with transverse steering for ribcage positioned at 40 mm, 55 mm, 70 mm, 85 mm, 100 mm and when the array axis crosses center of the rib (top row), intercostal space (bottom row), steered in x -direction (left column), y -direction (right column)

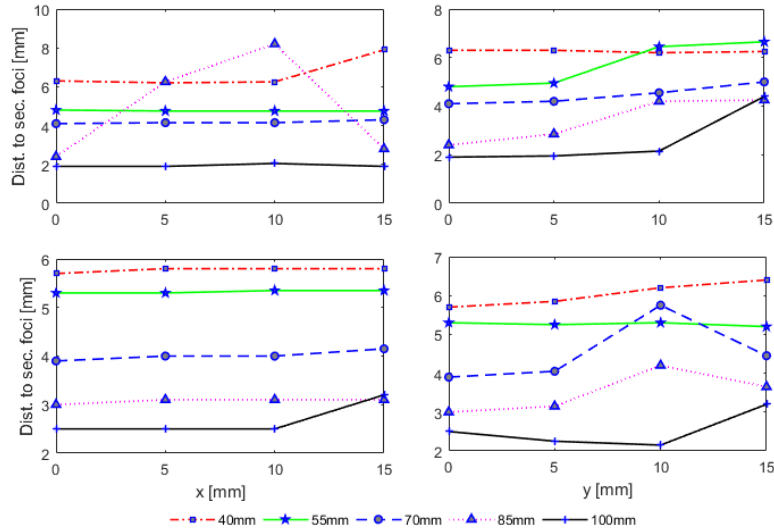


Figure 6.32: Effect on the distance to secondary foci from main focus with transverse steering for ribcage positioned at 40 mm, 55 mm, 70 mm, 85 mm, 100 mm and when the array axis crosses center of the rib (top row), intercostal space (bottom row), steered in x -direction (left column), y -direction (right column)

The ribcage was positioned at five different heights at 40mm, 55mm, 70 mm, 85 mm and 100 mm. The array axis passed either through the middle of the rib or the intercostal space. No axial steering was performed.

As expected, the intensity is highest along the axis and drops down away from the

axis. There is a variation in the peak intensity when the height of the rib cage is changed. When the ribcage is positioned at a depth of 100 mm, the intensity at focus point would be highest if the array axis passes through the ribs and lowest if it passes through intercostal space. Fig. 6.31 suggests that steering in either lateral or elevation directions has no adverse effect on the intensity in the secondary foci, however, low levels of intensity in secondary foci were observed when the ribcage is positioned at 40 mm. The intensity in secondary foci increases by increasing the distance between the transducer and the ribcage. The spacing between the main focus and the secondary foci does not change much while steering up to 10 mm in x- or y-direction. There is a significant variation in the spacing when the ribcage is positioned at different heights. Secondary foci are closest to the main focus when the ribcage is at 100 mm depth and move farther when the transducer gets closer to the ribcage (fig. 6.32).

Fig. 6.33 shows the distribution of active elements that are turned on when the array axis passes through the rib and through the intercostal space.

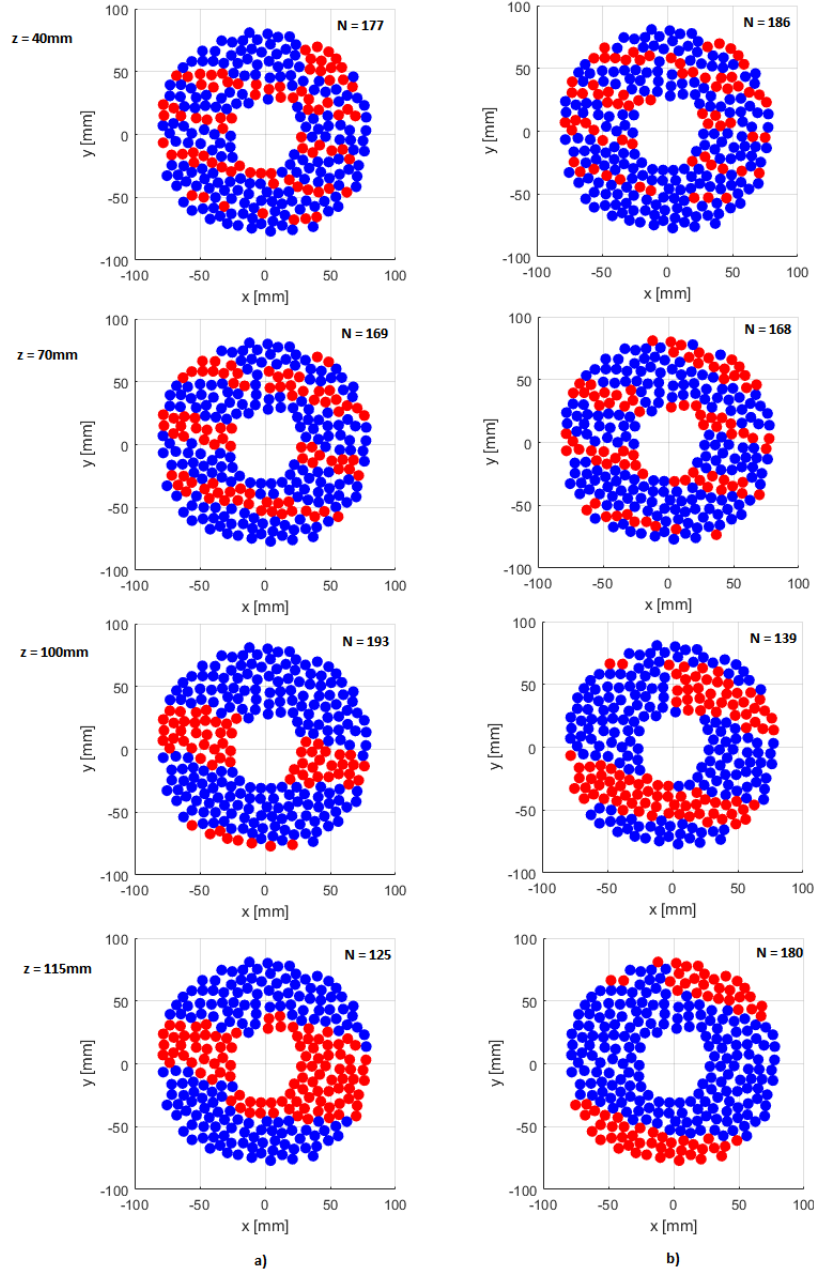


Figure 6.33: Active elements when the ribs are positioned at different heights [40,70,100,115]mm. Blue indicates elements that are turned ON for HIFU and Red indicates elements which are blocked by Ribs and turned OFF, N is the number of active elements a) When the array axis crosses the middle of rib 10. b) when the array axis crosses the middle of the space between ribs 10 and 11

6.4 Summary

In this chapter, acoustic modeling through the ribcage was discussed in detail. Both idealized parallel ribs phantom and anatomically correct human ribs were used to determine the set of active elements sparing the ribs, assess the focal quality in focal

plane and determine the intensity level in the ribs plane. The following points can be summarized from the observations:

- A single focus can be steered 1.5 cm off axis in lateral and elevation and 5 cm in axial direction with out any grating lobes. The peak intensity reduces to half if the focus is steered 15 mm off the axis in the focal plane. The intensity is mostly focused at the target and peak intensity in the HIFU beam at a distance of 10 mm along the axis is less than 5%.
- Patterns of multiple foci can be generated and steered (fig. 6.7). Set of five foci can be steered up to 10 mm off-axis with out any significant grating lobes. Peak intensity in the set of five foci decreases up to 5 times than for a single focus due to the fact that energy is distributed among multiple foci. The smaller the spacing between the foci, the higher would be the amplitude of the peak intensity.
- Ribs in the HIFU beam path not only get heated leading to skin burns but can also distort the focus quality significantly. The effect of idealized parallel strips on the focus quality was studied. It was found that intensity in the main focus is reduced due to the blockage of energy by the ribs. The intensity in the ribs plane also depends on its distance from the phased array. The closer the ribs plane to the geometric focus is, the higher the peak intensity in the ribs plane will be.
- Focus splitting is a significant effect caused by ribs. When the ribs are close to the phased array, the secondary lobes are formed away from the main focus with smaller amplitude. When the ribs are away from the transducer, the secondary lobes appear close to the main focus and have higher amplitude. Steering the focus in presence of idealized ribs effect the formation of secondary lobes. When the focus is steered against the direction of the ribs, the levels of secondary maxima are not uniform, however, when the focus is steered along

the direction of the stripes, the focus is split into three with uniform intensity amplitude in the secondary lobes.

- The width of the ribs has a pronounced effect on the intensity distribution. The wider the strips, the less number of elements are available for treatment leading to a lower intensity at the desired focus. Furthermore, the level of secondary foci is higher for wider strips. If the ribs plane is away from the transducer, fewer ribs would encounter the beam path resulting an increase in the focal intensity as compared to the ribs plane closer to the transducer where the number of spatial period of the ribs across the beam aperture would increase and will result in lower peak focal intensity.
- When the array axis passes through the intercostal space, fewer secondary lobes appear and intensity in the secondary lobes is smaller than when the array axis passes through the middle of one of the ribs.
- In case of the realistic human ribs, the distance of the ribs from the transducer has an important effect on the focus quality. Intensity in the secondary maxima would be higher for increased distance between the transducer and the ribcage. i.e. the closer the ribcage to the transducer is, the smaller will be the intensity in the secondary foci.
- For the targets closer to the ribcage, position of the transducer with respect to the ribcage is significantly important. If the HIFU beam is targeted at a depth of 3 cm or less inside the human body, effort should be made to align the beam axis such that it crosses the intercostal spacing, which would result in high intensity at the focus with negligible secondary maxima.

To summarize, a detailed and thorough study of acoustic field in the presence of idealized and realistic human ribs in the free-field was undertaken. The results described here not only validated the results described earlier by Bobkova *et al.* [99] and Khokhlova *et al.* [112] but also extended it to anatomically correct human ribs

and determined the effect of human ribcage on focus splitting, intensity distribution, secondary lobe level and overall quality of acoustic beam both in the plane of the ribs and focal plane.

Chapter 7

Improved multi-element Random Phased Array for Image guidance and Therapy

Though random distribution of the elements on the surface of a phased array result in avoiding formation of secondary hotspots, the unused surface area of the transducer results in lower intensity, therefore more power is required to obtain the required acoustic intensity to ablate the tumour. This leads to an increased energy transfer through the underlying tissue causing collateral damage. In this chapter, simulations are performed to improve the element distribution of the existing 256-elements random phased array. More elements are randomly distributed to fill the unused surface area of the array, which not only increased intensity at the desired focus but also extended the steering range without any increase in the grating lobes. It also extends the capability of the modeling suite to transducer design. Synthetic aperture imaging technique was used to obtain simulated images of a wire phantom, thus allowing the transducer to operate both in therapeutic as well as imaging mode. Simulation results of the proposed design were compared to the existing transducer

discussed in the previous chapters and improvements in terms of increased acoustic energy, reduced side lobes and image resolution were observed.

7.1 The Transducer Array

The proposed transducer array consists of 277 elements which are randomly distributed on a spherical shell with diameter of 170 mm and radius of curvature is 130 mm. The simulated array has a low f_{number} of 0.76 to maximize the focusing gain at the desired focus point. The elements are circular in shape and 7 mm in diameter. The spacing between elements varies from 7.9 mm to a maximum of 10 mm. The circular aperture intended for imaging transducer is filled with randomly positioned elements. The array is operated at 1 MHz frequency. These design parameters are in line with the theory described by Gavrilov *et al.* [65]. Fig. 7.1 shows the element distribution of the random phased array.

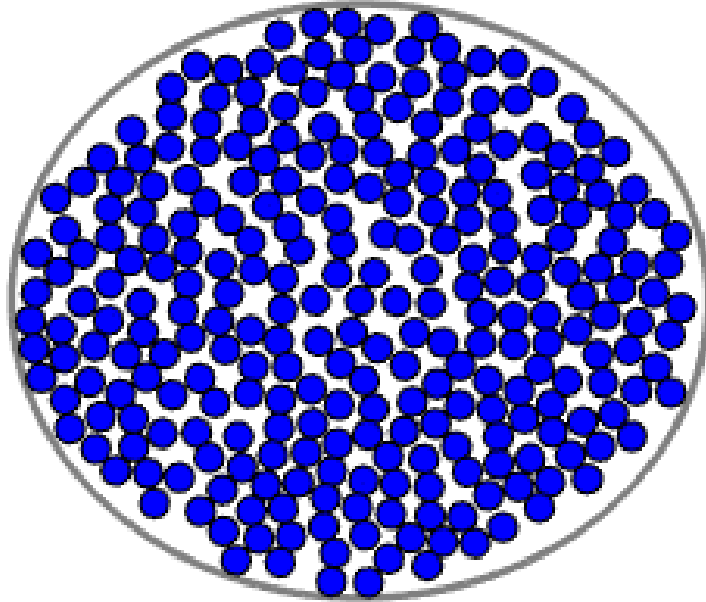


Figure 7.1: Front view of the proposed random phased array, 277 circular elements each with diameter of 7 mm are randomly distributed across the spherical surface of the array

7.2 Acoustic Field Distribution

Intensity field distribution was calculated using the analytical method discussed in section 6.1. A nominal acoustic power of 15 W was used to evaluate the field distribution in simulation which produced an average intensity of 0.14 W/cm^2 at each of the 277 elements. A single focus was generated at the geometric center of the array and the peak intensity predicted in the focal plane was 421 W/cm^2 with a corresponding maximum pressure amplitude of 3.55 MPa. Lateral and axial intensity profiles for the single focus are shown in the fig 7.2.

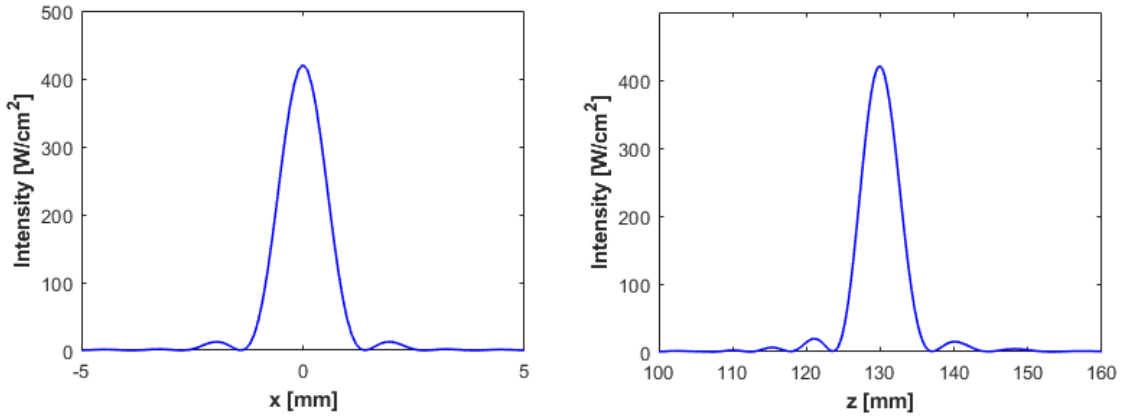


Figure 7.2: Lateral and axial intensity profiles for a single focus targeted at $(x,y,z) = (0,0,130)\text{mm}$

Spatial pressure distributions were also calculated in a 3D field with dimensions of $400 \times 400 \times 400$ with a grid spacing of 0.25 mm. Intensity distribution in the lateral yz plane and in the focal xy plane perpendicular to the axis passing through the array center are shown in fig. 7.3. Intensity distribution is shown for two cases: for a single focus generated at the geometric focus and when the focus is steered 18 mm away from the geometric focus. The peak intensity (I_{peak}) of the beam for un-steered focus was 421 W/cm^2 . Peak intensity in the main beam is reduced when the focus is steered 18 mm away from the focus and secondary hotspots start to appear. I_{peak} in the steered beam is 159 W/cm^2 , whereas the maximum intensity amplitude in the grating lobes is 16 W/cm^2 of the amplitude in the main beam, which is 10% of the peak intensity in the main beam and is thus in the safe region.

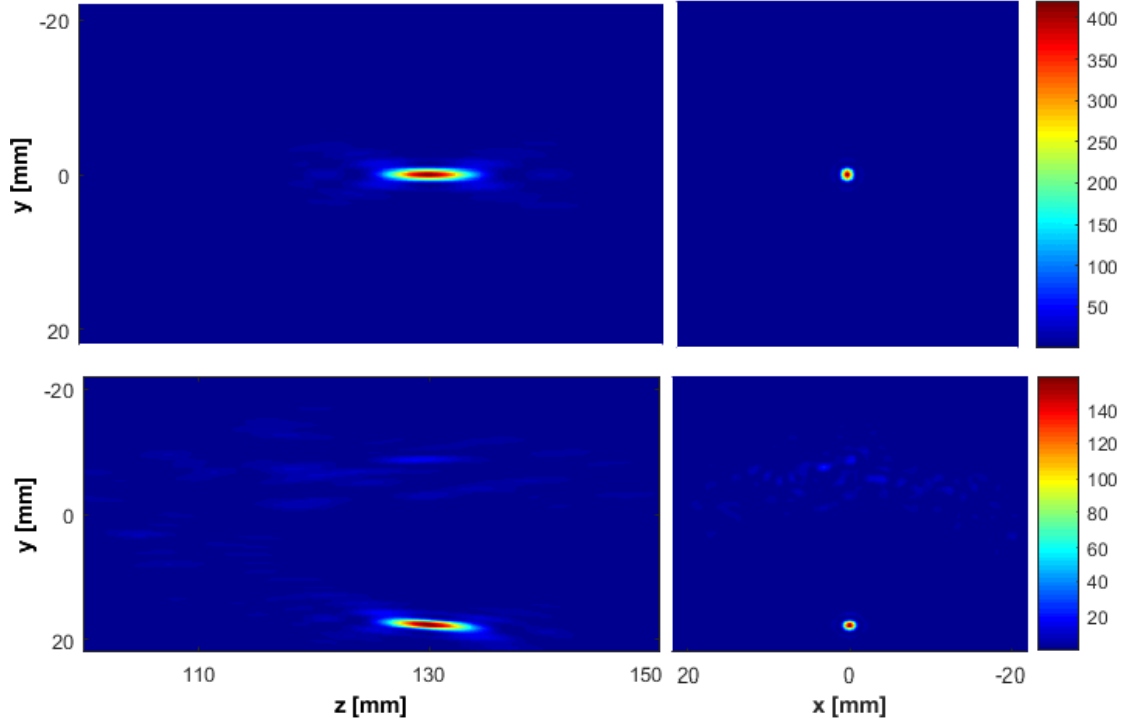


Figure 7.3: a) Simulated 2D intensity distribution in the axial yz (left) and focal xy (right) planes, when the focus is positioned at the geometric centre (top) and when steered 18 mm off the axis (bottom), secondary hotspots can be seen in the field with intensity less than $0.1I_{peak}$ which is considered as safe. Peak intensity in the beam is reduced when steered. Colorbar indicates intensity in W/cm^2

Grating lobes appear when the focus is steered away from the geometric focus. It was observed that there are no significant grating lobes when the focus is steered 15 mm each side of the axis, after which some grating lobes start to appear. Moreover, the intensity in the main beam also reduces when the focus is moved away from the axis. The array used in this simulation study is a modified version of that being used in the previous chapters, which contains a central hole of diameter 38 mm to accommodate an imaging transducer. Since no imaging transducer is being utilized, the central hole was filled with more elements. The increase in number of elements results in delivery of more energy for the same input power. It also reduces the sidelobes which were prominent in the existing array due to the unused surface. Amplitude of intensity profile and side lobe levels of both arrays is compared in fig. 7.4, which shows an increase in the peak intensity and reduction of side lobes. The sidelobe level to peak focal intensity ratio is reduced from 6.5% for the existing array to 2.3% for the proposed array

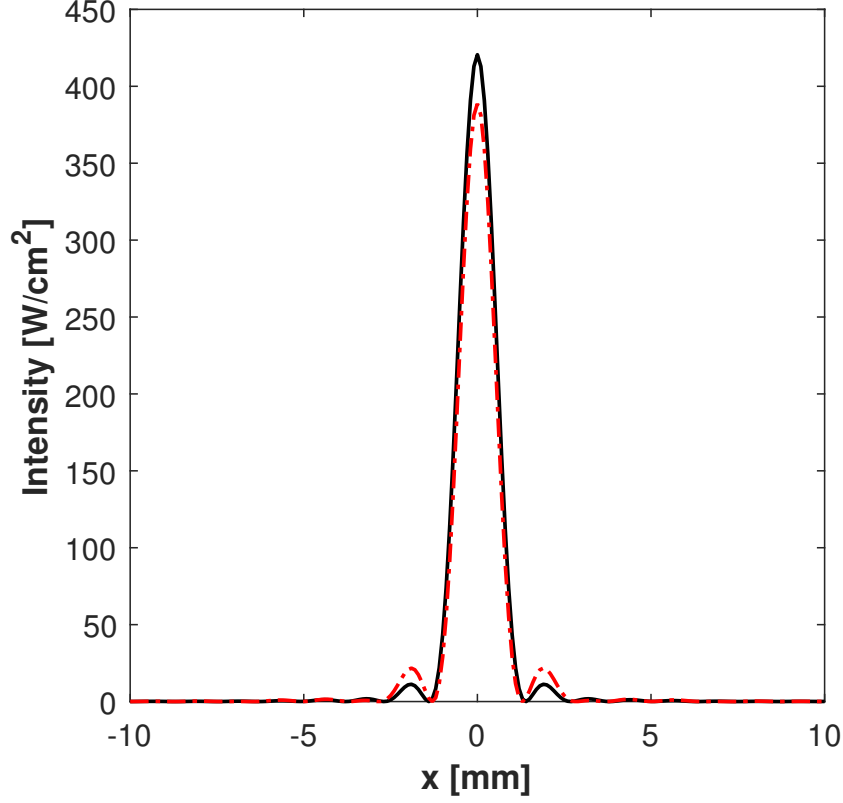


Figure 7.4: Amplitude of intensity profile along x -axis for 256 elements random array (dashed line) and 277 elements modified random array used in this study (solid line). The proposed array has higher peak intensity and lower side lobes than the existing one

The proposed array also performed better in terms of peak pressure at the focus. For a single focus at the geometric center, the ratio of peak pressure at the geometric centre to the pressure at the source (p_{focus}/p_{source}) is 55.4. For the existing 256-element array, this ratio is 50.5. The proposed array thus offers 1.2 times higher focal intensity than the existing one. When the focus point is steered 10 mm laterally, the ratio reduces to 46 and 42 for the new and old arrays, respectively. The sidelobes are also significantly reduced. The peak side lobe level at the geometric focus are 2.5% and 5.3% of the main lobe for the proposed and existing arrays, respectively. The effect of steering the focus for the 277-element array can be observed in fig. 7.5, where grating lobes of magnitude of up to 14% appear when the focus is steered 20 mm off axis in the focal plane.

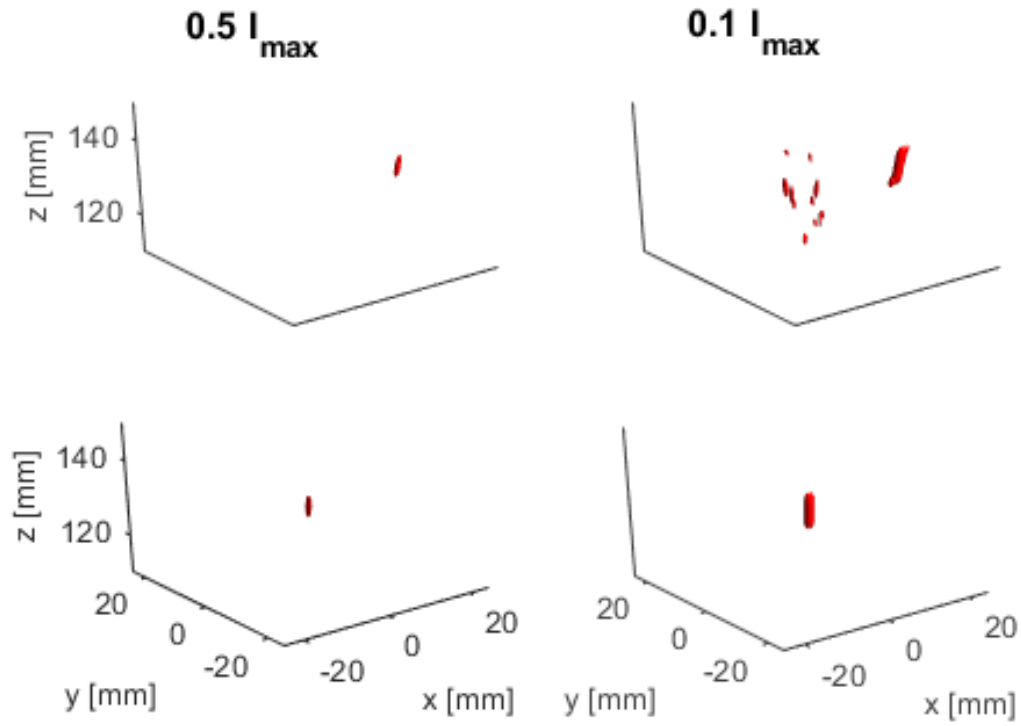


Figure 7.5: Effect of steering a single focus in the focal plane. The top row shows a single focus steered 20 mm away from the axis. The bottom row is when the beam is focused at the geometric centre, when intensities of 50% and above of the peak intensities are included (left) and 10% included (right)

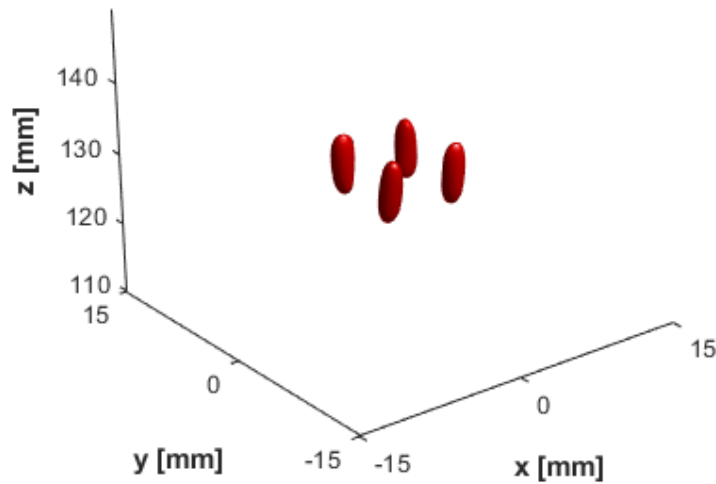


Figure 7.6: 3D view of the pattern of 4 simultaneous foci with coordinates $(-3, 3, 130)$, $(3, 3, 130)$, $(3, -3, 130)$ and $(-3, -3, 130)$ mm is shown. This would ablate a volume of approx. 216 mm^3

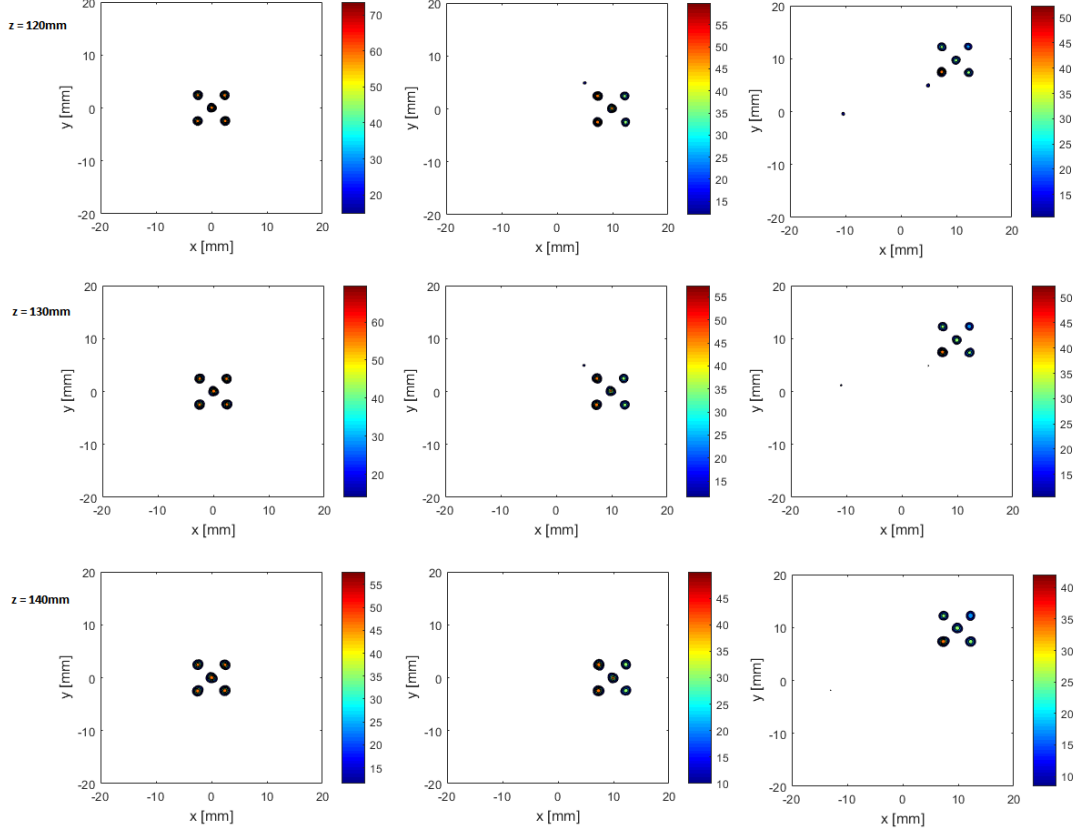


Figure 7.7: Predicted intensity distributions in $x - y$ planes at $z = 120\text{mm}$ (top row), $z = 130\text{mm}$ (middle row) and $z = 140\text{mm}$ (bottom row) for a set of five foci on axis and steered at $(x,y) = (0,0)\text{mm}$ (left column), $(x,y) = (10,0)\text{mm}$ (middle column) and $(x,y) = (10,10)\text{mm}$ (right column). Colorbar indicates intensity in W/cm^2

7.2.1 Patterns of multiple foci

By varying the amplitudes and phases of individual elements of the array, sets of multiple simultaneous foci were generated and steered without heating the underlying medium [92]. The larger the number of foci, the smaller the intensity in the beams is as the energy delivered is distributed among all the foci for a given input power. Pattern of four foci is generated at the geometric center with 3 mm distance between each focus. A 3D view of the pattern is shown in fig. 7.6. Another set of five simultaneous foci was generated with foci separated by 2.5 mm (fig. 7.7). The sets of foci were steered in transverse direction by 10 mm in x-direction and 10 mm in both azimuth directions. The foci are generated in $z = 120, 130$ and 140 mm planes. No side lobes are observed and all grating lobes are well below 20% of the

peak intensity.

7.2.2 Intensity distribution through the ribcage

The effect of ribs on ultrasound focusing of the proposed array was demonstrated in simulations as in the previous chapter but in less detail. Only two rib geometries were considered. Parallel strips with equal width and spacing, positioned at 40 mm depth from the transducer and anatomically correct human ribs. The normalized intensity distribution in the plane of the ribs for idealized ribs geometry consisting of parallel strips is shown in fig. 7.8. The number of active elements is 138 and the maximum intensity observed in the intercostal space in the ribs plane is 0.075 W/cm^2 . The peak intensity in the focal plane is 209.5 W/cm^2 .

Intensity distribution was also calculated in a 3D volume for anatomically correct ribs positioned at 40 mm depth from the transducer. The number of active elements was 190 and the peak intensity at the focus point was 288 W/cm^2 . No focus splitting was observed. Intensity distribution in the plane of the ribs and the focal plane is shown in fig. 7.9. A single focus could be seen in the focal plane with maximum intensity whereas intensity in the intercostal space is minimal suggesting that the ribs are being spared.

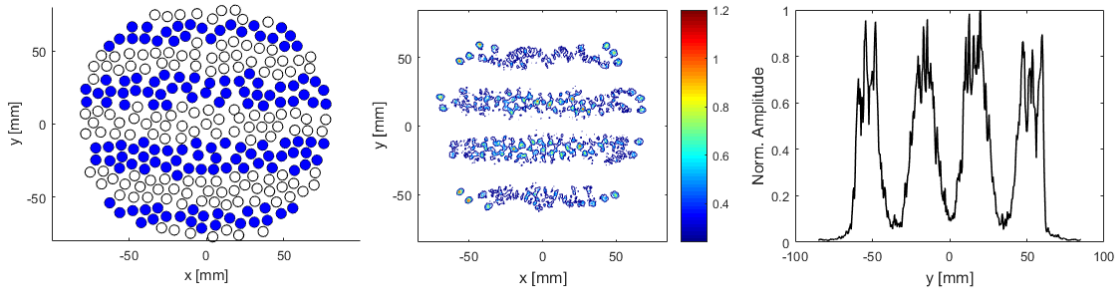


Figure 7.8: Normalized intensity distribution when the ribs are located at 40 mm. Active element are shown in blue (left), intercostal intensity distribution in the ribs plane in 2D (middle) and 1D plot (right). The striped intensity distribution confirms the intercostal delivery of acoustic energy.

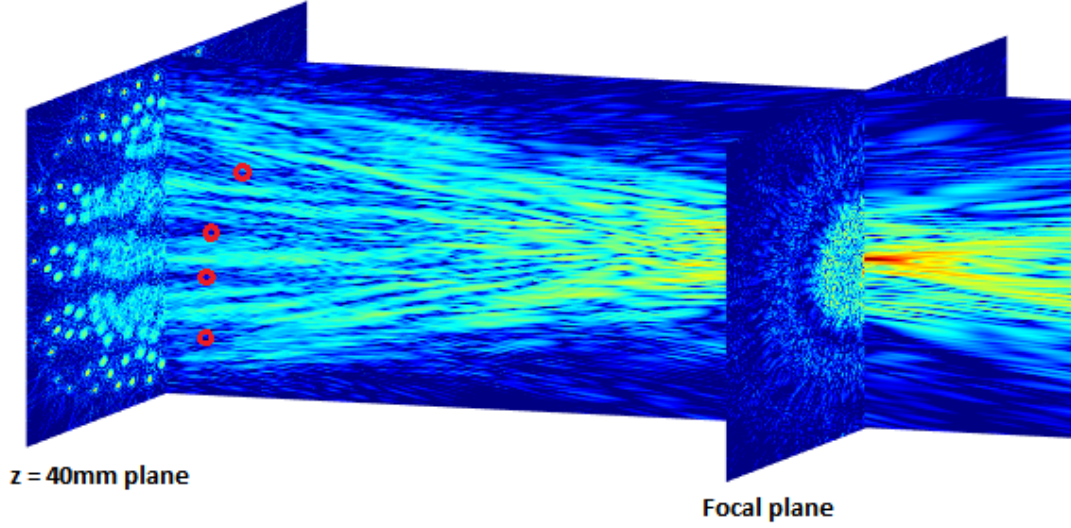


Figure 7.9: Normalized intensity distribution in focal plane and plane at $z = 40$ mm, position of the ribs is shown with red circles. Maximum peak intensity is observed at the focus.

7.3 Imaging with the proposed array

Variants of synthetic aperture imaging algorithms were implemented with random phased array in Chapters 4 and 5 and it was concluded that Synthetic Transmit Aperture (STA) imaging offered the best resolution. STA is thus used to determine the imaging capability of the proposed random phased array. In STA, a single element transmits a signal and the echo is received by all elements [127]. Time delays are calculated for all elements to focus at a single point. Dynamic focusing can thus be achieved both in transmit and receive. For an N element array, N echo recordings are required for image reconstruction in conventional beamforming, whereas, $N \times N$ echo recordings are required to synthesize STA image.

The image pixel at (x_p, y_p, z_p) is computed using [125]:

$$I(x_p, y_p, z_p) = \sum_{i=1}^N \sum_{j=1}^N y_{i,j} [(r_{ip} + r_{jp})] / c \quad (7.1)$$

Where $y_{i,j}$ is the echo received by element j when transmitting with element i . r_{ip} and r_{jp} are the distances to the point from the transmit and receive elements, respectively. The first and second summation corresponds to transmit and receive beamforming.

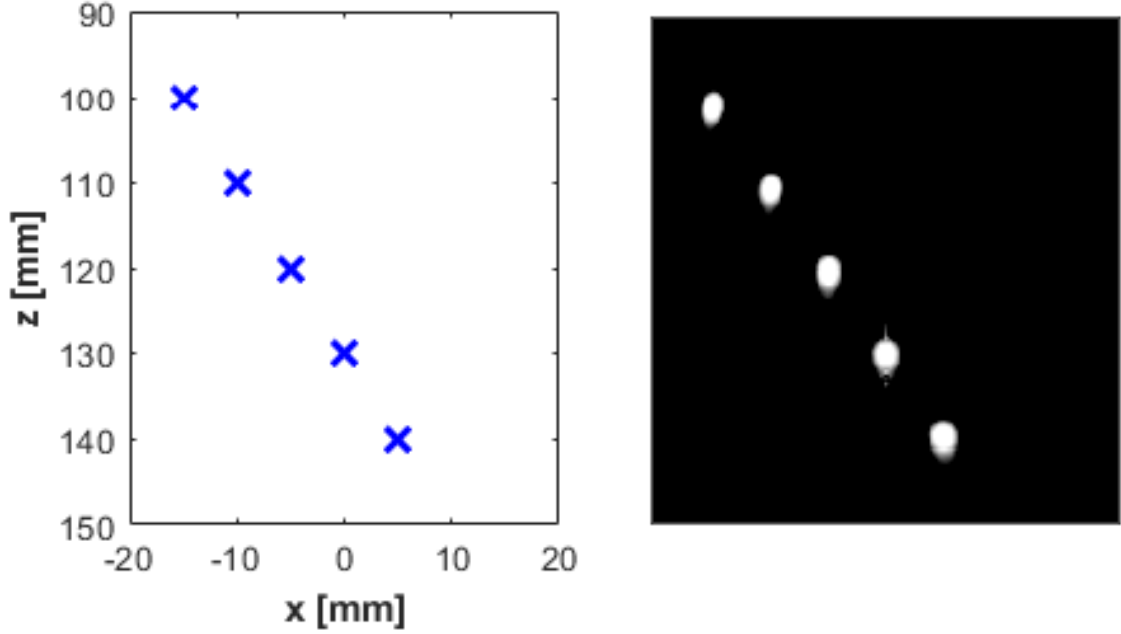


Figure 7.10: A wire phantom showing position of wires spaced 5 mm apart laterally and 10 mm apart axially (left), grayscale image obtained with synthetic transmit aperture imaging and normalized to -35dB (right). All the wires are displayed in the Bmode image with out any side or grating lobes.

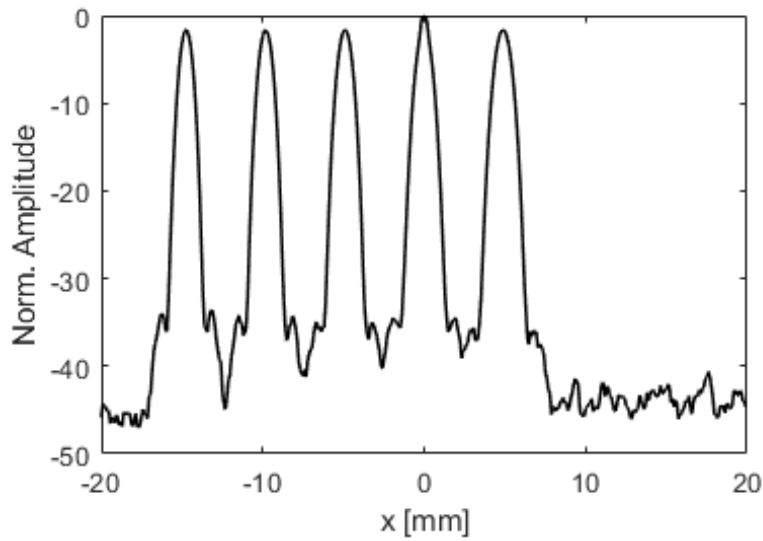


Figure 7.11: Normalized cross-section of lateral beamprofile of STA beamforming for the wire targets in fig. 7.10. The side lobe level for all the wires are below -36 dB

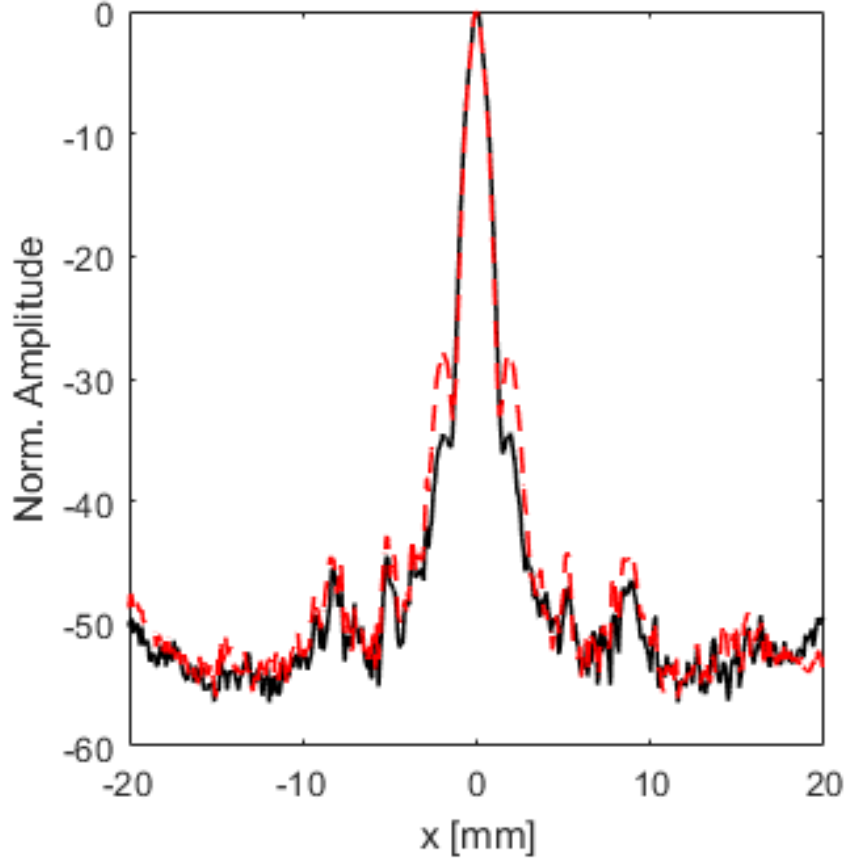


Figure 7.12: Comparison of the normalized cross-section of the beamprofile of synthetic transmit aperture technique corresponding to a scatterer located at the geometric focus for the existing 256-elements array (dashed line) and the proposed 277-elements array (solid line). Width of main beam for both arrays is same whereas the side lobe level is -29 dB and -36 dB for the existing 256-elements and the improved 277-elements, respectively.

Synthetic Transmit Aperture beamforming was used in simulation to image a wire phantom which consists of 5 wires spaced 10 mm axially and 5 mm laterally as shown in fig. 7.10. Normalized cross-section of 1D lateral beamprofile is shown in fig. 7.11. In fig. 7.12, lateral beamprofiles corresponding to a single scatterer at the geometric center of the array are compared for both the existing and proposed arrays. Side lobes which were present due to the breakage of the continuity of elements in the existing array (-29 dB) [146] are significantly reduced (-36 dB) in the proposed array indicating that the proposed array offers better lateral resolution than the existing one.

7.4 Summary

The performance of an improved random phased array was investigated via simulation. Since maximizing the power of phased arrays is an important factor in HIFU applications, more elements were incorporated to fill the unused space of the array. The filling factor of the device was increased from 38% to more than 42%. The modification resulted in an increased intensity at the desired focus. Peak intensity for the modified array was 1.2 times higher than the existing array. It also resulted in reduction of the size of side lobes. The level of side lobes was reduced to almost one third when focusing at the geometric center of the arrays. Steering range is also an important factor that needs to be considered while designing therapeutic arrays. The steering capability of the proposed array was observed to extend by 6 mm in comparison to the existing array while the grating lobes were still in the safe zone (intensity in the grating lobes less than 0.1% of that in the main beam). In terms of imaging resolution, the cross-section of beam profile showed that the side lobe level was reduced by 7 dB in comparison to the existing array that would help in improving the contrast resolution of the array.

Chapter 8

Conclusion

High Intensity Focused Ultrasound has the ability to deposit acoustic energy into the body non-invasively. With phased arrays, the acoustic energy can be focused and steered to the desired location. Patterns of multiple foci can be generated and steered to deposit optimal energy for a given therapeutic application. Due to the non-invasive nature of HIFU, imaging of the therapy procedure is necessary. The imaging modality must be able to outline the target region and identify the available acoustic window for the HIFU beam path. Moreover, it must be able to detect lesion formation and provide feedback to avoid unnecessary damage to the surrounding healthy tissue. To date, MRI, X-Ray and Ultrasound have been used for imaging the HIFU procedure but all have their limitations in terms of cost, complexity, frame rate and resolution. Imaging with the therapeutic array has the advantage of inherent registration between imaging and therapeutic transducer thus not only strong scattering objects can be detected in real time but also the therapeutic procedure can be monitored with suitable imaging techniques. HIFU therapy of liver tumor requires avoidance of thermal damage to the ribs, a problem that can be overcome by imaging with the therapeutic array. The research presented in this thesis aimed to investigate the capability of a random phased array to deliver therapy as well as perform image

guidance for treatment planning. The studies performed during the course of this research provided many insights into imaging and therapy with focused ultrasound which are summarised below.

8.1 Combined Imaging and Therapeutic Random Phased Array

A HIFU system capable of both image guidance and therapy was developed by integrating a random phased array with a research ultrasound scanner via custom connectors. The performance of the random phased array in delivery of high intensity was modeled to validate the previous results. The ultrasound scanner was then programmed to transmit imaging signals to the transducer and receive the backscattered echoes on each array element simultaneously. The collected data were beamformed using a high performance CPU to reconstruct 3D images of the medium of interest. Different synthetic aperture imaging methods were reviewed and implemented, in simulation and experimentally, with a linear imaging probe and for the first time with a therapeutic random phased array. The performance of these synthetic aperture imaging methods including, Synthetic Aperture Focusing, Synthetic Receive Aperture and Synthetic Transmit Aperture, was investigated with wire phantoms. It was established that STA offers the best imaging resolution and was thus used as an imaging technique in the rest of the thesis. The imaging capability of the random phased array was evaluated across a variety of phantoms and *ex vivo* tissue. The image quality was highly dependent on the location of the target. Image resolution near the vicinity of the geometric focus was best due to the concave nature of the transducer and the highly directive elements facing the geometric center. Rib phantoms made of metallic and acrylic cylindrical bars, in which the bars were placed parallel and non-parallel to each other to mimic the ribs and the phantoms were oriented parallel and inclined with respect to the phased array, were 3D imaged. Moreover, data were acquired for ex-vivo ovine ribs immersed

in degassed water and images were reconstructed using synthetic transmit aperture imaging indicating its potential to image bones with the therapeutic random phased array.

Imaging with a therapeutic array is previously demonstrated by Ebbini *et. al* [125, 126], however, their work is limited to a linear, convex and regular phased array. Moreover, detailed comparison of different synthetic aperture techniques with a therapeutic array has not been presented previously. It was thus important to determine the imaging potential of a therapeutic random phased array by analyzing and comparing variants of synthetic aperture imaging techniques and establish the benefit of using the array both for image guidance and therapy. It was shown for the first time that the therapeutic random phased array is capable of producing 3D images of the medium of interest which would be very helpful in image guidance and treatment planning.

8.2 Treatment planning in the presence of Ribcage

It has been observed that acoustic obstacles in the path of ultrasound beam distorts the focus by splitting it into three or more foci. For a periodic structure such as human ribcage, this phenomenon becomes more prevalent and practically relevant. Moreover, the ribs absorb acoustic energy, get heated and cause skin burns, therefore a technique to avoid them during HIFU treatment should be part and parcel of the HIFU treatment planning. The physical nature of the focus splitting and technique to avert heating of the ribs were thus investigated in detail.

Idealized flat parallel strips were first considered to reveal the effect of ribs on ultrasound focusing and to determine the intensity distribution in the focus plane and in the plane of the ribs. Binarized apodization based on geometric ray tracing approach was used to determine the optimal driving pattern for HIFU delivery through

the ribcage while preventing heat accumulation on the strips. It was observed, in simulations and experiments, that the strips were impeded from being heated and the acoustic energy was only delivered in the space between them. Parameters of focus splitting were also determined for various geometrical configurations.

Focus deterioration as a result of the ribs in the HIFU beam path was discussed by Bobkova *et al.* [99] and Khokhlova *et al.* [112] but their study was limited to idealized rib phantoms and the effects of human rib cage on focus quality was not taken into account. In addition to the idealized ribs geometries, the previous work was extended in this thesis to determine the effect of anatomical correct human ribcage model on the quality of focus and therapy in the presence of realistic ribcage was analyzed in detail. It was observed that unlike the parallel strips, the triad splitting of the focus does not always occur in the presence of a human ribcage but other factors including spacing between transducer and the ribcage, depth of the tumor behind the ribcage and orientation of the ribcage in front of the transducer define the quality and shape of the focus and intensity in the main HIFU beam. Ultrasound energy was thus focused through the ribcage and intensity distributions were calculated in plane of the ribs in simulation, whereas, temperature in the intercostal space was observed with an infrared camera. The effects of focus splitting when the HIFU beam passes through the ribcage was studied in detail. Various scenarios that can be faced during a clinical HIFU procedure were taken into consideration and the effects on the quality of focus and intensity in the HIFU beam at the target focus was calculated. Recommendations on adjusting the HIFU beam to treat liver tumors intercostally were made.

8.3 Improved Random Phased Array

It was observed that switching off the elements during HIFU therapy to minimize heating on the ribs also causes a decrease in the intensity at the focus. The inten-

sity at the focus can be increased by maximizing the input power but this would lead to near-field heating causing skin burns. Since the random phased array was also operated in imaging mode, the external imaging transducer embedded in the centre of the array could be removed and it was thus proposed that the element distribution of the phased array be optimized to fill the unused space by introducing more elements. The filling factor of the proposed array was increased to 42% in comparison to 38.6% for the existing array. The benefits of array modification were threefold: First, the intensity at the focus was increased for the same input acoustic power at each element. Secondly, the steering range of the array was extended and finally, the sidelobes present in the beam were reduced which would help improving the imaging resolution of the system. The increase in the focal peak pressure to the sidelobe ratio was seen as a major advantage of phased arrays without an imaging aperture to the existing phased arrays accommodating an imaging aperture.

8.4 Future Work

8.4.1 GPU parallelization

The full synthetic transmit aperture approach requires that an Ultrasound pulse is transmitted by a single element and the received echo train is recorded on every element. Since the process is repeated by transmitting on every element in turn, for N elements there are N^2 ultrasound echo trains. Each echo train is a signal of approximately 1024 data points depending on the depth of imaging field. In practice, the transmit and receive fields of all element pairs do not always intercept, so the number of usable element pairings is less than N^2 but is still a considerable amount of data. It has been demonstrated in this work that useful images from the therapeutic array can be obtained, however, to make this technique clinically useful, the processing time of the image reconstruction needs to be shortened significantly. With GPU parallelization, the beamforming computing time per pixel could be

significantly reduced. The advantages of using GPU for synthetic aperture imaging are twofold:

- First, GPU has hundreds of processing cores which are specifically developed to facilitate single instruction, multiple thread (SIMT) computation. The beamforming operation can thus be accelerated with the help of parallelism without any power wall issues being faced by current microprocessors.
- Secondly, It is easy to implement algorithms with computed unified device architecture (CUDA) for execution on a GPU through high level programming language such as C and is a good alternative to FPGA which is configured with low level hardware description language such as VHDL.

Synthetic aperture beamforming algorithm involves operation on a large volume of signals in a repetitive manner and is therefore a good candidate for GPU computation as the algorithm can be cast in a parallel form. The following strategy may be used to maximize the efficiency:

- To reduce the noise during the acquisition, band pass filter can be applied in parallel by launching one thread of execution on GPU for each received signal.
- 3D Beamforming is the most computationally expensive step. Parallelization can be achieved by launching a thread for each image pixel that would calculate corresponding value for that pixel based on the time of flight. This would significantly reduce computation time.
- Hilbert transform is applied to each line of the signal for envelope detection. One thread can be launched per image line taking benefit of the GPU FFTs.
- The generated image can be displayed using OpenGL libraries.

Processing speed can be further optimized by efficiently managing memory access thus reducing latency overheads. Both shared memory and global memory should be used properly to lower the processing latency. Thus the time taken to reconstruct the volumetric images can be significantly reduced and the imaging can be performed in near real-time.

8.4.2 Improved HIFU Device Design

For imaging with therapeutic transducer, the central hole left for accommodating the imaging transducer is no longer needed. The large discontinuity reduces the focusing efficiency and increase the sidelobe level to peak focal pressure ratio. Thus phased array should be designed with elements tightly packed and randomly distributed to maximize energy delivered to the tissue with reduced sidelobes and no grating lobes. The transducer should be able to operate with tone bursts of few milliseconds to perform operation such as histotripsy and transcostal sonication. Advances in transducer technologies can be exploited to design arrays with tight packing, large bandwidth and low cross-coupling making them suitable for imaging and therapy, both. The array can thus be used to image in real-time and to interrogate the tissue response to the high intensity HIFU beam. The available RF generator can support only 256 channels, however, switching off some elements from a dense array with more elements to spare the ribs will make it possible to use the improved design with the existing RF generating system.

8.4.3 Non-linear acoustic modeling

During the calculation of intensity distribution in this work, the input acoustic power was restricted to 15 W in simulation and the non-linear effects were not taken into account. For HIFU experiments and clinical practice, a high acoustic power is required which results in the generation of higher harmonics due to non-

linear propagation. For calculating intensity distribution at high powers, non-linear effects should also be considered. The simple numerical methods such as *Rayleigh Sommerfield integral* are computationally efficient, easy to implement and use features of wave propagation in human tissue, they do not address the challenge of actual scattering and diffraction phenomena involved in complex, inhomogeneous medium, however. Full wave 3D models should thus be implemented that would account for the effects of non-linear propagation associated with the HIFU field in a heterogeneous medium. The full wave models provide more realistic representation of wave propagation in a complex, inhomogeneous medium, however, computational challenges are the limiting factor in implementing such models which need to be addressed in order to implement full wave 3D numerical models which are useful in treatment planning for HIFU therapy.

In future, the existing system can be connected to a steerable histotripsy system. The system can be used to provide high amplitude ultrasound pulses suitable to treat tumors via the mechanical damage caused by boiling histotripsy. Modeling of the acoustic field can be done via linear Huygens and Westervelt equations to predict the ultrasound field distribution and optimise the drive conditions. This would require modification of the existing RF generator to produce the required drive signals for each element, and produce short pulses rather than continuous wave and an addition of impedance matching circuitry to each channel. Thermal effects on the ribs will be lower when using boiling histotripsy due to the low duty factor and the highly non-linear response of histotripsy with ultrasound pressure. The ribs can be totally spared by imaging with the therapeutic transducer, the inherent registration of imaging and therapeutic frames of reference will enable elements whose beams intersect the ribs to be accurately identified and excited with tailored time delayed drive signals to minimise the effect of the ribs. Synthetic aperture imaging techniques can be used to image the ribs and Passive Acoustic Mapping (PAM) to image and monitor the cavitation based therapeutic procedure. The benefit of using PAM with

the therapeutic transducer is the achievement of optimal imaging resolution due to the large aperture size and ability to perform 3D cavitation mapping without moving the array mechanically.

Bibliography

- [1] W. J. Fry, W. H. Mosberg, J. W. Barnard, and F. J. Fry, “Production of Focal Destructive Lesions in the Central Nervous System With Ultrasound,” *Journal of Neurosurgery*, vol. 11, no. 5, pp. 471 – 478, 1954.
- [2] V. Auboiroux, E. Dumont, L. Petrusca, M. Viallon, and R. Salomir, “An MR-compliant phased-array HIFU transducer with augmented steering range, dedicated to abdominal thermotherapy,” *Physics in Medicine & Biology*, vol. 56, no. 12, pp. 3563–82, 2011.
- [3] P. B. Rosnitskiy, B. A. Vysokanov, L. R. Gavrilov, O. A. Sapozhnikov, and V. A. Khokhlova, “Method for designing multielement fully populated random phased arrays for ultrasound surgery applications,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 65, no. 4, pp. 630–637, 2018.
- [4] J. W. Hand, A. Shaw, N. Sadhoo, S. Rajagopal, R. J. Dickinson, and L. R. Gavrilov, “A random phased array device for delivery of high intensity focused ultrasound,” *Physics in Medicine & Biology*, vol. 54, no. 19, pp. 5675–93, 2009.
- [5] H. T. O’Neil, “Focusing radiators,” *The Journal of the Acoustical Society of America*, vol. 21, no. 1, pp. 60–60, 1949.
- [6] W. J. Fry and F. J. Fry, “Fundamental neurological research and human neurosurgery using intense ultrasound,” *IRE Transactions on Medical Electronics*, vol. ME-7, pp. 166–181, July 1960.

- [7] K. Hynynen and R. M. Jones, “Image-guided ultrasound phased arrays are a disruptive technology for non-invasive therapy,” *Physics in Medicine & Biology*, vol. 61, pp. R206–R248, Aug. 2016.
- [8] C. J. Diederich and K. Hynynen, “The feasibility of using electrically focused ultrasound arrays to induce deep hyperthermia via body cavities,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 38, no. 3, pp. 207–219, 1991.
- [9] A. D Maxwell, G. Owens, H. Gurm, K. Ives, D. Myers, and Z. Xu, “Noninvasive treatment of deep venous thrombosis using pulsed ultrasound cavitation therapy (histotripsy) in a porcine model,” *Journal of Vascular and Interventional Radiology : JVIR*, vol. 22, pp. 369–77, Dec. 2010.
- [10] T. Wang, Z. Xu, T. L. Hall, J. B. Fowlkes, and C. A. Cain, “An efficient treatment strategy for histotripsy by removing cavitation memory,” *Ultrasound in Medicine & Biology*, vol. 38 5, pp. 753–66, 2012.
- [11] J. C. Simon, O. A. Sapozhnikov, V. A. Khokhlova, Y.-N. Wang, L. A. Crum, and M. R. Bailey, “Ultrasonic atomization of tissue and its role in tissue fractionation by high intensity focused ultrasound,” *Physics in Medicine & Biology*, vol. 57, pp. 8061–8078, Nov. 2012.
- [12] V. A. Khokhlova, J. B. Fowlkes, W. W. Roberts, G. R. Schade, Z. Xu, T. D. Khokhlova, T. L. Hall, A. D. Maxwell, Y.-N. Wang, and C. A. Cain, “Histotripsy methods in mechanical disintegration of tissue: towards clinical applications,” *International Journal of Hyperthermia*, vol. 31 2, pp. 145–62, 2015.
- [13] K. B. Bader, E. Vlaisavljevich, and A. D. Maxwell, “For whom the bubble grows: Physical principles of bubble nucleation and dynamics in histotripsy ultrasound therapy,” *Ultrasound in Medicine & Biology*, vol. 45, no. 5, pp. 1056 – 1080, 2019.

- [14] M. Hoogenboom, D. Eikelenboom, M. H. den Brok, A. Heerschap, J. J. FÄtterer, and G. J. Adema, “Mechanical high-intensity focused ultrasound destruction of soft tissue: Working mechanisms and physiologic effects,” *Ultrasound in Medicine & Biology*, vol. 41, no. 6, pp. 1500 – 1517, 2015.
- [15] A. Eranki, N. Farr, A. Partanen, K. V. Sharma, H. Chen, C. T. Rossi, S. V. V. N. Kothapalli, M. Oetgen, A. Kim, A. H. Negussie, D. Woods, B. J. Wood, P. C. W. Kim, and P. S. Yarmolenko, “Boiling histotripsy lesion characterization on a clinical magnetic resonance imaging-guided high intensity focused ultrasound system,” *PLOS ONE*, vol. 12, pp. 1–23, 03 2017.
- [16] T. D Khokhlova, Y. Wang, J. Simon, B. Cunitz, F. Starr, M. Paun, L. Crum, M. Bailey, and V. Khokhlova, “Ultrasound-guided tissue fractionation by high intensity focused ultrasound in an in vivo porcine liver model,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, pp. 8161–6, 05 2014.
- [17] A. Khanna, R. T. C. Nemes, N. Gougoulis, N. Maffulli, and J. Gray, “The effects of LIPUS on soft-tissue healing: a review of literature,” *British Medical Bulletin*, vol. 89, pp. 169–182, Nov. 2008.
- [18] H. Fang, K. Tsai, W. Cheng, M. Shieh, P. Lou, W. Lin, and W. Chen, “The effects of power on-off durations of pulsed ultrasound on the destruction of cancer cells,” *International Journal of Hyperthermia*, vol. 23, pp. 371–380, June 2007.
- [19] T. D. Khokhlova, M. S. Canney, V. A. Khokhlova, O. A. Sapozhnikov, L. A. Crum, and M. R. Bailey, “Controlled tissue emulsification produced by high intensity focused ultrasound shock waves and millisecond boiling,” *The Journal of the Acoustical Society of America*, vol. 130, no. 5, pp. 3498–3510, 2011.
- [20] M. S. Canney, V. A. Khokhlova, O. V. Bessonova, M. R. Bailey, and L. A. Crum, “Shock-induced heating and millisecond boiling in gels and tissue due to

- high intensity focused ultrasound,” *Ultrasound in Medicine & Biology*, vol. 36, no. 2, pp. 250 – 267, 2010.
- [21] G. E. Tupholme, “Generation of acoustic pulses by baffled plane pistons,” *Mathematika*, vol. 16, no. 2, pp. 209–224, 1969.
- [22] P. R. Stepanishen, “Transient radiation from pistons in an infinite planar baffle,” *The Journal of the Acoustical Society of America*, vol. 49, no. 5B, pp. 1629–1638, 1971.
- [23] P. R. Stepanishen, “The time-dependent force and radiation impedance on a piston in a rigid infinite planar baffle,” *The Journal of the Acoustical Society of America*, vol. 49, no. 3B, pp. 841–849, 1971.
- [24] R. J. McGough, T. V. Samulski, and J. F. Kelly, “An efficient grid sectoring method for calculations of the near-field pressure generated by a circular piston,” *The Journal of the Acoustical Society of America*, vol. 115, no. 5, pp. 1942–1954, 2004.
- [25] J. W. Goodman, *Introduction to Fourier optics*. Roberts and Company, Greenwood village,, 3rd ed., 2005.
- [26] M. E. Schafer and P. A. Lewin, “Transducer characterization using the angular spectrum method,” *The Journal of the Acoustical Society of America*, vol. 85, no. 5, pp. 2202–2214, 1989.
- [27] A. Kyriakou, *Multi-physics computational modeling of focused ultrasound therapies*. PhD thesis, ETH Zurich, 2015.
- [28] D. Belgroune, J. de Belleval, and H. Djelouah, “Modelling of the ultrasonic field by the angular spectrum method in presence of interface,” *Ultrasonics*, vol. 40, no. 1, pp. 297 – 302, 2002.
- [29] C. J. Vecchio, M. E. Schafer, and P. A. Lewin, “Prediction of ultrasonic field propagation through layered media using the extended angular spectrum

- method,” *Ultrasound in Medicine & Biology*, vol. 20, no. 7, pp. 611 – 622, 1994.
- [30] Y. Jing, T. Wang, and G. Clement, “A k-space method for moderately non-linear wave propagation,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 59, pp. 1664–73, Aug. 2012.
- [31] G. F. Pinton, J. Dahl, S. J. Rosenzweig, and G. E. Trahey, “A heterogeneous nonlinear attenuating full-wave model of ultrasound,” *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control*, vol. 56, pp. 474 – 88, Mar. 2009.
- [32] J. Gu and Y. Jing, “Modeling of wave propagation for medical ultrasound: A review,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 62, pp. 1979–1992, 11 2015.
- [33] P. J. Westervelt, “Parametric acoustic array,” *The Journal of the Acoustical Society of America*, vol. 35, no. 4, pp. 535–537, 1963.
- [34] A. Gawande, “Two hundred years of surgery,” *New England Journal of Medicine*, vol. 366, no. 18, pp. 1716–1723, 2012.
- [35] E. S. Ebbini and C. A. Cain, “Multiple-focus ultrasound phased-array pattern synthesis: optimal driving-signal distributions for hyperthermia,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 36, no. 5, pp. 540–548, 1989.
- [36] S. Dijkgraaf, “Spallanzani’s unpublished experiments on the sensory basis of object perception in bats,” *Isis*, vol. 51, no. 1, pp. 9–20, 1960.
- [37] J. W. Richard, “Measuring the speed of sound in water,” *Physics Education*, vol. 50, no. 6, pp. 727–732, 2015.

- [38] V. A. Koptsik and I. S. Rez, “Pierre curie’s works in the field of crystal physics (on the one-hundredth anniversary of the discovery of the piezoelectric effect),” *Soviet Physics Uspekhi*, vol. 24, no. 5, p. 426, 1981.
- [39] K. F. Graff, *A History of Ultrasonics*, vol. 15, pp. 1–97. Academic Press, 1981.
- [40] M. A. Shampo and R. A. Kyle, “Karl theodore dussik-pioneer in ultrasound,” *Mayo Clinic Proceedings*, vol. 70, no. 12, p. 1136, 1995.
- [41] C. Hill, J. Bamber, and G. t. Haar, *Physical Principles of Medical Ultrasonics*. John Wiley & Sons, ProQuest Ebook Central, 2004.
- [42] J. J. Wild and J. M. Reid, “Application of echo-ranging techniques to the determination of structure of biological tissues,” *Science*, vol. 115, no. 2983, pp. 226–30, 1952.
- [43] J. H. Holmes, “Diagnostic ultrasound during the early years of A.I.U.M.,” *Journal of Clinical Ultrasound*, vol. 8, no. 4, pp. 299–308, 1980.
- [44] K. Baba, K. Satoh, S. Sakamoto, T. Okai, and S. Ishii, “Development of an ultrasonic system for three-dimensional reconstruction of the fetus,” *Journal of Perinatal Medicine*, vol. 17, pp. 19–24, 02 1989.
- [45] M. C. Fyfe and M. I. Bullock, “Therapeutic ultrasound: some historical background and development in knowledge of its effect on healing,” *Australian Journal of Physiotherapy*, vol. 31, no. 6, pp. 220–4, 1985.
- [46] D. O. J. William, “Assessing the risks for modern diagnostic ultrasound imaging,” *Japanese Journal of Applied Physics*, vol. 37, no. 5S, p. 2781, 1998.
- [47] W. J. Fry, F. J. Fry, J. W. Barnard, R. F. Krumins, and J. F. Brennan, “Ultrasonic lesions in the mammalian central nervous system,” *Science*, vol. 122, no. 3168, pp. 517–518, 1955.
- [48] M. Oka, “Application of intense focused ultrasound in brain surgery and other fields,” *Clinical All-Round*, vol. 13, pp. 1514–1523, 1964.

- [49] R. Meyers, W. J. Fry, F. J. Fry, L. L. Dreyer, D. F. Schultz, and R. F. Noyes, "Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders," *Journal of Neurosurgery*, vol. 16, no. 1, pp. 32–54, 1959.
- [50] W. J. Fry, W. H. Mosberg Jr., J. W. Barnard, and F. J. Fry, "Production of focal destructive lesions in the central nervous system with ultrasound," *Journal of Neurosurgery*, vol. 11, no. 5, pp. 471–8, 1954.
- [51] P. N. Wells, "Ultrasonics in medicine and biology," *Physics in Medicine & Biology*, vol. 22, no. 4, pp. 629–69, 1977.
- [52] F. W. Kremkau, "Cancer therapy with ultrasound: a historical review," *Journal of Clinical Ultrasound*, vol. 7, no. 4, pp. 287–300, 1979.
- [53] M. G. Vaughan, G. R. T. Haar, C. R. Hill, R. L. Clarke, and J. W. Hopewell, "Minimally invasive cancer surgery using focused ultrasound: a pre-clinical, normal tissue study," *The British Journal of Radiology*, vol. 67, no. 795, pp. 267–274, 1994.
- [54] R. Warwick and J. Pond, "Trackless lesions in nervous tissues produced by high intensity focused ultrasound (high-frequency mechanical waves)," *Journal of Anatomy*, vol. 102, no. Pt 3, pp. 387–405, 1968.
- [55] I. H. Rivens, R. L. Clarke, and G. R. t. Haar, "Design of focused ultrasound surgery transducers," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 43, no. 6, pp. 1023–1031, 1996.
- [56] R. S. Foster, R. Bihrlé, N. T. Sanghvi, F. J. Fry, and J. P. Donohue, "High-intensity focused ultrasound in the treatment of prostatic disease," *European Urology*, vol. 23 Suppl 1, pp. 29–33, 1993.
- [57] R. Bihrlé, R. S. Foster, N. T. Sanghvi, F. J. Fry, and J. P. Donohue, "High-intensity focused ultrasound in the treatment of prostatic tissue," *Urology*, vol. 43, pp. 21–26, 1994.

- [58] N. T. Sanghvi, R. S. Foster, R. Bihrlé, R. Casey, T. Uchida, M. H. Phillips, J. Syrus, A. V. Zaitsev, K. W. Marich, and F. J. Fry, “Noninvasive surgery of prostate tissue by high intensity focused ultrasound: an updated report,” *European Journal of Ultrasound*, vol. 9, no. 1, pp. 19–29, 1999.
- [59] A. Gelet, J. Y. Chapelon, R. Bouvier, C. Pangaud, and Y. Lasne, “Local control of prostate cancer by transrectal high intensity focused ultrasound therapy: preliminary results,” *Journal of Urology*, vol. 161, no. 1, pp. 156–62, 1999.
- [60] A. Gelet, J. Chapelon, J. Margonari, Y. Theillere, F. Gorry, R. Souchon, and R. Bouvier, “High-intensity focused ultrasound experimentation on human benign prostatic hypertrophy,” *European Urology*, vol. 23 Suppl 1, pp. 44–7, 02 1993.
- [61] E. S. Ebbini and C. A. Cain, “Experimental evaluation of a prototype cylindrical section ultrasound hyperthermia phased-array applicator,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 38, no. 5, pp. 510–20, 1991.
- [62] J. W. Hand, E. Ebbini, D. O. Keeffe, D. Israel, and S. Mohammadtaghi, “An ultrasound linear array for use in intracavitary applicators for thermotherapy of prostatic diseases,” in *Proceedings IEEE Ultrasonics Symposium*, vol. 2, pp. 1225–1228, 1993.
- [63] E. B. Hutchinson, M. T. Buchanan, and K. Hynynen, “Design and optimization of an aperiodic ultrasound phased array for intracavitary prostate thermal therapies,” *Med Phys*, vol. 23, no. 5, pp. 767–76, 1996.
- [64] E. B. Hutchinson and K. Hynynen, “Intracavitary ultrasound phased arrays for noninvasive prostate surgery,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 43, no. 6, pp. 1032–1042, 1996.

- [65] L. Gavrilov and J. Hand, “Design and experimental evaluation of an endocavitary linear phased array for ultrasound surgery of prostate,” *Acoustical Physics*, vol. 46, pp. 144–152, Mar. 2000.
- [66] L. R. Gavrilov, J. W. Hand, P. Abel, and C. A. Cain, “A method of reducing grating lobes associated with an ultrasound linear phased array intended for transrectal thermotherapy,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 44, no. 5, pp. 1010–1017, 1997.
- [67] M. Skolnik, *Introduction to Radar Systems*. McGraw-Hill, 2001.
- [68] S. D. Sokka and K. H. Hynynen, “The feasibility of MRI-guided whole prostate ablation with a linear aperiodic intracavitary ultrasound phased array,” *Physics in Medicine & Biology*, vol. 45, no. 11, pp. 3373–83, 2000.
- [69] J. Tan, L. Frizzell, N. Sanghvi, R. Seip, J. Wu, and J. Kouzmanoff, “Design of focused ultrasound phased arrays for prostate treatment,” vol. 2, pp. 1247 – 1251 vol.2, Nov. 2000.
- [70] J. S. Tan, L. A. Frizzell, N. Sanghvi, S.-j. Wu, R. Seip, and J. T. Kouzmanoff, “Ultrasound phased arrays for prostate treatment,” *The Journal of the Acoustical Society of America*, vol. 109, no. 6, pp. 3055–3064, 2001.
- [71] L. Curiel, F. Chavrier, R. Souchon, A. Birer, and J. Y. Chapelon, “1.5-D high intensity focused ultrasound array for non-invasive prostate cancer surgery,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 49, no. 2, pp. 231–42, 2002.
- [72] R. Seip, W. Chen, R. Carlson, L. Frizzell, G. Warren, N. Smith, K. Saleh, G. Gerber, K. Shung, H. Guo, *et al.*, “Annular and Cylindrical Phased Array Geometries for Transrectal High-Intensity Focused Ultrasound (HIFU) using PZT and Piezocomposite Materials,” in *AIP Conference Proceedings*, vol. 754, pp. 229–232, 2005.

- [73] R. T. Held, V. Zderic, N. Thuc Nghi, and S. Vaezy, “Annular phased-array high-intensity focused ultrasound device for image-guided therapy of uterine fibroids,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 53, no. 2, pp. 335–348, 2006.
- [74] G. Chen, H. Chang, Y. Kuo, W. Lin, W. Chen, and W. Tseng, “Design and Fabrication of a Wide-Aperture HIFU Annular Array Transducer for the Treatment of Deep-Seated Tumors,” *AIP Conference Proceedings*, vol. 1359, no. 1, pp. 215–220, 2011.
- [75] K. Ocheltree, P. J. Benkeser, L. A. Frizzell, and C. A. Cain, “An ultrasonic phased array applicator for hyperthermia,” *IEEE Transactions on Sonics and Ultrasonics*, vol. 31, pp. 526– 526, 10 1984.
- [76] C. A. Cain and S. Umemura, “Concentric-ring and sector-vortex phased-array applicators for ultrasound hyperthermia,” *IEEE Transactions on Microwave Theory and Techniques*, vol. 34, no. 5, pp. 542–551, 1986.
- [77] S. Umemura and C. A. Cain, “The sector-vortex phased array: acoustic field synthesis for hyperthermia,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 36, no. 2, pp. 249–257, 1989.
- [78] E. S. Ebbini and C. A. Cain, “A spherical-section ultrasound phased array applicator for deep localized hyperthermia,” *IEEE Transactions on Biomedical Engineering*, vol. 38, no. 7, pp. 634–643, 1991.
- [79] F. Xiaobing and K. Hynynen, “A study of various parameters of spherically curved phased arrays for noninvasive ultrasound surgery,” *Physics in Medicine & Biology*, vol. 41, no. 4, p. 591, 1996.
- [80] D. R. Daum, N. B. Smith, R. King, and K. Hynynen, “In vivo demonstration of noninvasive thermal surgery of the liver and kidney using an ultrasonic phased array,” *Ultrasound in Medicine & Biology*, vol. 25, no. 7, pp. 1087–98, 1999.

- [81] G. T. Clement, J. White, and K. Hynynen, “Investigation of a large-area phased array for focused ultrasound surgery through the skull,” *Physics in Medicine & Biology*, vol. 45, no. 4, pp. 1071–83, 2000.
- [82] G. T. Clement, S. Jie, G. Tonia, and H. K., “A hemisphere array for non-invasive ultrasound brain therapy and surgery,” *Physics in Medicine & Biology*, vol. 45, no. 12, p. 3707, 2000.
- [83] G. T. Clement and K. Hynynen, “A non-invasive method for focusing ultrasound through the human skull,” *Phys Med Biol*, vol. 47, no. 8, pp. 1219–36, 2002.
- [84] G. T. Clement, P. J. White, R. L. King, N. McDannold, and K. Hynynen, “A magnetic resonance imaging-compatible, large-scale array for trans-skull ultrasound surgery and therapy,” *Journal of Ultrasound in Medicine*, vol. 24, no. 8, pp. 1117–25, 2005.
- [85] J. White, G. T. Clement, and K. Hynynen, “Transcranial ultrasound focus reconstruction with phase and amplitude correction,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 52, no. 9, pp. 1518–1522, 2005.
- [86] C. M. Tempany, E. A. Stewart, N. McDannold, B. J. Quade, F. A. Jolesz, and K. Hynynen, “MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study,” *Radiology*, vol. 226, no. 3, pp. 897–905, 2003.
- [87] A. Pulkkinen, Y. Huang, J. Song, and K. Hynynen, “Simulations and measurements of transcranial low-frequency ultrasound therapy: skull-base heating and effective area of treatment,” *Physics in Medicine & Biology*, vol. 56, no. 15, pp. 4661–83, 2011.
- [88] L. Gavrilov and J. Hand, *High-Power Ultrasound Phased Arrays for Medical Applications*. Nova Science Publishers., 2014.

- [89] S. A. Goss, L. A. Frizzell, J. T. Kouzmanoff, J. M. Barich, and J. M. Yang, "Sparse random ultrasound phased array for focal surgery," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 43, no. 6, pp. 1111–1121, 1996.
- [90] J. Hand and L. Gavrilov, "Ultrasound transducer arrays. Great Britain Patent No. GB2347043 (23 August 2000).," Jan. 2000.
- [91] J. Hand and L. Gavrilov, "Array of quasirandomly distributed ultrasound transducers. US Patent 6488630 (3 December 2002).," Jan. 2002a.
- [92] L. R. Gavrilov and J. W. Hand, "A theoretical assessment of the relative performance of spherical phased arrays for ultrasound surgery," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 47, no. 1, pp. 125–139, 2000.
- [93] P. Gelat, G. Ter Haar, and N. Saffari, "The optimization of acoustic fields for ablative therapies of tumours in the upper abdomen," *Physics in Medicine & Biology*, vol. 57, no. 24, pp. 8471–97, 2012.
- [94] M. Pernot, J. Aubry, M. Tanter, F. Marquet, G. Montaldo, A. Boch, M. Kujas, D. Seilhean, and M. Fink, "High power phased array prototype for clinical high intensity focused ultrasound: applications to transcortical and transcranial therapy," *Conf Proc IEEE Engineering in Medicine & Biology Society*, vol. 2007, pp. 234–7, 2007.
- [95] M. Pernot, J. F. Aubry, M. Tanter, J. L. Thomas, and M. Fink, "High power transcranial beam steering for ultrasonic brain therapy," *Physics in Medicine & Biology*, vol. 48, no. 16, pp. 2577–89, 2003.
- [96] F. Marquet, A. L. Boch, M. Pernot, G. Montaldo, D. Seilhean, M. Fink, M. Tanter, and J. F. Aubry, "Non-invasive ultrasonic surgery of the brain in non-human primates," *Journal of Acoustical Society of America*, vol. 134, no. 2, pp. 1632–9, 2013.

- [97] L. Marsac, D. Chauvet, B. Larrat, M. Pernot, B. Robert, M. Fink, A. L. Boch, J. F. Aubry, and M. Tanter, “MR-guided adaptive focusing of therapeutic ultrasound beams in the human head,” *Medical Physics*, vol. 39, no. 2, pp. 1141–9, 2012.
- [98] N. Ellens, A. Pulkkinen, J. Song, and K. Hynynen, “The utility of sparse 2D fully electronically steerable focused ultrasound phased arrays for thermal surgery: a simulation study,” *Physics in Medicine & Biology*, vol. 56, no. 15, pp. 4913–32, 2011.
- [99] S. Bobkova, L. Gavrilov, V. Khokhlova, A. Shaw, and J. Hand, “Focusing of high-intensity ultrasound through the rib cage using a therapeutic random phased array,” *Ultrasound in Medicine & Biology*, vol. 36, no. 6, pp. 888–906, 2010.
- [100] V. Khokhlova, P. Yuldashev, P. B. Rosnitskiy, A. D. Maxwell, W. Kreider, M. Bailey, and O. Sapozhnikov, “Design of hifu transducers to generate specific nonlinear ultrasound fields,” *Physics Procedia*, vol. 87, pp. 132–138, Dec. 2016.
- [101] B. I. Raju, C. S. Hall, and R. Seip, “Ultrasound therapy transducers with space-filling non-periodic arrays,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 58, no. 5, pp. 944–954, 2011.
- [102] L. Gavrilov, O. Sapozhnikov, and V. Khokhlova, “Spiral arrangement of elements of two-dimensional ultrasonic therapeutic arrays as a way of increasing the intensity at the focus,” *Russian Academy of Sciences Physics*, vol. 79, pp. 1232 – 1237, 2015.
- [103] P. Ramaekers, M. Ries, C. T. Moonen, and M. de Greef, “Improved intercostal HIFU ablation using a phased array transducer based on Fermat’s spiral and Voronoi tessellation: A numerical evaluation,” *Medical Physics*, vol. 44, no. 3, pp. 1071–1088, 2017.

- [104] P. Ramaekers, M. de Greef, R. Berriet, C. T. W. Moonen, and M. Ries, “Evaluation of a novel therapeutic focused ultrasound transducer based on Fermat’s spiral,” *Physics in Medicine & Biology*, vol. 62, no. 12, pp. 5021–5045, 2017.
- [105] J. F. Aubry, M. Pernot, F. Marquet, M. Tanter, and M. Fink, “Transcostal high-intensity-focused ultrasound: ex vivo adaptive focusing feasibility study,” *Physics in Medicine & Biology*, vol. 53, no. 11, pp. 2937–51, 2008.
- [106] S. A. Goss, L. A. Frizzell, and F. Dunn, “Ultrasonic absorption and attenuation in mammalian tissues,” *Ultrasound in Medicine & Biology*, vol. 5, no. 2, pp. 181–6, 1979.
- [107] Y. Y. Botros, E. S. Ebbini, and J. L. Volakis, “Two-step hybrid virtual array ray (VAR) technique for focusing through the rib cage,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 45, no. 4, pp. 989–1000, 1998.
- [108] F. Wu, Z. B. Wang, W. Z. Chen, H. Zhu, J. Bai, J. Z. Zou, K. Q. Li, C. B. Jin, F. L. Xie, and H. B. Su, “Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma,” *Annals of Surgical Oncology*, vol. 11, no. 12, pp. 1061–9, 2004.
- [109] J. Civalé, R. Clarke, I. Rivens, and G. ter Haar, “The use of a segmented transducer for rib sparing in HIFU treatments,” *Ultrasound in Medicine & Biology*, vol. 32, no. 11, pp. 1753–61, 2006.
- [110] H. L. Liu, H. Chang, W. S. Chen, T. C. Shih, J. K. Hsiao, and W. L. Lin, “Feasibility of transrib focused ultrasound thermal ablation for liver tumors using a spherically curved 2D array: a numerical study,” *Medical Physics*, vol. 34, no. 9, pp. 3436–48, 2007.
- [111] B. Quesson, M. Merle, M. O. Kohler, C. Mougenot, S. Roujol, B. D. de Senneville, and C. T. Moonen, “A method for MRI guidance of intercostal high

- intensity focused ultrasound ablation in the liver,” *Medical Physics*, vol. 37, no. 6, pp. 2533–40, 2010.
- [112] V. A. Khokhlova, S. M. Bobkova, and L. R. Gavrilov, “Focus splitting associated with propagation of focused ultrasound through the rib cage,” *Acoustical Physics*, vol. 56, no. 5, pp. 665–674, 2010.
- [113] E. Cochard, C. Prada, J. F. Aubry, and M. Fink, “Ultrasonic focusing through the ribs using the DORT method,” *Medical Physics*, vol. 36, no. 8, pp. 3495–503, 2009.
- [114] P. Gelat, G. Ter Haar, and N. Saffari, “Modelling of the acoustic field of a multi-element HIFU array scattered by human ribs,” *Physics in Medicine & Biology*, vol. 56, no. 17, pp. 5553–81, 2011.
- [115] P. Gelat, G. Ter Haar, and N. Saffari, “A comparison of methods for focusing the field of a HIFU array transducer through human ribs,” *Physics in Medicine & Biology*, vol. 59, no. 12, pp. 3139–71, 2014.
- [116] J. Gao, S. Cochran, Z. Huang, L. Shi, and A. Volovick, “Effect of focus splitting on ultrasound propagation through the rib cage in focused ultrasound surgery,” in *4th International Conference on Biomedical Engineering and Informatics (BMEI)*, vol. 4, pp. 2327–2330, 2011.
- [117] J. Gao, A. Volovick, R. Cao, G. Nabi, S. Cochran, A. Melzer, and Z. Huang, “Optimizing sonication protocols for transthoracic focused ultrasound surgery,” *AIP Conference Proceedings*, vol. 1503, pp. 146–151, Nov. 2012.
- [118] J. Gao, A. Volovick, Y. Pekelnny, Z. Huang, S. Cochran, and A. Melzer, “Focusing through the Rib Cage for MR-guided Transcostal FUS,” *AIP Conference Proceedings*, vol. 1481, pp. 94–99, Oct. 2012.

- [119] S. Qiao, G. Shen, J. Bai, and Y. Chen, “Transcostal high-intensity focused ultrasound treatment using phased array with geometric correction,” *Journal of Acoustical Society of America*, vol. 134, no. 2, pp. 1503–14, 2013.
- [120] M. Gyongy and C. C. Coussios, “Passive spatial mapping of inertial cavitation during HIFU exposure,” *IEEE Transactions on Biomedical Engineering*, vol. 57, no. 1, pp. 48–56, 2010.
- [121] C. Simon, P. VanBaren, and E. S. Ebbini, “Two-dimensional temperature estimation using diagnostic ultrasound,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 45, no. 4, pp. 1088–1099, 1998.
- [122] M. A. Lewis, R. M. Staruch, and R. Chopra, “Thermometry and ablation monitoring with ultrasound,” *International Journal of Hyperthermia*, vol. 31, no. 2, pp. 163–81, 2015.
- [123] C. Maleke and E. E. Konofagou, “Harmonic motion imaging for focused ultrasound (HMIFU): a fully integrated technique for sonication and monitoring of thermal ablation in tissues,” *Physics in Medicine & Biology*, vol. 53, no. 6, pp. 1773–93, 2008.
- [124] L. Curiel, Y. Huang, N. Vykhodtseva, and K. Hynynen, “Focused ultrasound treatment of VX2 tumors controlled by local harmonic motion,” *Physics in Medicine & Biology*, vol. 54, no. 11, pp. 3405–19, 2009.
- [125] Y. Wan and E. S. Ebbini, “Imaging with concave large-aperture therapeutic ultrasound arrays using conventional synthetic-aperture beamforming,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 55, no. 8, pp. 1705–18, 2008.
- [126] E. S. Ebbini, H. Yao, and A. Shrestha, “Dual-mode ultrasound phased arrays for image-guided surgery,” *Ultrasonic Imaging*, vol. 28, no. 2, pp. 65–82, 2006.
- [127] J. A. Jensen, S. I. Nikolov, K. L. Gammelmark, and M. H. Pedersen, “Synthetic aperture ultrasound imaging,” *Ultrasonics*, vol. 44, pp. e5–e15, 2006.

- [128] S. Nikolov, B. Tomov, and J. Jensen, “Real-time synthetic aperture imaging: Opportunities and challenges,” in *Proceedings 11th Asilomar Conference on Circuits, Systems and Computers*, pp. 1548 – 1552, Dec. 2006.
- [129] M. Karaman, L. Pai-Chi, and M. O. Donnell, “Synthetic aperture imaging for small scale systems,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 42, no. 3, pp. 429–442, 1995.
- [130] M. O’Donnell, “Efficient parallel receive beamforming for phased array imaging using phase rotation (medical US application),” in *IEEE Symposium on Ultrasonics*, pp. 1495–1498 vol.3, Dec 1990.
- [131] R. R. Entrekin, B. A. Porter, H. H. Sillesen, A. D. Wong, P. L. Cooperberg, and C. H. Fix, “Real-time spatial compound imaging: Application to breast, vascular, and musculoskeletal ultrasound,” *Seminars in Ultrasound, CT and MRI*, vol. 22, no. 1, pp. 50 – 64, 2001.
- [132] T.-J. Shan and T. Kailath, “Adaptive beamforming for coherent signals and interference,” *IEEE Transactions on Acoustics, Speech, and Signal Processing*, vol. 33, pp. 527–536, June 1985.
- [133] E. Lyka, C. M. Coviello, C. Paverd, M. D. Gray, and C. C. Coussios, “Passive Acoustic Mapping Using Data-Adaptive Beamforming Based on Higher Order Statistics,” *IEEE Transactions on Medical Imaging*, vol. 37, pp. 2582–2592, Dec 2018.
- [134] P. Stoica, Z. Wang, and J. Li, “Robust Capon beamforming,” *IEEE Signal Processing Letters*, vol. 10, pp. 172–175, June 2003.
- [135] R. N. Thomson, “Transverse and longitudinal resolution of the synthetic aperture focusing technique,” *Ultrasonics*, vol. 22, no. 1, pp. 9–15, 1984.
- [136] M. O. Donnell and L. J. Thomas, “Efficient synthetic aperture imaging from a circular aperture with possible application to catheter-based imaging,” *IEEE*

Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, vol. 39, no. 3, pp. 366–380, 1992.

- [137] N. Milen and V. Behar, “Simulated annealing optimization of multi-element synthetic aperture imaging systems,” in *Proceedings 11th Asilomar conference on Circuits, Systems and Computers*, pp. 585–592, June 2007.
- [138] L. F. Nock and G. E. Trahey, “Synthetic receive aperture imaging with phase correction for motion and for tissue inhomogeneities. i. basic principles,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 39, no. 4, pp. 489–495, 1992.
- [139] V. Behar and D. Adam, “Optimization of sparse synthetic transmit aperture imaging with coded excitation and frequency division,” *Ultrasonics*, vol. 43, no. 10, pp. 777–88, 2005.
- [140] C. H. Frazier and W. D. O. Brien, “Synthetic aperture imaging with a virtual source element,” in *Proceedings IEEE Ultrasonics Symposium. Proceedings*, vol. 2, pp. 1555–1558, 1996.
- [141] T. A. Shoup and J. Hart, “Ultrasonic imaging systems,” in *Proceedings IEEE Ultrasonics Symposium Proceedings.*, vol. 2, pp. 863–871, Oct 1988.
- [142] S. A. Ilyin, P. V. Yuldashev, V. A. Khokhlova, L. R. Gavrilov, P. B. Rosnitskiy, and O. A. Sapozhnikov, “Analytical method for evaluating the quality of acoustic fields radiated by a multielement therapeutic array with electronic focus steering,” *Acoustical Physics*, vol. 61, no. 1, pp. 52–59, 2015.
- [143] M. Itagaki, “Left ribs - bone model stl file from converted CT scan 1.0.0.” <https://www.embodi3d.com/files/file/12492-left-ribs-bone-model-stl-file-from-converted-ct-scan/>, 2018. Accessed: 30-06-2018.
- [144] S. Patil and B. Ravi, “Voxel-based representation, display and thickness analysis of intricate shapes,” in *Ninth International Conference on Computer Aided Design and Computer Graphics (CAD-CG’05)*, p. 6, Dec. 2005.

- [145] A. H. Aitkenhead, “Mesh voxelisation,” *MATLAB Central File Exchange*, 2017.
- [146] M. Zubair, S. Harput, and R. J. Dickinson, “3D Ultrasound Image Guidance and Therapy Through the Rib Cage with a Therapeutic Random Phased Array,” in *Proceedings IEEE International Ultrasonics Symposium (IUS)*, pp. 1–9, IEEE, 2018.

Appendices

Appendix A

Paper I

The following paper was presented in IEEE Ultrasonics Symposium, held in Kobe, Japan in Oct. 2018.

M. Zubair, S. Harput and R. J. Dickinson, "3D Ultrasound Image Guidance and Therapy Through the Rib Cage with a Therapeutic Random Phased Array," 2018 IEEE International Ultrasonics Symposium (IUS), Kobe, 2018, pp. 1-9, doi: 10.1109/ULT-SYM.2018.8579835.

Appendix B

Paper II

The following paper was presented in IEEE Symposium on Biomedical Imaging, held in Venice, Italy in April 2019.

M. Zubair and R. J. Dickinson, "Simulation of a Modified Multielement Random Phased Array for Image Guidance and Therapy," 2019 IEEE 16th International Symposium on Biomedical Imaging (ISBI 2019), Venice, Italy, 2019, pp. 1137-1140, doi: <https://dx.doi.org/10.1109/ISBI.2019.8759169>.