Transcranial Focused Ultrasound: New Methods and Applications

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Medical Biophysics
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Abstract
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Transcranial focused ultrasound is a rapidly-advancing therapeutic modality. In recent years, clinical trials have begun for a number of neurological conditions, including Essential Tremor, Obsessive Compulsive Disorder, and Neuropathic Pain. These clinical trials follow decades of intensive laboratory research programs to understand the mechanisms behind ultrasound interaction with brain tissue and to develop clinical devices that are capable of delivering the therapeutic ultrasound to a wide range of targets. Looking to the future, however, there remain many obstacles to the further implementation of focused ultrasound to a number of pathologies: limited steering range in the brain using a hemispherical array, secondary control over the spatial manifestation of the focus transcranially, and possible temperature-dependent acoustic effects.

Recent clinical data of thermal lesions from treatments of Essential Tremor using MR-guided transcranial focused ultrasound have shown that in many cases the focus is oblique to the main axis of the phased array. Chapter 3 presents the pertinent clinical data and attempts to explain the phenomenon. Numerical simulations were performed on clinical data to analyze the causes of the oblique focus and determine appropriate correction methods. It was found that the focal obliquity could be replicated with the numerical simulations to within $23.2 \pm 13.6^\circ$ of the clinical cases. It was then found that a major cause of the focal obliquity was the presence of sidelobes, caused by an unequal deposition of power from the different transducer elements in the array at the focus. In addition, it was found that a 65% reduction in focal obliquity was possible using phase and amplitude corrections in comparison to the clinical phase corrections alone.

Extending the results of Chapter 3, in Chapter 4 a technique was developed for the generalized rotation of a focus using a phased array of ultrasound transducers. In this chapter, the concept of focusing an ultrasound phased array is expanded to include a method to control the orientation of the focus using a Tikhonov regularization scheme. It is then shown that the Tikhonov regularization parameter used to solve the ill-posed focus rotation problem plays an important role in the balance between quality of focusing and array efficiency.

In Chapter 5, clinical data were analyzed to indicate a reduction in the induced energy-temperature...
efficiency relationship during clinical treatments at higher acoustic powers; to establish its relationship with the spatial distribution of the focal temperature elevation; and to explore its cause. Computer simulations, animal experiments, and clinical system tests were performed to determine the effects of skull heating, changes in brain properties and transducer acoustic output, respectively. The reduction in the energy-efficiency relationship during treatment was found to correlate with the increase in size of the focal volume at higher sonication powers (p-value < 0.01), supporting the hypothesis that transient skull and tissue heating causes acoustic aberrations leading to a decrease in efficiency. Changes in thermal conductivity, perfusion, absorption rates in the brain, as well as ultrasound transducer acoustic output levels were found to have minimal effects on the observed reduction in efficiency.

Chapter 6 focuses on the mechanical effects of focused ultrasound to open the blood-brain barrier. The restricted steering range of current clinical devices limits the regions of the brain that are considered treatable by ultrasound. A new array design was developed, therefore, to enable high levels of beam steering and increased transmission throughout the brain by using concave transducers normal to the outer-skull surface in a patient-specific configuration to target within the skull. Using pulsed ultrasound waves timed to arrive in-phase at the desired target, sufficient levels of acoustic energy were delivered for blood-brain barrier opening throughout.

In this thesis, these problems are introduced and solutions are described. Collectively, the developments achieved in this thesis could help to speed the implementation of transcranial focused ultrasound in clinic.
To my dad.
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Abbreviations

2D ............... 2-Dimensional
3D ............... 3-Dimensional
3T ............... 3-Tesla
Aβ ............... Amyloid β-Peptide
AC ............... Amplitude Corrections
AD ............... Alzheimer’s Disease
AP ............... Anterior-Posterior
APC ............. Amplitude and Phase Corrections
BBB .............. Blood-Brain Barrier
CFL .............. Courant-Friedrichs-Lewy
CNS .............. Central Nervous System
CT ............... Computed Tomography
dB ............... deciBel
DBS .............. Deep Brain Stimulation
EIS .............. Equal Intensity on the Skull Surface
EIT .............. Equal Intensity on the Transducer Surface
ET ............... Essential Tremor
FDTD ............ Finite Difference Time Domain
FFT .............. Fast Fourier Transform
GB ............... Gigabytes
IS ............... Inferior-Superior
LR ............... Left-Right
MR ............... Magnetic Resonance
NMR ............ Nuclear Magnetic Resonance
PAM ............ Passive Acoustic Mapping
PC .............. Phase Corrections
PD .............. Parkinson’s Disease
PRF ............. Pulse Repetition Frequency
RF .............. Radiofrequency
SNR ............. Signal-to-Noise Ratio
US .............. Ultrasound
VIM ............. Ventral Intermediate
Symbols

\( \alpha \) ................. Absorption
\( \alpha_L \) ................. Longitudinal Mode Attenuation
\( \alpha_S \) ................. Shear Mode Attenuation
\( \alpha_{Temp} \) ............. Temperature Sensitivity Coefficient
\( \alpha_{Tikhonov} \) ........ Tikhonov Regularization Parameter
\( \gamma \) ................... Gyromagnetic Ratio
\( \Delta \phi \) ................. Phase Shift between Two Magnetic Resonance (MR) Images
\( \epsilon \) .................... Strain Tensor
\( \eta \) ..................... First Viscosity Parameter
\( \theta \) ..................... Polar Angle
\( \lambda \) .................... Wavelength
\( \lambda_L \) .................. First Lamé Coefficient
\( \xi \) ....................... Second Viscosity Parameter
\( \xi_{Bulk} \) ............... Bulk Susceptibility
\( \rho \) ..................... Density
\( \rho_b \) .................... Density of Blood
\( \sigma_{Shield} \) ........... Shielding Constant
\( \sigma \) ..................... Stress Tensor
\( \Sigma \) .................... Weighted Sample Covariance Matrix
\( \phi \) ..................... Azimuthal Angle
\( \omega_{Larmor} \) ........... Larmor Frequency
\( \omega \) .................... Angular Frequency
\( \Im(x) \) ................. Imaginary component of \( x \)
The desired pressures at all control points

Constant Magnetic Field

Radiofrequency Magnetic Pulse

Speed of Sound

Specific Heat Capacity of Tissue

Specific Heat Capacity of Blood

Coefficient of Thermal Conductivity of Tissue

Treatment Efficiency, defined as $\frac{\Delta T}{P}$ for temperature rise $\Delta T$ and applied power $P$

Fundamental Frequency

Water Pulse Repitition Frequency (PRF)

Prescribed Transducer Oscillation Function

Obliquity of the Focus

Maximum Array Gain

Minimum Array Gain

Spatial Discretization Step Size

An $N \times K$ vector specifying the pressures at $K$ control points from $N$ transducers

The Rotated Analogue of $H$

Imaginary Number ($\sqrt{-1}$)

Normal Vector

Acoustic Pressure

Pressure Field after Performing Rotation

The pressure contribution from the $m^{th}$ transducer element in the array at point $x$

Maximum Focal Pressure Amplitude

Minimum Focal Pressure Amplitude

Absorbed Power Density

Position Vector

Rotation Matrix

Reference MR Image

Subsequent MR Image
\( t \) ................. Time

\( T \) ................. Temperature

\( T_b \) ................. Blood Temperature

\( T_{ref} \) ................. Reference Temperature for Thermal Dose Calculations (43°C)

\( u \) ................. Particle Displacement

\( W_b \) ................. Tissue Perfusion Rate

\( w_i \) ................. Temperature at \( i^{th} \) Voxel

\( V_i \) ................. The \( i^{th} \) Focal Volume

\( x_{\mu} \) ................. Voxel of Peak Temperature at Focus

\( x_i \) ................. Position of \( i^{th} \) Voxel
Chapter 1

Introduction

1.1 The Need for New Therapies for Neurological Conditions

According to Canada’s National Population Health Study of Neurological Conditions, an estimated 3.6 million Canadians are affected by fourteen neurological conditions, including brain tumours, Parkinson’s Disease (PD), and Alzheimer’s Disease (AD) [7]. The high incidence of neurological conditions negatively impacts the quality of life of many Canadians and brings with it considerable costs to the Canadian economy [7,8]. Consequently, a strong incentive exists from both public health and economic perspectives to develop efficient and lasting treatments for these neurological conditions.

Current treatments for neurological conditions are generally either invasive surgical procedures or pharmaceutical therapies [9–11]. Treatment is therefore not universally available; patients may be ineligible for surgical procedures or they may not tolerate the side effects of prescribed drugs or an effective treatment may not yet exist. For example, the surgical treatment of brain tumours often involves a highly-invasive craniotomy, with a number of exclusion criteria [12]. On the other hand, patients with Essential Tremor (ET) may be prescribed Alprazolam or Botulinum toxin A injections, which can cause serious side effects [11].

Although this thesis is primarily concerned with the technical aspects of focused ultrasound technology, the clinical motivation behind the work is essential to understanding the therapeutic role of focused ultrasound. Therefore, three general types of neurological conditions will first be introduced: movement disorders, brain tumours, and AD. The epidemiology, demographics, and clinical background of these neurological conditions will be discussed before studying the role that focused ultrasound can play in their treatment.

1.1.1 Epidemiology, Demographics, and Clinical Background of Movement Disorders, Brain Tumours, and Neurodegenerative Disorders

Movement Disorders

Although the term “Movement Disorders” encompasses a much larger range of conditions, the term will refer only to ET and PD in this thesis. These two conditions are currently actively-researched clinical targets for focused ultrasound therapy [13–16].

Both ET and parkinsonian tremor, the tremor associated with PD, are defined by involuntary, rhythm-
mic oscillations of a body part [9]. As a result, ET and parkinsonian tremor will often have very similar clinical presentations. In fact, ET and parkinsonian tremor were long believed to be the same disease [9, 17]. It was actually James Parkinson, the discoverer of PD, who distinguished between the two diseases in 1817 [17]. Even today, ET is often misdiagnosed as parkinsonian tremor and vice versa [9].

The cause of ET is still unknown, but a hereditary link has been established: 50% of ET sufferers have a positive family history of the disease [9]. As a result of its unknown physiological origins, a diagnosis of ET must be made from clinical observation. Subtle differences between the types of observed tremor as well as their manifestation with other pathological conditions are the prime methods of differentiation between these two similar diseases [9]. For example, a “pill-rolling”, resting tremor of the hand is much more common in PD than in ET. On the other hand, ET can be excluded by the clinical observation of rigidity, bradykinesia, and shuffling gait, which would confirm PD to the clinician [9].

There have been few studies on the prevalence of ET in Canada [18, 19]. An estimate in a rural community population performed in 1989 found that of 80 000 people, 0.008% had postural tremor, one of the manifestations of ET [20]. A study five years later, following similar methodology in the province of Saskatchewan, showed that the incidence rate of ET in patients aged over 65 is 14% [21].

On the other hand, the incidence rates of PD in Canada are much better established [7]. The Canadian National Population Health Study of Neurological Conditions performed a meta-analysis of the prevalence of PD among different age groups including 47 studies and found prevalence rates ranging from 40.5 cases per 100 000 population between the ages of 40-49 years old and 1 903 cases per 100 000 population in the 80+ age group [7].

Current Treatments of Essential Tremor  
Pharmacological treatments are usually the first line of attack when the clinician suspects ET. These treatments include Alprazolam, Botulinum A toxin, Gabapentin, Primidone, Propranolol, and Topiramate, among others [22]. The efficacy of these drugs, however, vary significantly between patients and specific tremors. In addition, all of these drugs induce some side effects, with the most common being fatigue, weakness, and decreased alertness. Another drug, Nadolol, does not induce substantial side effects when used at 120-240 mg a day [22]. Nadolol, however, has been given a Level C rating by the American Neurological Association, indicating only possible effectiveness in the treatment of ET [23].

Various studies have been conducted to analyze the varying efficacy of different drugs in treating ET [22,24,25]. It was recently recommended that better drugs need to be developed for the treatment of ET and controlled trials conducted to analyze patient safety when treating in the nucleus ventrointermedius and neighbouring subthalamic structures [10].

In addition, various surgical treatments for ET have been investigated for patients whose tremor is not sufficiently alleviated by pharmacotherapy [9]. Stereotactic thalamotomy results in over 80% of patients experiencing long-term, complete or near-complete alleviation of tremor symptoms [26]. Gamma knife radiosurgery has been investigated for the treatment of essential tremor, with a long-term follow-up study following patients for more than 60 months post-treatment [27]. Gamma knife radiosurgery, however, was recently found by the American Neurological Association to have a rating of Level U, indicating that there was insufficient evidence into its efficacy [23]. Deep brain stimulation (DBS) is also used in the treatment of ET [28]. DBS was found to have a Level C clinical rating, indicating the possibility for efficacy in the treatment of essential tremor [23]. Both of these treatments involve the targeting of regions of the brain supposed to be the cause behind the tremor.
Current Treatments of Parkinson’s Disease Although the non-motor symptoms of PD are treated using a variety of techniques [29], the motor symptoms are of interest here. In fact, the resting tremor, bradykinesia, rigidity, and loss of postural reflexes are considered the hallmarks of PD during diagnosis [30]. Initial pharmacological treatments of PD include neuroprotectants, agents that block glutamate-mediated toxicity, calcium channel blockers, anti-inflammatory agents, and steroids, among others [31]. These neuroprotectants protect or rescue vulnerable neurons from disease progression [31]. Beyond neuroprotective therapy, other drug therapies, typically involving Levodopa, offer significant clinical benefit [32]. There is substantial risk, however, that PD patients receiving Levodopa for 5-10 years will experience motor complications [31,33].

In addition, various surgical treatments exist for PD management, including thalamotomy, pallidotomy, and Deep-Brain Stimulation (DBS) [34]. In cases of severe asymmetric tremor, thalamotomy directed to the ventral intermediate (VIM) nucleus is highly successful in decreasing the tremor [34]. On the other hand, DBS is recommended for bilateral tremor [34].

Brain Tumours

In Canada, brain and central nervous system (CNS) cancers were the leading cause of cancer deaths in patients aged 0-29 years between 2008 and 2012, accounting for 35% of cancer deaths between the ages of 0-14 and 16% of cancer deaths between the ages of 15-29 [35]. There is a 0.8% lifetime chance of developing a brain or CNS cancer for males and a 0.7% lifetime chance for females. However, brain and CNS cancers accounted for 3.2% of all cancer deaths in males and 2.7% of all cancer deaths in females in 2017.

There are several major types of primary brain tumours which are categorized based on histology and location. These major brain tumour types include Gliomas, Meningiomas, Medulloblastomas, Glioschialgiomas, Schwannomas, and Chordomas [36]. The biology and treatment of brain tumours has been intensively studied during the twentieth and twenty-first centuries [37, 38]. For the purposes of this thesis, the genetic make-up and exact nature of the brain tumour will be of minimal significance to the results presented here: more relevant is the tumour’s location and volume within the brain.

The American Brain Tumor Association has also published a general overview for the layman of the various surgical options available for brain tumour patients [12]. The current range of treatments is vast and encompasses both highly-invasive traditional craniotomies for removal of operable tumors as well as gamma knife radiosurgery and pharmacological treatments. It is now standard practice to administer adjuvant chemotherapy with radiation therapy on many types of brain tumors. Previous meta-analysis studies have demonstrated its efficacy [39, 40]. Chemotherapies include Carmustine, Lomustine, and Methyl Iomustine, among others. Prior to administration of chemotherapy and radiation treatment, partial or full resection of the tumor mass is often attempted [40].

Alzheimer’s Disease

Alzheimer’s Disease (AD) is a neurodegenerative disorder and the most common type of dementia. Clinically, AD is characterized by a gradual loss of function for the patient.

In 2006, it was forecasted that by 2050, 1 in 85 people will be affected by the disease worldwide [41]. The same study found that a 1-year delay in disease onset and progression could reduce the global incidence by 9.2 million worldwide in 2050. According to a 2016 Statistics Canada Health Reports publication, the prevalence of dementia in Canadians aged 45 and older varied significantly between
private households and long-term residential care facilities. 0.8% of individuals aged 45 and older living in private households were affected by dementia and 45% in long-term residential care facilities were affected [42].

The World Health Organization 2012 report on Dementia indicated that beyond the individual afflicted with the disease, the disease had physical, psychological, social, and economic impacts on caregivers, family and society [43]. Besides the direct and indirect impact on health and society, AD also incurs substantial economic costs. The total worldwide costs of dementia were estimated at US$604 billion in 2010 [44]. For these reasons, small advances to disease treatment could have incredible benefits to human health.

AD is characterized physiologically by the presence of amyloid \( \beta \)-peptide (A\( \beta \)) in plaques, intracellular aggregates of tau protein, the formation of neurofibrillary tangles, and progressive neuronal loss [45]. Current pharmacotherapies for AD include cholinesterase inhibitors and the N-methyl-D-aspartate receptor (NMDA) receptor antagonist memantine, which provide symptom alleviation but do not help reduce the progression of the disease [46]. Although AD is not fully understood and treatments remain nascent, the current theory suggests that the buildup of A\( \beta \) in plaques in the brain may hold the key to lasting treatment [45, 47]. This theory, though, has been challenged recently based on inconclusive clinical trials [45]. Still, the desire to develop “disease-modifying” drugs that prevent the progression of AD beyond the pre-symptomatic stage remains [46].

1.1.2 The Potential Role of Focused Ultrasound in Neurosurgery

The reader should now be convinced that there is room for improvement in treating the aforementioned neurological conditions. This thesis will focus on technical developments that reinforce the potential role of focused ultrasound in bridging the gap between current interventions and better treatments. The potential for clinical success using focused ultrasound neurosurgery has been demonstrated in recent years through several landmark studies [13–16,48–50].

Focused ultrasound has potential to improve two broad forms of current neurological treatment: surgery and pharmacotherapy. In this thesis, the discussion of surgical methods will focus on improvements in current focused ultrasound interventions for the treatment of ET, PD, and brain tumours in Chapters 3, 4, and 5. In these discussions, the thermal effects of ultrasound will be of interest. The discussion of pharmacotherapy applications will occur in Chapter 6, with the development of a novel ultrasonic phased array for the opening of the Blood-Brain Barrier (BBB). In Chapter 6, the mechanical effects of ultrasound will be of interest, which allow for the ability to deliver neurotherapeutics which would not normally be able to traverse the BBB.

Current thermal applications of transcranial focused ultrasound aim to induce substantial temperature elevations (temperatures \( \gtrsim 60^\circ \text{C} \)) for short time periods [13–16,48–50] or mild temperature elevations (39.5 – 43°C) for longer durations, for therapeutic benefit [51]. A focused ultrasound beam can target with millimetre precision to cerebral targets in a highly-controlled manner [52]. As a result, thermal applications of focused ultrasound in the brain provide great promise to the future of neurosurgical interventions.

The mechanical effects of transcranial focused ultrasound promise an even larger range of applications. One such application is for the temporary disruption of the BBB to allow for the delivery of macromolecular therapeutics [53,54]. The BBB is a physical barrier between the brain and the cerebral circulation, which prevents the passage of large molecules, rendering drug delivery particularly challeng-
ing [54]. There have been a number of preclinical focused ultrasound studies performed on the feasibility of increasing the permeability of the BBB in animal models [55–58]. BBB disruption using focused ultrasound has also become the subject of ongoing clinical trials [59]. The ability of FUS to allow for the passage of these previously-impenetrable therapeutics opens the door for improved pharmacotherapeutic neurological treatment.

Other mechanical applications of focused ultrasound include inducing cell necrosis with the aid of contrast agents [60–62]; use of ultrashort pulses of ultrasound at very high peak negative pressures to induce cell lysis [63–65]; and the dissolution of clots using focused ultrasound for the treatment of stroke [66–73]. A more in-depth discussion of the mechanical and thermal applications of focused ultrasound is given in Section 1.2.5.

1.2 Background to MR-guided Focused Ultrasound

Given this clinical background and motivation for ongoing development of focused ultrasound therapy methods, it is useful at this point to introduce the more technical aspects of transcranial focused ultrasound. The following section focuses on the physics essential to understanding transcranial focused ultrasound propagation, the generation of ultrasound using ultrasonic transducers, current techniques for focusing ultrasound through the skull, the bio-effects of focused ultrasound, and monitoring techniques for transcranial therapies.

1.2.1 Ultrasound Basics

Ultrasound is defined as sound above a frequency of 20 kHz, which falls outside of the audible range for humans (20 Hz - 20 kHz). Although the range of ultrasound frequencies is quite large (up to 100 MHz), all ultrasound is governed by a few fundamental principles.

The propagation of ultrasound must occur through a medium; that is, ultrasound cannot propagate in a vacuum. For simplicity, propagation is best explained with reference to acoustic particles, which are considered to be subwavelength pieces of matter that interact in a well-defined way under ultrasonic excitation. An acoustic particle is a discrete volume much larger than the intermolecular spacing of the medium and much smaller than the wavelength of the ultrasound. In this thesis, the medium of propagation will entirely consist of water and biological tissue.

In addition, it is important to note that ultrasound behaves as a mechanical wave with both longitudinal and transverse wave components. Longitudinal waves are defined as oscillations in the direction of the wave velocity, while transverse waves are defined as oscillations perpendicular to the wave velocity. Longitudinal waves manifest in gases and fluids, whereas both types of waves can manifest in solid materials.

Longitudinal waves can be demonstrated using two simple models, as illustrated in Figure 1.1: temporal oscillations of a single particle; and relative rates of compression and rarefaction between neighbouring particles. The compression and rarefaction illustrates the transmission of the wave through layers of acoustic particles in the medium. Depending on the wavelength of the incoming ultrasonic wave, neighbouring particles will be in various stages of transmitting the wave along the wavefront path, and the transmission of the ultrasonic energy occurs as a theoretically lossless transfer of potential energy from one particle to the next. This lossless assumption is never valid in tissue, but is a good
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Figure 1.1: Different representations of longitudinal waves. The black circular acoustic particle in A and B oscillates in the \( x \) direction over time. This is represented temporally in A and spatially in B. The sound wave is indicated to travel from right to left by the arrow in B, resulting in the displacement of the particle from “1” to “2” to “3”.

Figure 1.2: An illustration of shear wave propagation within a solid described as a collection of connected acoustic particles. The wave propagation direction is defined by “1”. Longitudinal waves propagate along direction “1”. Shear waves propagate in direction “2”.

Shear waves are less intuitive, but are critically important considerations when propagating ultrasound through a solid medium, such as cranial bone \[74\]. Figure 1.2 illustrates the basic idea behind shear wave propagation. Both longitudinal and shear waves propagate along direction “1”. When considering a longitudinal wave, the particles will also oscillate along direction 1. However, the particles will oscillate perpendicular to the wave propagation direction, direction 2, when considering shear waves. The shear waves are an important consideration in transcranial ultrasound propagation for several reasons. First, shear waves generally attenuate at a higher rate than longitudinal waves, and therefore contribute to skull heating while resulting in little energy deposition at the target. However, several studies have investigated the potential advantageous role that shear waves could play in transcranial therapy \[75\] and imaging \[76\].

1.2.2 Ultrasound Transducers

Ultrasound transducers are devices that provide the link between an electrical driving signal and the generation of a mechanical wave. All of the results in this thesis assume that by modifying the electrical signals to appropriately designed transducers, different acoustic field patterns can be generated.
The conversion of electrical to mechanical energy by an ultrasound transducer is accomplished through the inverse piezoelectric effect, which was discovered by Jacques and Pierre Curie in 1880 [77]. A time-varying applied electric field oscillates the unit cell structure of a crystal, in turn generating mechanical waves [6]. The first application of the inverse piezoelectric effect to generate ultrasound was most likely during World War I by Langevin [6, 78].

A piezoelectric plate has electrodes leading to a radiofrequency (RF)-line connected to both the front and back surfaces. By convention, the majority of the ultrasound will be generated from the “front” surface [77]. The electrical excitation frequency is chosen such that the wavelength is double the thickness of the plate [6, 77] for maximum transmission. This frequency, \( f_0 \), is called the fundamental frequency of the transducer. The transducer can also be operated at odd-integer multiples of the fundamental frequency, \( f_0 \), but the efficiency of conversion between electrical and mechanical energy is reduced at these frequencies [77].

To give preferential transmission through the front face of the transducer, the acoustic impedance of the material in contact with the back face of the transducer is made much smaller than the backing of the front face [77]. Using this thinking, air-backed transducers are generally used in therapy transducers to maximize the output mechanical energy from the front surface of the transducer [77, 79]. By constructing an array of ultrasound transducers and generating individual electrical signals stimulating the inverse piezoelectric effect on each transducer, it becomes possible to target the ultrasound much more flexibly than the geometry of the array would normally allow.

In the last several decades, there have been many advances in ultrasound transducer fabrication technology [80–82] and driving systems for ultrasound transducer arrays [83–85] for a variety of transcranial therapy applications. By increasing the number of transducer elements in an array and allowing for various transducer excitation methods, it has become possible to increase the steering range of focused ultrasound in the brain and permit more precise focal control.

1.2.3 Ultrasound Imaging

Before delving into the therapeutic applications of ultrasound, it is informative to introduce ultrasound imaging. The therapeutic and imaging applications of ultrasound developed together throughout the twentieth century, and therefore many of the developments between the two applications crossed over [86, 87]. Although an in-depth overview of all the technologies associated with ultrasound imaging is outside the scope of this thesis, the imaging methods that relate to phased array ultrasonics are relevant.

Conventional ultrasound imaging is characterized by the transmission and reception of an ultrasound wave by a transducer. Using a variety of signal processing techniques, it becomes possible to infer the nature of human tissue based on the characteristics of the received wave and a precise knowledge of the transmitted wave. There are a variety of ultrasound imaging methods, which are conventionally categorized as A-, B-, C-, and M-Modes.

A-Mode imaging involves the transmission and reception of a pulse-echo signal and is displayed as amplitude-versus-time or amplitude-versus-distance [6]. The 2-dimensional (2D) corollary of an A-Mode scan is the B-Mode scan, where a sequence of scan lines is stacked to form a 2D image. Due to advances in computer processing speeds and ultrasound technology, even 3- [88] and 4-dimensional [89] scans are now possible in this manner.

C-Mode ultrasound imaging is analogous to B-Mode imaging, except that the images formed are perpendicular to the B-Mode image. C-Mode imaging has the advantage of superior resolution to
conventional B-Mode imaging. C-Mode images are formed from a specific depth on a A-Mode line, followed by 2D scanning of the transducer [6].

A-, B-, and C-Mode imaging work under the assumption of a static medium to construct an image. M-Mode (Motion) imaging, which was developed by Edler and Hertz in 1954 for cardiac applications [90], allows for the imaging of moving targets. By transmitting the same ultrasound pulses to a moving target – such as the heart – it is possible to map the spatial variation in motion over time.

The advent of ultrasound arrays stemmed from the development of antenna array technology at the turn of the twentieth century [6]. The use of ultrasound transducer arrays, as opposed to a single transducer, transformed both imaging and therapeutic ultrasound. It became possible to break free from the geometric constraints imposed by a single transducer and improve focusing quality through complex media. Following the development of the first ultrasound array [91], the first medical ultrasound arrays, which were developed for ophthalmic imaging, arose in 1965 [92]. Further developments in the 1970s [93, 94] led to the predecessors of the modern ultrasound imaging arrays seen in clinical settings today [6, 95, 96].

In addition to the conventional methods of ultrasound imaging, more advanced imaging methods have been developed [97], including plane-wave ultrasonography [97–99], shear imaging [100–103], functional imaging [104, 105], vibro-acoustic spectrography [106], radiation force imaging [107], and elastography [98, 108–111]. Using these techniques, it is possible to monitor thermal therapy using focused ultrasound [100, 109, 112], rapidly scan a volume of tissue [97], image tuning forks with different resonance frequencies [106], and analyze changes in the brain [104, 105].

1.2.4 Therapeutic Ultrasound

As mentioned, ultrasound has therapeutic applications in addition to the imaging applications discussed in the previous section. Although there are therapeutic applications of unfocused ultrasound beams [113], therapeutic applications of focused ultrasound are the major focus of the thesis.

Focused ultrasound can be used to deposit energy in tissue in a targeted and controlled manner [77]. Since the early experimental tests and theoretical developments, focused ultrasound is currently applied to a wide range of pre-clinical and clinical uses, and research is being conducted to treat almost every region of the body [114]. Some current applications include a range of neurological applications [13, 48, 51, 58, 115–117], the treatment of uterine fibroids [118–121], prostate cancer treatment [122–124], diseases of the liver and kidney [125–129], bone metastases [130–132], and the ablation of cardiac tissue for the treatment of abnormally conducting cardiac muscle tissue [133, 134].

In addition to the range of anatomical targets in the body, there are a wide variety of mechanisms of action for therapeutic ultrasound. These applications range from low energy, contrast agent-enhanced therapy [135, 136], to thermal ablation techniques [77], to high power lithotripsy and histotripsy applications [72, 137–141]. In the following section, the mechanisms of action will be described in more detail, by focusing on the mechanical and thermal effects of a focused ultrasound beam.

1.2.5 The Bio-Effects of Ultrasound

Mechanical Effects of Ultrasound

The mechanical effects of ultrasound rely on the interaction of the ultrasound with tissue at both the target and in the intervening tissue. Ultrasound can induce these mechanical effects independently
The most important distinction relevant to this thesis is the difference between high- and low-power ultrasound. Low-power ultrasound is predominantly a linear phenomenon, whereas high-power ultrasound is characterized by nonlinear effects on tissue.

High- and low-power ultrasound can induce mechanical effects with widely divergent results. Low-power mechanical therapies currently centre around neuromodulation [143,146,147] and the temporary opening of the BBB for a range of therapeutics, including the delivery of macromolecular therapeutics [54], targeted genes [148], natural killer cells [116], and ultrasound-stimulated drug release [149,150]. In these cases, the temporary increase in the permeability of the BBB is achieved using bursts of ultrasound that interact with microbubble contrast agents injected into the blood stream. Although the mechanism of ultrasonic action to open the BBB is not fully understood, strides forward are being made [151,152].

High pressure amplitude exposures, on the other hand, are used in sonothrombolysis for the breaking apart of clots [71,153–155] and histotripsy for the fractionation of tissue [72,138,156,157]. In both low power and high power cases mentioned above, the thermal effects are not considered significant. In low-power applications, any accumulation of thermal energy is rapidly dissipated by blood perfusion. In high-power applications, shorter, lower duty cycle pulses on the order of a wavelength are used, preventing any accumulation of thermal energy, assuming a sufficiently low duty cycle.

Thermal Effects of Ultrasound

The thermal effects of ultrasound applied to the body rely on the absorption of ultrasound energy in the tissue, resulting in a temperature rise. This temperature elevation can cause levels of heating in the hyperthermia range (39.5 – 43°C) [158], which can work as an adjunct to radiation therapy [51] and has other therapeutic effects [159]. It is also possible to achieve ablative temperatures (> 60°C) with focused ultrasound, which causes thermal tissue necrosis.

The thermal effects can be quantified by both the temperature rise as well as the thermal dose [160], a concept analogous to radiation dose in radiotherapy which seeks to characterize tissue damage from heat exposure as a function of both time and temperature. Using these metrics, it becomes possible to relate the desired bio-effects of ultrasound treatments across patients and different tissue types. For instance, a thermal dose of 240 equivalent minutes at 43°C signifies complete cell death in all tissue types [160].

The ultrasound absorption coefficients of different parts of the body vary significantly [1]. Of the highest importance here is the large difference in absorption between brain tissue (low absorption) and cranial bone (high absorption). Because it is highly desirable to elevate the temperature in an efficient manner in the neurological target, the high absorption in bone becomes a potential safety issue. This idea will be expanded on in Chapters 3 and 5.

1.2.6 Focusing Ultrasound Through the Skull for Therapy

The transmission of high-intensity ultrasound through the skull had been considered a challenge for decades since the mid-twentieth century. It was initially found that treatment through the skull was not feasible [161] and ultrasound treatments following these preliminary studies required removing the cranial bone to treat the brain. Using a four-transducer array, targeted lesions were performed in animal brain [162,163] and humans [164].
Figure 1.3: An illustration of the focusing of a hemispherical array to a central brain target using independently-driven ultrasound transducers. (a) First, the wave is propagated backwards from the target, and the phases recorded on all the transducer elements. (b) The phases are then inverted and the focus is created at the target. In the case of time-reversal, the full signal received on each element in (a) is time-reversed before being forward-transmitted in (b).

The development of transcranial focused ultrasound began with the first experiments which demonstrated that it was possible to create lesions in a lucite block by transmitting ultrasound at high enough powers [165]. Once the acoustical properties of human skull [74] were characterized, experiments involving transcranial transmission to a feline brain [166] demonstrated the first ablation in live brain tissue through a human skull.

Early experiments were performed using between one and four focused transducers [165, 166]. However, setups using few transducers caused difficulties in focusing the beam, and caused high levels of skull heating. The use of phased arrays of ultrasound transducers to focus inside the skull proved essential. Phased arrays consist of a set of ultrasound transducers in some configuration with independent driving controls. Phased arrays had been used previously with antennas [167], radar [168], optics [169], and imaging ultrasound [6]. Phased array ultrasonics has advantages over a single ultrasound transducer because the increased number of degrees of freedom allows for electronic steering of the beam, the compensation for acoustic aberrations when propagating through heterogeneous media, and dissipation of heat load across more of the skull surface. Phased arrays required several innovations for therapeutic applications of ultrasound through the skull, however.

The development of a hemispherical array to propagate ultrasound through the skull was a landmark achievement, compensating for the acoustic heterogeneity of the skull bone [52, 170–172], maximizing the surface area of the skull used for transmission [173], and minimizing the deposition of acoustic energy in the cranial bone. The deposition of acoustic energy leads to heating and therefore potential thermal damage to tissue on the inner and outer surfaces of the skull [79, 164, 174–180].

There are a variety of techniques which have been developed over the years for computating the
phase and amplitude corrections to correct for skull-induced acoustic aberrations. Figure 1.3 illustrates the general process of determining the phase corrections through the skull using any compensation technique. First, the ultrasound waves are propagated backwards from the target numerically [181], through an implanted ultrasound source [182,183], or using a bubble cloud [184], as illustrated in (a). Next, the phase delays on each element are read and the phases inverted to generate the temporal signals to be propagated forward, as in (b). The resulting ultrasound waves will then converge at the focal point.

The first technique developed for correcting transcranial aberrations is the “time reversal” method [183,185–195]. The advantage of the time reversal methodology stems from the ability to invert a signal over all incoming frequencies, so that the inverted wave is in-sync with all frequencies represented in the spectrum. The time reversal technique relies on mathematical reversibility of the signal in time, however. As a result, the solutions are technically only fully valid for non-attenuating media, although excellent phase corrections can still be obtained.

The second technique, which is implemented into clinical transcranial focused ultrasound phased array setups today, is the use of time-delay summation to compensate for the linear acoustic propagation of a single frequency of ultrasound [196,197]. The time-delay summation technique uses the mapping of acoustic densities derived from CT scans to acoustic parameters to generate time delays non-invasively [198–202]. This technique is a sufficient approximation of ultrasound transmittance through bone in current clinical therapies because higher harmonics are not generated at sufficiently low powers and generally become attenuated before transmitting.

Using the technological innovations to focus a beam through the skull non-invasively, pre-clinical testing was performed to study the effectiveness of focusing [175,203,204] and the safety concerns arising from skull heating [4,174,175]. Recent clinical trials, including the treatments of ET [13,14,16], obsessive compulsive disorder [205], PD [15], brain tumors [48], and neuropathic pain [49], have now demonstrated the clinical promise of MR-guided focused ultrasound as a non-ionizing, non-invasive neurosurgery tool. A range of potential future applications of transcranial focused ultrasound have also been described in the literature, including the treatments of trigeminal neuralgia [206], AD [58,117], PD [50], epilepsy [207], third ventriculostomy [139], and sonothrombolysis for the treatment of stroke [68,71,153,208].

1.2.7 Treatment Monitoring in Transcranial Focused Ultrasound

The ability to focus ultrasound through the skull is only one half of the provision of efficient and safe therapy. It is also critically important that the clinician administering the therapy is aware of the neurological targets and that the potential safety risks of the treatment are minimized. There are two essential treatment monitoring methods in current clinical applications of transcranial focused ultrasound: Magnetic Resonance (MR) thermometry and cavitation detection. By using these two methods, it is possible to provide effective and safe feedback to the treatment by determining the treatment outcomes as well as providing warning of potential adverse events. Although direct application of these techniques will not be covered in this thesis, these two methods are described below to provide clinical context.

Magnetic Resonance Thermometry

MR imaging was initially discovered in 1946 [209,210] and applied to condensed matter physics. The first MR image using linear gradients was formed in 1973 [211]. MR is now present in hospital imaging
departments around the world. In the physics and chemistry fields to this day, Nuclear Magnetic Resonance (NMR) is the employed term, whereas Magnetic Resonance (MR) is the term used in imaging and medical physics [212] and is therefore the term used throughout this thesis.

The generation of MR images, despite widely-varying applications, proceeds along the same lines in every case. A strong magnet, as used in conjunction with clinical focused ultrasound systems, maintains a constant magnetic field, $B_0$, at all times. This static field aligns the magnetic moment vectors predominantly of hydrogen nuclei in water molecules of biological tissues. These magnetic moments resonate at a fixed frequency, termed the Larmor Frequency, $\omega_{\text{Larmor}}$, according to the relationship

$$\omega_{\text{Larmor}} = \gamma B,$$

where $B$ is any magnetic field and $\gamma$ is the gyromagnetic ratio of the hydrogen nucleus. In the case of an MR machine before a scan begins, $B = B_0$. The generation of MR images, however, requires the use of spatial gradients in addition to $B_0$ to selectively scan a specific region of space. By adding a sequence of radiofrequency magnetic pulses, $B_1$, it is then possible to infer PRF-dependent differences in the scanning region to generate an image. These MR scans follow the same procedure: excitation of the field, measurement of the signal, relaxation, followed by a return to the steady state.

In addition to the generation of static images, MR has also been used to map temperature changes over time since the early 1980s [213, 214]. MR thermometry, as it is called, relies on the temperature-dependent properties of MR signal contrast parameters. As a result of these temperature-sensitive properties, it becomes possible to map temperature changes over time by subtracting sequential MR images from baseline imaging data acquired before ultrasound energy is deposited in tissues [77, 204].

The most common method of MR thermometry used in monitoring transcranial focused ultrasound is based on the temperature sensitivity of the water proton chemical shift [77]. Since the initial theoretical and experimental results presented in 1966 characterizing the water proton chemical shift at different temperatures [215], the proton chemical shift was calibrated to the change in temperature for focused ultrasound surgical applications [216]. Although we will only discuss temperature mapping based on the proton resonance shift of water, it must be noted that other techniques of MR-based thermometry include exploiting the temperature-sensitivity of the spin-lattice relaxation time and the temperature sensitivity of the molecular diffusion coefficient of water [77].

In focused ultrasound applications, MR thermometry relies on mapping proton resonances throughout space and time. Changing temperatures in tissue result in changes to the molecular structure of water; at higher temperatures, there are fewer hydrogen bonds between adjacent water molecules. This decreased overall hydrogen bonding leads to increased bonding within the water molecule between the hydrogen and oxygen. This central oxygen molecule then shields the hydrogen atoms from the induced magnetic field, and the Proton Resonance Frequency (PRF) will shift [77].

More formally, the relationship between the water PRF shift, which will be denoted $\Delta f_{\text{PRF}}$, and the change in temperature, denoted $\Delta T$, is described by [77]

$$\Delta f_{\text{PRF}} = \gamma B_0 \alpha_{\text{Temp}} \Delta T,$$

where $\gamma$ is the gyromagnetic ratio, $B_0$ is the static magnetic field, and $\alpha_{\text{Temp}}$ is the temperature sensitivity coefficient. The value of $\alpha$ is mostly affected by temperature-dependent changes in the shielding constant, termed $\Delta \sigma_{\text{Shield}}$, with some shift contribution from the change in bulk magnetic susceptibility,
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termed $\Delta \xi_{Bulk}$ [77].

The phase shift, $\Delta \phi$, between two images as a result of a temperature-induced shift in the resonance frequency, $\Delta f_{PRF}$, can be written as [77]

$$
\Delta \phi = 2\phi \Delta f_{PRF} \cdot TE = 2\pi \gamma B_0 \alpha_{Temp} \Delta T \cdot TE,
$$

(1.3)

where TE is the echo time (measurement time) of the thermometry imaging sequence. Using the phase differences between subsequent images, temperature differences between a reference image ($S_0$) and a subsequent image ($S_1$) can be measured using Equation 1.4:

$$
\Delta T = \frac{\Delta \phi}{2\pi \gamma B_0 \alpha_{Temp}} = \frac{\arg(S_0^* S_1)}{2\pi \gamma B_0 \alpha_{Temp}}.
$$

(1.4)

The strengths of this phase difference technique for MR thermometry come from the speed at which the images can be obtained, which allows for real-time thermometry monitoring in clinical treatments [216,217] (3.5 s).

Cavitation Detection

Another technique used during the application of focused ultrasound to the brain is acoustic cavitation detection. The application of the high acoustic powers required for thermal therapies at the relatively low frequencies used clinically can cause cavitation events to occur [218]. Acoustic cavitation is the mechanical excitement of a gas bubble by an applied acoustic field [218, 219]. Cavitation events during the course of a thermal ablation treatment are potentially dangerous to the patient if undetected and uncontrolled [220,221] and can result in vascular damage in the brain. As a result, cavitation detectors are integrated into almost all focused ultrasound systems [77]. The detection of a cavitation event above a threshold halts the treatment, preventing any damage from occurring [77].

Cavitation is generated at substantially high acoustic pressures when sonicating ultrasound through tissue. There is a nonlinear relationship between the applied acoustic pressure and the threshold amplitude onset of the cavitation signal. In low-power, high-frequency applications of focused ultrasound, the cavitation issue becomes minimized, whereas for high-power, low-frequency applications, as is the case with many FUS clinical therapies, cavitation is likely and must be monitored [221] to ensure treatment safety. The frequency- and pressure amplitude-dependence of cavitation events was described in dog thigh [222], allowing for the fast determination of these thresholds for each application. Further studies sought to image these cavitation events [223].

Controlled cavitation, in contrast to the unintended cavitation described above, can be used as a therapy technique. In particular, cavitation can be used at high energies to cause tissue fractionation [139,141,156,224–226], whereas cavitation can be used to temporarily open the BBB at lower energies [53,145,227–229].

A cavitation detection technique called Passive Acoustic Mapping (PAM) [230] is an area of research being developed for the increased safety and efficacy of focused ultrasound therapy. Rather than simply detecting whether a cavitation event has occurred, the use of PAM seeks to localize the cavitation event and map the activity in space. PAM has been applied to transcranial ultrasound [85,231–233] and with advances in computer processing speeds, may be integrated into clinical systems in the near future.
1.2.8 Current Commercial Clinical Devices

The treatment of the brain using focused ultrasound has proceeded through several iterations of therapy devices. Recently, a clinically-approved ultrasound device has been developed and is the subject of ongoing trials. As much of this thesis will focus on replicating, analyzing, and modifying the treatment parameters of this clinical device, it is essential to introduce the specific device technology.

The ExAblate 4000 (Insightec, Haifa, Israel) is an ultrasound transducer phased array consisting of 1024 independently-driven ultrasound transducers in a 15 cm radius hemispherical configuration (Figure 1.4). The image in Figure 1.4 was taken prior to experimental validation work performed using MR thermometry, and as a result an ex vivo skull filled with phantom material [234] is shown affixed to the device.

There are two versions of the device, enabling operation with transducers at either 230 or 650 kHz. The ExAblate brain arrays for transcranial focused ultrasound therapy are a natural evolution from the work over several decades (since the 1990s) when the first transcranial hemispherical arrays were constructed with the goal of causing thermal ablation [52, 204]. The 650 kHz device is generally used for thermal ablation studies in clinical centres worldwide [13–16, 49, 50], whereas the 230 kHz device is currently in the pre-clinical [145] and clinical [235] stages of testing for BBB disruption studies. As a result, the 650 kHz device is described in this thesis, as pertinent to the work undertaken in Chapters 3 and 5.

Clinical treatments using the ExAblate array proceed through a series of sequential steps. First, pre-
treatment imaging is performed on the patient using Computed Tomography (CT) and MR imaging. The CT images provide excellent bone density contrast, to determine acoustic properties of the patient’s skull [201], whereas the MR images provide excellent soft tissue contrast and allow the clinician to plan the treatment and determine potential treatment targets.

MR scans on the day of the treatment occur after the patient is fixed with a stereotactic frame to the treatment device (see Figure 1.5 for an illustration of the MR images obtained) and the co-registration of the CT images and the therapy device are then performed manually by the clinical staff. The treatment software then plans the treatment parameters depending on the targets selected by the clinician.

Figure 1.6 illustrates the interactive clinical interface of the ExAblate array. The thermometry images are obtained at 3.5-s intervals throughout the treatment. The images at each time point are illustrated in panel A and the peak and mean voxel temperatures over the course of the treatment are plotted in panel B. In addition to the therapy transducers, which are illustrated schematically in panel D, the ExAblate system has integrated cavitation detectors. The cavitation spectrum during this particular treatment is illustrated in panel C. The narrow peak observed in the spectrum comes from the sonication frequency (650 kHz) of the therapy transducers. Figure 1.6 is performed on an \textit{ex vivo} skull filled with phantom material [234], whereas Figure 1.7 illustrates the temperature rise in a clinical case, showing both a coronal thermometry imaging slice (A) and the temperature rise over the course of a single sonication (B).

Chapters 3 and 5 will analyze data obtained from clinical trials using the ExAblate array. The next section discusses the seminal transcranial focused ultrasound treatment and clinical focus of Chapters 3 and 5.

1.2.9 Focused Ultrasound Thalamotomy for Essential Tremor

In 2012, clinical trials of focused ultrasound treatments for ET commenced [13, 14]. Treatment sites around the world have now treated hundreds of patients and the Insightec ExAblate 4000 is clinically-approved for this pathology [236]. Although the success of these treatments has led to investigation into potential future treatments using the same technology [206, 237], the trials have led to interesting, unforeseen findings that provide some of the inspiration for this thesis.
Chapter 1. Introduction

Figure 1.6: A screenshot of the Insightec ExAblate 4000 clinical interface. (A) Real-time MR thermometry images obtained during the course of treatment, (B) The mean and peak temperature rises at the intended target, (C) the cavitation spectrum, and (D) the distribution of acoustic powers among the array elements.

Figure 1.7: (A) A coronal MR thermometry map of the entire treatment domain obtained during a clinical trial of MR-guided FUS for the treatment of ET. (b) The average (dashed line) and peak (solid line) temperatures obtained over the course of a 12-s sonication during the same treatment.
Chapter 1. Introduction

Figure 1.8: 1 day post-treatment gradient echo MR image of a patient treated for ET by focused ultrasound thalamotomy. The site of the thermal lesion is indicated by the white arrow.

The target in the treatment of ET is the site of the Ventral Intermediate (VIM) nucleus, which is located in the thalamus. The location of the VIM nucleus is determined by the neurosurgeon from anatomical landmarks. The treatment planning then occurs for the clinically-indicated target and sonications of increasing power are administered with MR thermometry feedback under the direction of the neurosurgeon. Low-power sonications are first used to confirm registration and positioning of the target without causing thermal damage to the tissue. Higher power sonications are then administered to cause thermal ablation at the target. Before, during, and after treatment, the patient is fully awake and his/her tremor is consistently being evaluated by the clinician. The resulting lesion at the site of the VIM nucleus is illustrated 1 day after treatment in Figure 1.8.

Although the treatment of ET using focused ultrasound has paved the way for future transcranial ultrasound therapies in the brain, there remain substantial obstacles to the treatment of new targets. In the next three sections, these limitations will be introduced. These limitations provide the entire motivation for this thesis.

1.3 Clinical Limitations and Motivation

Focused ultrasound has several advantages over other neurosurgical interventions: it is non-invasive, it uses non-ionizing radiation (the ultrasound itself), and provides clinicians with real-time feedback of the progress being made. However, the reliance on mechanical waves which aberrate and attenuate in biological tissue comes with certain problems. These problems are not insurmountable, but they do require careful control.
1.3.1 Skull Heating

Skull heating is a substantial issue in the deposition of focused ultrasound transcranially due to the high rate of acoustic absorption in bone. This acoustic absorption leads to temperature rises in the skull which can cause thermal damage in the cranium and adjacent tissues – especially at the high acoustic powers (500 - 1200 W) required for thermal therapy. Skull heating is illustrated with the white arrow in panel (a) in Figure 1.9 with experimental MR thermometry images obtained using an ex vivo skull and tissue-mimicking phantom material [234]. In this image, the imported CT image is shown in green and overlayed on the MR thermometry image to illustrate the heating relative to the position of the skull.

The issue of skull heating was first highlighted by Connor and Hynynen [4]. Further studies were conducted to quantify the temperature rise as a function of power [174] and to correct for this effect using power amplitude controls [175]. Skull heating, though, was found to be less of a concern at lower frequencies (220 kHz) [178]. Although early innovations sought to use the maximum available skull surface to minimize heating at any given point [170, 173], the instances of skull heating so far observed in clinical trials suggest that future work in this area is still needed to improve treatment safety.

Heating at the base of the skull is an additional concern. By targeting the ultrasound close to the skull base, the high heating propensity of bone has been found to limit the ability to treat [238]. The risk of thermal damage to surrounding structures is nontrivial. Skull base heating is illustrated in panel (b) in Figure 1.9 at a target much closer to bone than in panel (a). Techniques for the reduction of heating at the base of the skull include a strain-elimination method in bone [238], as well as an on-off power scheme to reduce the direct application of ultrasound in line with the transducers [206]. Both these techniques exploit the degrees of freedom granted by a hemispherical 1024-element array to control the acoustic field away from the focus. The potential downsides of these methods include the long time required to perform the computer simulations for the corrections, and the potential issues in the application at the
base of the skull, as well as the potential for high levels of skull heating. The treatment of these targets still remains an open challenge.

1.3.2 Off-Centre Targets

The targeting of off-centre locations in the brain with MR-guided focused ultrasound remains challenging. Although there are a number of desired targets deep and lateral in the brain [206,237], the issues of skull heating (described above) and focal control (described below) remain substantial obstacles. As a result, the treatment envelope [239] of focused ultrasound in the brain remains limited.

The treatment of deep and lateral targets is not unique to focused ultrasound, however. The American Brain Tumor Association makes the distinction between operable and inoperable brain tumours [12]. Deep tumours located close to the thalamus and brain stem, in particular, remain generally inoperable tumours due to the high risk of brain damage and other complications resulting from surgery. The ideal outcomes, then, would see the treatment range of focused ultrasound overlap with some of these inoperable targets and allow for the treatment of these tumour locations.

1.3.3 Control of the Focus

In addition, for clinical applications of focused ultrasound where significant temperature elevations are involved, complete control of the deposition of heat in the brain is imperative for safe and effective therapy. The close proximity of critical nerve structures and functional areas in the brain to any given target render extremely precise control even more important, to avoid peripheral thermal damage. Assuming that a hemispherical phased array were to sonicate to the geometric focus through a homogeneous medium, it is expected from symmetry that the focus would be oriented along the main axis of the array. Previous studies in transcranial focused ultrasound have investigated the targeting accuracy of brain therapy [240], by comparing the relative locations of the target focus and the actual focus in the three Cartesian directions. Various studies from other brain therapy modalities, such as gamma knife radiosurgery, have been performed to determine the targeting accuracy [241–244], and to discuss the effects of errors in targeting [244]. It is argued here that the obliquity of the focus observed in transcranial focused ultrasound treatments is an important indicator of targeting accuracy. The spatial orientation of the deposition of heat in the brain should be studied in a similar fashion to the effects of radiation dose contours in radiosurgery.

1.3.4 Treatment Efficiency at Higher Acoustic Powers

During the course of transcranial focused ultrasound treatment for ET, multiple ultrasound sonications are performed to cause a small focal thermal coagulation of brain tissue at the anatomically-determined location of the VIM nucleus [13]. The power of the repeated sonications is gradually increased over the course of treatment to achieve focal ablation of the targeted brain tissue. Theoretically, it is expected that the temperature will rise linearly with increasing acoustic power, because these short-duration sonications are not substantially influenced by changes in the blood perfusion [245]. However, it has been observed in recent clinical trials that the relationship is more complicated – implying that the existing scientific understanding of focused ultrasound treatment delivery needs to be modified. In this thesis, clinical data are presented where the high power sonications during many ET treatments do not
follow the expected linear relationship and the power-temperature efficiency decreases over the course of the treatment. Work undertaken to explain these effects will also be presented.

1.4 General Aims

With the current clinical limitations of transcranial focused ultrasound described above, the aims of the thesis are as follows:

1. to control the distribution of acoustic energy at the focus during transcranial focused ultrasound surgery and to develop a framework to allow for the rotation of single and multiple foci in any focused ultrasound phased array application;

2. to develop a scientific understanding of the unexpected temperature profiles generated during transcranial focused ultrasound thalamotomy for ET; and

3. to design a novel, patient-specific phased array for the opening of the BBB using focused ultrasound.

1.5 Specific Aims

The General Aims of this thesis can be more precisely stated as Specific Aims as follows:

1. to solve the focus rotation inverse problem using a regularization scheme (Chapters 3 and 4);

2. to analyze independently the effects of brain tissue heating, cranial bone heating, and transducer performance on the clinical observation of the decrease in acoustic energy-temperature at higher acoustic powers (Chapter 5); and

3. to compare the performance of a conformal, patient-specific phased array of ultrasound transducers to a conventional hemispherical array to generate acoustic fields which would allow for BBB opening (Chapter 6).

With these developments, it should become possible to improve the safety and efficacy of clinical treatments of ET using focused ultrasound and to allow for the disruption of the BBB at all locations in the brain using a novel, patient-specific phased array.

1.6 Outline

This thesis is divided into seven chapters. The first chapter has provided introductory motivation; the second chapter introduces the mathematical background and the numerical methods used in the thesis. The third, fourth, fifth, and sixth chapters describe the efforts made towards the three aims listed in Section 1.5 above. Finally, the seventh chapter provides a summary of the work performed in this thesis and opinions on the future of the field of transcranial focused ultrasound therapy.

Critical to any transcranial focused ultrasound therapy is the ability to accurately target a location in the brain. As described above, basic targeting accuracy through the skull has been analyzed in previous studies. Here, we introduce an additional obliquity metric with which to measure focal quality. The large number of critical structures close to any target in the brain necessitates the use of phased array
controls that optimally control both the position and the orientation of the focus. The observation, replication, and correction of an oblique focus in clinical transcranial studies is performed in Chapter 3. In this chapter, clinical data is first presented from a clinical trial investigating focused ultrasound for the treatment of ET. These clinical cases illustrate the first instances of an oblique focus in transcranial focused ultrasound. Numerical modeling is then performed to replicate the observed foci in the clinical cases. Finally, a method using phased array controls is introduced to control the deposition of acoustic energy at the focus and illustrate how these corrections can be used to replicate the focus in water.

In Chapter 4, we extend the findings in Chapter 3 towards the ability to control this focus and create multiple independently-rotated foci in space using phased array controls. In this way, the control over the focus is used to potentially create focal patterns that conform to certain shapes with resolution finer than the wavelength of the ultrasound being applied. Thus, the rotation of the focus allows for sub-wavelength precision in control when avoiding heating different regions of the brain. The problem is formulated as an inverse problem and a Tikhonov regularization method is shown to allow for the complete control of the focus in space, given a sufficient number of degrees of freedom. With these two chapters, Chapters 3 and 4, the reader should be convinced that Aim 1 is accomplished.

Towards Aim 2, a study was performed on the manifestation of the observed reduction in efficiency at high powers during transcranial FUS for the treatment of ET and provides several possible explanations for the phenomenon.

The design of a novel patient-specific array that would allow for improved treatments using pulsed ultrasound to open the BBB and deliver therapeutics is covered in Chapter 6. In this chapter, the design of a patient-specific array from clinical CT data is presented and possible construction techniques are discussed. In addition, numerical modeling of pulsed ultrasound is performed to test the treatment range and the variability of the pulse lengths permitted for use with the new array design. With these developments, the reader should be convinced that Aim 3 is complete.

Finally, Chapter 7 provides perspectives on the future developments in transcranial focused ultrasound and the role that focused ultrasound can play in the future treatment of neurological diseases. Hopefully, the reader will be convinced that the goal of fulfilling the unmet need for efficient, safe, and non-invasive neurosurgical techniques illuminated in Section 1.1 will be advanced in this thesis.
Chapter 2

Mathematical Background and Numerical Modeling of Focused Ultrasound

The majority of the work performed in this thesis involves the numerical modelling of acoustic fields by an array of transducers to propagate ultrasound through the skull. It is therefore informative to devote some discussion to numerical modeling of focused ultrasound for transcranial therapy. In this section, the principles behind numerical modeling of ultrasound and the current state of transcranial focused ultrasound numerical simulations will be reviewed. The numerical methods used in this thesis will then be introduced.

2.1 Background

2.1.1 Governing Equations of Ultrasound Propagation and the Diffusion of Heat

The Wave Equation

The wave equation is defined as

\[ \partial_{tt} p = c^2 \nabla^2 p, \]  

(2.1)

where \( p \) is the pressure and \( c \) is the speed of sound. In this simple approximation, the region of interest is homogeneous and isotropic. In the human body, the assumption of homogeneity is invalid: acoustic properties vary between different types of tissues, and tissues are highly heterogeneous themselves. In addition, the assumption of isotropy is invalid: ultrasound refracts and attenuates in different directions due to the geometry of the tissues. Due to the relative simplicity of Equation 2.1, it is possible to obtain closed-form solutions in 1-, 2-, and 3-dimensional space, although in 3-dimensional space the solutions are complex and involve rather intensive calculations. The wave equation, however, can not accurately represent complex acoustic phenomena observed in biological tissue.
The wave equation can be modified to represent real-world phenomena more accurately by including attenuation (which consists of absorption and scattering components). In this way, the wave equation can demonstrate the complex ultrasound wave propagation in the highly heterogeneous, attenuating human body. This modified wave equation is written as

\[ (\partial^2_t + 2\alpha_L c\partial_t)p = c^2(\nabla^2 - \frac{1}{\rho}\nabla \rho \cdot \nabla)p, \]  

(2.2)

where \( \alpha_L \) is the attenuation and \( \rho \) is the density of the medium. This wave equation models the longitudinal propagation of ultrasound in fluid domains. Soft tissues, including cerebral white matter, can be modeled accurately as fluids, because in these media the transverse ultrasonic component is insignificant at the acoustic powers and frequencies used in transcranial focused ultrasound therapy. For solid media, however, an even more complex implementation is required that uses particle displacement fields to characterize solid interactions with acoustic waves.

The Viscoelastic Wave Equation  In solid domains, the governing equation is given by [247]

\[ \rho \partial^2_t \mathbf{u} = (\mu_L + \eta \partial_t)\nabla^2 \mathbf{u} + (\lambda_L + \mu_L + \xi \partial_t + \frac{\eta}{3} \partial_t)\nabla(\nabla \cdot \mathbf{u}), \]  

(2.3)

where \( \mathbf{u} \) is the vector field of the particle displacements in the three Cartesian directions, \( \lambda_L \) and \( \mu_L \) are the first and second Lamé coefficients, and \( \eta \) and \( \xi \) are the first and second viscosity parameters. Bone must be modeled as a solid and as a result, this equation is integral to several chapters in this thesis. In this version of the wave equation, the vector \( \mathbf{u} \) describes the acoustic particle displacement in all three Cartesian coordinates as a function of time. This representation becomes important when modeling both longitudinal and transverse waves.

With Equations 2.2 and 2.3, it is possible to model acoustic phenomena in the human body with reasonable accuracy. Chapters 3, 4, and 5 also require the modeling of temperature fields in the body arising from acoustic waves, however. This is achieved using the diffusion equation, as described below.

The Diffusion Equation

The diffusion equation can be written as

\[ \rho C_t \partial_t T = \kappa \nabla^2 T, \]  

(2.4)

where \( \rho \) is the density, \( C_t \) is the coefficient of thermal conductivity, and \( T \) is the temperature. In this simplified approximation, there is no heat source and no perfusion. Certain initial conditions and boundary conditions are assumed, and the resultant temperature profile \( T \) at some time \( t > 0 \) is obtained. However, a link is required between the acoustic absorption in tissue and the resultant thermal fields.

In 1948, Pennes developed a modified diffusion equation, now called the Pennes bioheat equation [248]. This equation takes into account perfusion of a tissue by blood as well as diffusion from a constant heat source, according to

\[ \rho C_t \partial_t T = \kappa \nabla^2 T - \rho_b C_b W_b (T - T_b) + Q, \]  

(2.5)

where \( \rho \) is the tissue density, \( C \) is the specific heat capacity of the tissue, \( \kappa \) is the tissue thermal conductivity, \( \rho_b \) is the blood density, \( C_b \) is the specific heat capacity of blood, \( W_b \) is the perfusion rate
in the tissue, \( T_b \) is the blood temperature, and \( Q \) is a constant heat source. The absorbed power density, \( Q \), is measured in W / m\(^3\) and is generated from the acoustic field and is determined based on the variable absorptions among the different tissues.

In fluid domains, the absorbed power density is calculated from the pressure map using the relation

\[
Q = \frac{\alpha}{\rho c} |p|^2, \tag{2.6}
\]

where \( \alpha \) is the absorption in the tissue. Since brain tissue is modeled as a homogeneous medium, one can take \( \alpha = \alpha_L \). The relation

\[
Q = -\frac{\omega}{2} \Im(\sigma_i \epsilon_i), \tag{2.7}
\]

applies in solid media, where \( \omega \) is the angular frequency of the ultrasound wave, \( \sigma \) denotes the stress tensor, \( \epsilon \) denotes the average strain tensor \([247]\), and \( \Im \) denotes the imaginary component.

Sapareto and Dewey developed the concept of the thermal dose to normalize different heat exposures as functions of both time and temperature \([160]\). The thermal dose, \( TD \), is defined as

\[
TD = \int_0^t R(T(t')) (T_{ref} - T(t')) dt', \tag{2.8}
\]

for sonication duration \( t \) and \( T_{ref} = 43{\degree}C \), where \( R(T) = 0.25 \) for \( T < 43.0{\degree}C \) and \( R(T) = 0.5 \) for \( T \geq 43.0{\degree}C \). The thermal dose will be pertinent to Chapter 3, where the clinical 1-day post-treatment lesions will be compared to numerically-simulated thermal dose maps to confirm accuracy of the simulation model in replicating the clinical cases.

Now that the governing equations used in this thesis have been introduced, it is necessary to discuss the methods available for solving them. Using Equations 2.2, 2.3, and 2.5, it should be possible to determine completely the acoustic fields generated from an ultrasound transducer in any part of the body and the resultant temperature rise. However, closed form solutions to these equations do not exist. As a result, numerical modeling is used to simulate the generation of these fields and temperatures over time.

Figure 2.1 illustrates the discretization of the simulation domain. Although the domain macroscopically mirrors the continuous reality that a clinician would see on a medical image or in real life, by continually zooming in to the field of view, illustrated by the arrows, the discretization of the simulation domain becomes apparent. The discretization of the domain allows for two things to happen: first, the spatial coordinate is discretized; second, each voxel within the simulation domain can specify acoustic (or thermal) parameters at that point, which then tell the governing equations which parameters to use, or indeed, which of the equations to use to solve for the field at that point. Note that the discretization is of sufficiently high resolution such that biophysical features are represented well and simulation errors are minimized.

A 3D representation of the image slice presented in Figure 2.1 is illustrated in Figure 2.2. The different components of the simulation domain are represented by different colours, according to the different material properties within the field of view.
Figure 2.1: An illustration of the discretization used during the simulation of ultrasound in the head. The skull is first segmented and positioned inside the hemispherical array (far left). By zooming in close to the target, one can begin to see the discretized domain indicating tissue in blue and bone in yellow (middle). The individual voxels are indexed based on density and the corresponding acoustic parameters (density ($\rho$), speed of sound ($c$), attenuation ($\alpha$)) are obtained (far right).

Figure 2.2: A 3D representation of the segmented simulation volume featured in Figure 2.1.
2.1.2 Overview of Simulation Methods

Recently, there has been rapid advancement in the software packages available to simulate ultrasound from both imaging and therapeutic perspectives. These simulation packages involve various assumptions and sacrifices, with varying levels of complexity and hardware requirements. Three broad categories of ultrasound simulation are of interest here: full-wave, angular spectrum, and ray acoustic approaches.

**Full-wave Approaches**

Full-wave approaches to modeling ultrasound are, in general, the most accurate, the most computationally intensive, and the most complex. The accuracy and complexity of the solutions derive from the universal treatment of the domain of interest, guided by the governing equations introduced in Section 2.1.1, among other more complex variations (including nonlinear simulation). Full-wave simulation methods involve the definition of a geometry, either as a series of interconnected points in a mesh or a fully-populated array of points, with each voxel or vertex specified as having a specific location and specific properties. In the case of transcranial acoustic simulations, it is important to determine whether a specific voxel corresponds to brain tissue or cranial bone, and then to determine what the resultant speed of sound and attenuation characteristics are for the associated acoustic particle.

Once the geometry is well-defined, the initial conditions and the governing equations of the physical processes (i.e. the wave and diffusion equations) fully determine the resultant field and temperature map. In the case of a single governing equation, as is often the case in the simulation of soft tissue, the output can be mapped as a spatio-temporal pressure or velocity field. In the case of different governing equations, as in the case of fluid-solid full-wave simulations, coupling rules between the different equations are required. For instance, in the case of transcranial simulations, the conversion between fluid and viscoelastic wave equations at tissue-solid boundaries can be governed by the continuous propagation of the normal force [251].

**Angular Spectrum Approaches**

Angular spectrum methods are often used for their speed and accuracy in modeling both linear and nonlinear ultrasound. In these simulations, the acoustic transfer function is used to forward propagate the pressure field in Fourier space to a parallel plane further afield. The most notable angular spectrum approach currently in use is the k-wave model [252]. A number of recent studies have used the k-wave toolbox in MATLAB and C to simulate both ultrasound transmission and photoacoustic reception [180,253,254].

**Ray Acoustic Approaches**

Ray acoustic approaches to ultrasound propagation are often used because they are fast, easily parallelizable, and accurate for linear ultrasound propagation, which generally will apply to lower frequencies and lower acoustic pressures.

The predecessor to the ray acoustic method originates in the study of geometrical optics, where the path of light can be described through a series of reflections and refractions.

Ray acoustic methods originate from the principles described in O’Neil’s classical 1949 paper on the theory of focusing radiators [255]. In this paper, O’Neil describes the Rayleigh-Sommerfeld integral,
Table 2.1: Simulation parameters used in the full-wave simulation of the acoustic and thermal fields [1–4].

<table>
<thead>
<tr>
<th>Material</th>
<th>$\rho$ (kg m$^{-3}$)</th>
<th>$c_L$ (m s$^{-1}$)</th>
<th>$\alpha_L$ (Np m$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1000</td>
<td>1500</td>
<td>0</td>
</tr>
<tr>
<td>Brain</td>
<td>1037</td>
<td>1400</td>
<td>4.28</td>
</tr>
<tr>
<td>Water</td>
<td>0.62</td>
<td>4180</td>
<td>0</td>
</tr>
<tr>
<td>Brain</td>
<td>0.53</td>
<td>3640</td>
<td>$8.33 \times 10^{-4}$</td>
</tr>
<tr>
<td>Skull</td>
<td>0.43</td>
<td>1440</td>
<td>$3.33 \times 10^{-4}$</td>
</tr>
<tr>
<td>Blood</td>
<td>1030</td>
<td>3620</td>
<td>37</td>
</tr>
</tbody>
</table>

For point source $(r')$

$$p(r) = \int_S \frac{jk_c \rho c}{2\pi \|r - r'\|} e^{-jk_c \|r - r'\|} u(r') dr', \quad (2.9)$$

where $p$ is the acoustic pressure, $r$ corresponds to a point in space, $S$ is the transducer surface, $j$ is the imaginary number $\sqrt{-1}$, $k_c$ is the wave number, $\rho$ is the density of the propagation medium, $c$ is the speed of sound in the medium, and $u$ is the transducer surface velocity. In this way, it becomes possible to discretize an ultrasound transducer as a set of point sources, and to propagate ultrasound using the additive principle of the assumed linear field. Therefore, the computation of the resultant ultrasound field in a layered problem becomes a summation over the possible combinations of point source-control point pairs over each pair of adjacent layers.

This approach was first described in ultrasound applications in 1994 [256] and resulted in its application to a wide range of therapeutic and monitoring work. The approach has also been used to describe the passive acoustic signals through the intact skull [231].

### 2.2 Numerical Methods used in this Thesis

The numerical simulation methods used in this thesis can be broken down broadly into two categories: acoustic and thermal simulations. The acoustic simulations are used to determine the acoustic field at a given timepoint based on initial conditions set at an array of ultrasound transducer elements. The thermal simulations, on the other hand, use the time-averaged acoustic field to compute the resultant temperature rise.

#### 2.2.1 Acoustic Simulations

The acoustic simulations used in this thesis are further divided into full-wave simulations and ray acoustic simulations. In the brain, with transcranial simulations, full-wave simulations are performed due to their high accuracy in attenuating and scattering media. In the homogeneous media described in Chapter 4, ray acoustic simulations are performed, due to the speed and accuracy of this simulation technique when studying propagation in a homogeneous medium at low acoustic pressures.

**Full-wave Simulations**

Full-wave simulations are performed in Chapters 3 and 5 to represent accurately the propagation of ultrasound through cranial bone. To obtain the acoustic pressure field inside the treatment geometry,
a previously-introduced numerical model is used [251] that combines finite difference simulations [246] with the grid method [257]. This hybrid model calculates the pressure field in the brain and the particle displacement field in the cranial bone. The governing equations of acoustic propagation for fluid and solid domains are given in Equations 2.2 and 2.3. Further details of the numerical implementation of Equations 2.2 and 2.3 are given in the Appendix of [258]. The longitudinal speed of sound, \( c_L \), and attenuation, \( \alpha_L \), in skull, are found using a spline interpolation of previously-obtained acoustic data over a range of frequencies [201]. Scaling factors are used to describe the shear speed and attenuation data in bone as functions of density, so that \( c_s = \frac{440}{2700} c_L(\rho) \) and \( \alpha_s(\rho) = \frac{90}{85} \alpha_L(\rho) \) [259]. A time step size of 10.5 ns combined with a spatial voxel size of dimensions 0.23 mm is used to obtain a maximum CFL value [260] of 0.15, where CFL is calculated as \( \text{CFL} = \frac{c \Delta t}{\Delta h} \), for spatial discretization step size \( \Delta h \) and temporal step size \( \Delta t \). The CFL is calculated in each domain separately and for both longitudinal and shear wave speeds in bone. The spatial discretization is chosen to have at least seven points per wavelength in water. Acoustic and thermal parameter values for water, brain, and bone are listed in Table 2.1.

Each sonicating transducer element is driven with a sinusoidal signal that increases linearly from zero amplitude to the prescribed sonication amplitude in five cycles. The Neumann boundary condition, defined as

\[ \partial_n p = g, \] (2.10)

is used on interfaces between transducer faces and water, where \( n \) is the normal to the transducer surface, \( p \) is the pressure, and \( g \) is a term describing the prescribed oscillation of the transducer surfaces. The absorbing boundary condition is used on other boundaries.

A Fast Fourier Transform (FFT) of the final two cycles of the acoustic field is taken to obtain a stable average pressure field over the treatment domain. The total size of the treatment domain varied between 938 × 954 × 643 and 938 × 954 × 693 voxels, and each simulation is executed over 20085 temporal steps, allowing enough time to simulate the propagation of ultrasound 30 cm in water.

Ray Acoustic Simulations

In Chapter 4, a homogeneous treatment domain is simulated. Therefore, a modified Rayleigh-Sommerfeld equation is used to model ultrasound propagation in this volume [255, 261]. The Rayleigh integral, described by Equation 2.9, was solved numerically. The surface of the transducer elements was broken into surfaces of infinitesimal area, which could be considered point sources, given the relative scale of the propagation distance to the transducer size. Equation 2.9 is then expressed as a summation over the infinitesimal point source transducers. This technique is elucidated in [256]. Table 2.2 lists the parameter values used in these specific acoustic and thermal simulations.

2.2.2 The Simulation of Pulsed Ultrasound

In addition to the above-described continuous wave ultrasound simulation methods used in this thesis, simulations of pulsed ultrasound were also performed in Chapter 7. A CT scan (LightSpeed VCT, GE Healthcare, Chalfont St Giles, UK) of a human cadaver skull was obtained and used in each of these simulations (512 × 512 × 328 voxels with uniform voxels of size 625 \( \mu \text{m} \) × 625 \( \mu \text{m} \) × 625 \( \mu \text{m} \)). The density was obtained using a linear relation with the Hounsfield Units, using knowledge of the densities of water
Table 2.2: Simulation parameters used in solving Equation 2.9 and Equation 2.5, obtained from [1,5,6].

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c$</td>
<td>Speed of sound in soft tissue</td>
<td>1545 m s$^{-1}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Soft tissue density</td>
<td>1030 kg m$^{-3}$</td>
</tr>
<tr>
<td>$C_t$</td>
<td>Specific heat capacity of tissue</td>
<td>3600 J kg K$^{-1}$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Tissue attenuation coefficient</td>
<td>5.0 Nep m$^{-1}$ MHz$^{-1}$</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Thermal conductivity of tissue</td>
<td>0.6 W m$^{-1}$ K$^{-1}$</td>
</tr>
<tr>
<td>$T_0$</td>
<td>Body temperature</td>
<td>37.0°C</td>
</tr>
<tr>
<td>$\rho_b$</td>
<td>Blood density</td>
<td>1030 kg m$^{-3}$</td>
</tr>
<tr>
<td>$C_b$</td>
<td>Specific heat capacity of blood</td>
<td>3620 J kg K$^{-1}$</td>
</tr>
<tr>
<td>$W_p$</td>
<td>Perfusion rate in soft tissue</td>
<td>0.5 kg m$^{-3}$ s$^{-1}$</td>
</tr>
</tbody>
</table>

and air in the CT scan [198]. The skull CT data were then segmented in MATLAB (The Mathworks Inc., Natick, MA, USA) and interpolated such that the discretization in the numerical simulations was $\lambda/10$, where $\lambda$ was the wavelength of the ultrasound in water.

A previously-introduced numerical model [251], which combines finite difference simulations [246] with the grid method [257], was modified to allow for ultrasound bursts of variable length to be emitted from the transducer elements in the array. Details of the numerical implementation of these acoustic simulations are given elsewhere [251, 262]. An FFT of the peak cycle of the acoustic field was taken to obtain the time-averaged pressure field over the treatment domain. Each simulation was run over a sufficient number of temporal steps to allow the ultrasound wavefront from each element to reach the target. The phasing of each transducer element was obtained by first sending a pulse from the target focus in the brain, and delaying the transmission pulse based on the time-of-flight obtained to each element. Each sonicating transducer element was then driven with the time-delayed Gaussian-enveloped sinusoidal signal obtained from the reversed problem.

Thermal simulations were performed in the cranial bone, using the absorbed power density obtained from [250]. The absorbed power density was then used as a heat source in the Pennes bioheat equation [248]. The temporal evolution of this equation was solved using a finite-difference time-domain (FDTD) technique. A computer cluster consisting of eight Intel Xeon processors was used to perform the FDTD simulations and a standard desktop computer was used to analyze and process the data.

### 2.2.3 Thermal Simulations

To study the heating resulting from the absorpton of acoustic energy, the Pennes bioheat equation [248] is solved. The absorbed power density, calculated from Equations 2.6 and 2.7, in the entire domain is used as a time-independent heat source in Equation 2.5.

In cases where the tissue is homogeneous, as in Chapter 4, Equation 2.5 is solved using a Fourier transform method introduced in [263]. For heterogeneous domains, as in Chapters 3 and 5, a full-wave implementation of the bioheat equation is solved. The convergence of the full-wave simulation is based on the spatiotemporal discretization criterion set out in a previous study for numerical simulations of the Pennes equation [263]. In this way, the Pennes bioheat equation is allowed to run for domains with various conductivities, allowing for the simulation of bone-tissue interfaces and for assessment of the role of circulating cool water on skull heating.
Chapter 3

Controlling an oblique focus in transcranial therapies

During clinical trials for MR-guided focused ultrasound for the treatment of ET beginning in 2012, a strange focusing effect was observed to occur: in some clinical cases, the focus at the site of the VIM nucleus was aligned oblique to the main axis of the array. This chapter presents the results of a numerical study performed to replicate and analyze the cause of the observed focal obliquity and forms the first study performed as a part of this thesis.

3.1 Introduction

In clinical applications of focused ultrasound where significant temperature elevations are involved, complete control of the deposition of heat in the brain is imperative to a safe and effective therapy. The close proximity of critical nerve structures and functional areas in the brain to any given target render this level of control even more important, to avoid peripheral thermal damage. Assuming that a hemispherical phased array were to sonicate to the geometric focus through a homogeneous medium, it is expected that the focus would be oriented along the main axis of the array, from symmetry. In this chapter, it is shown that the heating at the focus during clinical treatments of essential tremor is often oblique to the main axis of the array when performing sonications through the skull, and the various causes of the oblique focus and their effects are investigated in this retrospective analysis.

Previous studies in transcranial focused ultrasound have investigated the targeting accuracy of brain therapy [240], by comparing the relative locations of the target focus and the actual focus in the three Cartesian directions. In addition, various studies from other brain therapy modalities, such as gamma knife radiosurgery, have been performed to determine the targeting accuracy [241–244], as well as discussion on the effects of errors in targeting [244]. It is argued here that the obliquity of the focus observed in transcranial focused ultrasound treatments is another indicator of targeting accuracy. The spatial orientation of the deposition of heat in the brain could then be studied in a similar fashion to the effects of radiation dose contours in radiosurgery.

---

Using clinical data exported from a clinical trial of essential tremor using focused ultrasound [13], consisting of imaging data and treatment parameters, it will first be shown using numerical modeling that the presented real-time MR thermometry images and 1-day post-treatment MR images showing the oblique focus can be replicated, further validating a previously-introduced full-wave numerical model [258]. It will then be shown that by using combinations of full-wave phase [171, 177] and amplitude corrections [171], it is possible to reduce the focal obliquity, as well as the more conventional metrics of the peak sidelobe ratio and the volume of heating.

3.2 Materials and Methods

3.2.1 Numerical Modelling

Patient Treatment Modeling

Full-wave acoustic simulations were performed to obtain the stable acoustic pressure fields in the brain, as described in Section 2.2.1.

From the generated acoustic fields, the absorbed power density, defined by Equations 2.6 and 2.7, was calculated. The absorbed power density in the entire domain was then used as a time-independent heat source in the Pennes bioheat equation (Equation 2.5). Simulation parameters are defined in Table 2.1.

Clinical Phase Corrections

The phase corrections used in the clinical trial follow previous work to correct the phase [199]. In this case, the direct line between the transducer face and the focus is drawn, and the phase delay calculated from the CT data is computed along this straight ray path. The focus is then steered to the target focus location.

Clinical Amplitude Controls to Reduce Skull Heating

Amplitude controls designed to reduce skull heating [173] were used during the clinical trials. These amplitude controls distributed the deposition of energy evenly in the skull during the treatment in order to utilize the entire skull surface to minimize skull heating.

3.2.2 Patient Imaging Data

Six MR and CT imaging datasets were obtained from a clinical trial of MR-guided focused ultrasound for the treatment of essential tremor [13]. In the clinical trial, the VIM nucleus was targeted, and the patient was positioned such that the target focus was in close proximity to the geometric focus of the hemispherical phased array. The sonication powers and durations were such that a therapeutic level of heating could be obtained to cause a thermal lesion. The sonication powers and durations of the analyzed cases are listed in Table 3.1, along with the low levels of steering used to target the precise location of the VIM nucleus. The resolution of the CT scans (Brilliance 40, Philips Healthcare, the Netherlands) used for the segmentation of the skull into simulation grid points was 1 mm × 0.49 mm × 0.49 mm. Fast-spin echo T2-weighted MR images were used for image registration during the clinical trials, and obtained from a 3T scanner (General Electric, Milwaukee, WI, USA). An example of the
Figure 3.1: The sagittal and coronal MR images obtained during a treatment, demonstrating the location of the head inside the transducer array (T2 3-plane fast spin echo, TR = 2300ms, TE = 82ms).

Table 3.1: A summary of the acoustic powers and durations for each of the simulated patients A-F, taken from the clinical treatment data. In addition, the steering of the focus from the geometric center of the array in the left-right (LR), anterior-posterior (AP), and inferior-superior (IS) directions is listed.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Power (W)</th>
<th>Duration (s)</th>
<th>Focus Shift (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>750</td>
<td>13</td>
<td>-2.9</td>
</tr>
<tr>
<td>B</td>
<td>1100</td>
<td>20</td>
<td>-2.1</td>
</tr>
<tr>
<td>C</td>
<td>850</td>
<td>20</td>
<td>1.3</td>
</tr>
<tr>
<td>D</td>
<td>950</td>
<td>30</td>
<td>0.6</td>
</tr>
<tr>
<td>E</td>
<td>600</td>
<td>24</td>
<td>4.2</td>
</tr>
<tr>
<td>F</td>
<td>350</td>
<td>27</td>
<td>0.2</td>
</tr>
<tr>
<td>G</td>
<td>754</td>
<td>27</td>
<td>-1.0</td>
</tr>
<tr>
<td>H</td>
<td>754</td>
<td>24</td>
<td>1.0</td>
</tr>
<tr>
<td>I</td>
<td>656</td>
<td>24</td>
<td>0.0</td>
</tr>
<tr>
<td>J</td>
<td>549</td>
<td>24</td>
<td>-0.7</td>
</tr>
<tr>
<td>K</td>
<td>593</td>
<td>24</td>
<td>-0.7</td>
</tr>
<tr>
<td>L</td>
<td>803</td>
<td>24</td>
<td>0.3</td>
</tr>
<tr>
<td>M</td>
<td>750</td>
<td>24</td>
<td>-1.0</td>
</tr>
<tr>
<td>N</td>
<td>754</td>
<td>24</td>
<td>-2.6</td>
</tr>
<tr>
<td>P</td>
<td>500</td>
<td>27</td>
<td>-0.3</td>
</tr>
<tr>
<td>Q</td>
<td>996</td>
<td>40</td>
<td>0.3</td>
</tr>
</tbody>
</table>
exported MR data is shown in Figure 3.1 in the sagittal and coronal planes, showing the location of the skull inside a superimposed hemispherical transducer array.

1 day post-treatment 3D fast spoiled gradient echo MR images (TR = 8.3ms, TE = 3.3 ms) were obtained from each of the six treatment cases, labeled as Patients A-F. Coronal slices of these images through the lesion site are shown in Figure 3.2 and demonstrate the clinical oblique focus cases. The white arrows highlight the location of the created lesions. For clarity, Figure 3.3 illustrates a 3D rendering of the oblique lesion volume for Patient C. This figure demonstrates the spatial orientation of the lesion in space using standard spherical coordinates.

### 3.2.3 Therapy Device

A phased array (ExAblate 4000, InSightec, Israel) consisting of 1024 independently-driven ultrasound transducers in a hemispherical configuration of 15 cm radius of curvature was modeled. The transducer locations in space were determined from the treatment export data and were assumed to operate as circular piston transducers, with maximum possible radius such that no two transducers would overlap. The resultant radius of each transducer was approximately 5 mm, where all transducers had the same size. The transducer elements operated at 650 kHz. The co-registration of the CT images and the therapy device were performed manually by the clinician during treatment, and the registration information was exported and used in the modeling.

### 3.2.4 Investigation of Causes of the Oblique Focus

The effect of the distribution of transducer element powers used to distribute heating evenly on the surface of the skull, and the heterogeneity of the skull, which will be considered skull aberration effects, on the focus obliquity were studied. After determining the relative magnitude of each of these effects, it was then determined whether it was possible to compensate for these effects using the degrees of freedom.
Three independent metrics were used to quantify the magnitude of these various effects on the focal obliquity: the peak relative sidelobe intensity of the acoustic pressure field with respect to the main lobe, the full-width half maximum of the temperature distribution, and the orientation of the focus in space, termed the obliquity of the focus.

Quantification of Obliquity

The obliquity of the focus was measured by fitting the normalized temperature distribution of the focus to a 3D Gaussian distribution, defined as

$$ G = (2\pi)^{-3/2} |\Sigma|^{-1/2} e^{-1/2(x-x_\mu)^T \Sigma^{-1} (x-x_\mu)}, $$

(3.1)

where \( x_\mu \) denotes the location of the peak temperature, and \( \Sigma \) is the weighted sample covariance matrix, defined as

$$ \Sigma = \frac{\sum w_i}{(\sum w_i)^2 - \sum w_i^2} \sum w_i (x_i - x_\mu)(x_i - x_\mu)^T, $$

(3.2)

where \( w_i \) corresponds to the temperature, and \( x_i \) the position, of the \( i \)th voxel. The unit eigenvector corresponding to the maximum eigenvalue of the covariance matrix was taken as the major axis of the distribution, and the unit spherical representation of this eigenvector, defined by \((\theta, \phi)\), was used to quantify the oblique angles. In this case, \( \theta \) is the polar angle and \( \phi \) is the azimuthal angle. In the following, the obliquity will refer to \( \theta \), the tilt from the main axis. Figure 3.3 illustrates the obliquity metric on the 3D clinical lesion volume.

The real-time MR thermometry images are only available in certain planes for the clinical treatments, and as a result, the obliquity measured from the numerical simulations was compared to the 3D
Transcranial therapies

Table 3.2: The five cases simulated to extract the causes of the oblique focus.

<table>
<thead>
<tr>
<th>Simulated Case</th>
<th>Description</th>
<th>Phase</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 EIS</td>
<td>Equal Intensity on the Skull Surface</td>
<td>Clinical</td>
<td>Clinical</td>
</tr>
<tr>
<td>2 EIT</td>
<td>Equal Intensity on the Transducer Surface</td>
<td>Clinical</td>
<td>Equal</td>
</tr>
<tr>
<td>3 AC</td>
<td>Amplitude Corrections</td>
<td>Clinical</td>
<td>Inverse</td>
</tr>
<tr>
<td>4 PC</td>
<td>Phase Corrections</td>
<td>Full-Wave</td>
<td>Clinical</td>
</tr>
<tr>
<td>5 APC</td>
<td>Amplitude and Phase Corrections</td>
<td>Full-Wave</td>
<td>Inverse</td>
</tr>
</tbody>
</table>

volumetric lesion data provided by the 1-day post-treatment MR images.

Transducer Power Effects

The transducer powers during clinical treatments are such that the deposition of acoustic power is equal across the surface of the skull [173]. In order to determine the effect of this distribution of power on the focusing quality, the treatment was simulated assuming equal transducer powers on all elements, and the focusing quality was analyzed.

Skull Aberration Effects

The effect of the heterogeneity of the skull manifests in two ways during transcranial focused ultrasound therapy: through phase changes in the transmitted acoustic field, and through variable transmission to the focus from different elements in the array. We seek to investigate both these effects.

To determine the effect of the temporal shifts in the acoustic field over different regions of the skull, a full-wave phasing scheme was used. In this way, it was deemed possible to determine the optimal phasing solution, resulting in all element fields arriving in-phase at the target focus. To obtain the phases in this case, a source was placed at the focus and backwards propagated to the transducer faces, where the phase was read off. The inverted phase was then used as the optimal phase for transmission.

To determine the effect of the variable transmission to the focus, a similar inversion scheme was employed. Instead of the phase, the average acoustic power was determined at the transducer faces, and this value was reciprocated, such that the deposition of acoustic power at the focus is identical for all elements, as has been previously proposed [171]. This was termed the “inverse amplitude correction” by White et al.

3.2.5 Simulated Cases

Five different cases were simulated to extract the independent effects of the skull aberration and distribution of transducer power, as listed in Table 3.2. EIS refers to the clinical replication, where the transducer powers distribute power evenly on the surface of the skull [173]. In this case, the clinical export phase and amplitude were used. EIT is the distribution of equal intensity on the transducers, where the clinical phase corrections are coupled with an even distribution of power on the surface of the transducer. The third case, AC, refers to the use of amplitude corrections coupled with the clinical phase corrections. The fourth case, PC, uses the clinical amplitude export with full-wave phase corrections, and APC, the fifth case, refers to the use of both amplitude corrections and full-wave phase corrections.
Figure 3.4: A comparison of the clinical and numerical simulation results for Patient E, illustrating the clinical and numerical results. The numerically-simulated thermal dose contours are superimposed on the 1-day post-treatment MR image for comparison.

3.3 Results

3.3.1 Replication of Clinical Data

Figure 3.4 illustrates qualitatively the ability to replicate the focus morphologies observed during clinical treatments for Patient E. The simulated acoustic pressure field is shown in the bottom right of the figure (Acoustic Pressure), and the temperature map at the focus generated from this pressure field, using Equations 2.6 and 2.5, is shown in the bottom left (Temperature). The 1-day post-treatment MR image first presented in Figure 3.2 is magnified and shown in the upper righthand corner (MR Imaging), clearly illustrating the outline of the thermal lesion. The numerically-simulated thermal dose lesions are superimposed, with contours at 0.1, 1, 5, 10, and 60 minutes thermal dose, where the power was normalized to obtain the peak temperature obtained from the clinical export data in order to have a fair comparison. In addition, the real-time thermometry image taken 24s after the start of the sonication, is shown in the upper lefthand corner (MR Thermometry). It is important to note the morphological similarities between the simulated temperature map and the real-time MR thermometry map; including the obliquity demonstrated in both cases. The thermal lesion, in particular, clearly demarcates the
extent of the ablated tissue, manifesting as an oblique focus.

Figure 3.5 summarizes the numerically-simulated heating maps for Patients A-F. It is useful to compare these heating maps to the focal lesions illustrated in Figure 3.2, demonstrating morphological similarities between the temperature maps at the end of heating and the resultant thermal lesions. Particular attention should be paid to Patients C and E, where the oblique focus is most notable in both the clinical and simulated images.

To add to these qualitative findings, Table 3.3 provides a quantitative comparison of the clinical oblique foci and the numerically-simulated cases (Case 1, as described in Table 3.2). The \((\theta, \phi)\) spherical representation of the major axis of the oblique focus, first introduced in Section 3.2.4, is listed for all six cases. For the clinical cases, since the MR thermometry maps were only taken in one plane at a time, the 3D 1-day post-treatment MR images delineating the lesion were used to measure the clinical focal obliquity. It should be noted that in all six cases, there is agreement between the directionality of the oblique foci from the clinical export data and the numerical simulations. It was found that it was possible to correctly replicate the obliquity observed clinically to within \(23.1\pm19.5^\circ\).

Using the qualitative similarities between the simulated temperature fields and the post-treatment MR images and real-time thermometry MR images, as demonstrated in Figures 3.4 and 3.5, as well as the quantitative comparison between the clinical and numerical results outlined in Table 3.3, it appears that the numerical simulations are able to replicate many of the morphological features demonstrated clinically, and allow for the further study of the causes of the oblique focus.
Table 3.3: A quantitative comparison of the obliquity measured from 1-day post-treatment MR lesion information and the numerically-simulated results, listing the clinical and numerically-simulated obliquity, as well as the angle between these unit spherical vectors.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Data $(\theta, \phi)$</th>
<th>Numerical Simulation $(\theta, \phi)$</th>
<th>Angle $(^\circ)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(64.2, 102.2)</td>
<td>(49.1, 107.1)</td>
<td>15.3</td>
</tr>
<tr>
<td>B</td>
<td>(69.6, 20.4)</td>
<td>(54.3, -46.9)</td>
<td>32.9</td>
</tr>
<tr>
<td>C</td>
<td>(32.3, 78.2)</td>
<td>(79.4, 97.5)</td>
<td>47.8</td>
</tr>
<tr>
<td>D</td>
<td>(77.4, 80.6)</td>
<td>(79.4, 97.5)</td>
<td>6.0</td>
</tr>
<tr>
<td>E</td>
<td>(42.3, 122.5)</td>
<td>(40.6, 111.9)</td>
<td>8.1</td>
</tr>
<tr>
<td>F</td>
<td>(48.1, 122.6)</td>
<td>(63.7, 129.4)</td>
<td>16.0</td>
</tr>
<tr>
<td>G</td>
<td>(62.4, 130.7)</td>
<td>(62.4, 142.0)</td>
<td>5.2</td>
</tr>
<tr>
<td>H</td>
<td>(38.4, 74.0)</td>
<td>(62.6, 113.0)</td>
<td>33.7</td>
</tr>
<tr>
<td>I</td>
<td>(40.9, 60.3)</td>
<td>(70.3, 96.3)</td>
<td>34.7</td>
</tr>
<tr>
<td>J</td>
<td>(38.3, -89.0)</td>
<td>(57.0, -106.0)</td>
<td>21.8</td>
</tr>
<tr>
<td>K</td>
<td>(55.3, 78.8)</td>
<td>(44.2, 90.4)</td>
<td>13.4</td>
</tr>
<tr>
<td>L</td>
<td>(54.8, -164.5)</td>
<td>(60.9, 102.3)</td>
<td>45.7</td>
</tr>
<tr>
<td>M</td>
<td>(62.8, 139.1)</td>
<td>(76.6, 148.4)</td>
<td>14.1</td>
</tr>
<tr>
<td>N</td>
<td>(49.4, -96.2)</td>
<td>(27.6, -100.7)</td>
<td>22.1</td>
</tr>
<tr>
<td>P</td>
<td>(65.9, -165.2)</td>
<td>(72.4, 144.7)</td>
<td>18.3</td>
</tr>
<tr>
<td>Q</td>
<td>(61.3, 47.7)</td>
<td>(82.1, -148.7)</td>
<td>36.3</td>
</tr>
</tbody>
</table>

**Mean** 23.2 ± 13.6

Figure 3.6: The simulated pressure fields at the focus for patients A-F. The contours are at 10% intervals.
Chapter 3. Controlling an oblique focus in transcranial therapies

3.3.2 Investigation of Causes of the Oblique Focus

It was hypothesized that the oblique focus observed during clinical treatments was partially caused by the presence of sidelobes in the direction of the focal obliquity. The simulated acoustic pressure maps for Patients A-F are shown in Figure 3.6. It can be seen from these pressure maps that the sidelobes of the acoustic field are in the direction of the oblique foci illustrated in Figures 3.2 and 3.5.

This observation is further supported by Figure 3.7, where the temperature evolution over time is demonstrated for Patient E, where it appears that the manifestation of the oblique focus arises from the sidelobes, as highlighted by the white arrow in the leftmost panel at t = 0.1 s. These sidelobes become masked over time as the diffusion of heat generates a single focus, whereby the lesion forms, as can be seen after 5s of heating.

Interestingly, there also existed clinical data which suggested the existence of a main lobe, as opposed to side lobe, effect on the focal obliquity. As illustrated in Figure 3.8, using phase corrections has a minimal effect on the focal obliquity, while amplitude and phase corrections appear to re-align the main axis of the focus in the inferior-superior direction. In addition, it is clear from the acoustic pressure field illustrated in (a) that the sidelobes in this case appear to have minimal effect on the observed focal obliquity, illustrated with the time-temperature evolution in Figure 3.9. This demonstrates that there are clinical cases in which either sidelobes or the main lobe can independently affect the observed focal obliquity.

Figure 3.10 illustrates the effect of each parameter on the focal obliquity, peak sidelobe ratio, and
Figure 3.9: The simulated temperature maps in the coronal plane after 0.1, 5, 10, and 20 s of heating, showing obliquity resulting from the main lobe in Patient K.

Figure 3.10: The composite effects of the power amplitude distribution and the skull aberration on peak sidelobe intensity, full-width half maximum, and obliquity. 1: clinical replication (EIS), 2: distribution of equal intensity on the transducers (EIT), 3: amplitude corrections, 4: full-wave phase corrections with EIS amplitude distribution, and 5: inverse amplitude and phase corrections. The solid line is the respective value when sonicating through a homogeneous medium with no skull. The heating volume is the region heated above 50% of the peak temperature at the focus. The error bars are one standard deviation.
Table 3.4: Summary of values presented in Figure 3.10. 1: clinical replication (EIS), 2: distribution of equal intensity on the transducers (EIT), 3: amplitude corrections, 4: full-wave phase corrections with EIS amplitude distribution, and 5: inverse amplitude and phase corrections.

<table>
<thead>
<tr>
<th></th>
<th>EIS</th>
<th>EIT</th>
<th>AC</th>
<th>PC</th>
<th>APC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Sidelobe Ratio (a.u.)</td>
<td>0.47±0.07</td>
<td>0.52±0.07</td>
<td>0.45±0.06</td>
<td>0.37±0.03</td>
<td>0.32±0.03</td>
</tr>
<tr>
<td>Heating Volume (mm³)</td>
<td>15.8±3.4</td>
<td>17.6±4.7</td>
<td>14.8±2.4</td>
<td>11.2±1.2</td>
<td>9.8±1.1</td>
</tr>
<tr>
<td>Obliquity (degrees)</td>
<td>32.7±12.4</td>
<td>39.3±15.0</td>
<td>15.6±6.2</td>
<td>34.4±10.3</td>
<td>9.1±5.3</td>
</tr>
</tbody>
</table>

Figure 3.11: A demonstration of the effects of amplitude and phase corrections, showing the simulation results for Case 1 (left), Case 4, (center), and Case 5 (right).

heating volume in the numerical simulations. The values used in the plots are summarized in Table 3.4. Figure 3.10 demonstrates that it is the aberration effects of the skull that lead to the oblique focus. From the figure, it appears that amplitude corrections, labeled as AC and APC, significantly reduce the focal obliquity by 52 and 72%, respectively, whereas full-wave phase corrections, as labeled PC and APC, contribute the most to the heating volume (29 and 38% reductions, respectively) and the peak sidelobe ratio (21 and 32% reductions, respectively).

On the other hand, the distribution of transducer power used to reduce heating on the surface of the skull appears to play little role in the observed focal obliquity, as can be seen when setting all element powers equally; that is, when moving from EIS to EIT in Figure 3.10. The distribution of power among the elements, however, does play a role in the correction of the oblique focus by compensating for the skull aberration effects which lead to variable deposition of power at the focus. This subtle distinction is important to note.

Figure 3.11 shows the simulated temperature maps, comparing the heating resulting from full-wave and clinical phase corrections. In this case, it is clear that there are improvements in the spatial resolution of the focus when using full-wave phasing corrections, since, intuitively, improved phase corrections lead to a higher concentration of deposited energy at the target focus. The obliquity of the focus, however, remains. In the righthand panel, when using amplitude corrections, the focus orients in the inferior-superior direction, thereby reducing the obliquity from this axis.

The combination of full-wave phase and amplitude corrections, therefore, leads to a focus resembling the focus obtained without the skull, as shown in Figure 3.12. It is emphasized in this figure that the distribution of power has minimal effect, while the full inversion of phase and amplitude leads to a focus with a similar morphology to the water-only case.
Figure 3.12: A comparison of the acoustic pressure fields at the focus when using full-wave and clinical phase corrections.

Figure 3.13: Heating maximum-image projection maps normalized to the peak focus temperature. The arrows indicate locations of heating in excess of the focus temperatures.

3.3.3 Skull Heating Considerations

It is important to note that manipulation of the power distribution among the elements can lead to uneven skull heating levels, since the clinical power distribution (EIS) is designed to distribute heat evenly on the surface of the skull. Figure 3.13 demonstrates the increased skull heating when using amplitude corrections on Patient C. It is shown that there are multiple regions on the inner surface of the skull, adjacent to brain tissue, where the temperature elevation exceeds the temperature elevation at the focus. As a result, full inversion of power may be infeasible, particularly with patients that require significantly more total power to achieve therapeutic temperature elevations.

3.4 Discussion

It was first shown that a hybrid numerical model was able to replicate some of the trends of the focal obliquity observed in clinical treatments of essential tremor. It was then shown that the occurrence oblique focus in MR-guided transcranial focused ultrasound can be attributed to the intensity of sidelobes in the acoustic pressure field. It was found that a reasonable configuration to reduce focal obliquity is by
using amplitude corrections to deposit acoustic power evenly at the focus from all elements in the array. Combined with full-wave phase corrections that take into account the refraction due to the skull along the ray path, it is possible to also reduce the peak sidelobe ratio and the heating volume of the focus.

The analysis in this paper was performed for a relatively central target within the brain, namely the VIM nucleus in the thalamus. It was assumed that the focus was well within the steering range of the phased array. Future studies may look at the effect of phased array controls on focusing at targets at the extreme regions of the steering range.

By using amplitude corrections, the total deposition of power at the focus is lower for a constant total array power, since the powers of the transducer elements that contribute more to the temperature rise at the focus are being reduced, and the powers of the transducer elements with low transmission efficiency are being increased [171]. As a result, it may be infeasible to use amplitude corrections with the powers required for thermal ablation. Further retrospective analysis of skull heating in clinical trials and prior [174,175] and future experimental studies may indicate general trends of maximum acoustic power deposition on the surface of the skull. Using these safety guidelines as an upper bound to the acoustic power assigned to a single element, the amplitude corrections could then be used safely.

Reinforcing previous studies [173, 189, 264, 265], it was also shown that phasing corrections are critically important to focusing quality in transcranial focused ultrasound. The clinical phase corrections [199] use average CT-derived corrections in a ray model, and only compensate along the direct ray path from the transducer element to the focus. It was found that by using full-wave phase corrections [177], it is possible to reduce the presence of sidelobes and the heating volume significantly. Combining the phase and amplitude corrections, it is possible to correct the focus close to the case with no skull present. It has been generally assumed that amplitude corrections should play minimal role at this frequency [197] to achieve high focusing quality, but it is shown here that the manifestation of the oblique focus in clinical results as a result of imperfect phase corrections can be somewhat rectified by the use of amplitude corrections.

With increasing computer processor speed and memory capabilities, it is becoming more feasible to implement complex acoustic models for transcranial treatment planning. As a result, it may be possible to integrate more accurate models to minimize sidelobes and optimize the deposition of energy at the target focus.

The implementation of amplitude controls is, of course, a very delicate matter. Since the EIS algorithm is used to minimize skull heating during treatment, any deviation from this power distribution will necessarily increase temperature at some point in the skull. Therefore, a balance may be found based on retrospective analysis of patient skull heating, as well as treatment efficacy studies, to determine the optimal phased array controls to use in each case.

In some patients, the treatment involved the sonication of slightly shifted points, in addition to the target point. The shift, if at all, was typically on the order of a millimeter, and hence it is believed that there should be minimal impact on the obliquity observed.

### 3.4.1 Limitations of the Obliquity Metric

The focus was assumed to be non-spherical, in the characteristic cigar shape in focused ultrasound. In this study, this was found to be a rather good approximation due to the use of a hemispherical phased array. In the case where the focus approaches a spherical volume, the concept of obliquity as defined here becomes increasingly poorly defined. One potential solution is the use of the ratio of minimum and
maximum eigenvalues as a secondary metric to determine the extent to which the focus is oblique. If the ratio is close to 1, then the focus is almost spherical, and hence not oblique. In the case where the ratio is small, then the focus is oblique, and the proposed metric defines the obliquity.

3.4.2 Discrepancies between Numerical Modeling and Clinical Data

The existence of some discrepancy in Table 3.3 will be discussed. The correspondence between the numerical simulations and the clinical data ranges from between 5.2 to 47.8°. There are numerous potential sources of discrepancy. First, the simulated thermometry maps were compared to the 3D 1-day post-treatment MR images, since real-time thermometry is done in a single plane. As a result, biological effects and variable brain tissue response to different heating levels could explain some discrepancy in the lesion obtained after completion of the treatment. Second, there was no direct registration between the post-treatment images and the images obtained during treatment, aside from anatomical landmarks. These discrepancies could account for some translation and rotation errors. Given these potential sources of error, it is quite clear from the resultant mean angle discrepancy of $23.2 \pm 13.6$ that there is good correspondence between the simulated and clinical data.

3.5 Conclusions

In this chapter, it was demonstrated that a full-wave numerical simulation model was able to replicate the focal obliquity observed during clinical trials. In addition, it was shown that by using full-wave phase and amplitude corrections, it was possible to significantly reduce the manifestation of the oblique focus. In future, it is imperative that other phasing techniques are studied, and their effect on focusing quality analyzed. In the next chapter, the obliquity metric introduced here will be formalized and we will discuss methods for the complete control over the spatial orientation of the focus during focused ultrasound surgery.
Chapter 4

Rotating a Focus$^1$

As a corollary to Chapter 3, this chapter seeks to formalize the definition of the *oblique focus* and develop a theoretical basis for the complete control over the spatial manifestation of a focus in any clinical ultrasound array. Conventional focusing techniques rely only on the specification of the acoustic energy deposition at a single point. Here, we take a region in the neighbourhood of this target to control the spatial orientation of a single focus or multiple foci.

4.1 Introduction

As the use of focused ultrasound phased arrays continues to grow, increasing efforts have been expended in optimizing treatments and postulating methods for improved patient outcomes, including the use of quantitative temperature images to predict the optimal power for focused ultrasound surgery [267], the application of Zernike polynomials to adaptive focusing [268], optimizing thermal dose distribution using numerical models [269], investigating standing wave formation in transcranial focused ultrasound [270], and a study on the effect of near- and far-field heating on patient safety in uterine fibroid treatments [121]. In addition, new techniques have been introduced to control the acoustic field emitted from a phased array [271, 272]. This chapter aims to expand on the ideas presented in [271] to control the spatial manifestation of the focus generated from a phased array.

The idea of steering and focusing an ultrasound phased array can be formulated as an inverse problem: determining the phase delays required on a set of elements to produce a tight focus at a desired location. This problem has been well-studied [6, 185]. The focus is therefore treated as a single point in space. The inverse of the backwards propagation from the focus then determines the required phase delays to produce the forward problem. Using this technique, there is always a unique solution. Whether this focus is satisfactory, however, is a much more complex consideration, and is based on many factors, including transducer element spacing and steering range [6].

The spatial manifestation of the focus is highly variable and can change based on the array f-number, propagation through an aberrating medium, as well as steering off the main axis of the array. Therefore, the focus can be elongated or rotated. Since focused ultrasound relies heavily on the precision of the beam and the ability to induce biological changes in a limited space, the ability to control the spatial

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manifestation of the focus allows for additional control over the beam. This work adds to a growing volume of literature on phased array controls [273–275].

In reality, the focus does not manifest as a point in space, but rather as a considerable volume of heating, typically on the order of a wavelength. The manifestation of the focus can be considered a Gaussian distribution in three dimensions. Using this idea, the focus can then be described as having an "orientation" in space, by considering how the focus is distributed relative to a fixed coordinate system. Therefore, by sampling points around the focus and solving the inverse problem with multiple control points [271], it should be possible to control the spatial distribution of the focus.

Taking a sample of points around the focus poses an additional problem, however, since the focusing problem can become ill-posed. This is always the case, for instance, when a larger number of points are sampled at the focus than there are transducers in the array. Tikhonov regularization has been used successfully to solve numerous inverse problems in a range of fields [276], and has previously been applied to focused ultrasound to minimize heating at the base of the skull by using the concept of the anti-focus [238]. In this paper, the focusing problem is expanded to include the desired orientation of the focus in space.

At deep locations, the focus can exceed 1-2cm in length [277]. In addition, the orientation of the focus is dictated by the distance from the center of the array, and can overlap with nerves and other critical structures due to the length of the focus. By controlling the orientation of the focus, it is then possible to more accurately target a volume for therapy while sparing surrounding tissue. More specifically, it is shown here that the problem can be posed as a rotation on the focal volume in 3-dimensional space. As an immediate application, this paper focuses on thermal surgery using a 2D focused ultrasound phased array, as proposed in [277].

4.2 Materials and Methods

4.2.1 Transducer Geometry

Figure 4.1: The transducer array with $\lambda/2$ center-to-center element spacing and outer diameter of 12 cm, showing the pressure field at 50 mm in the z-direction.

Following [277], a transducer array consisting of 4572 individually-driven elements in a ring config-
uration was simulated. The outer diameter was 120 mm, and the inner diameter was 20 mm. The centre was left empty with the idea that it may be filled with an imaging transducer. This geometry is illustrated in Fig. 4.1. The transducer elements had a center-to-center spacing of $\lambda/2$, where $\lambda$ is the wavelength of ultrasound in water, in order to ensure full steering capabilities [6]. The domain grid, including the transducer elements, was subdivided into voxels of size $\lambda/5$, in order to ensure low errors in the pressure field estimation. The transducer was sonicating at 500 kHz through tissue in all cases presented, so that the voxel dimensions were 0.6 mm $\times$ 0.6 mm $\times$ 0.6 mm.

4.2.2 Numerical Model

The ultrasound is assumed to propagate in a homogeneous medium and therefore the ray acoustic models described in Section 2.2.1 were performed. In order to study the resultant heating, the Pennes bioheat equation (Equation 2.5) was solved. Table 2.2 lists the parameter values used in the acoustic and thermal simulations.

4.2.3 Theory

The conventional focusing of ultrasound arrays consists of calculating the phase delays required to steer the beam to one [185] or more [271] points. It is argued here that by expanding the region of interest at the focus to encompass a volume with dimensions on the order of the wavelength, it is possible to manipulate the "orientation" of the focus in space, and as a result, rotate the focus freely as desired.

Quantifying a focal volume

In order to quantify focus orientations and rotations, it is necessary to introduce some formalism. It was assumed that the focused ultrasound acoustic pressure field could be well-fitted to a 3-dimensional Gaussian distribution. The Gaussian distribution was defined in Equations 3.1 and 3.2, but is repeated here for reference:

$$G(x) = (2\pi)^{-3/2} |\Sigma|^{-1/2} e^{-\frac{1}{2}(x-x_\mu)^T \Sigma^{-1} (x-x_\mu)},$$  \hspace{1cm} (4.1)

where $x_\mu$ is the location of the peak ultrasound intensity, and $\Sigma$ is the weighted sample covariance matrix, defined as

$$\Sigma = \frac{\sum_i w_i}{(\sum_i w_i)^2 - \sum_i w_i^2} \sum_i w_i (x_i - x_\mu)^T (x_i - x_\mu).$$  \hspace{1cm} (4.2)

The weighted sample covariance matrix is defined such that $w_i = |p(r_i)|$, where $p(x_i)$ is the pressure at sample point $x_i$, so that (4.2) may be rewritten as

$$\Sigma = \frac{\sum_i |p(x_i)|}{(\sum_i |p(x_i)|)^2 - \sum_i |p(x_i)|^2} \times \sum_i |p(x_i)| (x_i - x_\mu)^T (x_i - x_\mu).$$  \hspace{1cm} (4.3)

It can then be thought that $x_\mu$ describes the focus, and $\Sigma$ describes the focal volume. In this way, by arbitrarily thresholding the value of $G$, it is possible to extract a focal volume with the shape of an ellipse. From the natural definition of an ellipse in 3-dimensional space, it is then possible to assign major and minor axes, which can be taken as the eigenvectors of the covariance matrix defined in (4.2). The eigenvector corresponding to the largest eigenvalue is considered the major axis. Representing the
Chapter 4. Rotating a Focus

Figure 4.2: A schematic describing the treatment of the focus as a Gaussian distribution, with orientation described by its major axis.

major axis eigenvector in spherical coordinates, the orientation is naturally defined as $(\theta, \phi)$. This is illustrated in Figure 4.2. In future reference, the value of $\theta$ will be referred to as the obliquity. The meaning of the major axis eigenvalue is more ambiguous, and its precise definition will not be of concern here.

Since the focus is traditionally considered a point source, the phases assigned to the transducer elements are such that there is constructive interference at this point. In this paper, it is argued that there are benefits to considering the problem where the focal volume is considered. In this paper, the set of sampled points, called $\{x_i\}$, are taken in a regular Cartesian grid surrounding the target focus, with a sampling rate of 5 points per wavelength. Since the set of points is taken on the order of a wavelength, a total of $(2 \times 5 + 1)^3 = 11^3 = 1331$ points are taken. That is, $N = 1331$. It is assumed that there are $K = 4752$ independent elements, but the following formalism is valid for all $K$. Each transducer element corresponds to a specific $u = u(x)$ describing the phasing vector, which is subdivided into points of size $\lambda/5$.

**Formalisms**

The phasing problem when considering a set of points in the focal region can be described as solving the equation [271]

$$Hu = b,$$  \hspace{1cm} (4.4)
for the phasing vector $u = u(x)$, where

$$H = \begin{pmatrix} H_p(x_1) \\ \vdots \\ H_p(x_N) \end{pmatrix}_{N \times K},$$

(4.5)

and

$$H_p(x_n) = (p^1(x_n) \ldots p^K(x_n))_{1 \times K}$$

(4.6)

and

$$b = \begin{pmatrix} p(x_1) \\ \vdots \\ p(x_N) \end{pmatrix},$$

(4.7)

where $p^m(x_n)$ describes the pressure contribution at $x_n$ from element $m$, so that

$$p^m(x) = \int_{S_m} \frac{j k \rho c}{2\pi \|x - x'\|} e^{-jk\|x-x'\|} u_m(x') dx',$$

(4.8)

and $S_m$ is the surface of the transducer of element $m$.

**Rotation of a Focus**

Let $R$ be a rotation matrix such that $\tilde{p}(x) = p(R^{-1}x)$, where $\tilde{p}$ is the pressure field after application of the rotation. That is, the pressure field has been rotated by $R$. The problem may then be stated as follows: Given a focal volume $V$, what distribution of power and phase, $\tilde{u}$, would return $V$ rotated by some rotation matrix $R$? Using the above formalism, it is possible to define a matrix problem

$$H[R]\tilde{u} = b,$$

(4.9)

where

$$H[R] = \begin{pmatrix} H[R]_1(x_1) \\ \vdots \\ H[R]_N(x_N) \end{pmatrix}_{N \times K},$$

(4.10)

and

$$H[R]_p(x_n) = (p^1(R^{-1}(x_n - x_\mu) + x_\mu), \ldots, p^K(R^{-1}(x_n - x_\mu) + x_\mu))_{1 \times K}$$

(4.11)

and $b$ is defined as in (4.7). $H[R]$ corresponds to the forward propagator mapping the transducer velocity phasors, $\tilde{u}$, to the focal volume $V$.

The solution to this problem may be obtained using a Tikhonov regularization. Assuming that $u$ is the solution to (4.4), then $\tilde{u}$ in (4.9) can be found by minimizing the functional

$$f(\tilde{u}) = \|H[R]\tilde{u} - b\|^2 + \alpha_{Tikhonov}\|\tilde{u} - u\|^2,$$

(4.12)

for some regularization parameter $\alpha_{Tikhonov}$. The regularization parameter, in this case, takes units of Pa$^2$, since $u$ is the velocity phasor and $H$ is measured in Pascals, and $b$ is measured in Pa·m/s$^2$.

In this case, $\alpha_{Tikhonov}$ plays the role of a Tikhonov regularization parameter, and can be considered
a cost function for deviations of \( \tilde{u} \) from \( u \). The minimum norm solution to (4.12) is given by [238]

\[
\tilde{u} = (H[R]^*H[R] + \alpha_{Tikhonov}I)^{-1}(H[R]^*b + \alpha_{Tikhonov}u),
\]

where \( I \) is the identity matrix of size \( K \) and \( * \) denotes the Hermitian transpose. It is important to note here that the result for general isometries would be derived identically, since isometries in a 3-dimensional Cartesian space are linear operators.

**Generalizations**

Given a sufficient number of degrees of freedom, it is possible to also define independently-rotated multiple foci. In this case, suppose that there are \( M \) focal volumes, labeled as \( V_i \), for \( i = 1 \ldots M \). Then (4.11) can be written

\[
H[R] = \begin{pmatrix}
H_{V_1}[R_1] \\
\vdots \\
H_{V_i}[R_i] \\
\vdots \\
H_{V_M}[R_M]
\end{pmatrix}_{(\sum_{i=1}^M N_i) \times K},
\]

and

\[
H_{V_i}[R]^p(x_{i,n}) = (p^1(R_i^{-1}(x_{i,n} - x_{\mu_i}) + x_{\mu_i}), \ldots, p^K(R_i^{-1}(x_{i,n} - x_{\mu_i}) + x_{\mu_i}))_{1 \times K},
\]

where \( R_i \) and \( x_{\mu_i} \) correspond to the rotation matrix and mean position of the \( i \)th focal volume, \( V_i \), respectively. It is assumed here that \( x_{n,i} \neq x_{m,j} \) for \( m \neq n \), for all \( i, j \).

**4.2.4 Error Analysis**

The effect of error in the phasing controls on the resultant acoustic field was analyzed. Various levels of random error were added to the transducer power assigned to each element in the array, as well as the phasing used. Low (<\text{SNR}> = 5), moderate (<\text{SNR}> = 2), and high (<\text{SNR}> = 4/3) levels of error were analyzed, and the resultant pressure field normalized to the intensity of the error-free case, were described.

**4.3 Results**

**4.3.1 Focus Rotations**

Figure 4.3 demonstrates the distribution of temperature resulting from the rotation of a focus to predetermined angles, where in each case the normalized temperature distribution is shown. As a reference, Figure 4.3a shows the original focus without rotation, using the conventional point-source phasing technique. Figs. 4.3b, 4.3c, and 4.3d show the rotation of the focus by 15\(^\circ\), 30\(^\circ\), and 45\(^\circ\) about the y-axis, respectively. In all three cases, the inverse problem was solved with \( \alpha_{Tikhonov} = 10^3 \). To give an idea of the spatial distribution of heating using this method, Figure 4.4 provides a 3-dimensional representation of a 45\(^\circ\) rotation in the yz-plane, contrasted to the focus distribution using conventional phasing techniques. In this case, the temperature is thresholded at half the maximum temperature in the focal
Figure 4.3: A demonstration of the rotation of the focus at a depth of 50 mm, along the main axis of the array, by (a) 0°, (b) 15°, (c) 30°, and (d) 45°. The normalized temperature profile is shown.

Figure 4.4: A 3-dimensional representation of the new focusing technique introduced, demonstrating (a) conventional focusing techniques, and (b) the focusing technique introduced here which allows for the focus to reorient spatially.

region. From this figure, it is evident that the focusing is maintained while the focal volume is rotated. An issue of note is that the volume of heating increases as the angle of rotation increases. In the three cases presented in Figure 4.3, a 15° rotation results in an 18% increase in the focal volume, a 30° rotation results in an 60% increase in the focal volume, and a 45° rotation results in an 141% increase in the focal volume, as compared to the focus obtained from standard focusing. The focal volume in all three cases was taken as the volume inside the 50% contour of the peak temperature.

Fig. 4.5 demonstrates the role of the regularization parameter $\alpha_{Tikhonov}$ on the quality of the focusing and the rotation of the focus, as well as the distributions of transducer velocities and phases to obtain these pressure maps. In this case, the problem is set up such that the focus should be rotated 30° about the y-axis. The first row illustrates the focus obtained for various $\alpha_{Tikhonov}$-values. The second and third rows show the transducer velocity magnitude and phase, respectively, of the transducer elements in the array, determined by solving (4.9).

The focus obtained using conventional point-source focusing is shown in Figure 4.5a. It is shown in
Figure 4.5: The effect of varying $\alpha_{\text{Tikhonov}}$ when attempting to rotate the focus $30^\circ$ about the y-axis. The top row illustrates the resultant normalized acoustic fields. The second and third rows show the transducer velocity magnitude and phase, respectively, of the transducer elements in the array, determined by solving (4.9).

Figure 4.5b that in the underregularized case, since the problem is ill-posed, the focusing disappears, and there is a large deposition of energy in the peripheral regions. On the other hand, with a sufficiently high $\alpha_{\text{Tikhonov}}$, the cost of deviation from the initial phasing is too high, and hence there is minimal change from the initial pressure pattern, as shown in Figure 4.5d. Figure 4.5c shows that for certain intermediate $\alpha_{\text{Tikhonov}}$, it is possible to obtain a good balance between focusing and the desired focal rotation. This is also illustrated by contrasting Figs. 4.5e and 4.5i to Figs. 4.5h and 4.5l. The high $\alpha_{\text{Tikhonov}}$-value results in a phase and amplitude plot nearly identical to the case of conventional phasing. The intermediate cases of $\alpha_{\text{Tikhonov}} = 10^{-4}$ and $\alpha_{\text{Tikhonov}} = 10^4$ in Figs. 4.5f and 4.5g illustrate significant amplitude deviations from the original cases. It is clear from the phase plots in Figs. 4.5j and 4.5k that in the underregularized case, the phase deviates significantly from the conventional phasing case, resulting in the non-existent focusing illustrated in Figure 4.5b. Figs. 5b–d are normalized about the mean transducer velocity, and thresholded below twice this mean, in order to have sufficient contrast.

Figure 4.6 plots the normalized peak pressure, $|p|$, the focal obliquity, $\theta$, and the standard deviation of the element powers for a range of values of $\alpha_{\text{Tikhonov}}$. The values are normalized such that the total
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Figure 4.6: The role of $\alpha_{Tikhonov}$: The normalized peak pressure, $|p|$, the focal obliquity, $\theta$, and the standard deviation of the element powers, $\sigma(P)$, are plotted. Note the logarithmic scale of $\alpha_{Tikhonov}$.

Power outputs of the transducer array are identical for different $\alpha_{Tikhonov}$. In addition, the standard deviation is normalized to the maximum deviation of powers. As suggested in Figure 4.5, there is a complex relationship between $\alpha_{Tikhonov}$, $\theta$, $P$, and $|p|$. Ideally, the solution to the problem should render a high peak pressure, minimal change in the distribution of power amongst the elements, and the focus should be oriented in the exact direction spatially. As shown in Figure 4.6, however, the peak pressure is considerably lower as the angle of obliquity increases, and the powers vary more significantly. This is to be expected, of course, since the problem posed in (4.12) is a balance between the conventional phase controls and the minimum-norm solution of the obliquity problem, which can be ill-posed.

Figure 4.7: The effect of $\alpha_{Tikhonov}$ on the peak acoustic pressure at the focus for various rotation angles, at locations 50 and 100 mm in front of, and 0, 20, and 40 mm laterally from the transducer array.

Figure 4.7 quantifies the effect of $\alpha_{Tikhonov}$ on the peak acoustic pressure for $x = 0$, 20, and 40 mm.
Figure 4.8: The effect of $\alpha_{\text{Tikhonov}}$ on the achieved focal obliquity for various target rotation angles, at locations 50 and 100 mm in front of, and 0, 20, and 40 mm laterally from the transducer array.

Laterally, and at depths of $z = 50$ and 100 mm. As can be seen from the figure, a higher $\alpha_{\text{Tikhonov}}$ value, corresponding to higher levels of regularization, leads to a higher peak pressure. Although it has been previously been shown that the pressure magnitude of lateral targets is lower than central targets for this transducer array configuration [277], for a given rotation, the relative amplitude for each rotation remains relatively constant.

Figure 4.8 demonstrates the achieved rotation angle for each target angle at various positions. It can be seen that for lower $\alpha_{\text{Tikhonov}}$, the obtained obliquity is closer to the target angle of obliquity, illustrated by the diagonal line in the figure, which indicates an optimal attainment of the target angles between 0 and 45°. The peak achievable angle of rotation, however, is greatly diminished for lateral positions, illustrated at x = 20 and 40 mm.

Fig. 4.9 demonstrates the ability of this focusing method to re-orient the focal volume along the z-direction of the array. In Figure 4.9a, foci at depths of 50 and 100 mm, and 0, 20, and 40 mm laterally were simulated using conventional focusing. Consistent with [277], the foci off-axis are oblique, and the angle of obliquity increases as the steering angle increases, as expected. By fitting each focus to a Gaussian, it is possible to determine the rotation matrix $R$ that will re-orient the focus along the z-axis. Figure 4.9b illustrates the re-orientation of the foci along the z-axis of the array using this method. In all six cases, a value of $\alpha_{\text{Tikhonov}} = 10^3$ was used.

### 4.3.2 Multiple Independent Rotations

The synthesis of multiple independently-rotated foci using (4.14) is illustrated in Figure 4.10. Figure 4.10a demonstrates the phasing pattern using the conventional multiple focus synthesis technique introduced in [271]. The rotation of the left and right foci by 45° and $-45^\circ$, respectively, is demonstrated in Figure 4.10b. In this case, a value of $\alpha_{\text{Tikhonov}} = 10^3$ was used.
4.3.3 Near-Field Heating Analysis

The potential for near-field heating is a substantial concern for focused ultrasound treatments, and has been studied previously for conventional phasing techniques and uterine fibroid ablation [121]. Figure 4.11 demonstrates the role of $\alpha_{Tikhonov}$ on near field heating, for $\alpha_{Tikhonov}$ values of $10^3$, $10^4$, and $10^5$. It can be seen from the figure that a decreased level of regularization, manifesting as smaller $\alpha_{Tikhonov}$, has the effect of increased near-field heating. This is of concern to any clinical application of this technique for ablation, where the use of high temperature elevation at the focus must be accompanied by low levels of heating elsewhere, in the interest of patient safety.

4.3.4 Error Analysis

Figure 4.12 illustrates the effect of additive noise on the resultant acoustic pressure field, showing (a) the focus obtained through traditional focusing, (b) the rotated focus solved with error-free information from Eq. 4.13, (c) the solution to Eq. 4.13 with 20% additive noise, and (d) the solution to Eq. 4.13 with 50% additive noise. The error was added to the velocity of the transducer elements. As can be seen, the peak acoustic pressure at the focus drops with added error, in a similar fashion to the traditional focusing case, and the sidelobes are more pronounced.

4.4 Discussion

The method introduced here to perform an isometry on a focal volume provides an additional degree of control over the manifestation of the focus when performing a thermal focused ultrasound treatment. The possibility of heating extraneous structures necessitates an understanding of the focal orientation and the ability to spare surrounding tissue. As can be seen from the results of the paper, $\alpha_{Tikhonov}$ plays a critical role in the rotation of a focus.
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Figure 4.10: (a) Multiple focus synthesis using the technique outlined in Ebbini1989, and (b) independently rotating the left and right foci by 45° and −45°, respectively. The images and scales depict normalized \( |p|^2 \). The relative (c) and normalized (d) pressure profiles along the y-axis before (solid line) and after (dashed line) rotation are also plotted, in order to compare the relative peak pressures and the relative sidelobe effects, respectively.

4.4.1 The role of \( \alpha \)

The phasing technique presented here relies heavily on the value of \( \alpha_{\text{Tikhonov}} \) used in each solution to (4.12). In particular, the optimal value of \( \alpha_{\text{Tikhonov}} \) is problem-specific, and its role as both a Tikhonov regularization parameter and a cost factor between the original phasing pattern and the desired focus isometry further complicates matters. As was demonstrated in Figure 4.5, a sufficiently large \( \alpha_{\text{Tikhonov}} \)-value will result in the focus obtained from conventional phasing, whereas a sufficiently small \( \alpha_{\text{Tikhonov}} \)-value will result in a complete loss of focusing of the ultrasound. Ideally, it would be useful to develop a technique to implicitly determine the precise value of \( \alpha_{\text{Tikhonov}} \) for each geometry; however, an optimization over the solution space to each specific problem is more likely to garner useful, albeit less insightful, results. It must be noted that the computational cost of the inverse problem was found to be heavily-dependent on the generation of \( H \) and \( H_R \) in (4.5) and (4.12), rather than the determination of the solution for each \( \alpha_{\text{Tikhonov}} \).

A judicious choice of \( \alpha_{\text{Tikhonov}} \) for any given rotation must balance the desired obliquity, the peak pressure amplitude, and the standard deviation of power. An example of these variables as a function
Figure 4.11: The effect of rotation on the near field of the transducer array compared to (a) conventional focusing, for (b) $\alpha_{Tikhonov} = 10^3$, (c) $\alpha_{Tikhonov} = 10^4$, and (d) $\alpha_{Tikhonov} = 10^5$.

of $\alpha_{Tikhonov}$ is plotted in Figure 4.6. In this particular case, a reasonable choice of $\alpha_{Tikhonov}$ would lie between $10^3$ and $10^6$, since it is between these values that there is still a significant obliquity while maintaining a relatively equal distribution of power among the elements and a high peak pressure amplitude. The precise value of $\alpha_{Tikhonov}$, however, must be determined using a metric that quantifies the desired balance between the three factors.

4.4.2 Limitations

It must be noted that there are several limitations to the presented technique for rotating foci.

Firstly, only a rudimentary analysis of the effect of error was implemented. It appears, however, that in Figure 4.12, random error added to the inverse phasing controls does not significantly affect the focusing quality. There are multiple potential sources of error that could arise in an experimental implementation: transducer surface imperfections, imperfect impedance matching, and errors relating to amplifier gain, to name a few. In addition, as described in [276], the presence of unknown error severely complicates the determination of the Tikhonov regularization parameter, $\alpha_{Tikhonov}$. If it is assumed
that the norm of the error can be well estimated, then the Morozov discrepancy principle can be applied to determine an initial estimate for $\alpha_{Tikhonov}$ [276], which we will call $\alpha_{Morozov}$. This initial estimate will ignore the secondary role that $\alpha_{Tikhonov}$ plays in this application: namely, as a cost parameter. Further deviations from $\alpha_{Tikhonov}$ can then be considered as $\alpha_{Tikhonov} = \alpha_{Tikhonov}' + \alpha_{Morozov}$, where $\alpha_{Tikhonov}' \in (-\alpha_{Morozov}, \infty)$, in order to achieve the focus isometries presented here.

The second limitation is the potential for no good $\alpha_{Tikhonov}$ value to manifest. Naturally, it is possible that there are insufficient degrees of freedom to achieve the desired focal orientation, or to obtain the desired focal orientation without physically unrealistic parameters. It is also possible that the transducer geometry does not allow for the desired angle to be reached. For instance, from the distribution of power illustrated in Figure 4.5g, there appears to be a geometric component to the rotation of the focus. As a result, it would seem that a curved or hemispherical transducer array would present a more desirable geometry for rotation to higher angles. In addition, it is possible that by increasing sufficiently $N/K$, such that the number of transducer elements is significantly greater than the number of control points, it may be possible to increase the maximum rotation angle achievable, up to a limit.

Figure 4.12: The effect of additive noise on the resultant acoustic pressure field for a focus rotated by 30°, with regularization parameter $\alpha_{Tikhonov} = 10^4$. 

(a) No Noise

(b) Low Noise: $<\text{SNR}> = 5$

(c) Moderate Noise: $<\text{SNR}> = 2$

(d) High Noise: $<\text{SNR}> = 4/3$
In the same light, the value of $\alpha_{\text{Tikhonov}}$ has been shown to control multiple aspects of focusing quality, including near-field heating and peak acoustic pressure. From Figure 4.8, it is clear that for sufficiently high rotation angle $\theta$, there is no $\alpha_{\text{Tikhonov}}$ that allows the focus to reach this obliquity. The maximum attainable angle with the presented geometry appears to be approximately $35^\circ$. A curved transducer array could potentially increase the maximum angle achievable because the natural geometry is more conducive to focus rotations.

A third limitation relates to the case presented in Figure 4.9, where the foci were re-aligned with the z-axis for steered positions. As can be seen from comparing the foci at $(x = 40, z = 100)$ in Figure 4.9a and Figure 4.9b, the focal volume thresholded at $60^\circ\text{C}$ in the latter case encompasses a larger area than the former. When using conventional phasing techniques. This shows that as the focus is steered further away from the transducer array, the focus rotations become more costly to the focusing, and the focusing quality can diminish. This is a similar effect as when comparing the focusing at $z = 50$ mm and $z = 100$ mm from the array: as the focus is steered further from the transducer, the focus quality decreases.

As has been shown in transcranial focused ultrasound, the use of amplitude and phase corrections at the focus minimizes the focal volume and concentrates the energy in the most efficient manner. Naturally, one would then assume that as the distribution of power among the array elements increases in range, the deposition of energy at the focus becomes wider. As has been shown in Figure 4.8, a lower value of $\alpha_{\text{Tikhonov}}$ yields a higher rotation, while the distribution of power among the elements deviates further from the mean. As a result, using this technique, it appears that an increased focal volume is an additional cost. Future techniques may overcome this limitation.

In a similar light, it is evident from Figure 4.3 that there are limitations on the achievable angles of obliquity given a transducer array geometry and degrees of freedom. It is possible that other array geometries could be tested in future work for their efficacy in rotating focal volumes.

### 4.4.3 Comparison to Existing Phased Array Control Techniques

Several past works have investigated the used of phased array controls to modify the phasing pattern generated from a phased array of ultrasound transducers [271,275]. In particular, Hertzberg and Navon demonstrate that it is possible to position multiple foci in order to obtain a desired ultrasound field map using holographic techniques [275], and Ebbini and Cain [271] proposed an iterative multiple focus synthesis technique that allows for an even distribution of acoustic power. The techniques presented here, demonstrated in particular in Figure 4.10, can complement these techniques, by adding control on a sub-wavelength scale, allowing for the control of the spatial manifestation of each focus in the acoustic field pattern.

### 4.4.4 Computational Aspects

The implementation of this technique to real-time applications must be considered. Using an NVIDIA GPU for parallel processing and a dual-core computer, the computation of the phasing controls for a single point requires on Matlab (2015a, The MathWorks, Natick, MA, USA) approximately eight minutes. In addition, for a simulation domain spanning $28 \times 28 \times 28$ cm$^3$ and $470^3$ grid points, the computation requires approximately 1.6 GB of memory to compute. In future applications, parallelization and faster numerical methods could potentially be explored in order to reduce the computation time for experimental implementation.
4.5 Conclusions

A method to control the orientation of a focus generated by an ultrasound phased array was introduced in this chapter. It was shown that, in most cases, by using a Tikhonov regularization with a judicious choice of the hybrid regularization-cost parameter $\alpha_{Tikhonov}$, it was possible to freely rotate the focus while maintaining a relatively high peak pressure amplitude and having a high array efficiency. It was shown that it is possible to re-orient a steered focus along the main axis of the transducer array using a clinically-relevant focused ultrasound array. It was also shown that it is possible to perform focus isometries on multiple foci independently. Limitations to this technique include the assumption of minimal error, the possibility that no good $\alpha_{Tikhonov}$-value will manifest, and the diminishing efficacy of the method further from the transducer array, in a manner similar to the conventional point-source focusing technique.

In the next chapter, we return to clinical data for inspiration. Chapter 5 presents the clinical observation of unexpected temporal heating profiles observed during MR-guided focused ultrasound surgery for the treatment of ET.
Chapter 5

Unexpected Temperature Profiles

This chapter follows a similar structure to Chapter 3, where clinical experience has led to interesting observations, which are reported for the first time, followed by a thorough analysis of the probable causes of this phenomenon and possible corrective techniques. We will introduce the concept of a heating plateau. The plateau occurs when the resulting temperature rise from focused ultrasound surgery begins to drop below the expected levels, and in some cases remains stagnant, as will be demonstrated. This chapter covers several techniques of biomedical research, starting from clinical experience and moving towards numerical modeling, benchtop experimental procedures, and animal experiments.

5.1 Introduction

During the course of the FUS treatment, multiple ultrasound sonications are performed to cause a small focal thermal coagulation of brain tissue at the anatomically-determined location of the VIM nucleus [13]. The power of the repeated sonications is gradually increased over the course of treatment to achieve focal ablation of the targeted brain tissue. From the Pennes bioheat equation [248], it is expected that the temperature will rise linearly with increasing acoustic power, since these short-duration sonications would not be substantially influenced by changes in the blood perfusion [245]. However, we present clinical data where the high power sonications during many ET treatments do not follow the expected linear relationship and the total increase in temperature per Joule of applied energy, which we call here energy-temperature efficiency, decreases over the course of the treatment.

It is hypothesized that this reduction in energy-temperature efficiency is the result of changing acoustic parameters along the path of the beam as a function of increasing temperature, on top of the expected aberrations due to variations in skull thickness and density, which de-phase the acoustic beam at the focal volume. In this study, we have quantified these effects and explored the causes of the temperature saturation. Understanding this reduction in efficiency may lead to more effective thalamotomy treatments in the future. In addition, the ability to prevent the expanse of the focal volume would improve the degree of control the operator has over the treatment. These results could have an impact on a wide range of current and future clinical FUS brain therapies.

1Parts of this section appear as Alec Hughes, Yuexi Huang, Michael L Schwartz, and Kullervo Hynynen. Focus de-phasing correlates with the reduction in treatment efficiency at high acoustic powers during MR-guided transcranial focused ultrasound thalamotomy for essential tremor. Medical Physics, Submitted, 2018
The aim of the study is to analyze clinical data indicating a reduction in the induced energy-temperature efficiency relationship during transcranial FUS ET thalamotomy treatments at higher acoustic powers, establish its relationship with the spatial distribution of the focal temperature elevation, and explore its cause.

5.2 Materials and Methods

Clinical data were obtained with approval from the Research Ethics Board at Sunnybrook Health Sciences Centre (Toronto, ON, Canada) and all patients provided free and informed consent prior to their participation in the study. In addition, all animal procedures were approved by the Sunnybrook Research Institute Animal Care and Use Committee and conformed to the guidelines set out by the Canadian Council on Animal Care.

MATLAB (R2016b with Statistical Toolbox, The Mathworks, Inc., Natick, MA, USA) was used to perform all statistical analyses. The multivariate Pearson correlation coefficients were computed in MATLAB to determine correlation coefficients and their respective P values. A P value of 0.05 was used for significance.

5.2.1 Clinical Data

Nineteen patient treatments were analyzed retrospectively. These patients were treated between July 2015 and August 2016 at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada and consisted of the entire cohort treated for a clinical trial of focused ultrasound for the treatment of ET FUS thalamotomy. The treatment procedures and inclusion/exclusion criteria followed previous ET FUS thalamotomy studies [13,14,16].

All patients were treated with a hemispherical, 30-cm-diameter ultrasound phased array operating at a frequency of 670kHz. The array consisted of 1024 transducer elements with independent phase and amplitude control (ExAblate 4000, 670 kHz; InSightec, Haifa, Israel). All hair was removed and a stereotactic frame was affixed to the head for immobilization during the treatment. The patient was then placed on an MRI system patient table and the transducer array placed around the head. A flexible membrane was secured around the head and fixed to the opening of the array such that a water tight volume was formed between the array and the patients head. Cooled, degassed water was then circulated in this space to provide skin and skull cooling and to provide a coupling medium for the ultrasound propagation between the array elements and the skin. T2-weighted MRI was used to localize the brain landmarks for targeting and to allow prior CT scans of the skull bone to align with the patient setup. The CT scans were used to correct the beam distortions induced by the skull bone such that a sharp focus was achieved [197,199,279].

Treatment sonications were performed under the direction of a neurosurgeon (M.L.S.). Low power (100-250 W) sonications were performed first for targeting accuracy. The power was then gradually increased until the peak temperature reached ablative temperatures (approximately 54-60°C), if it was possible. The 2-dimensional (2D) axial temperature map and temporal temperature profile for a single sonication are shown in Figure 5.1, as well as a schematic of the hemispherical phased array used to perform the FUS thalamotomy, emphasizing the traversal of the different beam paths through skull and brain tissue. The temperature maps were taken at 3.7 s intervals and contained noise of approximately ±0.5°C.
Figure 5.1: (A) A schematic of the hemispherical transcranial focused ultrasound (FUS) device sonicating
in the brain from multiple elements, (B) the temperature rise in the focal region as a function of time,
illustrating the peak (solid line) and average (dotted line) temperature rises. The change in temperature,
$\Delta T$, the duration, $\Delta t$, and the calculation of power, $W$, are also illustrated to elucidate the calculation
of the efficiency metric in Equation 1. (C) The 2D axial temperature map through the focus, with the
focal region magnified in the inset. Scale bar = 10 mm.

5.2.2 Image Processing

The temperature rise for each sonication was measured in one of the axial, coronal, or sagittal planes.
To control for the natural diffusion effects of longer duration heating, the image slice at the 9 s timepoint
was used during the analysis. To reduce the impact of noise, the mean temperature over $3 \times 3$ voxels
at the focus was taken as the temperature rise. Temporal filtering of each voxel was performed using a
Table 5.1: A summary of the clinical cases. The number of sonications performed, the peak temperature achieved, the peak applied acoustic power, the maximum sonication duration, and the calculated power-efficiency correlation are listed along with their respective p-value. Patients with non-significant (p-value > 0.05) power-efficiency correlation coefficient are marked with an asterisk (*).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of Sonications</th>
<th>Sonications Included in Analysis</th>
<th>Peak Temperature (C)</th>
<th>Peak Power (W)</th>
<th>Peak Energy (J)</th>
<th>Maximum Duration (s)</th>
<th>Energy-Efficiency Pearson Correlation Coefficient</th>
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<td>4563</td>
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<td>800</td>
<td>19152</td>
<td>24</td>
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<td>14388</td>
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</tr>
<tr>
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<td>19176</td>
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<td>900</td>
<td>24327</td>
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<td>47.4</td>
<td>600</td>
<td>24940</td>
<td>43</td>
<td>-0.90 (P &lt; 0.01)</td>
</tr>
</tbody>
</table>
moving average filter with a window size of 11.1s (3 time points) over the course of treatment. Low power sonications where the focus was not resolvable from the noise and aborted sonications were excluded from the analysis. The total number of sonications and the number of included sonications is outlined in Table 5.1. A list of all performed sonications for each patient can be found in Appendix 7.3.

The focal size was defined as the 50% area around the peak temperature voxel for each sonication. To determine the 50% area, the temperature map was normalized to the peak temperature, and the local 2 cm × 2 cm area around the focus was thresholded and segmented.

5.2.3 Correlation of Efficiency with Other Treatment Parameters

The efficiency, $E$, of each sonication was defined as

$$E = \frac{\Delta T}{W},$$

(5.1)

where $\Delta T$ is the temperature rise and $W$ is the applied energy, so that $E$ is measured in $^\circ C / J$. Assuming a linear response between power and temperature, then, one would expect $E$ to remain constant for each patient for a fixed sonication duration [280, 281]. The percentage changes in treatment efficiency and focal size between the minimum and maximum acoustic energies were taken to quantify decreases in efficiency and increases in focal size for each patient.

Correlations were then assessed between changes in treatment efficiency and the peak temperatures obtained during the treatment, the peak applied acoustic powers, the peak deposited acoustic energy, the peak sonication durations, the total number of sonications, and the changes in focal size. When assessing the correlation between the change in treatment efficiency and the focal spot size, only those sonications performed in the axial (perpendicular to the main axis of the array) plane were included, because in all analyzed patients, most imaging scans were performed in the axial plane and the axial plane provides the best estimate of the tissue temperature.

5.2.4 Experimental Studies to Explain the Observed Phenomena

To determine the cause of the clinically-observed reduction in energy-temperature efficiency and focal expansion, a series of experiments was also performed.

There are several competing hypotheses to explain the observed reduction in energy-temperature efficiency in the clinical cases. First, it is possible that as the skull heats, either temporary or permanent thermal damage to the skull and scalp causes the acoustical impedance to change, resulting in lower acoustic transmission to the bone in regions of high heating. To test this hypothesis, computer simulations were performed using temperature-dependent acoustic parameters and the results compared to the clinical data.

It is also possible that after repeated sonication, there are changes in the tissue in the focal region that cause absorption to decrease, perfusion to change, or the delivery of energy to already-heated regions to decrease due to changes in acoustic impedance between ablated and non-ablated tissue. To this effect, rabbit experiments were performed using a single transducer, replicating the timescales of the clinical treatments.

Finally, it is possible that the transducer array output decreases over time and the energy being delivered is reduced over longer, higher power sonications. To test this hypothesis, transducer experiments
Figure 5.2: The longitudinal (solid line) and shear (dashed line) speeds of sound (A) and attenuation (B) used in the temperature-dependent numerical simulations.

were performed using the clinical phased array and a hydrophone at the focus. The pressure measured on the hydrophone was analyzed as a function of applied acoustic power from the array.

With these experiments performed, the effects of skull heating, tissue heating, and transducer engineering were analyzed for their independent effects to explain the clinical observations.

**Computer Simulations on The Effects of Skull Heating**

If uniformly applied over the skull, temperature changes in the cranial bone would not explain the observed plateau, since the acoustic phase delays from all elements would experience the same temporal shift. The skull thickness and density, however, vary spatially and cause non-uniform skull heating [4] that could result in the observed defocusing. We sought to explore the effect of this non-uniform heating on the transcranial focusing problem.

Using previously-developed computer simulations [201, 251], the temperature rise in the skull was simulated for Patient 8 for clinical sonication parameters (600 W power, 24 s duration) to illustrate the effect of temperature-dependent speed-of-sound and attenuation changes on the manifestation of the focus. The temperature fields at 1-s intervals between 0 and 24 s were recorded, assuming constant parameters over each 1-s period. The change in the speed of sound and attenuation as functions of temperature in the skull bone were taken to be ratios relative to the standard acoustic measurements taken at room temperature (20°C) [201], using the mean values over the samples obtained from Nicholson and Bouxsein [282]. The speed of sound and attenuation were therefore taken to be separable functions of both density and temperature: $c = c(\rho, T) = c_0(\rho) \beta(T)$ and $\alpha = \alpha(\rho, T) = \alpha_0(\rho) \gamma(T)$, as constant factors scaled from a previous study in the calcaneus bone [282]. In the case of speed of sound, $\beta(T) = (15962.2T)/1552$, whereas in the case of attenuation, $\gamma(T) = (47.15 + 0.75T)/62.15$, where $T$ was the temperature in Celsius. Figure 5.2 illustrates the values of $c_0(\rho)$ and $\alpha_0(\rho)$ for longitudinal and shear waves, taken from a previous study [201].

Assigning each voxel representing bone in the 3-dimensional simulation grid to a temperature-dependent speed of sound and attenuation, the acoustic simulations were then re-run in a stepwise fashion, assuming constant temperature for 1 s at a time. The absorbed power density was then recorded.
High Power

Figure 5.3: The experimental setup during the in vivo rabbit experiments. The rabbit is placed supine and the transducer \((f = 1.5 \text{ MHz})\) is positioned using a 3-axis positioner to sonicate a central target close to the surface of the brain, to avoid skull base heating. Radiofrequency (RF) coils are placed close to the target for localized thermometry with a 3T MRI system during the treatment. Outside of the magnet room, a custom-built computer interface is used to perform the sonication and provide thermometry feedback. Also illustrated are examples of low and high power sonication thermometry results overlaid on anatomical MR images.

for each timepoint and the temperature rise over the 1-s interval was simulated using the Pennes bioheat equation [248].

**In Vivo Rabbit Experiments to Determine the Effect of Brain Absorption, Perfusion Rates and Thermal Conductivity**

To determine if there were changes in the brain tissue during multiple sonications, experiments were performed on a New Zealand white rabbit, obtained from Charles River Laboratories (Sherbrooke, QC, Canada) and weighing between 2.5-3 kg at the time of the experiment. These experiments were used to compare the power-temperature efficiencies after 6 and 15 s of heating, to determine whether brain absorption, perfusion, and thermal conductivity changed substantially upon the repeated application of ultrasound with increasing acoustic powers. A craniotomy was performed 9 days prior to experiments for ultrasound coupling with the brain without skull impediment, so that the effect of brain heating alone could be analyzed. The animal was anesthetized with a cocktail of ketamine (50 mg/kg) and xylazine (5 mg/kg) and maintained on isoflurane (2-2.5%) for the duration of the surgery. The skin over the removed bone was sutured and the wound healed prior to the experimental procedure.

A concave transducer \((f = 1.513 \text{ MHz}, \text{ f-number} = 0.8, \text{ focal length} = 10 \text{ cm})\) was used in the experiments. The transducer was moved using a 3-axis positioning system and positioned such that the focus was near to the brain surface, so that skull base heating was of minimal concern. The experimental setup is illustrated in Figure 3, as well as an illustration of the temperature rises recorded using
Table 5.2: Correlations of Changes in Efficiency with Treatment Parameters. Correlations of various treatment parameters with the percentage change in the power-temperature efficiencies, taken for all nineteen (19) clinical cases, listed with their associated P values. Also included is the multiple linear regression over all five variables. The percentage change in the focal size is marked with an asterisk, since in this regression the power-temperature efficiency was calculated, instead of the energy-temperature efficiency, since all temperature maps were taken at the 9-s timepoint. In addition, the change in focal size only considered axial sonication.

<table>
<thead>
<tr>
<th>Correlation with Change in Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak temperature</td>
</tr>
<tr>
<td>Peak energy</td>
</tr>
<tr>
<td>Peak power</td>
</tr>
<tr>
<td>Peak time</td>
</tr>
<tr>
<td>Multiple Linear Regression over all Variables</td>
</tr>
<tr>
<td>Percentage Change in Focal Size*</td>
</tr>
</tbody>
</table>

MR thermometry for low and high powers. Lower frequency (f = 0.558 MHz) sonications were also tested. However, due to the longer focus at 0.558 MHz, scalp burning and skull base heating became insurmountable issues in the rabbit model, and these analyses were not included here.

Transducer Array Power Experiments

It was hypothesized that there could be an effect of the transducer elements or the driving electronics and their response at higher acoustic powers. To test this hypothesis, experiments were performed with the clinical system sonicating into degassed water. A 125-µm fiber-optic hydrophone with an active sensor diameter of 10 µm (Precision Acoustics, Dorchester, U.K.) was placed at the geometric focus of the transducer array to measure the acoustic pressure. In the interest of maintaining hydrophone integrity and accuracy, 30% apodization of the transducer array was used, such that only 68 elements were sonicating. The apodization was calculated as a solid angle of the hemispherical array, similar to a previous study [270]. Transducer powers were set to be equal among all array elements. The acoustic power on each element ranged from 0.37-1.03 W, such that the total acoustic power on the array ranged from 25-70 W. If the full array were used at this level, then the total array power would range from 379-1055 W, covering most of the range of the clinical treatments.

5.3 Results

5.3.1 Correlation of Efficiency with Other Treatment Parameters

Table 5.2 shows the correlation between the reduction in efficiency in the nineteen patients with various treatment parameters. The results show significant correlation between the reduction in efficiency observed and the peak temperature achieved (P = 0.02), the peak power (P < 0.01), the peak energy (P < 0.01), and the peak duration (P < 0.01). The multiple linear regression has an R-squared of 0.82 (P < 0.01). This shows that as the peak power, peak energy, and peak duration increased, the efficiency of the treatment would decrease. This is to be expected, since a treatment with lower efficiency at higher powers would typically yield less success, as indicated by the positive correlation between the peak temperature and the efficiency. These data indicate that the efficiency of the treatment correlates negatively with less desirable treatment outcomes, since the ideal treatment is fast, efficient, and targeted.
Figure 5.4: The clinical sequences of sonications as functions of power, with sonication order indicated by the arrow directions. Patients 1 and 8 are presented. There is no significant reduction in efficiency over time for Patient 1 (P = 0.06), while there is a significant reduction in efficiency for Patient 8 (P < 0.01). The box highlights the reduction in efficiency as a function of time for a constant power level.

Table 5.1 summarizes the nineteen clinical cases analyzed in this clinical trial, emphasizing the power-efficiency correlation coefficients. In eighteen (18) of the patients, there is significant (P < 0.05) negative correlation between the applied acoustic power and the efficiency. That is, in these patients the efficiency decreased as a function of power. For one (1) patient there was no significant correlation between power and efficiency (Patients 1) and no significant decrease in efficiency. Interestingly, this patient also had the lowest deposited energy.

Figure 5.4 shows examples of the energy-temperature efficiency achieved during each of the sonications during a treatment as a function of applied acoustic power. The examples are presented for a patient with a relatively constant efficiency over time (Patient 1) and a patient with a decreasing efficiency over time (Patient 8) to illustrate the patient variability within the data. The directions of the arrows indicate the order of the sonications in time. This figure demonstrates that in some patients, the efficiency is decreasing with the power and number of sonications.

Considering the variation between patients in more detail, the power-temperature efficiency was constant between low and high powers for Patient 1, whereas there was a 60% decrease in efficiency between low and high powers for Patient 8. Clinical MR thermometry images taken at a timepoint of 9 s are illustrated for these patients in Figure 5.4, as well as a summary of the relationships between power and efficiency for all sonications. Figure 5.5 illustrates the relationship between the size of the
focus and different power levels for Patient 8, where the focal size increases as the power increases.

In addition, Figure 5.5 summarizes the relationship between the rate of change in the power-temperature efficiency and the focal size as a function of applied acoustic power, for all nineteen clinical cases. There is a significant negative correlation ($P < 0.01$). Therefore, the less efficient the treatment, the more dispersed the focus at higher powers.

### 5.3.2 Experimental Studies to Explain the Observed Phenomena

**Computer Simulations on The Effects of Skull Heating**

Figure 5.7 illustrates the reduction in focal temperature rise as a function of time with changing acoustic parameters as a function of temperature, the increase in the focal volume, and the absorbed power density over time. The temperature rise is 12% lower and the focal dispersion is 8% higher over time. Although the general trend is observed in the numerical simulations, the effect was larger in the analyzed clinical cases. From the clinical case, the temperature rise is 68% lower and the focal dispersion is 47% higher over time.

**In Vivo Rabbit Experiments to Determine the Effect of Brain Absorption, Perfusion Rates and Thermal Conductivity**

Although the Spearman correlation coefficient between acoustic power and efficiency was -0.40 ($P = 0.04$), there is only a 2.8% reduction in efficiency at 15 s between 2 and 15 W of applied acoustic power.

Figure 5.8 illustrates the efficiency recorded at 6 and 15 s timepoints for transducer powers ranging between 2-15 W. In this way, the effects of perfusion, thermal conduction, and absorption on treatment efficiency were analyzed. Although the Spearman correlation coefficient was -0.40 ($P = 0.04$), there is only a 2.8% reduction in efficiency at 15 s between 2 and 15 W of applied acoustic power. Since the duration was held fixed in each case, both the power- and energy-efficiencies are included in subfigures B and C. In both cases, the temperature rise is linear with power (or energy for a fixed duration). However, as a result of diffusion over longer duration heating, the energy-efficiency decreases between 6 and 15-s
Figure 5.6: The linear correlation between the percentage decrease in efficiency and the percentage increase in the size of the focus for all 19 clinical cases. R-squared = 0.52, P < 0.01. In this case, the efficiency was calculated using acoustic power, since the focal spot size was taken at 9 s in all cases.

Transducer Array Power Experiments

Figure 5.9 demonstrates the relationship between acoustic power emitted from each element in the array, and the pressure-squared. The linear fit corresponds well (R-squared = 0.996) and shows that the transducer acoustic response is linear with power.

5.4 Discussion

With the ongoing development of transcranial FUS for the treatment of a range of diseases and disorders [16, 48, 49, 283], it is imperative to understand the relationship between the applied acoustic energy and the resultant temperature elevation during treatment. From the Pennes bioheat equation [248], one would expect a linear relationship between the applied acoustic power of the transducer array and the temperature rise at the focus in a FUS thermal treatment. Clinical data were presented here to illustrate the unexpected reduction in the energy-temperature efficiency at higher powers during MR-guided FUS.
Chapter 5. Unexpected Temperature Profiles

Figure 5.7: Computer simulations on the effect of skull heating on the temperature rise at the focus and the focal volume for Patient 8 for (A) a 24-second sonication (black line) and the simulated temperature rise assuming changing speed of sound (thick red dashes). There is a 12% decrease in the simulated peak temperature at 24 s when accounting for temperature-dependent speed-of-sound changes. (B) The increase in the focal volume assuming skull heating (red dashed line) compared to the focal volume with constant acoustic parameters (solid black line). There is an 8% increase in the focal volume when including temperature-dependent acoustic parameters. (C) Normalized temperature (relative to 37°C body temperature) plotted across the simulated focus assuming skull heating (red dashed line) compared to the focal volume with constant acoustic parameters (solid black line). (D) The evolution of the power absorption (W/cm³) measured at the focus for timepoints of 6, 12, 18, and 24 s, showing a decrease in absorption during skull heating.

Thalamotomies for the treatment of ET. This reduction in efficiency was then correlated with the observed dispersion of the focus during treatment. This article presents clinical evidence of power-dependent focal dispersion, which builds upon previous studies into the focal quality during transcranial FUS [240,262].

The natural suspicion when observing reduced power-temperature efficiency is that there is an increase in the rate of perfusion at higher powers, due to a larger disparity between the focal temperature and the blood temperature, as predicted by the perfusion term in the Pennes bioheat equation [248]. A previous study showed that ignoring blood perfusion in a transcranial model results in a 4% increase in the focal temperature elevation [251]. The rabbit experiments presented here illustrate that perfusion effects causing a decrease in efficiency are minimal. However, the rabbit experiments were performed at 1.513 MHz using a single focused transducer, while the clinical treatments were performed at 670 kHz using a 1024-element hemispherical array. As a result of these geometric and frequency differences, the extrapolation of these results may be limited and would require further study.

Changes in tissue thermal conductivity could also explain the results presented here. By analyzing the temperature dependence of various tissues, Valvano et al developed a linear fit describing this relationship [284]. It was found that the conductivity increased by 0.3% per degree Celsius, so that in the present context, between 37 and 50°C, conductivity likely increased by 4%. This linear fit, however, did not cover near-coagulation-inducing temperature ranges of tissue and therefore may not fully describe the effects presented here.
Figure 5.8: An analysis of the effects of blood perfusion, thermal conduction and absorption on the reduction in the power-temperature efficiency during treatment using a rabbit model (N = 1 rabbits, N = 21 sonications). The 6-s (black) and 15-s (red) efficiency curves as functions of (A) temperature rise, (B) power, and (C) energy are shown, with the 95% confidence intervals shown in dashed lines. The Spearman cross correlation between power and efficiency on the difference between the 6- and 15-s sonications is -0.40 (P = 0.04), indicating that changes in perfusion, thermal conduction, and absorption play a role in reducing efficiency at higher powers, although it is not described by a linear fit (P = 0.29). There is only, however, a 2.8% reduction in efficiency at 15 s between 2 and 15 W of applied acoustic power, indicating that changes in perfusion, conduction and absorption play minimal roles in the reduced efficiency. Computing the Spearman cross correlation between temperature rise and efficiency on the difference between the 6- and 15-s sonications, it is found that there is no correlation (P = 0.11).

It is infeasible, however, that as the power is increased, there is a decrease in the absorption in the tissue of the heated target volume leading to reduced energy-temperature efficiency. It is expected that the absorption should increase at higher acoustic powers due to the increase in absorption [285] and the reduced effect of perfusion once the thermal dose [160] at the target reaches coagulation. In addition, the positive correlation between peak temperature and change in efficiency presented in Table 1 would suggest that between patients, the higher the focal heating, the lower the observed reduction in energy-temperature efficiency. It would appear then that changes in focal absorption at higher powers would not be the cause of the phenomena observed here. These results suggest that changes in perfusion, thermal conductivity, and absorption are not substantial causes of the observed efficiency reduction at higher powers. Whether the treatment-related edema from heating has an effect, however, remains an open question.

A further explanation was that the skull and brain tissue along the beam paths could heat under sufficient power levels to cause acoustic parameters to change, and therefore cause the observed blurring (de-phasing) of the focus and reduction in the treatment efficiency. A number of previous studies have confirmed changes in the velocity and attenuation of ultrasound in water [286], bone marrow [287], and bone [282], among others, as a function of temperature. Although skull heating during FUS treatments is a well-documented ongoing concern [4,174,288], it would appear unlikely that brain tissue away from the focus would heat sufficiently to cause any changes in the acoustic parameters, as evidenced by tight transcranial acoustic focusing confirmed in previous studies [178].

The negative correlation between power and efficiency presented in Table 5.1 indicates that skull heating correlates negatively with efficiency since power exhibits a linear, positive relationship with skull heating. This would lead us to believe that the heating of the skull at higher acoustic powers is potentially causing additional acoustic aberrations, leading to focal spot expansion, thereby reducing the energy-temperature efficiency. In addition, the phase corrections through the skull are computed assuming
constant acoustic parameters over time [199]. If the rise in skull heating resulting from increased power causes changes in the ultrasound speed in the skull non-uniformly, then the focus would disperse, since the ability to target precisely would decrease. The power-temperature efficiency would likewise decrease from this de-phasing. The dispersion of the foci presented here and reduction in energy-temperature efficiency is consistent with this hypothesis. Because previous studies have consistently found the speed of sound in bone to decrease at higher temperatures [282,289] with the exception of water-filled bone [290], the phase distortion induced by the skull bone would change during the exposure depending on the local heating of the skull. If skull heating is the cause of the focal volume de-phasing and decrease in energy-temperature efficiency observed, then future work could analyze the relationship between temperature and acoustic properties, following previous studies [201]. These results could then be used to develop time- and power-dependent phased array corrections that consider the changing acoustic parameters as a function of temperature for better focusing. Future transcranial therapies could rely on more sophisticated treatment planning software, so that the potential impact of skull heating on treatment outcomes could be pre-determined.

Finally, the acoustic efficiency of transducers using the clinical array sonication into water was found to be constant between lower and higher acoustic powers, indicating non-significant transducer effects.

Figure 5.9: The transducer power experiments illustrating the linear pressure-squared rise with the applied power per element in the array (R-squared = 0.996). The 95% confidence intervals of the linear fit are indicated by the dashed lines.
The effect of registration between CT and MR images, however, was not analyzed.

The use of axial MR images to quantify the changes in the focal size as a function of applied power has notable limitations. Full analysis would require 3D volumetric MR imaging to quantify the total deposition of energy in the focal region. As described previously [262], should an oblique focus manifest in the coronal or sagittal planes, the axial quantification of the focal volume would underestimate the true size of the focus. During analysis of some coronal images in the 19 patients included in this study, it was found that the focus was oblique to the main array axis. However, the focal obliquity manifested at both low and high power sonications. Since Figure 6 included only the percentage decrease in the focal size, it is possible that the measured change in the focal size would still be accurate should a 3D volumetric analysis be performed. Future work with a larger volume of coronal and sagittal images could confirm this hypothesis.

The effect of MR noise was suppressed in this study using a series of filters. The noise, however, played a noticeable role, particularly at lower power sonications, where the temperature rise was sometimes on the order of the observed noise in the image. Although the corrective methods were largely successful, some sonications needed to be excluded from analysis. Since the effect of noise was more of an issue at lower power sonications, the size of the foci in some of the lower power sonications could have been overestimated in this analysis. This, however, would not alter the conclusions of this study. Invasive in vivo and ex vivo experiments, however, would be required to determine more absolutely the true nature of the relationships between skull heating, temperature rise, and focal dispersion. Tissue heating resulting from FUS, causing geometric distortions in the MR temperature maps, could also contribute to the observed phenomena [291], and was not considered in this analysis.

5.5 Conclusions

In this chapter, it was observed that the reduction in energy-temperature efficiency during high-power focused ultrasound thalamotomy for Essential Tremor correlated with increases in the size of the focal volume and is likely caused by transient and semi-permanent changes in the tissue and skull during heating. Further studies should be conducted to develop temperature-dependent compensation methods for improved treatment efficiency.

This chapter marks the end of three chapters focusing on thermal applications of transcranial focused ultrasound. In the next chapter, we seek to break from conventional clinical arrays and design a novel brain array for the temporary opening of the BBB and shift tracks to the mechanical applications of focused ultrasound.
Chapter 6

The design of patient-specific ultrasound arrays

This chapter constitutes the final study performed as a part of this thesis. Here, we depart substantially from the use of conventional brain array devices and present a novel brain array design which aims to expand the treatment range of focused ultrasound in the brain for the treatment of a variety of neurological conditions by temporarily opening the BBB.

6.1 Introduction

The application of focused ultrasound to the brain through the intact skull has a long history leading up to the clinical implementations of the present day. Since the first successful ablation of animal brain tissue transcranially using a single transducer in 1980 [166], to the present day clinical treatments of essential tremor using hemispherical phased arrays consisting of more than one thousand elements [16], new phased array designs have been conceptualized to overcome previous challenges. Previous developments include skull aberration correction [52, 189, 199], standing wave reduction [270], skull heating minimization [173, 293], and dual-frequency blood-brain barrier (BBB) opening [294].

Most of the current clinical work in transcranial focused ultrasound involves continuous wave ultrasound to cause thermal ablation [16, 48, 49, 205]. Early animal studies, however, have shown that burst ultrasound could be used for BBB opening [55, 295]. This has led to studies involving BBB opening in conjunction with drug delivery to treat brain tumors [56] and Alzheimer’s disease [58] and deliver immune cells to metastatic brain tumors [116], among others. A recent study has even shown that mechanical tissue destruction is possible with lower intensity pulsed ultrasound when used in conjunction with microbubbles [60, 61]. In these applications, skull heating is of minimal concern due to the low duty cycle.

To obtain maximal energy transmission through the skull, the wave should enter the skull at normal incidence [199]. This limits the areas of skull that can be used for ideal power transmission to the target region - especially for targets that are not in the central regions of the brain. Here, we propose...
Figure 6.1: The treatment workflow using a patient-specific array: (1) 3-dimensional patient imaging for scaffold design; (2a) the construction of a phased array scaffold for transducer placement; (2b) the placement of focused transducer elements within the scaffold, where the inset illustrates the concept of focusing inside the skull at normal incidence to increase the steering range and transmission; and (3) computer-assisted treatment planning to control the time delays on each element in the array to steer the beam to a lateral target in the brain, shown as a maximum-intensity projection of the time delays on each element.

A new approach using concave transducers focusing their beam inside the skull, such that the planar wave at the focus penetrates the skull at normal incidence. With the proper design, the planar waves propagate through the skull and exit the brain as diverging waves, thereby minimizing the impact of the impedance mismatch with bone. By using an array of such transducers and timing the bursts such that they arrive at the desired target simultaneously, one would expect an acoustic focus to be generated. In this numerical study, the feasibility of this idea in a realistic skull geometry is explored.

In clinical practice, an array scaffold would be constructed from imaging data to fit the patient, followed by the placement of the curved transducer elements within the scaffold. Finally, upon fixing the array to the patient head at the time of treatment, a final imaging sequence would be obtained for use in computer-assisted treatment planning. The workflow of the proposed treatment process is outlined in Figure 6.1.
6.2 Materials and Methods

6.2.1 Array Design

Transducers were optimally spaced [296] to reduce the formation of grating lobes, placed the same distance from the skull, and rotated independently such that each transducer was normal to the skull surface. The concept of the array design and resultant treatment workflow is illustrated in Figure 6.1, where a concave transducer is positioned such that the natural focus of the transducer is inside the skull. In this way, the brain is within the far-field of the transducer. With proper transducer design, the majority of trans-skull transmission should be planar waves in the process of converting from convergent to divergent wavefronts. This planar transmission at normal incidence should then theoretically result in higher trans-skull transmission and a larger steering range, compared to a hemispherical array with the same number of elements. All sonications were performed with a 3-cycle pulse unless otherwise specified.

6.2.2 Patient Treatment Modeling

Numerical simulations were performed using both continuous wave and pulsed ultrasound. Since the domain consisted of heterogeneous media, full-wave simulations were performed, as in Sections 2.2.1 and 2.2.2. In addition, thermal simulations were performed using the Pennes bioheat equation (Equation 2.5).

A computer cluster consisting of eight Intel Xeon processors was used to perform the simulation of the FDTD simulations, while a standard desktop computer was used to analyze and process the data.

6.2.3 Safety Analysis

In order to assess the potential safety of the sonications to brain tissue, the ratio of the peak pressure amplitude at the focus to the maximum pressure at the inner-surface of the skull was analyzed, in order to assess the acoustic energy deposition away from the focus. This ratio was described as the array gain, $G_{MAX}$.

6.3 Results

Emphasizing the wave conversion presented in Figure 6.1, Figure 6.2 illustrates the propagation of the ultrasonic wave through the skull, emphasizing the conversion to plane wave propagation. The transducer (f-number=1, radius=10 mm, f=500 kHz) is focused inside the skull. The outline of the skull is shown in white. At 16.4 $\mu$s, the converging spherical wave is converted to a planar wave which then propagates at normal incidence through the skull, as highlighted at $t = 16.8, 17.2$, and $17.8 \mu$s with the white arrows. At 56.8 $\mu$s, the attenuated wave is shown inside the head as a diverging spherical wave. The particle displacement fields inside the skull are scaled for visual contrast with the pressure field.

To illustrate the increased transmission resulting from this wave conversion in the skull, Figure 6.3a compares a concave transducer focused inside the skull to a flat $\lambda/2$-diameter element. Both transducer powers are normalized to the same value, and the pressure fields are taken as ratios to the maximum pressure in the focused transducer case. The panels in each subfigure illustrate schematics of the geometry through the coronal plane, with the arrows pointing to the position of the transverse plane through which the pressure maps are displayed. It is clear in this example that the curved transducer transmits a higher
Chapter 6. The design of patient-specific ultrasound arrays

Figure 6.2: An illustration of the temporal wave propagation of a 5-cycle pulse emitted from a single curved transducer (f-number=1, radius=10 mm, f=500 kHz) focused inside the skull, at timepoints 11.3, 16.4, 16.8, 17.2, 17.8, and 56.8 µs.

intensity acoustic field through the skull, with a more disperse acoustic field than the flat transducer of size $\lambda/2$. Figure 6.3b demonstrates the effect of the focal lengths listed in the legend on the angle of dispersion of the acoustic field for a transducer of diameter 20 mm. It is clear that the -3 dB and -6 dB beamwidths are increased when the transducer is more concave, as highlighted by the arrows.

Figures 6.2 and 6.3 demonstrate that focusing a wavefront through the skull allows for dispersion of the wave within the head, as well as an increased transmission as compared to a single small element.

Figure 6.4 summarizes the advantages of a conformal array to a hemispherical array. The -3dB isosurfaces for a conformal (Figure 6.4a) and a hemispherical (Figure 6.4b) array illustrate the improvement in focusing when using only 128 elements. Figure 6.4c shows the percentage increase in the transmitted intensity at a lateral brain target when using a conformal array as compared to a hemispherical array. Figure 6.4d shows the percentage change in the -3dB (white) and -6dB (black) volumes, illustrating the improvement in focal quality when using a conformal array.

6.3.1 Safety Analysis

The primary safety concern is the deposition of acoustic energy at locations away from the target focus. Figure 6.5a illustrates the effect of the duty cycle on the focusing quality, for duty cycles of 75, 50, 25, and 10 %. In each case, the pulse length is fixed at 3 cycles. Therefore, for a duty cycle of 50%, for example, the burst would consist of 3 cycles on, followed by 3 cycles off. The red indicates the -6 dB isosurface, and the blue indicates the -3 dB isosurface. In all four cases, the -3 dB isosurface is contained to the vicinity of the target, whereas the -6 dB isosurface is widely dispersed for 50 and 75 % duty cycles, and minimal for less than 25 % duty cycles. It is therefore imperative that the sonication duty cycle be reduced in order that acoustic energy is not deposited to central regions of the brain when targeting to
lateral positions. Figures 6.5b, 6.5c, and 6.5d further this point, by presenting the peak pressure in the brain compared to the target focus for bursts of 3, 5, and 10 cycles, and continuous-wave sonication. These figures demonstrate that shorter pulse lengths are ideal for more lateral targets in the brain, to avoid accumulation of acoustic energy away from the target focus.

With sufficient temporal spacing to allow for skull cooling, in conjunction with present-day skull cooling mechanisms during treatment, it appears that skull heating would not be a limitation to potential treatments with this device. Using a 256-element array sonating at 100 W at a frequency of 500 kHz, a single 1000-cycle burst, representing a continuous wave sonication of duration 2 ms, led to a temperature rise of approximately 0.03 °C, while the focal pressure amplitude ranged between 0.24-1.4 MPa for the different steered positions. Naturally, a duty cycle lower than 100% would lead to a smaller temperature rise. In addition, Table 6.1 illustrates the effect of the number of transducers on the minimum ($G_{MIN}$) and maximum ($G_{MAX}$) gain values throughout the head, as well as the minimum ($p_{MIN}$) and maximum ($p_{MAX}$) focal pressure amplitudes.

Figure 6.3: (a) A comparison between a focused (left) and flat, $\lambda/2$-diameter (right) transducer and (b) a comparison between the beamwidths of transducers with different focal lengths for a 20 mm-diameter transducer, with the -3dB and -6dB widths indicated by the arrows.
Figure 6.4: The -3 dB isosurfaces for (a) the conformal array and (b) the hemispherical array, with 128 elements, and the percentage change in (c) the intensity and (d) the -3dB (white) and -6dB (black) volumes, as a function of the number of elements, when comparing the conformal array to a hemispherical array. In all cases, the focus is positioned at (AP = +60 mm, LR = 0, IS = 0), where (0, 0, 0) is the geometric center of the brain, to demonstrate the steering capabilities of the conformal array.

6.4 Discussion

A novel phased array design for transcranial focused ultrasound therapy was presented. This design could extend the limited electronic steering range in the brain by reducing the impact of the high acoustic impedance of the skull on the propagation window and using focused array elements focused in the skull such that the plane waves generated were propagated through the skull. With a sharply-focused transducer, the wave in the far field in the brain diverges, providing an increased steering range. This study also introduced the novel idea of placing the array elements in a patient-specific scaffold, designed to fit tightly around the patients head. This patient-specific transducer helmet could potentially be formed by rapid prototyping it based on MR- or CT-derived head geometry.

There is potential that this new array design could be used in higher frequency applications requiring low-power, low-duty-cycle applications, including BBB opening. The use of a conformal array of focused transducer elements allows for tight focusing at lateral targets in the brain, with sufficient acoustic
pressures for a number of therapies involving relatively short ultrasound pulses, including BBB opening, where sonications were performed at a pressure of 0.54 MPa [297], which is within the range of acoustic pressures presented in Table 6.1. These studies were performed at 1.18 MHz, however, and the required pressures at 500 kHz could be different as a result. Other studies found that at 558 kHz, targeted antibodies reduced Amyloid-β plaque loads while sonicating in 10 ms bursts at 0.3 MPa [58], and blood-brain barrier opening was possible at 0.52 MPa at 600 kHz [294]. Both of these acoustic pressures are within the pressure ranges presented in this study.

Clinical transcranial therapies are currently performed using hemispherical arrays [16,48,205], and the performance of conformal arrays compared to hemispherical arrays was summarized in Figure 6.4. Most importantly, it was shown that with only 64 or 128 channels, precise targeting and high transmission was achieved. With the increased electronic complexity associated with many independent channels, the ability to focus with few elements would make for an array with relatively simple driving electronics. This advancement could allow for ease of adoption of the technology. Interestingly, the margins of improvement in transmission and focusing quality with a conformal array over a hemispherical array

Figure 6.5: (a) The effect of duty cycle on the -3 dB (blue) and -6 dB (red) isosurfaces, and (b-d) the ratio between the maximum acoustic pressure in the brain compared to the target focus, for a 256-element conformal array targeted to \( \text{AP} = +60 \text{ mm}, \text{LR} = 0, \text{IS} = 0 \).
Table 6.1: A summary of the minimum ($G_{MIN}$) and maximum ($G_{MAX}$) gains, and minimum ($p_{MIN}$) and maximum ($p_{MAX}$) focal pressure amplitudes, for different numbers of elements.

<table>
<thead>
<tr>
<th>Number of Elements</th>
<th>64</th>
<th>128</th>
<th>256</th>
<th>512</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_{MAX}$</td>
<td>2.8</td>
<td>3.9</td>
<td>9.6</td>
<td>26.5</td>
</tr>
<tr>
<td>$G_{MAX}$</td>
<td>7.3</td>
<td>11.3</td>
<td>56.9</td>
<td>140.5</td>
</tr>
<tr>
<td>$p_{MAX}$ (MPa)</td>
<td>0.34</td>
<td>0.63</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>$p_{MIN}$ (MPa)</td>
<td>0.13</td>
<td>0.19</td>
<td>0.24</td>
<td>0.35</td>
</tr>
</tbody>
</table>

The question of how to optimize this configuration for a given patient geometry then arises. For each patient geometry, there is a limited surface area over which to distribute elements in such a conformal configuration. That is, the number of elements is limited by the diameter of each transducer, and the f-number of each transducer is limited by the allowable distance to the skull. In addition, the distance of each element from the skull, for a given f-number, dictates how the wavefront will propagate through the skull, affecting both the transmission as well as the dispersion of the wave inside the head.

Figure 6.3b illustrates the effect of different transducer focal lengths on the dispersion of the pressure wave transmitted through the skull. The advantage of a relatively wide dispersion is that the steering range is increased, since there is minimal natural concentration of acoustic energy in any point in the brain, allowing for tight focusing anywhere in the brain. In addition, Figure 6.3a clearly demonstrates the benefits of focusing a transducer in the skull to achieve higher transmission and better focus resolution, compared to a $\lambda/2$-diameter flat element. The optimal array design that balances degrees of freedom from having more elements with the increased transmission from a larger, more sharply-focused element, remains to be understood.

A limitation of the proposed array construction is the duration of the bursts that can be safely sonicated, as well as the duty cycle of these bursts. Figure 6.5 showed that with reducing duty cycle, the targeting becomes more accurate, and the peripheral -6 dB volumes decrease. In addition, it seems that only short-duration pulses would allow for precise targeting and the elimination of acoustic depositions at unintended locations in the brain. With a duty cycle of less than 10%, however, acoustic deposition away from the focus was shown to be minimal. As a result, sonications using a short pulse with 10% duty cycle could potentially be used. Skull heating for burst ultrasound was analyzed and found to not cause any safety limitations.

6.4.1 Numerical Limitations

The model presented here is a linear simulation of the acoustic field and is valid for the low pressure amplitude sonications investigated here. The utility of the array design for nonlinear applications, including histotripsy and higher power therapies have thus not been simulated. The use of nonlinear simulations, however, would come with additional convergence issues, particularly when coupling the finite-difference simulations with the grid method as performed in this study.
6.5 Conclusions

This chapter presented a study on a novel phased array design for transcranial focused ultrasound therapy. The use of a conformal array of focused transducer elements allows for tight focusing at lateral targets in the brain, with sufficient acoustic pressures for BBB opening and drug delivery.

The final chapter in this thesis follows. In Chapter 7, a summary of the results presented in this and the previous three chapters will occur as well as insights into the future of transcranial focused ultrasound.
Chapter 7

Conclusions and Future Directions

Transcranial focused ultrasound is limited by several factors including focusing quality, skull heating, and steering range of conventional phased arrays. As computers become faster and more powerful, it is feasible that numerical methods will be integrated into treatment planning algorithms in future clinical applications. As a first step, it is important to understand the role that these numerical methods can play and understand clinical treatments as they occur at present.

7.1 Summary of Results

A wide range of results were presented in the four research chapters of this thesis. Here, the results of each chapter are summarized in turn and discussed.

In Chapter 3, results from clinical trials for the treatment of ET using MR-guided focused ultrasound were compiled. It was observed during treatment and confirmed from 1-day post-treatment MR images that the focus was oblique to the main axis of the transducer array in many patients. The potential for this obliquity to extend the focus into lateral regions of the brain led to speculation as to the cause of the oblique focus and whether it is possible to realign the focus.

Numerical simulations were performed on the clinical export data to analyze the causes of the oblique focus and to determine whether realignment was possible. It was found that the focal obliquity could be replicated with the numerical simulations to within $23.2 \pm 13.6^\circ$ over all clinical cases. It was then found that a major cause of the focal obliquity was the presence of sidelobes, caused by an unequal deposition of power from the different transducer elements in the array at the focus. In addition, it was found that a 65% reduction in focal obliquity was possible using phase and amplitude corrections. Potential drawbacks associated with this correction include the higher levels of skull heating required when modifying the distribution of power among the transducer elements and the difficulty at present in obtaining ideal phase corrections from CT information alone. However, the techniques for the reduction of focal obliquity can be applied to other applications of transcranial focused ultrasound involving lower total energy deposition, such as blood-brain barrier opening, where the issue of skull heating is minimal.

After introducing the concept of obliquity and illustrating its clinical origins, a generalized theory for the complete control of the spatial manifestation of the focus was introduced in Chapter 4. It has long been known that by using an array of individually-driven transducer elements, it is possible to steer a focus through space electronically and to compensate for acoustically heterogeneous media with phase
delays. In this chapter, a method was introduced to control the orientation of the focus using a Tikhonov regularization scheme. The ability to control the focus depended largely on the choice of regularization parameter, \( \alpha \), to solve the ill-posed inverse problem. Using these techniques, it was then shown that the theory generalizes to multiple foci, allowing for multiple independent spatial rotations.

Chapter 5 presented the clinical observation of unexpected temperature temporal profiles during MR-guided focused ultrasound surgery for ET in 19 patients. In this chapter, the temperature plateau was defined as a reduction in the efficiency of transmission over time at higher acoustic powers. The relationships between the applied power, the resultant peak temperature achieved in the brain and the dispersion of the focal volume were analyzed and it was found that a linear relationship exists showing that a decrease in treatment efficiency correlates positively with an increase in the focal size over the course of treatment (\( P \leq 0.01 \)). This observation and supporting simulations and animal experiments are consistent with the hypothesis of transient skull and tissue heating causing acoustic aberrations leading to a decrease in efficiency. It was also found that changes in thermal conductivity, perfusion, absorption rates in the brain, as well as ultrasound transducer acoustic output levels had minimal effects on the observed reduction in efficiency.

The results from these chapters could have applications to future clinical treatments of Movement Disorders, AD, and brain tumours using focused ultrasound, providing better control of the ultrasound focus and therefore more efficient deposition of thermal energy for ablative therapy.

Chapter 6 investigated the application of the mechanical effects of ultrasound for the temporary opening of the BBB. The steering range of current clinical devices limits the regions of the brain that are considered treatable by ultrasound. As a result, a new patient-specific array design was developed. This new array design was introduced that allows for high levels of beam steering and increased transmission throughout the brain. These improvements were achieved using concave transducers normal to the outer-skull surface in a patient-specific configuration to target within the skull, so that the far-field of each beam was within the brain. It was shown that by using pulsed ultrasound waves timed to arrive in-phase at the desired target, sufficient levels of acoustic energy were delivered for BBB opening throughout the brain.

### 7.2 Future Work

The field of transcranial focused ultrasound is in a nascent stage. There is tremendous opportunity for clinical applications, however, there are also several areas at present where improvements are needed so that the promise of transcranial focused ultrasound can be broadly fulfilled.

The need for accurate numerical models is crucial to the development of new ultrasound devices and treatments, since computers offer a relatively low-cost, reproducible basis for experimentation as well as the ability to tune parameters finely to study their effect on treatment outcome. In addition, numerical modeling provides insights which are difficult to obtain using experimental and clinical procedures, such as the measurements of the temperature rise in cranial bone during clinical treatments and the acoustic pressure fields in brain tissue during treatment. However, numerical modeling of transcranial focused ultrasound is limited by several factors: the accuracy of numerical models, the speed and memory of computers, and the accuracy of acoustic properties of biological tissues.

Numerical models of transcranial ultrasound propagation have largely focused on linear propagation at relatively low frequencies [181]. There has been a preliminary study of the simulation of nonlinear
propagation in transcranial focused ultrasound [298], but the lack of accurate nonlinear acoustic parameters for cranial bone and models for the accurate propagation of ultrasound in cancellous bone remain substantial limitations.

In addition, there has recently been investigation into the role that Biot waves [299, 300] can play in the propagation of ultrasound in cancellous bone [301]. Since Gibson’s seminal paper which first studied the mechanical behaviour of cancellous bone as a cellular material [302], great strides have been made in understanding the numerical and experimental characterization of these “slow” Biot waves [303–305]. With an accurate understanding of the role of Biot waves in transcranial therapy, more accurate treatment planning may be possible.

The integration of numerical treatment planning with clinical focused ultrasound treatments is an important development that will allow for more precise therapies and the targeting of new pathologies and neurological structures. This mindset has guided much of the recent research in the field, with the development of ultrasonic controllers for hyperthermia, treatment planning algorithms, and numerically-efficient shortcuts to bypass multimodal imaging technologies. The application of these technologies to transcranial ultrasound has been limited, however. Although numerical methods for the correction of the focus have been developed [181, 202], the complex problems of skull base heating [238], outer skull heating [4, 174, 178], and complex focal patterns have been nearly untouched. Due to the limited target range of current clinical brain devices [239] and the repeated clinical desire to treat a number of pathologies outside this treatment range [206, 237], this area of research remains a fruitful path to take.

Future developments in transcranial focused ultrasound will seek to minimize the limitations currently experienced during clinical treatments, including the possibility of possible bone thermometry and 3D volumetric MR theramometry during treatment, as well as the translation of many current pre-clinical studies to clinic. For example, the ability to measure bone temperatures during treatment directly using ultrashort MR sequences could substantially improve the clinical safety of transcranial treatment and allow for pre-clinical models to more accurately measure the impact of treatment [306]. Further, the observation of a reduction in the power-temperature efficiency during transcranial ET treatments as reported in this thesis, could drive temperature-dependent phase corrections and compensation techniques to be developed.

7.3 Conclusion

Focused ultrasound is a growing therapeutic modality for neurosurgical and neurological applications. Its clinical adoption is progressing at a high rate, with early-phase treatments for Essential Tremor, Parkinson’s Disease, Alzheimer’s Disease and Obsessive Compulsive Disorder being developed, among others. As more potential therapies are investigated in pre-clinical models and novel bioeffects are being discovered, further technological developments are needed to expand the treatment range of current clinical devices, develop future devices, and optimize the application of ultrasound to the brain.
Bibliography


Appendices
### Appendix A

### Patient Data

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