

Multi-functional Holographic Acoustic Lenses for Modulating Low- to High-Intensity Focused Ultrasound

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(ABSTRACT)

Focused ultrasound (FUS) is an emerging technology, and it plays an essential role in clinical and contactless acoustic energy transfer applications. These applications have critical criteria for the acoustic pressure level, the creation of complex pressure patterns, spatial management of the complicated acoustic field, and the degree of nonlinear waveform distortion at the focal areas, which have not been met to date. This dissertation focuses on introducing experimentally validated novel numerical approaches, optimization algorithms, and experimental techniques to fill existing knowledge gaps and enhance the functionality of holographic acoustic lenses (HALs) with an emphasis on applications related to biomedical-focused ultrasound and ultrasonic energy transfer. This dissertation also aims to investigate the dynamics of nonlinear acoustic beam shaping in engineered HALs. First, We will introduce 3D-printed metallic acoustic holographic mirrors for precise spatial manipulation of reflected ultrasonic waves. Optimization algorithms and experimental validations are presented for applications like contactless acoustic energy transfer. Furthermore, a portion of the present work focuses on designing holographic lenses in strongly heterogeneous media for ultrasound focusing and skull aberration compensation in transcranial-focused ultrasound. To this end, we collaborated with the Biomedical Engineering and Mechanics Department as well as Fralin Biomedical Research Institute to implement acoustic lenses in transcranial neuromodulation, targeting to improve the quality of life for patients with brain disease by

minimizing the treatment time and optimizing the ultrasonic energy into the region of interest. We will also delve into the nonlinear regime for High-Intensity Focused Ultrasound (HIFU) applications, this study is structured under three objectives: (1) establishing nonlinear acoustic-elastodynamics models to represent the dynamics of holographic lenses under low- to high-intensity acoustic fields; (2) validating and leveraging the resulting models for high-fidelity lens designs used in generating specified nonlinear ultrasonic fields of complex spatial distribution; (3) exploiting new physical phenomena in acoustic holography. The performed research in this dissertation yields experimentally proven mathematical frameworks for extending the functionality of holographic lenses, especially in transcranial-focused ultrasound and nonlinear wavefront shaping, advancing knowledge in the burgeoning field of the inverse issue of nonlinear acoustics, which has remained underdeveloped for many years.

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(GENERAL AUDIENCE ABSTRACT)

Ultrasonic waves are sound waves that have frequencies higher than the upper audible limit of human hearing. The versatility and non-invasive nature of ultrasonic waves make them a valuable tool in numerous scientific, medical, and industrial applications. In healthcare, ultrasonic waves are employed in diagnostic imaging techniques, such as ultrasound scans, to create images of internal body structures. Ultrasonic waves are also used for non-destructive testing (NDT) of materials, detecting flaws or cracks within structures without causing any damage. Furthermore, this technology finds applications in the field of material science for the manipulation of particles and in biomedical research for drug delivery systems. Focused ultrasound sound is an emerging non-invasive therapeutic modality that uses focused ultrasound waves to target tissue within the body without damaging the surrounding tissue. This technology allows for precise delivery of ultrasound energy to a specific region, where it can induce various desired therapeutic effects depending on the targeting location and parameters. Therapeutic focused ultrasound has the advantage of being non-invasive, reducing the risks and recovery time associated with traditional surgery. It can be precisely controlled and monitored in real-time with imaging techniques such as ultrasound or MRI, ensuring the targeted treatment of pathological tissues while sparing healthy ones. Applications of therapeutic are broad and include tumor ablation, facilitation of drug delivery across the blood-brain barrier, relief of chronic pain, and treatment of essential tremor and other neurological disorders. The domain of therapeutic focused ultrasound is continually

advancing, driven by research that seeks to extend its applications. Recent developments in acoustic engineering and 3D printing have led to the creation of acoustic holograms, or holographic acoustic lenses, which allow for more refined control over the spatial structure of the acoustic field. These technological advancements hold the promise of enhancing FUS by improving the accuracy of acoustic field localization and providing a more cost-effective solution compared to conventional systems like phased array transducers. However, the accuracy and applicability of existing models and techniques are constrained by assumptions, including the uniformity of the propagation medium and the linearity of the acoustic field, which limits the functionality and restricts the potential applications of acoustic holograms. In this dissertation, we present novel numerical techniques, algorithms, and proof-of-concept experiments to fill those knowledge gaps and expand the functionality of acoustic holograms in crucial applications.

Dedication

To my dear parents, Mohamed and Maha (Abu Em Mo'men), whose sacrifices laid the foundation for my and my brothers' character and success. Thank you for your support, selflessness, and love. To M'omen, my older brother, since our childhood, You blazed the trails, making each step easier for me to take. To Abdelrahman, my younger brother, of whom I am infinitely proud.

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Chapter 1

Introduction

Monolithic holographic acoustic lenses (HALs) or acoustic holograms is an emerging technology for precise and elaborate manipulation of acoustic fields. HALs enabled an unprecedented level of spatial control in the ultrasonic range using a single acoustic transducer [1–8]. Such a precise control wasn’t previously possible using more common techniques such as phased array transducers (PATs). The investigations in this dissertation focused on introducing and validating experimental, computational, and numerical techniques to improve and expand the functionality of HALs with a focus on applications related to ultrasonic energy transfer and biomedical focused ultrasound. A significant portion of the work is also dedicated to extending the capabilities of HALs to the nonlinear regime for high-intensity focused ultrasound (HIFU) applications by introducing novel physical insights and numerical methods. This chapter includes the background and motivation for the present work and finally concludes with the dissertation outline and an overview of each chapter.

1.1 Background and Motivation

Ultrasonic waves are a form of mechanical vibration beyond the range of human hearing and have long been harnessed for various applications in science and technology [9]. These waves, with frequencies above 20,000 Hertz, enable fascinating capabilities due to their unique properties and versatility, such as their ability to penetrate matter and generate detailed

images or induce unique effects. Recent advances in ultrasonic technology have opened up a plethora of novel research applications spanning a wide range of disciplines [9, 10].

Perhaps one of the most widely recognized applications of ultrasonic waves is in the field of medical imaging. Ultrasonic imaging, often referred to as ultrasound or sonography, has become a cornerstone of modern healthcare, enabling non-invasive visualization of the human body's internal structures [11]. The principles of ultrasonic imaging rely on the transmission and reception of high-frequency sound waves, which bounce off tissue interfaces and return as echoes. These echoes are then processed to generate detailed, real-time images that aid in the diagnosis and monitoring of various medical conditions. In addition to its prominent role in healthcare, ultrasonic imaging has found applications in industrial settings for non-destructive testing and flaw detection. By analyzing the reflected ultrasonic waves, engineers and inspectors can identify structural defects, measure material thickness, and ensure the integrity of critical components in different industries, including aerospace, manufacturing, and civil engineering [12].

Moreover, ongoing research has expanded the utility of ultrasonic waves in minimally invasive treatments, namely, focused ultrasound (FU) therapy [10, 13, 14]. This transformative therapeutic technology harnesses the precise delivery of focused ultrasonic waves to non-invasively target and ablate tumors, alleviate neurological disorders, and enhance drug delivery. One of the most significant advantages of FU is its non-invasive nature. FU does not require incisions or the insertion of instruments into the body, reducing the risk of complications, infection, and the need for extended recovery periods associated with traditional surgical procedures. The treatment parameters, such as intensity and duration, can also be tailored to each patient's specific needs, ensuring that the therapy is both effective and safe for individual cases. Medical professionals can also precisely control the location and depth of treatment, minimizing damage to healthy surrounding tissue.

Acoustic radiation force is a phenomenon that occurs when sound waves exert a force on objects in a fluid medium [15]. Through radiation force, ultrasonic waves can exert forces on particles at the microscale, which can be used to concentrate, separate, sort, or align specific particles within the fluid. This fundamental phenomenon drove research in areas such as acoustophoresis, where precise control of particle motion and assembly can lead to advancements in drug delivery systems, microfluidics, and materials science [16].

Contactless ultrasonic energy transfer leverages the piezoelectric effect to transmit energy through the propagating medium over short distances [17–19]. A piezoelectric transmitter converts electrical energy into ultrasonic waves, which carry the energy to a receiver equipped with another piezoelectric transducer. There, the incoming ultrasonic waves are converted back into electrical energy. This approach eliminates the need for physical connections and offers advantages such as powering devices in remote or hard-to-reach locations for various applications, including wireless charging of electronic devices, medical implants, and self-sustaining sensor networks.

Improved control over the spatial distribution of ultrasonic fields can greatly enhance the aforementioned applications and can open up opportunities for novel technologies. The recent advances in 3D printing and acoustic engineering technologies have given rise to the 3D-printed acoustic holographic lens [1, 8, 20, 21]. This remarkable innovation has enabled scientists and engineers to manipulate ultrasonic wavefronts in unprecedented resolution with an order of magnitude more degrees of freedom (DOF) than has been possible with conventional techniques, offering novel opportunities for diverse applications across various domains. By harnessing the power of computer-generated holography (CGH) and 3D printing, researchers can design and create robust and cost-effective intricate structures capable of shaping, focusing, and steering ultrasonic waves with remarkable precision using a single transducer. Such technology is currently driving new opportunities in fields like targeted

medical treatments [2, 22, 23], shaping sound fields for ultrasonic levitation [15] and manipulation of particles, and contactless ultrasonic energy transfer [3, 17].

HALs have been previously demonstrated for shaping transmitted low-intensity ultrasonic wavefronts through homogeneous mediums. The objective of this work is to enable and improve potential applications by extending and enhancing the functionality of HALs through the development of novel holographic algorithms, numerical methods, and experimental techniques. The majority of the research on HALs has been limited to modeling and proof-of-concept experiments in transmission mode. In this work, we will show lenses for manipulating reflected wavefronts. Furthermore, HALs have been investigated extensively for free propagation in homogeneous media. In this dissertation, we will address precise ultrasound patterning through strongly aberration layers with a focus on transcranial-focused ultrasound. Finally, in the realm of High-Intensity Focused Ultrasound (HIFU) therapy, we venture into the nonlinear regime, introducing effects such as harmonic generation and shock waves. Holograms can be engineered to modulate the acoustic pressure distribution, enabling the precise concentration of energy on therapeutic targets while concurrently mitigating the risk of collateral damage. The stretch towards nonlinear acoustic holography represents a significant paradigm shift in HALs. However, this shift into the nonlinear regime also brings forth a set of challenges. Calibration and validation of nonlinear holograms necessitate advanced modeling and experimental techniques due to the complexity of nonlinear acoustic interactions.

1.2 Outline of Research

This research broadly addresses two themes. Firstly, the manipulation of low-intensity ultrasonic fields in the linear regime (Chapters 2&3). Secondly, high-intensity focused ultrasound

that exhibits nonlinear behavior is considered (Chapters 4-6). The outcome of each chapter aims to enhance the functionality of HALs in different highly desired applications by filling knowledge gaps, introducing computational and numerical algorithms, and demonstrating novel proof-of-concept experimental techniques.

- **Chapter 2** introduces and experimentally validates the concept of 3D-printed metallic acoustic holographic mirrors for intricate spatial manipulation of reflected ultrasonic waves. This chapter includes the optimization algorithms implemented for designing the holographic mirror, namely the iterative angular spectrum algorithm. The proposed holographic mirror is investigated for intricate patterning and for constructing multi-focal areas for contactless acoustic energy transfer applications. Experimental results were compared with numerical models and COMSOL simulations. The errors due to mirror and transducer misalignments were also investigated.
- **Chapter 3** proposes new optimization algorithms for designing HALs for strongly heterogeneous propagation media and through aberrating layers, specifically for transcranial-focused ultrasound applications. In this work we designed HALs capable of transcranial focusing of ultrasound waves at desired volumes and locations while simultaneously compensating for the aberrations of the skull. Inspired by previous approaches in optics, an iterative acoustic volumetric holography algorithm is implemented. A non-convex gradient descent optimization algorithm is integrated with the modified mixed domain method to carry out iterative ultrasound forward and backward propagation simulations in strongly heterogeneous media. The proposed algorithm is more computationally efficient compared to previous methods, enabling iterative optimization schemes. In addition, the proposed algorithm implements custom weighing functions, which allows optimizing for preferred FU parameters, such as total coverage, uniformity, or leakage. This work concludes by validating the numerical approach with

hydrophone measurements of underwater experiments using a 3D-printed skull model.

- **Chapter 4** In this chapter, we numerically investigate the interplay of complex physics arising from the constructed complex holographic modulated ultrasound and the cumulative nonlinear distortion of the waveforms that emerge at high intensities. Currently, acoustic holograms are computed using linear propagation techniques and have only been demonstrated in the linear regime. As a result, a significant potential role for acoustic holograms has yet to be explored: creating precise and complex high-intensity focal regions. We show that the nonlinear waveform distortion leads to pronounced effects on the spatial structure of the sound field. In this chapter, we investigated the effect of nonlinearities on important acoustic parameters such as peak positive and peak negative pressures, acoustic intensity, and size of cavitation zones. The findings lay the groundwork for informed and educated utilization of HALs in high-intensity applications.
- **Chapter 5** Introduces a novel adaptive algorithm for simulating high-intensity ultrasound efficiently. Since nonlinear effects are highly localized, solving nonlinear simulations using uniform spatial and temporal is inefficient and quickly leads to large and computationally expensive simulations, especially in three-dimensional coordinates and around shock fronts. The proposed algorithm employs a monitoring function that tracks the harmonic content of the acoustic signal and adjusts the discretization parameters accordingly. We show how the adaptive algorithm leads to a 50-fold speed-up in simulation time compared to uniform mesh implementations. We also show that this algorithm can be applied for forward and backward nonlinear propagations, making it suitable for designing HALs in the nonlinear regime. We also demonstrate the algorithm for weakly heterogeneous media for nonlinear propagation in soft tissue, which is of great interest for medical applications.

- **Chapter 6** In this chapter, we numerically explore the utilization of HALs in the nonlinear regime. We propose that HALs could provide the opportunity for intricate spatial control of not just the fundamental field but also the higher harmonics. Iterative optimization and direct error minimization techniques are implemented for designing thickness profiles that can encode the phase information of a single or multiple harmonics. We numerically show amplitude patterning of multiple harmonics using a single acoustic lens. Such an approach could improve applications that utilize higher harmonics, such as harmonic imaging and acoustic communication.
- **Chapter 7** will summarize the findings and significant contributions of the research contained in this dissertation and provide suggestions for future directions.

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Chapter 2

Holographic mirrors for spatial ultrasound modulation in contactless acoustic energy transfer systems

2.1 Details of publication

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2.2 Abstract

This work introduces and investigates a flat acoustic mirror capable of efficiently manipulating wavefront and creating an arbitrary pressure pattern in a target plane using the sound reflection phenomenon. The mirror is a metallic holographic lens that performs as a spatial ultrasound modulator by introducing a relative phase shift to the reflected wavefront. The phase-shifting lens is designed using an iterative angular spectrum algorithm and 3D-printed

from powdered aluminum through direct metal laser melting. The lens’s capabilities to construct diffraction-limited complex pressure patterns underwater are tested numerically and experimentally. The proposed holographic mirror design can drive immense improvements in applications involving contactless acoustic energy transfer, which is investigated in this letter.

2.3 Introduction

The intricate acoustic wave manipulation and focusing have gained significant attention due to their broad applications in the fields of medical ultrasound [1–5], contactless acoustic energy transfer (AET) [6–10], nondestructive evaluation (NDE) [11, 12] and sensing. In the scope of reflected acoustic wave tailoring, acoustic metamaterials have shown significant capabilities to manipulate reflected waves such as wavefront transformation [13, 14], extraordinary sound reflection [15], and amplitude and phase modulation [16]. Using an ultrathin reflective metasurface based on locally resonant Helmholtz-like elements, Qi et al. [17] showed theoretically that a metasurface can confine acoustic intensity to about ten times the intensity of a free plane wave field. Similar acoustic focusing effects have also been realized by coiling up space [18] and by using labyrinthine units [19]. Still, most of these capabilities have been demonstrated for a range of frequencies between 1 – 17 kHz. Since metamaterials are made of labyrinths or arrays of unit cells of sub-wavelength size [20, 21], extending their implementation to the ultrasonic range is challenging and requires complicated fabrication techniques.

Recently, Prat-Campts et al. [22] introduced a manually reconfigurable reflective phase modulation device to manipulate ultrasonic waves. The reflective device consisted of a rectangular array of variable depth piston waveguides. One distinct advantage of such a device

is the real-time control over the sound field whereby the phase delay can be continuously modified because each piston can be separately controlled. The experiments were performed in air at an operating frequency of 40 kHz. We hypothesize that extending such a device to the MHz range can make it very complex and expensive. Also, electronically controlling each piston by an array of micro stepper motors or solenoid magnets adds more complications for underwater operation. Despite the intriguing features provided by artificially structured acoustical materials, the spatial control over the reflected wavefront in ultrasound frequencies and in water to generate arbitrary and elaborate wave fields, i.e. multifocal point beamforming, remains unexplored. In contrast, passive acoustic mirrors have been used to reflect and spatially focus sound waves. These mirrors are based on specific curved paraboloid or ellipsoid shapes that bend the sound beams for acoustic source localization [23, 24]. Melde et al. [25] demonstrated a 3D-printed lens for levitating fluid droplets and solid particles in the air. The lens was designed to generate a standing wave field with multiple transverse traps in a cavity geometry.

Using holographic techniques, we report on the theoretical design, numerical simulation, and experimental demonstration of a 3D-printed metallic Holographic Acoustic Mirror (HAM). For comparison purposes, 3D-printing of the metallic lens with a lateral resolution of $304\text{--}\mu\text{m}$ [26] can yield approximately 68000 acoustic pixels compared to the 1024 elements in the design of [22]. The higher pixel density enables finer wave manipulation up to 2.3 MHz (with a pixel size of $\lambda/2$, where λ is the wavelength). The HAM acts as spatial sound modulator. Because the phase shift imposed by the mirror is depending on the wavelength, the operation is narrow-band around the design frequency. As schematically shown in Fig. 2.1, the HAM reflects an acoustic wave generated by a cylindrical acoustic transducer located between itself and the target plane. The unique thickness map of the HAM introduces a phase shift distribution to the reflected wavefront that propagates downstream and generates the

desired pressure pattern at the target plane. The configuration, shown in Fig. 2.1, utilizes the reflected acoustic energy that would have been otherwise wasted. As such, higher power outputs can be achieved due to the more efficient and selective energy transfer, which is especially attractive for acoustic energy transfer and sensing applications.

2.4 Theoretical Analysis

The first step in designing the mirror is to determine the reflected complex pressure. Due to the difficulty of experimentally measuring the reflected pressure and evaluating errors at the mirror plane, we base the mirror design for under water implementation on simulations using COMSOL Multiphysics 5.4. The transmitter disc parameters used in the simulations were obtained from an experimental parameter identification based on electromechanical impedance and acoustic pressure measurement data [see Figs. A2 and A3, and disc parameters in the supplementary material]. These covered a broad range that included the resonant frequency at 780 kHz. The size of the transmitter disc was chosen based on the acoustic field aperture and resonant frequency of the disk. The simulation analysis was then carried out using the Acoustic-Piezoelectric interaction and Frequency Domain acoustic-electro-elastic multiphysics interface. The domains were meshed with tetrahedral elements with a maximum size of $\lambda/6$. A spherical radiation boundary condition was applied to the external boundaries. The reflected pressure was calculated using $p_{\text{ref}} = p_{\text{tot}} - p_{\text{inc}}$, where p_{inc} and p_{tot} are respectively the incident pressure generated by the piezoelectric disc and total pressure, both at the mirror plane. The simulation was first performed in the absence of the mirror to obtain the incident pressure that was also verified experimentally [see Fig. A4 in the supplementary material]. The mirror was then placed in the computational domain to obtain the total pressure. The simulated mirror had the following elastic properties: a modulus of

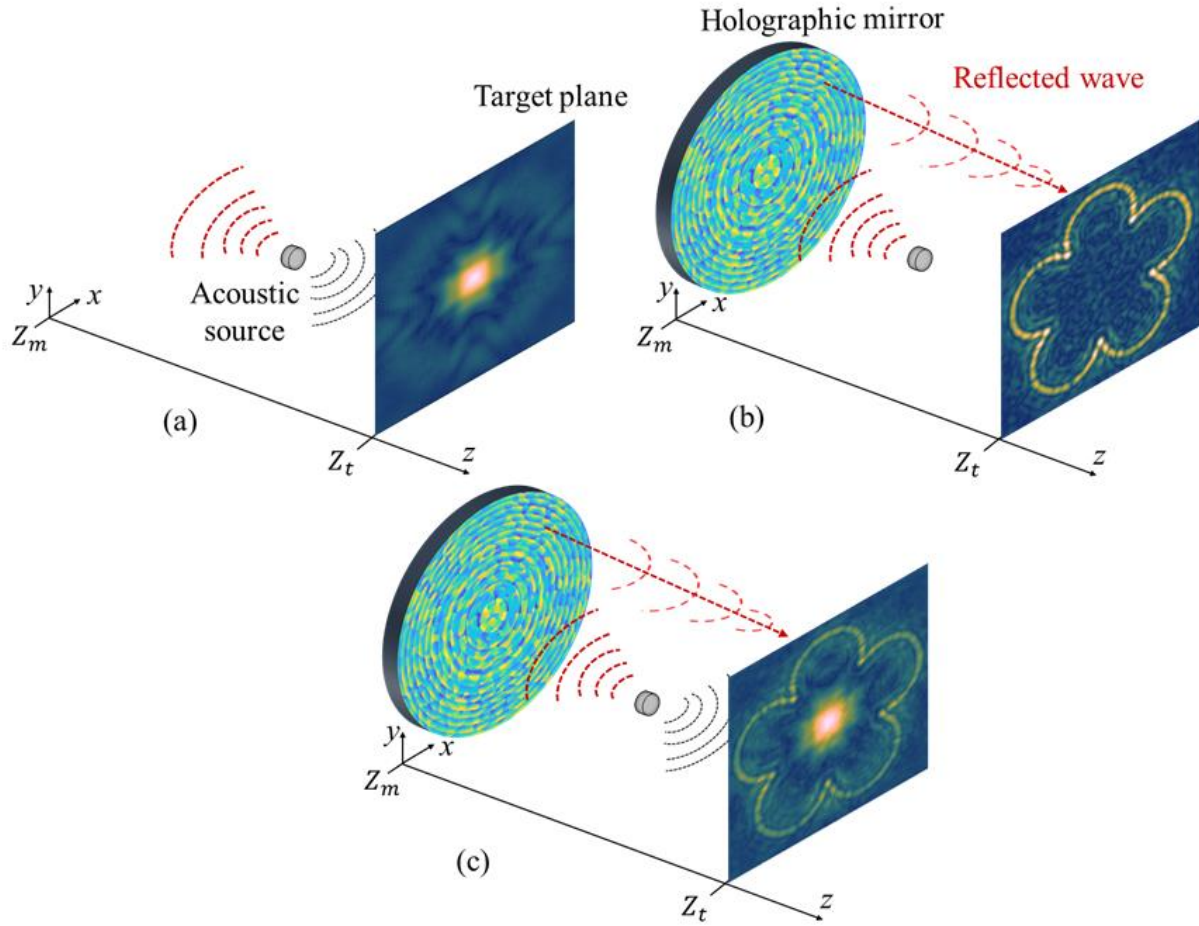


Figure 2.1: Schematic representation of acoustic pressure distribution in the target plane at $z = Z_t$, (a) when there is no holographic mirror, i.e. forwarded incident wave, and (b) in the presence of the reflective mirror at $z = Z_m$, i.e. guided reflective wave. The mirror reflects the incoming acoustic wave from the cylindrical acoustic source and modulates its phase to construct the desired pressure pattern (flower shape) at the target plane. (c) Total acoustic pressure i.e. forward and reflected fields at the target plane.

elasticity of 68.3 GPa, a density of 2.67 g/cm³ and Poisson's ratio of 0.35. Subtracting the two complex pressures resulted in the reflected pressure at the mirror plane, which was then used as an input to the iterative algorithm. The metallic holographic mirror was 3D-printed with powdered aluminum (AlSi10Mg) by Stratasys using direct metal laser melting (DMLM) with a theoretical printing resolution of 20 μm in the z-direction [26]. The material of the mirror was chosen to have high impedance mismatch with water to achieve efficient reflection. The printed mirrors are flat and disc-shaped with a diameter of 90 mm and a nominal thickness of 10 mm. After fabrication, the surface was treated with media blasting to get a smoother surface and consequently less diffusion in the reflected wavefront. The process provides a satin finish of approximately 2.5 – 6 μm Ra surface roughness [26] where Ra is the arithmetic average of the surface roughness profile [27]. For the present study, the typical surface roughness is much smaller than the wavelength and, as such, the scattering is comparable to that of a smooth surface [28, 29].

2.5 Results and Discussion

Two sets of experiments were performed to demonstrate the use of holographic mirrors. In the first set, the mirror, shown in Fig. 2.2(a), was designed to generate the flower-shaped pressure pattern presented in Fig. 2.1(b) in a target plane 70 mm away from the mirror in the z-direction at an operating frequency of 780 kHz. Since the acoustic field constructed by the mirror is diffraction-limited, the location of the target plane should be at a distance in which the minimum feature size of the pattern can be resolved. The corresponding thickness map for this mirror, as determined from the simulations and algorithm, is shown in Fig. 2.2(c). This pattern was chosen to demonstrate the capability of the reflective mirror in generating elaborate pressure fields. The mirror was illuminated by an acoustic field generated by a

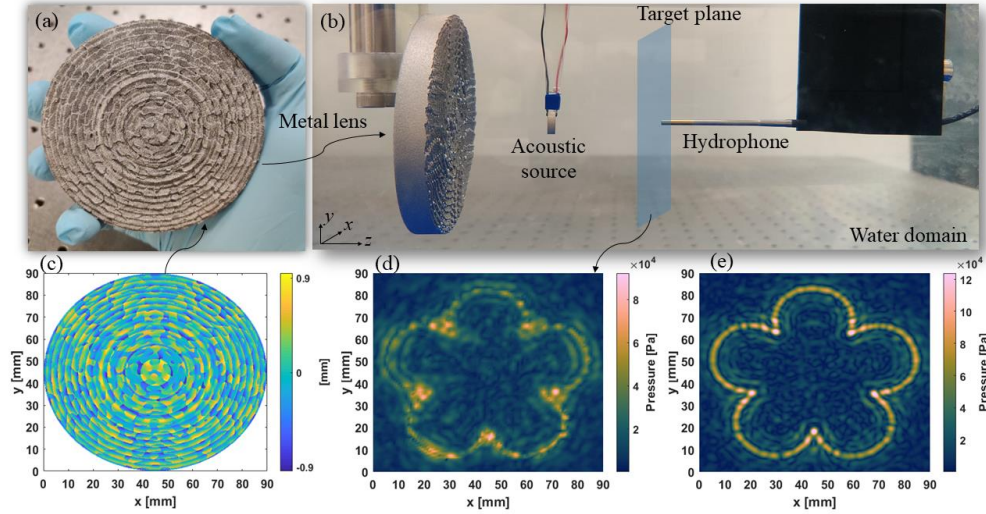


Figure 2.2: (a) Printed holographic acoustic mirror (lens), (b) the experimental setup with the printed mirror located at 35 mm from the acoustic source, hydrophone, and piezoelectric cylindrical acoustic source, and (c) the lens thickness map. (d) Experimentally measured pressure amplitude distribution at the target plane at 780 kHz. (e) Theoretical pressure amplitude distribution at the target plane. The target plane is located at a 70 mm distance from the mirror in the z -direction.

piezoelectric disc having a diameter of 9 mm and a thickness of 3 mm and placed 35 mm away from the mirror. The location of the mirror with respect to the source should be at the distance far enough to avoid the multiple reflections from the mirror and the cylindrical source surface that result in the formation of standing waves[7]. The disc was fixed by a 3D printed holder that was printed using VeroClear, a transparent photopolymer material. The transmitter was excited by a sinusoidal pulse signal (25 cycles) with an actuation amplitude of 103 V that is provided by a signal generator (Keysight 33500B) and an amplifier (Electronics & Innovation A075). The actuation amplitude was chosen in order to realize appreciable pressure amplitudes at the target plane.

The mirror and the acoustic transmitter were mounted in degassed and deionized water in a tank that was partially covered with Aptflex F28 acoustic absorbing sheets manufactured by Precision Acoustics Ltd. The pressure field on a specified target plane was mapped with the ONDA HNR-0500 needle hydrophone attached to a custom-built in-house 3D positioning

system, as shown in Fig. 2.2(b). The uncertainty in the sensitivity of the hydrophone (calibration factor) was defined within $\pm 1.5\text{dB}$ ($\approx 19\%$). A spatial sampling resolution of $\lambda/2$ was employed to avoid aliasing. The measured signal from the hydrophone was sampled and digitized by a Tektronix TBS2104 oscilloscope and averaged 64 times to increase the signal-to-noise ratio. To eliminate the effect of any DC bias and higher frequency noises, the signal was post-processed using MATLAB by performing an FFT on the time series. The amplitude and phase corresponding to the operating frequency were obtained. A MATLAB program was used to control the positioning system and triggering of the function generator. The obtained voltage amplitude was then converted into acoustic pressure according to the calibration factor provided by the manufacturer. To map the reflected pressure at the target plane without the interference of the incident wave generated from the other side of the transducer, we exploited the time delay caused by the difference in the propagation distances. The measurements were carried out when the reflected pulse was arriving at the target plane sufficiently long after the departure of the incident pulse.

Figure 2.2(d) shows the experimentally measured pressure amplitude distribution at the target plane. By comparing it with the theoretical prediction, shown in Fig. 2.2(e), we note that a good agreement is achieved in the general pattern of the target and that the locations of high-pressure points in the experiment match closely those in the theoretical prediction. The results also show that the experimental pressure pattern is not as clean as the theoretical prediction and that there is a difference of less than 25% in the pressure amplitude. These errors can be attributed to misalignments, uncertainties in hydrophone sensitivity, fabrication imperfections, and material inhomogeneities.

In the second set of experiments, we considered a pattern with four uniform focal areas defined by circles with a diameter of 15 mm, as shown in Fig. 2.3(a). The experimental setup with the printed mirror, hydrophone, and piezoelectric cylindrical acoustic source is

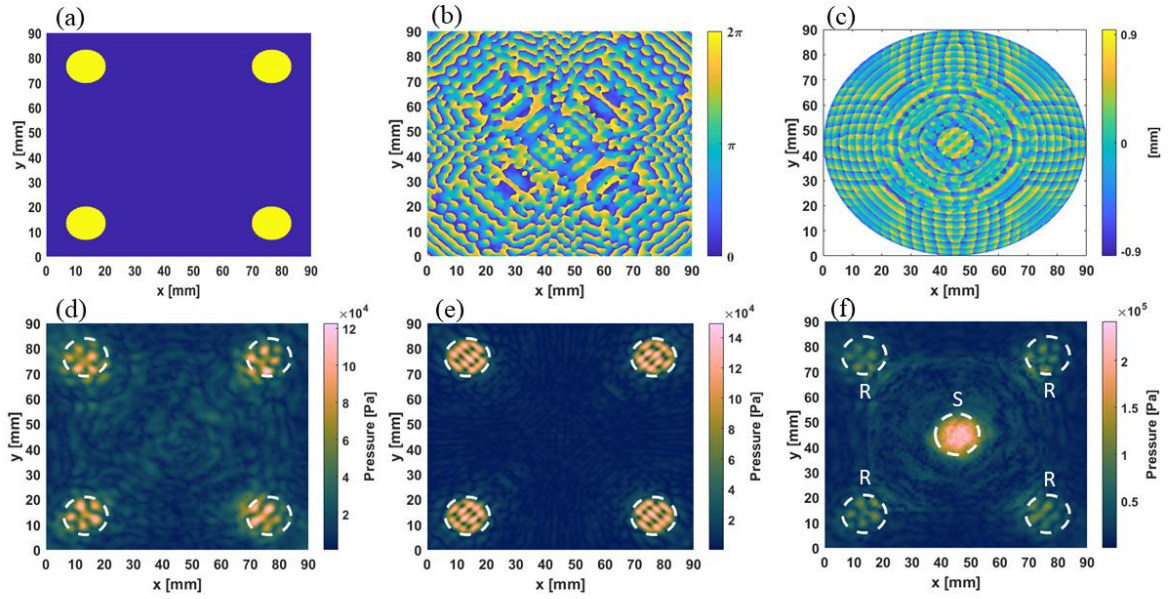


Figure 2.3: (a) The desired amplitude map at the target plane. (b) Calculated phase distribution at the mirror plane at 780 kHz. (c) The mirror thickness map. (d) Experimentally measured reflected pressure amplitude distribution at the target plane. (e) Theoretical pressure amplitude distribution at the target plane. The target plane is located at a 70 mm distance from the mirror in the z-direction. The dashed circles in (d) and (e) represent the desired locations of the receivers in the target plane which is of interest for the AET applications. (f) Experimentally measured total pressure amplitude (i.e. forward and reflected) fields at the target plane.

similar to the setup presented in Fig. 2.2(b). The corresponding phase distribution and thickness map of the holographic mirror are presented in Figs. 3(b) and 3(c), respectively. The experimentally measured and the theoretical prediction of the pressure pattern are shown in Fig. 2.3(d) and Fig. 2.3(e), respectively, which show a good agreement. Figure 2.3(f) shows total acoustic pressure i.e. forward and reflected fields at the target plane. The total pressure was experimentally obtained by sending long-pulsed signals and measuring the pressure when both the reflected and forward waves were present at the target plane.

To measure the overall reconstruction quality of the experimental results, we implement a metric equivalent to the diffraction efficiency in optics [30, 31]. The reconstruction efficiency is obtained by relating the experimentally measured acoustic power in the focal non-zero regions of the binary target pattern to the total acoustic power in the whole target plane. The plane-traveling wave is assumed in the calculations of the acoustic intensity and power. The acoustic intensity of each sampling point is calculated from the experimental pressure amplitudes as

$$I(x, y, Z_t) = \frac{p(x, y, Z_t)^2}{2\rho c} \quad (2.1)$$

while the acoustic power at the target plane, Π , is the summation of all intensities over the sampling points multiplied by their corresponding areas:

$$\Pi = A_s \sum I(x, y, Z_t) \quad (2.2)$$

Because the spatial sampling resolution Δd_s is constant along with the x and y coordinates (i.e. $\Delta d_s = \Delta x_s = \Delta y_s$), the sampling area is defined as $A_s = \Delta d_s^2$. Finally, the reconstruction efficiency is expressed as

$$\eta = \frac{\Pi_{focal}}{\Pi_{total}} = \frac{\sum p_{focal}^2(x, y, Z_t)}{\sum p^2(x, y, Z_t)} \quad (2.3)$$

where $p_{focal}(x, y, Z_t)$ and Π_{focal} are the acoustic pressure distribution and the acoustic power in the focal regions in the target plane, respectively, and Π_{total} is the total acoustic power in the target plane. The total acoustic power is due to the constructive and destructive interference between the forward and reflected pressure fields. The theoretical efficiency was calculated to be 61%, while the experimental efficiency is 34%. The results reveal that the experimental pattern did not align perfectly with the desired pattern. We attribute this inconsistency to the misalignments [see Fig. A5 in the supplementary material]. To quantify the errors and evaluate the sensitivity of the pressure at the target plane to misalignments, a set of numerical simulations was performed. The results show that lateral misalignments have a more significant effect on reconstruction efficiency compared to axial misalignments. The efficiency drops by 53% for a lateral shift of 2.25 mm and by 5% for the same shift in the axial direction. It is noteworthy to mention that relaxing the alignment criteria and considering a larger target area, e.g. extending the target circle radius by 75%, will increase the experimental reconstruction efficiency from 34% to 56% [see Fig. A6 in the supplementary material].

By localizing the acoustic energy to desired focal areas, efficient and selective power transfer can be achieved. For instance, the circles in Fig. 2.3(f) can be considered to represent locations of piezoelectric receivers operating in the 33-mode with the fundamental resonant frequency of 780 kHz and connected to an external load resistance. Shahab et al. [8] derived the coupled electro-elastic equations for fluid-loaded longitudinal vibrations of the receivers assuming linear piezoelectricity and neglecting elastic coupling and dissipative nonlinearities and showed that the electrical power-output response, E_{out} , is proportional to the input acoustic power on the receivers at the target plane, i.e. $E_{out} \propto \Pi_{focal}$ [See Eq. A7 in the supplementary material]. Using that analysis, employing the mirror in the AET setup leads to a 2860% increase in the power output for receivers R in Fig. 2.3(f) and 146% increase for

the total electrical power output in the target plane (receivers R and S). The focal acoustic power imposed on the receivers R and S are presented in Table 2.1. The ratio of electrical power output from the receivers, E_{out} , with HAM to the case of without HAM, is also presented.

Table 2.1: Focal acoustic power and electrical power output in AET

Without HAM Π_{focal} [W]	Receivers R	0.0066
	Receiver S	1.5944
With HAM Π_{focal} [W]	Receivers R	0.1890
	Receiver S	1.6011

E_{out} (with HAM)/ E_{out} (without HAM)		
Receivers R	Receiver S	All the receivers
28.6	1	1.46

2.6 Conclusions

We demonstrated the use of a 3D-printed metallic holographic acoustic mirror for the manipulation of reflected ultrasonic waves under water, generated by a single acoustic transmitter. Two different flat acoustic mirrors were designed using IASA, fabricated, and experimentally tested. The capabilities of the mirrors for spatial complex pressure patterning and multi-focal point wave focusing were evaluated. We envision that the mirroring concept has the potential to extend the realm of critical applications that employ acoustic manipulation of reflective waves. Notably, the ability to focus sound on multifocal areas with just a single acoustic source is desirable for AET-based wireless powering and communication in sensing networks. This configuration allows the utilization of both incident and reflected acoustic energy and increasing the total acoustic power available for receivers in AET systems. By compensating for the aberrations using phase conjugation and time-reversal techniques, wave patterning

through aberrating layers using acoustic holograms is possible and has been shown in medical applications[4, 3]. Another interesting concept is integrating this reflective mirror with the transmission acoustic holograms for phase and amplitude modulation [32]. If needed the forward wave can also be patterned by using a transmission hologram on the other side of the transmitter disc in conjunction with the reflective mirror. Thus, the reflected and forward wave can be patterned to different regions of interest achieving a very efficient AET system.

See the supplementary material for the summary of the IASA algorithm, experimental verification of the COMSOL simulations and further misalignment and error analysis.

2.7 Acknowledgment

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2.A

The algorithm starts by imposing two constraints, the reflected pressure amplitude at the mirror plane, shown in Fig. A1(a), and the desired amplitude pattern at the target plane, shown in Fig. A1(b). No constraints are imposed on the phase. The amplitude pattern is defined as a binary image where the values of ones and zeros represent the maximum

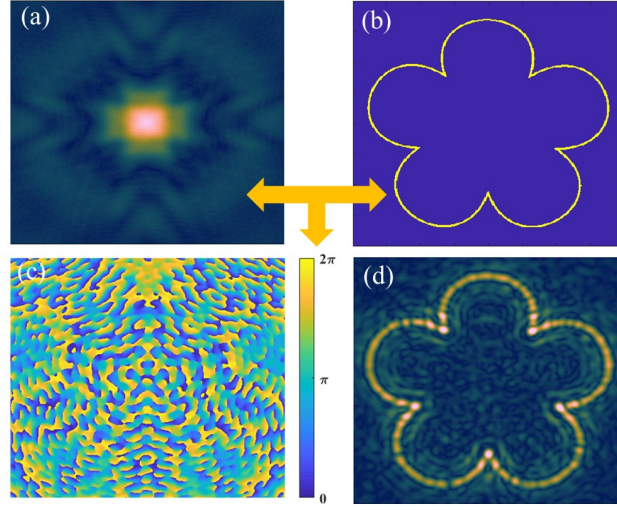


Figure 2.A.1: The scheme of generating phase distribution using IASA. (a) Reflected pressure amplitude at the mirror plane at $z = Z_m$. (b) Desired amplitude map at the target plane at $z = Z_t$. (c) Obtained phase distribution at the mirror plane. (d) Theoretical prediction of the pressure amplitude at the target plane. Multiple iterations of front and back propagations between (a) and (b) give the output as the (c) phase and (d) amplitude from the final step.

and minimum regions of the desired pressure, respectively. Multiple iterations of front and back propagations between the two planes, Fig. A1(a) and (b), are then carried out until a phase map, Fig. A1(c), that corresponds to a satisfactory pressure pattern, Fig. A1(d), is achieved.

Similar to the procedure investigated by Melde et al. [24], the pressure distribution is propagated from the mirror plane downstream to the target plane using

$$p(x, y, Z_t) = \text{IFT} \left[FT [p(x, y, Z_m)] e^{i(Z_t - Z_m) \sqrt{(k^2 - k_x^2 - k_y^2)}} \right]$$

and for backpropagation using

$$p(x, y, Z_m) = \text{IFT} \left[FT [p(x, y, Z_t)] e^{-i(Z_t - Z_m) \sqrt{(k^2 - k_x^2 - k_y^2)}} \right]$$

where FT and IFT are the Fourier transform and its inverse, respectively, i is the unit imaginary number and $p(x, y, z_m)$ and $p(x, y, z_t)$ are the pressure distributions at the mirror and target planes, respectively. Here, $k^2 = k_x^2 + k_y^2 + k_z^2$, where $k = \omega/c$ is the wavenumber, ω is the angular frequency and c is the speed of sound of the propagation medium. FIG. A1. The scheme of generating phase distribution using IASA. (a) Reflected pressure amplitude at the mirror plane at $z = Z_m$. (b) Desired amplitude map at the target plane at $z = Z_t$. (c) Obtained phase distribution at the mirror plane. (d) Theoretical prediction of the pressure amplitude at the target plane. Multiple iterations of front and back propagations between (a) and (b) give the output as the (c) phase and (d) amplitude from the final step.

The output of this iterative process is the phase distribution, as shown in Fig. A1(c), required to achieve the theoretical prediction of the pressure at the target image in Fig. A1(d). The obtained phase can be translated to the thickness map of the mirror using $t(x, y) = t_0 + \Delta\phi(x, y)/2k$ where $t(x, y)$ is the thickness map, t_0 is the initial thickness of the flat mirror and $\Delta\phi(x, y)$ is the phase change. The phase change represents the phase shift that is introduced to the initial phase distribution of the reflected pressure, which is calculated by $\Delta\phi(x, y) = \phi(x, y) - \phi_0(x, y)$ where $\phi_0(x, y)$ is the initial phase distribution of the reflected pressure and $\phi(x, y)$ is phase distribution obtained from IASA.

The steps for designing the holographic mirror are summarized in Fig. A1 and given here:

- (1) Propagate the reflected complex pressure from the mirror plane to the target plane.
- (2) Evaluate the quality of the propagated amplitude map at the target plane.
- (3) Impose the desired amplitude map while retaining the phase information.
- (4) Propagate the pressure back to the mirror plane and obtain the phase information.
- (5) Repeat steps (1) to (4) until a satisfactory result is achieved.

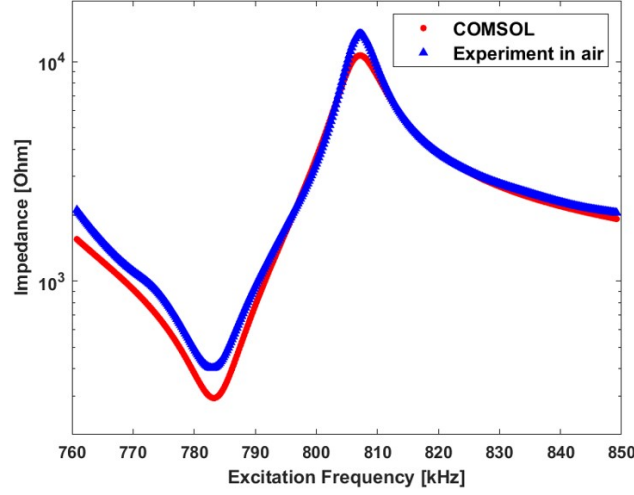


Figure 2.A.2: In-air electromechanical impedance frequency response function of the piezoelectric transmitter disk in free-free boundary conditions showing the agreement between experimental data and model (COMSOL) prediction.

(6) Compute the thickness map of the mirror.

Figure A2 shows the modeling and experimental impedance frequency response functions for inair actuation. The impedance measurement captures the resonance and anti-resonance, which are also called the short- and open-circuit resonance frequencies. The disk was coated with an electrically insulating to avoid electrical shorting under water. The impedance measurement and experimental identification were performed to capture the transmitter disk parameters used in the model simulations. The acoustic transmitter used in the experiments and modeling was a piezoelectric disk (APC #444) with a diameter of 9.5 mm and a thickness of 3.0 mm. The transmitter was modeled in COMOSL using the "Acoustic-Piezoelectric interaction, frequency domain" module with parameters of $\rho = 7800 \text{ kg/m}^3$, $\eta_s = 0.01$, $\epsilon_{33r} = 1000$, $C_{33}^E = 1.27 \times 10^{11} \text{ Pa}$, and $d_{33} = 20 \text{ C/m}^2$. Here, ρ is the mass density, η_s is the isotropic loss factor, ϵ_{33r} is the longitudinal relative permittivity, C_{33}^E is the longitudinal elasticity and d_{33} is the longitudinal

Figure A3 shows the normalized acoustic pressure measured by an ONDA HNR-0500 needle hydrophone attached to a custom-built in-house 3D positioning system. To identify the

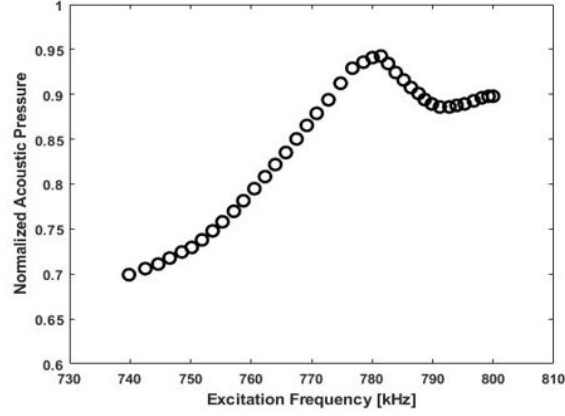


Figure 2.A.3: Normalized absolute pressure vs. frequency measured by the needle hydrophone to identify the fluid-loaded resonant frequency.

fluid loaded resonant frequency of the transmitter disk, we measured the sound pressure for different excitation frequency. The tests were conducted for a set of frequency values covering a broad range that is expected to include the resonant frequency at 780kHz. Figure A4 shows the simulation performed in the absence of the mirror to obtain the incident pressure. The results were verified with the experiment. The tests were conducted by an ONDA HNR-0500 needle hydrophone attached to a custom-built in-house 3D positioning system at 780

Figure A5 shows the normalized reconstruction efficiency vs. misalignment with respect to the origin ($x' = y' = z' = 0$ in Fig. 1). To quantify the errors and evaluate the sensitivity of the pressure at the target plane to misalignments, a set of numerical simulations were carried out. The mirror location was systematically moved with respect to the origin in the x, y, z and the $-z$ directions in steps of 0.45 mm as shown in the schematic illustration in Figure A5. The reconstruction efficiency was calculated in each step and then normalized by the efficiency at the origin where the mirror has zero misalignments. Misalignments in the x and y axes are equivalent due to the symmetry of the pattern and phase map. Figure A5 shows that lateral misalignments have more significant effect on the reconstruction efficiency

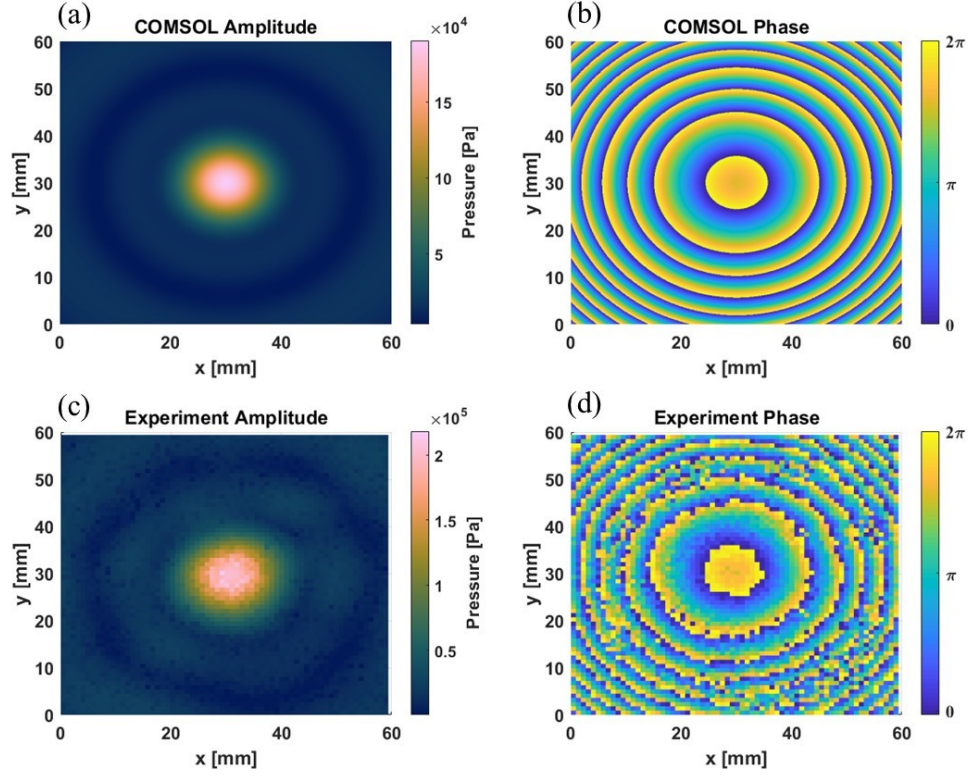


Figure 2.A.4: Pressure amplitude and phase obtained from the simulation (a and b) and experiment (c and d) performed in the absence of the mirror to obtain the incident pressure.

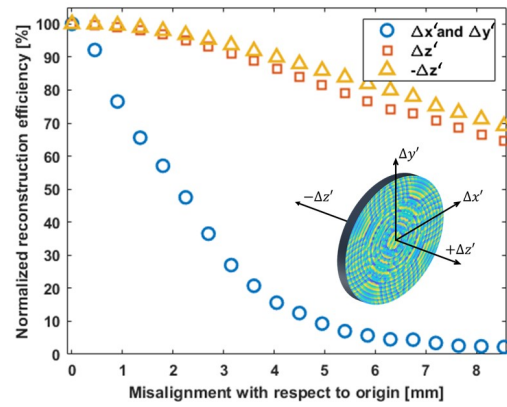


Figure 2.A.5: Normalized reconstruction efficiency vs. misalignment with respect to the origin ($x' = y' = z' = 0$) in Fig. (1).

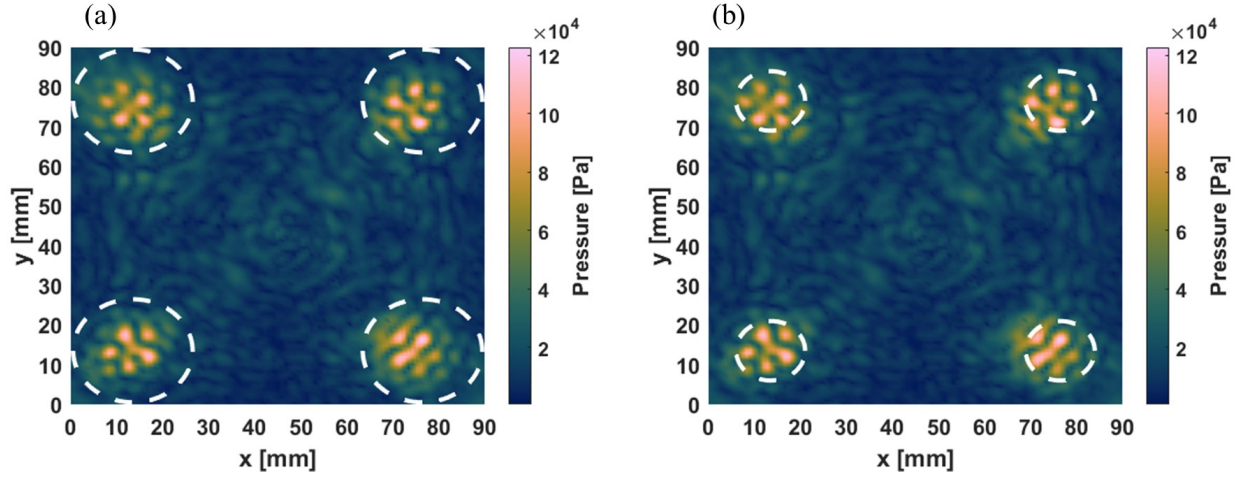


Figure 2.A.6: Experimentally measured reflected pressure amplitude distribution at the target plane. The dashed circles represent the extended desired locations of the receivers in the target plane.

compared to axial misalignments. The normalized efficiency drops to 47% for a lateral shift of 2.25 mm and to about 95% for the same shift but axially. It is also worth noting that we expect this geometry to be more sensitive to misalignments compared to the transmission holograms due to the distance the reflected wave has to travel. The longer the distance the more magnified the error would be due to the shift in projection at the mirror or target plane. Angular misalignment will result in a poor reconstruction efficiency as well as dislocation of the constructed image due to the changes in the propagation direction of the incident and reflection waves.

Fig. A6 shows relaxing the alignment criteria and considers a larger target area, for example extending the target circle radius by 75%. Then the experimental reconstruction efficiency is increased from 34% to 56% in the experiments.

In our theoretical study, the locations of piezoelectric receivers connected to an external load resistance are defined in Fig. 3(f). Following the theoretical modeling presented by Shahab et al. [33] and Bakhtiari-Nejad et al. [3], coupled electro-elastic equations for fluid-loaded

longitudinal vibrations of the receivers operating in the 33-mode of piezoelectricity with free-free boundary conditions are used and given here. In this model, linear piezoelectricity is assumed and elastic coupling and dissipative nonlinearities were neglected. The electrical power-output is given as [6, 8]

$$|E_{\text{out}}| = \prod_{\text{focal}} \left(\left(\frac{2\rho c}{AR_l} \right) \times \left| \frac{j\omega\kappa A [\varphi(0) - \beta\varphi(L)e^{-j\psi}] [\varphi(0) - \varphi(L)]}{[\{\{\omega_n^2 - \omega^2 + j\omega[2\zeta\omega_n + R_r(\varphi^2(0) + \varphi^2(L))\}](1/R_l(\omega) + j\omega C_p) + j\omega\kappa^2(\varphi(L) - \varphi(0))^2\}]} \right| \right)^2$$

Here E_{out} is electrical power output of the piezoelectric receiver, $\prod_{\text{focal}}$ is the total acoustic power on the receiver's area, ρ is the density of the propagation medium, c is the speed of sound of the propagation medium, ω is the excitation frequency, A is the cross-sectional area of the receiver, κ is the electromechanical coupling term in physical coordinates, β is the ratio of the acoustic pressure on the bottom surface to that on the top surface, ψ is the phase angle between the excitation forces at the top and bottom surfaces, ω_n is the natural frequency, and ζ is the strainrate damping ratio. The parameters C_p and R_l respectively represent the internal capacitance of the piezoelectric receivers and the external load resistance. Moreover, the dissipative term R_r is the resistive component of the fluid radiation impedance. Here φ is the mass-normalized eigenfunction, that is evaluated at the top surface $\varphi(0)$ and the bottom surface $\varphi(L)$ of the receiver and can be expressed as:

$$\begin{aligned} \varphi(\eta) &= \left[\cos(\alpha\eta/L) - \alpha \frac{m_r}{mL} \sin(\alpha\eta/L) \right] \times \\ &\left[\int_0^L m \left(\cos(\alpha\eta/L) - \alpha \frac{m_r}{mL} \sin(\alpha\eta/L) \right)^2 d\eta + m_r \left(\cos(\alpha) - \alpha \frac{m_r}{mL} \sin(\alpha) \right)^2 + m_r \right]^{-1/2} \end{aligned} \quad (2.4)$$

where the eigenvalue, α , of the fundamental mode is the first non-zero root of the transcendental equation $\left[\alpha^2 \left(\frac{m_r}{m_L}\right)^2 - 1\right] \sin \alpha - 2\alpha \frac{m_r}{m_L} \cos(\alpha) = 0$, where $m_r = X_r/\omega$ is the radiation mass, i.e., added mass, due to reactive component of fluid radiation impedance X_r [6].

From equation A3, it can be seen that the electrical power output is directly proportional to the acoustic power input, i.e., $E_{\text{out}} \propto \prod_{\text{focal}}$. By employing the acoustic mirror, the total pressure on receivers R increases and as a result, the total acoustic power increases by 2860%. Since the electrical power-output is directly proportional to acoustic power input, it is consequently increased by 2860%.

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Chapter 3

Volumetric holography for transcranial focused ultrasound

3.1 Details of publication

Co-authors: Ceren Cengiz, Mihir Pewekar, Eric Hoffmann, Wynn Legon, Eli Vlaisavljevich, and Shima Shahab.

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3.2 Abstract

Acoustic holographic lenses, also known as acoustic holograms, can change the phase of a transmitted wavefront in order to shape and construct complex ultrasound pressure fields, often for focusing the acoustic energy on a target region. These lenses have been proposed for transcranial focused ultrasound (tFUS) to create diffraction-limited focal zones that target specific brain regions while compensating for skull aberration. Holograms for tFUS are currently designed using time-reversal approaches in full-wave time-domain numerical simulations. However, such simulations need time-consuming computations, which severely limits

the adoption of iterative optimization strategies. Furthermore, in the time-reversal method, the number and distribution of virtual sources can significantly influence the final sound field. Because of the computational constraints, predicting these effects and determining the optimal arrangement is challenging. This study introduces an efficient method for designing acoustic holograms using a volumetric holographic technique to generate focused fields inside the skull. The proposed method combines a modified mixed-domain method for ultrasonic propagation with a gradient descent iterative optimization algorithm. This approach enables substantially faster holographic computation than previously reported techniques. The iterative process uses explicitly defined loss functions to bias the ultrasound field’s optimization parameters to specific desired characteristics, such as axial resolution, transversal resolution, coverage, and focal region uniformity, while eliminating the uncertainty associated with virtual sources in time-reversal techniques. Numerical studies are conducted on four brain structures: the anterior insula, hippocampus, caudate nucleus, and amygdala. The findings are further validated in underwater experiments with a realistic 3D-printed skull phantom.

3.3 Introduction

Transcranial focused ultrasound (tFUS) is a transformative technology that employs concentrated ultrasound energy to treat various neurological conditions. [1, 2]. Non-ionizing acoustic beams can penetrate through the skull and precisely target specific structures deep within the brain. The energy of the ultrasound beam elicits thermal and mechanical effects in brain tissue. Those effects are utilized for a variety of therapeutic treatments and procedures. At lower intensities, tFUS can accurately transmit energy to specific regions in the brain and induce local modulation of neural activity [3–6]. Furthermore, tFUS has been demonstrated to locally disrupt the blood-brain barrier (BBB) [7–10], allowing for improved

delivery of therapeutic drugs. High-intensity ultrasound is also leveraged in tFUS to treat various diseases and disorders [1], for which ultrasound energy can be used to thermally ablate diseased tissue [11], and high pressures can be used for histotripsy [12–14], in which targeted tissues are mechanically fractionated.

Focusing the ultrasound beam in tFUS is challenging due to the highly stiff skull. The high acoustic impedance, irregular geometry, and nonuniform thickness of the skull bones strongly scatter and attenuate the propagating ultrasound beam. This phenomenon is known as skull-induced aberrations [15, 16], and it causes severe defocusing and phase distortion of the beam, resulting in inefficient and out-of-target focusing. To address this issue, 3D-printed acoustic holographic lenses, known as acoustic holograms, have been recently proposed for tFUS and compensation of skull aberrations [17–23]. Acoustic holograms act like phase plates, modulating the phase of the wavefront with unique thickness maps. The thickness map enables the reconstruction of complicated acoustic fields with a desired spatial distribution of pressure or phase using a single-element acoustic transducer. These lenses have been shown to modulate reflected and transmitted wavefronts [24–27], forming multi-focal spots or arbitrary complex patterns for applications such as contactless ultrasound energy transfer [28], particle manipulation [27, 29], controlling cavitation zones [30], and hyperthermia [31]. These intricate modulation and manipulation capabilities make them ideal for tFUS applications. The acoustic lens compensates for skull aberrations and creates highly localized pressure fields that direct the ultrasound beam to specific brain areas within the skull. Acoustic holograms provide an order of magnitude higher resolution and acoustic pixel density than phased array transducers at a substantially lower cost and simpler fabrication procedure [27]. They have been tested successfully in bench-top setups using 3D-printed phantoms and ex-vivo human skulls [22, 23], as well as in-vivo mouse models [20, 21] for neuromodulation and BBB opening procedures.

Time-reversal numerical simulations and direct error minimization techniques are currently employed to generate an appropriate thickness map that accounts for skull aberrations and directs the ultrasonic field to the target structure in the brain. In the numerical domain, monopole virtual sources are introduced at the target regions of the skull. The ultrasound is then transmitted from the simulated sources to the hologram plane outside of the skull, where the acoustic signal is recorded. The extracted signal is subsequently processed to determine the phase and amplitude distributions in the hologram plane. The phase and amplitude information are then used to construct the lens thickness map. Ultrasound propagation in strongly heterogeneous media is often carried out using full-wave numerical simulations, namely the pseudospectral time-domain method implemented in the open-source software k-Wave [32]. However, full-wave numerical simulations are computationally expensive, lasting up to 20 hours when using CPU parallel processing [22]. The long computation time also prevents the use of iterative optimization techniques, which could help improve focusing quality and allow the implementation of explicitly specified loss functions to bias the ultrasound field's optimization parameters to specific desired characteristics, such as axial resolution, transversal resolution, coverage, and focal region uniformity. Furthermore, iterative algorithms take into account the transducer's experimental amplitude output, improving the accuracy of the thickness map and eliminating the need for error diffusion schemes. Acoustic holography is a technique that allows for the reconstruction of 3-D acoustic fields by projecting measured or simulated 2-D data from a measurement plane to the remainder of the volume [33]. Because of its computing efficiency, holography is used in iterative optimization techniques such as the Gerchberg-Saxton (GS) and iterative angular spectrum algorithms to compute and design the thickness map of holographic lenses [27, 29]. In those techniques, the wavefront is iteratively propagated forward and backward between the hologram and target planes until a satisfying boundary condition is obtained. However, such techniques are intended for freely propagating media and optimizing planar pressure patterns. This paper introduces

an analogous iterative optimization approach that takes into account strongly heterogeneous media and aberrating layers, including the effects of reflection, transmission, scattering, and attenuation. Furthermore, the proposed method optimizes for volumetric targets, such as directing sound to specific volumetric components in the brain. The modified mixed domain method (MMDM) [34–36] is used to simulate the forward and backward propagation inside the strongly heterogeneous media. In addition, a non-convex gradient descent optimization algorithm is used to find the optimal phase for targeting a specific volume. The proposed technique is substantially more efficient, allowing for the creation of a hologram in less than 50 minutes while also allowing for the explicit defining of loss functions. The proposed algorithm is evaluated numerically by considering four test cases that target different brain structures: the anterior insula, hippocampus, caudate nucleus, and amygdala. Each target resides at a different depth in the brain and has a distinct complex volume and geometric structure in 3D space. The holographic lenses obtained for each target are then 3D printed and tested in underwater trials and on a 3D-printed skull phantom.

3.4 Methods

3.4.1 Acoustic propagation

The MMDM [36, 34, 35] is implemented to execute computationally efficient forward and backward propagations through the strongly heterogeneous domain, which includes the skull and water. This methodology is based on the generalized Westervelt equation and can be thought of as an expanded form of the angular spectrum method. The acoustic field is calculated by marching in the spatial domain along the axis that is normal to the source plane.

Using the generalized Westervelt equation as a starting point:

$$\rho \nabla \cdot \left(\frac{1}{\rho} \nabla p \right) - \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} + \frac{\delta}{c^4} \frac{\partial^3 p}{\partial t^3} + \frac{\beta}{\rho c^4} \frac{\partial^2 p^2}{\partial t^2} = \gamma \frac{\partial p}{\partial t} \quad (3.1)$$

where p is the acoustic pressure, ρ is the ambient density, c is the speed of sound, δ is the sound diffusivity and β is the nonlinearity coefficient. The frequency-independent absorption term $\gamma \partial p / \partial t$ accounts for the absorption layer close to the computational boundaries. Applying the normalized wavefield $f = p / \sqrt{\rho}$, assuming homogeneous density, and performing the Fourier transform with respect to X , Y , and t yields:

$$\begin{aligned} \frac{\partial^2}{\partial Z^2} \tilde{P} + K^2 \tilde{P} = \\ F_{XY} \left\{ \left[-\frac{\omega^2}{c_0^2} \left(\frac{c_0^2}{c^2} - 1 \right) + \frac{i\delta\omega^3}{c^4} + i\omega\gamma \right] F_t(p) \right\} \\ + F_{XY} \left(\frac{\beta\omega^2}{\rho c^4} F_t(p^2) \right) \end{aligned} \quad (3.2)$$

where $\tilde{P}$ is the Fourier transform (FT) of p , F_{XY} is the FT operator in X - and Y -dimensions, F_t is the FT operator in the time domain, c_0 is the background sound speed and $K^2 = \omega^2/c_0^2 - k_X^2 - k_Y^2$, k_X and k_Y are the wavenumbers in X - and Y -dimensions, respectively. An implicit, one-way propagation can be derived from the 1-D Green's function in the form of an integral equation, such that

$$\tilde{P}(Z) = \tilde{P}(0)e^{iKZ} + \frac{e^{iKZ}}{2iK} \int_0^Z e^{-iKZ'} M(p(Z')) dZ' \quad (3.3)$$

where,

$$\begin{aligned}
 M(p) = & \\
 & F_{XY} \left\{ \left[-\frac{\omega^2}{c_0^2} \left(\frac{c_0^2}{c^2} - 1 \right) + \frac{i\delta\omega^3}{c^4} + i\omega\gamma \right] F_t(p) \right\} \\
 & + F_{XY} \left(\frac{\beta\omega^2}{\rho c^4} F_t(p^2) \right)
 \end{aligned} \tag{3.4}$$

Equation (5.3) is solved by using a Simpson-like rule.

The pressure distribution on the source plane or any arbitrary plane is reconstructed using the backward projection. By changing Z in (5.3) to $-Z$, the backward projection is obtained as:

$$\tilde{P}(-Z) = \tilde{P}(0)e^{-iKZ} - \frac{e^{-iKZ}}{2iK} \int_0^{-Z} e^{iKZ'} M(p(-Z')) dZ' \tag{3.5}$$

The Kramers-Kronig dispersion relation is applied directly by replacing the speed of sound c with c_p and $c_p = (1/\hat{c} + \alpha_0 \tan(\pi y/2)\omega^{y-1})^{-1}$, where $\hat{c}$ is the sound speed at zero frequency, y is the power-law exponent, α_0 is the absorption in nepers per megahertz^{-y} per meter and $\alpha_o = \alpha_{NP}\omega^{-y}$. Using this model, wave effects such as full-wave diffraction, attenuation, and dispersion are considered. However, this model is only accurate for weakly heterogeneous media [35, 34]. To have a more general model that could be applied to strongly heterogeneous media, phase correction and transmission compensation are introduced.

Assuming 1D propagation through an inhomogeneous media with a varied speed of sound distribution, the following phase correction term is added:

$$\begin{aligned}
 (P_{z+\Delta z})_{\text{corr}} = & (P_{z+\Delta z}) \\
 & + P_z e^{iK'\Delta z} \left(1 - e^{i(K-K')\Delta z} \frac{1 + \frac{M_z}{4iK}\Delta z}{1 - \frac{M_{z+\Delta z}}{4iK}\Delta z} \right)
 \end{aligned} \tag{3.6}$$

Where P_z is the wave pressure at z , $(P_{z+\Delta z})_{\text{corr}}$ is the phase corrected pressure, K' is the

wave number, and $K' = \omega/c_2$ with a frequency of ω .

Moreover, the original formulation does not take into account the transmission coefficient caused by variations in sound speed. In order to handle the density and speed of sound heterogeneities, amplitude correction is employed. The compensation term:

$$T(x, y, z) = \frac{2\rho(x, y, z + \Delta z)c(x, y, z + \Delta z)}{\rho(x, y, z)c(x, y, z) + \rho(x, y, z + \Delta z)c(x, y, z + \Delta z)} \quad (3.7)$$

where $c(x, y, z)$ and $\rho(x, y, z)$ are the speed of sound and density at plane z , respectively, and $c(x, y, z + \Delta z)$ and $\rho(x, y, z + \Delta z)$ are the speed of sound and density at plane $z + \Delta z$, respectively.

Finally, reflections are further added to the formulation by using the following equation:

$$P_{\text{reflection}} = P_{\text{incident}} (T - 1), \quad (3.8)$$

Here, P_{incident} is the incident wave used for calculating the reflected wave. The second-order reflection field is formed by propagating the resulting $P_{\text{reflection}}$ in the forward direction. This process is repeated until the intended maximum order of reflection is achieved. This makes it possible to model scattering from multilayer interfaces and distributed scattering events. Superposing each solution yields the final wave field.

3.4.2 Holograms computation

Computer-generated holography (CGH) can be implemented to construct desired 3D pressure patterns by altering the wavefront of a coherent acoustic beam [29]. CGH determines

the spatial phase and amplitude distribution of an incident wavefront, which, upon diffraction, forms the target volume. Computing the 2D phase mask that yields certain intensity patterns is generally a non-trivial and ill-posed task [37]. Most three-dimensional intensity patterns are not physically viable. The wave field must diffract through space in a way that is consistent with Helmholtz's equations and maintains intensity conservation at each depth plane. Furthermore, resolution is limited due to the finite numerical aperture (NA). The phase-only hologram constraint also compounds these limitations further. As a result, any required 3D pressure pattern cannot be precisely reproduced. The optimal thickness map is determined by optimizing the output acoustic field under experimental limitations such as incident beam profile, source NA, and wave shaping modality. Following prior efforts in acoustics and optics, we use a gradient descent optimization approach in the present investigation [37, 29].

The defined loss function greatly influences the outcomes of 3D CGH, where there is no exact solution but numerous approximate solutions. Our algorithm searches for optimal holograms using custom cost functions that users can select to best suit a certain application. The optimization aims to obtain a phase distribution ϕ at the hologram plane that minimizes a specified error function $L[P_{3D}(\phi), T]$ between the generated acoustic field $P_{3D}(\phi)$ in the volumetric domain and the volumetric target pattern T , with the constraint that the pressure amplitude at the transducer plane must always equal to the experimental pressure $|p_0| = A_0$. The numerical solution of this optimization problem necessitates calculating the gradient of the loss function with respect to the decision variables. By implementing Wirtinger subdifferential calculus and following the derivation in [29], the gradient of the loss function L is calculated as:

$$\nabla_p L = 2A^* \left(\frac{A\mathbf{p}}{|A\mathbf{p}|} \circ \nabla_x \ell(\mathbf{x}, \mathbf{T}) \Big|_{x=|A\mathbf{p}|} \right) \quad (3.9)$$

Here A is a linear parameter representing the propagation of the acoustic field at the transducer plane to the rest of the volume, such that $A\mathbf{p} = P_{3D}$. Correspondingly, A^* represents the inverse propagation from each plane in the volume to the transducer plane such that $A^*P_{3D} = \mathbf{p}$. Note that the propagation is implemented using the MMDM. Here $\circ$ denotes the element-wise product. Assuming square loss

$$L(\mathbf{x}, \mathbf{T}) = \frac{1}{2} \sum_{i=1}^{n_x} \sum_{j=1}^{n_y} (x_{ij} - T_{ij})^2 \quad (3.10)$$

Substituting equation (10) into (9) yields:

$$\nabla_p L = 2A^* \left(A\mathbf{p} - \mathbf{g} \circ \frac{A\mathbf{p}}{|A\mathbf{p}|} \right) \quad (3.11)$$

Thus the iterative gradient descent algorithm update rule becomes

$$p^{k+1} = \mathcal{P}_U \left[A^* \left(\mathbf{T} \circ \frac{A\mathbf{p}^k}{|A\mathbf{p}^k|} \right) \right] \quad (3.12)$$

where $\mathcal{P}_U(\mathbf{p}) := \mathbf{u} \circ \mathbf{p}/|\mathbf{p}|$ is the Euclidean projection onto the constrain set U .

This algorithm is analogous to the GS algorithm and follows similar steps. However, with the aid of the MMDM, this algorithm correctly takes into account the heterogeneity of the media and uses adaptive step sizes with the aid of the Armijo line-search parameters β and σ as shown in Algorithm 1 below following [29]. In words, the algorithm's steps are as follows: (1) propagate the pressure from the transducer plane to the rest of the volume, (2) calculate the gradient of the loss function and back propagate each plane in the volume back to the hologram plane and obtain the new phase distribution at the transducer plane, (3) impose the new phase distribution and the initial transducer amplitude at the transducer plane, and

(4) repeat steps 1-3 until the desired convergence criterion is met.

The algorithm output provides a phase map for the holographic element, which we translate it into a surface map for fabrication. The resulting thickness map is then calculated as[27]: The holographic plate starts with an initial thickness T_0 . Removing material at pixel position (X, Y) causes a relative phase change

$$\Delta\phi(X, Y) = (k_m - k_h) \Delta T(X, Y)$$

Where $T(X, Y) = T_0 - \Delta T(X, Y)$ is the thickness of the pixel positioned at coordinates (X, Y) in the hologram plane and k_h, k_m are the wave numbers in the hologram plate and its surrounding medium, respectively.

Algorithm 1 Gradient descent with line search for computer-generated volumetric holography

Result: Phase pattern $\phi = \arg(p)$
Initial field configuration $p = p_0$;
Initial stepsize $\tau = 1.0$;
Armijo line-search parameters $\beta = 0.5, \sigma = 0.1$;
while not converged **do**
 $\partial p = 2A^* \left(\frac{Ap}{|Ap|} \circ \nabla_x \ell(x, T) \Big|_{x=|Ap|} \right)$
 $p_{\text{new}} = \mathcal{P}_U(p - \tau \partial p)$
 while $\ell(p_{\text{new}}) > \ell(p) - \sigma \frac{\tau}{2} \|\partial p\|^2$ **do**
 $\tau = \beta \tau$
 $p_{\text{new}} = \mathcal{P}_U(p - \tau \partial p)$
 end while
 $p = p_{\text{new}}$
end while

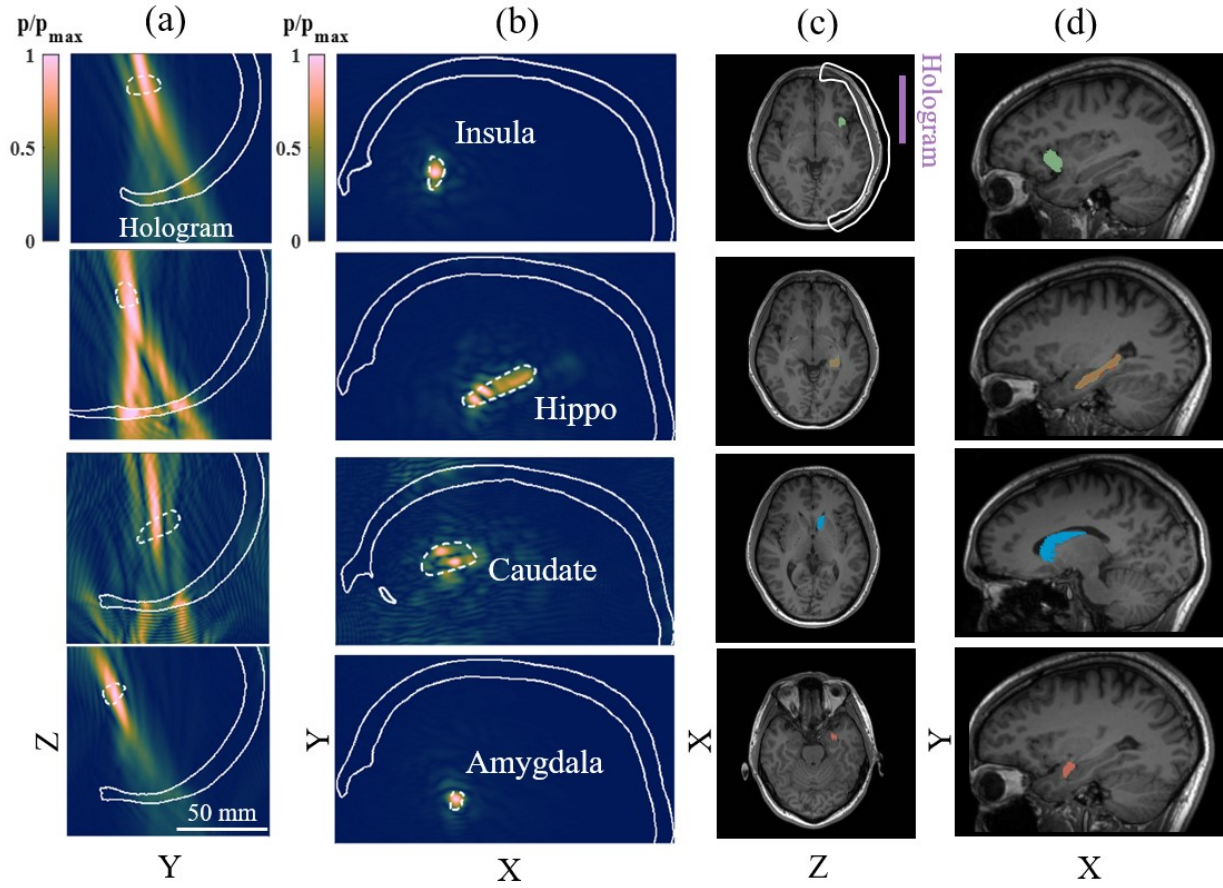


Figure 3.5.1: Summary of the numerical findings for targeting the desired volumes within the skull phantom. Columns (a) and (b) depict axial and transverse sections of the normalized pressure field, respectively. The dashed line represents the desired volume, whereas the solid white line represents the skull phantom. Columns (c) and (d) depict the axial and transverse sections of the MRI scans, respectively. The target volumes' geometries are emphasized in distinctive colors.

3.5 Numerical results

In this section, we numerically generate four acoustic holograms using the aforementioned optimization techniques to target four distinct human brain areas via the temporal window. A flat single-element transducer combined with an acoustic hologram can correct for skull aberrations and create a focal point tailored to a certain target location and volume. The geometry of the skull is derived from a computed tomography (CT) scan and processed to a resolution of the numerical grid. The skull geometry is sliced along a plane parallel to the sagittal plane to match the 3D-printed skull in the experimental setting. The skull section is integrated into the numerical simulations with a resolution of 0.5 mm, which corresponds to $\lambda/6.67$ for the transducer drive frequency in water. The numerical grid's resolution is uniform in all directions ($dX = dY = dZ$). The geometry and placement of the therapeutic targets chosen for this investigation have been retrieved from the Magnetic resonance imaging (MRI) scans and fitted and mapped into their proper locations in the cranial cavity. The flat circular transducer and hologram are situated at the temporal bone window, at a distance of 15 mm between the hologram's surface and the skull's surface. The transducer's output is experimentally evaluated in a water tank, with hydrophone measurements taken at an excitation frequency of 444 kHz. The numerical algorithm is constrained by the transducer's measured experimental amplitude, and the thickness map is designed using the initial experimental phase, as detailed in Algorithm 1. In all simulations, the average amplitude at the transducer's surface is normalized to 1Pa. Water is assumed everywhere else in the numerical domain since it is a good approximation of soft tissue and to match the water-submerged experiments. The domain size is 384X212X199 grid points in the X, Y, and Z directions, respectively. The Armijo line-search parameters in Algorithm 1 are set to $\beta = 0.9$ and $\sigma = 0.002$ with an initial step size of $\tau = 1$. The target volume T in Algorithm 1 is a binary volumetric matrix with nonzero values at the targeted brain structure. The

numerical simulations of acoustic propagation are performed using the MMDM and implemented in the open-source toolbox mSOUND on MATLAB R2019b [36]. A computational node equipped with AMD EPYC 7702 2.5 GHz (total of 18 cores) and 36 GB of RAM is used for all simulations. The backward propagation step in Algorithm 1 is the most computationally time-consuming. In Algorithm 1, the backward propagation stage consumes the most processing time. The pressure at each plane in the entire volume must be propagated back to the transducer plane. Because each propagation is independent, a parallel back-propagation technique was created using MATLAB's *parfor* function, which considerably accelerated the procedure. In the current study, each iteration lasted an average of 380 seconds, and each simulation produced satisfactory results after seven iterations on average. The average overall simulation time was 44 minutes, which is much faster than previously reported time-reversal techniques.

To assess the proposed algorithm's performance, we investigate four separate test cases involving various targets inside the brain. We created four distinct holograms that focus the ultrasound field on the anterior insula, hippocampus, caudate nucleus, and amygdala. Each of these targets has distinct properties in terms of shape, volume, orientation, and spatial placement within the brain structure. This diversity allows for a more comprehensive and general assessment of the holograms' performance capabilities. We shall look at the axial and transversal distribution of the ultrasonic field within the brain. In addition, we look into the sonication volume and peak focal pressure gain inside and outside the target regions. Sonication volumes are calculated as the region with a pressure gain of at least -3 dB with respect to the peak pressure in the brain for each test instance. Normalized peak pressure is calculated as the pressure gain relative to the average pressure at the transducer surface. The results of the numerical simulations for all the test cases are summarised in Fig. 3.5.1 and quantitatively in Table 3.1.

3.5.1 Anterior Insula

The anterior insula is a brain area that processes taste, emotions, and interoceptive awareness, including hunger and pain. It also plays roles in autonomic functioning and sensory processing, including auditory and vestibular functions, and is essential for empathy and social cognition [38, 39]. In the present simulation, the insula's volume is 0.875 cm^3 , and it is positioned at a depth of 8.32 cm from the hologram's surface along the axial direction, making it the deepest target among all the test cases. The dimensions of the insula extend to lengths of 0.9 cm, 1.9 cm, and 1 cm along the X, Y, and Z axes, respectively. The normalized cross-section of the maximum pressure field in the YZ and XY planes are shown in the first row of Fig. 3.5.1 (a) and (b), respectively. Each cross-section intersects the centroid of the target volume. The cartesian axes are aligned with the axes of the source. The segmented MR image with the highlighted geometry of the anterior insula is illustrated in 3.5.1 (c) and (d). As illustrated in the axial and transversal cross-sections, the pressure is concentrated on the Insula volume, which is marked by the white dashed line. Good coverage is obtained, with the main focal encompassing the majority of the volume. However, while the energy is focused on the Insula, significant acoustic pressure occurs both before and after the focal zone. The maximum normalized pressures inside and outside the target volume are close, at a value of 4.55 and 4.67, respectively. A total of 0.45 cm^3 of the Insula was sonicated, representing 51.4% of the total volume. While 2.25 cm^3 was sonicated outside the target. It is also crucial to note the low-pressure amplitudes seen in the skull (which is outlined by solid white lines). This is crucial since it reduces the possibility of skull heating effects, which improves the therapeutic technique's safety profile.

3.5.2 Hippocampus

The hippocampus, located in the temporal lobe of the brain, is responsible for memory formation and storage, spatial navigation, and stress and mood regulation. It also affects the learning process. Dysfunction in this area can lead to memory issues, spatial disorientation, and emotional problems [40]. The volume of the segmented Hippocampus is 3.85 cm^3 , and it is located at a depth of 7.55 cm from the hologram's surface along the axial direction. The dimensions of the Hippocampus extend to lengths of 4.45 cm, 2.55 cm, and 1.55 cm along the X, Y, and Z axes, respectively. The normalized cross-section of the maximum pressure field in the YZ and XY planes are shown in the second row of Fig. 3.5.1 (a) and (b), respectively. MRI scans, presented in Fig. 3.5.1 (c) and (d), show that the hippocampus extends more prominently in the transversal plane along the X-axis. At 4.45 cm, the hippocampus is the largest in terms of length in the X direction among all the target volumes investigated. The axial and transverse cross-sections clearly show the pressure focus within the hippocampus volume. The transverse cross-section shows that pressure is effectively contained inside the intended area. However, axially, substantial pressure exists outside the target zone. The maximum normalized pressure inside and outside the target volume are close, at a value of 2.97 and 3.15, respectively. Using the hologram 1.61 cm^3 or 41.8% of the Hippocampus is sonicated. However, a significant portion of the sonicated volume, amounting to 8.1 cm^3 , occurs outside the targeted region, with 83.4% of the total sonicated volume falling outside the intended area. Furthermore, high-pressure amplitudes in the skull increase the risk of causing unwanted skull heating effects when performing therapeutic operations.

3.5.3 Caudate Nucleus

The caudate nucleus in the brain's basal ganglia is crucial for motor control, procedural learning, reward processing, decision-making, and emotional processing. Its dysfunction is associated with various neurological and psychiatric disorders, including Parkinson's and Huntington's diseases [41]. The volume of the segmented caudate nucleus is 4.73 cm^3 , and it is positioned at a depth of 6.2 cm from the hologram's surface along the axial direction, making it the largest target and the closest to the hologram surface among all the targets considered in the present investigation. The dimensions of the caudate extend to lengths of 4.1 cm, 2.3 cm, and 1.75 cm along the X, Y, and Z axes, respectively. The normalized cross-section of the maximum pressure field in the YZ and XY planes are shown in the third row of Fig. 3.5.1 (a) and (b), respectively. MRI scans, as presented in Fig. 3.5.1 (c) and (d), show that the caudate also extends more prominently in the transversal plane along the X-axis. The axial and transverse cross-sections show the pressure concentration inside the caudate's volume, however there is less effective coverage of the target area than in earlier tests. This is emphasized by the relatively smaller sonicated volume of the caudate, amounting to 1.2 cm^3 or 25.4% of its total volume. This level of sonication is notably the lowest among all the considered test cases. The sonicated volume outside of the target volume is 8.81 cm^3 which is 86.3% of the total sonicated volume. The maximum normalized pressure inside and outside the target volume are close, at a value of 3.32 and 3.38, respectively.

3.5.4 Amygdala

The amygdala, a tiny region in the brain, is critical in emotional processing, notably fear and aggression. It is essential for developing emotional memories and influencing decision-making. The amygdala is also involved in stress and anxiety reactions, as well as social

interactions through the interpretation of social cues. Amygdala dysfunction can cause emotional disorders, memory problems, and difficulties with social behavior[42]. The volume of the segmented Amygdala is 0.491 cm^3 , and it is positioned at a depth of 7.49 cm from the hologram's surface along the axial direction. The dimensions of the amygdala extend to lengths of 0.8 cm, 1.2 cm, and 1.15 cm along the X, Y, and Z axes, respectively. The amygdala is the smallest and most contained target volume among all the test cases, as highlighted by the MRI scans in Fig. 3.5.1 (c) and (d). The normalized cross-section of the maximum pressure field in the YZ and XY planes are shown in the fourth row of Fig. 3.5.1 (a) and (b), respectively. The axial and transversal cross-sections demonstrate adequate coverage and containment of the focus zone in the target region. This is highlighted by the high sonication rate within the amygdala with a total sonication volume of 0.32 cm^3 or 65.3%, which is the highest sonication percentage among all the test cases. The sonicated volume outside of the target volume is 1.93 cm^3 , which represents 85.8% of the total sonicated volume. The maximum normalized pressure inside and outside the target volume is the same, at 5.49, which is the largest gain achieved among all test cases. Low-pressure amplitudes in the skull were also observed when targeting the amygdala.

Table 3.1: Summary of the Numerical Results

	Volume [cm^3]	Total sonicated volume [cm^3]	Sonication inside target [cm^3]	Percent of target sonication [%]	Gain inside target	Gain outside target
Insula	0.875	2.7	0.45	51.4	4.55	4.67
Hippocampus	3.85	9.9	1.61	41.8	2.97	3.15
Caudate	4.73	8.81	1.2	25.4	3.32	3.38
Amygdala	0.491	2.22	0.321	65.3	5.49	5.49

3.5.5 Discussion

The pressure fields created by acoustic holograms are inherently constrained by the diffraction limit and must adhere to the Helmholtz equation and the principle of energy conservation. This implies that sound fields that do not conform to these fundamental principles are not physically viable. As a result, there will inevitably be differences between the theoretically desired target field and the actual field that is physically realized due to these inherent limitations and principles governing acoustic propagation. The sound field can be significantly improved and optimized by carefully considering key parameters such as the numerical aperture, operating frequency, and the location and orientation of both the transducer and the hologram in relation to the size, position, orientation, and geometry of the target volume. This rigorous calibration guarantees that the acoustic field is fine-tuned to meet the appropriate targeting characteristics, maximizing the treatment process's efficacy, precision, and safety.

The numerical results clearly show that acoustic holograms are more effective at restricting the focal region within the transversal portion than in the axial section, especially for bigger targets such as the hippocampus and caudate. The wider the target's extent and cross-sectional area in the transversal plane, the weaker the field's focus is, resulting in a lower gain and a focused zone that is more elongated and distributed in the axial direction, causing greater sonication outside the target volume. This impact can be minimized by increasing the numerical aperture (transducer size) or adjusting the operating frequency, albeit both of these modifications have limitations. Another technique is to orient the transducer so that its axis is parallel to the target's longest dimension, resulting in an elongated focal area that is substantially contained inside the target volume. However, this strategy has limitations; for example, targeting the hippocampus will necessitate passing through the parietal bone, which is thicker and more curved, which could lead to new complications and issues such as

skull heating and mode convergence.

These constraints are inherent in acoustic holographic lenses, not the optimization algorithm itself. However, the optimization methodology provided here, with its explicitly defined loss function, provides a method for somewhat overcoming these limits. Different loss and weighting functions can be used to direct the optimization algorithm to prioritize specific ultrasonic parameters. For example, to promote axial resolution by giving axial errors more weight than transversal errors. This approach could provide better axial confinement at the expense of transversal containment. Other parameters, such as pressure uniformity and coverage, can also be optimized to fit specific therapeutic demands and objectives, resulting in a more specialized optimization process that improves the efficacy of ultrasonic applications. The loss functions can be customized further by designating regions with low pressure, directing the algorithm to avoid sonication in these areas. This adjustment provides more precise control over pressure distribution, protecting vital or sensitive areas from unwanted ultrasonic wave exposure. Furthermore, the proposed algorithm effectively eliminates the uncertainties inherent in time-reversal techniques, where the impact of the number, distribution, and locations of virtual sources on focusing parameters is unclear. Determining the optimal distribution of virtual sources for specific desired focusing parameters can be challenging due to the non-iterative nature of these techniques and the computational limitations associated with them [43].

3.6 Experimental verification

3.6.1 Experimental Setup

The experimental setup is submerged in a water tank, as shown in Fig. 3.6.1. The walls of the tank are partially covered with Aptflex F28 acoustic absorbing sheets manufactured by Precision Acoustics, Ltd. The water tank is filled with degassed and deionized water in a temperature-controlled environment. A custom-made holder is fabricated to hold the skull, the ultrasound transducer, and the holographic lens. The position of the transducer can be moved manually relative to the skull in the X, Y, and Z directions. The transducer is custom-made and composed of a single circular piezoelectric disc with a diameter of 60 mm and an operating frequency of 444 kHz. The transducer is excited with a sinusoidal pulse signal (20 cycles) by a signal generator (Keysight 33500B) and an amplifier (Electronics and Innovation A075). The pressure field on a specified target plane is mapped with the ONDA HNR-0500 needle hydrophone attached to a custom-built in-house 3D positioning system. The measured signal from the hydrophone is sampled and digitized by a Tektronix TBS2104 oscilloscope and averaged 64 times to increase the signal-to-noise ratio. To eliminate the effect of any DC bias and higher frequency noises, the signal is post-processed using MATLAB by performing an FFT on the time series. A MATLAB program is used to control the positioning system and triggering of the function generator. The obtained voltage amplitude is then converted into acoustic pressure according to the calibration factor provided by the manufacturer (-250.13 dB). The geometry of the skull is obtained using a segmented CT scan. A section of the skull is then 3D-printed with Polycarbonate (PC) FDM by STRATASYS (F270, Eden Prairie, MN) with a smooth hand finish. The acoustic properties of PC have been previously investigated underwater [44] with $c = 2380$ m/s, $\rho = 1153$ kg/m³, and $\alpha = 12.23$ dB/cm at 1.1 MHz. A Formlabs (Formlabs, Somerville, MA, US) Form 3 grey resin was used for

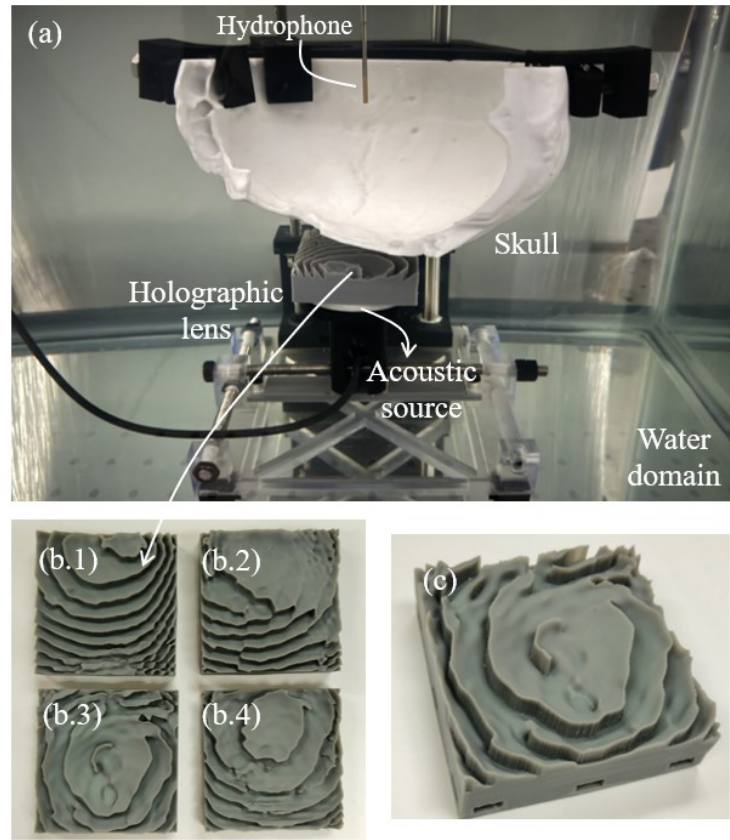


Figure 3.6.1: (a) shows the experimental setup, including the acoustic source, 3D-printed acoustic hologram, 3D-printed skull phantom, and the hydrophone. The 3D-printed holograms for targetting the insula (b.1), hippocampus (b.2), caudate (b.3), and the amygdala (b.4). (c) closeup of the 3D-printed hologram.

printing the acoustic lenses with a lateral and axial resolution of 25 microns. The acoustic properties of the resin were previously reported in an underwater experimental study [45] with $c = 2591$ m/s, $\rho = 1178$ kg/m³, and $\alpha = 2.922$ dB/cm at 1 MHz.

3.6.2 Experimental results

Four holograms are designed based on the numerical results to validate the proposed algorithm. Underwater pressure scans in both the transversal and axial directions are carried out for each target using a hydrophone attached to a positioning system. Due to the hy-

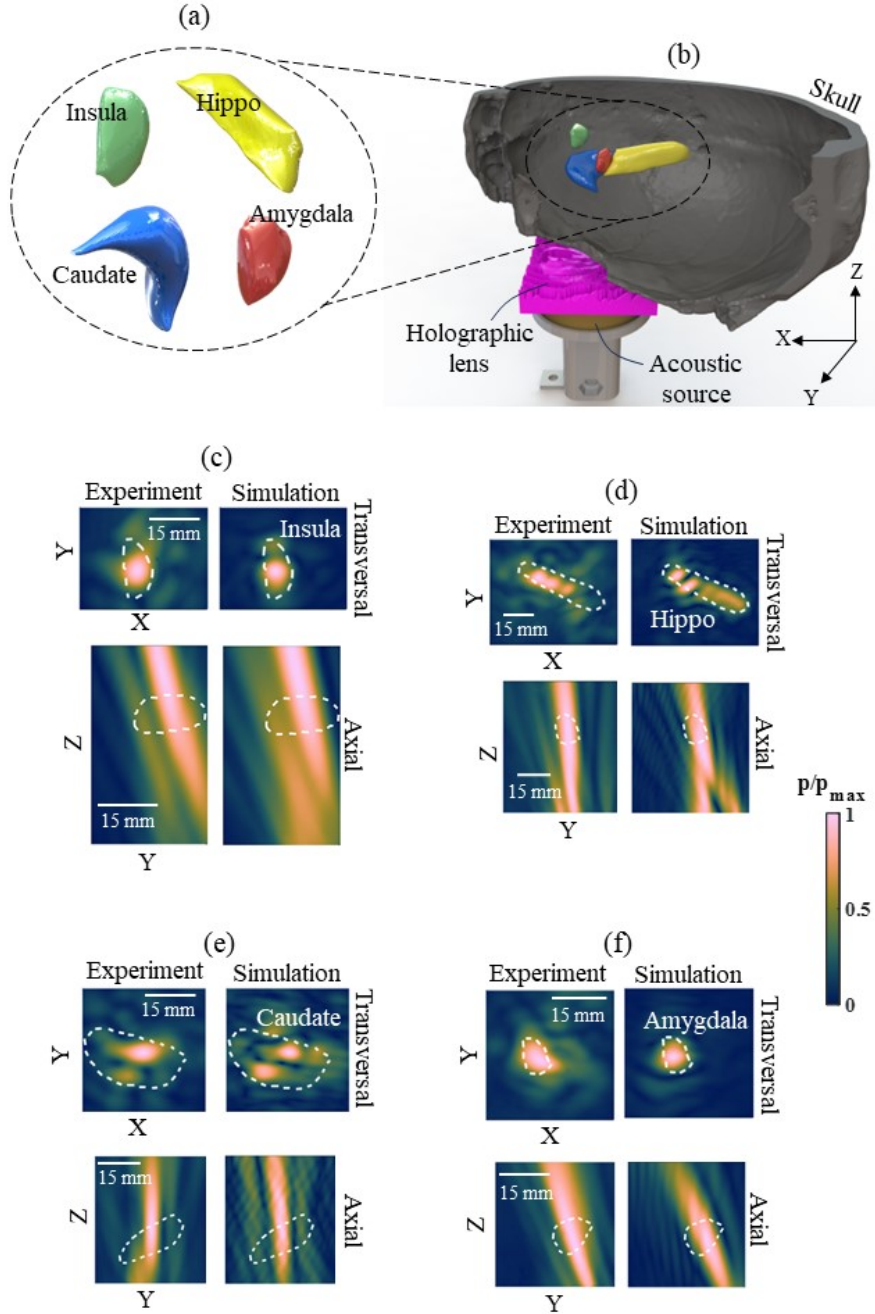


Figure 3.6.2: (a) The geometry of each target evaluated in the current study. (b) Schematic of the experimental setup, with the targets positioned in their proper placements within the cranial cavity of the skull phantom. (c), (d), (e), and (f) show the experimental and numerical results for the test cases of the insula, hippocampus, caudate, and amygdala.

drophone's limited mobility range within the skull, only smaller portions surrounding the target location are scanned. The experimental measurements are then compared to numerical simulations. Figure 3.6.2 (a) and (b), respectively, show the geometry of the four target volumes and their corresponding location inside the 3D-printed skull phantom. Figure 3.6.2 (c), (d), (e), and (f) respectively compare the experimental measurements and their corresponding numerical results for the insula, hippocampus, caudate, and amygdala. Good overall agreement is observed between the experimental measurements and the numerical results. The maximum experimental pressures measured in the transversal plane were 85.2 kPa for the insula, 98.5 kPa for the Hippocampus, 127 kPa for the Caudate, and 98.2 kPa for the Amygdala with an excitation input of 200 V_{pp} .

For a quantitative comparison between experimental and numerical results, we calculated the focusing efficiency [24] in the transversal section. By comparing the acoustic power within the focal region to the total acoustic power in the entire plane. The calculations assume planar wave propagation. The focusing efficiency is given as:

$$\eta = \frac{\Pi_{focal}}{\Pi_{total}} = \frac{\sum P_{focal}^2(X, Y, Z_0)}{\sum P^2(X, Y, Z_0)} \quad (3.13)$$

Where $P_{focal}(X, Y, Z_0)$ and Π_{focal} are the acoustic pressure distribution and the acoustic power in the focal regions, respectively. Π_{total} is the total acoustic power in the transversal plane. Examining Fig. 3.6.2 (c), which presents insula results, we notice more pressure leakage outside of the focal region in the experimental data. This is evident from the disparity in focusing efficiency, with the simulations calculated at 76.5% compared to 46.1% in the experimental measurements. A similar pattern is observed in other test cases: the hippocampus has a numerical efficiency of 84.2% compared to an experimental efficiency of 49.2%, and the amygdala with a numerical efficiency of 70.1% against an experimental efficiency of 41.6%. Interestingly, the caudate is the only test case where the experimental

results outperform the simulations, with an efficiency of 64.2% versus 57.1%, potentially due to a more pronounced top lobe in the experimental data as shown in Fig. 3.6.2(e). The differences between experimental and numerical results could be attributable to factors such as measurement mistakes, alignment challenges, variances in material qualities, and flaws in the produced skull phantom and hologram.

3.7 Conclusions

We introduced an efficient volumetric holographic technique for creating 3D-printed acoustic holograms specifically for low-intensity non-thermal tFUS applications. The fundamental goal of these acoustic lenses is to generate precise FUS fields within the brain while successfully compensating for aberrations induced by the skull's structure. The proposed optimization strategy uses the modified mixed domain method to perform efficient ultrasonic propagation in strongly heterogeneous media, which is then incorporated into a gradient descent iterative volumetric holography optimization algorithm. The holographic approach outperforms the previously reported time-reversal strategies used in full-wave time-domain numerical simulations. Using the proposed approach, a hologram can be created in less than 50 minutes. Furthermore, due to the more efficient propagation, iterative optimization techniques can be used with explicitly assigned loss functions. The optimization technique can be fine-tuned to prioritize individual ultrasound characteristics by using different loss and weighting functions. For example, increasing axial resolution entails giving greater weight to axial errors than transversal ones, which improves axial containment but may reduce transversal containment. Other factors like pressure uniformity and coverage can also be adjusted to suit particular therapeutic requirements, enabling a more customized optimization process. The loss functions can also be specifically tailored to designate regions where

minimal pressure is crucial, thereby directing the algorithm to prevent sonication in those sensitive areas, ensuring a more precise and effective ultrasound treatment. We applied the proposed algorithm to target four brain structures: the anterior insula, hippocampus, caudate nucleus, and amygdala. Verification was done through underwater experiments using realistic 3D-printed skull phantoms. Good agreement was observed between the numerical results and the measured experimental data. Our results demonstrate that the acoustic holograms achieved effective coverage and confinement in the transversal plane. However, in the axial direction, sonication leakage varied depending on the target geometry, orientation, and volume, with lower axial containment observed in larger and transversely elongated targets like the hippocampus and caudate. The proposed approach enables more rapid computation of acoustic holograms, enabling quicker administration of therapeutic procedures and allowing for more flexibility in tailoring ultrasound fields for specific therapeutic requirements.

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Chapter 4

On nonlinear effects in holographic-modulated ultrasound

4.1 Details of publication

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4.2 Abstract

Holographic acoustic lenses (HALs), also known as acoustic holograms, are used for generating unprecedented complex focused ultrasound (FU) fields. HALs store the phase profile of the desired wavefront, which is used to reconstruct the acoustic pressure field when illuminated by a single acoustic source. Nonlinear effects occur as the sound intensity increases, leading to distorted and asymmetric waveforms. Here, the k-space pseudospectral method is used to perform homogeneous three-dimensional nonlinear acoustic simulations with power law absorption. An in-depth analysis is performed to study the evolution of holographic-modulated FU fields produced by HALs as the excitation amplitude increases. It is shown

that nonlinear waveform distortion significantly affects the reconstruction of the pressure pattern when compared to the linear condition. Diffraction and nonlinear effects result in an asymmetric waveform with distinct positive and negative pressure patterns at the target plane. Peak positive pressure distribution becomes more localized around the areas with the highest nonlinear distortion. The peak signal-to-distortion ratio (PSDR) at the target plane falls while the non-uniformity index (NUI) rises. As a result of harmonic generation, the heat deposition distribution becomes highly localized with a significant increase in the NUI. Nonlinear effects have also been shown to flatten the peak negative pressure distribution while having minimal effect on the PSDR or NUI. However, nonlinear effects are shown to be critical for accurately predicting cavitation zones. Findings will pave the way for HALs implementation in high-intensity applications and prompt the incorporation of nonlinear acoustics into the notion of computer-generated holography.

4.3 Introduction

Focused ultrasound (FU) is an emerging non-invasive and non-ionizing therapeutic technology that has the potential to treat a variety of medical conditions.

FU can heat up, destroy, or change target tissue while minimizing damage to tissue outside the target area by precisely focusing ultrasonic beams [1, 2]. FU has been shown as an effective tool for tumor ablation [3, 4], lithotripsy [5, 6], histotripsy [7–9], drug delivery [10–12] and contactless ultrasound power transfer [13]. The current FU technology focuses ultrasound energy using curved single-element or phased-array transducers (PATs). Single-element transducers can only target a single location, whereas PATs have limited fidelity and require expensive and complex hardware. Holographic acoustic lenses (HALs), i.e. acoustic holograms, have been proposed as a simple, robust, and cost-effective method for creating

highly localized ultrasound fields [14–19]. HALs, which are often 3D printed, act as phase plates and can be used to reconstruct ultrasound onto a desired spatial distribution deep inside living tissue. As a result, acoustic holograms are being rapidly investigated for various biomedical applications with the potential to enable low-cost therapeutic procedures such as transcranial neuromodulation [20], blood-brain barrier opening [21], ultrasound-induced hyperthermia [22], and burst-wave lithotripsy [5]. Furthermore, HALs have also been proposed for producing precise cavitation patterns [23] for various therapeutic applications. Many FU therapeutic techniques capitalize on the rise of nonlinear effects at high intensities to enhance the desired thermal and mechanical effects. At higher intensities, nonlinear propagation effects cause a sharp increase in ultrasound energy absorption resulting in accelerated and more localized thermal tissue ablation [24]. Short ultrasound pulses with shocks can also be used to generate purely mechanical liquefaction of tissue [25, 26]. Acoustic holograms, on the other hand, are currently computed using linear propagation techniques and have only been demonstrated in the linear regime.

If the acoustic amplitude is sufficiently large, the linearity assumptions are no longer valid and will result in significant errors in the predicted sound field. Studies that highlight the interaction of complex physics between the constructed holographic sound field and nonlinearities are absent. As a result, a significant potential role for acoustic holograms has yet to be explored: creating precise and complex high-intensity focal regions, particularly for clinical treatments. The current study investigates numerically the effects of increasing acoustic intensity on holographic modulated ultrasound. Modeling three-dimensional nonlinear ultrasound is a physically and computationally demanding problem. As such several difficulties coexist: the complex diffraction structure necessitates the use of accurate diffraction models and a fine spatial numerical grid. Furthermore, strong nonlinear effects necessitate the inclusion of a large number of harmonics in simulations with fine temporal and spatial grids.

[27, 28]. In general, three-dimensional nonlinear simulations require large memory (RAM) and lengthy computation time.

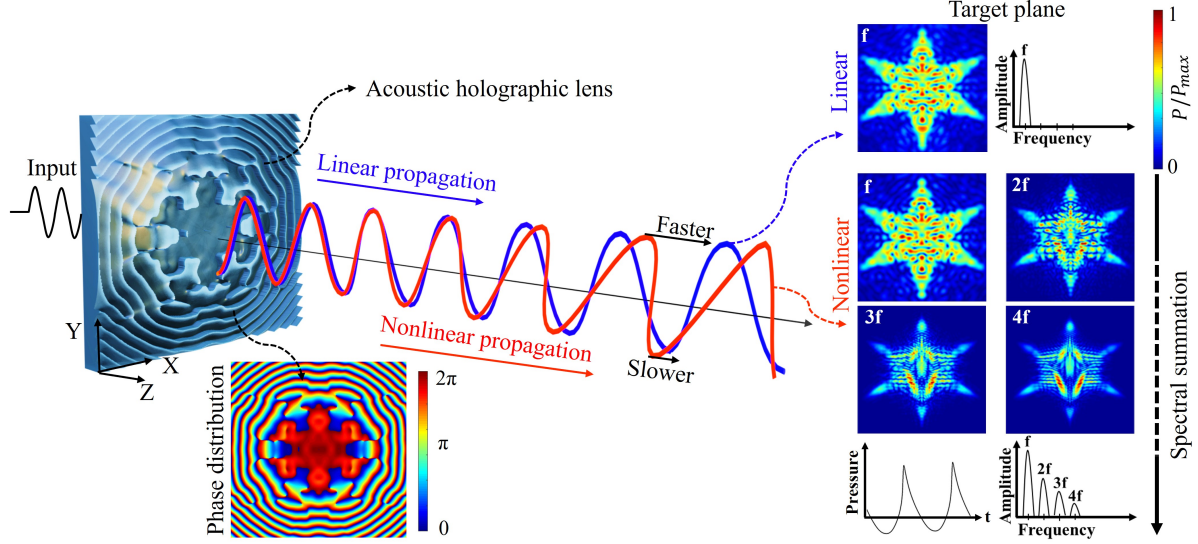


Figure 4.3.1: The schematic representation of the acoustic propagation of a holographic-modulated ultrasound wave from the hologram plane (left) to the target plane (right) to form a star-shaped amplitude pattern. The time waveforms' linear (blue) and nonlinear (red) evolutions are depicted. The linear monochromatic pressure amplitude distribution at the target plane (top right) is also shown, as are the fundamental and higher harmonic amplitudes for the broadband nonlinear field (bottom right). The nonlinear asymmetric distorted waveform and its broadband spectrum are depicted (bottom right).

4.4 Results and Discussion

In this work, the k-space pseudospectral method was used to perform homogeneous three-dimensional nonlinear acoustic simulations with power law absorption [28]. The numerical model solves a set of coupled partial differential equations equivalent to a generalized Westervelt equation. The accuracy and validity of this numerical model have been previously verified with analytical solutions and experimental measurements [29, 30]. The simulations were run in an optimized C++ implementation that makes use of the OpenMP interface for

parallelized execution across multiple cores. The C++ implementation is an extension of the open-source K-wave MATLAB toolbox, available online[31]. See the supplementary material for verification of the present numerical approach by previously published experimental data. The simulations were carried out on a high-performance computing cluster hosted on the Virginia Tech campus (Blacksburg, VA, USA). The used computational node has 128 cores (two AMD EPYC 7702 64-core processors) and 1024 GB of RAM. The largest simulation in this study took 56 hours to run, with a spatial discretization of 60 grid points per wavelength (supporting up to 30 harmonics) and a Courant-Friedrichs-Lewy (CFL) number of 0.3. The calculations were carried out in water using the appropriate physical parameters: $\rho_0 = 1000$ kg/m³, $c_0 = 1481$ m/s, $\beta = 3.6$, $\alpha_0 = 0.0022$ dB/MHz and $\gamma = 2$ for excitation frequency of $f_0 = 1$ MHz. Here ρ_0 , c_0 , β , are the density, ambient speed of sound, and nonlinearity coefficient, respectively. While α_0 and γ , respectively, are the absorption coefficient and the power law exponent. The size of the spatial domain is $50 * 50 * 30$ mm in addition to the size of the perfectly matched layers (PMLs). To ensure that a steady state is reached throughout the computational domain, the temporal domain is extended to 12000 time steps (50 time periods with respect to the excitation frequency). All simulations in this paper used the same set of parameters. To investigate the nonlinear effects in holographic-modulated ultrasound, the iterative angular spectrum algorithm (IASA) [14] was first used to create a star-shaped amplitude pattern 25 mm from the hologram plane, as shown in Fig. 4.3.1. The algorithm was initialized with a uniform phase and amplitude input, then used to iteratively calculate the required phase map at the hologram plane (50 iterations). Figure 4.3.1 shows the computed phase map at the hologram plane and the simulated linear pressure field at the target plane. The computed phase was then used as a Dirichlet boundary condition in the nonlinear simulations. The linear sound field was first calculated with a uniform source pressure amplitude of $P_0 = 0.1$ MPa. The source pressure was then increased to $P_0 = 1.8$ MPa to investigate the emergence of nonlinearities and their effects on the sound field. The

compressional phase in a propagating nonlinear wave travels at a speed of $c_0 + \beta u$ faster than the speed of the rarefaction phase $c_0 - \beta u$, where u is the particle velocity [32, 33]. As a result, the sinusoid shape is distorted to a steeper waveform as the wave propagates further. Harmonics at integer multiples of the fundamental frequency are generated as a result of waveform distortion, resulting in enhanced heating and streaming effects. Furthermore, in the nonlinear problem, diffraction and focusing effects cause a relative phase shift in the harmonics with respect to the fundamental component, resulting in an asymmetric waveform and a discrepancy between the peak positive pressure (PPP) and the peak negative pressure (PNP). The effects mentioned above are depicted schematically in Fig. 4.3.1. The

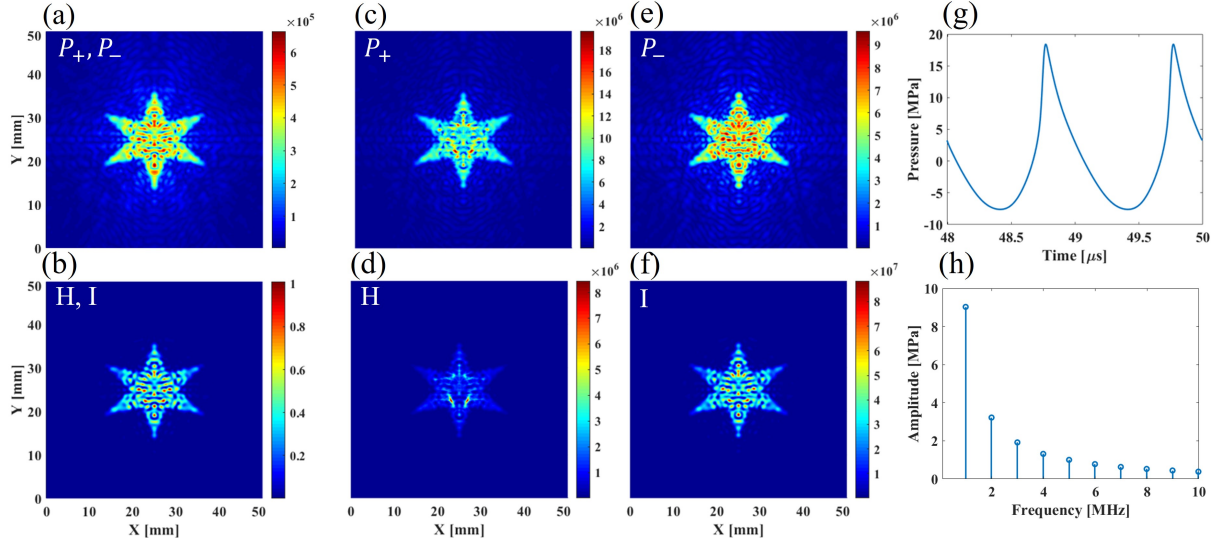


Figure 4.4.1: Nonlinear distortion effects on the spatial structure of the PPP, PNP, heat deposition, and intensity. The distributions of linear amplitude [Pa] (a) and normalized heat deposition/intensity (b) at the target plane for a source pressure of $P_0 = 0.1$ MPa are shown. PPP [Pa] (c), heat deposition [W/cm^2] (d), PNP [Pa] (e), and intensity [W/cm^2] (f) distributions at the target plane for a $P_0 = 1.8$ MPa source pressure. The maximum PPP point at the target plane has a distorted time waveform (g), and the corresponding spectrum is (h).

PPP is connected to the heat effect in therapeutic ultrasound, whereas the PNP controls the cavitation effect. Understanding and characterizing such effects is essential to ensuring that therapies are administered at the proper place and intensity, as required by FDA and IEC

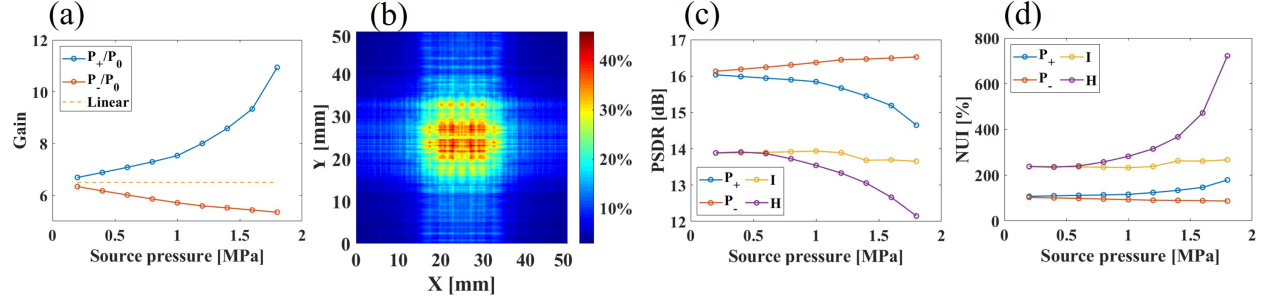


Figure 4.4.2: The effects of nonlinear distortion on the spatial structure of key acoustic parameters are quantified. (a) As source pressure is increased, the linear gain is compared to the nonlinear positive and negative gains. THD at the target plane (b). As the source pressure is increased, the PSDR (c) and NUI (d) at the target plane increase.

rules [34]. The spatial distributions of important acoustic parameters at the target plane in the linear and nonlinear regimes are depicted in Fig. 4.4.1. For linear $P_0 = 0.1$ MPa (a, b) and nonlinear $P_0 = 1.8$ MPa (c-f) conditions, the PPP (P_+), PNP (P_-), intensity, and heat deposition are shown. The PPP and PNP are spatially identical in the linear case. Furthermore, the linear spatial structure of wave intensity and heat deposition are identical. As a result, only the pressure amplitude is shown in (a), whereas the intensity and heat deposition are both shown in a single normalized plot in (b). The spatial structure of the acoustic parameters deviates from the initial linear prediction due to nonlinear distortion at higher intensities. When compared to the linear field, the PPP (c) and especially heat deposition (d) are more localized and less uniform in space in the nonlinear regime. The nonlinear spatial structure of the PNP (e) deviates from the linear prediction as well, though to a lesser extent. In contrast, the intensity distribution differs only slightly between the linear (b) and nonlinear (f) conditions. The spatial structures and magnitudes of the PPP and PNP are no longer identical in the nonlinear regime. It is also clear that the intensity cannot be used to estimate heat deposition in the nonlinear regime. Furthermore, due to the nonlinear distortion and diffraction, the nonlinear waveform shown in Fig. 4.4.1 (g) exhibits top-bottom asymmetry, and the wave is no longer monochromatic as the corresponding spectrum shows, Fig. 4.4.1 (h). As a consequence of the waveform's distorted asymmetric profile,

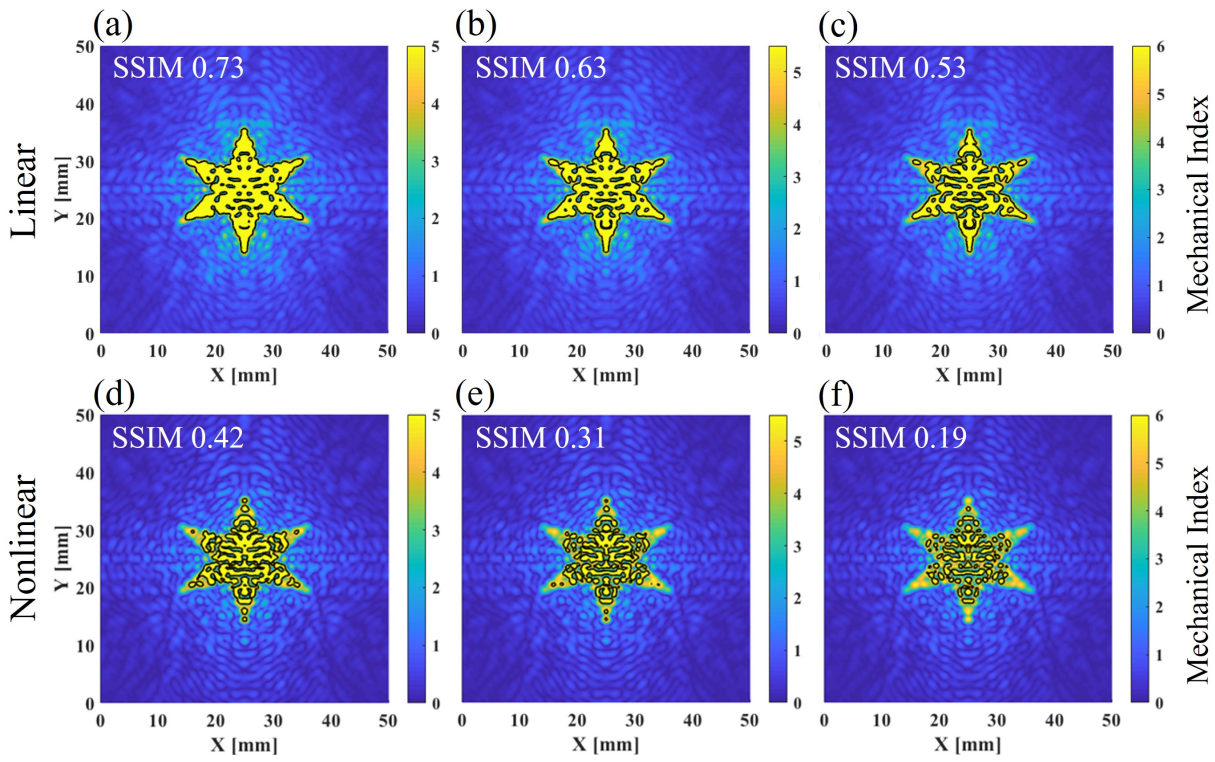


Figure 4.4.3: Effects of nonlinear distortion on the inertial cavitation zones at the target plane. The black contour line contains the saturated MI zones i.e cavitation zone. The linear (top row) and nonlinear (bottom row) predictions are compared at varying MI. Cavitation zones for an MI of 5 (a,b), 5.5 (c,d) and 6 (e,f).

the real gain of the PPP (P_+/P_0) increases while the gain of the PNP (P_-/P_0) decreases with respect to the linear value. Figure 4.4.2 (a) compares the gain of the PPP and PNP to the linear gain as the amplitude of the source pressure increases. The values of the maximum peak pressures at the target plane were normalized by the amplitude of source pressure and thus represent the real gain. The gain of the PPP and PNP at low source pressure is that of linear propagation. However, under nonlinear conditions, the PPP gain grows larger than the linear gain to a maximum of 11. Meanwhile, as the source pressure increases, the gain for PNP decreases. As a result, where there are highly distorted waveforms, the maximum PPP grows faster while the maximum PNP grows more slowly. In the nonlinear regime, this is the underlying mechanism that results in a spatial structure that is more localized for the PPP and flattened for the PNP. Since higher harmonics increase wave energy absorption, it is critical to investigate the spectral distribution of acoustic energy at the target plane. Total harmonic distortion (THD) is defined as the ratio of all harmonic component powers to fundamental frequency power [35].

$$THD = 100 \cdot \frac{\sqrt{\sum_{n=2}^{\infty} A_n^2}}{A_1} \quad (4.1)$$

Here A is the amplitude, and n is an integer representing multiples of the fundamental frequency. Nonlinear distortion of the waveforms due to the harmonics and relative phase shift is highest at the points that exhibit the maximum THD in the domain[34]. Figure 4.4.2 (b) shows the distribution of THD at the target plane. The points with the maximum THD have harmonics with a total power that is 45% that of the fundamental. When compared to the PPP, the heat deposition has a more localized distribution due to the higher harmonics. It can also be seen that the points with the highest THD also have the highest heat deposition. To quantify the deviation of the spatial structure of the acoustic parameters as the source

pressure is increased, two metrics were used. Equations (2) and (3) define the peak signal-to-distortion ratio (PSDR) and the non-uniformity index (NUI), respectively.

$$\begin{aligned} PSDR &= 10 \log_{10} \frac{\max[m(X, Y)]^2}{MSE} \\ MSE &= \frac{1}{m} \sum_{i=0}^{n_X-1} \sum_{j=0}^{n_Y-1} [m(i, j) - g(i, j)] \end{aligned} \quad (4.2)$$

Here m is the data matrix of the field, and g is the binary matrix of the star-shaped pattern (ground truth). While n_X and i are respectively the number and index of the rows in the data matrix, and n_Y and j are respectively the number and index of the columns.

$$NUI = 100 \cdot \left[\frac{\max[m(X, Y)] - \text{mean}[m(X, Y)]}{\text{mean}[m(X, Y)]} \right]_{ROI} \quad (4.3)$$

Here the mean and the max of the data matrix were calculated for the region of interest (ROI), which is the area enclosed by the star pattern. NUI was selected to study the effect of nonlinear distortion on the spatial localization of the acoustic parameters, while PSDR is used to assess the effect of the distortion on the reconstruction quality. PSDR and NUI were calculated as the source pressure gradually increased from $P_0 = 0.1$ MPa to $P_0 = 1.8$ MPa. Figure 4.4.2 (c) shows the PSDR drops by 1 dB for the PPP and by 2 dB for the heat deposition. The PSDR for the intensity is essentially constant, while it increases slightly for the PNP. Figure 4.4.2 (d) depicts a similar story where the NUI for the PNP and intensity change only slightly. However, the NUI increases for PPP and more rapidly for heat deposition, with a maximum value of 700%.

Cavitation can cause significant desired or unintended bio-effects in the tissue in medical acoustics [23]. The mechanical index (MI) was used to calculate the inertial cavitation zones within the target plane. The MI is calculated by dividing the PNP in MPa by the square root

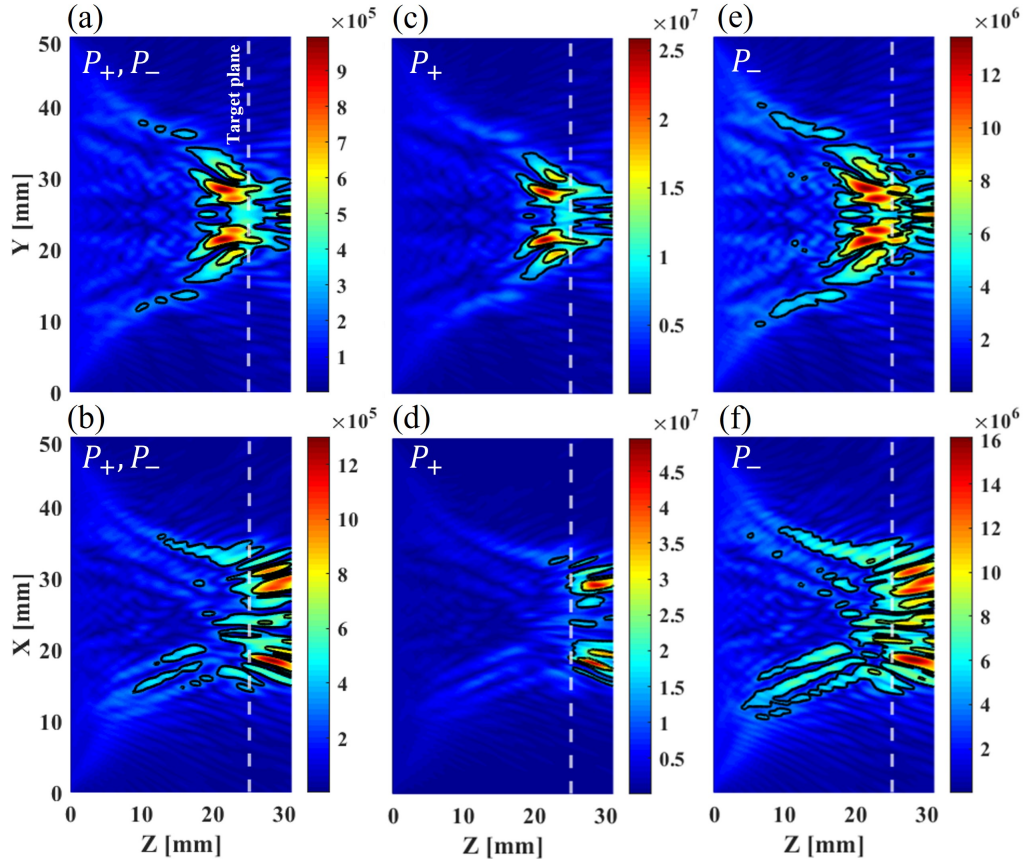


Figure 4.4.4: Nonlinear distortion effects on the spatial distributions of peak pressures in the axial planes: YZ (top row) and XZ (bottom row). The spatial distribution at the YZ plane for linear amplitude (a) for $P_0 = 0.1$ MPa. The PPP (c) and PNP (e) for $P_0 = 1.8$ MPa. The spatial distribution at the XZ plane for the linear amplitude (b) for $P_0 = 0.1$ MPa. The PPP (d) and PNP (f) for $P_0 = 1.8$ MPa.

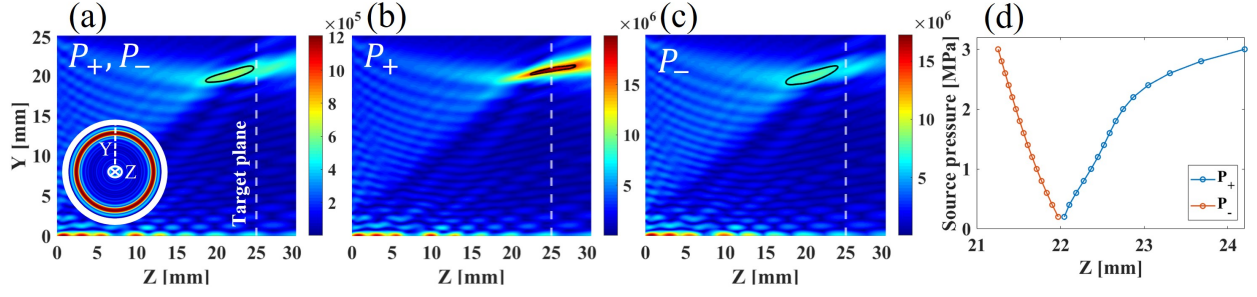


Figure 4.4.5: Nonlinear distortion effects on axisymmetric holographic patterns. (a) Linear amplitude distribution in the axial plane and amplitude snapshot in the target plane for $P_0 = 0.2$ MPa. The nonlinear distributions of the PPP (b) and PNP (c) at the axial plane for $P_0 = 0.2$ MPa. (d) The focal location of the PPP and PNP as the source pressure increases.

of the excitation frequency in MHz [36]. As the MI involves a trade-off between PNP and excitation frequency, the MI can be a more comprehensive and reliable measure than PNP alone [37]. The cavitation zones were calculated for the simulated nonlinear field and a linear prediction with a source pressure of $P_0 = 1.8$ MPa. Fig. ?? depicts the predicted saturated pixels with a contour line encapsulating the cavitation zones. The structural similarity index (SSIM) between the star pattern and the obtained cavitation zones was also calculated. The predicted cavitation zones for the linear (top row) and nonlinear (bottom row) fields can be seen. The focusing gain of the PNP decreases due to nonlinear distortion. As a result, in the linear case, larger cavitation zones are predicted. The MI saturation levels were selected according to experimentally tested cavitation thresholds of ex vivo tissue [38]. In Fig. ??, (a) & (b) depict MI saturation level of 5, (c) & (d) depict saturation level of 5.5, and (e) & (f) depict saturation level of 6. When nonlinear effects in the sound field were taken into account, the SSIM decreased by an average of 0.32. As a result, nonlinear modeling is critical to avoid overestimation of the PNP and, as a result, cavitation effects. Therefore, nonlinear modeling is essential to avoid overestimation of the PNP and consequently the cavitation effects.

As opposed to a spherically focused ultrasound field which has a clear focal point and focal length, a holographically modulated ultrasound field has a complex spatial distribution with intricate regions of high and low pressure. As a result, it is critical to consider the acoustic parameters of the entire field rather than just the target plane. Figure 4.4.4 shows two cross-sections of the sound field, the YZ plane (Top row) and the XZ plane (Bottom row) both extend from the hologram plane at $Z = 0$ mm to $Z = 30$ mm (5 mm beyond the target plane). Two contour lines are also plotted at a pressure drop of -3 and -6 dB. When compared to the linear distributions in (a) and (b), the PPP in (c) and (d) show higher localization, while the PNP in (e) and (f) show significant spreading. The plots also highlight focal areas that occur before the target plane, as shown in the YZ plane, or after, as shown in the XZ plane. Because nonlinear effects are inherently cumulative, it is critical to examine the entire sound field. In computing acoustic holograms, the pressure field is only constrained at the target plane, thus, significant bio-effects or shock wavefronts may form before or after the target plane at undesirable locations.

Finally, as a special case of holographic modulation, we will consider an axisymmetric ring pattern. Previously reported experimental and numerical studies on spherically focused transducers have revealed a spatial focal shift of the PPP and PNP at high intensities [39–41]. It would be interesting to look into axisymmetric holographic ultrasound fields and investigate whether they exhibit similar behavior. An axisymmetric simulation for a ring pattern, as shown in Fig. 4.4.5, was also implemented to this end. IASA was used to construct the desired pressure by imposing a binary amplitude ring pattern with a radius of 20 mm at the target plane. The simulations were more memory efficient due to the axisymmetric geometry, and up to 60 harmonics were included. The spatial domain had dimensions of 25 mm in the radial direction and 30 mm in the axial direction, with the target plane located at $Z = 25$ mm in the axial direction. The axial cross-section of the

linear sound field with a snapshot of the ring pattern at the target plane is shown in Fig. 4.4.5 (a). Figures 4.4.5 (b) and (c) show the PPP and PNP with a black contour line at -1 dB. A couple of nonlinear effects can be deduced from observing Figs. 4.4.5 (a-c). The PPP focal region becomes narrower and spatially shifts further from the source (right), while the PNP slightly shifts towards the direction of the source (left). The curves in Fig. 4.4.5 (d) represent the spatial location of the maximums of the peak pressures as the source pressure increases. At a source pressure of 3 MPa, the maximum PPP shifts by 2 mm away from the source, while the maximum PNP shifts by 0.8 mm toward the source. The behavior of the maximum pressures presented in Fig. 4.4.5(d) is due to the effects of nonlinear refraction. Compressive phases travel faster and self-defocus, while rarefaction phases travel slower and self-focus[40]. As nonlinear effects increase at the target plane, the beamwidth of the focal decreases by 50% for the PPP and remains constant for the PNP.

4.5 Conclusions

In conclusion, we have numerically examined the effects of nonlinear distortion on holographically modulated ultrasound generated by HALs. Using the k-space pseudospectral method, we have performed homogeneous three-dimensional nonlinear acoustic simulations with power law absorption. Due to the computationally intensive nature of the problem, the model was implemented in C++ on a high-performance computing cluster. The 3D spatial distribution of the PPP, PNP, intensity, heat deposition and cavitation zones were then analyzed for a range of excitation levels. It was shown that the nonlinear waveform distortion leads to pronounced effects on the spatial structure of the sound field. Due to diffraction and focusing effects, the waveform becomes asymmetric with different PPP and PNP patterns. The areas of maximum nonlinear distortion become increasingly focused in

terms of PPP distribution, the NUI rises to 190%, and the PSDR drops by 1 dB. Harmonic generation also causes the heat deposition distribution to become extremely confined, with a NUI of 700%. Nonlinear effects have also been shown to flatten the peak negative pressure distribution with minimal impact on the PSDR or NUI. In addition, nonlinear effects were shown to be vital for correctly estimating cavitation zones. When designing HALs for high-power therapeutic ultrasound techniques, it is crucial to consider the dynamic behavior of the spatial structure of various acoustic parameters in a nonlinear field. Our findings contribute to the informed use of HALs in high-intensity applications. We also envision that this investigation can be a precursor for encompassing nonlinear effects in the realm of computer-generated holography, allowing for the creation of specific nonlinear acoustic fields to improve the efficacy and precision of therapeutic procedures. Furthermore, manipulating the amplitudes or phases of higher harmonics could improve applications such as harmonic imaging and enhancing peak positive or peak negative pressures. The present investigation considered a homogeneous domain with the physical parameters of water. Our findings are also applicable to other nonlinear domains, however, according to the power law absorption, larger acoustic absorption will reduce the amplitude of the harmonics while a higher nonlinearity parameter will lead to faster harmonic generation[42]. In addition, in heterogeneous domains such as biological tissue, transmission, reflection, and refraction at the interfaces should also be considered.

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Chapter 5

Nonlinear acoustic holography with adaptive sampling

5.1 Details of publication

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5.2 Abstract

Accurate and efficient numerical simulation of highly nonlinear ultrasound propagation is essential for a wide range of therapeutic and physical ultrasound applications. However, due to large domain sizes and the generation of higher harmonics, such simulations are computationally challenging, particularly in three-dimensional problems with shock waves. Current numerical methods are based on computationally inefficient uniform meshes that require the highest harmonic to be resolved across the entire domain. To address this challenge, we present an adaptive numerical algorithm for computationally efficient nonlinear acoustic

holography. At each propagation step, the algorithm monitors the harmonic content of the acoustic signal and adjusts its discretization parameters accordingly. This enables efficient local resolution of higher harmonics in areas of high nonlinearity while avoiding unnecessary resolution elsewhere. Furthermore, the algorithm actively adapts to the signal’s nonlinearity level, eliminating the need for prior reference simulations or information about the spatial distribution of the harmonic content of the acoustic field. The proposed algorithm incorporates an upsampling process in the frequency domain to accommodate the generation of higher harmonics in forward propagation and a downsampling process when higher harmonics are decimated in backward propagation. The efficiency of the algorithm was evaluated for highly nonlinear three-dimensional problems, demonstrating a significant reduction in computational cost with a nearly 50-fold speedup over a uniform mesh implementation. Our findings enable a more rapid and efficient approach to modeling nonlinear high-intensity focused ultrasound wave propagation.

5.3 Introduction

Acoustic holography is a technique that enables the reconstruction of three-dimensional acoustic fields by projecting measured or simulated two-dimensional data from the hologram plane to the rest of the volume. Accurate and efficient nonlinear acoustic holography of high-intensity ultrasound is an essential tool for a wide range of applications in the fields of medical and physical acoustics [1? –5]. In high-intensity focused ultrasound (HIFU) therapy, it is critical to characterize and model the nonlinear pressure field to establish therapeutic protocols and to predict the ultrasound-induced biological effects [6–8].

Acoustic holography is also widely used in source synthesis and identification due to its exceptional ability to visualize and analyze complex three-dimensional sound fields. Holographic

techniques are used to compute the necessary phase and/or amplitude maps to create desired sound-field structures. These structures are then physically realized using either phased array transducers or passive acoustic devices such as holographic lenses or metasurfaces, which enable arbitrary sound beam shaping and patterning. [9–16]. Such techniques have been used in various applications, including particle levitation and lithotripsy [17, 18], in which nonlinear effects such as acoustic streaming and harmonic generation are present. Nonlinear acoustic holography is also utilized for source identification, allowing for the examination of the locations and characteristics of radiating surfaces for high-level noise diagnostics and shock-wave control [19]. Additionally, nonlinear acoustic holography is used for computing the propagation of higher harmonics, which is essential in nonlinear imaging applications, such as harmonic imaging and diagnostics [20].

However, simulating the propagation of nonlinear acoustic fields is a computationally challenging problem [6, 21, 1]. Often the computational domain is much larger than the smallest wavelength present. Moreover, the nonlinear problem requires the use of extremely fine spatial and temporal discretization to accurately capture the generated harmonics. As a result, the computational cost quickly escalates, especially for three-dimensional problems. Large number of harmonics should be considered when steep shock-wave fronts are present. Resolving up to several hundred harmonics is required if the propagating medium is highly nonlinear with low frequency-dependent attenuation, such as water. However, in media such as soft tissue, where higher harmonics are more strongly attenuated, the requirements for the number of harmonics are less stringent [21]. Significant efforts have been made to reduce the computational cost of such simulations.

Tavakkoli *et al.* [22, 23] introduced computationally efficient models based on a second-order operator splitting approach, with a fractional step-marching scheme, capable of simulating finite-amplitude ultrasound beam propagation in water and in tissue. Wherein linear and

nonlinear effects are propagated separately over incremental steps, and the computation of the diffractive substeps is based on an angular spectrum technique for accurate and efficient implementation of diffractive propagation from non-axially symmetric sources. However, modeling of the shock fronts often requires a very dense temporal sampling[24]. Adaptive meshes and nonuniform step sizes may further reduce computational cost [25], especially when considering full 4D (three dimensions of space and time) field simulations.

Since nonlinear effects are highly localized around the focal point [26], very fine discretization is only required locally in the computational domain at the regions that exhibit the highest nonlinearity and harmonic content. Recent techniques used computationally efficient nonuniform spatial meshes with more refined numerical discretization in regions with the highest nonlinearity [27, 6, 28]. Overall, this can result in a significant reduction in the total number of grid points, and thus memory and execution time without compromising accuracy. However, current techniques for designing nonuniform meshes require prior knowledge of the spatial distribution of the harmonics in the ultrasound field. Because the ultimate goal of such techniques is to eliminate the need to carry out reference simulations on computationally inefficient uniform meshes, a reference simulation on *a priori* basis is assumed to be unavailable. In addition, such simulations would require mesh convergence investigations since the actual harmonic content of the signal can't be predicted accurately, adding to the computational burden. Furthermore, when patterns with complex focal zones are considered, or when backward propagation is used to identify sources of unknown locations or characteristics, the problem of designing a non-uniform mesh becomes increasingly difficult.

The Adaptive Nonlinear Acoustic Holography (ANAH) algorithm is introduced in this paper as a novel approach to nonlinear acoustic holography simulations. At each propagation step, the ANAH algorithm actively monitors the harmonic content of the wavefront and adjusts the

discretization parameters as needed. Other than basic parameters like propagation medium and fundamental excitation frequency, such implementation eliminates the need for reference simulations or prior knowledge of the ultrasound field. We will demonstrate ANAH for capturing shock-wave fronts in three dimensions, which is a significant challenge in nonlinear acoustics. In addition, we will show how ANAH can be used for backward propagation in source identification applications.

This article is structured as follows: Section II A outlines the mathematical model employed for the nonlinear forward and backward propagation, and Section II B introduces the proposed adaptive algorithm. In section III, we validated and investigated the performance of the ANAH algorithm for forward and backward propagation. We also discuss the most important parameters in the algorithm and their effects on the computation speed and accuracy. Finally, in Section IV, we summarise, conclude the present work, and discuss future directions.

5.4 Theory

5.4.1 Forward and Backward Projection

The wave-vector-frequency-domain method [29–31] is implemented to carry out the nonlinear forward and backward propagations. This approach is based on the generalized Westervelt equation and can be considered an extended version of the angular spectrum method. The acoustic field is computed by marching in the spatial domain along the axis normal to the source plane.

Starting with the generalized Westervelt equation:

$$\rho \nabla \cdot \left(\frac{1}{\rho} \nabla p \right) - \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} + \frac{\delta}{c^4} \frac{\partial^3 p}{\partial t^3} + \frac{\beta}{\rho c^4} \frac{\partial^2 p^2}{\partial t^2} = \gamma \frac{\partial p}{\partial t} \quad (5.1)$$

where p is the acoustic pressure, ρ is the ambient density, c is the speed of sound, δ is the sound diffusivity and β is the nonlinearity coefficient. The frequency-independent absorption term $\gamma \partial p / \partial t$ accounts for the absorption layer close to the computational boundary [32]. Applying the normalized wavefield $f = p / \sqrt{\rho}$ and performing the Fourier transform with respect to X , Y , and t yields:

$$\begin{aligned} \frac{\partial^2}{\partial Z^2} \tilde{F} + K^2 \tilde{F} = & \\ F_{XY} \left\{ \left[\sqrt{\rho} \nabla^2 \frac{1}{\sqrt{\rho}} - \frac{\omega^2}{c_0^2} \left(\frac{c_0^2}{c^2} - 1 \right) + \frac{i \delta \omega^3}{c^4} + i \omega \gamma \right] F_t(f) \right\} & \\ + F_{XY} \left(\frac{\beta \omega^2}{\rho c^4} F_t(f^2) \right) & \end{aligned} \quad (5.2)$$

where $\tilde{F}$ is the Fourier transform of f , F_{XY} is the Fourier transform operator in X - and Y -dimensions, F_t is the Fourier transform operator in the time domain, c_0 is the background sound speed and $K^2 = \omega^2 / c_0^2 - k_X^2 - k_Y^2$, k_X and k_Y are the wavenumbers in X - and Y -dimensions, respectively. An implicit, one-way propagation can be derived from the 1-D Green's function in the form of an integral equation [31], such that

$$\tilde{F}(Z) = \tilde{F}(0) e^{iKZ} + \frac{e^{iKZ}}{2iK} \int_0^Z e^{-iKZ'} M(f(Z')) dZ' \quad (5.3)$$

where,

$$\begin{aligned}
 M(f) = & \\
 & F_{XY} \left\{ \left[\sqrt{\rho} \nabla^2 \frac{1}{\sqrt{\rho}} - \frac{\omega^2}{c_0^2} \left(\frac{c_0^2}{c^2} - 1 \right) + \frac{i\delta\omega^3}{c^4} + i\omega\gamma \right] F_t(f) \right\} \\
 & + F_{XY} \left(\frac{\beta\omega^2}{\sqrt{\rho}c^4} F_t(f^2) \right)
 \end{aligned} \tag{5.4}$$

Equation (5.3) is solved by using a Simpson-like rule [29, 33].

The pressure distribution on the source plane or any arbitrary plane is reconstructed using the backward projection. By changing Z in (5.3) to $-Z$, the backward projection is obtained as:

$$\tilde{F}(-Z) = \tilde{F}(0)e^{-iKZ} - \frac{e^{-iKZ}}{2iK} \int_0^{-Z} e^{iKZ'} M(f(-Z')) dZ' \tag{5.5}$$

Using this model, wave effects such as full-wave diffraction, attenuation, dispersion, and nonlinearity are considered, including nonlinearity in arbitrary directions, making it particularly accurate for highly focused transducers[31]. The present formulation only includes one-way propagation with no reflections making it only accurate for modeling wave propagation in weakly heterogeneous media [33]. Phase correction, amplitude compensation, and multiple reflections were later incorporated with the one-way model to improve the accuracy for strongly heterogeneous media such as transcranial ultrasound propagation[34].

The Kramers-Kronig dispersion relation is applied directly by replacing the speed of sound c with c_p and $c_p = (1/\hat{c} + \alpha_0 \tan(\pi y/2) \omega^{y-1})^{-1}$, where $\hat{c}$ is the sound speed at zero frequency, y is the power-law exponent, α_0 is the absorption in nepers per megahertz $^{-y}$ per meter and $\alpha_o = \alpha_{NP} \omega^{-y}$.

5.4.2 The Adaptive Algorithm

The acoustic field calculations are performed in both the temporal and frequency domains by numerically propagating the field onto parallel projection planes along the propagation axis. The axial distance between each projection plane, i.e. the step size ΔZ , should be small enough to ensure the stability and accuracy of the numerical scheme [30]. In the temporal domain, the time resolution Δt should adhere to the Nyquist-Shannon sampling theorem, which states that under perfect conditions, a harmonic signal can be perfectly reconstructed when sampled at a rate of two points per period of its highest frequency $\Delta t = 1/2f_{max}$. In this case, f_{max} is the frequency of the highest generated harmonic. In the case of highly nonlinear fields with shock-waves, a large number of harmonics must be considered (up to hundreds of harmonics for shock-wave modeling) as such an extremely small step size ΔZ and temporal resolution Δt is necessary, which could lead to unfeasible long computation time, especially in three-dimensional problems. In addition, the Gibbs effect occurs when insufficient harmonics represent shock waves. The errors are typically manifested as high-frequency oscillations near the shock discontinuity. This causes instability in the numerical scheme along with amplification and accumulation of errors along the planar projection [35].

To this end, we present an adaptive algorithm that adjusts the discretization parameters ΔZ and Δt according to the highest harmonic detected in the acoustic signal. The adaptive algorithm implements a monitoring function that tracks the frequency of the highest harmonic f_{max} in the signal at each propagation step. This maximum is extracted by finding the frequency of the highest harmonic with an amplitude larger than a threshold value. The threshold value A_{Th} is directly related to the amplitude of the fundamental and can be expressed as $A_{Th} = A_F R_h$, where A_F is the amplitude of the fundamental and R_h is a chosen fraction value. A smaller R_h means a lower threshold value which leads to more harmonics being included.

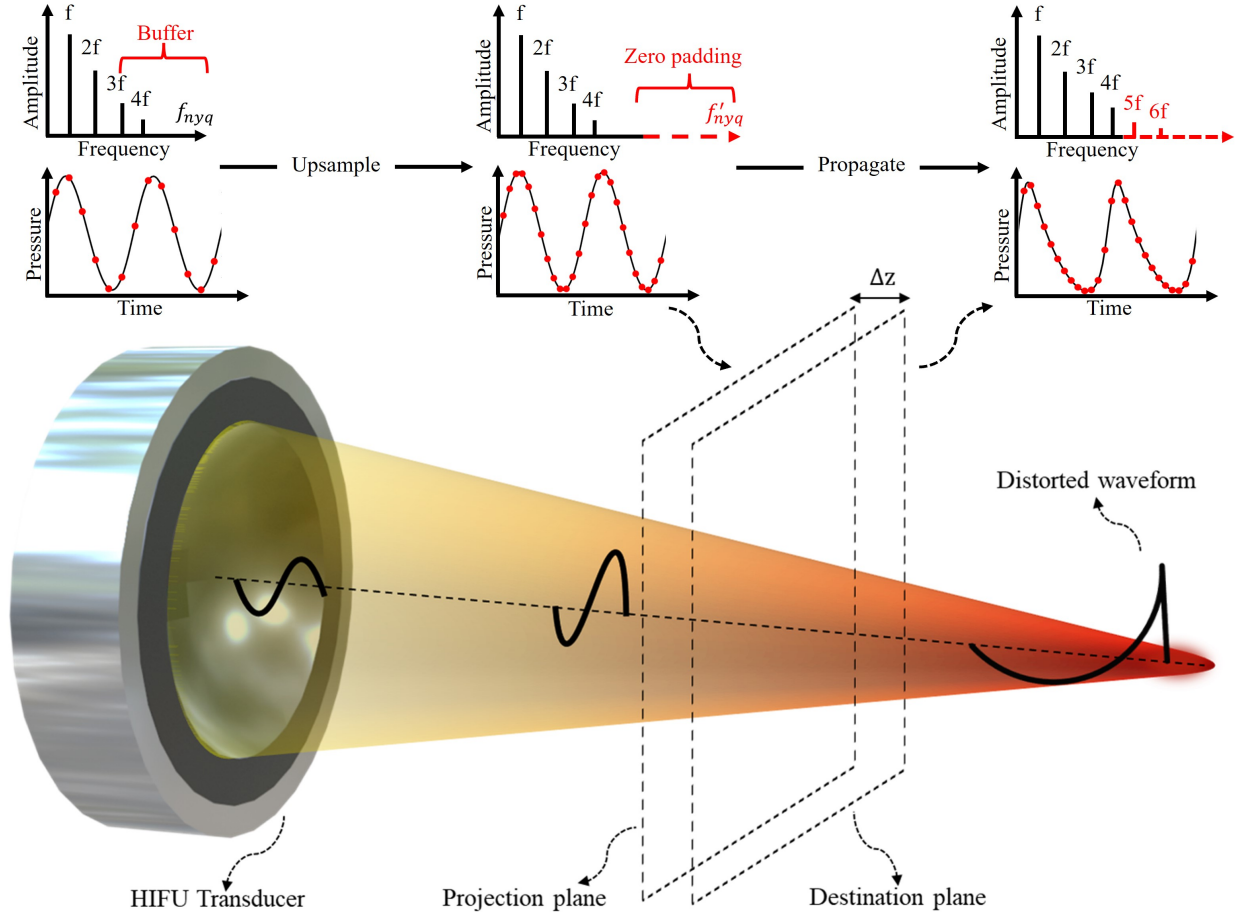


Figure 5.4.1: Schematic representation of focused ultrasound nonlinear acoustic wave propagation of an initially linear wave (bottom left) to a highly distorted waveform at the focal point (bottom right). The upsampling of the signal in the frequency domain is also illustrated (Top). As the higher harmonics overstep into the spectral buffer zone (top left), the signal is interpolated by zero-padding the spectrum (top middle). The wave is then nonlinearly propagated forward from the projection plane to the destination plane, and the newly generated higher harmonics can be resolved due to the upsampling process.

To avoid aliasing errors and minimize the Gibbs effect, the algorithm maintains a spectral buffer b between the frequency of the highest harmonic f_{max} , and the Nyquist frequency f_{Nyq} , such that $f_{Nyq} > f_{max} + b$. As the wave propagates and more harmonics are generated f_{max} increases and oversteps into the buffer region such that $f_{Nyq} > f_{max} \geq f_{Nyq} - b$. To accommodate the newly generated harmonics and maintain the accuracy of the simulation, the original time signal is interpolated to increase the original sampling rate and Nyquist frequency such that $\Delta t' = \frac{1}{2(f_{max} + n_h f_0)}$ and $f'_{Nyq} = f_{max} + n_h f_0$. Where $\Delta t'$ and f'_{Nyq} are respectively the sampling rate and Nyquist frequency of the interpolated signal and f_0 is the fundamental frequency. The size of the spectral padding $n_h f_0$ is a function of the fundamental frequency f_0 and the positive integer n_h , such that, at each adaptive step, the Nyquist frequency is increased by n_h harmonics. For computational efficiency, the interpolation is carried out in the frequency domain by zero-padding the original spectrum of the signal [36, 37]. Let us consider an initial wave signal $p[n]$, $n = 0, 2, \dots, L - 1$ where n is the time index, and L is the sample length. The discrete Fourier transform (DFT) of $p[n]$ is defined as:

$$P[k] = \sum_{n=0}^{L-1} p[n] e^{-2\pi j k n / L} \quad (5.6)$$

where $P[k]$ is the complex frequency-domain representation of the signal, k is the frequency index, and j is the imaginary unit. In addition, the inverse discrete Fourier transform (IDFT) is defined as:

$$p[n] = \frac{1}{L} \sum_{k=0}^{L-1} P[k] e^{2\pi j k n / L} \quad (5.7)$$

Notice that the scaling by $1/L$ is included in the IDFT, which is the same choice as in MATLAB's FFT and IFFT implementations.

When the spectrum of a signal is appended with zeros, the inverse DFT (IDFT) effectively applies the aliased sinc function for time-domain interpolation [36]. The original spectrum

is zero-padded, as illustrated in Fig. 5.4.1. The modified spectrum $P'[k]$, has length $N' = N(\Delta t/\Delta t')$ where N is the number of samples in the original spectrum. The modified spectrum P' retains all information of the original spectrum P and is padded with exactly $N' - N - 1$ zeros filling the high-frequency part of the spectrum.

The construction of the modified spectrum is described in the following equations [36, 37]:

$$P'(k) = \begin{cases} (\Delta t'/\Delta t)P(k), & 0 \leq k < \frac{N}{2} \\ \frac{1}{2}(\Delta t'/\Delta t)P\left(\frac{N}{2}\right), & k = \frac{N}{2} \\ 0, & \frac{N}{2} < k < N' - \frac{N}{2} \\ \frac{1}{2}(\Delta t'/\Delta t)P\left(\frac{N}{2}\right), & k = N' - \frac{N}{2} \\ (\Delta t'/\Delta t)P(k - N' + N), & N' - \frac{N}{2} < k < N', \end{cases} \quad (5.8)$$

Such construction retains Hermitian symmetry; thus, the result of the IDFT is a real-valued signal.

In backward propagation, the initially nonlinear signal is propagated back to the source plane, causing higher harmonics to be decimated. As a result, the signal is downsampled by the adaptive algorithm to account for the reduction in harmonic content. This downsampling approach improves computational efficiency while maintaining accuracy in nonlinear acoustic holography simulations. The downsampling is also accomplished in the frequency domain by truncating part of the spectrum. Only the spectral information up to the new Nyquist frequency is retained. The monitoring function triggers the downsampling process when the relation $G < f_{Nyq} - f_{max}$ is true. G represents the maximum allowed spectral gap between the Nyquist frequency f_{Nyq} and the frequency of the highest harmonic f_{max} before the signal is truncated. The new sample rate and Nyquist frequency of the truncated signal are expressed

as $\Delta t' = \frac{1}{2(f_{Nyq} - G)}$ and $f'_{Nyq} = f_{Nyq} - G$. The spectral truncation process is described in the following equation [36, 37]:

$$P'(k) = \begin{cases} (\Delta t' / \Delta t) P(k), & \text{for } 0 \leq k < \frac{N'}{2} \\ 0, & \text{for } k = \frac{N'}{2} \\ (\Delta t' / \Delta t) P(N - N' + k), & \text{for } \frac{N'}{2} < k \leq N' - 1, \end{cases} \quad (5.9)$$

Finally, in both the back and front propagations, the value of the step size ΔZ is also updated according to the new Nyquist frequency such that $\Delta Z' = c/2f'_{Nyq}$. The spatial resolutions ΔX and ΔY are fixed throughout the propagation process since the discretization requirements aren't as strict when the propagation direction is mainly along the axis of the transducer. [30, 31].

5.5 Results and discussion

5.5.1 Validation

To verify our approach, we simulated a single-element spherically focused ultrasound transducer. The simulation results of the ANAH algorithm were examined by comparing the obtained data with full-wave numerical simulations based on the k-space pseudospectral method [38]. The numerical model solves a set of coupled partial differential equations equivalent to a generalized Westervelt equation. The accuracy and validity of this numerical model have been previously verified with analytical solutions and experimental measurements [39, 40]. The pseudospectral method was implemented using the open-source MATLAB Toolbox k-wave, which is available online[41] (The performance of the C++ version when running

axisymmetric simulations with non-square domains is orders of magnitude slower due to peculiarities with the discrete trigonometric transforms in Intel MKL[42]). The pseudospectral method was used to perform homogeneous axisymmetric nonlinear acoustic simulations with power law absorption [43]. The numerical computations were carried out at an excitation frequency of 1 MHz, and the propagation medium was modeled using the following physical parameters: $\rho_0 = 1000 \text{ kg/m}^3$, $c_0 = 1500 \text{ m/s}$, $\beta = 3.6$, $\alpha_0 = 0.05 \text{ dB/MHz}$ and $\gamma = 2$. Here ρ_0 , c_0 , β , are the density, ambient speed of sound, and nonlinearity coefficient, respectively. While α_0 and γ , respectively, are the absorption coefficient and the power law exponent. The medium parameters are close to those of water. Highly attenuating media, such as soft tissue, are considered later in this paper. The spatial dimensions of the computational domain are $20 \text{ mm} \times 20 \text{ mm}$, corresponding to the radial and axial directions with a spatial discretization of 500 grid points per wavelength ($dx = 3\mu\text{m}$) and a Courant-Friedrichs-Lewy (CFL) number of 0.25. In addition, perfectly matched layers (PMLs) were added to prevent any reflections at the boundaries. The modeled focused transducer has a focal length and outer diameter of 18 mm ($F_\# = 1$). The pressure data at a plane with an axial offset of $z = 4 \text{ mm}$ away from the source is obtained from k-wave simulations and was used as an input to the ANAH algorithm, as shown in Fig. 5.5.1.

For computational efficiency, k-wave simulations were computed in axisymmetric coordinates. However, all the ANAH simulations were carried out in the full spatial domain with the three-dimensional coordinates (i.e. X, Y, and Z) with $n_h = 20$ and $R_h = 0.002$. Here, we note that the axisymmetric cases are considered to enable efficient validation study, ANAH isn't limited to axisymmetric acoustic fields or geometries. Hence, ANAH allows the computation of more complex nonlinear ultrasound propagation and the inclusion of elaborate geometries in the computational domain. Two simulations were carried out for the cases of a moderately nonlinear field at a source pressure of $P_0 = 2 \text{ MPa}$ and a highly

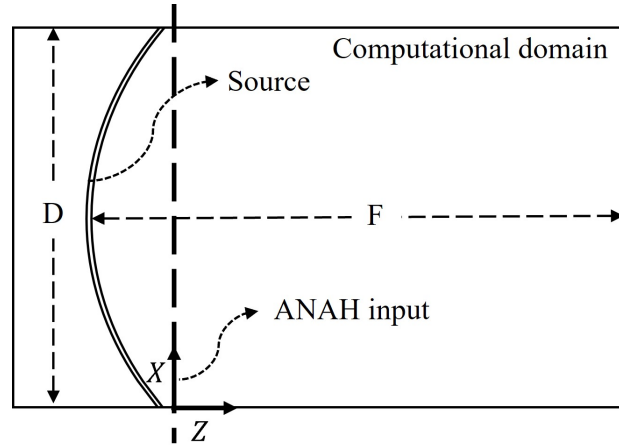


Figure 5.5.1: Schematic illustration of the computational domain, the simulated focused ultrasound transducer, and the input plane used to initialize the ANAH algorithm.

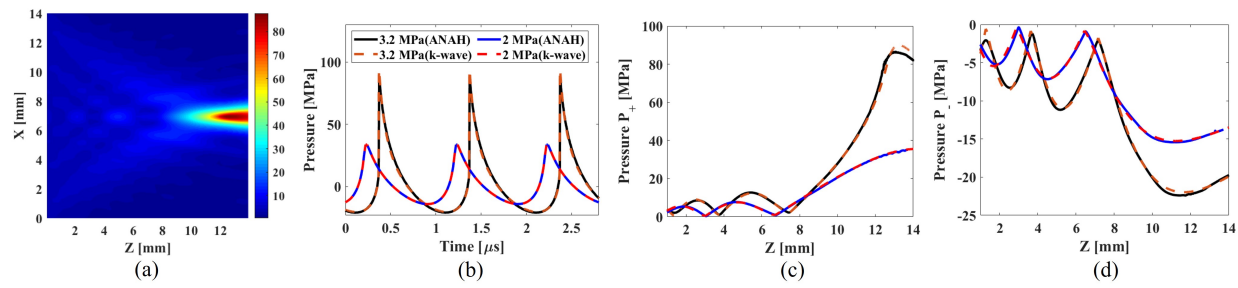


Figure 5.5.2: Comparison of the ANAH algorithm with k-wave results. (a) Axial cross-section of the obtained peak positive pressure using ANAH for a source pressure of $P_0 = 3.2$ MPa. Comparison of the (b) pressure time waveforms, (c) axial peak positive pressure, and (d) axial peak negative pressure for source pressures of $P_0 = 2$ and $P_0 = 3.2$ MPa.

nonlinear field with shock-fronts at a source pressure of $P_0 = 3.2$. Planar sources with these amplitudes correspond to Gol'dberg numbers [44] ($\bar{z}/\ell_\alpha$, where $\bar{z}$ is the shock formation distance and ℓ_α is the absorption length) of 380 and 606, respectively. Fig. 5.5.2 (a) shows the axial cross-section of the simulated field using the ANAH algorithm for $P_0 = 3.2$ MPa. The steady-state time waveforms at the point of maximum peak positive pressure are compared in Fig. 5.5.2 (b). Good agreement is observed between the k-wave simulations and ANAH for the case of moderate and high nonlinearity. Furthermore, the peak positive and peak negative axial pressures are compared in Fig. 5.5.2 (c) & (d), respectively. To compare the axial pressures quantitatively, the L_2 norm errors of the peak positive and peak negative axial pressures were calculated. Here, the relative error norm L_2 is defined as $L_2 = \|p_{\text{ref}}(z_i) - p(z_i)\|_2 / \|p_{\text{ref}}(z_i)\|_2$. For $P_0 = 2$ MPa, the errors norms calculated were $L_2 = 1.6\%$ and $L_2 = 2.3\%$ for the axial peak positive and peak negative pressures, respectively. When the source pressure is increased to $P_0 = 3.2$ MPa, the errors norms calculated were $L_2 = 3.8\%$ and $L_2 = 2.59\%$ for the axial peak positive and peak negative pressures, respectively. It is noted that for the highly nonlinear case, the k-wave results show approximately 4% higher peak positive pressure around the focal region, as shown in Fig. 5.5.2 (b) & (c). We attribute this error to the observed Gibbs oscillations and overshoot at the shock front in the k-wave simulations. Including more harmonics in the k-wave simulations would minimize such effects. However, it is computationally prohibitive to include more harmonics. In the current study, 250 harmonics were considered in the k-wave simulations with a total simulation time of 92 hrs. Nevertheless, simulation results of the ANAH and k-wave are in overall good agreement for the moderately and highly nonlinear cases.

5.5.2 ANAH performance

In order to showcase the effectiveness of the proposed ANAH in enhancing the computational efficiency of nonlinear simulations, a comparison is made between its performance and that of equivalent simulations carried out on uniform meshes. To examine the effect of nonlinearity level on the performance of the algorithm, the simulations were carried out for source pressures that range from $P_0 = 0.2$ MPa to $P_0 = 3.2$ MPa. Fig. 5.5.3 (a) illustrates the maximum harmonic detected within the computational domain via the monitoring function as the source pressure increases. As expected, the rise in acoustic intensity results in an increase in nonlinearity level and the generation of more harmonics. Fig. 5.5.3 (b) shows the evolution of the detected harmonic content in the acoustic field as the wave propagates to the focal point. The ANAH algorithm progressively adjusts the Nyquist frequency to resolve higher harmonics only when they are detected by the monitoring function. This is in contrast to a uniform mesh where the highest harmonic (illustrated dotted red line) must be resolved throughout the entire computational domain. In Fig. 5.5.3 (b), it can also be observed that when approaching shock, a large number of harmonics are generated with much smaller amplitudes compared to the fundamental. This could lead to erroneous detection of the highest harmonics in a single spatial step. As we will show later, this behavior is not observed when highly attenuating media are considered. Furthermore, since the harmonic content decreases post-shock, implementing a two-way re-sampling scheme to reduce sampling beyond the focal region is possible and could improve computational performance. This is, however, more challenging to apply for more complex fields with multifocal regions. In addition, the stability of the adaptive algorithm is essential for applying such a scheme appropriately. The effectiveness of the ANAH algorithm, in comparison to a uniform mesh implementation, is directly related to the degree of localization of the nonlinear effects. To evaluate the degree of localization, we implement the frequency reduction measure (FRM),

which is defined as:

$$FRM = \frac{1}{z} \int_0^z 1 - f_{nyq}(z')/f_{\max} dz' \quad (5.10)$$

where $f_{nyq}(z')$ is the Nyquist frequency at each propagation step. FRM varies between 0 for the linear case where the local Nyquist frequency equals the maximum overall frequency in the whole domain (i.e., the adaptive algorithm wasn't active) and 1 in the case where the local Nyquist frequency was infinitely smaller than the maximum frequency, in this case, the adaptive algorithm will have the highest performance improvement.

Fig. 5.5.3 (c) shows the calculated FRM as the source pressure increases. Initially, when the acoustic field is linear, the FRM equals zero since the local nonlinear effects aren't present. However, as the source pressure is increased, nonlinearities and their localization increase, and an FRM of 0.82 is calculated at $P_0 = 3.2$ MPa.

As expected, the simulation times shown in Fig. 5.5.3 (d) illustrate how using uniform meshes scales unfavorably as nonlinearities grow compared to the ANAH implementation. Furthermore, Fig. 5.5.3 (e) shows the speedup in the simulation time when using the ANAH versus the uniform mesh. This speedup follows a similar trend to the FRM, revealing the ANAH's effectiveness, particularly at high nonlinearities, where the ANAH simulation executes nearly 50 times faster than the equivalent uniform mesh implementation at a source pressure of $P_0 = 3.2$ MPa. Furthermore, the results also show that the monitoring function has minimal computational overhead, as both implementations exhibit almost identical execution times when the field is linear for $P_0 = 0.2$ MPa. We should point out that the uniform mesh simulations were only run for the first ten propagation steps. By taking into account the total number of propagation steps in the entire simulation, the total simulation time using a uniform mesh can be predicted. The computation time required to run the full simulations with a uniform mesh is prohibitively long (up to 1500 hours).

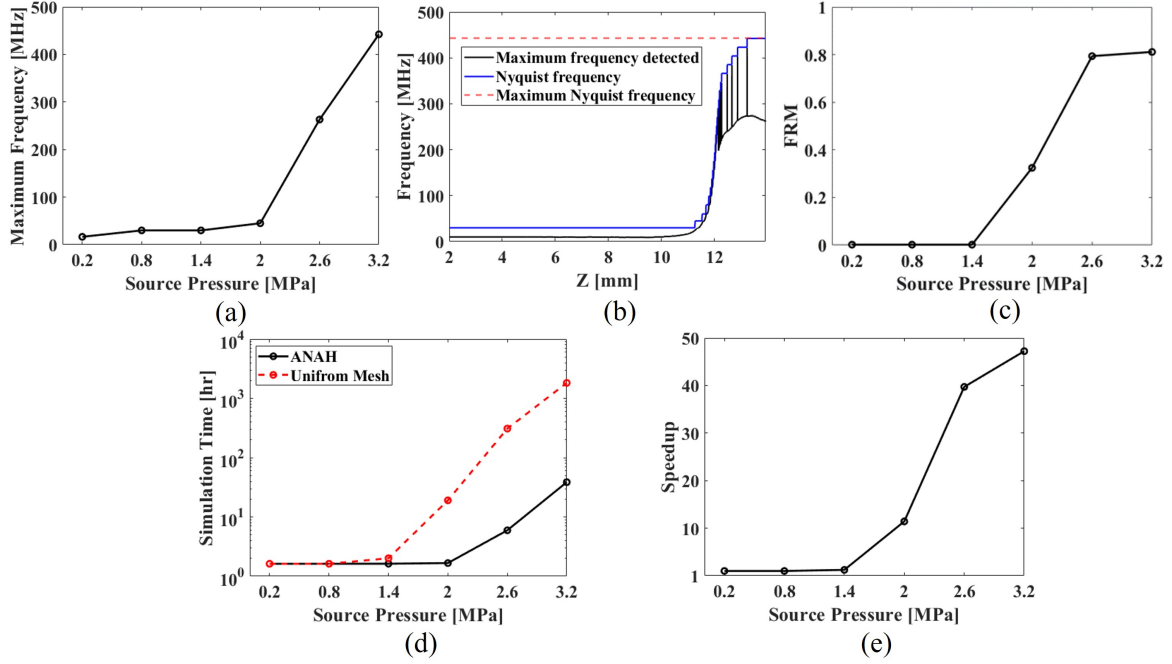


Figure 5.5.3: Evaluation of the ANAH performance compared to a uniform mesh implementation. (a) The frequency of the highest detected harmonic as the source pressure increases. (b) The harmonic content and the adjusted Nyquist frequency as the acoustic field is propagated towards the focal point for $P_0 = 3.2$ MPa. (c) The FRM as the source pressure increases. (d) Comparison between the simulation times of the ANAH and uniform mesh implementations as the source pressure increases. (e) The speedup of the simulation time when ANAH is implemented as the source pressure increases.

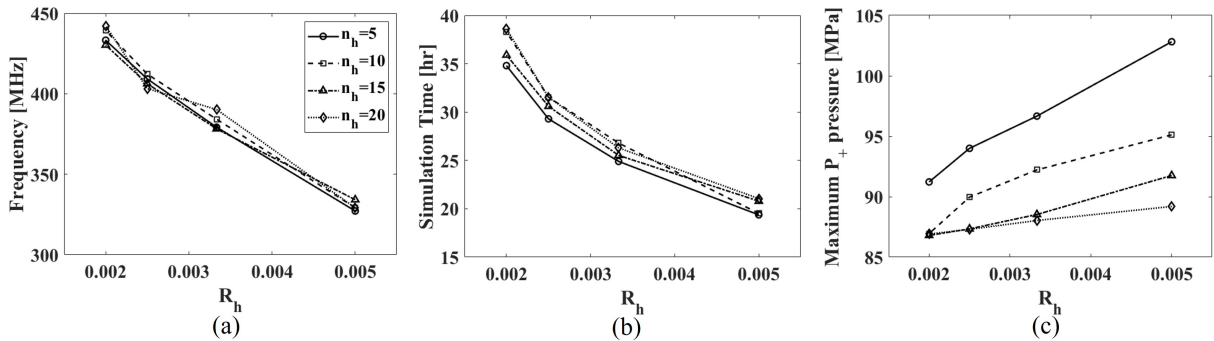


Figure 5.5.4: Effects of the adaptive parameters on the simulation time and accuracy of ANAH at $P_0 = 3.2$ MPa. (a) Maximum Nyquist frequency (b) total execution time, and (c) convergence of the maximum peak positive as a function of the adaptive parameters.

To gain a better understanding of the adaptive behavior of the algorithm, we investigate the influence of its primary parameters, namely n_h and R_h , on the simulation time and accuracy. This investigation focuses on the highest nonlinearity level, with $P_0 = 3.2$ MPa. As depicted in Fig. 5.5.4 (a) & (b), the maximum Nyquist frequency and the simulation time are mainly influenced by the selection of R_h . However, when the convergence of the maximum peak positive in the simulation is considered, Fig. 5.5.4 (c) clearly shows that the value of n_h has a significant impact on the simulation accuracy.

When $n_h = 20$ is considered, the maximum convergence error is calculated to be 2.3% for the largest value of $R_h = 0.005$. However, for $n_h = 5$, the convergence error increases significantly and ranges from 18.5% to 5% for $R_h = 0.005$ and $R_h = 0.002$, respectively. As such, convergence wasn't achieved for $n_h = 5$ even when R_h is minimized. For $n_h = 10$ and $n_h = 15$, the large convergence error is diminished when the R_h is minimized to a value of $R_h = 0.002$. When n_h is set to a value that is too low, the adaptive algorithm fails to match the actual generation rate of the harmonics in the domain, leading to significant inaccuracies in the simulation and a large convergence error. Furthermore, it should be noted that increasing the value of n_h may be a more advantageous approach in achieving accurate simulation results, as opposed to solely minimizing R_h . This is due to the fact that, as we showed, an increase in n_h does not significantly affect the computational time, yet has a significant impact on the accuracy of the simulation results. This investigation highlights that employing a larger spectral buffer (represented by a larger value of n_h) offers the potential to achieve accurate simulations without the need for overly sensitive detection (indicated by a smaller value of R_h). This approach allows for better accuracy while maintaining manageable simulation time. Therefore, choosing the appropriate values for n_h and R_h is crucial for achieving accurate and efficient simulations.

5.5.3 Weakly heterogeneous media

To validate and demonstrate the performance of the proposed ANAH algorithm for more realistic heterogeneous media and highly attenuating soft tissue, two cases are considered. In the first case, we consider a multi-layer geometry with a water-like medium in the first layer and liver tissue in the second layer, as shown in Fig. 5.5.5 (a). In the second case, a water-like background medium is considered with a cylindrically shaped tumor tissue, as shown in Fig. 5.5.5 (d). The corresponding acoustic properties of each medium are summarised in Table 5.1 [45]. A power law exponent of 2 is assumed for all media due to the limitations of the k-wave axisymmetric formulation[43]. For source pressure of $P_0 = 3.2$ MPa, the peak axial positive pressures obtained using ANAH and k-wave are compared in Fig. 5.5.5 (b) & (e). Good agreement is observed with a norm error of $L_2 = 6.2\%$ for the multi-layer domain and an error of $L_2 = 4.1\%$ for the tumor case. Fig. 5.5.5 (c) & (f) show the detected harmonics at each propagation step. Due to the significant attenuation of soft tissue, the harmonic content is approximately an order of magnitude lower compared to the homogeneous water-like domain in Fig. 5.5.3 (b). For the multi-layer domain, a speed-up of 7.7 was achieved using the ANAH compared to the uniform mesh implementation with a calculated FRM value of 0.53. For the tumor domain, the speed-up was 9.5 with an FRM of 0.56. This investigation highlights the performance enhancement achieved by using ANAH even when highly attenuating media are considered, and as a result, a relatively lower number of harmonics are generated. The implemented mixed-domain formulation is only accurate for weak heterogeneity and only considers the forward wave with no reflections [33]. For strongly heterogeneous media such as bone, phase and amplitude corrections should be implemented in addition to reflections to achieve accurate results [34]. Strongly heterogeneous media are going to be considered in the context of ANAH in future work.

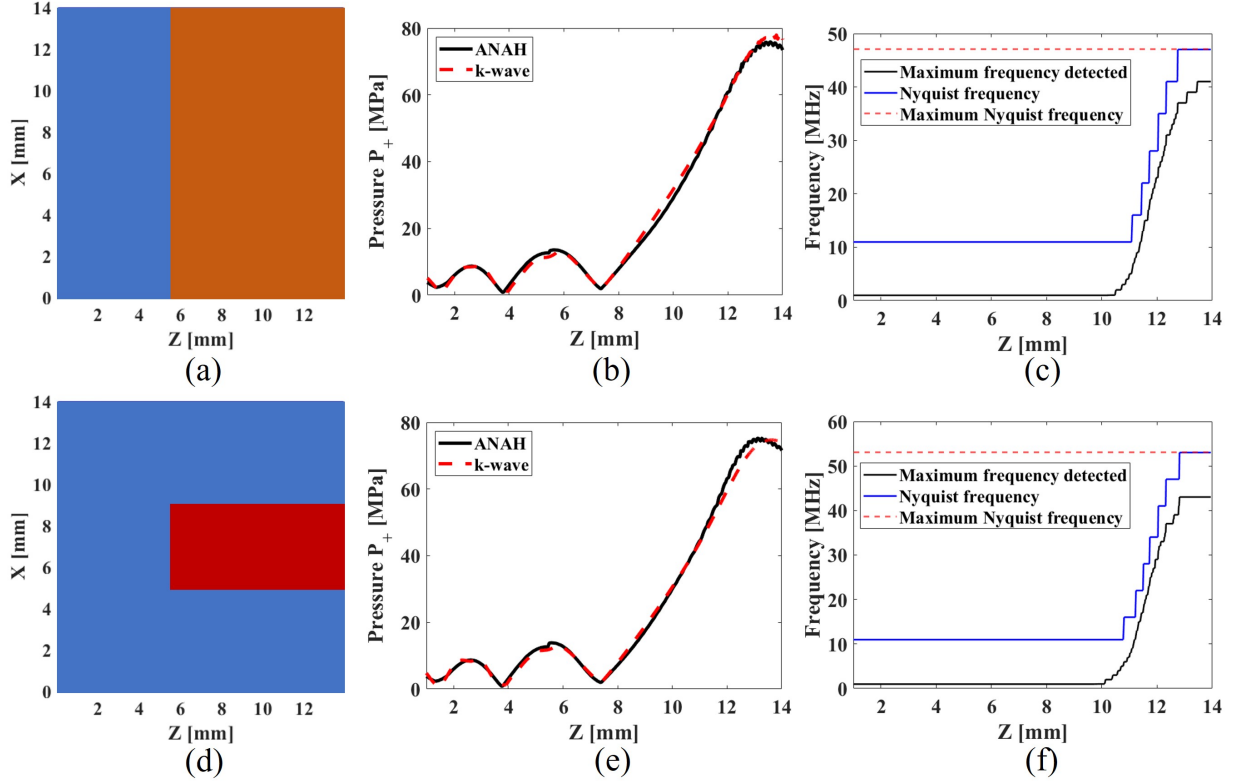


Figure 5.5.5: Evaluation of ANAH for weakly-heterogeneous propagation media. (a) the geometry of the multi-layer case, the blue part is the water-like medium, and the orange part represents the liver tissue. (b) & (c) are, respectively, the axial peak positive pressure and the harmonic content of the simulated multi-layer medium. (d) the geometry of the cylindrical tumor, the blue part is the water-like medium, and the red part represents the tumor. (e) & (f) are, respectively, the axial peak positive pressure and the harmonic content of the simulated water-tumor medium.

Table 5.1: Tissue Acoustical Properties

	Nonlin. coefficient	Speed of sound m/s	Density kg/m ³	Atten. coef.@ 1MHz (dB/cm)	Power law exponent
Water	5.8	1500	1000	0.05	2
Liver	4.3	1595	1060	0.5	2
Tumor	4.5	1563	1070	0.57	2

5.5.4 Backward propagation

In this section, we demonstrate ANAH for backward propagation. Here, the signal is down-sampled as higher harmonics are decimated, and the field is propagated back to the source plane. This technique has potential applications in efficient nonlinear nearfield acoustic holography [19], sound focusing and aberration correction [46], and cavitation mapping [47]. A desired field could also be generated synthetically and then projected backward to provide information on the source. Forward and backward iterations are used to obtain the geometry of acoustic holographic lenses or metasurfaces. [9]. Implementing ANAH in this context can significantly reduce the computation time required to generate the necessary geometry for generating complex high-intensity nonlinear ultrasound fields.

Time reversal techniques are first used to obtain an image amplitude pressure distribution with an "ANAH" shape at a plane 25 mm away from the source plane, as shown in Fig. 5.5.6 (a). The distribution of the peak positive pressure and phase of the source are shown in Fig. 5.5.6 (b) & (c), respectively. ANAH is then implemented to back propagate the field from the image plane back to the source plane. The pressure and phase values along the dashed line are compared in Fig. 5.5.6 (d) & (e), respectively. The dashed line intersects the image

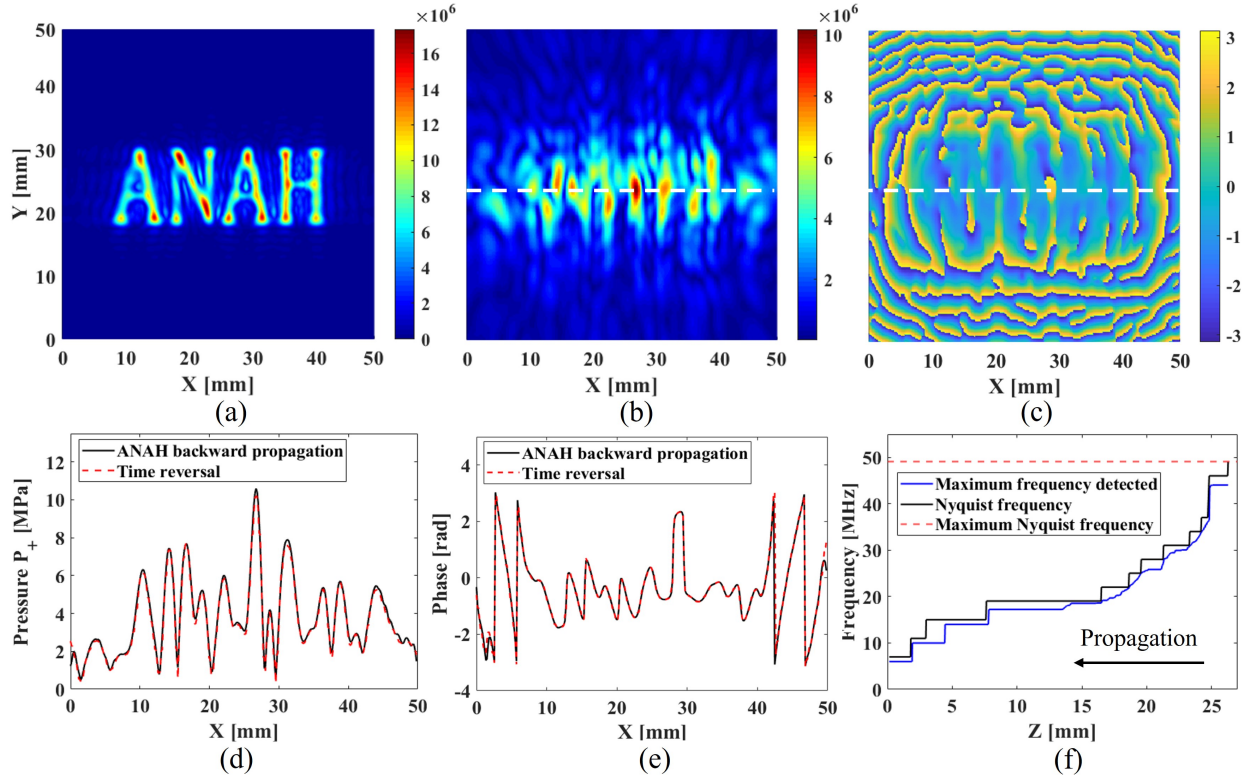


Figure 5.5.6: Illustrating ANAH for backward propagation of nonlinear acoustic fields. (a) "ANAH" shaped amplitude structure at the image plane constructed by time reversal. (b) & (c) Peak positive pressure and phase at the source plane obtained using time reversal. (d) & (e) Comparison of the peak positive pressures and phases along the dashed line of the initial source pressure and the backward projected field using ANAH. (f) The harmonic content and the adjusted Nyquist frequency as the acoustic field is back propagated to the source plane.

plane's maximum peak positive pressure. The back propagation using ANAH produces good agreement with the initial source pressure, with a calculated norm error of $L_2 = 6.45\%$. The phases at the source plane are also in good agreement. To investigate the harmonic levels of the back propagated signal at the source plane, the total harmonic distortion [48] at each point was calculated. The signal exhibits low harmonic level with an average total harmonic distortion of 0.93%, showing accurate decimation of the harmonics in the back propagation. This indicates that ANAH is an effective tool for efficiently projecting a desired nonlinear field backward to provide information on the source. Finally, Fig. 5.5.6 (f) illustrates the downsampling process where the Nyquist frequency gradually decreases as harmonics are decimated and the signal is propagated back to the source plane.

5.6 Conclusion

An adaptive numerical algorithm for computationally efficient nonlinear acoustic holography is presented in this paper. At each propagation step, the algorithm implements a monitoring function that tracks the harmonic content of the acoustic signal. The algorithm then adjusts the discretization parameters, namely, the step size and the temporal sampling rate, according to the frequency of the highest detected harmonic. The signal is upsampled in the frequency domain to accommodate the generated harmonics by maintaining a spectral buffer and zero-padding the signal's spectrum. This ensures that the discretization parameters are gradually refined and that the higher harmonics are only resolved locally in regions of high nonlinearity. Our results demonstrate that the proposed implementation can significantly reduce the computational cost for highly nonlinear three-dimensional problems, achieving a speedup of up to nearly 50 times compared to a uniform mesh. Furthermore, the proposed adaptive algorithm was also employed for backward propagation, which involves projecting

the signal back to the source while gradually downsampling the signal as higher harmonics are decimated. To perform downsampling, the spectrum of the acoustic signal was truncated based on its harmonic content at each propagation step. The developed algorithm has numerous practical applications in nonlinear medical and physical acoustics. It allows for accurate HIFU source characterization and identification, as well as the prediction of sonication dosage and ultrasound-induced thermal effects. It can also be used to efficiently generate acoustic holographic lenses or metasurfaces for use in nonlinear applications. The adaptive algorithm for strongly heterogeneous media will be implemented in the future to allow accurate modeling of therapeutic procedures through aberrating layers.

The algorithm can be readily integrated with the MATLAB open-source toolbox mSOUND. The current implementation for 2D and 3D problems as well as the instructions for integrating it with mSOUND, are freely available [49].

5.7 Acknowledgment

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Chapter 6

Design of acoustic holograms for modulating higher harmonics in nonlinear ultrasound

6.1 Abstract

This study focuses on the design of acoustic holograms for manipulating higher harmonics in nonlinear ultrasound. In this work, we use modified iterative optimization algorithms and error minimization techniques to encode phase information of multiple harmonics onto a single acoustic lens thickness profile. This approach allows for precise modulation of fundamental and second harmonic frequencies, aiming to expand the capabilities of acoustic holograms to the nonlinear regime. The paper presents case studies that illustrate the application of these acoustic holograms in generating specific patterns for different harmonic frequencies at targeted locations. The results demonstrate the hologram's ability to realize target amplitudes for both the fundamental and second harmonic. This work contributes to the field of nonlinear ultrasound by offering a method for controlling higher harmonics, indicating directions for future research and potential improvements in ultrasound imaging and therapy applications.

6.2 Introduction

The intricate shaping and precise focusing of acoustic fields is an area of significant research interest owing to its promising applications in various fields such as biomedical ultrasound and physical acoustics. Traditionally, phased array transducers (PATs) are used to achieve real-time wave-shaping capabilities by exciting each transducer with specified amplitude and phase delay. However, recent advancements in 3D printing technologies and acoustic engineering have led to the emergence of passive acoustic devices, such as metamaterials and holographic lenses [1, 2]. A key innovation in this area is the development of acoustic holograms[1]. These are 3D-printed phase plates that reconfigure the wave output from a single-element transducer or an array into a desired phase map [1, 3]. This is achieved using a thickness profile designed and computed through holographic techniques. By exploiting the differences in the speed of sound between the propagation medium and the lens, these specially designed thickness profiles effectively diffract the wavefront to create a precise acoustic pressure distribution or pattern at targeted locations. Acoustic holograms present several benefits over phased array transducers (PATs). One key advantage is their reliance on a single-element transducer, which eliminates the need for complex and power-intensive circuitry. This not only significantly reduces the cost but also accelerates the fabrication process. Moreover, the resolution of acoustic holograms is constrained only by the diffraction limit and the resolution of the 3D printing techniques utilized. As a result, acoustic holograms typically boast an acoustic pixel density that is an order of magnitude higher than that of PATs [1]. This enables them to precisely manipulate acoustic fields at operational frequencies in the MHz range [4, 5]. The versatility of acoustic holograms has been demonstrated in shaping both transmitted and reflected ultrasound wavefronts for various applications [6]. Including transcranial-focused ultrasound [7], contactless ultrasonic energy transfer [15, 6], particle manipulation [3], hyperthermia treatment [8], and patterning cav-

itation zones[9]. Using acoustic holograms to generate complex pressure patterns at the fundamental frequency has been well documented and demonstrated for various applications at lower acoustic intensities. The compressional phase in a propagating finite-amplitude nonlinear wave travels at a speed faster than the speed of the rarefaction phase [10–12] as shown in 6.2.1. As a result, the sinusoidal shape is distorted to a steeper waveform, and higher harmonics at integer multiples of the fundamental frequency are generated. The notably high fidelity of acoustic holograms opens up the opportunity for modulating the higher harmonics not just the fundamental, thereby expanding the potential applications of this technology.

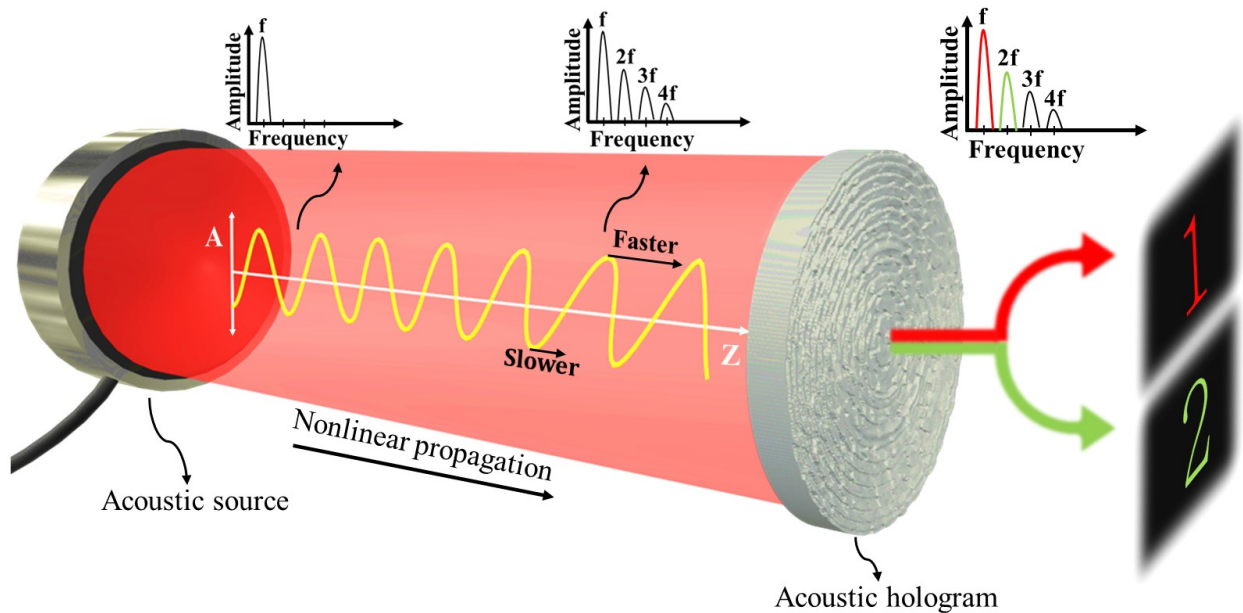


Figure 6.2.1: Schematic that illustrates the concept of an acoustic hologram that modulates the fundamental and second harmonic of a propagating nonlinear ultrasound wave. (on the left) A transducer transmits an acoustic signal. The acoustic signal then accumulates nonlinearities as the propagation distance increases, leading to a distorted waveform and a broadband spectrum due to the generated harmonics. (On the right) The acoustic hologram modulates the ultrasound signal in such a way that uniquely shapes the amplitude of the fundamental and second harmonic of the signal.

Tissue harmonic imaging (THI) takes advantage of the harmonic components generated

through nonlinear propagation in biological tissue[13]. Unlike classic imaging modes that rely on the fundamental frequency, THI captures these higher-order harmonics, which can be superior to the fundamental imaging mode due to improved spatial resolution and suppression of side lobe levels [14–16]. THI is a development in medical imaging techniques and is used in various applications, including abdominal, cardiac, and vascular imaging [13]. Furthermore, the synergistic effects between the fundamental and the second harmonic have been investigated for sonochemical reactions and threshold reduction for inducing cavitation and tissue damage [17–19]. It was found that acoustic cavitation can be significantly enhanced by superimposing the second harmonic on the fundamental through in vitro and in vivo experiments. The intensity threshold for producing focal tissue damage and sonochemical reaction was significantly lowered by second-harmonic superimposition. Precise insonation with second harmonic superimposition can be used for selective tumor treatment [17] and has the potential to significantly improve the erosion rate in lithotripsy [19]. In acoustic levitation experiments, it has been observed that when transducers are operated at high voltage amplitudes, the generation of harmonic frequencies and the resulting nonlinear effects become increasingly significant [20, 21]. These experiments have demonstrated that at elevated excitation amplitudes, there is a notable transfer of energy from the fundamental frequency to the higher harmonics. This energy shift can lead to the formation of a high amplitude second harmonic components, which is thought to contribute to the instability observed in the levitated particles [21]. Therefore, the ability to precisely manipulate the spatial distribution of higher harmonics opens up new possibilities for enhancing existing applications and exploring novel avenues in these fields.

In this work, we propose using acoustic holograms to manipulate higher harmonics in finite-amplitude nonlinear acoustic fields. To design the thickness profile of the acoustic lenses we introduce modified iterative optimization algorithms and error minimization techniques

to precisely modulate the amplitude of one or multiple generated harmonics using a single acoustic lens. Two case studies are considered to demonstrate the realization of the proposed concept. In the first case, an acoustic lens is designed to modulate two separate frequencies, namely the fundamental and the second harmonic. In the second case, we also consider manipulating two harmonics, but for this case, we will consider different target plane locations for each harmonic.

6.3 Numerical methods

Optimization and error minimization techniques are implemented with the objective of designing an acoustic lens with a thickness map $T(x, y)$ that encodes the required phase distributions $\Delta\phi_n(x, y)$ of one or multiple harmonics of interest f_n which when propagated to their respective target depths z_n diffract to the desired pressure distributions $p_n(x, y, z_n)$. Here, n is an integer representing the index of each harmonic.

To this end, in the first step, we follow an approach similar to the previously reported iterative angular spectrum algorithm (IASA) [1, 6]. However, in the present study, we include the nonlinear effects associated with finite-amplitude propagation. Forward and backward propagation steps are implemented using efficient adaptive nonlinear acoustic holography (ANAH) algorithm [22] executed in the open source MATLAB toolbox mSOUND [30]. The acoustic field is first propagated from the transducer plane z_t to the hologram plane z_h , at which higher harmonics are generated due to the cumulative nonlinear effects, as shown in Fig. 6.2.1. The algorithm starts by specifying the constraints for each harmonic considered. At the hologram plane, the amplitude of each harmonic $|p_n|(x, y, z_h)$ is set according to the transducer output. The constraints for each harmonic at their respective target planes are set separately, where the pressure amplitudes of the desired patterns are imposed, and the phase

distributions are left unconstrained. Each frequency is then separately iteratively forward and backward propagated between the hologram and target planes. The iterative steps are repeated until a desired tolerance is achieved. The optimization steps are summarized below:

- (1) Propagate the nonlinear field from the transducer plane to the hologram plane.
- (2) Propagate each harmonic separately to their corresponding target planes.
- (3) Evaluate the quality of the reconstruction for each harmonic at their corresponding target planes.
- (3) Impose the desired amplitudes for each harmonic at their corresponding planes and retain the phase information.
- (4) Separately propagate the field of each harmonic back to the hologram plane.
- (6) Compute the phase of each harmonic at the hologram plane.
- (7) Impose the initial transducer amplitude at the hologram plane.
- (8) Repeat from step 2 and exit when satisfactory results are obtained.

The output of the iterative scheme is the required phase difference $\Delta\phi_n(x, y)$ of each harmonic to achieve the desired amplitudes at the target planes. The next step involves finding a thickness profile that satisfies the phase requirements of each harmonic. Various algorithms have been proposed to address similar problems in optics and acoustics [5, 23]. In this work, we implement a direct error-minimization process with the goal of reducing the total phase error at each pixel. First, minimum and maximum values of the thickness profile are selected. The minimum thickness T_{min} is chosen to be sufficiently large to guarantee structural integrity and maintain the rigidity of the lens. On the other hand, the maximum thickness T_{max} is carefully determined to avoid excessive pixel height that can lead to notable deviations from the thin element approximation, which is a fundamental assumption in the

IASA model [5, 23]. By considering discrete steps between T_{min} and T_{max} , all the possible thicknesses of each pixel are calculated. The corresponding phase of each possible thickness is then calculated using the expression $\Delta\phi_h = T(k_0 - k_h)$. Where k_0 and k_h are, respectively, the wave numbers in the propagating media and the hologram. Thus, the thickness of each pixel is the thickness that minimizes the total error of the phases of each harmonic considered. This can be expressed as:

$$T(x, y) = \operatorname{argmin}[\Sigma_h(|\Delta\phi_h(x, y) - \bar{T}(k_0 - k_h)|)] \quad (6.1)$$

where $\bar{T}$ is a discrete vector of all possible thicknesses.

6.4 Results and discussion

The two case studies are designed to generate two patterns, the shape of the numeral "1" at the fundamental frequency and the numeral "2" at the second harmonic. In the first case, both of the target planes are 25 mm away from the hologram plane. In the second case, the target plane for the fundamental frequency is at 25 mm, and the target plane for the second harmonic is at 45 mm. The source considered has a circular aperture with a diameter of 50 mm and a fundamental operating frequency of 1 MHz. The distance between the transducer and hologram planes is 25 mm. The simulated propagation media is water with a speed of sound 1500 ms^{-1} and a nonlinearity parameter $\beta = 3.6$. The acoustic hologram has a minimum thickness of 3 mm and a maximum thickness of 10 mm and is discretized using steps of $20 \mu\text{m}$ with a speed of sound 2424 ms^{-1} .

The numerical results for the first case study are shown in Fig. 6.4.1. The desired target amplitudes for the fundamental and the second harmonic are clearly realized. As discussed

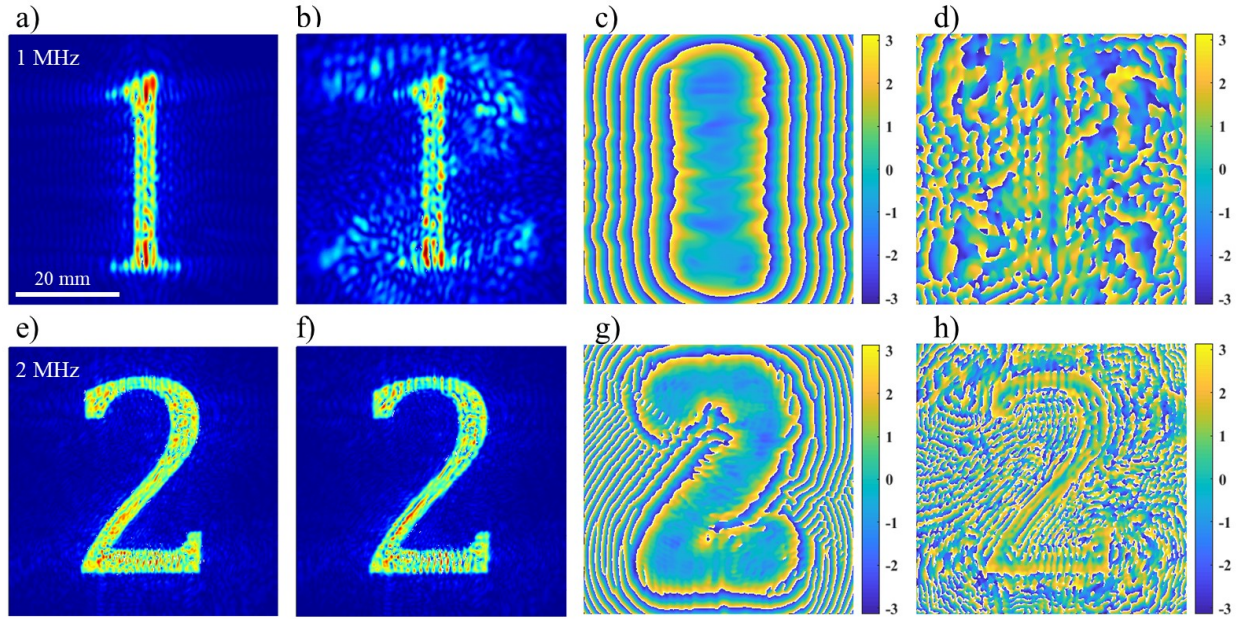


Figure 6.4.1: Summary of the numerical results of the first case study. (a) and (e) are the output pressures of the iterative optimization algorithm at the target plane for the fundamental and second harmonic, respectively. (b) and (f) are respectively, the obtained pressures at the target plane for the fundamental and second harmonic after encoding the phase maps onto a single thickness profile. (c) and (g) are the output phases of the iterative optimization algorithm at the target plane for the fundamental and second harmonic, respectively. (d) and (h) are respectively, the obtained phases at the target plane for the fundamental and second harmonic after encoding the phase maps onto a single thickness profile.

in the previous section, the harmonics are first optimized separately, and the required phases are obtained for each harmonic. Here, (a) and (c) respectively show the output amplitude and phase of the optimization process for the fundamental frequency while (e) and (g) show the optimization output of the second harmonic. To generate both patterns using a single thickness profile, the aforementioned direct error minimization technique is then applied to the phases in (c) and (g). By encoding the initial phases onto the same thickness profile, the phases in (d) and (h) are obtained. Since each phase can't be exactly realized, a deviation between each phase before and after the encoding is observed. This will lead to crosstalk artifacts and lower construction efficiencies in the amplitudes, as shown in (b)

and (f). Those effects are clear in (b), where a background artifact of the numeral "2" is observed even at the fundamental frequency. Ref [23] reported on the relation between the ratio of the design frequencies and the level of crosstalk. Their results suggest that for higher modulation depths, harmonics should be avoided. However, in this study, we strictly consider the generated harmonic due to the nonlinear phenomenon, thus, harmonic frequencies can't be avoided. Finally, we consider the second case study shown in Fig. 6.4.2. The desired target amplitudes for the fundamental and the second harmonic at their corresponding depth are clearly realized. The crosstalk effects are also observed when inspecting Fig. 6.4.2 (b)

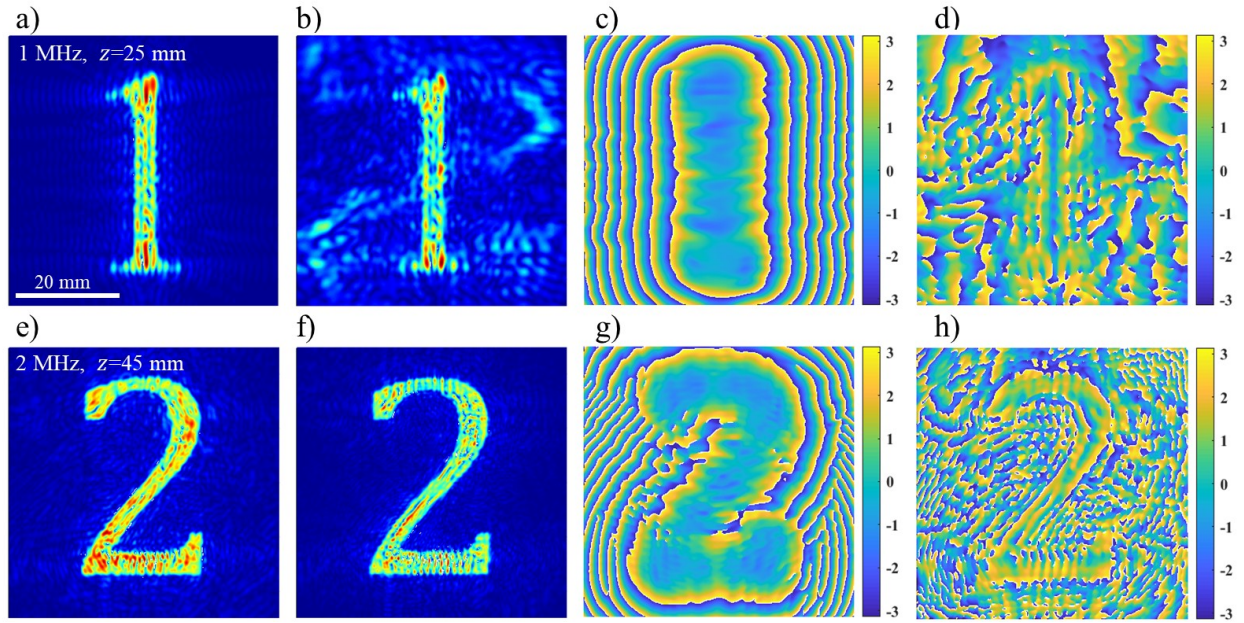


Figure 6.4.2: Summary of the numerical results of the second case study in which the target plane is at a depth of 25 mm for the fundamental and at 45 mm for the second harmonic. (a) and (e) are the output pressures of the iterative optimization algorithm at the corresponding target planes for the fundamental and second harmonic, respectively. (b) and (f) are respectively, the obtained pressures at the corresponding target planes for the fundamental and second harmonic after encoding the phase maps onto a single thickness profile. (c) and (g) are the output phases of the iterative optimization algorithm at the corresponding target planes for the fundamental and second harmonic, respectively. (d) and (h) are respectively, the obtained phases at the corresponding target planes for the fundamental and second harmonic after encoding the phase maps onto a single thickness profile.

despite the distinct depths of each pattern. Here the harmonics are patterned at two different depths. This could be of interest for applications that benefit from the high penetration of the lower frequencies and the high resolution of the higher harmonics. The inherent cause of the observed crosstalk is the deviation between the ideal phases obtained from the optimization techniques and the equivalent phase obtained after the error minimization and encoding procedures. The maximum thickness could be increased to allow more spatial frequencies and minimize phase errors and, thus, the crosstalk between the harmonics. However, the thin element approximation used for the IASA model becomes increasingly inaccurate with increasing the maximum thickness, leading to a breakdown in the optimization model [23]. Furthermore, we expect the reconstruction quality and crosstalk to deteriorate further as the number of design harmonics increases. This deterioration is attributed to the increased complexity of encoding more information onto the same thickness profile. The additional data incorporated into a limited spatial dimension can lead to more pronounced errors and interference.

6.5 Conclusions

In this study, we proposed and numerically investigated the use of acoustic holograms for controlling single or multiple higher harmonics in nonlinear ultrasound. We applied iterative optimization methods and error minimization techniques to encode the phase information of each harmonic onto a single thickness profile. Our research included two case studies: in the first, we aimed to pattern the fundamental and second harmonic amplitudes onto the same target plane, while in the second, we targeted two different planes at varying depths. In both cases, we successfully achieved the desired amplitudes at the specified target planes. However, we observed the existence of crosstalk and background pressure, particularly at the

fundamental frequency. Finally, to compute acoustic holograms for synthesizing arbitrary spatio-temporal specified nonlinear fields, it's necessary to further develop the algorithm to incorporate solutions of the inverse boundary value problem in nonlinear ultrasound.

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Chapter 7

Scientific contributions, conclusions and future work

This dissertation investigates novel numerical and experimental techniques for constructing complex ultrasonic fields using holographic acoustic lenses for focused ultrasound applications. Specifically, this research (1) proposes holographic acoustic mirrors for shaping reflected ultrasonic wavefronts; (2) proposes novel optimization algorithms and modeling techniques to design holographic acoustic lenses for transcranial-focused ultrasound; (3) investigates the effect of nonlinearities on holographically modulated high-intensity focused ultrasound; (4) develops novel algorithms and numerical approaches for efficient nonlinear acoustic holography to simulate high-intensity ultrasound; (5) finally, we will also explore utilizing acoustic holograms for manipulating higher harmonics in nonlinear ultrasound. The research presented in the thesis advances the functionality and understanding of holographically modulated ultrasound and acoustic lenses.

In Chapter 2, we showcased the utilization of 3D-printed metallic holographic acoustic mirrors for controlling underwater ultrasonic waves generated by a single acoustic transmitter. Two distinct flat acoustic mirrors were designed, fabricated, and experimentally verified. We assessed the mirrors' abilities to create complex pressure patterns and achieve multi-focal point wave focusing. This innovative mirroring approach has promising applications, expanding the possibilities in acoustic wave manipulation. Specifically, it allows the concentration

of sound onto multiple focal points with a single acoustic source, which is advantageous for applications like wireless powering and communication in sensing networks based on AET. This configuration optimizes both incident and reflected acoustic energy, thereby increasing the available acoustic power for AET receivers. Another intriguing concept is integrating the reflective mirror with transmission acoustic holograms for phase and amplitude modulation. Moreover, if necessary, the forward wave can also be shaped by employing a transmission hologram on the opposite side of the transmitter disc in combination with the reflective mirror. This enables precise pattern control for the reflected and forward waves in different regions of interest, achieving an exceptionally efficient AET system.

In Chapter 3, We proposed and showcased an efficient volumetric holographic technique for generating 3D-printed acoustic holograms for low-intensity tFUS applications. The proposed approach uses the modified mixed domain method incorporated into a gradient descent iterative volumetric holography optimization algorithm. Furthermore, due to the more efficient propagation, using the proposed approach, a hologram can be created in less than 50 minutes, significantly faster than previously reported techniques. The iterative optimization technique uses explicitly assigned loss functions, allowing more flexibility and fine-tuning capabilities in the optimization. We applied the proposed algorithm to target four brain structures: the anterior insula, hippocampus, caudate nucleus, and amygdala. Verification was done through underwater experiments using realistic 3D-printed skull phantoms. The proposed approach enables more rapid computation of acoustic holograms, enabling quicker administration of therapeutic procedures and allowing for more flexibility in tailoring ultrasound fields for specific therapeutic requirements.

In Chapter 4, this study conducted a numerical analysis of the impact of nonlinear distortion on holographically modulated ultrasound. The research involved three-dimensional simulations of nonlinear acoustics using the k-space pseudospectral method, with power law

absorption. The simulations, implemented in C++ on a high-performance computing cluster, examined the spatial distribution of various parameters like peak positive pressure (PPP), peak negative pressure (PNP), intensity, heat deposition, and cavitation zones across different excitation levels. The results indicated that nonlinear distortion significantly affected the spatial characteristics of the sound field, causing waveform asymmetry and localized nonlinear effects. Furthermore, harmonic generation led to confined heat deposition and influenced cavitation zones. These findings underscore the importance of considering nonlinear effects when designing HALs for high-power therapeutic ultrasound applications. They also suggest potential applications in computer-generated holography for creating specific nonlinear acoustic fields and improving procedures like harmonic imaging.

In Chapter 5, this paper introduces an adaptive numerical algorithm designed to enhance the efficiency of nonlinear acoustic holography. The algorithm continually monitors the harmonic levels of the acoustic signal during propagation and adjusts key discretization parameters, such as step size and temporal sampling rate, based on the highest detected harmonic frequency. It employs frequency domain upsampling to accommodate generated harmonics, thereby gradually refining discretization parameters and locally resolving higher harmonics in regions of nonlinearity. The results reveal a substantial reduction in computational costs for three-dimensional nonlinear problems, achieving nearly a 50-fold speedup compared to a uniform mesh. Moreover, the adaptive algorithm is extended to backward propagation, downsampling the signal as higher harmonics are eliminated. This versatile algorithm finds applications in nonlinear medical and physical acoustics, facilitating precise HIFU source characterization, sonication dosage prediction, and the generation of acoustic holographic lenses or metasurfaces for nonlinear applications.

Finally, in Chapter 6, We proposed that acoustic holograms could provide the opportunity for the manipulation of not just the fundamental field but also the higher harmonics. The

proposed concept was numerically demonstrated by applying iterative optimization methods and error minimization techniques to encode the phase information of one or multiple harmonics onto a single thickness profile. Two case studies were considered: in the first, the fundamental and second harmonic amplitudes were patterned onto the same target plane, while in the second, we targeted two different planes for each harmonic at varying depths. The numerical results clearly showed that the desired amplitudes were realized for each harmonic at their corresponding target planes. Such an approach can be utilized in applications such as harmonic imaging and nonlinear ultrasonic nondestructive evaluation.

7.1 Future directions

Several promising directions for future research can build upon and expand the findings of this dissertation. These include, but are not limited to, the following:

- Extending the proposed ANAH algorithm in Chapter 5 to include strongly heterogeneous media. Such a task isn't trivial and will require the implementation of phase and amplitude correction techniques and the inclusion of reflections. In this problem, simulating a large number of reflections poses a significant computational challenge that requires the investigation of more efficient techniques and strategies. Extending the algorithm successfully allows efficient simulation of HIFU through dense structures like bones for therapeutic procedures such as transcranial and through-ribs histotripsy.
- Acoustic holograms have been demonstrated extensively for modulating longitudinal pressure waves in fluid media. However, controlling and steering elastic waves through solid materials is desired for various applications. Unlike fluid media, for elastic waves manipulation, both the propagation of longitudinal and shear waves must be considered

when designing the hologram. Thus, expansion of the current models and optimization techniques is required. Progress in this direction can enable precise through-wall contactless acoustic energy transfer for charging sensors or devices [1] and could allow the utilization of elastic-guided waves for transcranial ultrasound [2].

- Acoustic holograms for transcranial ultrasound have been demonstrated in controlled laboratory bench-top representative experiments using either 3D printed skull phantoms and human skull cadavers or *in-vivo* animal studies. Looking ahead, the progression to human studies is essential, yet it introduces a unique set of challenges. Key among these are ensuring effective acoustic coupling between the hologram and the human skull and achieving the necessary transcranial acoustic intensity to meet therapeutic objectives. Addressing these challenges will be critical for the successful application of acoustic holograms for human treatment.
- Deep learning and neural networks have been proposed to rapidly generate acoustic holograms for pressure patterning in free propagation media [3]. Extending these innovative approaches to transcranial ultrasound could lead to a more universal and rapid generation of acoustic holograms. However, this task is inherently more complex, as it must account for the skull shape and size variations among different patients.
- Finally, the algorithms proposed in Chapter 6 can be extended to allow the computation of holograms when placed near the transducer surface preceding the accumulation of nonlinearities. This will require advancing the understanding and mathematical formulation of the inverse boundary value problem in nonlinear ultrasound. This problem involves complex mathematical formulations to compute a radiating source that is specifically synthesized to generate the desired highly nonlinear spatio-temporal acoustic field [4].

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