Simulation Methods in Transcranial Ultrasound Therapy

Aki Pulkkinen

Publications of the University of Eastern Finland
Dissertations in Forestry and Natural Sciences
AKI PULKKINEN

Simulation methods in transcranial ultrasound therapy

Publications of the University of Eastern Finland
Dissertations in Forestry and Natural Sciences
No 143

Academic Dissertation
To be presented by permission of the Faculty of Science and Forestry for public examination in the Auditorium L21 in Snellmania Building at the University of Eastern Finland, Kuopio, on August, 9, 2014, at 12 o’clock noon.

Department of Applied Physics
ABSTRACT

Focused ultrasound is an emerging therapeutic modality that has found clinical use for the treatment of a number of serious medical conditions. It is an attractive treatment modality due to its nonionizing and noninvasive nature. Active research is currently taking place worldwide, both to improve existing applications and to discover and develop novel applications of the technique. One of the most demanding applications is transcranial focused ultrasound therapy. During transcranial ultrasound therapy, acoustic energy is delivered through the intact skull and into the brain, where thermal and mechanical bioeffects can take place. In the brain, these biological effects can be harnessed for a variety of purposes, including thermal ablation, targeted drug delivery and neurostimulation, to name a few. The development of these techniques to a point where they are readily employed in a clinical environment is a tedious task due to the experimental nature associated with the complex biological targets. One approach, that can be used as an aid in such experimental research is the use of numerical simulations, where mathematical models are used to gain insight into the problem of interest. The main advantages of performing numerical simulations, in comparison with experimental measurements, is that each physical parameter affecting the results can be independently and accurately controlled. However, a numerical model can be only as good as the understanding of theoretical principles on which it has been developed. Flaws in the underlying theory can lead to inaccuracies in the simulations, when compared with real measurements. On the other hand, a good match between a numerical model and corresponding experimental measurements increases the certainty that a given theory is strong, and that the understanding of the physical principles behind the problem are well understood.

This thesis investigates the use of numerical simulations in transcranial focused ultrasound therapy. An overview of the principal physics associated with therapeutic ultrasound in the context of brain treatments is provided, followed by a review of the relevant
numerical studies and simulation approaches commonly applied in the field of therapeutic ultrasound. Additionally, the treatment protocol for transcranial ultrasound therapy is described, together with a review of the clinical studies published to date.

This thesis contains four original publications describing different numerical approaches to simulate the propagation of ultrasound. The first paper investigates the nonlinear propagation of ultrasound in soft tissues using a Khokhlov-Zabolotskaya-Kuznetsov equation based simulation model. The second publication investigates skull base heating during transcranial ultrasound therapy using sequentially coupled simulation models. The third publication investigates the standing wave phenomenon associated with reverberant cavities, such as the human skull, using a spectral element based simulation approach. The fourth publication describes a novel hybrid full-wave simulation model, which is used to simulate clinical transcranial ultrasound therapy patient treatments. Each of the developed simulation models are compared with real world experiments.

AMS Classification: 92C50; 65M60; 35Q53
NLM Classification: WB 515, WN 185
Universal Decimal Classification: 615.837, 534-6, 534-8

Library of Congress Subject Headings (LCSH): Ultrasonic waves; Therapeutics; Simulation methods; Modelling; Computer simulation

Medical Subject Headings (MeSH): Computer Simulation; Models, Anatomic; Models, Biological; Ultrasonography, Doppler, Transcranial/ methods High Intensity Focused Ultrasound Ablation/methods Ultrasonic; Therapy/instrumentation Skull/ultrasonography Humans

Yleinen suomalainen asiasanasto (YSA): matemaattiset mallit; numeeriset menetelmät; ultraääni; ultraäänihoito; hoitomenetelmät; mallintaminen; lääketieteellinen fysiikka; aivot; pehmytkudokset
ACKNOWLEDGEMENTS

This work was mainly carried out during my stay at Sunnybrook Research Institute, Toronto, Canada during 2008-2011. Following that the work was continued while at Department of Applied Physics at the University of Eastern Finland, Kuopio, until 2014.

I thank my supervisor Kullervo Hynynen for the opportunity to work on the subject of therapeutic ultrasound. I have learned much while working under his supervision.

The reviewers Gregory T. Clement and Jean-Francois Aubry deserve an expression of gratitude for the effort they put into the review process.

I thank my coauthors, Yuexi Huang, Junho Song, Beat Werner, and Ernst Martin, for the fruitful collaboration we have had so far. In addition, I thank Jonathan Lao, Eyal Zadicario, and Insightec Ltd. for their help during the work related to publications II and III.

A great deal of the work was made while staying in Toronto. I am grateful to the members of the Focused Ultrasound Group, and especially to Meaghan O’Reilly and Ryan Jones for all the help provided.

Tero Karjalainen and Jarkko Leskinen, members of the UEF Biomedical Ultrasound Group, are two of the main characters who led me to work in this research field. I thank them both, for all the help, guidance, and discussions we have had along the way. I also express my gratitude for the members of the UEF Inverse Problems Group for the support I have had during my stay in Kuopio.

In addition, I express my gratitude to: the O’Donnell family, Kyle Bailey, Timo & Saara Lähivaara, Jukka & Minna Antikainen, Timo & Maarit Liimatainen, Joni-Pekka Pietikäinen, Janne Huttunen, Tanja Tarvainen, Kimmo Karhunen, my big sisters Satu & Sari Rantonen, the Räbinä family, and my mother. There are more people to be thankful to, but let’s keep it short.

This study, and the publications presented, was supported by Saastamoisen Säätiö through the University of Kuopio (currently
University of Eastern Finland), funding from the Ontario Research Fund, the Canadian Research Chair program, and grants from the National Institutes of Health (no. R01EB003268). In addition I wish to thank the Finnish IT Center for Science for the computational resources provided.

Kuopio, July 3, 2014

Aki Pulkkinen
LIST OF PUBLICATIONS

This thesis consists of an overview of the following four original articles which are referred to in the text by their roman numerals I-IV:


The original articles have been reproduced with permission of their copyright holders.
AUTHOR’S CONTRIBUTION

The publications selected in this dissertation are original research papers on therapeutic ultrasound. The study design for the research presented in Publications I-IV originated from the co-author and main thesis supervisor, Prof. Kullervo Hynynen.

In all publications the author has carried out the development of the simulation tools and has performed the numerical simulations. In addition to the simulation work, the author was involved in planning the measurements in Publications II and III, and in performing the measurements in Publication II. The treatment data in Publication IV originated from the co-authors Dipl. phys. Beat Werner and Prof. Dr. med. Ernst Martin.

The author has written the manuscripts to Publications I, II and IV. The author wrote the simulation component of Publication III, which was principally written by co-author Dr. Junho Song.
Contents

1 INTRODUCTION

2 FUNDAMENTAL PHYSICS OF THERAPEUTIC ULTRASOUND
   2.1 Ultrasound propagation in soft tissues
   2.2 Ultrasound propagation in bone
   2.3 Transmission of ultrasound at tissue-bone interfaces
   2.4 Heating due to ultrasound
   2.5 Bioheat model
   2.6 Thermal dosimetry
   2.7 Acoustic cavitation
   2.8 Correcting phase and amplitude aberrations

3 SIMULATION METHODS IN THERAPEUTIC ULTRASOUND
   3.1 Ray acoustics
   3.2 Angular spectrum method
   3.3 KZK equation
   3.4 Full-wave models
   3.5 Higher order numerical approaches

4 CLINICAL FOCUSED ULTRASOUND BRAIN THERAPY
   4.1 Treatment setup
   4.2 Treatment flow
   4.3 Transcranial ultrasound studies

5 REVIEW OF PUBLICATIONS I-IV

6 CONCLUSIONS

REFERENCES
ABBREVIATIONS

KZK Khokhlov-Zabolotskaya-Kuznetsov
MR Magnetic resonance
CT Computed tomography
FDTD Finite difference time-domain
tPA Tissue plasminogen activator

NOMENCLATURE

| : | Absolute value
j | Imaginary unit \( j = \sqrt{-1} \)
\( \mathbb{R}\{\cdot\}, \mathbb{I}\{\cdot\} \) | Real and imaginary parts
\( \cdot^\top \) | Matrix transpose
I | Identity matrix
\( \mathcal{F}\{\cdot\}, \mathcal{F}^{-1}\{\cdot\} \) | Fourier and inverse Fourier transform
\( \delta(\cdot) \) | Dirac \( \delta \)-function
\( \partial_s f, \partial^2_s f, \partial^3_s f \) | Derivatives \( \partial_s f = \frac{\partial f}{\partial s}, \partial^2_s f = \frac{\partial^2 f}{\partial s^2}, \partial^3_s f = \frac{\partial^3 f}{\partial s^3} \)
\( \nabla_s \) | Gradient of scalar
\( \nabla^2_s \) | Laplacian of scalar
\( \nabla_s \) | Gradient of vector
\( \nabla \cdot s \) | Divergence of vector
\( \nabla^2 \) | Laplacian of vector
\( \nabla \cdot \tau \) | Divergence of tensor
\( \tau \cdot n \) | Product of tensor and vector
\( \text{Tr}\{\cdot\} \) | Tensor trace

SYMBOLS

\( t \) | Time
\( t' \) | Retarded time \( t' = t - z/c \)
\( r \) | Position vector \( r = (x, y, z)^\top \)
\( n \) | Normal vector to surface
\( p \) | Acoustical pressure in time-domain
\( \hat{p} \) | Acoustical pressure in frequency-domain
\( u \) | Particle displacement
\( \hat{u} \) | Particle displacement in frequency-domain
\( T \) | Temperature
$D$ Thermal dose
$\rho$ Soft tissue or bone density
$c$ Sound speed in soft tissue
$\alpha$ Attenuation in soft tissue
$\alpha_0$ Proportionality coefficient of power law attenuation
$\alpha_1$ Exponent parameter of power law attenuation
$\beta$ Coefficient of nonlinearity in soft tissue
$\lambda$ First Lamé parameter
$\mu$ Second Lamé parameter
$\eta$ First viscosity parameter
$\xi$ Second viscosity parameter
$\tau$ Stress tensor
$\epsilon$ Strain tensor
$c_L$ Longitudinal sound speed in bone
$\alpha_L$ Longitudinal attenuation coefficient in bone
$c_S$ Shear sound speed in bone
$\alpha_S$ Shear attenuation coefficient in bone
$\lambda'$ Complex first Lamé parameter
$\mu'$ Complex second Lamé parameter
$\tau'$ Complex stress tensor
$\epsilon'$ Complex strain tensor
$C$ Specific heat capacity
$\kappa$ Thermal conductivity
$Q$ Absorbed power density
$\rho_b$ Density of blood
$\kappa_b$ Thermal conductivity of blood
$C_b$ Specific heat capacity of blood
$W$ Perfusion rate of blood
$T_b$ Blood temperature
$\mathbf{v}$ Velocity field of blood circulation in vessels
$R$ Tissue heat sensitivity parameter
$f$ Frequency
$\omega$ Angular frequency $\omega = 2\pi f$
$k$ Wave-number $k = \omega / c$
$k'$ Complex wave-number $k' = k - j\alpha$
1 Introduction

Neurological diseases are common and include Alzheimer’s, Parkinson’s, and chronic pain disorders, to name a few. The brain and central nervous system are also a common place for primary tumours with an estimated 175000 cases diagnosed per year worldwide [1]. In addition to primary tumors, approximately 10% of other cancer patients develop brain metastases [2]. In children, tumors of the brain and central nervous system are surpassed only by leukaemia in occurrence [3]. No definite cures for any of these neurological diseases exist, and existing treatments are typically accompanied with a poor chance of survival. For example, only 3.3% of glioblastoma patients survive for more than 5 years after the time of their diagnosis, with the median survival time being 9-15 months [4]. The treatment of these diseases might benefit from the use of therapeutic ultrasound [5]. For a review of focused ultrasound therapy see [6–12].

Noninvasive transcranial ultrasound therapy is based on delivering ultrasonic energy through the intact skull into the patient’s brain. It was assumed for a long time that the only method to deliver ultrasound into the brain was to perform a craniectomy on the patient, thus forming an acoustic window in the skull through which the ultrasound could be delivered [13]. However, advances in transducer development led to the possibility of building large-scale ultrasound phased-arrays that are capable of generating and steering an ultrasonic focus within the brain without the use of a craniectomy [14–17]. The physical principles and devices used in therapeutic ultrasound are reviewed in [18,19].

The overall goals of this thesis was to investigate various aspects of ultrasound therapy, with an emphasis on brain treatments, through the use of numerical simulations. In order to carry out the research for the publications included in this thesis, four separate numerical models were developed for different simulation pur-
poses. In Publication I, a nonlinear propagation model based on the Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation was used to perform simulations in soft tissues. In Publication II, a hybrid model combining a Rayleigh integral-based model, a full-wave soft tissue-bone model, and an angular spectrum model was developed for transcranial simulations. In Publications III and IV two separate full-wave soft tissue-bone models were developed for transskull applications, one solved using a spectral element approach (Publication III) and the other with a hybrid approach composed of a grid method and a finite difference method (Publication IV). The developed simulation models have been used to gain new insights into the use of therapeutic ultrasound.

Following the introduction, the physics of ultrasound propagation, with an emphasis on the transcranial focused ultrasound therapy, is reviewed in Chapter 2. A description of the common simulation approaches used in the field of therapeutic ultrasound together with a review of corresponding simulation studies is presented in Chapter 3, along with a brief discussion of some higher order numerical methods that may gain further adoption in the future. Chapter 4 is devoted to describing the practical aspects of ultrasound therapy in the brain, and reviewing the clinical studies published to date. In Chapter 5 the results obtained in the publications included in this thesis are reviewed, and concluding remarks are made in Chapter 6.
In this chapter, the fundamental physics associated with therapeutic ultrasound is briefly reviewed.

2.1 ULTRASOUND PROPAGATION IN SOFT TISSUES

An equation describing the nonlinear propagation of ultrasound in an inhomogeneous fluid medium can be written in terms of the acoustical pressure field $p$ as [20,21]:

$$\frac{1}{c^2} \partial_{tt}^2 p = \nabla^2 p - \frac{1}{\rho} \nabla \rho \cdot \nabla p + \frac{2\alpha_0}{c} \partial_{tt}^3 p + \frac{\beta}{\rho c^4} \partial_{tt}^2 p^2, \quad (2.1)$$

where $\rho$ is the density, $c$ is the sound speed, $\alpha_0$ is related to attenuation, and $\beta$ is the coefficient of nonlinearity of the medium of interest. Equation (2.1) is often referred to as the Westervelt equation [20]. Typical values of these material parameters for some soft tissues are presented in Table 2.1.

In heterogeneous media, ultrasound will be partially reflected and transmitted at boundaries separating tissues with differing acoustical properties. The transmission and reflection are based on the requirement of continuous pressure (or stress) and particle displacement (or velocity) along the boundary interface. The propagation direction of the transmitted and reflected waves are determined by Snell’s law [21]. Mathematically, these requirements can be expressed as:

$$p_i + p_r = p_t,$$

$$\frac{1}{\rho_i c_i} \partial_n (p_i + p_r) = \frac{1}{\rho_t c_t} \partial_n p_t, \quad (2.2)$$

and

$$\frac{\sin \theta_i}{c_i} = \frac{\sin \theta_r}{c_i} = \frac{\sin \theta_t}{c_t}, \quad (2.3)$$
Table 2.1: Acoustical properties of some soft tissues [22–25]. \( c \) is the sound speed, \( \rho \) is the density, \( \alpha_0 \) is the amplitude attenuation coefficient\(^†\) and \( \alpha_1 \) is the power law exponent, and \( \beta \) is the coefficient of nonlinearity.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>( c ) (m/s)</th>
<th>( \rho ) (kg/m(^3))</th>
<th>( \alpha_0 ) (Np/m/MHz(^T))</th>
<th>( \alpha_1 )</th>
<th>( \beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1532–1573</td>
<td>1040</td>
<td>7</td>
<td>1.14</td>
<td>4.28</td>
</tr>
<tr>
<td>Fat(^*)</td>
<td>1436–1476</td>
<td>950</td>
<td>1.6</td>
<td>2.1</td>
<td>6.14</td>
</tr>
<tr>
<td>Kidney</td>
<td>1560</td>
<td>1050</td>
<td>10</td>
<td>1.09</td>
<td>5.49</td>
</tr>
<tr>
<td>Liver</td>
<td>1522–1607</td>
<td>1060</td>
<td>8</td>
<td>1.13</td>
<td>4.38</td>
</tr>
<tr>
<td>Muscle(^*)</td>
<td>1568–1580</td>
<td>1050–1060</td>
<td>20.4 / 7.2</td>
<td>0.82 / 0.93</td>
<td>4.72</td>
</tr>
</tbody>
</table>

\(^†\) Note that the attenuation values are given in terms of frequency, whereas equation (2.1) takes parameters in terms of angular frequency.

\(^*\) Attenuation parameters for fat and muscle tissue were estimated based on the data in the references. Values of attenuation and nonlinearity parameters are along the fibers (before slash) and across the fibers (after slash).

where \( p_i, p_r \) and \( p_t \) are the incident, reflected and transmitted pressure waves, \( \rho_i, c_i, \rho_t \) and \( c_t \) are the material parameters on the incident and transmitted sides of the boundary, respectively, \( \partial_n \) is the normal derivative on the boundary interface, and \( \theta_i, \theta_r \) and \( \theta_t \) are the incident, reflected, and transmitted propagation angles with respect to the vector oriented normal to the boundary interface. Figure 2.1 displays the refraction of acoustic wave on tissue interface. When the speed of sound in the incident medium is smaller than in the transmitted medium propagating sound wave can experience total reflection at incident angles beyond the critical angle \( \theta_{\text{crit}} \), defined for fluid-fluid interfaces as:

\[
\theta_{\text{crit}} = \sin^{-1} \frac{c_i}{c_t}. \tag{2.4}
\]

The transmitted sound wave becomes evanescent for angles beyond the critical angle. For interfaces between soft tissues in Table 2.1 the critical angle can be as low as 63° for fat-liver interface.

Equation (2.1) describes the power law attenuation mechanism
Fundamental physics of therapeutic ultrasound

of form

\[ \alpha(\omega) = \alpha_0 \omega^{\alpha_1}, \tag{2.5} \]

where \( \alpha(\omega) \) is the attenuation of the pressure at angular frequency \( \omega \) and \( \alpha_1 \) is the power law exponent. For the classical attenuation mechanism in (2.1), \( \alpha_1 = 2 \). In practice, soft tissues have exponents closer to \( \alpha_1 = 1 \) in value (see Table 2.1.) It can be shown, through the Kramers-Kröning relations [26], that non-quadratic [27–29] (i.e. \( \alpha_1 \neq 2 \)) power law attenuation results in small variations of sound speed as a function of the ultrasound frequency, a phenomenon known as acoustic dispersion, which has been studied both theo-

![Figure 2.1: Refraction of acoustic wave on fluid-fluid (top left) and fluid-solid (top right) interfaces, and refraction of longitudinal wave (bottom left) and shear wave (bottom right) on solid-fluid interface.](image)

Dissertations in Forestry and Natural Sciences No 143
retically and experimentally [27–30]. Modifications to the acoustic wave equation exist which incorporate more realistic attenuation mechanisms [31]. Common modifications include the modeling of relaxation mechanisms [21,32–34], as well as approaches based on fractional derivatives [35,36]. The relaxation methods offer a computationally simple and attractive way of approximating the power law attenuation, whereas the fractional derivative approaches provide an exact power law attenuation mechanism at a potentially high computational cost.

The attenuation of ultrasound is not to be confused with acoustic absorption. The difference between attenuation and absorption is that the latter describes how much energy is transferred from the wave into tissue, whereas the former incorporates both absorption and additional mechanisms of amplitude reduction, such as scattering of sound caused by small-scale inhomogeneities. Attenuation can be up to $2 - 5$ times larger than absorption in some soft tissues [23], and determining the value of attenuation can be difficult as different measurement setups can yield different values. For example, one study found a factor of three difference between two experimental setups for measuring attenuation [23].

As a finite amplitude ultrasound wave propagates, it generates nonlinearities. This is caused by the nonlinear thermodynamical relationship between the material density of the medium and the acoustic pressure. The effect is such that at high acoustical pressure the ultrasound wave will propagate faster than at the low pressure. This leads to generation of harmonic frequency components and a general sharpening of the wavefront as a function of the propagation distance, as illustrated in Figure 2.2. In attenuating media the propagation of ultrasound becomes more complex. As nonlinearities are generated, energy is shifted into higher frequency components. However, these higher frequencies are more quickly attenuated in most biological media.

For sonications in the linear power regime, the nonlinearity-term in (2.1) can be ignored by setting $\beta = 0$. For monofrequency, or narrow-band sonications, a further simplification is possible. The
Fundamental physics of therapeutic ultrasound

attenuation mechanism can be simplified by transferring the attenuation term into the angular frequency-domain resulting in attenuation term $-2\alpha_0\omega^2 c^{-1} j \omega \hat{p}$ with $\hat{p}$ being the complex pressure in the angular frequency-domain. It becomes apparent that in frequency-domain coefficients $\alpha_0\omega^2$ correspond to power law attenuation with cubic dependence on frequency (equation (2.5) with $\alpha_1 = 2$). Replacing the term now with arbitrary constant (frequency independent) attenuation $\alpha$ results in $-2\alpha c^{-1} j \omega \hat{p}$ which can be Fourier transformed back into time-domain resulting in linear, inhomogeneous, attenuating wave equation for narrow-band sonications:

$$\frac{1}{c^2} \partial_t^2 p = \nabla^2 p - \frac{1}{\rho} \nabla \rho \cdot \nabla p - \frac{2\alpha}{c} \partial_t p.$$ (2.6)

Equation (2.6) describes the power law attenuation with $\alpha_1 = 0$, i.e. constant attenuation for all frequencies. The use of this simplified attenuation mechanism results in a reduced computational complexity since the implementation of a numerical scheme with at

![Figure 2.2: Top: Nonlinear ultrasound pressure field as a function of distance from the sound source located on the left in a non-attenuating medium. Bottom: A spectrogram of the acoustic pressure as a function of distance from the sound source for the first 20 harmonics of the base frequency. Data based on the solutions presented in [37]. The propagation distance x is normalized by the acoustic wavelength λ at the principal frequency.](image)

Dissertations in Forestry and Natural Sciences No 143
most second order temporal derivatives requires less memory than implementing higher order (e.g. third order in this case) temporal derivatives.

Boundary conditions commonly used with equations such as (2.1) and (2.6) include the homogeneous Dirichlet boundary condition \[38, 39\]

\[ p = 0, \quad (2.7) \]

and the inhomogeneous Neumann boundary condition \[38, 39\]

\[ \frac{1}{\rho} \nabla p \cdot \mathbf{n} = -a, \quad (2.8) \]

where \( \mathbf{n} \) is the normal on the boundary and \( a \) is the acceleration of the boundary as a function of time. The Dirichlet and Neumann boundary conditions are also referred to as sound-soft and sound-hard boundaries, respectively, due to their physical interpretations: the Dirichlet boundary describes an exterior domain that is very light (e.g. tissue-air), whereas the Neumann boundary describes heavy exterior domain (e.g. tissue-transducer). The Neumann boundary condition is typically used to simulate the transducer’s surface and to emit ultrasound. Another commonly used boundary condition is the Robin boundary condition \[38, 39\]

\[ \frac{1}{c} \partial_t p + \nabla p \cdot \mathbf{n} = 0, \quad (2.9) \]

which operates as an absorbing boundary condition: sound hitting the boundary will reflect at reduced amplitude back into the main domain. The Robin boundary condition is commonly used to limit the size of computational domains in large-volume simulations, where the region of main interest is confined within a small volume. The efficiency of the Robin boundary (i.e. the amplitude of the wave reflecting from it) depends on the propagation direction of the incident wave. Due to the imperfect absorption of sound with (2.9), higher order absorbing boundary conditions and methods to reduce the boundary reflections have been developed \[40–43\].
Fourier transforming (2.6) into the frequency-domain results in the inhomogeneous Helmholtz equation:

\[ \nabla^2 \hat{p} - \frac{1}{\rho} \nabla \rho \cdot \nabla \hat{p} + k'^2 \hat{p} = 0, \]  

(2.10)

where \( \hat{p} \) is the complex pressure and \( k' \) is the complex wave-number defined as \( k'^2 = k^2 - \frac{j2\alpha \omega}{c} \), with \( k = \omega / c \). In situations where \( \alpha \ll k \), the complex wave-number can be approximated as \( k' \approx k - j\alpha \). Equation (2.10) can be used to compute steady-state solutions of monofrequency sonifications.

### 2.2 ULTRASOUND PROPAGATION IN BONE

An isotropic viscoelastic wave equation of solids, such as the skull bone, can be written in terms of the particle displacement \( u \) as [44, 45]:

\[ \rho \partial_{tt}^2 u = (\mu + \eta \partial_t) \nabla^2 u + (\lambda + \mu + \zeta \partial_t + \frac{\eta}{3} \partial_t^3) \nabla \nabla \cdot u, \]  

(2.11)

where \( \rho \) is the density, \( \lambda \) and \( \mu \) are the first and second Lamé coefficients, and \( \eta \) and \( \zeta \) are the first and second viscosity parameters of the medium of interest.

Solid media supports the propagation of two modes of acoustic waves: longitudinal, or compressional waves, such as those present in soft tissues, as well as shear, or transverse waves. As such, wave propagation in solids is characterized by both the longitudinal and shear sound wave speeds \( c_L \) and \( c_S \), and their corresponding attenuations coefficients \( \alpha_L \) and \( \alpha_S \). The relationship between the Lamé and viscosity parameters and \( c_L \), \( c_S \), \( \alpha_L \), and \( \alpha_S \) is given as follows [45]:

\[ c_L = \sqrt{\frac{\gamma^2 + \nu^2 \omega^2}{\rho} \sqrt{\frac{2}{\gamma + \sqrt{\gamma^2 + \nu^2 \omega^2}}}} \]  

(2.12)

\[ c_S = \sqrt{\frac{\mu^2 + \eta^2 \omega^2}{\rho} \sqrt{\frac{2}{\mu + \sqrt{\mu^2 + \eta^2 \omega^2}}}} \]  

(2.13)
\[ \alpha_L = \frac{\omega^2}{\sqrt{2}} \sqrt{\frac{\rho}{\gamma^2 + v^2\omega^2}} \frac{v}{\sqrt{\gamma + \sqrt{\gamma^2 + v^2\omega^2}}} \]  
\[ \alpha_S = \frac{\eta \omega^2}{\sqrt{2}} \sqrt{\frac{\rho}{\eta^2 + \eta^2\omega^2}} \frac{1}{\sqrt{\mu + \sqrt{\mu^2 + \eta^2\omega^2}}} \]  

(2.14) 

(2.15)

where \( \gamma = \lambda + 2\mu \), and \( \nu = \xi + \frac{4}{3} \eta \) are auxiliary parameters that are introduced for a more compact notation.

The acoustical properties of human skull bone have been investigated in [46–48]. Figure 2.3 shows the longitudinal and shear sound speeds and attenuation coefficients as a function of skull density in the range of 1200 – 2600 kg/m\(^3\). Generally speaking, the shear wave sound speed in the skull is much closer to the sound speed of longitudinal waves in soft tissues, when compared with the longitudinal sound speed in skull bone. The shear wave attenuation coefficient is higher than its longitudinal counterpart, and both are generally much higher than the attenuation coefficient in soft tissues.

Figure 2.3: From left to right: sound speeds \( c_L \) (–) and \( c_S \) (– –), and attenuation coefficients \( \alpha_L \) (–) and \( \alpha_S \) (– –). Top row (bottom row) displays the acoustical properties of the skull at 230 kHz (650 kHz). Parameters displayed as a function of skull density \( \rho \). Data based on values presented in [48, 49].
Equation (2.11) can be derived from a differential form of Newton’s second law [44]
\[ \rho \partial_{tt}^2 \mathbf{u} = \nabla \cdot \mathbf{\tau}, \] (2.16)
where \( \mathbf{\tau} \) is the stress tensor for isotropic viscoelastic solids defined as [44]:
\[ \mathbf{\tau} = \left( \lambda + (\xi - \frac{2}{3} \eta) \partial_i \right) \text{Tr}\{\mathbf{e}\} \mathbf{I} + 2(\mu + \eta \partial_i) \mathbf{e}, \] (2.17)
where \( \text{Tr}\{\cdot\} \) is the trace operator, \( \mathbf{I} \) is the identity matrix and \( \mathbf{e} \) is the strain:
\[ \mathbf{e} = \frac{1}{2} \left( \nabla \mathbf{u} + \nabla \mathbf{u}^\top \right). \] (2.18)

The frequency-domain form of (2.11) is obtained through a Fourier transformation and is given by:
\[ \rho \omega^2 \hat{\mathbf{u}} + \mu' \nabla^2 \hat{\mathbf{u}} + (\mu' + \lambda') \nabla \nabla \cdot \hat{\mathbf{u}} = 0, \] (2.19)
where \( \hat{\mathbf{u}} \) is the frequency-domain particle displacement, \( \mu' = \mu + j \omega \eta \) and \( \lambda' = \lambda + j \omega (\xi - \frac{2}{3} \eta) \) are the complex Lamé parameters, and the corresponding stress and strain tensors are:
\[ \mathbf{\tau}' = \lambda' \text{Tr}\{\mathbf{e}'\} \mathbf{I} + 2\mu' \mathbf{e}', \] (2.20)
and
\[ \mathbf{e}' = \frac{1}{2} \left( \nabla \hat{\mathbf{u}} + \nabla \hat{\mathbf{u}}^\top \right). \] (2.21)

One alternative model for propagation of ultrasound in the skull bone could be Biot’s model for porous solids [50]. This model describes the propagation of sound in a porous material that is partially saturated with fluid. The skull diploë is indeed such a structure, forming a spongy solid support structure between the outer and inner layers of the skull [51]. Cancellous diploë contains more fluidic bone marrow, and is found in occipital, parietal, and frontal bones. It may be possible to couple (2.11) with Biot’s porous wave equations such that the propagation of ultrasound in dense, cortical bone structures (i.e. the inner and outer surfaces) is simulated using (2.11) while propagation in soft, cancellous structures is modeled using the porous wave equation. In addition to possibly creating a
more physically realistic ultrasound propagation model, the computational burden would increase, and new material parameters would have to be defined for the porous wave equation.

### 2.3 TRANSMISSION OF ULTRASOUND AT TISSUE-BONE INTERFACES

The transmission of sound at tissue-bone interfaces, i.e. the coupling of equations (2.1) and (2.11), is handled by requiring the continuity of the normal pressure in soft tissue and the stress in the bone

\[ p \mathbf{n} = -\tau \cdot \mathbf{n}, \quad (2.22) \]

and the normal component of particle displacement (or velocity)

\[ \frac{1}{\rho} \nabla p \cdot \mathbf{n} = -\partial_{tt}^2 \mathbf{u} \cdot \mathbf{n}, \quad (2.23) \]

where \( \mathbf{n} \) is the normal of the interface. The refraction of ultrasound on the interface follows Snell’s law:

\[ \frac{\sin \theta_i}{c_i} = \frac{\sin \theta_L}{c_L} = \frac{\sin \theta_S}{c_S}, \quad (2.24) \]

where \( \theta_i \) and \( c_i \) are the angle and speed of propagation of sound in the soft tissue, \( \theta_L, c_L \) and \( \theta_S, c_S \) are the angles and speeds of propagation of the longitudinal and shear wave in the bone. As an ultrasound beam encounters an interface between the soft tissue and bone, it can transmit both longitudinal and shear wave components in the bone medium, depending on the angle of incidence. This dual-mode generation is referred to as shear-mode conversion [49,52,53]. Similarly, both longitudinal and shear waves will generate a longitudinal pressure wave in soft tissue if incident upon a bone-soft tissue interface. Figure 2.1 displays the refraction of acoustic wave on tissue-skull bone interface. On soft tissue-bone interface critical angles can be defined for transmission, similar to equation (2.4) for transmission in soft tissues, beyond which the transmitted longitudinal or shear sound waves become evanescent.
The longitudinal and shear critical angles, $\theta_{\text{crit},L}$ and $\theta_{\text{crit},S}$ respectively, can be defined as:

$$
\theta_{\text{crit},L} = \sin^{-1} \frac{c_i}{c_L}, \quad \theta_{\text{crit},S} = \sin^{-1} \frac{c_i}{c_S}.
$$

(2.25)

For soft tissues with sounds speed in range of those presented in Table 2.1 and skull bone with sound speeds in range of those in Figure 2.3 the longitudinal critical angle varies between 26° and 73° depending on the bone density and speed of sound in the soft tissue. Similarly, for shear waves the critical angle varies between 61° and 90°.

As the shear wave sound speed in bone is close to that of soft tissues, the part of the ultrasound beam that is transmitted as a shear wave is less distorted than the part transmitted as longitudinal wave [49,52]. This effect can be used for transcranial ultrasound applications [53–55].

Due to the strong acoustic impedance mismatch between soft tissues and bone, strong reflections are generated on the interfaces. The reflected ultrasound beam will interact with the incident beam and, in some circumstances, can lead to the formation of standing waves. As standing waves often have higher pressure amplitude than just the incident-wave, this can contribute to heating close to tissue interfaces. A wave propagating through a bone, on the other hand, reflects on the interface between the soft tissue and the bone forming a standing-wave within the bone itself.

Using plane wave studies of transmission and reflection at an interface between soft tissue and bone, from the perspective of the incident ultrasound-wave, it has been found that at close to normal incident angles the main source of heating on the interface comes from the attenuation of the longitudinal wave generated in the bone [56,57]. As the angle of incidence becomes more oblique, shear mode conversion starts to contribute to heating, and becomes the dominant source of heating at angles beyond the critical transmission angle for longitudinal waves [57]. At incident angles greater than the critical angle for shear waves, the main source of heating
on the interface is the interaction between the incident and reflected sound waves in the soft tissue [57].

2.4 HEATING DUE TO ULTRASOUND

The attenuation of acoustic energy from the ultrasound wave increases the tissue temperature. The heating can be described by the absorbed power density, $Q$, which characterizes the amount of energy transferred into the volume of tissue. Typical sonication times to achieve thermal effects with ultrasound range from milliseconds to minutes. Since the typical biological targets are on the scale of centimeters in length, a steady-state pressure field is rapidly formed during these therapeutic sonications. The heating caused by the ultrasound beam is hence commonly approximated as that generated by a steady-state field, by ignoring the initial pressure build up and post-sonication pressure fall off. The contribution to heating caused by both of these effects is minimal during long duration sonications. As the steady-state acoustical fields are sinusoidal, they can be written in terms of the complex pressure $\hat{p}$ and particle displacement $\hat{u}$. These quantities can be approximated through the Fourier transformation of the temporal pressure and particle displacement data, respectively.

In soft tissues the absorbed power density for continuous harmonic sonications can be expressed as [21]:

$$Q = \frac{\alpha}{\rho c} |\hat{p}|^2,$$

(2.26)

where $\alpha$ is the attenuation coefficient of the medium at the sonication frequency, and $|\hat{p}|$ is the absolute amplitude of the complex ultrasound pressure.

In the skull the conversion of a continuous mechanical wave into absorbed power density is expressed as [44, 58]:

$$Q = \frac{\omega}{2} \Im\{\tau' : e'\},$$

(2.27)

where $\Im\{\cdot\}$ refers to imaginary component and $\tau' : e'$ is a tensor product summing products of elements of $\tau'$ and $e'$. 

Dissertations in Forestry and Natural Sciences No 143
2.5 BIOHEAT MODEL

What is nowadays commonly referred to as the bioheat equation within the field of therapeutic ultrasound was introduced in [59]. The inhomogeneous bioheat transfer equation describing the evolution of the temperature field $T$ can be written as:

$$\rho C \partial_t T = \nabla \cdot (\kappa \nabla T) - \rho_b C_b W (T - T_b) + Q, \quad (2.28)$$

where $\rho$, $C$ and $\kappa$ are the density, specific heat capacity, and the thermal conductivity of tissue, respectively, while $\rho_b$, $C_b$, $W$ and $T_b$ represent the density, specific heat capacity, perfusion rate, and temperature of blood. $Q$ is the absorbed power density and can be computed using (2.26) or (2.27). Typical values for the thermal parameters of various tissues are shown in Table 2.2. Simulations of the bioheat equation are often computed using finite difference methods [60], though semi analytical approaches also exist [61].

The bioheat transfer equation (2.28) takes into account the diffusion of heat in inhomogenous media, and the heat transfer caused

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\rho$ (kg/m$^3$)</th>
<th>$C$ (J/kg $\cdot$ °C)</th>
<th>$\kappa$ (W/m $\cdot$ °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1040</td>
<td>3600-3680</td>
<td>0.503-0.576</td>
</tr>
<tr>
<td>Fat$^\dagger$</td>
<td>950</td>
<td>3590</td>
<td>0.200-0.334</td>
</tr>
<tr>
<td>Kidney</td>
<td>1050</td>
<td>3600-3890</td>
<td>0.513-0.564</td>
</tr>
<tr>
<td>Liver</td>
<td>1060</td>
<td>3600</td>
<td>0.467-0.527</td>
</tr>
<tr>
<td>Muscle</td>
<td>1050-1060</td>
<td>3720</td>
<td>0.449-0.562</td>
</tr>
<tr>
<td>Bone</td>
<td>-</td>
<td>1300</td>
<td>0.230-0.496</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\rho_b$ (kg/m$^3$)</th>
<th>$C_b$ (J/kg $\cdot$ °C)</th>
<th>$\kappa_b$ (W/m $\cdot$ °C)</th>
<th>$T_b$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>1030</td>
<td>3600-3720</td>
<td>0.484-0.530</td>
<td>37</td>
</tr>
</tbody>
</table>

$^\dagger$ For heat capacity of fat, value for cow is shown, for lack of measured value in human known to author.
by the vasculature. The perfusion is implemented in a way that the circulation of blood is modeled as a heat sink: the vasculature will remove excess heat from the tissue at a rate proportional to its temperature difference with respect to that of the blood. A more accurate way to model the blood circulation close to larger vessels, is to implement convection of heat that is based on the geometry of the vasculature. Convective heat transfer due to blood circulation can be implemented by coupling (2.28) with:

\[ \rho_b c_b \left( \partial_t T + \mathbf{v} \cdot \nabla T \right) = \kappa_b \nabla^2 T + Q, \quad (2.29) \]

where \( \mathbf{v} \) is the velocity field of the blood flow and \( \kappa_b \) is the thermal conductivity of the blood [62, 63]. The coupling of equations (2.28) and (2.29) is done by solving (2.28) in the tissue domain and (2.29) within the blood vessels, with the requirement of continuous heat flux on the tissue-vessel interface:

\[ \kappa \nabla T \cdot \mathbf{n} = \kappa_b \nabla T \cdot \mathbf{n}, \quad (2.30) \]

where \( \mathbf{n} \) is the unit vector normal to the interface. Taking the convective transfer of heat into account increases complexity of the thermal model, as it requires more material parameters as well as the geometrical information of the blood vessels. The bioheat equation without the velocity field estimates the tissue temperature well when the amount of energy transferred by perfusion is small compared with the heat transfer via thermal conduction. This means that short (a few second) focused ultrasound exposures can be predicted well away from large blood vessels [64] provided the ultrasound field is accurately simulated [65].

2.6 THERMAL DOSIMETRY

Thermal dose is a quantity that can be used to predict the degree to which thermal bioeffects occur in tissues as a result of heating [66,67]. In its continuous limit, the thermal dose \( D \) can be written as

\[ D = \int R^{T(t)} \ dt \quad (2.31) \]
Table 2.3: Examples of thermal dose thresholds (in equivalent time at 43°C) and the level of tissue damage for some soft tissues [67].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dose (min)</th>
<th>Tissue damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>25</td>
<td>Neuronal pyknosis</td>
</tr>
<tr>
<td>Fat</td>
<td>240</td>
<td>Necrosis, fibrosis</td>
</tr>
<tr>
<td>Kidney</td>
<td>20</td>
<td>Necrosis of glomeruli and tubules</td>
</tr>
<tr>
<td>Liver</td>
<td>30</td>
<td>Hepatocyte loss, fibrosis</td>
</tr>
<tr>
<td>Muscle</td>
<td>240</td>
<td>Necrosis, fibrosis</td>
</tr>
</tbody>
</table>

where the integral is carried over the duration of heating, \( T(t) \) is the temperature of tissue as a function of time in °C, and \( R \) is a parameter describing the sensitivity of tissue to heat, which has been empirically determined to be:

\[
R = \begin{cases} 
4, & T(t) \leq 43°C \\
2, & T(t) > 43°C.
\end{cases}
\]  

(2.32)

For an arbitrary exposure, the thermal dose model describes the duration of an exposure held at the temperature of 43°C that would produce equivalent bioeffects, and therefore allows for thermal exposures of tissues undergoing different temperature elevation trajectories to be quantitatively compared with one another. Table 2.3 shows examples of thermal dose thresholds for some soft tissues.

### 2.7 ACOUSTIC CAVITATION

At high enough pressure amplitudes, the ultrasonic pressure will start to interact with the inert gases present in soft tissues. The gas can form bubbles, which will in turn begin to oscillate within the ultrasound field [68]. This process is often referred to as acoustic cavitation [69]. At low pressures, the gas bubbles oscillate, scattering energy at harmonic, ultraharmonic, and subharmonic frequencies in addition to the frequency of the excitation ultrasound.
field. This is often referred to as stable cavitation. At higher pressure amplitudes of the ultrasound, the gas bubbles begin to oscillate chaotically in a highly nonlinear fashion, ultimately collapsing under the inertia of its surroundings [68, 69]. This phenomenon, typically referred to as inertial cavitation, is associated with wide-band acoustic emissions [70, 71]. Due to the frequency-dependent attenuation characteristics of soft-tissues (e.g. see (2.5)), the acoustic emissions associated with both stable and inertial cavitation can contribute significantly to the heating caused by the incident ultrasound wave [72–78].

Active, passive, and combined methods for monitoring bubble activity have been developed. Active monitoring methods are based on measuring the sound reflected by the bubbles, which can be seen e.g. in B-mode ultrasound images as hyperechoic regions [79]. Passive monitoring methods typically involve the use of a broad-band hydrophone in order to detect potential cavitation emissions during sonication [76, 80]. An example of combined active and passive detection system was presented in [81]. It is possible to use all of these methods to spatially map the location of cavitation activity over time [79, 82–85].

During long sonications, acoustic cavitation can occur due to the formation of standing waves, as they can lead to elevated pressure amplitudes in situ [86]. Due to the potentially hazardous nature of cavitation, methods to reduce the formation of standing waves within the skull cavity have been developed [87–90]. These methods are based on modulating the driving signal that is sent to the ultrasound transducers.

2.8 CORRECTING PHASE AND AMPLITUDE ABERRATIONS

As ultrasound beams from a phased array propagate through strongly inhomogeneous tissues, such as skull bone, they will experience refraction, differences in propagation speed within different media (e.g. skull bone vs. water and brain tissue), scattering, attenuation, and reflections. This leads to cumulative phase and ampli-
tude aberration of the ultrasound beams as they reach the intended target, causing a distortion of the acoustic focus [91].

The effect of this phase aberration is depicted in Figure 2.4. The figure shows the mean and standard deviation of the normalized peak pressure amplitude in the vicinity of the geometric focus of a phased array, as a function of the phase error amplitude. The phase error for each of the phased array elements is drawn from uniform distribution defined in $[-e, e]$ with $e$ being the error amplitude in degrees. The mean and standard deviation are computed based on samples of the pressure field for a number of different randomized phase errors. As the phase error increases, the focal pressure amplitude tends to decrease, while the uncertainty of the focal pressure amplitude increases.

There are two principle methods to perform phase correction with phased arrays:

- If the phase of the pressure field at the intended focus due to each element of the phased array is known, or can be estimated, the focus can be restored by applying phase shifts (phase corrections) to the driving signals, such that the phases will be the same at the desired focus [91, 92].

- If a sound source is present at the intended focus, and the pressure it forms on each of the phased array elements can be determined, then the measured phases can be used to calculate the phase corrections required to restore the focus [93, 94].

Both methods have been verified experimentally in transcranial applications, by inserting a hydrophone inside the skull cavity [91–94]. Instead of using an invasive source to emit sound from the intended target, it is possible to use an oscillating gas bubble as the sound source. Based on the scattered wave field of the bubble, the phase corrections can be determined [95, 96]. One potential weakness of the method is that the location of the gas bubble might be hard to control in vivo. Also, attempts to use this method through nucleation (i.e. without contrast agents) required dangerously high acoustic pressure through the skull (about 20 MPa) [83].
Other noninvasive methods to achieve phase correction include using magnetic resonance (MR) imaging to detect the focal displacement caused by the ultrasound and adjust the driving phases until a maximal focal displacement is achieved [97], or use coded sonications to determine the optimal elemental phasing [98]. Additionally, it might be possible to determine the phase shifts caused by the skull based on ultrasound signals reflecting from the skull [99].

Currently, the clinically implemented method for noninvasive phase correction is based on a simulation approach. Using acoustical simulations based on human skull morphology, it is possible to perform the focal pressure estimation [100] in order to achieve

![Diagram](image_url)

**Figure 2.4:** Top left: The phased-array (312 element, 15 cm radius of curvature, 7.5 cm diameter and 500 kHz frequency) used for the phase-aberration demonstration. Top right: The mean focal pressure amplitude as a function of the phase error $e$. The vertical lines denote standard-deviation limits of the computed means. Bottom: Undistorted pressure-amplitude at the focus on the acoustical axis ($-$) and perpendicular to it ($--$) with black line, as well as an example of the distorted pressure-amplitude with $e = 90^\circ$ on the acoustical axis ($-$) and perpendicular to it ($--$) with thick gray line.
experimentally valid phase corrections.

For amplitude correction of the aberrations two approaches have been presented in [101]: the amplitude and inverse amplitude correction methods. In the amplitude correction the driving amplitude of the phased array elements is adjusted such that the pressure amplitude reaching the focus from each individual element is the same. However, this approach may not be optimal as it favors giving strong amplitudes to elements which contribute negligibly to the focal pressure amplitude. This can create highly uneven sonication amplitudes over the phased array, and can potentially lead to unwanted skull heating. On the other hand, the inverse amplitude approach is based on driving the phased array elements with amplitudes proportional to each element’s focal pressure amplitude, i.e. elements which contribute minimally to the focal pressure are essentially turned off. Experiments have shown that the inverse amplitude correction approach, combined with a phase correction method, lead to better focal quality than with phase corrections alone, and that applying only the phase corrections will lead to a better focusing than with the amplitude correction approach and phase correction methods combined [101]. It should be pointed out, that the amplitude and inverse amplitude correction methods can be seen similar to time reversal based amplitude compensation method analyzed more thoroughly in [102], and the spatio-temporal inverse filter [103–105].
3 Simulation methods in therapeutic ultrasound

In the following chapter, simulation methods that are commonly employed in the field of therapeutic ultrasound are briefly reviewed.

3.1 RAY ACOUSTICS

Ray acoustical simulation methods based on the approach presented in [106] are commonly used in therapeutic ultrasound, for example, as an aid in transducer design [107, 108]. The idea is to divide a finite-sized source into a series of smaller sub-elements, and compute the total acoustic field as the sum of sound coming from each sub-element, which are made small enough to be approximated as point sources. For time-harmonic sound waves, this process can be expressed using the Rayleigh integral [106]:

$$p(r, t) = \frac{j\omega \rho}{2\pi} \int_S \frac{v}{||r-r'||}e^{j\omega t-jk||r-r'||} \, dr',$$

where $j$ is the imaginary unit, $\omega$ is the angular frequency, $S$ is the surface of integration (i.e. the transducer), $v$ is the normal velocity on surface $S$, $r$ is the position vector where the pressure field is to be computed, $k = \omega/c$ is the wave number, and $r'$ is the integrated position vector on $S$. On its own, (3.1) neglects effects such as diffraction caused by curvature of the surface $S$, spatially varying acoustical parameters in the medium of interest, attenuation (unless complex wave number $k'$ is used), as well as nonlinear propagation.

The ray acoustics approach described above has been extended to model multi-layered geometries [109]. This situation is realized in geometries where, for example, a water-tissue interface is insonified. As the acoustic wave from each transducer sub-element reaches the interface, its transmission across the interface can be
approximated using the boundary conditions for plane waves incident obliquely upon a planar interface (2.2)-(2.3). After repeating this process for each transducer sub-element, a new vibrating surface is created along the interface, and equation (3.1) can then be re-applied to further propagate the pressure field into the tissue medium.

The model presented in [109] was later expanded to irregular transcranial geometries [110, 111]. These papers used MR images of the head to derive the geometry of the human skull and demonstrated, through simulations, that transcranial focusing and steering could be achieved using phased arrays with driving frequencies between 500 kHz and 1.5 MHz combined with a phase correction technique. In the latter of these two studies, it was shown that the pressure amplitude on the skull surface can be minimized, by maximizing the acoustic window through which the ultrasound is delivered to the brain [111]. The pressure amplitude distribution on the skull surface is an indirect measure of the skull heating problem associated with transcranial ultrasound, and this result indicates one of the main benefits of using large-aperture phased arrays for transcranial ultrasound therapy.

In [112] the ray acoustics approach was taken to investigate the steerability of a low-frequency (250 kHz) hemispherical phased array. Using geometry derived from computed tomography (CT) scans of three human skulls it was demonstrated, through simulations, that transcranial focusing and steering could be achieved at lower ultrasonic frequencies without applying any aberration corrections. This is due to the short propagation path length within the skull relative to the acoustic wavelength at these lower frequencies [112].

Within the context of therapeutic ultrasound, ray acoustics models have been extended to account for shear wave propagation in the skull bone [53,113]. In [53] focusing ultrasound to targets in the brain located close to the inner skull surface, through shear-mode conversion was found feasible although a significant variation in the focusing quality was observed over the different skulls investi-
Simulation methods in therapeutic ultrasound

gated. In [113] the ray acoustics approach was used to numerically demonstrate feasibility of transcranial passive acoustic cavitation mapping.

The ray acoustics models have also been extended to incorporate effects of spatially varying heterogeneities within the skull bone [113–115]. The effect is essentially simulated in ray acoustics approaches by computing the cumulated phase shift caused by heterogeneous variation in sound speed along a ray path through the skull.

In addition to transcranial ultrasound applications, the ray acoustics approach has been applied to targets found elsewhere in the body. In [116] the ray acoustics method was expanded to the multi-layered irregular geometry found in abdominal applications, and it was shown that even targets composed of heterogeneous soft tissue layers can greatly benefit from the use of a phase correction method for transmit focusing. A ray acoustics model has also been applied to simulate ultrasound-induced lesions in cardiac muscle by using an endoesophageal phased array [117].

Although easy to implement and fairly fast to compute, ray acoustics models are not without issues. In more complex, heterogeneous media, as the number of layers within the simulation domain is increased in order to accurately represent the system, the corresponding computational time tends to increase exponentially. Through experiments it has been shown that thermal simulations based on ray acoustics tend to overestimate the focal temperature elevations [65]. These discrepancies could potentially be avoided by calibrating the model using experimental measurements. In addition to thermal measurements, the accuracy of the ray acoustics method has also been investigated through comparisons of the simulated spatial and temporal pressure data with hydrophone measurements [118,119], where it was shown that the Rayleigh integral propagation models are accurate only for piezocomposite transducers.
3.2 ANGULAR SPECTRUM METHOD

A 3D time-harmonic pressure field can be expressed by a 3D spatial inverse Fourier transformation as follows:

\[
p(x, y, z, t) = e^{j\omega t} \mathcal{F}^{-1} \{ p(k_x, k_y, k_z) \} (x, y, z) = e^{j\omega t} \int p(k_x, k_y, k_z) e^{jk_x x + jk_y y + jk_z z} \, dk_x \, dk_y \, dk_z,
\]

where the integration is carried over 3D wave number space and \( p(k_x, k_y, k_z) \) is the 3D spatial Fourier transform of the pressure field \( p(x, y, z, t) \). The inverse Fourier transformation in (3.2) can be thought of as a summation of plane waves propagating in direction \( \mathbf{k} = (k_x, k_y, k_z) \) at amplitudes and phases defined by \( p(k_x, k_y, k_z) \), which is a complex-valued function. It can be seen, through substitution, that in order for (3.2) to be a solution of the homogeneous Helmholtz equation (and represent an acoustic field):

\[
(\nabla^2 + k^2) p = 0,
\]

the wave number, \( k \), must obey the following relationship: \( k^2 = k_x^2 + k_y^2 + k_z^2 \) \( \iff \) \( k_z = \sqrt{k^2 - k_x^2 - k_y^2} \) with \( k = \omega / c \). This means that the Fourier transformed pressure field \( p(k_x, k_y, k_z) \), can be expressed as:

\[
p(k_x, k_y, k_z) = p(k_x, k_y) \delta(k_z - \sqrt{k^2 - k_x^2 - k_y^2}),
\]

where \( \delta(\cdot) \) is the Dirac \( \delta \)-function. Substituting (3.4) into (3.2) and integrating over \( k_z \) results in:

\[
p(x, y, z, t) = e^{j\omega t} \int p(k_x, k_y) e^{jk_x x + jk_y y + j\sqrt{k^2 - k_x^2 - k_y^2}} \, dk_x \, dk_y,
\]

where the integral is carried out over the \( k_xk_y \)-plane. Equation (3.5) indicates that the pressure field at any point in space can be obtained from the 2D inverse Fourier transformation of \( p(k_x, k_y) \). Furthermore, by examining equation (3.5) with \( z = 0 \), it can be seen that \( p(k_x, k_y) \) is nothing more than the 2D Fourier transform of the...
pressure field in the $xy$-plane at $z = 0$. This is the essence of the angular spectrum method.

The angular spectrum method described by equation (3.5) offers a fast way to compute the propagation of ultrasound beams: in order to compute the pressure field at an arbitrary plane $z$, one simply needs to:

1. form $p(k_x, k_y)$ by computing the 2D Fourier transformation of $p(x, y, z = 0, t)$, and
2. multiply $p(k_x, k_y)$ by $\exp(j \sqrt{k^2 - k_x^2 - k_y^2 z})$ and take the inverse 2D Fourier transformation to obtain $p(x, y, z, t)$.

Computing the Fourier transformations numerically can be performed efficiently by using fast Fourier transformation algorithms [120]. Depending on the application, the initial pressure field at $z = 0$ can be obtained from either experimental measurements or simulations. For information regarding the practical implementation of the angular spectrum method, including discretization requirements, see [121, 122].

In the context of therapeutic ultrasound the angular spectrum method has been extended to simulations of multi-layered media in both linear [123] and nonlinear pressure regimes [124]. The transmission of ultrasound beams through layered media can be taken into account, using the angular spectrum method, by adding a transmission coefficient that is dependent on the propagation direction $(k_x, k_y)$ into equation (3.5). Further, the angular spectrum method has been extended to include effects caused by spatially inhomogeneous material parameters [125].

The angular spectrum method can also be used for transducer characterizations [126, 127]. By measuring the pressure field of a transducer in a plane parallel to its acoustical axis, the vibration amplitude of the transducer surface can be estimated. Additionally, the angular spectrum method has been extended to computations with spherically curved acoustic sources [128]. With the angular spectrum method, it has been found that mechanical steering of the
focus can result in reduced near-field tissue heating in comparison to electrical steering of the focus [129].

In [100, 130] the transmission of sound through non-parallel multi-layered media was incorporated into the angular spectrum method. This modified angular spectrum method was applied successfully to compute the element driving signals required to focus a phased array through a human skull noninvasively, based on CT-derived geometry of the skull [100]. The methods that are currently used to perform transcranial focusing using the clinical phased array devices are based on this initial work.

### 3.3 KZK EQUATION

An attractive model for simulating nonlinear ultrasound propagation is the KZK equation, which can be defined in the time-domain as [131]:

$$\partial_{tt'}^2 p = \frac{c^2}{2} \nabla_{\perp}^2 p + \alpha_0 \partial_{tt'}^3 p + \frac{\beta}{2\rho c^3} \partial_{tt'}^2 p,$$  \hspace{1cm} (3.6)

where $p = p(x, y, z, t')$, $t' = t - z/c$ is the retarded time and $\nabla_{\perp}^2 = \partial_{xx}^2 + \partial_{yy}^2$ is Laplacian operator perpendicular to the propagation direction $z$. All other parameters are as found in equation (2.1). The KZK equation is a parabolic approximation of the full nonlinear wave equation (2.1). It can be derived by approximating the solution of (2.1) as a pulse that is both spatially wide in the $xy$-plane and short in $z$-direction, and by neglecting small amplitude terms in the resulting partial differential equation.

The KZK equation (3.6) accurately describes the propagation of highly directed (i.e. quasi-planar) acoustic waves. However, since it is a parabolic approximation of the wave propagation, it does not support the simulation of highly-focused ultrasound fields. In its simplest form, the KZK equation is only valid in homogeneous media. A method for solving equation (3.6) in the time-domain is presented in [131]. KZK equation-based models have been compared to measured pressure fields produced by piston [132] and focused [133] transducers with good agreement, even at very large
pressure amplitudes [134].

Modifications to the KZK model exist, which include replacing the parabolic computation of diffraction with ray acoustics [135] or angular spectrum methods [136], or making modifications that allow the simulation of weak inhomogeneities [137, 138]. Time-domain KZK with ray acoustic diffraction and frequency-domain KZK with parabolic diffraction approximation were compared to measurements in [139]. Good agreement between the models and the measurements was observed.

In therapeutic ultrasound KZK equation-based models have been used to investigate the enhancement of heating caused by the generation of nonlinearities in the propagating ultrasound field [63, 140, 141]. In addition, the effects of both acoustic cavitation and boiling on lesion formation were studied using a KZK model in [142–144].

### 3.4 FULL-WAVE MODELS

Full-wave modeling of therapeutic ultrasound fields obeying the Westervelt equation can be achieved by solving (2.1) using, for example, finite difference time-domain (FDTD) approaches [145]. FDTD methods are based on approximating spatial and temporal derivatives using finite differences. As an example, the centered second order accurate finite difference approximation of a second order derivative can be written as follows:

\[
\frac{\partial^2}{\partial x^2} f(x) \approx \frac{1}{\Delta x^2} \left( f(x - \Delta x) - 2f(x) + f(x + \Delta x) \right).
\]

Substituting (3.7) into the linearized 1D wave equation:

\[
\frac{1}{c^2} \frac{\partial^2}{\partial t^2} p = \frac{\partial^2}{\partial x^2} p
\]

results in numerical integration of form

\[
p_x^{t+\Delta t} = \frac{c^2 \Delta t^2}{\Delta x^2} \left( p_x^{t-\Delta x} - 2p_x^t + p_x^{t+\Delta x} \right) + 2p_x^t - p_x^{t-\Delta t},
\]
where pressure $p^t_x = p(x, t)$ has been discretized into a grid with temporal and spatial discretizations given by $\Delta t$ and $\Delta x$, respectively. In order for the FDTD simulation to be stable the discretizations $\Delta t$ and $\Delta x$ have to fulfill

$$\frac{c\Delta t}{\Delta x} < \text{CFL},$$

(3.10)

where CFL is the Courant-Friedrichs-Lewy number and the inequality is called Courant-Friedrichs-Lewy condition [146, 147]. Value of CFL is dependent on the discretization scheme and the number of spatial dimensions of the simulation.

Equation (3.9) provides means of computing the acoustical pressure field at a future time instance, based on the recent temporal history of the acoustical field. The Westervelt (2.1) equation can be discretized using the FDTD method in a similar fashion. In [34] the FDTD approach, applied to the Westervelt equation, was expanded to include a more complex treatment of acoustic attenuation by modeling multiple relaxation mechanisms. The study also introduced numerical dispersion reducing finite difference stencils for the approximation of the Laplacian operator.

The FDTD approach has been applied to investigate thermal lensing during ultrasound therapy in soft tissues [148, 149]. As the temperature of soft tissues increases during ultrasound exposure due to acoustic attenuation, a change of the tissue’s acoustical properties, namely speed of sound and attenuation, results due to their respective temperature dependences [150]. This process, known as thermal lensing, affects the propagation of the ultrasound beam, and can lead to small shifts of the acoustic focus.

In [151] it was demonstrated that the linearized wave equation is capable of producing the necessary phasing information for multi-element phased arrays to create a focus transcranially based on skull morphology derived from CT scans of the head. The use of ray acoustics models to speed up FDTD computations has also been studied [152]. Furthermore, the linearized form of (2.1) has been used to study the formation of standing waves within the skull bone itself, and the localized heating that can occur as a results of
this phenomenon [153].

In order to investigate potential causes for the intracranial hemorrhages observed in clinical trials of low-frequency (300 kHz) sonothrombolysis treatments [154], a simulation study with similar geometries was carried out [86]. The numerical study deduced that the standing waves that formed within the brain, caused by reflections from contralateral parts of the skull, might offer an explanation for the detected bleeding, since the simulated pressures in the presence of standing waves exceeded the estimated cavitation thresholds.

Standing wave phenomena was further investigated in [90], where FDTD computations of the linear attenuating wave equation were used to simulate acoustical fields in both primate and human skull cavities. The study demonstrated adequate focusing quality using single element transducer operating at 550 kHz for the purpose of blood-brain barrier opening.

The cavitation threshold level was further investigated with FDTD simulations at 220 kHz and 1 MHz using a hemispherical phased array enclosing the human calvaria [155]. The study demonstrated that for equal absorbed power density levels at the focus (i.e. when the thermal bioeffects are comparable), the lower-frequency sonications resulted in acoustic fields that could exceed the cavitation threshold in soft tissues, whereas the high frequency sonications did not.

A nonlinear, relaxational loss model wave equation [34] has been used to investigate the effects of nonlinear ultrasound propagation in transcranial ultrasound at 1 MHz [156]. The study found that nonlinear heating was present at the transcranial focus.

Simulations of ultrasound propagation and the associated heating in small bone fragments by solving first order hyperbolic viscoelastic equations coupled with an artificial attenuation was performed in [157]. The paper concluded that the majority of the ultrasonic attenuation in the skull bone is caused by reflections, scattering, and mode conversions taking place within heterogeneous bone fragments, and that only a small part of the attenuation is
attributed to absorption. A similar model, based on first order hyperbolic equations of motion for the acoustic pressure, has been used to simulate the propagation of short pulses in low-frequency (60 kHz and 120 kHz) transcranial applications to very good accuracy [158].

3.5 HIGHER ORDER NUMERICAL APPROACHES

In addition to the commonly applied simulation approaches discussed above, higher order numerical methods exist, which have yet to receive wide use in the field of therapeutic ultrasound. Some of these methods are briefly described below.

Within homogeneous regions of a simulation domain, the acoustic propagation problem can be expressed as a problem of solving the unknown pressure, or the pressure gradient on the boundaries of the region. From these it is possible to compute (by integration) the pressure within any locations of the region. A method solving the ultrasound propagation problem in such a way is the boundary element method, which has been applied to transcostal ultrasound treatments [159].

The ultra-weak variational formulation for modeling fluid-solid interactions is based on solving the frequency-domain acoustic (2.10) and viscoelastic wave equations (2.19) by splitting the simulation domain into multiple subdomains [160]. Within each subdomain the acoustical fields have to satisfy equations derived from (2.10) and (2.19), which are coupled on the respective subdomain interfaces using appropriate boundary conditions. Within each subdomain the acoustic fields are approximated using a group of plane waves propagating in different directions.

Similar to ultra-weak variational formulation, discontinuous Galerkin methods split the computational domain into smaller subdomains and locally approximate the solutions [161,162]. The local approximation is typically based on a set of orthogonal basis functions, such as Legendre polynomials.

Spectral element approaches are based on the formalism of fi-
nite element methods, however, instead of approximating the solutions using linear basis functions, the solutions are approximated with a sum of polynomials, resulting in a higher order approximation. One attractive formulation of the spectral element method is the Gauss-Lobatto-Legendre spectral element approach [163, 164], where the polynomial basis is chosen to be orthogonal, similar to discontinuous Galerkin methods.

Another class of methods for simulating the full-wave propagation of ultrasound are the $k$-space propagation models [165–167]. The main idea behind the $k$-space methods is to transfer the time-domain wave equations to spatial frequency-domain, where accurate temporal integration methods can be employed. It is possible to achieve very sparse spatial and temporal discretization using this type of numerical approach. The $k$-space models have been extended to incorporate effects of power law attenuation [168], simulate nonlinear propagation of ultrasound [169, 170], and has been demonstrated capable of fast computation of phase aberration corrections in ex vivo skulls [171].
Aki Pulkkinen: Simulation methods in transcranial ultrasound therapy
4 Clinical focused ultrasound brain therapy

In the following chapter, the typical treatment protocol for transcranial focused ultrasound therapy in human patients is outlined, along with a review of the relevant pre-clinical and clinical studies published to date which have investigated the use of therapeutic ultrasound in the brain.

4.1 TREATMENT SETUP

Figure 4.1 displays the treatment environment during clinical focused ultrasound brain therapy. The figure depicts the treatment room, the electronics compartment, and the operator area. The treatments are performed while the patient is located within the MR imaging system, in order to perform real-time MR thermometry [68] throughout the operation. The treatment room contains the MR bore, the treatment table, and the matching circuitry and driving electronics used to operate the clinical phased array device. The electronics compartment contains, among other things, the control electronics and amplifiers of both the focused ultrasound and MR systems. The operator area is where the treatment is controlled. Two workstations, one for the ultrasound device and one for the MR imaging system, are used to control the procedure.

The treatment table is shown in Figure 4.2. The treatment table is a standard MR-compatible table, on which the patient can lay, modified to hold the transducer array. The treatment table contains the phased array, mounted on a four-dimensional manual positioning device, as well as a panic button, which the patient can press in case of an emergency. The panic button immediately stops any ongoing sonication.
A close-up of the phased array and the patient is shown in Figure 4.3. The patient is positioned such that the calvaria is within the volume enclosed by the phased array, and that the treatment target is close to the geometric focus of the phased array. The patient’s head is fixed by a stereotactic frame to prevent any movement during the treatment, and a membrane is placed between the patient’s scalp and the phased array. The volume enclosed by the phased array and the membrane is filled with water to ensure good ultrasonic coupling between the phased array and the patient, and to provide cooling for the phased array and the scalp.

4.2 TREATMENT FLOW

The treatment protocol for transcranial focused ultrasound therapy proceeds as follows.

Initial decision to perform treatment: CT/MR scanning

Once the medical personnel have decided to utilize focused ultrasound therapy to treat a patient, CT and MR scans are taken. The CT scan is used to accurately capture the geometry of the skull.
Clinical focused ultrasound brain therapy

Figure 4.2: The treatment table.

Figure 4.3: A closeup of the phased-array and the patient. The patient's head is depicted with a combined CT and MR image.

and to estimate the heterogeneous density and speed of sound in the skull bone for phase aberration correction purposes [172], while the MR scan provides images of the soft tissue. The treatment planning is performed based on these initial scans. The patient’s hair is shaved to prevent any air being trapped on the path of the ul-
trasound beam and to increase the efficacy of ultrasound transmission [173].

**Treatment planning**

Based on analysis of the CT and MR imaging scans and decisions of medical personnel, medical physicists will perform the ultrasound treatment planning. Parameters to be determined in the treatment planning process include: the location of the target, the volume of the desired treatment, and the detection of any abnormalities seen in the CT or MR images. An example of such an abnormality is scar tissue left behind by prior surgical operations. Further parameters decided on by the medical physicists include: the patient’s orientation, an estimation of the sonication duration and power, the optimal sonication targets, and potentially determining which part of the phased array to disable in the case of, e.g., scarring of the scalp. Further considerations to take into account during the treatment planning include: the sonication power and duration at which the treatment device is capable of operating at, the estimated focal pressure with respect to the cavitation threshold of various brain tissues, and any potential sources of reflections of the acoustical beams, which can be particularly important when the intended sonication targets are close to the inner skull surface.

**Pre-treatment equipment testing**

Prior to treatment, the functionality of both the therapy device and the MR imaging scanner are assessed by performing test sonications in a quality assurance phantom. These tests are performed for quality control purposes in order to verify that the devices are operating within the correct parameters.

**Patient positioning**

Once the operating personnel are confident that the devices are working properly, the patient is brought into the treatment room
and positioned on the treatment table. In order to perform efficient sonications, the patient is positioned such that the treatment target is located close to the geometrical focus of the phased array. The head of the patient is fixed into a stereotactic frame in order to eliminate any movement during the treatment. A rubber membrane is placed between the patient’s head and the phased array in order to form a sealed container in order to enable water coupling between the patient and the ultrasound device.

**MR imaging of the head and registration with CT**

Once the patient has been positioned on the treatment table and fixed to the phased array device, the table is brought into the MR-bore. MR imaging scans of the patient and the phased array are taken to check for proper phased array-patient orientation, and to verify the location of the treatment target. If deemed necessary, reorientation of the phased array and the patient is performed at this stage.

Once the patient positioning is satisfactory, the CT scans of the head are registered with the MR imaging scans in order to provide the correct geometry of the skull and the derived information of the acoustic properties for input into the treatment software [172]. The information is used to determine the optimal driving phase and amplitude for each phased array elements through numerical simulations [100].

**Precooling**

During the whole operation except during the MR scanning of the patient, the circulation of cooled water is maintained in the volume between the patient’s head and the phased array. The cooled water is circulated constantly when the phased-array is turned off, that is, between the sonications, but not during pre- and post-treatment imaging scans.
Performing calibration sonications to verify correct focusing

Before the actual treatment sonications, calibration sonications are performed. These are low-power sonications intended to elevate the temperature at the target only by a few degrees Celsius. The calibration sonications are used to verify that the phased array controlling system is producing a focus at the intended location, and to verify the expected temperature elevation at the target with respect to the applied sonication power and duration. Once the desired focusing and temperature elevation have been confirmed, the higher-power therapeutic sonications can be performed. Throughout the treatment the patient is in visual and vocal contact with the treatment personnel as an additional safety measure.

Post-treatment follow-up using MR imaging

After the treatment sonications, follow-up MR imaging scans are performed to verify that therapeutic effects have been achieved. These scans are performed either immediately, or in days to months after the treatment, or both.

4.3 TRANSCRANIAL ULTRASOUND STUDIES

The feasibility of using large area phased arrays to focus ultrasound beams through the human skull and steer the focus within the skull cavity has been demonstrated [14–16]. The ability of focused ultrasound to create lesions in vivo, under MR-guidance, has been demonstrated by sonications through a human skull specimen in both rabbit brain and thigh muscle [174]. A similar study through an intact animal skull has been performed in sheep [94] and non-human primates [175, 176]. The first study also demonstrated that it is imperative to use pre-cooling of the skin and skull bone in order to avoid undesired soft tissue damage during brain treatments [175]. Fresh human cadaver heads were used to demonstrate the targeting accuracy of the MRI-guided focused ultrasound [177]. The feasibility of using MR imaging to assess tissue damage has
Clinical focused ultrasound brain therapy

been shown in vivo, in pre-clinical studies [178, 179]. It has also been shown that the heating of therapeutic targets in the brain can be enhanced through the use of ultrasound contrast agents [180].

Human subjects that underwent a craniectomy were treated with sonications from low-focusing transducers in [181]. Three people were enrolled in the study, and thermal coagulation was successfully achieved in two of these patients. The dural substitute prevented coagulation from taking place in the third patient. In one of the thermocoagulated subjects, a secondary focus was observed, which resulted in hemiparesis. The secondary focus was attributed to potential reflections of the ultrasound beam. In large-scale phased array studies with human skull phantoms, no such foci have been seen under 3D thermal imaging [182].

The use of transcranial focused ultrasound to treat brain tumors has been studied in three glioblastoma patients [183]. The study found that transcranial focusing was feasible in vivo. Unfortunately however, no thermocoagulation was achieved, as the output power of the device used was limited. The study also estimated that at higher power levels the treatment should be feasible without excess heating of the skin or the brain tissue located adjacent to the skull. Transcranial focused ultrasound has been successfully used for the noninvasive treatment of nine patients with chronic neuropathic pain using a hemispherical phased array [184], and the treatments were well tolerated by the patients. Further, treatments were performed in 12 patients, and in one of these subjects bleeding at the intended target was observed [185]. This adverse effect led to the introduction of two additional safety measures during clinical transcranial focused ultrasound treatments: acoustic emissions monitoring using a cavitation detection system composed of two single-element hydrophones, and altering the treatment protocol such that the maximum temperature during any sonication is not to exceed 60 °C. More recently, two clinical trials on investigating the treatment of essential tremors using MR-guided focused ultrasound have been published [186, 187]. Both studies demonstrated the feasibility of treating patients with essential tremors using transcranial
focused ultrasound, with promising one year follow-up results in one of the publications [187], and indicated that larger clinical trials are required to properly assess the efficacy of the approach.

In addition to thermal coagulation treatments using high-intensity focused ultrasound, low-intensity applications have been investigated, an example of which is focused ultrasound-induced blood-brain barrier opening. The blood-brain barrier operates as a protector of the brain, preventing larger molecules from entering the brain through the blood circulation [188]. However, it also prevents therapeutic agents from entering the brain parenchyma. Through pre-clinical studies it has been shown that focused ultrasound in combination with intravascular microbubble contrast agents can be used to locally open the blood-brain barrier [189]. The exposure parameters can be set such that the opening is transient, and therefore does not have a lasting effect on the brain [190]. However, non-optimal sonication parameters can result in undesirable soft tissue damage [191]. For a more thorough review of focused ultrasound-induced blood-brain barrier opening see [192–194].

Stroke is a common functional neurological disorder caused by a disruption of the blood circulation in the brain. Stroke can be either ischemic, where the supply of blood to parts of the brain is reduced due to the formation of a thrombus, or hemorrhagic, where bleeding occurs inside the brain [195]. Surgery is often required for the treatment of hemorrhagic stroke, whereas the standard treatment modality for ischemic stroke is the administration of tissue plasminogen activators (tPA), which helps to dissolve blood clots. In vitro studies have shown that tPA in combination with ultrasound enhances the recanalization of the clotted area [196, 197]. Patient trials using tPA in combination with ultrasound have shown promise [198, 199]. In addition sonothrombolysis has been investigated by using focused ultrasound alone [200–202]. For a review of sonothrombolysis see [203].

Neurostimulation can be defined as the modulation of neuronal activity. Current clinical approaches to perform neurostimulation for diseases such as movement disorders, epilepsy and severe de-
pression [204–206] include transcranial magnetic stimulation [207] and electrical brain implants [206, 208]. Focused ultrasound could prove to be an alternative approach to achieve neurostimulation [209–211]. Both mechanical and thermal effects of ultrasound propagation have been shown to be factors in neurostimulation achieved via focused ultrasound [211]. Focused ultrasound has potential advantages over the current clinical approaches for neurostimulation, in that it is able to precisely localize the focus to a confined area within the brain in a noninvasive manner. To date, experiments using ultrasound for neurostimulation have been predominantly limited to pre-clinical studies. In vitro experiments on bullfrog nerves demonstrated that ultrasound is capable of both temporarily and permanently suppressing neural conduction [211]. Stimulation of the motor cortex using focused ultrasound along with subsequent muscle contraction and movement has been observed in vivo in a mouse [212] and rat models [213]. The application of ultrasound has also been shown to suppress chemically induced epileptic activity in rats [214], and cause localized neurostimulation in rabbits [215]. Simulation results on neurostimulation in rats have demonstrated the complexity of the pressure fields within the rat brain which might cause difficulty in assessing the mechanisms causing the neurostimulation effect [213]. Further, a study performed on monkeys has demonstrated the technique feasible for primates [216]. In a recent study, the feasibility of transcranial ultrasonic neuromodulation was demonstrated in humans for the first time [217].

In addition to the treatment of brain disorders, focused ultrasound has many other applications that are currently under clinical investigation. These include breast cancer therapy [218, 219], palliative treatment of bone metastases [220], and the treatment of prostate cancer [221, 222]. One of the most successful applications of focused ultrasound therapy has been for the treatment of uterine fibroids [223–225].
5 Review of publications I-IV

In the following chapter, the main findings of the publications included in this thesis are briefly reviewed.

PUBLICATION I

A numerical model based on the KZK equation was derived and used to simulate thermal measurements previously performed in dog thigh muscle [226]. Four different ultrasound transducers were simulated with $f$-numbers between 1 and 3.6. The transducers were driven at 1 MHz, with power levels ranging from 1 to 300 W. The KZK equation-based model showed good agreement with the measurements performed with high $f$-number transducers. However, the model failed to predict the measured focal temperatures of low $f$-number transducers, rendering the model unsuitable for clinical transcranial hyperthermia applications where the typical $f$-number is close to 0.5 [14, 16, 17, 174, 183–185]. The study also showed that nonlinearities generated outside the treatment object (e.g. in the water path between the transducer and the dog thigh, in the case of this study) can significantly enhance focal heating, and that these nonlinearities can potentially be exploited to lower treatment times, as well as to reduce unwanted heating of the skin, which has previously been reported during focused ultrasound therapy for uterine fibroid ablation [227].

PUBLICATION II

A hybrid simulation model, which combined a ray acoustics model, a finite element method-based full-wave model, and an angular spectrum method, was developed and used to study skull base heating during ultrasound-induced thermal ablation in the brain. Comparison of the model output with corresponding thermal mea-
measurements of sonifications performed with a clinical transcranial ultrasound therapy device operating at 230 kHz through an *ex vivo* human skull were used to justify further use of the numerical model. The model was then employed to investigate skull base heating in five different human skulls specimens. It was found in the simulations that without applying any aberration correction to the phased array, the closest targets to the skull base that were treatable were located 19.1 ± 2.6 mm away from the skull base. Targets located at least 41.2 ± 5.3 mm away from the skull base were found to be always treatable. When phase correction was applied, however, the closest treatable distance reduced to 16.0 ± 1.6 mm and all sonifications beyond 38.8 ± 3.8 mm from the skull base were determined to be treatable. In an attempt to minimize skull base heating, three concepts were introduced: active pre-cooling of the skull base through the nasal cavities, an anti-focus method in skull medium, and a regularized phasing method. The active pre-cooling was found to expand the treatment envelope within the brain when phase correction was not applied. However, when the phase correction was applied, pre-cooling had little impact on the treatment envelope. The anti-focus and regularized phasing methods were investigated in one sonication location, and both methods were found promising in terms of reducing undesired heating at the skull base.

**PUBLICATION III**

A full-wave simulation model based on the spectral element method [163, 164] was developed to investigate standing wave formation during transcranial focused ultrasound therapy. The model was found to agree well with acoustic measurements made of sonifications performed using a low-frequency (230 kHz) hemispherical transcranial focused ultrasound phased array through an intact, *ex vivo* human skull. Further simulations demonstrated that the formation of standing waves are greatly reduced when the effective aperture of the therapy device is increased or, in other word, when the $f$-number is reduced.
PUBLICATION IV

A novel hybrid model combining the so-called grid method [228] and a FDTD method was developed to simulate acoustic wave propagation during transcranial focused ultrasound treatments. The model was utilized to simulate clinical treatments performed at University Children’s Hospital Zurich, Zürich, Switzerland, in five patients suffering from chronic neuropathic pain. It was found that the simulated focal temperature elevations were on average 24 ± 13% lower than what was observed using MR-thermometry during the treatments. The size of the simulated focus was found to be on average 40 ± 13% smaller in the anterior-posterior direction and 22 ± 14% smaller in the inferior-superior direction than in the treatments. The location of the simulated thermal focus had an average offset of 0.3 ± 0.1 mm in comparison to the prescribed focus (intended target) of the treatments, whereas the measured thermal focus had an offset of 1.6 ± 0.6 mm. The publication provides discussion on the discrepancies observed between the simulations and the measurements. The main points, which are thought to be the sources for the discrepancies, include:

- Acoustical properties of the intended target (thalamus) are not known accurately. It could be that the thalamus has higher attenuation than used in the simulations which could result in larger observed temperature elevations.

- The small size of the simulated thermal focus with respect to those observed in the treatments could indicate that additional heating mechanisms might be present in vivo. These mechanisms could rise from enhanced heating due to scattering and/or cavitation.

- The actual sonication power of the treatments, as reported by the therapy device, could be inaccurate due to accuracy of the calibration of the individual phased array elements. It could as well be, that the reflection of the ultrasound beam from the skull back to the phased array elements could affect their...
power output. These effects would reflect as a difference in the simulated sonication power and the true sonication power during the treatments.

- The accurate simulated location of the thermal focus, with respect to the prescribed focus, is believed to be due to accurate geometric and similar material parameter match between the simulations and the software of the therapy device computing the phase aberration corrections. Shift of the thermal focus with respect to the measured thermal focus could perhaps be explained by differences between the acoustic material parameters of the skull bone used in the simulations and the software of the device and the true acoustic parameters of the patients.

- The simulated focal temperature was found to be sensitive to the acoustic parameters as the focal temperature elevation could vary as much as 30 – 35 % when the acoustic attenuation or the speed of sound in the skull bone was varied by 10 %.

Regardless of the observed discrepancies between the simulations and the treatments the developed model serves as a step towards quantitatively accurate tool for transcranial focused ultrasound treatment planning. The model could already find uses, for example, by providing auxiliary information for the treatment planning personnel during the initial stages of the treatment. Additionally the exact control of the parameters in the simulations allow experimentation with different treatment schemes. Further, the current usefulness of the model could be expanded with a more accurate characterization of the treatment device and the acoustical and thermal parameters of relevant biological tissues.
6 Conclusions

In this thesis the physical principles involved in transcranial focused ultrasound therapy have been reviewed. Common simulation methods in active use within the field of therapeutic ultrasound were briefly discussed, along with a short description of some higher order methods that may gain further use in the future. Potential improvements for the current numerical models, such as the Biot model for modeling acoustic propagation in the diploë, and convective heat transfer based on the geometry of the vasculature for improving thermal modeling near large vessels, were also discussed. The treatment protocol for clinical transcranial focused ultrasound therapy was outlined, along with a review of relevant studies investigating the use of therapeutic ultrasound in the brain.

The publications included in this thesis investigated four different approaches to simulate wave propagation during ultrasound therapy: a model based on the KZK equation, a hybrid model combining ray acoustics, a full-wave model and the angular spectrum method, and two different full-wave simulation models.

The results obtained in the publications included in this thesis will have an impact on future therapeutic ultrasound treatment procedures. Publication I demonstrated, through simulations, that nonlinear ultrasound propagation could be utilized for both the benefit of patient safety, and for faster treatment times. The high impact of the nonlinearities generated in the water path between the target and transducer was demonstrated. The publication also investigated the accuracy of the KZK model with respect to measurements of transducers with varying degrees of focusing. It was concluded that the KZK equation-based model was unsuitable for simulating nonlinear propagation of transducers with $f$-number lower than three, and that better models need to be developed for highly focused sources.

Publication II investigated the issue of skull base heating in
transcranial focused ultrasound, and suggested three new methods to counteract the issue: active pre-cooling of the skull base through the nasal cavities, an anti-focus method in the solid media, and a regularized phasing method. Skull base heating was observed in simulations performed in five human skulls, and was found to be a factor limiting the treatment envelope in which thermally significant dose can be delivered using focused ultrasound. While the anti-focus and the regularized phasing approaches are not currently practical for clinical use due to their high computational cost, they might prove to be useful in the future to protect soft tissue regions adjacent to the skull surface.

Publication III investigated standing wave formation during focused ultrasound therapy in the brain, a potential concern from a treatment safety standpoint. The results showed that the use of a large aperture area phased array, such as those currently found in clinical use, geometrically minimizes the formation of standing waves, thus improving patient safety.

A hybrid simulation method combining a grid method and FDTD method was introduced in Publication IV, and the developed model was used to simulate clinical focused ultrasound treatments in patients with chronic neuropathic pain. The simulation results obtained using the developed model showed discrepancies when compared directly with the treatment data, leaving room for improvement. However, multiple potential sources that might explain the discrepancies were identified. The results of the study would call for more accurate characterization of the acoustical properties of the skull bone and the calibration of the treatment device. The developed model might still find uses in initial treatment planning and by allowing experimentation between different treatment parameters. The possibility of exact control of the geometry, material properties, and sonication parameters in the simulations makes it possible to identify the most crucial parameters affecting the transcranial ultrasound patient treatment, as well as exploring new treatment schemes.

In the future, the research presented in the publications in-
cluded in this thesis could be taken forward by including nonlinear propagation within the skull bone into full-wave simulation models, as well as by developing more realistic models of attenuation. This would allow for the simulation of a more diverse range of problems related to transcranial focused ultrasound therapy. Incorporating a more accurate treatment of porous media into full-wave ultrasound propagation methods may result in more physically realistic simulation models. While making the simulation models more physically realistic, all of these modifications would increase the corresponding computational burden. In addition, the increased complexity of the simulation models would also increase the importance of properly characterizing the acoustical and thermal properties of both soft tissues and human skull bone, as more parameters would need to be introduced into numerical models.
References


References


References


[112] X. Yin and K. Hynynen, “A numerical study of transcra-
nial focused ultrasound beam propagation at low frequency,”

passive acoustic mapping with hemispherical sparse arrays
using CT-based skull-specific aberration corrections: a simu-

[114] D. Pajek and K. Hynynen, “The design of a focused ultra-
sound transducer array for the treatment of stroke: a simula-

in high frequency transcranial focused ultrasound therapy: a

distortion and treatment planning in abdominal focused ul-

[117] S. Pichardo and K. Hynynen, “Circumferential lesion for-
mation around the pulmonary veins in the left atrium with
focused ultrasound using a 2D-array endoesophageal device:

[118] D. Cathignol, O. A. Sapozhnikov, and J. Zhang, “Lamb waves
in piezoelectric focused radiator as a reason for discrepancy

[119] D. Cathignol, O. A. Sapozhnikov, and Y. Theillère, “Compar-
ison of acoustic fields radiated from piezoceramic and piezo-
(1999).


References


References


References


References


[218] H. Furusawa, K. Namba, S. Thomsen, F. Akiyama, A. Ben-
det, C. Tanaka, Y. Yasuda, and H. Nakahara, “Magnetic Resonance–Guided Focused Ultrasound Surgery of Breast Can-


References


Aki Pulkkinen

Simulation Methods in Transcranial Ultrasound Therapy

Transcranial ultrasound therapy is an emerging modality for noninvasive treatment of diseases of the brain. Simulation methods provide a technique to investigate the modality, in combination with different measurement methods. In this thesis, the principal physics associated with the treatment modality, various simulation techniques currently at use in the research field, a clinical treatment protocol, and the most relevant studies published to date on the subject, are reviewed. The thesis introduces new techniques to overcome some of the safety concerns related to the treatment modality, and quantitatively analyzes the current level of accuracy to which clinical patient treatments can be predicted with these simulation methods.