High intensity focused ultrasound (HIFU) ablation using the frequency sweeping excitation

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2017

Wang, M. (2017). High intensity focused ultrasound (HIFU) ablation using the frequency sweeping excitation. Doctoral thesis, Nanyang Technological University, Singapore.

<http://hdl.handle.net/10356/69935>

<https://doi.org/10.32657/10356/69935>

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**HIGH INTENSITY FOCUSED ULTRASOUND
(HIFU) ABLATION USING THE FREQUENCY
SWEEPING EXCITATION**

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SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING

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A thesis submitted the Nanyang Technological University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

2017

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor, Dr. ZHOU Yufeng, for his mentorship throughout my graduate studies, and I have benefitted greatly from him with such broad and deep knowledge and experience. This thesis will not be completed without his guidance and advice. I wholeheartedly acknowledge the financial support from the NTU Research Scholarship which makes this project possible. To my fellow team mates, Mr. Liu Chenhui, Mr. WANG Jen-chiech, and Mr. Yannapol Sripitkiat, thank you all for your help over the years, and it has been a wonderful experience of working with you all. I would also like to dedicate this thesis to my sister and my parents for their support and generosity over the years.

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Abstract

High intensity focused ultrasound (HIFU) because of its unique noninvasive capability has received the increasingly widespread interests. With this technique, sufficiently high ultrasound energy is brought into a tight focus, generating the well-controlled tissue necrosis while leaving the surrounding or overlying tissues unharmed. So far, it has been used in clinics for the treatment of liver, kidney, breast, bone, prostate and pancreas cancer and uterine fibroids with great success.

Although HIFU therapy is promising and has become more and more popular for cancer therapy in recent years, clinical adoption of this technique still faces some challenges, such as the relatively long procedure duration because of the small necrosis size and the long waiting time between two successive sonications and unexpected tissue injury (i.e., skin burn) in the prefocal region. To overcome these issues, some investigations to improve the efficacy and efficiency of HIFU therapy by reducing the pre-focal heating as well as enlarging the lesion size have been made.

To have a better understanding of the propagation of HIFU burst in the biological tissue, an angular spectrum approach (ASA) with a second-order operator splitting was proposed and applied to simulate the three-dimensional nonlinear acoustic field of a phased-array HIFU transducer in a multiple layered media with focus steering over a wide range of angles and the generation of multiple foci. The simulated harmonics distribution along and transverse to the transducer axis were compared to that by the KZK model and the measurement data. It is found that the proposed algorithm has a better performance than the KZK model, especially the locations of pressure nodes in the focal region and grating lobes in the pre-focal region, suggesting that the proposed method is accurate and efficient to simulate the nonlinear wave propagation of HIFU burst. Further study has shown that shifting and splitting the focus leads to the reduced acoustic pressure and lesion size, and increased pre-

focal region heating. Compensation of power loss due to the focal shifting or splitting enables the phased array to generate uniform lesions, but simultaneously increasing the pre-focal heating

To further understand the effect of electronically steering the beam of a phased array HIFU transducer on the grating lobe, the proposed algorithm was utilized thoroughly. It is found that the grating lobe and main lobe decreases and increases linearly with the steering distance, respectively. But the increase of the grating lobe is much more rapid than the decrease of the main lobe. The focal and near field temperature linearly decreases and increases with the steering distance, respectively, and the high-frequency results in high temperature dropping in the focal region but increasing in the near field.

To mitigate the pre-focal heating caused by focus steering, frequency modulation method (linear sweeping) has been proposed. By using this method, the driving frequency continuously changes in the process of ablation. As a result, heat accumulated in the pre-focal region was leveraged greatly. Numerical simulation and experimental measurement using various excitations (constant frequency excitation, upward frequency sweeping, and downward frequency sweeping) show that frequency sweeping excitations result in a temperature reduction in the pre-focal region. Additionally, the feasibility of ablation without the cooling period has also been evaluated. It is shown that it is possible to implement the HIFU ablation without cooling time using the chirp excitation. A parametric study shows that the long time and downward chirp is more effective in reducing the pre-focal heating.

Frequency sweeping excitation was further evaluated to show that it can enhance bubble cavitation. Both gel phantom and *ex vivo* experiment studies show that with a proper selection of the frequency sweep range and sweep time, a 50% enlargement of lesion size could be achieved because of the enhanced cavitation. Analysis of the bubble cavitation signal captured by passive cavitation detection (PCD) in the gel phantom and porcine muscle

with various approaches (i.e. STFT, filtered RMS of the cavitation signal, and the RMS between the harmonics) shows that both stable cavitation and inertial cavitation were enhanced by frequency chirp. Temperature rise correlated well with the enhanced bubble cavitation. The sweeping time and frequency sweeping range play different roles in the enhanced bubble cavitation. A short sweeping time and large frequency sweeping range are preferred in the HIFU ablation.

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Chapter 1 Introduction and Background

High intensity focused ultrasound (HIFU) is a non-invasive cancer therapy developed in the past several decades and has been used in the treatment of liver [1, 2], kidney [3], breast [4, 5], bone [6], prostate [7, 8], pancreas cancer [9-11] and uterine fibroids [12-14]. Compared with the other ablative modalities, such as radio-frequency (RF), microwave (MW) and laser, HIFU ablation is the only really non-invasive option that does not introduce incisions in the treatment and has the fewest side effects. Moreover, there is no upper limit of tissue tolerance to the repeated HIFU exposure. Although open surgery and laparoscopic surgery are the standard methods in the selected patients with solid tumors, some of tumors are unable to undergo the surgical resection due to the tumor sites, advanced stage, or poor health conditions of patient. Given that, HIFU techniques may be an ideal substitution. In addition to the potential for curative treatment and the extension of life expectancy, HIFU has been demonstrated to reduce or eliminate the tumor-related pain and thus improve the quality of life for patients with the cancer metastasis [15, 16]. Numerous clinical studies have indicated that HIFU ablation is a safe and effective method for cancer treatment. Since the first clinical trial in the 1990s, thousands of patients worldwide with various kinds of cancers, either benign or malignant type, have been treated by HIFU.

Broadly, there are three types of HIFU devices, extracorporeal, transrectal, and interstitial [14]. The extracorporeal device has been used to treat various organs (e.g. liver, breast and bones) and usually has a very large F-number in contrast to the other two. The transrectal devices are indicated for the treatment of benign and malignant prostate. Transducer usually lies close to the target volume, therefore, with less acoustic attenuation and loss of power during the propagation. Transrectal systems normally work at the low power and high frequencies (around 8 MHz) to maximize the precision of ablation [17].

Interstitial ultrasound applicators were applicable for some tumors that cannot be reached with the extracorporeal or transrectal devices. So far, the treatment of cholangiocarcinoma or oesophageal tumors by the interstitial ultrasound applicators has been reported [18]. Probes for percutaneous and laparoscopic treatment are still under investigation, and it is likely that the therapeutic indications will increase. Interstitial ultrasound applicators are also brought as close as possible to the target to minimize the effects of attenuation and phase aberration along the ultrasound pathway. Interstitial applicator offers a high speed of coagulation and is compatible with the image monitoring [19].

Up to date, two commercially available devices have been reported to treat the prostate cancer in the clinical practice, the Ablatherm (EDAP Technomed, France) [20] and the Sonablate (Focus Surgery, USA) [21]. MRI-guided HIFU device (ExAblate 2000, InSightec-TxSonics Ltd, Haifa, Israel) [22], has been approved by the Food and Drug Administration (FDA) in October 2004 for the treatment of patients with uterine fibroid in the United States; treatment of breast cancer by the same device has also been approved by FDA in 2013. In the fall of 2015, FDA has approved the HIFU therapy for the ablation of prostate cancers. Other ultrasound-guided HIFU device[23] (Mode-JC HIFU system, Haifu Technology Co. Ltd., Chongqing, China) has been approved by CFDA (China Food and Drug Administration) for the treatment of liver and kidney cancer. In Singapore, HIFU has been utilized to treat the uterine fibroids in 2006 and prostate cancer in 2011; other applications, such as facial and slimming treatment are still under the investigation [24].

1.1 Image-guidance of HIFU ablation

Clinical utilization of HIFU is typically performed in conjunction with imaging techniques in order to enable the planning and targeting prior to applying the ablative or therapeutic levels of ultrasound energy. To accurately monitor the treatment process, magnetic resonance (MR) [25] or ultrasound (US) image [26] has been incorporated into

the HIFU system. MR image can directly quantify the variations of temperature and thermal dose of the treated tissue. When MR is used to guide HIFU treatments, sub-lesioning ultrasound exposures are used to identify the target region first, the local temperature rises are subsequently used to affirm the ultrasound focal position and then higher intensity therapeutic exposures are employed for the actual treatment. When ultrasound is used to guide the treatment, diagnostic probe and therapeutic transducer are normally arranged confocally. The therapeutic focal position can, therefore, be reliably identified in the diagnostic B-mode image. The extent of treatment can be monitored by recording the post-treatment grey-scale changes [27-29].

Both imaging modalities have their own advantages and disadvantages. The US guided devices are cheap, extensively available, capable of real-time visualization, and compatible with almost all known treatment modalities. US guidance is also valuable in the treatment of organs such as the liver and kidney, which have significant respiration motion [13]. In addition, US guidance offers the benefit of utilizing the same form of energy which is being used for the therapy to verify the condition of the acoustic window. Therefore, it is unlikely that HIFU therapy will be effective if the target cannot be well visualized with US image [30]. The main disadvantages of US guidance are the lower imaging resolution compared to MR image in some patients and the poor lesion detection because of the low tissue contrast or the presence of overlying bone structures such as ribs. MRI can provide better spatial resolution and temperature data during the HIFU exposure [13]. MR guidance allows for target localization, and postprocedure imaging (typically with contrast-enhancement) to verify tissue destruction [31]. Most importantly, it can provide in vivo semi-real-time monitoring of temperature based on the proton resonance frequency (PRF) shift of water, offering more control over the treatment outcome [32-34]. However, high cost, low temporal resolution, and inability of tracking a moving target such

as the liver may limit its extensive application. Other forms of image mortalities, such as elastography and photoacoustic image are also being investigated for the HIFU treatment monitoring [35, 36], but none are clinically available till now.

1.2 HIFU principles

In a way analogous to focusing of light, ultrasound waves can be easily focused at a given point, resulting in a considerable amplification of the pressure amplitude at the focus (see Figure 1-1). Immediate thermal toxicity occurs as long as the tissue temperature is raised above 60-65°C for at least 1 second, leading to the irreversible cell death through coagulative necrosis with no damage to the surrounding or overlying tissues. The amount of thermal damage caused by the heat accumulation can be evaluated by the Cumulative Equivalent Minutes (CEM) [37]. The volume of ablation following a single HIFU exposure is usually small and vary according to the transducer's characteristics, but is typically on the order of 1–3 mm in width and 8–15 mm in length along the beam axis. The mechanisms involved in HIFU exposure are complex and still under investigation, but two predominant ones have been recognized. One is the thermal effect by converting the mechanical energy into the heat while the other is bubble cavitation [12].

Figure 1-1. (A) single-element spherically curved HIFU transducer, (B) phased-array HIFU transducer, (C) an example of a linear (sine) ultrasound wave; its frequency spectrum contains a single frequency f . (D) A distorted ultrasound wave is formed and the energy is transferred from the fundamental frequency f into the higher harmonics: $2f$, $3f$, etc [38].

Without the presence of bubbles, tissue is mainly heated by the absorption of the incident ultrasound, which usually follows a frequency power law in the biological tissues. Previously, linear approximations are often used to model the beam propagation; the importance of nonlinearity in the field of biomedical ultrasound was pointed out by Carstensen et al in 1980 [39]. In human tissue with a nonlinear stress-strain relationship, the acoustic wave travels faster during the high-pressure positive phase of the oscillation, leading to a distortion in the wave profile and transferring energy from the fundamental frequency to the higher harmonics. Eventually, a shock front or discontinuity in each period of the waveform develops. As the high-frequency components have high absorption, the nonlinear wave propagation always predicts a higher heating rate compared to that by the linear methods [40]. Numerically, it has been demonstrated that in a typical HIFU surgery, the nonlinearity improves the localized heating by approximately an order of magnitude, and subsequently, the maximal temperature at the focus exceeds the values obtained in the approximation of linear wave propagation by a factor of three [41]. Experimental measurement of the temperature rise *in vivo* in dog's thigh muscle from a focused ultrasound source has also confirmed that the temperature rise was 2-3.5 times larger than the expectation assuming linear acoustic propagation [42, 43]. In addition, the acoustic nonlinearity parameter in recent years has been proposed to derive the thermometry noninvasively since it is highly temperature sensitive [44-46], about 4 times more temperature sensitive compared to the speed of sound and thermal expansion in water [46].

1.3 Acoustic cavitation

Acoustic cavitation, stable and inertial cavitation, induced by ultrasonic irritations known to play a key role in a wide range of therapeutic ultrasound applications [47, 48]. Bubble oscillation about its equilibrium by the low acoustic pressure is termed as “stable

cavitation”. Whereas gas bubble grows during each cycle, and more gas diffuses into the bubble during the expansion phase than diffuses out during the compressive phase, which is known as “rectified diffusion”. When bubble reaches a certain size, it undergoes the collapse - rapid reduction in radius and the pressure change in the liquid accelerated by the mass of the liquid - the inertia around the bubble. Inertial bubble collapse released high energy increases the temperature of the vapor to several thousand kelvins and generates high pressure and/or high-speed jets, which may produce mechanical damages to the nearby tissues [49, 50].

Examples of successful bubble assisted ultrasound therapies include histotripsy in which inertial bubble collapse releases shockwaves capable of destroying cell membranes, mechanically fractionating the soft tissues, and in many cases even completely liquefying or annihilating them into subcellular components [51, 52]; thrombolysis in which the stable bubble oscillation in the vicinity of clots promotes the uptake of lytic agent and inertial bubble collapse produces the micro-jet and pitting to directly and mechanically damage the clot’s surface [53, 54]; the blood-brain barrier (BBB) opening in which the stable bubble expansion temporarily affects the integration of the tight junction and transiently reduces the blood flow [55].

Figure 1-2. Cavitation effect of HIFU. The high intensity focused ultrasound waves cause the tissue bubbles to oscillate steadily resulting in shear stresses that cause cell damage, known as “stable cavitation”. Above certain pressure, threshold bubbles explode vigorously resulting in localized high pressure that causes tissue damage, known as “inertial cavitation”[12].

Within the scope of HIFU, acoustic cavitation has been shown to accelerate the tissue heating. Both stable cavitation and inertial cavitation have been shown to play a significant role in the cavitation facilitated heating. The strong acoustic scattering by a bubble cloud at the HIFU focus extends the sonic propagation path, resulting in greater absorption by the viscous dissipation and thermal conduction. Moreover, with the presence of inertial cavitation, the frequency dependence of the absorption coefficient means that the broadband noise emissions produced by the collapsing bubbles will be very readily and locally absorbed [56].

Different types of nonlinear bubble oscillations lead to different signatures in the acoustic signal. Stable cavitation denotes the nonlinear volumetric and/or surface oscillation of the bubble, resulting in the emissions of harmonics, sub-harmonics, and ultra-harmonics. Inertial cavitation, characterized by the broadband emissions, refers to the violent bubble oscillation leading to the bubble collapse [57]. These acoustic signatures reflect the intensity of cavitation and thus are in line with the cavitation- based treatment outcome.

1.4 Acoustic focusing for HIFU

Focusing ultrasound waves is another key issue. The easiest and cheapest way is by self-focusing. A spherically curved ultrasound transducer has a fixed and single focus at the position determined by the geometrical specifications. To overcome its lack of versatility and facilitate the simplicity in the manufacturing process, a flat ultrasound transducer with an exchangeable acoustic lens system was then devised. Focusing properties of the acoustic lens, such as the focal length and geometry (e.g. sphere, cylindrical or ellipsoid), could be altered accordingly, thus increasing the flexibility of the device. However, the lens system has additional absorption of the ultrasound waves [58, 59], degrading the performance of the HIFU system. A phased array transducer for the

therapeutic ultrasound was first proposed by Charles A. Cain in the late 1980s [60, 61]. By the control of driving signals, such as the amplitude and phase, to each component, beam-shifting within physically allowable scopes and multiple foci formation could be achieved. Phased array HIFU transducer can be used not only for the conventional beam steering but also for the correction of ultrasonic beam degradation due to its propagation through inhomogeneous media, making it more versatile than the other systems.

1.5 Challenges of HIFU therapy

There are a number of technical challenges currently hindering the widespread clinical applications of HIFU ablation. Except for common issues, such as inadequate acoustic windows, motion artifact [62] due to the respiration and heartbeat, and the absence of ultrasound-based temperature monitoring methods that complicate the HIFU ablation [10], another key limitation that hampers the effective use of this modality in the clinical practice is the long procedure time caused by the small necrosis size [63] and the long waiting time between two successive sonications [64, 65]. Although tumor size poses no absolute limitation, the treatment duration will increase with the tissue volume to be ablated. A superficial 3 cm diameter breast tumor might take less than 1 hour to treat, whereas a 10 cm diameter liver tumor might take more than 6 hours [63].

Lesion size created by a single shot sonication, depending on the sonication time and the power applied, is usually 1–2 mm in diameter and approximately 1 cm in length which is much smaller than the size of detectable solid tumors and cancers that are typically several centimeters [14]. To ablate a clinically relevant volume of tissue, many lesions need to be placed side by side to cover the whole target tumor. This scanning can be achieved by either a mechanical movement of the transducer or electronic beam steering by using multi-element phased array applicators in a pattern of “dots” or “lines” [12]. For HIFU systems with a single element focused transducer, scanning of the small focus

through a clinically relevant volume of tissue is mainly achieved by mechanically translating the transducer. It is time-consuming and can lead to the clinical treatments with impractically long duration. More seriously, due to the overlapping of the sonication beam during focus scanning, the temperature in the pre-focal region may increase to a certain level that causes unwanted damages. To address this issue, a cooling period ranging from several seconds to tens of seconds are introduced between two successive sonications, allowing the pre-focal region temperature return to the normal value before the following sonication. In addition, to ensure a complete ablation of the whole tumor, treatment planning always requires an inclusion of 1–3 cm safety margins around the tumor, which elongates the treatment even more.

With a phased array HIFU transducer, the aforementioned problems could be alleviated due to its electronically focus steering and multiple foci synthesizing capability, which enables a fast and accurate movement of the focus and a wide spread of the energies. However, the phased array HIFU transducer shows some critical disadvantages. Except for the problem of high cost of fabrication and complexity of the driving circuits, the pre-focal heating due to the presence of the grating lobe or the secondary maxima is the main problem that challenges its clinical application.

Moreover, accurately representing the behavior of acoustic sources is an important part of ultrasound simulation. This is particularly challenging in the ultrasound therapy where multi-element arrays are used. So far, the study on the simulation of the nonlinear effect of therapeutic phased array transducer are quite rare, since most of the ultrasonic phased arrays are for imaging purpose and the nonlinear effect is not apparent. Most investigations of the phased array HIFU transducer modelling still concentrate on the free field simulation using either Khokhlov-Zabolotskaya-Kuznetsov (KZK) [66, 67] or Westervelt equations [68, 69]. There are no analytical solutions to these two equations and

they were usually solved numerically in time or frequency domain. Worse yet, the computational burden to numerically solve these two equations is considerable, especially with non-axisymmetric sources. Alternatively, a phenomenological model, describing the propagation of the effects of attenuation, nonlinearity, and diffraction separately over small incremental steps has been developed. This approach is valid for arbitrary media and has been applied to continuous wave (CW) and pulsed as well as axisymmetric [70] and non-axisymmetric sources [71-73]. In this thesis, this model with some improvements will be applied to simulate the acoustic field of a phased-array HIFU transducer in the multiple-layered media using different focusing strategies.

1.6 Overview of the thesis

The goal of this study contained herein is to examine the solution to the aforementioned problems in the following aspects.

- 1) Simulation of the nonlinear acoustic wave propagation from a phased-array HIFU transducer in the multiple-layered media using different focusing strategies through an angular spectrum approach (ASA) with a second-order operator splitting method. The accuracy of the proposed model was verified by comparing the simulation results with the by the KZK model and the measurement data.
- 2) Quantitative evaluation of the effects of electronically steering the focus of a phased array HIFU transducer on the paramount acoustical and thermal parameters hence providing the guidelines for the transducer design.
- 3) Pre-focal heating reduction caused by the electronically steering through frequency sweeping was proposed, and its effectiveness was examined in both single shot sonication and plane sonication. Optimal sweeping parameters have also been investigated, and a proof of concept experiment was conducted to prove the effectiveness of the proposed methods.

- 4) The ability of frequency sweeping to enhance bubble cavitation was further studied. Lesson size, bubble cavitation, and temperature rise under frequency sweeping excitation and constant frequency excitation were compared. The effect of the paramount parameter (i.e, sweeping time, frequency sweeping range, and sweep direction) was also evaluated.

Chapter 2 Simulation of nonlinear acoustic field and thermal pattern of phased-array high-intensity focused ultrasound (HIFU)

2.1 Introduction

Simulation of the propagation of focused finite-amplitude sound with the combined influences of nonlinearity, absorption, and diffraction and consequent lesion formation is of importance in the treatment planning and understanding the mechanism. The Khokhlov-Zabozotskaya-Kuznetsov (KZK) nonlinear wave equation [74, 75] is popular and accurate for moderately focused acoustic beams with high direction (where k is the wave number and a is the radius of the source) at distances beyond a few source radii and in the paraxial region (up to about 16° off the central propagation axis in the far field) [76]. However, the KZK model uses a parabolic approximation for the diffraction effect, which limits the validity to relatively weak diffraction and low focusing gains, and hampers its use in the field of modern medical ultrasound sources. The KZK equation can be solved in an explicit finite-difference (FD) algorithm using a marching scheme based on the operator-splitting method on a three-dimensional Cartesian grid [77]. As the code marches, all wave propagation effects including thermoviscous absorption, relaxation, and dispersion are accounted separately at the fractional steps and then simply summed, if the effect in each step is fairly weak to correct the waveform. The time-domain numerical model is efficient for the propagation of short pulses from an asymmetric source in multiple layers, and very good agreement was found between simulations and experiments [78]. In the frequency-domain or spectral method, a Fourier series of the sound pressure is substituted into the KZK equation and the resulting set of coupled equations are solved using FD methods [79]. The alternative wave equation is the Westervelt equation, which is derived from the

full equations of fluid motion by keeping terms up to quadratic order [80]. It can simulate the generation of grating lobes which are located far beyond the validity region of the KZK equation [81] in both linear and nonlinear cases [82]. However, the simulation of the non-axis-symmetric source is still quite challenging and computationally complex.

A much more efficient diffraction algorithm is based on the angular spectrum approach (ASA) [73] because it can be implemented by taking advantage of the fast Fourier transform (FFT) or the discrete Hankel transform. Diffraction is calculated using a spatial Fourier transform method while applying the Burgers equation to model nonlinear effects even in regions that do not satisfy the parabolic approximation [70]. In addition, in order to increase the computation efficiency, second-order operator-splitting scheme with a fractional step algorithm was applied [83] because relatively large steps could be used than those in a first-order operator splitting [70]. Step size could also be adaptive, large steps in the near field and smaller ones in the focal region. The ASA approach has been used for pressure fields generated by concentric ring arrays and sector-vortex arrays. The spectral propagator is preferred in the ASA over the spatial propagator for calculations in attenuating media or with an apodized pressure distribution [84]. In addition, the effects of reflection and refraction on wave propagation, especially in multi-layered media, could also be compensated using the ASA [85].

In this chapter, the ASA with a second-order operator splitting was applied to simulate the three-dimensional nonlinear acoustic field of a phased-array HIFU transducer in multiple layered media with a steered propagation axis varying over a wide range of angles and generation of multiple foci. The model was first validated by comparing the first 5 harmonics on the axis of a concave transducer with those using the KZK model, and good agreement was found between them. Then the simulations were compared with the measurement of an annular HIFU transducer. The proposed algorithm had a better

agreement of harmonics distribution along and transverse to the transducer axis than the KZK model in the locations of pressure nodes and side lobes in the pre-focal region. In order to apply the simulation to the HIFU phased array three cases were considered here: geometric focusing, transverse focus shifting, and four foci generation in the focal plane. Nonlinear acoustic wave propagation in three dimensions with the presence of harmonics and waveform distortion and grating lobes in the prefocal region are clearly shown. Then the subsequent thermal field for a 2-second continuous HIFU exposure was calculated using the BioHeat equation and lesion boundary was determined by the thermal dose. It is found that the shifting or splitting of focus will result in lower temperature elevation and smaller lesion size because of the reduced nonlinearity and the peak positive pressure. Altogether, our algorithm provides an accurate way to calculate the acoustic field with arbitrary source distribution, multiple media, and complex focus pattern and to predict the consequent lesion formation in the HIFU treatment planning.

2.2 Materials and methods

The effects of diffraction, attenuation, and nonlinearity on finite-amplitude acoustic wave are propagated separately over incremental distances in the operator-splitting scheme, which is based on a reduced evolution equation and is valid for one-way propagation of quasi-plane waves

$$\frac{\partial p}{\partial z} = L_A \cdot p + L_N \cdot p + L_D \cdot p \quad (2.1)$$

where p is the acoustic pressure, L_A , L_N , and L_D are operators representing the effect of attenuation, nonlinearity, and diffraction, respectively [86]. Here the second-order splitting scheme was used because of its high computational efficiency and accuracy, which was accomplished by first solving a half step with diffraction operator, then taking that solution

to the nonlinearity and attenuation operator for a full step, and finally completing the diffraction operator by another half step [83] as shown in Fig. 2-1,

$$p(x, y, z_2; t) \equiv \Gamma_{D+A+N, \Delta z} p(x, y, z_1; t) = \Gamma_{D, \Delta z/2} \Gamma_{N+A, \Delta z} \Gamma_{D, \Delta z/2} p(x, y, z_1; t) + O(\Delta z^3) \quad (2.2)$$

where Δz is the propagation step size.

Figure 2-1 . Illustration of the step-marching scheme and second-order operator splitting operator used in the nonlinear acoustic wave propagation plane-by-plane in incremental steps from the transducer. Each step involves the effect of diffraction (D), attenuation (A), and nonlinearity (N) [87].

To overcome the parabolic approximation in the KZK equation, full wave diffraction by the ASA was chosen. Briefly, the ASA could be defined through a transfer function in the spatial frequency domain for the pressure from one plane to another parallel plane. Similar to the method developed in [87], the point spread function of a source is given by

$$h_p(x, y, \Delta z; \omega) = \frac{\Delta z}{2\pi d^2} (1 - jkd) e^{jkd} \quad (2.3)$$

where $d = \sqrt{x^2 + y^2 + \Delta z^2}$, $k = \frac{2\pi}{\lambda}$ is the wave number, and $\omega = 2\pi f$ is angular frequency. So, the pressure could be derived from the 2D spatial convolution between the input pressure at z_0 and the spatial propagator h_p :

$$p(x, y, z_0 + \Delta z; \omega) = p(x, y, z_0) \otimes h_p(x, y, \Delta z; \omega) \quad (2.4)$$

Performing 2D Fourier transforms on both sides of Eq. (2.4) obtains:

$$P(k_x, k_y, z_0 + \Delta z; \omega) = P_0(k_x, k_y, z_0) \cdot H_p(k_x, k_y, \Delta z; \omega) \quad (2.5)$$

where $P(k_x, k_y, z_0 + \Delta z; \omega)$, $P_0(k_x, k_y, z_0)$ and $H_p(k_x, k_y, \Delta z; \omega)$ represent the 2D Fourier transform of the output plane pressure $p(x, y, z_0 + \Delta z; \omega)$, the input plane pressure $p(x, y, z_0)$, and the spectral propagator, respectively. $H_p(k_x, k_y, \Delta z; \omega)$ is given by the analytical Hankel transform of $h_p(x, y, \Delta z; \omega)$

$$H_p(k_x, k_y, \Delta z; \omega) = \begin{cases} e^{-j\Delta z \sqrt{k^2 - k_x^2 - k_y^2}} & k_x^2 + k_y^2 < k^2 \\ e^{-\Delta z \sqrt{k^2 - k_x^2 - k_y^2}} & k_x^2 + k_y^2 \geq k^2 \end{cases} \quad (2.6)$$

The input pressure field of $L_x \times L_y$ is first discretized into a grid containing $M_x \times M_y$ points with a spatial sampling of δ . This grid is zero-padded to a larger grid of $N_x \times N_y$, and the angular spectrum of the input plane is calculated using a 2D FFT. The discretized transverse wavenumbers are

$$\begin{aligned} k_x &= m\Delta k_x, \quad m = -N_x/2 + 1 + \phi_x, \dots, N_x/2 + \phi_x, \quad \Delta k_x = 2\pi/(N_x\delta) \\ k_y &= n\Delta k_y, \quad n = -N_y/2 + 1 + \phi_y, \dots, N_y/2 + \phi_y, \quad \Delta k_y = 2\pi/(N_y\delta) \end{aligned} \quad (2.7)$$

where ϕ_x, ϕ_y compensate for the offset induced by the odd number of grid points so that m and n are both integers.

$$\phi_x, \phi_y = \begin{cases} -1/2 & N_x, N_y = \text{odd} \\ 0 & N_x, N_y = \text{even} \end{cases} \quad (2.8)$$

Due to the intrinsic periodicity of the spectrum, under-sampling of the spectra propagator and the replication of the source, the spatial aliasing error often appears in the far field. To reduce such an error, a spatial frequency truncation technique is applied through the use of the Tukey window (a spatial low-pass filter to the spectral propagator with a window size of 512 and taper ratio of 0.1) [88] without increasing the size of the computational grid. This method removes the under-sampled angular spectra and prevents the leakage of high spatial frequency components into the propagating field.

Distortion of finite-amplitude wave occurs in the propagation due to convective and nonlinear effects over incremental steps, which can be expressed as [73]:

$$p_n(z + \Delta z) = p_n(z) + j \frac{\beta \omega}{2 \rho c^3} \left(\sum_{k=1}^{n-1} k p_k p_{n-k} + \sum_{k=n+1}^N n p_k p_{n-k}^* \right) \Delta z - \alpha_0 (n f_0)^b p_n \Delta z \quad (2.9)$$

where $N = 20$ is the number of harmonics to be retained in the simulation, β is the nonlinearity coefficient, f_0 is the driving frequency, and the frequency dependence of the attenuation coefficient is written in a general form $\alpha(f) = \alpha_0 f^b$. The first summation in parentheses represents the accretion of the n th harmonic by a nonlinear combination of other harmonics while the second one with conjugation can be interpreted as a depletion of the n th harmonic to other harmonics.

When the shock fronts develop in the pressure waveform, strong gradients appear in the transverse spatial field. These spatial gradients can cause artificial oscillations in the numerical solution. To eliminate them, an artificial absorption was introduced in the algorithm locally around the focus where shocks may present. Specifically, the exponential attenuation absorption coefficient is replaced by the function [70]

$$b(n) = b + [(n-1)q / N] \quad (2.10)$$

where q is a constant. This approach is accurate and relatively insensitive to variation in q for the propagation of continuous planar waves, but only with distortion in the highest harmonics.

The pressure waveform in the radiation space can be synthesized from all harmonics as

$$p(z, t) = \sum_{n=1}^N p_n(z) e^{j 2 \pi n f_0 (t - z/c)} \quad (2.11)$$

2.2.1 Multiple layer model

At an interface between two media with different acoustic impedances, the transmission coefficient in the frequency domain is given by [85]

$$T_p(k_x, k_y) = \frac{p_t}{p_i} = \frac{2}{1 + \frac{\rho_1 c_1 \cos \theta_i}{\rho_2 c_2 \cos \theta_t}} \quad (2.12)$$

where ρ_1, c_1 and ρ_2, c_2 are the density and the speed of sound in the adjacent medium, respectively, θ_i and θ_t are the incident and refraction angles determined by the Snell's law:

$$\cos \theta_i = \frac{\sqrt{k^2 - k_x^2 - k_y^2}}{k}, \quad \cos \theta_t = \sqrt{1 - \left(\frac{c_2}{c_1}\right)^2 \frac{k_x^2 + k_y^2}{k^2}} \quad (2.13)$$

Thus, the angular spectrum of the pressures P_1 and P_2 at the interface are related by

$$P_2(k_x, k_y, z) = P_1(k_x, k_y, z) \cdot T_p(k_x, k_y) \quad (2.14)$$

2.2.2 Thermal model

The Bio-Heat transfer equation (BHTE) was used to simulate the temperature elevation and lesion formation by HIFU [89, 90]:

$$\rho C_t \frac{\partial T}{\partial t} = \nabla \cdot \kappa \nabla T + C_b W_b (T - T_a) + Q_p \quad (2.15)$$

where ρ is the density of the tissue, C_t is the specific heat of the tissue, T is the temperature at time t , κ is the thermal conductivity, C_b is the specific heat of the blood, W_b is the blood perfusion rate, T_a is the temperature at large distances, which corresponds to the initial condition value, and Q_p is the power deposited from the focused ultrasound energy:

$$Q_p(x, y, z) = 2\alpha I = 2 \sum_{n=1}^N \alpha(f) I_n = \sum_{n=1}^N \alpha_0 (nf_0)^b \frac{p_n^2(x, y, z)}{\rho c} \quad (2.16)$$

The BHTE was solved using the finite-difference time-domain (FDTD) method with initial and boundary conditions of 37 °C. The thermal dose, an equivalent exposure time at 43 °C ($TD_{43^\circ\text{C}}$), is used to characterize the ablation outcome [91].

$$TD_{43^\circ\text{C}}(t) = \int_0^t R^{43-T(\tau)} d\tau \quad (2.17)$$

where R is 0.5 for $T \geq 43^\circ\text{C}$ and 0.25 for $T < 43^\circ\text{C}$. The lesion formation requires a thermal dose of a 240-min exposure at 43 °C.

2.2.3 HIFU Phased array

A concave HIFU phased-array consisting of 331 circular elements (diameter of 3.6 mm and driving frequency of 1 MHz) has a focal length of 10 cm and an aperture of 5 cm in radius and was used in the simulation (see Figure 2-2a). To simply mimic the human tissues, a model comprised of a layer of 4 cm water, 2 cm fat and 10 cm viscera is adopted (see Fig. 2-2b). The model is taken from a simplified human abdomen, and the data used are from literature [61]. The single focus beam forming is achieved by the Huygen's principle while the multiple foci beam forming is by the pseudo-inverse approach method which has been widely utilized for multi-focus synthesis in phased array [92]. For an array consisting of N elements with arbitrary geometry, the pressure at a specific point could be expressed as:

$$\frac{j\rho ck}{2\pi} \sum_{n=1}^N u_n \int_S \frac{e^{-jk(r_m - r_n')}}{|r_m - r_n'|} dS = p(r_m) \quad (2.18)$$

where u_n and S are the velocity and surface area of the n th element, respectively [93]. The equation above can be expressed in matrix form as

$$Hu = p \quad (2.19)$$

where u is the complex excitation vector of the array elements, $u = [u_1, u_2, \dots, u_n]'$, and the vector p denotes the complex pressure at the control points in the field,

$p=[p(r_1),p(r_2),\cdots p(r_n)]'$, and H is the forward propagation operator. When H is full rank, Eq. (2-19) has the weighted minimum norm solution as:

$$\hat{u}_w = H^{*t} (HWH^{*t})^{-1} p \quad (2.20)$$

where H^{*t} is the conjugate transpose of H , $\hat{u}_w$ is the final driving signals, W is a $N \times N$ real positive definite weighting matrix to reduce the dynamic range and improve the efficiency of the driving signals. An iterative weighting algorithm was utilized to achieve the specified power deposition at the control points. Although straightforward, this weighting algorithm can increase the array excitation efficiency to near 100% efficacy in most cases [92]. Furthermore, in order to compensate the refraction occurring at the tissue interface additional weight, ratio of the thickness of each layer to the total one [85] which is determined by backward propagating the acoustic field to the transducer surface [94, 95], is applied to the driving signal. All the simulation ran in MATLAB (R2010b, Mathworks, Natick, MA) on a PC (3.3 GHz Intel(R)-Core(TM) i5-2500 CPU, 8 GB RAM) with Windows 7 64 bits operating system.

Figure 2-2. Schematic diagram of (a) a 331-element concave phased-array HIFU transducer and (b) the 3 layered media model used in the simulation.

2.2.4 HIFU Field Scanning

To validate the proposed algorithm, the HIFU field was measured using an established protocol [96]. The overall experimental arrangement used for HIFU acoustic field scanning is depicted in Figure 2-3. An annular focused HIFU transducer (H102, outer diameter = 69.94 mm, inner diameter = 22 mm, $F = 62.64$ mm, $f = 1.1$ MHz, Sonic Concepts, Woodinville, WA) was mounted at the bottom of a Lucite tank ($L \times W \times H = 20$ cm $\times$ 20 cm $\times$ 35 cm) filled with degassed and deionized water at the room temperature ($O_2 < 4$ mg/L, $T = 25^\circ\text{C}$) and driven by sinusoidal bursts produced by a function generator (AF3021B, Tektronics, Beaverton, OR) together with a power amplifier (BT00250-AlphaA, Tomco Technologies, Adelaide, Australia). To map the acoustic field of HIFU transducer, a needle hydrophone (HNA-0400, Onda, Sunnyvale, CA) was connected to a three-dimensional positioning system (XSlide, Velmex, Bloomfield, NY), which has a minimum step size of 5 μm and a maximum scan range of 200 mm. The measured signal was first recorded by a digital oscilloscope (Wavesurfer MXs-B, LeCroy, Chestnut Ridge, NY) operated at 500 MHz sampling rate, and then transferred to a PC for off-line analysis. The first 5 harmonics of pressure waveform were calculated using FFT. A LabVIEW (National Instruments, Austin, TX) program was written to automatically control the output of the function generator, data acquisition, and transfer, and hydrophone scanning. To minimize temperature elevation and cavitation damage to the sensing element, the HIFU transducer was operated in burst mode with a low duty cycle (i.e., 10-20 cycles/burst). Averaging over 100 bursts was used to improve the signal-to-noise ratio of the measured pressure waveforms. The geometric focus was determined by searching for the location of maximum signal strength. For line scan along and transverse to the transducer axis, the range and step size was set as $x = -3$ – 3 mm, $z = -3$ – 3 cm, $\Delta x = 0.2$ mm, $\Delta z = 0.5$ mm, respectively.

Figure 2-3. The schematic of the experimental arrangement to scan the HIFU field. The HIFU transducer-aligned z-coordination is shown in the top illustration, where $z = 0$ is defined at the centre of the transducer.

2.3 Results

2.3.1 Model Validation

To validate the proposed algorithm, harmonics generated by a concave transducer in a two-layer media (3 cm water and 5 cm tissue) were compared with those simulated by using HIFU simulator [HIFU-Simulator v1.2, Food and Drug Administration (FDA), Silver Spring, MD] [97]. The HIFU simulator developed by FDA currently can only be used for single element axial symmetry source modelling due to its parabolic approximation. The acoustic properties of water and tissue are listed in Table 2-1 [61, 70]. The concave transducer has a driving frequency of 2.08 MHz, focal length of 5 cm, the diameter of the aperture of 1.9 cm, and the acoustic pressure at the transducer surface is 480 kPa. In the simulation, the spatial sampling interval in the transverse plane is 0.119 mm ($\lambda_{\text{water}}/6$), and the dimension of the source plane is 18.24 cm $\times$ 18.24 cm, corresponding to 768 $\times$ 768 grid points. The sampling interval in the axial plane is 0.356 mm ($\lambda_{\text{water}}/2$) and 0.39 mm ($\lambda_{\text{tissue}}/2$) in the water and tissue layer, respectively. The axial pressure amplitude for the

first 5 harmonics simulated by the KZK model (HIFU-Simulator) and by the second order splitting operator using the ASA is shown in Figure 2-4. It is found that these two results agree closely in the far field (amplitude of fundamental harmonic: 3.04 MPa vs. 3.16 MPa at the focus located at $z = 4.08$ cm vs. 4.12 cm, respectively) but differ largely in the near field, which may be due to the different approximation of diffraction effects, consideration of refraction at the interface, and the starting position of nonlinear effects. HIFU simulator assumes that the propagation within the concave bowl is linear and nonlinear propagation starts from the aperture of the HIFU transducer. In contrast, the algorithm used in this study calculated the non-linear effects from the bottom plane of the transducer by back-projecting the acoustic pressure at the transducer surface to it. No ripple was found in the far field, which showed good convergence using the Tukey window.

Table 2-1. Acoustical parameters of different media used in the simulation [61, 70].

	water	tissue	fat	viscera
Density, ρ	1000 kg/m ³	1050 kg/m ³	950 kg/m ³	1060 kg/m ³
The speed of sound, c	1500 m/s	1629 m/s	1460 m/s	1540 m/s
Nonlinearity, β	3.5	4.5	6.5	4.7
Attenuation, α_0	0.025 Np/m/MHz ^b	6.68 Np/m/MHz ^b	15 Np/m/MHz ^b	3.2 Np/m/MHz ^b
Attenuation law, b	2	1.3	1.0	1.25

Figure 2-4. Comparison of the first 5 harmonics on the axis of the HIFU transducer using the KZK equation through the HIFU simulator (solid line) and the angular spectrum approach with second-order operator splitting scheme (dashed line) in a two layered media model.

The numerical simulations were further compared with experimental results. The pressure waveforms at the focus were purposely aligned in the time domain to match the

peaks for easy comparison (see Figure 2-5). Good agreement was found between measured waveform and synthesized waveforms using both numerical models although the KZK model has the largest negative pressure (9.84 MPa vs. 8.62 MPa using 2nd order operator splitting and 8.07 MPa in the measurement, respectively). Furthermore, the distributions of first 5 harmonics along and transverse to the transducer axis measured by hydrophone were compared with the numerical simulations (see

Figure 2-6). The 2nd order operator splitting algorithm was found to have a better agreement than the KZK model, especially the locations of pressure nodes and more side lobes in the pre-focal region. Overall, the proposed algorithm is an accurate way to simulate the nonlinear wave propagation of HIFU burst. The calculation time of HIFU-Simulator and the proposed algorithm is similar, about 30 min. To enhance the calculation accuracy fourth-order, Runge-Kutta method was used to compute the nonlinearity due to

high pressure at the focus while the computation time was also increased to about 50 min.

A summary of the computation time by different computation method could be found in

Table 2-2.

Table 2-2. Comparison of the calculation time using different computation method

Computation method	2 nd order splitting with a 2 nd Runge-Kutta method	2 nd order splitting with a 4 th Runge-Kutta method	HIFU simulator
Calculation time (min)	30	50	30

Figure 2-5. Comparison of the pressure waveforms at the focus of an annular HIFU transducer measured by a needle hydrophone and numerical simulations using the 2nd order operator splitting algorithm and the KZK model.

Figure 2-6. Comparison of the first 5 harmonics (from left to right) distribution (a) along and (b) transverse to the transducer axis obtained from the measurement and simulations using the 2nd order operator splitting algorithm and the KZK model.

2.3.2 Acoustic field

The acoustic field (the distribution of the first five harmonics in axial and lateral directions and the pressure waveform at the focus) in water and multiple-layered media produced by the phased-array HIFU transducer with the initial acoustic intensity of $8.33\text{W}/\text{cm}^2$ (Spatial Average-Temporal Average) on the transducer surface (about 500 kPa acoustic pressure), which is considered as high input excitation ($p_0 > 0.4\text{ MPa}$) [83], was simulated (see Figure 2-7 and Figure 2-8). Peak pressures are summarized in Table 2-3 for easy comparison. Three cases were considered: geometrical focus (0, 0, 10) cm, transverse focus shifting (1, 0, 10) cm, and four foci in the focal plane (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm. The transverse sampling intervals were set at 0.2mm, and the axial at $\lambda/4$ in all layers. The computation discretization was $512 \times 512 \times 42$, $512 \times 512 \times 80$, and $512 \times 512 \times 130$ points grid in water, fat, and the viscera layer, respectively. The computation on the PC took about 10min. With the electrical steering on the focus, the peak positive pressure reduced by 11.4% in water (27.05–23.97 MPa) and 8.9% in tissue (13.54–12.33 MPa), respectively, but with less change to the peak negative pressure, 5.2% in water (7.33–6.95 MPa) and 4.4% in tissue (5.23–5.0 MPa), respectively. There was no significant change in the lateral distribution of harmonics with shifted focus, while the change in the axial direction, especially in the near field, was due to the definition of the axis through points of (1, 0, 10) cm and (1, 0, 0) cm. For the four foci case, the peak positive pressure was almost half shifted focus (10.09 versus 23.97 MPa in water and 6.11 versus 12.33 MPa in tissue, respectively), but the reduction of the peak negative pressure was much less (5.01 versus 6.95 MPa in water and 3.58 versus 5.0 MPa in tissue, respectively). Despite weak acoustic pressure for four foci in tissue, the presence of harmonics could still be illustrated clearly and the ratio of the second harmonic at the focal point to the fundamental frequency was more than 0.2.

The distributions of first 5 harmonics in the x - z plane using these three focusing strategies are shown in Figure 2-9. It is found that the grating lobes on the axis ($z = 4\text{--}5$ cm) occur mostly at the fundamental harmonics (ratio of pressure at the focus to that in the grating lobe is 6 dB), which is due to the presence of harmonics in the focal region. Shifting the focus slightly worsens the grating lobe (pressure ratio of 5.94 dB) while splitting into four foci has a significant influence on it, the pressure ratio of 4.71 dB and much wide area of multiple grating lobes with similar pressure. The corresponding pressure distributions in the x - z plane are shown in Figure 2-10. Although the patterns of peak positive and negative pressure distribution are quite similar, there are some discrepancies. First, the beam size of peak negative pressure is larger than that of peak positive pressure. Because of the acoustic nonlinearity the duration of the positive and negative pulse will decrease and increase, which means shifting towards low and high frequency correspondingly [96]. Second, the grating lobes of negative pressure are more significant than that of positive pressure.

Figure 2-7. The simulated harmonics generated by the phased-array transducer in water with an input acoustic intensity of 8.33 W/cm^2 (SATA) along the axial axis (left column) and the lateral axis (middle column), and the pressure waveform at the focus (right column) with different focusing strategies: (a) geometrically focusing at (0, 0, 10) cm, (b) transverse focus shifting at (1, 0, 10) cm, and (c) generation of four foci at (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm.

Figure 2-8. The simulated harmonics generated by the phased-array transducer in three-layer media model with an input acoustic intensity of 8.33 W/cm^2 (SATA) along the axial axis (left column) and the lateral axis (middle column), and the pressure waveform at the focus (right column) with different focusing strategies: (a) geometrically focusing at (0, 0, 10) cm, (b) transverse focus shifting at (1, 0, 10) cm, and (c) generation of four foci at (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm.

Table 2-3. Comparison of acoustic pressure at the focal point in water and the tissue generated by the different focusing pattern.

	Peak positive pressure (MPa)		Peak negative pressure (MPa)	
	water	tissue	water	tissue
On-axis focus	27.05	13.67	7.33	5.02
Off-axis focus	23.97	12.33	6.95	5.00
Four foci	10.09	6.11	5.01	3.58

Figure 2-9. The simulation distribution of the first five harmonics (from left to right) in the x-z plane generated by the phased-array transducer in three-layer media model with an input acoustic intensity of 8.33 W/cm^2 with different focusing strategies: (a) geometrically focusing at (0, 0, 10) cm, (b) transverse focus shifting at (1, 0, 10) cm, and (c) generation of four foci at (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm. The colour-bar represents the pressure amplitude in MPa.

Figure 2-10. The simulation distribution of (a) peak positive pressure and (b) peak negative pressure in the x - z plane generated by the phased-array transducer in three-layer media model with an input acoustic intensity of 8.33 W/cm^2 with different focusing strategies: geometrically focusing at $(0, 0, 10) \text{ cm}$ (left column), transverse focus shifting at $(1, 0, 10) \text{ cm}$ (middle column), and generation of four foci at $(1, 1, 10) \text{ cm}$, $(1, 1, 10) \text{ cm}$, $(1, 1, 10) \text{ cm}$, $(1, 1, 10) \text{ cm}$ (right column). The colour-bar represents the pressure amplitude in MPa.

2.3.3 Temperature map and lesion size

The thermal fields and thermal dose distribution in both the focal region (x - y and x - z plane) and pre-focal region (x - z plane) using the phased-array HIFU transducer at a source input acoustic intensity of 8.33 W/cm^2 with the three different focusing strategies are shown in Figure 2-11 and Figure 2-12, respectively. The presence of grating lobe in the pre-focal region with significant temperature rise (56.3°C , 57.5°C , and 44.1°C , respectively) was found, which may cause unexpected damage. For the four foci case, the presence of interference patterns in both the pre- and post-focal region could be figured out easily (as shown by the arrow in Figure 2-11c). Such interference resulted in broad and complicated patterns of the grating lobe. In addition, the temperature evaluation at the focal point using these three focusing strategies was also compared with each (Figure 2-13).

Linear acoustics model, which ignores the non-linear operator in Equations 2-1 and 2-9, was also included in the comparison with the same computation volume and the transverse sampling intervals. It shows that the nonlinear acoustic propagation resulted in a higher temperature in the HIFU ablation than that predicted by the linear model (i.e. 98.7°C versus 86.1°C for geometrically focusing) due to significant differences in the heating deposition rate by the harmonics. Because of the low acoustic pressure in the four foci case, the discrepancy of temperature rises between non-linear and linear models was quite small (only 1°C). However, the lesion boundary after HIFU ablation was not affected much by the non-linear effect (Figure 2-13a and Figure 2-13b), due to the quick dissipation of non-linearity away from the focus and low thermal conduction in the soft tissue. The thermal output in the focal region for these three cases is summarized in Table 2-3. The total lesion volume of four foci was much less than a single focus (47.2 mm³ versus 126.6 mm³ and 103.9 mm³ for geometric focusing and transverse shifting, respectively). Furthermore, if the peak positive pressure at the focus was adjusted to the same value for all focusing strategies, the comparison of thermal fields could be listed as in Table 2-5. The maximum temperatures induced by transverse focus shifting and four foci were a little smaller than that at the geometrical focus, and the lesion area and volume produced by transverse focusing shifting were slightly larger, which may be due to the large beam width. However, the maximum temperatures in the pre-focal region cannot be neglected (61°C and 74.3°C for transverse focus shifting and four foci, respectively). It suggests that great attention should be paid when shifting the focus or generation of multiple foci in HIFU ablation in order to avoid the unintended heating in the pre-focal region. In addition, transverse focus shifting and generation of four foci requires an increase of 1.15- and 5-fold, respectively, in the input acoustic intensity.

Figure 2-11. Comparison of the temperature maps in the x-y plane (left column) and x-z plane (middle column) and presence of grating lobes in the x-z plane (right column) after 2- second continuous HIFU ablation through three layered media with an input acoustic intensity of 8.33 W/cm^2 using different focusing strategies (a) geometrically focusing at (0, 0, 10) cm, (b) transverse focus shifting at (1, 0, 10) cm, and (c) generation of four foci at (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm. The colour-bar represents the temperature rise in °C, and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

Figure 2-12 Comparison of the thermal dose in the x-y plane (left column) and x-z plane (middle column) and presence of grating lobes in the x-z plane (right column) by the end of the 5- second continuous HIFU ablation through three layered media with an input acoustic intensity of 8.33 W/cm^2 using different focusing strategies (a) geometrically focusing at (0, 0, 10) cm, (b) transverse focus shifting at (1, 0, 10) cm, and (c) generation of four foci at (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm, (1, 1, 10) cm. The colour-bar represents the equivalent thermal dose in CEM43C° and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

Figure 2-13. Comparison of the lesion size in (a) x-y plane and (b) x-z plane and c) the temperature elevation at the focal point using different focusing strategies predicted by the linear (solid line) and nonlinear (dashed line) acoustic model after 2-second continuous HIFU ablation through three layered media with an input acoustic intensity of 8.33 W/cm^2 .

Table 2-4. Comparison of the maximum temperature at the focal point after 2 seconds HIFU ablation and the lesion size in the tissue generated by different focusing pattern using linear and nonlinear model.

	Maximum temperature ($^{\circ}\text{C}$)		Lesion area, xz (mm^2)		Lesion area, xy (mm^2)		Lesion volume (mm^3)		Thermal dose (CEM43 $^{\circ}\text{C}$)	
	nonlinear	linear	nonlinear	linear	nonlinear	linear	nonlinear	linear	nonlinear	linear
On-axis focus	98.7	86.1	53.7	48.8	8.9	8.2	126.6	111.3	2.36e15	4.70e12
Off-axis focus	89.3	80.0	47.6	43.9	7.7	7.3	103.9	93.1	1.05e14	5.36e10
Four foci	54.2	53.2	~12.5	~11.3	~1.95	~1.83	47.2	42.8	5.6e3	4.06e3

Table 2-5. Comparison of the maximum temperatures at the focal points and in the pre-focal grating lobes after 2 s HIFU ablation and the lesion size in the tissue generated by different focusing patterns when adjusting the acoustic pressure at the focus to the same value.

	Input acoustic Intensity (W/cm^2)	Maximum temperature ($^{\circ}\text{C}$)		Lesion area (mm^2)		Lesion volume (mm^3)	Thermal dose (CEM43 $^{\circ}\text{C}$)
		At focus	In grating lobe	xz	xy		
On-axis focus	8.33	98.7	56.3	53.7	8.9	126.6	2.36e15
Off-axis focus	9.59	98	61	55.3	9.0	129.7	3.59e15
Four foci	41.68	97.5	74.3	~53.7	~8.7	~123.5	1.05e15

2.4 Discussions and Conclusion

Nonlinear acoustics play a significant role in HIFU ablation, and the use of phased-array is becoming popular for compensation of phase aberration and flexibility of focusing pattern. In this chapter, a numerical algorithm has been adopted to investigate the pressure distribution and the corresponding thermal pattern of the phased-array HIFU with the geometric or off-axis focus or multiple foci. The second-order operator splitting scheme proposed here has better agreement with harmonics distribution of HIFU field in the

measurement than the KZK model. For pulsed excitation, attenuation was coupled with the half step of diffraction rather than the nonlinear substep [98]. In HIFU ablation, the burst duration is usually on the order of 100 ms, and the transient response at both the starting and termination of excitation is not important. Therefore, a different second-order operator-splitting scheme was used here. The presence of higher harmonics in the waveform spectrum due to acoustic nonlinearity can result in higher heat deposition rate [96]. However, there are far fewer differences between the boundaries of the lesions simulated by linear and non-linear models, which is due to the low thermal conductivity of the soft tissue. The increase in thermal conductivity in the tissue leads to an exponential decrease of the maximum temperature elevation at the focus but significant increase in the focal region [99]. Therefore, the HIFU-induced thermal ablation could be predicted easily and quickly using a simple linear model with promising accuracy. Meanwhile, the absorption of the acoustic wave increases with the frequency. Thus, although the non-linearity of tissue is higher than that of water, the waveform distortion at the focal point is not significant because of high attenuation. The absorption law was found to have less impact on the prediction of the fundamental frequency than high harmonics, and on the transverse distribution than the axial distribution [98]. The shifting of focus and generation of multiple foci patterns will decrease the non-linear effect and deposited acoustic energy, leading to the formation of smaller lesions. In addition, this algorithm was also used for the planar phased array HIFU transducer with a similar conclusion (data not shown). Overall, our numerical model can simulate the acoustic and thermal field of HIFU phased array in a high computational accuracy. Optimization of HIFU treatment planning is feasible to enhance the efficacy and safety but needs further investigation

Computational efficiency is another reason of using ASA. The computation burden for the ASA is in the order of $N_x N_y N_t \cdot \log_2(N_x N_y N_t / 2)$, where N_t is the number of

temporal samples, and solving the non-linear wave equation in the frequency domain has a complexity in the order of N^2 where N is the number of harmonics retained. Thus, the computation volume, the transverse and axial plane sampling intervals, and the number of harmonics are key parameters in the simulation and were chosen as the trade-off between accuracy and computation burden. The value of N can be dynamically adjusted according to the waveform distortion [70]. If no shocks are anticipated, then 5 to 10 harmonics can adequately describe a continuous wave field. Otherwise, 30 to 50 harmonics are required. The transverse plane sampling rate should be large enough to describe the significant spatial frequency component, otherwise, large wrap-around errors will occur. For unfocused fields, 1~2× the Nyquist rate of the fundamental works very well while 4× the Nyquist rate is used for focused transducer [100]. The axial sampling intervals and N can also vary accordingly in the simulation. At the beginning of the simulation large Δz and small N values can be used due to the weak nonlinear effect. As the wave propagates towards the focal region and nonlinear effect becomes significant, finer step size and large N values are gradually included. Δz in the focal or far-field region is that the resultant exponential attenuation across Δz for the highest harmonic is no smaller than 0.7, which ensures the accuracy of the joint effect of nonlinearity and attenuation in one-dimensional propagation and diffractive propagation. If all of these parameters are varied adaptively in the simulation (fixed in this study), the computation time would be reduced. Dynamic data allocation has been applied in three-dimensional acoustic field calculation to effectively implement the non-linear algorithms with the application of stream data processing and efficient memory organization [101]. The dynamic data allocation was achieved by dividing the calculation domain into several different echelons and each echelon has a specific number of harmonics for calculation. The size of k th echelon is determined as

$$L_k = L_1 \frac{2N-2k+1}{2N-1} \quad (2.21)$$

where k is the echelon number, N is the overall number of echelons, and L_I is the size of the first echelon. Subsequently, the resources of memory could be saved by a factor of tens while maintaining the calculation efficiency.

In the practical hyperthermia or ablation applications, several variations in the physical properties of tissue should also be considered. If the tissue has small variations in the density changes, then a new term $\nabla p \cdot \nabla \rho_0 / \rho_0$ will be introduced to the full wave equation[98]. Small scale variations in other parameters (i.e., nonlinearity, absorption, and dispersion) do not introduce extra terms into the second-order wave equation [98]. The density fluctuation in the transverse direction, $\rho_0(Z)$, could be incorporated into the diffraction term as first-order derivatives while that in the axial direction should be included into the operator splitting paradigm as a new ordinary first-order differential equation [98],

$$\frac{\partial p}{\partial z} = \frac{1}{2\rho_0} \frac{\partial \rho_0}{\partial z} p \quad (2.22)$$

The speed of sound in the tissue is a function of the temperature, increasing with temperature and exhibiting a maximum at around 50°C in non-fatty tissues but a negative dependence for fatty tissues [102]. Such variation constitutes a localized aberration, becomes significant as the progress of HIFU ablation, and causes the self-defocusing of the acoustic beam. The ultrasonic attenuation coefficient of fresh bovine and human soft tissue has asymmetric quasi-parabolic curves with temperature, being convex downward with their minimum at the turning temperature of around 40°C [102]. Furthermore, all the thermal parameters (specific heat capacity, thermal conductivity, and heat diffusivity) of *ex vivo* porcine liver heated from 20°C to 90°C had a similar relationship with the temperature [103]. Therefore, more work is required to improve the proposed algorithm for *in vivo*

application, compensate the aberrations for perfect and consistent focusing, and predict lesion formation accurately.

Skin burns could be found occasionally during the clinical HIFU treatment and is a concern for the HIFU safety [14]. One of the reasons may be the bad acoustic coupling at the wave entry site. Hair in the skin could trap bubbles in the coupling medium, degassed and deionized water or ultrasound coupling gel. Using the real-time sonography, the coupling condition could be checked frequently. When hyper-echoes show up, HIFU ablation should be terminated to remove these bubbles. The appearance of the grating lobe in the pre-focal region of HIFU field is another mechanism which is inherent to the transducer geometry and driving frequency. The pressure in the grating lobe is much larger than that in the first side lobe, which is more than 15 dB less than the pressure at the focus. Splitting the focus into multiple foci further worsens this phenomenon. If each split focus has a similar acoustic pressure to that at the geometrical focal point of the transducer, a large area of the grating lobes as shown in Figure 2-10 should be considered seriously because of the significant temperature rises as listed in Table 2-4. In this chapter, it was also found that the negative pressure created more significant grating lobes. If higher than the cavitation threshold, the negative pressure in the grating lobe will induce bubbles, which may shield the propagation of subsequent HIFU bursts towards the focal region and scatter them towards the transducer. The presence of bubbles in the acoustic field results in the enhanced heat deposition and formation of lesions [14].

In summary, the proposed algorithm allowed the calculation of nonlinear HIFU wave propagation from arbitrary excitation geometry through multiple tissue layers with different focusing strategies in an accurate and efficient way. Despite the popularity of the KZK model used in the HIFU simulation, the axially symmetric source and parabolic approximation limit its application, especially for phased array HIFU. Narrower beam size

along and transverse to the transducer axis is predicted by the KZK model than those by the proposed algorithm and measurement, which may be due to the underestimation of diffraction. The resultant thermal field, temperature elevation, and lesion formation can be used to evaluate the HIFU treatment plan in the practice quantitatively. Shifting and splitting the focus leads to reduced acoustic pressure and lesion size. In addition, the pre-focal region becomes worse. Compensation of tissue phase aberration, tracking of target motion due to respiration, and avoidance of unintended energy accumulation in a vital region by using a phased-array HIFU transducer will be further investigated on the basis of this simulation algorithm.

Chapter 3 Evaluation of the effect of electronically steering a phased array transducer

3.1 Introduction

Electronically steering the beam of a phased array transducer achieved by varying the phase applied to each element to compensate for the delay in the acoustic wave propagation with respect to the geometrical position of focus dramatically shorten the interval time of focus shifting, allowing a rapid dynamic control of the focusing and a real-time compensation of respiratory-induced motion in the organ (e.g. kidney and liver) [104]. Indeed, a number of studies have shown that the treatment time reduction and accurate focusing can be accomplished through the utilization of phased array transducer [105-107].

It is always desirable to suppress the grating lobes or the secondary maximum and maximize the electronic steering range in 3D and achieve a maximum pressure in the focal zone through the manipulation of the operation frequency and transducer configuration. As shown in the last chapter, electronically steering the beam can only be available within a certain range, typically on the order of 1 cm along a given direction. If the focus is electronically shifted far away from the geometrical focal point, a significant reduction in the acoustic intensity and simultaneous increase of the grating lobes will occur. The formation of large grating lobes is a serious safety concern if they are presented outside of the treatment region. The steering ability depends on the phased array itself and is a key metric for an array design with regard to its safety and efficacy in the surgical applications. A good understanding of the relationship between the steering distance and grating lobe or the main lobe can provide valuable guidelines for the design of phased array transducer, particularly in determining the trade-offs between the transducer complexity and the desired beam characteristics for a specific clinical application.

In this chapter, the effect of electronically steering the focus on the HIFU ablation was thoroughly studied. The important relationship between the main lobe, grating lobe, and steering distance were investigated by a nonlinear algorithm simulation proposed in the last chapter. Safety concerns working in the nonlinear regimes related to the grating lobe are also discussed.

3.2 Methods

Considering the deep-seated tumor ablation, a typical 256-element spherically focused phased array transducer (H-169, Sonic Concepts Inc., the focal length of 200 mm, the active diameter of 200 mm, a central opening of 64 mm) driven at different working frequencies was simulated. Circular elements with a dimension of 1 cm in diameter and a central working frequency of 1.0 MHz are regularly placed on the concave surface. A multiple layer media model modified from the human abdomen was used in the simulation (see Figure 3-1). Acoustic pressure at the transducer surface was fixed to 300 kPa (3 W/cm²) to show a pronounced nonlinear effect. To see the influence of the frequency on the performance of phased array, several different frequencies (e.g., 0.9 MHz to 1.1 MHz in a step size of 0.05 MHz) was investigated.

The acoustic calculation was performed with an initial pressure plane seated 1.5 mm in front of the transducer surface. To accelerate the calculation, a combination of the fast near-field (FNF) method [108] and the element response function array (ERFA) method [109] was used to calculate the initial plane pressure. The formula to compute the pressure field generated by a harmonically excited circular transducer by FNF is given by:

$$p(x, y, z) = \rho c u_0 \frac{a}{\pi} \int_0^\pi \frac{r \cos \psi - a}{r^2 + a^2 - 2ar \cos \psi} (e^{-jk\sqrt{r^2 + a^2 - 2ar \cos \psi + z^2}} - e^{-jkz}) d\psi \quad (3.1)$$

where a is the radius of the elements, u_0 is the velocity on the transducer surface, and ψ is the variable of integration. The benefit of the above formula is that the 1D integral over ψ can be easily evaluated by midpoint Riemann sum. To simplify the calculation of the

pressure field on the initial plane, the plane was transformed into the coordinate system centered at the element center. The rotation matrix with respect to y and z -axis could be given by:

$$ROT = \begin{bmatrix} \cos \theta \cos \beta & \cos \theta \sin \beta & \sin \theta \\ -\sin \beta & \cos \beta & 0 \\ -\sin \theta \cos \beta & -\sin \theta \sin \beta & \cos \theta \end{bmatrix} \quad (3.2)$$

where θ and β are respectively the rotation angles of the element along the y - and z -axis. The rotation matrix is the product of two rotation matrices, one is the rotation matrix with respect to the y -axis, and the other is the subsequent one with respect to the z -axis. For the ERFA method, the pressure of the boundary plane on all elements is pre-calculated with the unit amplitude and zero phase by the means of FNF method. At the running time, the appropriate phase and amplitude for the desired focus were applied to each element, and the pressure on the desired plane is accordingly modified by multiplying the phase and amplitude accordingly, and finally all acoustic fields are added together to get the final pressure on the plane.

Phase determination for each element was still based on the Huygen's principle. The spatial sampling interval on the transverse plane is both 0.2 mm along the x and y -direction. Axial spatial sampling intervals differ in the different media, $\lambda_{\text{water}}/4$ in water, $\lambda_{\text{skin}}/5$ in skin, $\lambda_{\text{fat}}/4$ in fat, muscle/4 and $\delta=\lambda_{\text{liver}}/3$ in liver, respectively. As a result, the total computational volume is discretized into $1024 \times 1024 \times 46$ grid for water, $1024 \times 1024 \times 12$ grid for skin, $1024 \times 1024 \times 39$ grid for fat, $1024 \times 1024 \times 52$ grid for muscle and $1024 \times 1024 \times 276$ grid, respectively. The maximum number of harmonics retained in the simulation was up to 20, which is large enough to include an apparent nonlinear effect. Physical parameters are from other literature [110-113], and details of the corresponding values used in the thermal simulation are listed in Table 3-1. Since high power short pulse heating can enable the ablation perfusion independent [114], the heating scheme for the

thermal simulation is still kept to 2 s heating and 3 s cooling, and a temporal step size of 0.01 s was used to solve the Penes' Bioheat equation. Near field heating was evaluated from the water and skin surface to a plane 3.5 mm away from the corresponding focus.

Focus shifting could be either in the axial direction or lateral direction, and shifting the focus in one direction will cause the grating lobe to grow in the opposite one. Therefore, steering the focus in the post-focal region will cause the grating lobe appear in the pre-focal region, which is the most unwanted. Hence, to evaluate the worst case of focus steering, the axial steering to the post focal region was studied in this chapter.

Studies in this chapter were performed in the following manners. First, the acoustic intensities at various frequencies and locations were computed. Based on the intensity calculated, the absorbed power was then determined. Finally, the Penes' Bioheat equation was solved to examine the temperature rise and the corresponding thermal dose in both the focal region and pre-focal region.

Figure 3-1. The multiple layered media model used in the simulation.

Table 3-1. Materials and their acoustic properties used in the simulation [110-113, 115]

Material	Thickness (cm)	c(m/s)	ρ (kg/m ³)	α_0 (Np/m MHz ^y)	y	β
Water	4	1500	1000	0.025	2	3.5
skin	0.5	1615	1090	14.46	1.05	7.87
fat	2	1460	950	8.0	1	6.5
muscle	3	1609	1050	6.5	1.1	4
liver	17.5	1609	10660	3.2	1.25	4.5

3.3 Results

An example of the acoustic intensity distribution was shown in Figure 3-2, where the focus was gradually shifted 2.5 cm away from the geometrical focal point. It could be seen that as the focus is shifted away from the geometrical focus, the grating lobe gradually becomes significant. Furthermore, when the same acoustic power was applied, high frequency led to a large level of grating lobe. Most importantly, the grating lobe shifts when the driving frequency changed. The level of the main lobe decreases with the distance of focus shifting, and the frequency has little effect on the main lobe. The important features of the main lobe (e.g. -6 dB beam size, main lobe amplitude, and location) almost remain the same. Overall, the grating lobe and main lobe have a strong relation with the steering distance.

Figure 3-2. The distribution of acoustic intensity along the axial axis at the steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm.

3.3.1 Acoustic field

To show a quantitative variation of the main lobe and grating lobe, detailed comparisons of the acoustic field and thermal patterns are made. First, the steering

abilities, the variation of the main lobe and grating lobe, were studied. Figure 3-3(a) and (b) shows the normalized variation of the main lobe and grating lobe with regards to the intensity without focus steering, respectively, and Figure 3-3(c) is the variation of the grating lobe level defined as the ratio of the acoustic intensity of grating lobe to that of the main lobe. It is seen that the focal intensity linearly decreases while the grating lobe intensity linearly increases with the focus steering distance. In average, as the focus steered 2.5 cm away from the geometrical focal focus, the main lobe decreased to roughly 57.5% of the corresponding value at the geometrical focus, while the grating lobe increased almost 4 to 5-fold. Hence, the grating lobe increases in a much more rapid speed than that of the decreasing speed of the main lobe. In addition, high driving frequency leads to a large increasing rate for the grating lobe and falling rate of the main lobe. The grating lobe level as shown in Figure 3-3(c) linearly increases with the steering distance as well. High frequency has a larger increasing rate. As the grating lobe is of great concern for the treatment safety, a more detailed relationship between the grating lobe and the frequency was shown in Figure 3-4. The red line corresponds to the relationship between the grating lobe the amplitude and the driving frequency while the black line was the one between the location and the frequency. It is noted that both the amplitude and location of grating lobe vary linearly with the frequency, except for the case on the focal plane. The grating lobe moves towards the transducer surface with the decrease of driving frequency. Moreover, the shifting rate of the grating lobe with frequency is independent of the focus location, all around 0.4 cm/MHz. Except on the focal plane, the grating lobe amplitude linearly increases with the frequency, and unlike the grating lobe location, the increasing rate grows with the focus steering distance. The slope of the grating lobe increased from $0.8\text{W/mm}^2 \cdot \text{MHz}$ to $7.8\text{W/mm}^2 \cdot \text{MHz}$ as the steering distance goes from 0.5 cm to 2.5 cm, suggesting

that the large steering distance should be avoided; otherwise, the grating lobe will rapidly rise.

Figure 3-3. Variation of the acoustic intensities of (a) main lobe and (b) the grating lobe, and the grating lobe level at the various steering distance from 0 cm to 2.5 cm.

Figure 3-4. Variation of the grating lobe amplitude and its location at the frequency from 0.9 MHz to 1.1 MHz at the axial steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm, respectively.

Overall, the amplitude of grating lobe and the main lobe, and the grating lobe level shows a strong linear relationship with the steering distance. But, the grating lobe amplitude rises in a much more rapid speed than the decreasing speed of the main lobe. The grating lobe amplitude and location are a function of frequency, and the shifting rate

of grating lobe location with the frequency is independent of steering range and always linearly moves away from the geometrical focus. The amplitude of grating lobe linearly increases with the frequency, and a large steering distance normally causes a fast increase of the grating lobe level.

3.3.2 Temperature maps

Besides the acoustic field, the temperature maps resulted from the corresponding acoustic field were further compared. Several paramount results (e.g. lesion area size on the lateral and axial planes, lesion volume, and temperature rise) in the both focal and pre-focal regions were examined. The results of the lesion area and lesion volume were shown in Figure 3-5(a) to (c), wherein Figure 3-5 (a) was the result for the focal area on the lateral (xy) plane, Figure 3-5 (b) for the focal area in axial (xz) plane, and Figure 3-5 (c) for the lesion volume, respectively.

Figure 3-5. Variation of (a) the lateral plane lesion area, (b) axial plane lesion area and (c) the whole lesion volume at the various steering distance from 0 cm to 2.5 cm and driving frequency from 0.9 MHz to 1.1 MHz.

Unlike the linear relationship between the acoustic intensity and the focus steering distance, the lesion volume, and focal area decrease quadratically with the focus steering distance, and a large steering distance results in a small focal volume and focal area. On average, the lesion area on the lateral plane reduced about 36%, and the frequency does not show a great impact on the lateral lesion area. The axial plane lesion area and the lesion

volume have almost the same falling rates at all frequencies since the variations tend to decrease in the same manner, and all curves are almost parallel to each other. It is worth noting that high-frequency results in a larger acoustic intensity, but a small lesion area and lesion volume. The lesion area and volume decrease with the frequency at all focus steering distances. The falling rate of the lesion area and volume vary in a very small range (about 6%), the falling rate of the axial lesion area increasing from $0.26\text{mm}^2/\text{MHz}$ to $0.36\text{mm}^2/\text{MHz}$ while lesion volume increasing from $0.05\text{mm}^3/\text{MHz}$ to $0.095\text{mm}^3/\text{MHz}$. The comparison of the focal temperature rise is shown in Figures 3-6 and 3-7. As expected, the temperature rise drops with the focus steering distance. But surprisingly, the maximum temperature rises almost linearly decrease with the focus steering distance (see Figure 3-7), and the high frequency has a large decreasing rate (ranging from $10.72^\circ\text{C}/\text{cm}$ to $15.72^\circ\text{C}/\text{cm}$). The high frequency leads to a large temperature rise at all focus steering distances. But it is found that the impact of frequency decreases with the steering distance, and the large focus steering distance leads to the small temperature discrepancy.

Figure 3-6. Temperature rise at the focus at the axial steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm and at the various driving frequency from 0.9 MHz to 1.1 MHz.

Figure 3-7. The maximum temperature rises at the focus at the various axial steering distance from 0 cm to 2.5 cm and driving frequency from 0.9 MHz to 1.1 MHz.

Besides the comparison of the focal temperature rise, the near field temperature rises, and thermal dose accumulation were compared as well. As shown in Figure 3-8 that near-field temperature rapidly increases with the focus steering distance. High frequency always has the highest temperature rise and the increasing rate (from 3.22°C/cm to 4.89°C/cm). A summary of the near field temperature rise (see Figure 3-9) surprisingly shows that the maximum near-field temperature rises also linearly with the focus steering distance. Comparison of the thermal dose distribution is shown in Figure 3-10. It could be seen that the thermal dose in the near-field also increases with the focus steering distance and high frequency also has a high increasing rate. But the relationship is no longer linear as shown in Figure 3-10 that high frequency has a larger growing rate. For the case with a 2.5 cm focus steering distance at the excitation of 1.05 MHz, although its intensity exceeds -10 dB of the main lobe which deems to be unsafe, the thermal dose was still less than the necrosis value threshold (240CEM43). Therefore, using the intensity to evaluate the grating lobe level is not accurate, and it is better to directly use the thermal dose value. Moreover, comparing the thermal dose produced at different frequencies, we can see that the thermal dose is very sensitive to the frequency variation and a low frequency has a low

thermal dose. The thermal dose generated by 1.1 MHz excitation with the focus steering distance of 2.5 cm is almost 15fold of that by the 0.9 MHz excitation. Therefore, there is a trade-off for the frequency selection in the reduction of the near-field heating. High frequency will accelerate the focal heating which is beneficial, but greatly speed up the undesirable near-field heating.

Figure 3-8. Temperature rises in the near field at the axial steering distance of 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm and driving frequency from 0.9 MHz to 1.1 MHz.

Figure 3-9. The maximum temperature rise in the near field at the various axial steering distance from 0 cm to 2.5 cm and driving frequency from 0.9 MHz to 1.1 MHz. The temperature rise was evaluated from the water and skin interface to a plane 3.5cm away from the corresponding focus.

Figure 3-10. The thermal dose accumulation in the near field at the various axial steering distance from 0 cm to 2.5 cm and driving frequency from 0.9 MHz to 1.1 MHz.

To retain a uniform lesion ablation, power compensation in the process of focal steering is always necessary to replenish the steering power loss. Figure 3-11 shows that the power compensation levels with respect to the geometrically focusing (non-steering case) increase exponentially with the axial focus shifting distance and high frequency needs large power compensation. Shifting the HIFU focus axially for 2.5 cm needs about 63%–130% more power in the compensation. However, as shown in [116] that the pre-focal heating increases linearly with the power applied to the HIFU transducer and the axial focus shifting distance, high power compensation results in high power accumulated in the near field. Consequently, more undesirable pre-focal heating would produce for the possible side effects. Therefore, there is another trade-off between the lesion uniformity and the near-field heating.

Figure 3-11. Power compensation level at the various axial steering distance from 0 cm to 2.5 cm and driving frequency from 0.9 MHz to 1.1 MHz.

In summary, the lesion area and volume decrease quadratically with the focus steering distance and high frequency leads to a large lesion volume and area because of high focal temperature rise. The focal and the near-field temperature linearly decreases and increases with the focus steering distance, respectively, and high frequency accordingly results in a small dropping rate for the focal temperature and near-field temperature rise. Thermal dose accumulation in the near field rapidly increases with the focus steering distance, and high frequency leads to fast heat accumulation. Power compensation due to the focus steering is not preferred because it will worsen the near-field heating.

3.4 Discussion

Comparing to the mechanical steering of the focus, the electronic approach offers the advantage of rapid alteration of size and shape of the ultrasound beam profile to correct the phase and amplitude-aberration caused by the heterogeneous tissue. Furthermore, electronically steering the focus enhances the ablation ability. As a result, the controlled hyperthermia and ablation are feasible and attractive for the deep targets that were previously considered unreachable by the single element focused ultrasound. However, the current study has shown that electronically steering a 256-element phased array can significantly increase the grating lobe levels even when steering in a small distance.

Conventionally, it is believed that the steering is safe if the maximum intensity of any grating lobe is less than -10 dB of the focal intensity [117, 118]. The -10 dB value nevertheless is retained in the linear wave propagation, but in the nonlinear regimes, the steering ability could be enlarged. Since the nonlinearity of wave propagation is pressure dependent, the intensity at the focus greatly increases while the intensity at the grating lobe does not change too much due to its low pressure. As shown in the previous part that the -10 dB safety criteria were not accurate since the thermal dose was below the necrosis threshold although the grating lobe level exceeds the safety value. Current consideration in the HIFU treatment and planning should include the absolute value in the pre-focal region, particularly when the nonlinear effects of the wave propagation are considered.

It has been found in the previous part that the focal intensity linearly decreases with the steering distance. But the energy loss in the process of focus steering is not all transferred to the grating lobe. Another simulation which compares the acoustic intensity of electronically steering beam to a mechanical move beam with a 1 cm steering distance shows that the beam attenuation is responsible for about 89% of the intensity loss. But one advantage of phased array is that the energy loss or beam distortion in the wave propagation can all be compensated dynamically.

The grating lobe level not only relies on the focus steering distance but also on phased array configuration and element size [119]. It increases with the element size or width. Small elements are less directional and thus provide better steering abilities in an array. Theoretically, building an array with element size less than half of the wavelength will give the best results in terms of the grating lobe level. However, selection of element size was currently overlooked. The reason is that fabrication of an array with small size ($< \lambda/2$) was very difficult and in most cases phased array are designed with the element size much larger than 2 wavelengths. Moreover, the number of elements increases dramatically

when the element size becomes smaller. To achieve a $\lambda/2$ spaced phased array, low frequency is usually employed. The low frequency not only produces the small grating lobe (see Figure 3-3b) due to the low attenuation but also enables an increased element size, hence alleviating the near-field heating (see Figure 3-11). So far, a flat array with $\lambda/2$ -spaced elements for the ultrasound therapy has already been examined, and a high steering ability was attained [120]. But the number of elements involved in that design is up to 1024, which is still considered impractical for the complex and high-cost construction.

Formation of the grating lobes also depends on the position of elements. It has been shown that regular and symmetric positioning of the elements results in a strong grating lobe and small steering distance of the beam [121]. The use of random or sparse populated phased array was suggested to suppress the grating lobe, hence enhancing the steering ability. But it is at the cost of high power output. To maintain a compatible output with a fully fired phased array, the randomly sparse phased array usually has a large number of elements, large aperture size and utilizes a high-power input. However, the near field heating almost linearly correlated with the acoustic power at the transducer surface [116] and a greater power input will give rise to an increased near field temperature rise.

The steering capability currently investigated is only limited to the case of single focus, but not multiple foci. As shown in the last chapter, the focus splitting has an even larger grating lobe level comparing to that of focal shifting. A comparison of heating strategies using single-focus scanning, multiple-foci scanning, and simultaneous multiple focusing without scanning has shown that multiple foci pattern can considerably reduce the treatment duration but increase the pre-focal heating due to the increased power employed [122].

3.5 Conclusion

In this chapter, the effect of electronically steering the focus has been assessed. It is found that the grating lobe and main lobe linearly decreases and increases with the steering distance, respectively. But the grating lobe rises much more rapidly than the decrease of the main lobe. The grating lobe level and location are frequency dependent. The grating lobe location shifting rate with the frequency is independent of steering range, and it always linearly moves away from the focus as the frequency decreases. The grating lobe amplitude linearly increases with the frequency, and a large steering distance normally causes a fast increase of the grating lobe level. The lesion area and volume quadratically decrease with the steering distance, and high frequency leads to a large lesion size and high focal temperature. The focal and near field temperature linearly decreases and increases with the steering distance, respectively, and high frequency results in high temperature falling in the focal region but increasing in the near field. The -10 dB criterion to evaluate the safety of the steering ability is not accurate, and it's strongly suggested to directly evaluate the thermal effect caused by the grating lobe.

Chapter 4 Frequency chirping to reduce the pre-focal heating caused by electronically steering for a phased array ultrasound transducer: A feasibility study

4.1 Introduction

Phased array transducer for its virtue of electronically steering the focus and multiple foci synthesis is capable of yielding a faster necrosis rate, significantly reducing the ablation time [105-107]. But numbers of prior studies have demonstrated that pre-focal heating becomes more pronounced when utilizing phased array transducer for ablation. Besides the heating due to beam overlapping, the presence of the grating lobe or other unwanted secondary maxima in the process of focus steering, particularly when performing deep-seated tumor ablation, has worsened the pre-focal heating.

To address this problem, several strategies have been implemented. The common way was to either optimize the scanning path or include a long enough delay between two successive sonications so that the effect of beam overlapping could be minimized. For example, Yiannakou et.al [123] has recently compared six different scanning algorithms in ablation and suggested that setting the successive step apart from each other can completely remove the pre-focal heating. Fan et. al [106] has compared three different scanning paths with different delays and suggested that 30–60 s delay between two successive sonications is essentially needed to reduce pre-focal heating. The delay time varies with transducers used for the ablation. Damianou et.al [124] was the first one who noticed the pre-focal heating problem, and they have suggested a 20 s or longer delay to overcome the pre-focal heating. In addition, using the sparse arrays or randomly positioned array can also effectively alleviate pre-focal heating and suppress the grating lobe level and

other secondary intensity maxima, but this method limits the energies delivered to the focus [125].

In this chapter, an alternative method to mitigate the near-field or pre-focal heating problem caused by electronically steering the acoustic beam is presented. This method is accomplished by continuously changing the driving frequency in the process of ablation; as a result, the heat accumulated in the pre-focal region may be leveraged. Frequency sweeping technology has already been widely used in ultrasound diagnosis and therapeutics. It has been shown that frequency chirp is able to improve the signal-to-noise ratio (SNR) and penetration depth without increasing the peak acoustic pressure in the medical imaging [126]. Furthermore, frequency chirp has been applied to suppress the standing wave formation in the transcranial ultrasound sonication [127, 128] and vibroacoustography [129]. Recently, the frequency chirping has been reported to enhance or quench the ultrasonic induced bubble cavitation [130].

Although the current technique is similar to previous studies in which frequency modulation or phase modulation was used to suppress the grating lobe on either lateral plane or axial plane [131-133], some key aspects are still different. First, all the previous investigations were confined to the acoustic field. The thermal effect by frequency modulation on the pre-focal heating reduction has not been examined. Second, they were limited to the linear wave propagation, which was impractical considering the high-pressure level used in the HIFU ablation. Third, the instantaneous frequency varies linearly with time in a very large range; however, in this study, the frequency varies very slowly in a very short sweep range.

The chapter is structured in the following way. First, the methods dealing with the reduction of pre-focal heating by frequency sweeping excitation was introduced so that pre-focal heating in each single sonication may be minimized. Second, frequency sweeping

excitation was applied to three ablation planes located on the focal plane, 1 cm, and 2 cm away from the focal plane, respectively, to show its influence on the pre-focal heating reduction in multiple spot sonication. Last, a proof of concept experiment was conducted to verify the hypothesis that pre-focal heating could be reduced by frequency sweeping without compromising the thermal conditions in the focal region.

4.2 Method

4.2.1 Pre-focal heating and frequency sweeping

It has been mentioned in the introduction part that pre-focal heating was mainly produced in the process of creating multiple lesions to cover the whole target because of beam overlapping or the presence of the grating lobe or both. To evaluate this heating, temperature rise and thermal dose in the pre-focal region ranging from the water and skin surface to the liver was evaluated. Both single-shot sonication and plane sonication were studied. For each single-shot sonication, 2 s heating with 3 s cooling, which enables the blood perfusion independent sonication, was chosen. Models used in this chapter are the same as use that used in the last chapter.

Frequency sweeping was achieved by linearly varying the instantaneous frequency from 0.9 to 1.1 MHz in a step size of 0.02 MHz, which was carefully selected to enable an efficient transducer output considering its limited bandwidth. The frequency sweeping was either downward (from the high frequency to the low frequency) or upward (from the low frequency to the high frequency) at different sweeping durations (e.g. sweeping in 2 s, 1 s, 0.5 s or 0.1 s). In addition, a random frequency excitation, an equivalent constant frequency (at 1 MHz) excitation with electronically steering is also simulated to evaluate the performance of different sweeping methods. All simulations ran in MATLAB (R2010b, Mathworks, Natick, MA) on a PC (3.3 GHz Intel V R Core™ i5-2500 CPU, 4 GB RAM) with Windows 10 64-bit operating system.

4.3 Results

4.3.1 Results by frequency sweeping

To effectively alleviate the pre-focal heating caused by focus shifting, the driving frequency was gradually changed so that heat accumulated in the pre-focal region was leveraged in a wide spatial range instead of focusing at a single fixed point. In this part, the results of the temperature and thermal patterns of a phased array were shown and compared with those by a constant frequency excitation.

Figure 4-1 shows the pre-focal temperature distribution along the axial axis at the end of the heating period using different chirping directions and time for the case of a 2.5 cm axial focus steering. It could be seen that upward chirping in 2 s and downward chirp in 2 s gives the highest and lowest temperature rise, respectively. Therefore, all future comparisons are made with the downward chirping since it has a better result. It is not difficult to understand the underlying mechanisms why downward chirping was better. It is shown in the previous chapter that the downward chirping causes the grating lobe move away from the high-temperature focus where the heating rate is maximum. Moreover, the amplitude of the grating lobe decreases with downward chirping, indicating a reduced heating source for the pre-focal heating.

Figure 4-1. Pre-focal temperature distribution along the axial axis driven by a downward and upward frequency chirping at different duration with a 2.5cm axial focus steering.

Figure 4-2 compares the temperature elevation in the pre-focal region by the end of the heating period using the frequency chirping and regular excitation. The temperature rise gradually increases with the focus steering distance, and a large shifting distance causes a high-temperature elevation for both types of excitations. But chirping frequency excitations at all steering distances always give the lowest temperature rise, and their temperature distributions show a reduced fluctuation.

For easy comparison, a summary of the maximum temperature rise is shown in Figure 4-4(a). A minor difference ($\sim 1^{\circ}\text{C}$) was found when ablating on the geometrical focal plane, but a distinctive reduction ($\sim 4^{\circ}\text{C}$) was seen with a 2.5 cm axial focus steering distance. Hence the pre-focal heating reduction by frequency chirp is more effective for large steering distance.

To further show the reduction, the thermal dose variations in the pre-focal region along the axial axis are shown in Figure 4-3, and a summary of the maximum thermal dose reduction is shown in Figure 4-4(b). Thermal dose increases with focus steering distance for both regular and chirping excitations, but the increasing rate by the regular one is much larger than the chirping ones. Furthermore, it is found that due to the heat leveraging effect by frequency chirping, a small difference in the temperature rise (4°C) surprisingly induces a 6-fold difference in the thermal dose ($65\text{CEM}43^{\circ}\text{C}$ Versus $10\text{CEM}43^{\circ}\text{C}$).

Figure 4-2. Pre-focal temperature distribution by the end of heating period along the axis by the regular and linear chirp frequency excitations with an axial focus steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 0.9 to 1.1 MHz in a step size of 0.02 MHz. The acoustic pressure at the transducer surface was fixed to 300 kPa (3 W/cm^2) and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

Figure 4-3. Pre-focal thermal dose distribution by the end of the cooling period along the axis by the regular and linear chirp frequency excitations with an axial focus steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 0.9 to 1.1 MHz in a step size of 0.02 MHz. The acoustic pressure at the transducer surface was fixed to 300 kPa (3 W/cm^2) and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

Figure 4-4. Comparison of the (a) pre-focal temperature and (b) thermal dose distribution at the end of the heating and cooling period by the regular and chirping frequency with the various axis focus steering distance from 0 cm to 2.5 cm. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 0.9 to 1.1 MHz in a step size of 0.02 MHz. The acoustic pressure at the transducer surface was fixed to 300 kPa (3 W/cm^2) and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

To further show the influence of the chirping frequency excitation on the ablation, the lesion size and the focal temperature elevation were examined. As shown in Figure 4-5 to Figure 4-7, no significant difference was found in the lesion size and focal temperature rise between frequency chirping excitations and the regular constant excitation. The chirping time also shows no significant effect on the lesion size and the focal temperature elevation. Overall, HIFU ablation by frequency sweeping excitation shows a temperature reduction in the pre-focal region but keeps the same performance in the focal region.

Figure 4-5. Comparison of the lateral plane lesion size generated by the regular and linear chirp frequency excitations with the axial steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm.

Figure 4-6. Comparison of the axial plane lesion size generated by the regular and linear chirp frequency excitations with the axial steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm.

Figure 4-7. Comparison of the focal temperature rise generated by the regular and linear chirp frequency excitations with the axial steering distance of (a) 0 cm, (b) 0.5 cm, (c) 1.0 cm, (d) 1.5 cm, (e) 2.0 cm, and (f) 2.5 cm.

4.3.2 HIFU scanning in a plane

To further show the efficiency of the proposed methods, three positions located on the focal plane, 1 cm, and 2 cm away from the focal plane were simulated (see Figure 4-8). Focus steering was along the trajectories consisting of multiple outward-moving concentric circles.

Figure 4-8. Illustration of (a) the location of the plane ablation and (b) trajectory. For each plane, the trajectory follows the pattern in (b).

Figure 4-9. Comparison of the lesion size created by (a) regular, (b) downward, (c) upward, and (d) random frequency at the axial focus steering of 2 cm.

Figure 4-10. Comparison of the maximum temperature rise (upper row from a to c) and thermal dose (bottom row from e to f) in the pre-focal region driven by different excitations in location 1 (left column), location 2 (middle column) and location 3 (right column). The red, blue, black and green line represent the regular, downward sweep, upward sweep and random frequency excitation, respectively. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 0.9 to 1.1 MHz in a step size of 0.02 MHz. The acoustic pressure was fixed to 300 kPa (3 W/cm^2) and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

Figure 4-11. The effect of sweeping duration (i.e. 0,0.5,1.0, and 2.0s) on the temperature rise (upper row from a to c) and thermal dose (bottom row from d to f) in the pre-focal region for the ablation plane in location 1 (left column), location 2 (middle column) and location 3 (left column). The red, blue, black line represent the downward sweep, upward sweep and random frequency excitation, respectively. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 0.9 to 1.1 MHz in a step size of 0.02 MHz. The acoustic pressure at the transducer surface was fixed to 300 kPa (3 W/cm^2) and the absorption coefficient used is $3.2 \text{ Np/m/MHz}^{1.25}$.

Figure 4-12. The effects of the cooling period (i.e. regular from 3s to 4s, downward from 1s to 3s and downward without cooling period) on the maximum temperature rise (upper row from a to c) and thermal dose (bottom row from d to f) in the pre-focal region for the ablation plane location 1 (left column), location 2 (middle column) and location 3 (left column). The red, dark blue, dark, green, purple and light blue line represent the regular from 3s to 4s, downward from 1s to 3s and downward without cooling period respectively.

Figure 4-13. Comparison of the lesion size driven by different excitations with the different cooling period at the location 1 to location 3 (from left to right).

A demonstration of lesions created by different excitation schemes is shown in Figure 4-9. It could be seen that the focal lesion sizes by the regular excitation, chirping and random frequency excitations are similar but differ significantly in the pre-focal region. A clear pre-focal burn was observed by the regular frequency excitation. To further show the difference, the maximum temperature rises and thermal dose in the pre-focal region were compared (see Figure 4-10). The temperature rise and thermal dose by chirping frequency excitation were clearly lower, especially at the location 2 and 3. At the location 2, the pre-focal region thermal dose clearly exceeds the safety value of 10 CEM43°C [134] at the late stage of ablation with a constant frequency regular, but the chirping ones remain around 4 CEM43°C, which still has a large margin to the unsafe threshold. In comparison, at the location three, even though the chirping frequency excitations have reduced the thermal dose, it is still beyond the safety threshold.

Furthermore, the maximum temperature rise and thermal dose by different sweeping directions (e.g., downward, upward, or random) was compared (see

Figure 4-11). It could be seen that frequency chirping upward still shows the highest temperature rise while sweeping downward shows the lowest one and randomly lies between them. Furthermore, the long chirping (e.g. 2s) still shows a low-temperature rise. In terms of thermal dose, there is not too much difference at the location 1 and 2, but at the location 3, and the random frequency seems to have the smallest difference.

Cooling time is always necessary for regular ablation to prevent the pre-focal heating (see Figure 4-9). Since frequency chirping excitation is capable of reducing the pre-focal heating, the cooling period with a chirping excitation could be accordingly reduced. A comparison of temperature rise and thermal dose for excitations with different cooling periods is shown in Figure 4-12. It is found that frequency chirping results always have a lower temperature rise even without cooling time between two successive sonications. Moreover, the cooling period has a very minor impact on the pre-focal heating when utilizing the chirping excitation. There is only a small improvement of pre-focal temperature rise for chirping excitation but a significant one for regular excitation when cooling period was reduced.

As cooling period could be significantly reduced utilizing frequency chirping excitations, high temperature as a result of the reduced cooling is expected. The benefit of the increased background temperature or high temperature by the end of the cooling is an enlarged lesion size as shown in Figure 4-13. Therefore, a reduction of pre-focal heating not only substantially reduces the treatment time because of the reduced cooling period but also increases the lesion size as a consequence of an increased background temperature. Overall, by frequency sweeping the energy in the pre-focal region is leveraged, thus unwanted thermal damages are minimized. As a result, the total treatment time could be substantially reduced.

4.3.3 Experiment validation

To validate the proposed methods, a proof of concept experimental validation was performed. The setup of the experiment is shown in Figure 4-14, where a single element concave transducer (H101, Sonic Concept) with an aperture of 6 cm and focal length of 6 cm and working frequency of 1.15 MHz was placed in front of the BSA gel phantom to compare the pre-focal heating conditions under three different excitations (i.e. regular, upward and downward frequency sweeping). A water tank filled with degassed water was used to house the transducer and the phantom (see Figure 4-14). The air-backed concave transducer was used to generate the HIFU bursts used in the experiment. The pressure distribution of the transducer along the axial axis was evaluated by a numerical simulation using the method of [135]. It is noted that the distinctive side lobes presented in front of the main lobe and its amplitude and location changes accordingly with the frequency (see Figure 4-14b).

Before measuring the temperature rise in the phantom, the bandwidth of the transducer was first measured by a calibrated hydrophone. The frequency response curve of the transducer is shown in Figure 4-15, where the frequency sweeping was performed

from 1.0 MHz to 1.3 MHz and the constant frequency was set to 1.15 MHz equivalent. To reaffirm that the same acoustic power was delivered, the acoustic output power of the transducer with various excitations was measured by a Radiation Force Balance (RFB-2000, ONDA, Sunnyvale, CA), and a 30 W output power was retained for all the excitations by adjusting the input voltages from the function generator.

Finally, three excitations (i.e. single frequency, downward sweeping and upward sweeping) were delivered to the transducer with the same time protocol (15 s heating plus 15 s cooling and 15 s chirping time for chirp excitation). The temperature rises in the pre-focal region with three different excitations were studied. To ensure a fair comparison, the power output by these three excitations was first measured by acoustic balance, and all the three excitations were at the same acoustic output (around 30 W). Finally, a type J thermocouple (TJ36-ICSS-020G-6, Omega Engineering Inc., Stamford, CT) with a 0.15 cm diameter was inserted 2.5 cm deep into the phantom to measure the temperature elevation during the HIFU ablation. Four measurement spots located 0.5 cm, 1 cm, 1.5 cm, and 2 cm away from the transducer surface were measured. The thermal artifacts, such as the viscous artifacts and thermal conduction along the thermocouple, were not considered for the comparison. The results are shown in Figure 4-16 and Figure 4-17. Sweeping the frequency always has the lowest temperature rise while the regular constant frequency excitation always has the highest one. Downward chirping results in a slightly lower temperature rise, but the difference between frequency chirpings is not significant. Overall, the results show that sweeping the frequency upward or downward in the excitations significantly reduce the pre-focal heating.

Figure 4-14. (a) Setup of the experiment and (b) the simulated beam profile at three different excitations.

Figure 4-15. Frequency response curve of the H101 transducer, frequency sweeping was performed from 1.0 MHz to 1.3 MHz and the constant frequency was set to 1.15 MHz equivalent.

Figure 4-16. Temperature rise measured by a fine needle thermocouple at (a) 3.5 cm, (b) 3.0 cm, (c) 2.5 cm, and (d) 2.0 cm away from the transducer surface excited by different excitations.

Figure 4-17. Comparison of the maximum temperature rises measured by a fine needle thermocouple using three different excitations at the various distances away from the transducer surface from 0.5 cm to 2.0 cm.

Furthermore, the lesions in the gel phantom produced by the 15-s HIFU exposure at the focus using different excitation strategies were also measured (see Figure 4-18). Both the downward and upward frequency sweeping could produce larger lesions than that using the constant frequency excitation (24.8 ± 3.8 and 28.9 ± 2.9 mm² vs. 13.4 ± 1.3 mm² in the side view and 6.5 ± 0.3 mm² and 10.7 ± 2.3 mm² vs. 3.7 ± 0.6 mm² in the top view) with significant differences ($p < 0.05$). It suggests that the frequency sweeping would not compromise the ablation capability at the main lobe, but reduce the grating lobe.

Figure 4-18. (a) Representative photo of lesions in the BSA polyacrylamide gel phantom produced by 15-s HIFU exposure at the focus using different excitation strategies, and (b) comparison of the lesion area from the side view and top view. C: constant frequency chirp, D: downward frequency chirp, U: upward frequency chirp.

Finally, a 30-s HIFU exposure (PRF of 1 Hz, duty cycle of 90%, voltage of 0.3 V) was applied to the ex vivo porcine muscle sample, an obvious lesion was found by the constant frequency excitation. In comparison, using the upward frequency sweeping the

lesion was much smaller, and there was no lesion generated by downward frequency sweeping (see Figure 4-19).

Figure 4-19. Representative photo of lesions in the porcine muscle in the prefocal region of HIFU transducer by different frequency excitation strategies: constant frequency, downward and upward frequency sweeping every 2 s.

4.4 Discussion

Electronically steering the acoustic beam of a phased array transducer enables a fast shift of the focus and switch between different phases and amplitudes, allowing the phase correction of beam shape and distortion. However, the presence of large grating lobe and the resultant pre-focal heating limit its steering abilities. In this chapter, a simple yet effective method for pre-focal heating reduction and hence to improve its focal steering ability was presented and evaluated both numerically and experimentally. Pre-focal temperature elevation and thermal dose accumulation with different types of excitations were examined. Frequency sweeping has been shown to be effective for pre-focal heating reduction in both single shot sonication and multiple shots plane ablation. By comparing the temperature rise in the pre-focal region when sweeping the frequency in different directions and in different durations, it is preferable to sweep the frequency downward in a long time.

The previous study has shown that with electronically steering of the ultrasound beam using a 256-element phased array, a significant increase of thermal dose was deposited in the pre-focal field when compared with the same beam trajectory by the mechanical steering [136]. To some extent, pre-focal heating was alleviated by the means of frequency sweeping, but in contrast to mechanical steering, electronic steering in the HIFU ablation still shows a higher temperature rise (data not shown). Some other simulations show that the pre-focal heating cannot compete with the mechanical motion, the focal ablation volume by the frequency sweeping was also inferior due to the energy transferred to the pre-focal region.

Pre-focal heating relates to not only the methods of excitation but also the power input and the configuration of the phased array. Previous studies have shown that pre-focal heating linearly increases with the driving power and the steering distance. The design of a HIFU phased array transducer also greatly affects the pre-focal heating, as mentioned in the introduction part that the optimized design is capable of reducing the grating lobe and subsequently, the pre-focal heating. Reducing the element size and reducing the driving frequency are the most frequently utilized methods [120, 125]. These methods, however, are at the cost of comprising the performance at the focus, the complexity of the driving system for a large number of elements, and high power consumption.

Focus spacing and cooling intervals between two successive sonications play a crucial role in the safety of the HIFU ablation [124]. To enlarge the ablation volume, multiple foci synthesis is usually adopted, but it brings an even higher pre-focal heating due to the overlapping of the grating lobe from each single focus, thus requesting a longer delay or large focus spacing. Frequency sweeping for multiple foci sonication has not been examined, further studies are essentially needed to show its feasibility.

The current model assumes an idealized homogenous tissue. However, for extracorporeal HIFU treatment, ultrasound usually has to transmit through many highly heterogeneous tissue layers. Most significantly, when it passes through the bone or the ribs, a considerable attenuation or wave distortion would be experienced. Hence, more complicated models that considering the heterogeneity of the tissue are essential needed for the future development.

It has been mentioned in the previous part that the selection of the sonication trajectory was of great importance in pre-focal heating generation. The pre-focal heating with sonication steps close to each other has a higher pre-focal heating while the sonication step apart with each other has a reduced pre-focal heating. The trajectory currently used belongs to the former algorithms; therefore, a further pre-focal heating could be expected if an optimal sonication trajectory is used. Furthermore, the heating protocols used in this study have the fixed heating and cooling period. If the optimal heating and interpulse cooling as shown in [64] are used, a further comparison is needed.

The capability of frequency sweeping depends on not only the sweeping direction and sweeping time but also the frequency range employed. It is expected that a large frequency sweeping results in a significant reduction of the pre-focal heating because of a large spatial leveraging range on the temperature. However, the frequency range that could be swept was always limited by the bandwidth of the ultrasound transducer. The current frequency range was only 0.2 MHz (20% of the central frequency), seems to be practical and feasible. Transducer with large fractional bandwidth will further enhance the temperature reduction. Recent advances in the piezo-composite transducer technology have made it possible for the transducer working in a large fractional bandwidth, and dual-mode array (DMUA) with therapeutic and imaging capabilities has been reported [137].

Pre-focal heating for a single-element focused ultrasound transducer ablation was mainly associated with the beam overlapping in the process of the focus shifting when mechanically moving the transducer. However, in the case of electronically steering the beam of a phased array transducer, pre-focal heating is contributed not only by the beam overlapping but also the presence of the grating lobe or unwanted secondary maxima. As such, the pre-focal heating becomes worse. Slow frequency sweeping ablation in a stair-step manner, the grating lobe level itself, in fact, was not removed but rapidly shifted, spreading the heating in a large spatial region.

Currently, the frequency sampling intervals used for the sweeping is only 20 kHz, which is relatively large, comparing to the values used elsewhere [133]. The main reason for the large frequency sampling interval is the heavy computation burden. If a finer frequency sampling interval is employed, the computation time will be dramatically increased. The current computation time for each single plane ablation was around 30 hours. If the sampling interval is reduced to 10 kHz, the computation time will be around 4 days, making the computations practically intractable on the classical hardware.

Although the experimental study in the gel phantom and ex vivo tissue has shown that the frequency chirping excitation can reduce the pre-focal heating, parameter studies were not performed. Chirping time and the frequency range was only limited to 30 s and -3 dB bandwidth, and the other chirping time and frequency ranges have not been studied.

The gel phantom experiment further confirmed that the temperature rises in the pre-focal region by the frequency chirp excitations measured by a fine needle thermocouple were decreased by ~40% while the lesion areas at the main lobe were surprisingly increased by ~2 folds. The enlarged lesion size found here was attributed to the enhanced bubble activities at the focus. The effects of frequency chirp excitations to the lesion

formation and bubble cavitation at the focus will be investigated in more details and presented in the next chapter.

4.5 Conclusion

In this chapter, the feasibility to reduce the pre-focal heating by linear frequency sweeping was evaluated. Pre-focal heating could be considerably reduced using the chirping signals. Paramount parameters that influence the chirping signals have also been evaluated. It has been shown that long time and downward chirping shows a better result despite the small difference between the other chirping options. Additionally, the feasibility of ablation without cooling period has also been evaluated. It is possible to implement the HIFU ablation without cooling time using the chirping excitations. A simple preliminary experiment was conducted to further show the performance of the proposed method. The temperature rise in the pre-focal region using the frequency sweeping measured by a fine needle thermocouple was always the lowest regardless of its locations and chirp directions. Overall, the numerical and experimental results suggest that it is viable to reduce the pre-focal heating by a linear frequency sweeping modulation excitation.

Chapter 5 Enhancement of the bubble cavitation for high intensity focused ultrasound by frequency sweep

5.1 Introduction

Acoustic cavitation caused by the radiation of incident ultrasound wave plays an important role in the tissue heating in the hyperthermia applications [56]. With the presence of the cavitation bubbles, a great enhancement of heating rate could be accomplished, which is attributed to two basic bubble oscillations. Stable cavitation denotes the nonlinear volumetric and/or surface oscillation of the bubble, resulting in emissions of harmonics, subharmonics, and ultraharmonics. Inertial cavitation, characterized by broadband emissions, refers to violent bubble oscillation leading to bubble collapse. The stable bubble oscillation causes the high shear stress between the bubble and the surrounding medium, and the inertial bubble collapse produces the broadband noise emission [56]. A comparison of different types of cavitation activities served to the enhanced heating has suggested that the enhanced heating effect in the HIFU ablation was mainly from the inertial cavitation for the emission of the broadband noise which can be more readily absorbed. A temperature rise measurement with thermocouples embedded in an agar tissue-mimicking phantoms at the multiple positions adjacent to the HIFU focus shows that the temperature rise at low pressure corresponds well to the heating from the classical thermoviscous absorption. But above a certain threshold, the heating was significantly greater than that predicted by the classical model [138].

Although acoustic cavitation plays such a vital role in the tissue ablation, a significant technology barrier to the realization of bubble-assisted HIFU in clinics is the lack of preexisting bubble nucleation in the region of interest as bubble nucleation is a necessary precursor to cavitation activity. To generate sufficient cavitation *in vivo* with

high efficiency, several techniques have been employed. Both ultrasound contrast agents (UCAs) and nanoparticles have been frequently studied to deliver cavitation nuclei into the target region. With the presence of UCAs or nanoparticles, several to ten fold of necrosis volume enhancement could be achieved [139-141]. Injection of percutaneous ethanol to the focal region or concurrently applies the laser illumination during the HIFU is able to lower the inertial cavitation threshold [142-144]. Mixing two or more frequencies for excitation has also been shown to reduce the inertial cavitation threshold, hence improving the efficiency of the heating [145, 146]. A high power and short triggering pulse followed by the normal continuous wave was found to initiate and sustain the controlled levels of cavitation activity[147]. Like the triggered scheme, the use of two consecutive ultrasound waves at different frequencies, has also been reported to enhance the cavitation [148].

In this chapter, we present a new method to enhance the bubble cavitation. Instead of using multiple frequencies at the same time or consecutively, we linearly sweep the frequency in the excitation. This method is based on the following assumptions. Bubbles should experience the resonance before growing to the maximum size followed by collapse. Hence, if a large frequency range matches the resonant frequency of the bubble population with a wide size distribution, a greater number of bubbles could be collapsed to accomplish an enhanced acoustic response.

So far, the broadband frequency chirping technique has a wide range of applications. It has long been used to increase the signal-to-noise ratio (SNR) and penetration depth in the ultrasound image [126], to reduce the grating lobe level of a phased array [127, 128], to increase the sonoporation efficiency of targeted microbubble populations [149], and to suppress the standing wave formation in the transcranial therapy [131-133]. Some prior studies of bubble cavitation [130, 150] using a pseudorandom or a broadband chirping excitation have also been reported, but all these studies are performed

in water and examined the intensity of the sonochemiluminescence and none of them have been studied *in vivo* or *ex vivo*. The main difference between the current study and the previous one which also investigated the bubble activity in HIUF by short range frequency sweep [130] are as follows. First, this study was performed in the tissue or phantom, which makes the bubble behavior distinctively different due to the presence of viscosity and elasticity. Second, the power (~150 W) used in the current study was much higher compared to the 17 W used in [130], which makes it similar to the real clinical case. Furthermore, a wide range of parameters (e.g. frequency sweep range and sweep time) was investigated in this study.

In this chapter, lesion formation, bubble cavitation, and temperature rise under regular constant frequency and linear frequency chirping excitations were studied in the tissue mimicking material and excised porcine muscle. Numerical simulation was first performed to compare the acoustic distribution using different excitations. Paramount parameters of the frequency sweeping signal (e.g. sweeping directions, sweeping time, and the frequency sweeping range) were then examined. Lesion formation process was captured by a camcorder; bubble cavitation activity was monitored by passive cavitation detection (PCD) and temperature rise in the focal region was measured by a fine needle thermocouple. Data analysis of the cavitation signals were performed with various approaches.

5.2 Materials and Methods

5.2.1 Experiment system

The setup used in the experiment is shown in Figure 5-1, where an annular focused HIFU transducer (H-102, outer diameter = 69.94 mm, inner diameter = 22.0 mm, F = 62.64 mm, Sonic Concepts, Woodinville, WA) working at its third harmonic frequency, 3.3 MHz, was used in the investigation. The input signals produced by the function generator

were amplified by a power amplifier (BT00250-AlphaA, Tomco Technologies, Adelaide, Australia) before delivering to the matching unit and the HIFU transducer. Both the HIFU transducer and the sample (phantom or muscle) were immersed in the degassed and deionized water ($O_2 < 4 \text{ mg/L}$, $T = 25^\circ\text{C}$, measured by DO700, Extech Instrument, Waltham, MA) of a Lucite tank ($L \times W \times H = 70 \text{ cm} \times 50 \text{ cm} \times 30 \text{ cm}$). A silicone rubber acoustic absorber was put at the end of the testing tank to minimize the ultrasound reflection. A three-axis positioning stage (BiSlide, Velmex, Bloomfield, NY) was employed to align the HIFU focus to the desired position (i.e., 1 cm from the sample surface). A 0.5 mm diameter thermocouple (TCs) (TJ36-ICSS-020G-6, Omega Engineering Inc., Stamford, CT)) was inserted into the sample in the focal region and was aligned perpendicular to the HIFU transducer axis to measure the temperature rise in the process of ablation. The tip of the thermocouple was positioned 2 mm axially behind the HIFU focus to reduce the possibility of bubble nucleation and heat conduction on the thermocouple. A data acquisition (DAQ) unit (NI-9214, National Instruments, Austin, TX) at a sample rate of 2000 Hz was connected to the TCs, and the data obtained were then transferred to PC and processed in OriginPro (V9.1, Northampton, MA). Bubble detection was performed with a 15-MHz focused transducer (focal length = 19 mm; aperture = 6.4 mm; -6 dB focal width = 0.29mm; -6 dB bandwidth = 12–19 MHz, V313, Olympus-IMS, Waltham, MA) by aligning it confocal and coaxially to the HIFU transducer. Methods to align these two transducers in the desired position could be found in [151]. The PCD transducer served as a pure receiver, and the signals captured was directly collected by a digital oscilloscope (Wavesurfer MXs-B, LeCroy, Chestnut Ridge, NY) at a sampling frequency of 50 MHz and finally transferred to a personal computer (PC) for data analysis. A 100 W white-light bulb under the water tank provided the illumination source through the gel phantom for the photography. The lesion formation process in the transparent gel

phantom was recorded by a digital video camera (Vixia HF M500, Canon, Tokyo, Japan) at a frame rate of 50 Hz and shutter speed of 1/2000 s. A LabView program (National Instruments, Austin, TX) was written to control the pulse delivery and translational motion.

Figure 5-1. Schematic diagram of the experimental system. The HIFU transducer and passive cavitation detection (PCD) transducer were aligned confocally and coaxially.

5.2.2 Gel phantom and tissue preparation

The optically transparent polyacrylamide (PA) gel with a 7% of bovine serum albumin (BSA) was prepared to study the lesion formation process and the bubble activity. The transparent gel at high temperatures over 60°C becomes white due to the thermally denatured BSA proteins serving as indicators for the thermal outcome induced by the HIFU ablation. The phantom was prepared with the established protocol [152]. Briefly, the liquid mixture of PA, BAS, and the Tris-Buffer was degassed for about 1 h in a descant chamber (Sap 420100000, Scienceware, Pequannock, NJ) by a vacuum pump (VTE8, Thomas, Sheboygan, WI) at a pressure of 150 mbars, then the degassed mixture was poured into a custom mold (2.5 cm wide, 2.5 cm tall and 6 cm deep). The polymerization was then finalized by the addition of a 10% (w/v) ammonium persulfate solution (APS, Sigma-Aldrich Co., St. Louis, Missouri, USA) and N,N,N',N'-tetramethylethylene/diamine (TEMED, Sigma, Singapore).

Porcine muscles were purchased from a commercial food market and then cut into the same size as the mold container. The surfaces were carefully peeled to provide a smooth water–tissue interface. All tissue samples were first immersed in the distilled, deionized water and degassed for approximately 1h before the experiments.

5.2.3 Linear frequency sweep

To compare the effects of frequency sweep on the acoustic field, several driving methods were assessed. The driving frequency of sinusoidal wave either linearly increases or decrease with the time. Generally, the driving signals are given by

$$S(t) = A * \sin(2\pi\varphi(t) * t) \quad (5.1)$$

where $\varphi(t)$ is a time domain function that describes the frequency sweep parameter and defined as

$$\varphi(t) = f_0 \pm \frac{\Delta f}{\Delta t} * t \quad (5.2)$$

where f_0 is the start frequency, Δf is the frequency sweeping range and Δt is the sweeping time. The plus sign in the equation means sweeping upward, while the minus sign means sweeping downward. Furthermore, the value of $\Delta f/\Delta t$ defines the sweeping rate.

5.2.4 Sonication protocol

In the experiments with the gel phantoms and *ex vivo* porcine muscles, the samples were carefully aligned so that the focus of the HIFU transducer was 1 cm below the sample surface. Alignment of the focus was achieved by first setting the focus onto the sample surface and then manually moved 1 cm forward by the translational stage. To accurately put the focus on the sample surface, the time delay between the pulse and echo is set as the acoustic propagation time. To suppress the influence of the viscous heating on the bulk acoustic absorption, pulsed HIFU exposures (100 ms bursts, 10% duty cycle and 50 s duration) with an *in-situ* pressure ($p^+ = 36$ MPa, $p^- = -9$ MPa) large enough to exceed the

inertial cavitation threshold (-1.7 MPa) [151] was applied. In addition, to avoid the boiling bubble formation, the pulse length was set to 100ms. After each exposure, the HIFU focus was moved by 8 mm to another spot within the same sample. Each sample was used for six exposures.

Figure 5-2. The frequency response of the HIFU transducer measured by a calibrated hydrophone.

The frequency sweeping was performed within a small frequency range due to the limited bandwidth of the transducer (see Figure 5-2). Paramount parameters of the frequency sweep signal (e.g. sweeping directions, sweeping time, and the sweeping frequency range) are investigated. An equivalent exposure at the single frequency (3.3 MHz) was also performed for comparison. 3 ranges of frequency sweeping (i.e., 3.1 to 3.5 MHz, 3.15 to 3.45 MHz and 3.2 to 3.4 MHz), 3 different sweeping times (i.e., 1 ms, 10 ms, and 100 ms) and two sweeping directions (upward or downward) are involved in the parameter study. The sweeping time was fixed to 1ms in the study of frequency sweeping range while the frequency sweeping range was fixed to 3.1 to 3.5 MHz in the study of sweeping time. To reduce the influence of bubble concentration among the samples, the sonication follows a sequence of the upward, constant and downward manner in every sample. 5–10 spots were sonicated for each excitation scheme. During each single sonication period, the PCD data, temperature rise, and video recording were

simultaneously collected. The video recording and thermocouple measurement started 1 s before the sonication, while the PCD acquisition was synchronized with the pulse on time to capture the whole duration of 100 ms. Due to the migration of the lesion location, a thermocouple during the frequency chirping was aligned 3 mm in front of the focus.

5.2.5 Numerical Simulation

Numerical simulation with the frequency sweeping excitation was studied using the *k*-wave tool box which uses a pseudospectral finite difference time domain method to solve the coupled first-order acoustic wave equations on a finite difference grid [153]. The governing equations for this method are given by

$$\frac{\partial u}{\partial t} = -\frac{1}{\rho_0} \nabla p \quad (5.3)$$

$$\frac{\partial \rho}{\partial t} = -\rho_0 \cdot \nabla u - u \nabla \rho_0 \quad (5.4)$$

$$p = c_0^2 (\rho + d \cdot \nabla \rho_0 + \frac{B}{2A} \frac{\rho^2}{\rho_0} + L\rho) \quad (5.5)$$

where u , d , p , ρ_0 , and ρ is the particle velocity, particle displacement, pressure, ambient density, and acoustic density perturbation, respectively; c_0 is the speed of sound, B/A is the nonlinearity parameter, and L is the linear integro differential operator that accounts for acoustic absorption (α) that follows a frequency power law relation in the form $\alpha = \alpha_0 \omega^\gamma$. To simplify the simulation, a 2D computation domain with a 3296×4096 grid size and a 0.023 mm resolution was used. The grid size used can ensure the simulation of nonlinear propagation up to the sixth harmonics with at least two points per wavelength, which may be accurate for the transducer surface pressure of 400 kPa. The computation domain was divided into two sub-domains, water, and either tissue or phantom. The simulation considers both the nonlinear effect of wave propagation and the power law attenuation. Parameters used in the simulation are listed in Table 5-1, and the values are mainly from literature [110, 115, 154].

Table 5-1. Material properties used in the simulation

Material	water	phantom	tissue
Nonlinear coefficient (B/A)	5	5	7
Power of attenuation (y)	2	2	1
Attenuation coefficient (α_0 -dB/cm. MHz)	0.0022	0.15	0.54
Sound speed (c-m/s)	1500	1544	1570
Density (ρ -kg/m ³)	1000	1044	1080

A concave transducer with its dimensions described in the previous part was used in the simulation. The transducer was placed on the left side of the grid and driven by three different types of time varying signals. The frequency sweeping scheme is the same as the one described in the previous part, but only the case with 1ms sweep time and frequency sweep range of 3.1 to 3.5 MHz was investigated. The rest sweeping time of 10ms and 100 ms and frequency sweeping range of 0.3 MHz and 0.2 MHz were not examined due to its impractical computation burden on a normal computer. Time steps size was set to 10ns to ensure a convergent simulation. As the positive pressure of acoustic wave determines how violently the bubble collapses, and the negative pressure is responsible for the generation or nucleation of the cavitation bubbles, both the peak negative pressure and positive pressure were recorded in the simulation. All Simulations were carried out on a 64-bit PC (Precision WorkStation T7610, Dell, Austin, TX) with Intel(R) Xeon(R) CPU E5-2630 v2 2.60 GHz processors, 64 GB of RAM and a 6 GB GPU board (Tesla C2075, NVIDIA, Santa Clara, CA, USA).

5.2.6 Data analysis

Data obtained in the experiment were divided into three categories: the photograph of the lesion, PCD data, and the temperature rise. The video data acquired by the camera were first edited in Movie maker to remove the useless start-up clips, then the remained video was imported into the Free studio (V6.3) to convert the video into the images and extracted every 5 s. Finally, the 10 extracted images were processed by the ImageJ software (National Institutes of Health, Bethesda, MD, USA) to obtain the lesion area size.

In the ImageJ, the measurement was started by setting the scale according to a known distance. Colour compensation, image smoothing, and contrast enhancement were then conducted. The lesion boundary detection in the image was accomplished using the edge detection function. Photos taken at the end of each sonication were processed in the same way.

During a series of 100-ms HIFU exposures, bubble activity signals were acquired by the PCD transducer and processed using a custom-made program in the MatLab (MatLab 2016a, The MathWorks, Natick, MA, USA). Several methods to interpret the bubble signals were used. The most straightforward way of evaluating the overall bubble cavitation is to examine the root mean square (RMS) of the cavitation signal captured by the PCD, which directly reflects the total strength of the bubble cavitation activity [155]. Next, inertial cavitation and the stable cavitation were separately studied. To quantify the variation of inertial cavitation, three different ways were utilized. First, the small-time Fourier transforms (STFT) (2048-points, zero overlapping window) were applied to the collected PCD data in MATLAB [156]. A specific frequency window, 7.5–9 MHz, whose central value is the mean value of the second and third harmonic frequencies, was chosen to quantify the amount of inertial cavitation-induced broadband noise during the HIFU exposure. The temporal average frequency-average amplitude of the corresponding window was calculated as the inertial cavitation dose (ICD). The second method employed evaluate the RMS value of the PCD signal after filtering the harmonic, ultra-harmonic and super-harmonic content. The filtration was achieved by applying a 100-kHz notch-shaped comb filter to the PCD signal [157]. The last method was by converting the acquired signal into the frequency spectrum. The RMS amplitude in the frequency domain within a frequency window (from 7.5 to 9 MHz) was then used to quantify the intensity of ICD[158]. Stable cavitation dose was examined in two ways. The first method employed

was by the STFT method with the 200 kHz window encompassing the third harmonics. The second method is by the evaluation of the RMS values of the frequency spectrum around its third harmonics. A demonstration of the method used for the cavitation data analysis is shown in Figure 5-3.

Figure 5-3. PCD data for (a) regular, (b) downward and (c) upward excitations; and the corresponding spectrum over the sonication time ((d), (e), and (f), respectively) and STFT spectrograms ((g), (h), and (i), respectively) with the colour-bar representing the decibel(dB) value normalized to 1mv.

The temperature rise in the focal region was measured during the whole process of exposure, but due to the limited sampling frequency and the short burst time, the maximum temperature rise by the end of the heating period was not examined, only the temperature rise by the end of the cooling period was presented. Thermocouple artifacts were still not considered for the comparison. The sample size for all measurement ranges from 5 to 8,

and the highest and lowest value in the measured data were removed for a reliable statistical analysis.

5.3 Results

5.3.1 Simulation

Simulation results of the peak positive and negative pressure distribution in the gel phantom and tissue are shown in Figure 5-4 and Figure 5-5, respectively. It is found that there is no obvious difference in the pressure distribution among the excitations, suggesting that the difference of lesions between the regular and chirp excitations are mainly due to the different frequency responses to the bubble activities. Comparison of the axial and lateral beam profiles is shown in Figure 5-6, and details of the maximum peak positive and negative pressure are summarized in Table 5-2. It is found that sweeping the frequency downward and upward can slightly influence the peak positive and negative pressure. A downward sweeping lead to a slightly higher peak positive pressure and lower negative pressure while sweeping upward only leads to a slightly lower peak negative pressure.

Figure 5-4. Simulated (a) peak negative pressure and (b) peak positive pressure in the gel phantom driven by a regular (left), downward (middle) and downward (right) excitation. The colour-bar represents the pressure amplitude in MPa. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 3.1 to 3.5 MHz within 1ms.

The acoustic pressure at the transducer surface was fixed to 400 kPa (5.33 W/cm^2) and the absorption coefficient used is 0.15 Np/m/MHz^2 .

Figure 5-5. Simulated (a) peak negative pressure and (b) peak positive pressure in the tissue driven by a regular (left), downward (middle) and downward (right) excitation. The colour-bar represents the pressure amplitude in MPa. Frequency sweeping was achieved by linearly varying the instantaneous frequency from 3.1 to 3.5 MHz within 1ms. The acoustic pressure at the transducer surface was fixed to 400 kPa (5.33 W/cm^2) and the absorption coefficient used is 0.54 Np/m/MHz .

Figure 5-6. (a) is the axial and (b) is lateral pressure distribution in the gel phantom (left) and tissue (right). Data are directly obtained from Figure 5-4 and 5-5.

Table 5-2. Peak positive and negative pressure obtained in the simulation

Material	Peak positive pressure (MPa)			Peak negative pressure (MPa)		
	Regular	Downward	Upward	Regular	Downward	Upward
Gel Phantom	9.6686	10.3759	9.5453	-4.0331	-4.1735	-4.3527
Tissue	7.6863	8.1376	7.7101	-3.4344	-3.4910	-3.4824

5.3.2 Lesion size variation

5.3.2.1 Lesions in the gel phantom

The progressive lesion formation process and a photograph of the typical lesions profile created by various excitations are shown in Figure 5-7 and Figure 5-8, respectively. It could be seen that lesions produced by frequency sweeping excitations are clearly larger than those of regular excitation when the same exposure time and similar intensity was employed. But due to the enhanced cavitation, lesions created by frequency chirping were migrated towards the transducer (~3 mm). Bubbles play a significant role in the lesion formation since all lesions are tadpole shaped. At the beginning of the ablation, a cigar-shaped lesion was formed due to the absorption of the incident ultrasound wave; then an apparent tadpole-shaped lesion was observed after the 10th pulse. The quantitative lesion size (i.e. the side view and top view lesion area) created by different excitations with various frequency sweeping ranges and sweeping time is shown in Figure 5-9. Lesions generated by the downward and upward sweeping are both significantly larger than the regular one with no statistical difference between them ($p > 0.05$).

Figure 5-7. An illustration of the progressive lesion formation process created by downwards chirping excitation.

Figure 5-8. A photograph of the lesion profiles created by different excitations in the gel phantom (top view).

Figure 5-9. Comparison of the lesion size in the top view (left) and side view (right) created by different excitations with the various a) frequency sweeping ranges, b) sweeping time (* means $p < 0.05$, ** > 0.05).

Figure 5-10. The real-time lesion formation process (in the top view) with respect to the pulse sequence created by different excitations with the various (a) sweeping frequency ranges (from left to right: 0.4 MHz, 0.3 MHz, and 0.2 MHz) and (b) sweeping time (from left to right: 1 ms, 10 ms, and 100 ms).

A further comparison shows that as the frequency sweeping range decreased from 0.4 MHz to 0.2 MHz, the enlargement of the lesion size gradually dropped by 50.04%, 43.13%, and 35.08% in the top view and 49.13%, 46.21%, and 32.8% in the side view with the downward chirping. However, the corresponding enlargement by upward chirping is quite similar with the corresponding dropping of 44.60%, 35.43%, and 23.7% in the top view and 44.6%, 43.66%, and 23.22% in the side view, respectively. With the increase of the sweeping time, the lesion size enlargement only drops slightly in the side view. The lesion size enlargement for the sweeping time from 1ms to 100ms was 50.4%, 43.03%, and 37.80% in the top view and 49.13%, 46.40%, and 45.86% in the side view in downward chirping, while 44.6%, 36.69%, and 37.43% in the top view and 44.60%, 43.57%, and 45.11% in the side view in upward chirping. Comparing the improvement rate of the lesion size in the side view, it is found that frequency sweeping range has a higher impact on the lesion size. Overall, large frequency sweeping range and short sweeping time are favorable for the lesion enlargement. The lesion size variation with the progress of the exposure was also investigated. Due to the small lesion size at the beginning of the HIFU exposure, the lesion size comparison started from the 10th pulse. Data were processed in SPSS to determine the statistical difference. All data between frequency chirping (both upwards and downwards) excitations and a regular one show a significant difference ($p > 0.05$) but no significant difference between the upward sweeping and downward sweeping ($p < 0.05$). Unlike the linear growth of lesions size created by the regular excitation[159], the frequency sweeping excitation is a quadratic manner. Conventionally, to enlarge the lesion size a longer sonication time will usually be utilized [159], but the quadratically variation means that this method becomes inefficient when a pulse excitation was utilized. In summary, the frequency sweep can enhance the bubble cavitation and hence lead to a

larger lesion size. With a proper selection of frequency sweep range and sweep time, a 50% enlargement of lesion size could be achieved.

5.3.2.2 Lesions in the *ex vivo* tissue

The lesions produced in the porcine kidney samples after 1 min-HIFU ablation are shown in Figure 5-11, the frequency sweeping range and time was 0.4 MHz and 2 s, respectively. The lesion areas in the axial direction produced by the downward and upward frequency chirp excitations were significantly larger than that by the constant frequency excitation ($9.4 \pm 1.5 \text{ mm}^2$ and $9.0 \pm 1.0 \text{ mm}^2$ vs. $7.2 \pm 1.4 \text{ mm}^2$, $p < 0.05$). The porcine kidney samples were used in the *ex vivo* lesion comparison because of higher image contrast of tissue for easy boundary detection.

Figure 5-11. (a) Representative photos of lesions in the porcine kidney samples using the constant frequency, downward frequency chirp, and upward frequency chirp excitations

*after 1 min-HIFU exposure (from left to right), and (b) comparison of the lesion areas. *: statistical difference with the conventional exposure at the constant frequency excitation, $p < 0.05$.*

5.3.3 Bubble cavitation variation

To find the possible underlying reasons for the enlarged lesion size with the frequency chirping excitations, cavitation throughout the process of exposures were monitored by PCD. Due to a large amount of data involved, PCD signals were collected every 5 pulses.

5.3.3.1 Cavitation in the gel phantom

Bubble cavitation in the gel phantom captured by PCD is shown in Figure 5-12 to Figure 5-16. The RMS values were first analyzed. Large standard deviation caused by the variation of the bubble concentration among the samples was observed. As expected, the cavitation overall sustains for the whole procedure of exposure. Both frequency sweeping range and sweeping time have a significant influence on the cavitation. The difference of PCD signals gradually diminished as the frequency sweeping range reduced from 0.4 MHz to 0.2 MHz and the sweeping time increased from 1ms to 100ms. As the frequency sweeping range goes from 0.4 MHz to 0.3 MHz, a minor difference could be observed (2mV). But when it goes to 0.2 MHz, the three signals almost overlap. In the cases of the sweeping time, all show no significant difference except for the 1ms case. Overall, it suggests that short sweeping time and large frequency sweeping range favors strong bubble cavitation. Furthermore, the sweeping direction does not show a significant difference in the RMS value.

Figure 5-12. The RMS value of the cavitation signal in the gel phantom with the various (a) frequency sweeping ranges (from left to right: 0.4 MHz, 0.3 MHz, and 0.2 MHz) and (b) the sweeping time (from left to right: 1 ms, 10 ms, and 100 ms). The data points represent an average of 5 to 10 measurements.

The influence of the frequency ranges on the inertial bubble cavitation is shown in Figure 5-13, where the decibel values were with respect to 1mV. It could be found that all methods show that the regular excitation has the lowest inertial cavitation level. And the methods used to quantify the bubble cavitation correlate well with each other. The inertial cavitation with a 0.3MHz frequency sweeping range keeps a steady level in the process of exposure and has the smallest variation, but inertial cavitation induced by the downward excitations with the frequency sweeping range of 0.2 MHz surprisingly increases with the exposure time. And sweeping direction still shows no difference except for the 0.2 MHz case, where the downward sweeping shows a better result.

Figure 5-13. The inertial cavitation level with the progress of the exposure in the gel phantom evaluated by (a) STFT, (b) filtered RMS of the cavitation signal and (c) the RMS of the frequency spectrum from 7.5 to 9.0 MHz with a frequency sweeping range of 0.4 MHz, 0.3 MHz and 0.2 MHz (from left to right). The data points represent an average of 5 to 10 measurements.

Figure 5-14. The inertial cavitation level with the progress of the exposure in the gel phantom evaluated by (a) STFT, (b) Filtered RMS of the cavitation signal and (c) the RMS of the frequency spectrum from 7.5 to 9.0 MHz with the sweeping time of 1 ms, 10 ms and 100 ms (from left to right). The data points represent an average of 5 to 10 measurements.

The influence of the sweeping time on the inertial cavitation is presented in Figure 5-14. It is found that the regular excitation still has the lowest inertial cavitation level. But the difference becomes smaller with the increase of the sweeping time. For the sweeping time of 1ms and 10ms, the difference is around 2 dB but reduced to about 0.4 dB in the case of 100ms. And the downward sweeping at the sweeping time of 10ms shows a clear difference to the other excitations. But the sweeping direction shows no difference between them.

Figure 5-15. The stable cavitation level with the progress of the exposure in the gel phantom evaluated by (a) STFT and (b) the RMS of the frequency spectrum within the third harmonics with the frequency sweeping range of: 0.4 MHz, 0.3 MHz and 0.2 MHz (from left to right). The data points represent an average of 5 to 10 measurements.

Figure 5-16. The stable cavitation level with the progress of the exposure in the gel phantom evaluated by (a) STFT and (b) the RMS of the frequency spectrum within the third harmonics with the sweeping time of 1 ms, 10 ms and 100 ms (from left to right). The data points represent an average of 5 to 10 measurements.

Stable cavitation dose evaluated with respect to the sweep frequency range and sweep time are shown in Figure 5-15 and Figure 5-16, respectively. Regular constant frequency excitation still shows the lowest level. The STFT method shows that the reduction of the frequency sweep ranges does not have a significant influence on the stable cavitation dose as the differences among different frequency sweep ranges are all close to 4dB. The methods by RMS values of the third harmonics also show the same trend except for the 0.2 MHz case, in which some pulses are shifted downwards (e.g. the 10th, 45th, and 50th pulse). As for the sweep time, it is found that the regular constant frequency excitation has the lowest stable cavitation dose except for the case of 100ms evaluated by the RMS of the third harmonics. Stable cavitation still reduces as the increase of the sweep time. With a 100ms sweep time, the PCD signals almost show no difference among the excitations. Furthermore, a preference still cannot be made for the sweep direction, since upward and downward show very similar performance.

Overall, the sweeping time seems to play a more important role in the bubble cavitation since both inertial cavitation and stable cavitation increases with it. The

frequency sweeping range does not show a great impact on the bubble activity due to its small variations. A short sweeping time induces a strong bubble cavitation. Furthermore, methods used to evaluate the inertial cavitation correlate well with each other but differ in the stable cavitation.

5.3.3.2 Cavitation in the ex vivo tissue

The RMS values of the cavitation signal collected in the porcine muscle tissue are shown in Figure 5-17. Even though all samples were degassed for the same time to ensure the same bubble concentration, an even larger standard deviation was still retained due to the heterogeneous of the tissue. The RMS value of PCD signal using the chirping excitations are similar to the regular excitation except for the case of 0.4MHz and 1ms. Frequency sweeping in 0.3MHz downward even shows a lower value than the regular excitation. Furthermore, all cavitation signals slightly increase with the exposure time, which means the bubbles recover more quickly in the tissue than that in the gel phantom.

Figure 5-17. The RMS value of the cavitation signal in the exercised porcine muscle with the various (a) frequency sweeping ranges (from left to right: 0.4 MHz, 0.3 MHz and 0.2 MHz), and b) sweeping time (from left to right: 1 ms, 10 ms, and 100 ms). The data points represent an average of 5 to 10 measurements.

Figure 5-18. The inertial cavitation level with the progress of the exposure in the exercised porcine muscle evaluated by (a) STFT, (b) filtered RMS of the cavitation signal and c) the RMS of the frequency spectrum from 7.5 to 9.0 MHz with the frequency sweeping range of 0.4 MHz, 0.3 MHz and 0.2 MHz (from left to right). The data points represent an average of 5 to 10 measurements.

Figure 5-19. The inertial cavitation level with the progress of the exposure in the exercised porcine muscle evaluated by (a) STFT, (b) filtered RMS of the cavitation signal and c) the RMS of the frequency spectrum from 7.5 to 9.0 MHz with the sweeping time of 1 ms, 10 ms and 100 ms (from left to right). The data points represent an average of 5 to 10 measurements.

Inertial cavitation dose with the various frequency sweeping range and sweeping time are shown in Figure 5-18 and Figure 5-19, respectively. Unlike the case in the gel phantom, the difference between frequency sweeping excitation and regular excitation become smaller as the frequency sweeping range reduced. With a 0.3 MHz frequency sweeping range, a small difference could still be seen; but as the sweeping range drops to 0.2 MHz, the three signals show almost no difference among them. The RMS values from 7.5 MHz to 9 MHz differ with the other methods, particularly in the 0.3 MHz case, where the downward sweeping was clearly larger than the other two. A careful check of the data has found that one group of data by this method have much larger mean value and standard deviation than the others. In addition, the 0.2 MHz case by evaluating the RMS within 7.5-9 MHz has very small variations from the 10th pulse.

Figure 5-19 illustrates the influence of the sweeping time on the inertial cavitation. The variation of inertial cavitation is similar to the case in the gel phantom, but different from the influence of the frequency sweeping range. All methods show that the regular excitation has the lowest inertial cavitation level and the sweeping time has a minor impact on the inertial cavitation. The 10ms results by the STFT method shows the smallest difference (~ 1 dB) between regular excitation and sweeping ones. For most cases, the inertial cavitation still increases with the exposure time, and the results by evaluating the RMS values from 7.5 to 9.0 MHz still show very small variations for 10 ms and 100 ms cases.

Figure 5-20. The stable cavitation level with the progress of HIFU exposure in the exercised porcine muscle evaluated by (a) STFT and (b) the RMS of the frequency spectrum within the third harmonics with the frequency sweeping range of 0.4 MHz, 0.3 MHz and 0.2 MHz (from left to right). The data points represent an average of 5 to 10 measurements.

Figure 5-21. The stable cavitation level with the progress of HIFU exposure in the exercised porcine muscle evaluated by (a) STFT and (b) the RMS of the frequency spectrum within the third harmonics with the sweeping time of 1 ms, 10 ms and 100 ms (from left to right). The data points represent an average of 5 to 10 measurements.

Stable cavitation influenced by the frequency sweeping range and sweeping time is shown in Figure 5-20 and Figure 5-21, respectively. With the STFT method, the regular excitation all shows the lowest stable cavitation level. The impact of the frequency

sweeping range and sweeping time in the tissue is similar to that in the gel phantom. But the discrepancy between the regular excitation and the chirping ones has increased from 4dB to 6dB. Like the cases in the gel, the differences among the excitations become smaller and even diminished with the sweeping time increased from 1ms to 100ms. The method of evaluating the RMS around the third harmonics still cannot provide a clear difference except for the 1ms and 0.4 MHz case.

Overall, the RMS values of PCD signals are not a good way to evaluate the cavitation since they cannot reflect the role of different bubble cavitations in the HIFU ablation. In the tissue, frequency sweeping range plays a more important role than the sweeping time. The method of evaluating the RMS from 7.5 MHz to 9.0 MHz in the tissue does not correlate well with the other methods in both inertial and stable cavitation evaluation. The large frequency sweeping range and short sweeping time again are favorable for the cavitation. Sweeping direction still shows no difference

5.3.4 Temperature elevation

The temperature rises in the tissue and gel phantom throughout the process of the ablation by different excitations were measured. The results in the gel phantom and porcine muscles are shown in Figure 5-22 and Figure 5-23, respectively.

Figure 5-22. The temperature rise measured by the needle thermocouple in the gel phantom with the various (a) frequency sweeping ranges (from left to right: 0.4 MHz, 0.3 MHz, and 0.2 MHz) and (b) sweeping time (from left to right: 1 ms, 10 ms, and 100 ms).

Figure 5-23. The temperature rise measured by the needle thermocouple in the exercised porcine muscle with the various (a) frequency sweeping ranges (from left to right: 0.4 MHz, 0.3 MHz, and 0.2 MHz) and (b) the sweeping time (from left to right: 1 ms, 10 ms, and 100 ms).

Figure 5-24. Comparison of the maximum temperature rise in the a) gel phantom and b) the exercise porcine muscle with the various sweeping frequency ranges (left) and sweeping time (right).

The temperature rises by frequency sweeping excitations are higher in the both gel phantom and porcine muscle. Large variations of the temperature elevation may be due to the uncertainty of the thermocouple location. Upward and downward sweeping results still vary with the excitation conditions. The temperature rises in the tissue were lower compared with those in the gel phantom due to its higher attenuation. Furthermore, the temperature rises prone to be stabilized around the 20th pulse in the gel phantom but continuously grows in the tissue. A detailed comparison of the temperature rise by the end of the HIFU exposure is shown in Figure 5-24. The temperature rise shows a similar trend with the result of the lesions size and decreases with the reduced frequency sweeping range or the increased sweeping time. The regular excitation always has the lowest temperature rises.

5.4 Discussion

In this chapter, cavitation-enhanced ablation by the frequency sweeping excitations was verified experimentally. Lesion size created by the regular excitation (constant frequency) was compared with those by frequency sweeping. A maximum of 50% enlargement of the lesion area was obtained. The enlargement relies on the frequency sweeping range and the sweeping time. Reduction of the frequency sweeping range and increase of the sweeping time result in a reduced improvement. PCD and thermocouples were also utilized to monitor the ablation process in various excitations. It is found that both stable cavitation and inertial cavitation and the consequent temperature rise are higher when using a frequency sweeping excitation.

The simulation results have shown that the pressure distributions by the regular excitation and frequency sweeping ones are similar in both peak negative pressure and positive pressure. Heat simulation was not performed due to the difficulties in the calculation of the effective power deposition since both the intensity and the absorption vary with the driving frequency. A simplified model by using the RMS value of the pressure to calculate the intensity shows that the temperature rise in the focal point has a minor difference. Hence, we assume that the difference in the lesion size is attributed to the difference of bubble cavitation.

It has been shown in the experiment that both upward and downward sweeping can enhance the bubble cavitation. The mechanism for the enhancement may be explained as follows. It is well known that the thermal effect is more effective by high-frequency excitation while the mechanical effect is more predominant by low-frequency one. For downward sweeping, due to the high starting frequency, high temperature will be produced initially. The raised initial temperature makes the sample super-saturated with air, resulting in the air molecules dissolved in the sample become unstable. Furthermore, vapor pressure

and surface tension increases and decreases with the temperature, respectively. Therefore, the high initial temperature is beneficial for the cavitation since it can improve the probability of cavitation formation. In the case of the downward sweeping, the initial low-frequency driving makes the bubble more prone to collapse comparing to the constant equivalent one due to the enlarged bubble expansion as a result of the long duration of the rarefactional phase. Therefore, by upward chirping, there is also a high chance of bubble formation.

Currently, PCD has been used to monitor the cavitation variation in the process of ablation. Except for the case with short sweeping time and large frequency sweeping range, where a distinctive difference between the regular excitation and the chirping ones was observed, PCD signals in the other case does not show a reliable correlation with the lesion size variation. Even though the PCD data have shown that the regular excitation has the lowest stable and inertial cavitation levels, the variation of bubble signals captured by PCD does not agree with the variation of the lesion sizes, particularly in the case of a long sweeping time and small frequency sweeping range.

PCD has been extensively used to monitor the cavitation during the HIFU ablation, but it cannot provide the spatial information of the cavitation. The current PCD data only provide very limited information of cavitation along the axial direction, cavitation in the other directions is missed. To have a full view of the bubble cavitation, other cavitation monitoring methods are required. An example of such technique is the use of the 2D arrays detectors [160] or the Doppler bubble images [161].

Comparing the cavitation in the tissue with that in the gel phantom, inertial cavitation in the tissue has a closer correlation with the lesion formation, attributing to the reduced intensity because of the large attenuation of the acoustic wave. It's known that the low intensity is desirable for bubble-facilitated heating because cavitation-enhanced

heating is most effective at the temperature well below the boiling as the elevated vapor pressures serve to mitigate the violent collapse [162]. In the boiling regime, the bubbles are filled with vapor and quite large, and the dominant mechanism for the enhanced heating becomes the viscous boundary layer heating.

Although the temperature rises in the gel or tissue were measured, thermocouple artifacts (e.g. the effect of viscous heating, heat conduction along the thermocouple and the bubble shield) are not corrected for the comparison. By examining the temperature rise by the end of the cooling period, the viscous heating and the bubble shielding effect were minimized but the heat conduction along the thermocouple was maximized. Nevertheless, the major reason for the discrepancy between the temperature rise and the lesion size with the various frequency sweeping ranges and sweeping time is the position uncertainty of the ultrasound beam with respect to the thermocouple tip. Because of the narrow beam size, precise localization of the thermocouple is difficult. Therefore, a more sophisticated or accurate method to align the thermocouple to the target is needed for the future investigation.

5.5 Conclusion

In this chapter, frequency sweeping excitation has been shown to enhance the bubble cavitation in the process of HIFU ablation and hence lead to an enlarged lesion size. With a proper selection of the frequency sweeping range and sweeping time, a 50% enlargement of lesion size could be achieved. Both stable cavitation and inertial cavitation dose could be enhanced by the frequency chirpings. Temperature rise correlates well with the enhanced bubble cavitation, and higher temperature rises were obtained using the frequency sweeping excitations. The sweeping time and frequency sweeping range play different roles in the gel and tissue; sweeping time acts a more important role in the gel while the frequency sweeping range is more important in the tissue. The sweeping

direction does not make a significant difference in the cavitation enhancement. A short sweeping time and large frequency sweeping range can lead to a larger enhancement.

Chapter 6 Conclusion and Future work

High intensity focused ultrasound (HIFU) thermal ablation due to its non-invasive characteristics has been used more and more widely in clinics for the treatment of a variety of cancers. Compared with the other minimally invasive surgery techniques, treatment with HIFU is currently the only truly non-invasive one [63]. Therefore, it has become increasingly attractive, particularly in the cases that the tumors cannot be treated with open surgery.

Although HIFU therapy was promising and has got its popularity in recent years, the clinical adoption of this technique is still challenging largely owing to the relatively long procedure durations caused by the small lesion size at a single spot and long waiting time between two successive sonications. To address this issue, some fundamental studies toward improving the HIFU therapy performance by reducing its pre-focal heating and enlarging the focal lesion have been numerically and experimentally made.

Chapter 1 briefly introduced the background of HIUF technology. Its current clinical status, mechanisms, the role of the acoustic bubble in the tissue heating, methods for acoustic focusing, and the clinical challenges were discussed.

Chapter 2 introduced a nonlinear acoustic wave propagation modeling method applied to simulate the performance of a phased-array transducer in the multiple-layered media. The acoustic field and thermal patterns by different focusing strategies with its concern for the treatment safety and plannings were also compared and discussed.

Chapter 3 utilized the nonlinear modeling algorithm developed in Chapter 2 to evaluate the effect of electronically steering the beam of a phased array transducer. The important relationship between the grating lobe and the focus steering distance were evaluated. Safety concerns regarding the electronically beam steering were also studied.

Based on the discussion in Chapter 3, frequency sweeping excitation was proposed to address the pre-focal heating issue in Chapter 4. Both numerical simulation using the nonlinear algorithm proposed in Chapter 2 and experiment valuation using a single element transducer have been used to show the feasibility of the proposed methods.

Chapter 5 evaluated the frequency sweeping excitation enhanced bubble cavitation and temperature elevation. Both numerical simulation and *ex vivo* experimental study have been conducted. Various methods have been used to show the effectiveness of the bubble enhancement by frequency sweeping excitation. Parameters related to the chirping signals are also optimized.

The major contributions of this thesis are summarized as the follows.

1. A second order operator splitting algorithm was proposed and applied to the simulation of nonlinear HIFU wave propagation from arbitrary excitation geometry through multiple tissue layers with different focusing strategies in an accurate and efficient way.
2. Comparing different focusing strategies, it is shown that shifting and splitting the focus leads to a reduced acoustic pressure and lesion size. In addition, the pre-focal heating becomes worse. Compensation of power loss due to the focal shifting or splitting enables a HIFU phased array to generate a uniform lesion; however, it simultaneously increases the pre-focal heating.
3. The relationship between the focus steering distance and the grating lobe has been thoroughly studied by using the second order operator splitting scheme. It is found that the grating lobe and main lobe linearly decreases and increases with the axial steering distance, respectively. But the grating lobe rises much more rapidly than the decrease of the main lobe. The grating lobe level and location depend on the frequency and the steering distance. The grating lobe location always linearly moves away from the focus, and its amplitude linearly decreases with the frequency. Large steering range has a fast

increase of the grating lobe level. The lesion area and volume decrease quadratically with the steering distance. The maximum focal and near field temperature linearly decreases and increases with the steering distance, respectively, and the high-frequency results in a high temperature dropping in the focal region but increasing in the near field.

4. The -10 dB criterion to evaluate the safety of the steering ability is not accurate, and it is better to directly evaluate the thermal effect caused by the grating lobe.
5. To reduce the pre-focal heating due to the presence of the grating lobe, the frequency sweeping excitation was adopted. It is shown that the pre-focal heating could be considerably reduced using the chirp signals. Parameter optimization of the chirp signal shows that long sweeping time and downward sweeping in a large range are preferred. Additionally, it is possible to implement the HIFU ablation without the cooling time using the chirping excitations. A simple proof-of-concept experiment in the gel phantom using a single element transducer further verified the feasibility of the proposed method. The temperature rise in the pre-focal region by the frequency sweeping measured by a fine needle thermocouple was always the lowest regardless of its location and chirp direction. Overall, the numerical and experimental results suggest that it is viable to reduce the pre-focal heating through linear frequency sweeping.
6. Frequency sweeping excitation not only reduces the pre-focal heating but also enhances the bubble cavitation. It is shown that with a proper selection of frequency sweeping range and sweeping time, a 50% enlargement of lesion size could be achieved. Both stable cavitation and inertial cavitation could be enhanced by the frequency sweeping excitation. Temperature rise correlated well with the enhanced bubble cavitation since high-temperature rise could be obtained by the frequency sweeping excitation. The sweeping time and frequency range play a different role in the enhanced bubble

cavitation. A short sweeping time and large frequency sweeping range can lead to a better outcome.

7. The sweeping direction, both upward and downward, does not make a difference in the cavitation enhancement.

Suggestions for the future work are listed below

1. To avoid the computational complexity of directly solving the nonlinear acoustic equations in 3D, simplification is normally made. In particular, one-way or evolution-type models have been used in simulating the HIFU fields in the homogeneous media. However, the real living tissues have a complex structure with significant heterogeneity. The heterogeneity of the tissues causes the deformation in the wavefront. Finite difference time domain (FDTD) methods or full wave k -space method have been predominantly implemented to simulate the wave propagation in the heterogeneous tissue media [163, 164]. Although they are powerful techniques to deal with the heterogeneous tissues, they are seriously limited to the maximum size of the voxels and time steps for the bearable computation burden. The most efficient way currently adopted is the Hybrid Angular Spectrum Method [165] which has been shown to be rapid and robust. It can result in a decrease in the calculation time by more than two orders compared with the FDTD technique while giving essentially the same pressure pattern. However, it is currently limited to only the linear wave propagation. Extension of this model to include the nonlinear effect and develop a fast yet accurate method to model the nonlinear effect in the inhomogeneous medium can provide a better understanding of the physical interaction between the ultrasound wave and the biological tissue.
2. The proof of concept of experimental study has shown that the frequency sweeping excitation is able to reduce the pre-focal heating, but the measurement result is limited

to a single element transducer. Beam steering and multiple foci beam forming have not been performed in this study. Therefore, a better way to compare the effects of excitation signals on the pre-focal heating of a phased-array with various strategies and directly measuring the temperature rise in the pre-focal region are needed. However, because of the lack of availability of an ultrasound HIFU phased-array, a single-element transducer was adopted here to simply verify the concept. In the future, a real evaluation of an ultrasound HIFU phased-array is requested.

3. Selection of the sonication trajectory plays a significant role in the pre-focal heating generation. It has been shown that the pre-focal heating with sonication steps close to each other results in a higher pre-focal heating, but with sonication step set apart with each other a reduced pre-focal heating could be produced [124]. But even with an optimal scanning algorithm (i.e. square, random, and square spiral), a cooling time between two successive moving steps was still necessary at the late stage of ablation. The trajectory currently used in HIFU scanning in Chapter 3 belongs to the traditional algorithms that set the sonication steps close to each other. Therefore, a further pre-focal heating reduction could be expected if an optimal sonication trajectory was used and an ablation protocol that without cooling time could be expected as well.
4. The simulation of the acoustic field by various excitations has been shown to be similar in both peaks negative pressure and positive pressure. However, the direct heat stimulation was not performed due to the difficulties in the calculation of effective power disposition since both the intensity and the absorption vary with the frequency sweeping. An alternative way to verify this assumption is by keeping the *in-situ* pressure well below the inertial cavitation threshold, hence causing the heating in the process of the lesion formation dominated by the viscous absorption of the incident

wave. If lesion size obtained is similar, it means that the acoustic field by the various excitations is also similar.

5. The cavitation in the gel phantom and porcine tissue by monitoring PCD signals has been enhanced by the frequency sweeping excitation. Both stable and inertial bubble cavitation have been enhanced, but the underlying mechanisms and their contributions have not been identified. One potential solution is to simulate the dynamics of single bubble or bubble cloud with response to the regular excitation and the frequency sweeping excitation. In viscoelastic materials, both viscosity and elasticity can potentially alter the nature of cavitation dynamics. Viscosity and elasticity are the key parameters controlling cavitation dynamics in the biological tissues. The bubble dynamics (e.g. bubble motion, inertial cavitation threshold, the rectified diffusion) can be modeled using the Keller-Miksis equation coupled with a Kelvin–Voigt viscoelastic model. More importantly, parameters that governing the bubble dynamics under the frequency sweeping excitation could be optimized. The modified Keller-Miksis equation that includes the compressibility and viscoelasticity of the surrounding medium is given by [166]

$$\left(1 - \frac{\dot{R}}{c}\right)R\ddot{R} + \frac{3}{2}\left(1 - \frac{\dot{R}}{3c}\right)\dot{R}^2 = \left(1 + \frac{\dot{R}}{c}\right)\left[\frac{p_B - p_\infty(t)}{\rho} - \frac{4\mu\dot{R}}{R} - \frac{2S}{\rho R} - E_{NT}\right] + \frac{R}{\rho c} \frac{d}{dt}(p_a - p_\infty) \quad (6.1)$$

where c is the constant speed of sound in the medium, ρ is the medium density, S is the surface tension coefficient, and μ is the viscosity of the medium. Kelvin–Voigt approach whose stress consists of both viscous and elastic contributions is used to model the tissue viscoelasticity. For the large deformations during the bubble growth, a hyperelastic (Neo-Hookean) constitutive relation could be utilized to yield the elastic term [167].

$$E_{NT} = \frac{G}{2} \left[5 - 4 \left(\frac{R_0}{R} \right) - \left(\frac{R_0}{R} \right)^4 \right] \quad (6.2)$$

where R_0 is the initial bubble radius, and G is the linear shear modulus. The solution of the above equations could be easily performed in Matlab with the ODE function modules.

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