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

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Abstract

Purpose: HIFU becomes an effective and noninvasive modality of solid tumor/cancer ablation. Simulation of the nonlinear acoustic wave propagation using a phased-array transducer in multiple layered media using different focusing strategies and the consequent lesion formation are highly required in the HIFU planning in order to enhance the efficacy and efficiency of treatment.

Materials and methods: Angular spectrum approach with the marching fractional steps was applied in the wave propagation from phased-array HIFU transducer, and diffraction, attenuation, and nonlinearity effects were accounted by a second-order operator splitting scheme. The simulated distributions of first 3 harmonics along and transverse to the transducer axis were compared to the hydrophone measurements. The Bioheat equation was used to simulate the subsequent temperature elevation using the deposited acoustic energy, and lesion formation was determined by the thermal dose.

Results: Better agreement was found between the measured harmonics distribution and simulation using the proposed algorithm than the Khokhlov-Zabozotskaya-Kuznetsov equation. Various focusing of the phased-array transducer (geometric focusing, transverse shifting and the generation of multiple foci) can be simulated successfully. It is found that the shifting and splitting of focus result in the significantly decreased temperature elevation at the focus and the subsequent lesion size, but increased grating lobe in the prefocal region.

Conclusions: The proposed algorithm could simulate the nonlinear wave propagation from the source with arbitrary shape and distribution of excitation through multiple tissue layers in high computation accuracy. The performance of phased-array HIFU can be optimized in the treatment planning.

Keywords: high-intensity focused ultrasound (HIFU), second-order operator splitting, angular spectrum approach, nonlinear acoustic field, thermal field

Introduction

High intensity focused ultrasound (HIFU) has become an emerging non-invasive modality for the treatment of the prostate, liver, kidney, breast, bone, pancreas cancer and uterine fibroids [38]. Most of the clinical trials have been carried out in Asia and Europe with great success. The principle of thermal ablation induced by HIFU is focusing ultrasonic wave at a specific location, rapid temperature rising of tissue in the focal region after absorbing the acoustic energy, and subsequently the formation of irreversible necrosis and death of cancer cells when the accumulated thermal dose is beyond a threshold. Furthermore, HIFU can also be used for various medical applications, such as local drug delivery and gene transfection, thrombolysis, tissue erosion [11, 31, 16]. A simple, reliable, and popular configuration of HIFU system is to mechanically move the focal point throughout the whole volume of a solid tumor/cancer by motors. HIFU transducer could be a single concave element, or several piston elements aligned on the same concave surface and all driven in phase, or a concave acoustic lens in front of the planar transducer. However, this configuration has several shortcomings. Because of the refractive inhomogeneities of tissue and the presence of multiple layers in the propagation pathway acoustic wave focusing *in vivo* is not perfect as in the free field [14]. Technical advance in the last decade witnessed the development and application of phased-array transducer which consists of hundreds or thousands of individually driven elements [2]. Electronic steering is achieved by varying the phase applied to each emitter to compensate for the delay in the acoustic wave propagation with respect to the focal point position. As a result, the interval time of focus shifting is dramatically reduced (from seconds to nanoseconds theoretically). Such a quick motion makes real-time compensation of the respiratory-induced motion in the organ (i.e., kidney and liver) possible. Phase aberration occurred in the tissue could also be compensated to

improve the focusing. The production of multiple foci and minimization of acoustic energy accumulated at the unintended organ (i.e., ribs for transcostal ablation, large artery, and nerve) are only feasible using the phased-array design. Although the cost and control complexity of a large-scaled phased-array transducer increase significantly, and the available range of focus shifting is typically on the order of 1 cm, the application of phased-array is definitely the choice of the next generation of HIFU system.

Simulating the propagation of focused finite-amplitude sound with the combined influences of nonlinearity, absorption, and diffraction and consequent lesion formation is of importance in the HIFU treatment planning and understanding the mechanism. The Khokhlov-Zabozotskaya-Kuznetsov (KZK) equation [34, 18] is popular and accurate for moderately focused acoustic beams with high direction ($ka \gg 1$, where k is the wave number and a is the radius of the source) at distances beyond a few source radii and in the paraxial region (up to about 16° off the central propagation axis in the far field) [21]. However, this model uses a parabolic approximation for the diffraction effect, which limits the validity to relatively weak diffraction and low focusing gains, and hampers its use in the field of modern medical ultrasound sources. The KZK equation can be solved in an explicit finite-difference (FD) algorithm using a marching scheme based on the operator-splitting method on a three-dimensional Cartesian grid [19]. As the code marches, all wave propagation effects including thermoviscous absorption, relaxation, and dispersion are accounted separately at the fractional steps and then simply summed, if the effect in each step is fairly weak to correct the waveform. The time-domain numerical model is efficient for the propagation of short pulses from a symmetric source in multiple layers, and very good agreement was found between simulations and experiments [3]. In the frequency-domain or spectral method, a Fourier series of the sound pressure is substituted

into the KZK equation and the resulting set of coupled equations are solved using FD methods [1]. The alternative wave equation is the Westervelt equation, which is derived from the full equations of fluid motion by keeping terms up to quadratic order [29]. It can simulate the generation of grating lobes which are located far beyond the validity region of the KZK equation [17] in both linear and nonlinear cases [7]. However, the simulation of a non-axis-symmetric source is still quite challenging and computationally complex.

A much more efficient diffraction algorithm is based on the angular spectrum approach (ASA) [35] because it can be implemented by taking advantage of the fast Fourier transform (FFT) or the discrete Hankel transform. Diffraction is calculated using a spatial Fourier transform method while applying the Burgers equation to model nonlinear effects even in regions that do not satisfy the parabolic approximation [5]. In addition, in order to increase the computation efficiency second-order operator-splitting scheme with a fractional step algorithm was applied [27] because relatively large steps could be used than those in a first-order operator splitting [5]. Step size could also be adaptive, large steps in the near field and smaller ones in the focal region. The ASA approach has been used for pressure fields generated by concentric ring arrays and sector-vortex arrays. The spectral propagator is preferred in the ASA over the spatial propagator for calculations in attenuating media or with an apodized pressure distribution [37]. In addition, the effects of reflection and refraction on wave propagation, especially in multi-layered media, could also be compensated using the ASA [36].

In this study, the ASA with a second-order operator splitting was applied to simulate the three-dimensional nonlinear acoustic field of a phased-array HIFU transducer in multiple layered media with a steered propagation axis varying over a wide range of angles and generation of multiple foci. The model was first validated by comparing the first 5 harmonics on the axis of a

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

Materials and methods

Nonlinear acoustic wave propagation

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

$$\frac{\partial p}{\partial z} = L_A \cdot p + L_N \cdot p + L_D \cdot p \quad (1)$$

where p is the acoustic pressure, L_A , L_D , and L_N is operator representing the effect of attenuation, diffraction and nonlinearity, respectively [26]. Here the second-order splitting scheme was used because of its high computational efficiency and accuracy, which was accomplished by first solving a half step with diffraction operator, then taking that solution to the nonlinearity and attenuation operator for a full step, and finally completing the diffraction operator by another half step [27] as shown in Fig. 1,

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

where Δz is the propagation step size.

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

$$h_p(x, y, \Delta z; \omega) = \frac{\Delta z}{2\pi d^3} (1 - jkd) e^{jkd} \quad (3)$$

where $d = \sqrt{x^2 + y^2 + \Delta z^2}$. So the pressure could be derived from the 2D spatial convolution between the input pressure at z_0 and the spatial propagator h_p :

$$p(x, y, z_0 + \Delta z; \omega) = p(x, y, z_0) \otimes h_p(x, y, \Delta z; \omega) \quad (4)$$

Performing 2D Fourier transforms on both sides of Eq. (4) obtains:

$$P(k_x, k_y, z_0 + \Delta z; \omega) = P_0(k_x, k_y, z_0) \cdot H_p(k_x, k_y, \Delta z; \omega) \quad (5)$$

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

$$H_p(k_x, k_y, \Delta z; \omega) = \begin{cases} e^{-j\Delta z \sqrt{k^2 - k_x^2 - k_y^2}} & k_x^2 + k_y^2 < k^2 \\ e^{-\Delta z \sqrt{k^2 - k_x^2 - k_y^2}} & k_x^2 + k_y^2 \geq k^2 \end{cases} \quad (6)$$

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

$$\begin{aligned} k_x &= m\Delta k_x, \quad m = -N_x/2 + 1 + \phi_x, \dots, N_x/2 + \phi_x, \quad \Delta k_x = 2\pi/(N_x\delta) \\ k_y &= n\Delta k_y, \quad n = -N_y/2 + 1 + \phi_y, \dots, N_y/2 + \phi_y, \quad \Delta k_y = 2\pi/(N_y\delta) \end{aligned} \quad (7)$$

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

$$\phi_x, \phi_y = \begin{cases} -1/2 & N_x, N_y = \text{odd} \\ 0 & N_x, N_y = \text{even} \end{cases} \quad (8)$$

Due to the intrinsic periodicity of the spectrum, under-sampling of the spectra propagator and the replication of the source, the spatial aliasing error often appears in the far field. To reduce such

an error, a spatial frequency truncation technique is applied through the use of the Tukey window (a spatial low-pass filter to the spectral propagator with a window size of 512 and taper ratio of 0.1) [30] without increasing the size of the computational grid. This method removes the under-sampled angular spectra and prevents the leakage of high spatial frequency components into the propagating field.

Distortion of finite-amplitude wave occurs in the propagation due to convective and nonlinear effects over incremental steps, which can be expressed as [35]:

$$p_n(z + \Delta z) = p_n(z) + j \frac{\beta \omega}{2 \rho c^3} \left(\sum_{k=1}^{n-1} k p_k p_{n-k} + \sum_{k=n+1}^N n p_k p_{n-k}^* \right) \Delta z - \alpha_0 (n f_0)^b p_n \Delta z \quad (9)$$

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

When the shock fronts developed in the pressure waveform, strong gradients appear in the transverse spatial field. These spatial gradients can cause artificial oscillations in the numerical solution. To eliminate them, an artificial absorption was introduced in the algorithm locally around the focus where shocks may present. Specifically, the exponential attenuation absorption coefficient is replaced by the function [5]

$$b(n) = b + [(n-1)q / N] \quad (10)$$

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

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

$$p(z, t) = \sum_{n=1}^N p_n(z) e^{j2\pi f_0(t-z/c)} \quad (11)$$

Multiple layer model

At an interface between two media with different acoustic impedances, the transmission coefficient in the frequency domain is given by [36]

$$T_p(k_x, k_y) = \frac{p_t}{p_i} = \frac{2}{1 + \frac{\rho_1 c_1 \cos \theta_t}{\rho_2 c_2 \cos \theta_i}} \quad (12)$$

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

$$\cos \theta_i = \frac{\sqrt{k^2 - k_x^2 - k_y^2}}{k}, \quad \cos \theta_t = \sqrt{1 - \left(\frac{c_2}{c_1}\right)^2 \frac{k_x^2 + k_y^2}{k^2}} \quad (13)$$

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

$$P_2(k_x, k_y, z) = P_1(k_x, k_y, z) \cdot T_p(k_x, k_y) \quad (14)$$

Thermal model

The Bio-Heat transfer equation (BHTE) was used to simulate the temperature elevation and lesion formation by HIFU [22]:

$$\rho C_t \frac{\partial T}{\partial t} = \nabla \cdot \kappa \nabla T + C_b W_b (T - T_a) + Q_p \quad (15)$$

where ρ is the density of the tissue, C_t is the specific heat of the tissue, T is the temperature at time t , κ is the thermal conductivity, C_b is the specific heat of the blood, W_b is the blood

perfusion rate, T_a is the temperature at large distances, which corresponds to the initial condition value, and Q_p is the power deposited from the focused ultrasound energy:

$$Q_p(x, y, z) = 2\alpha I = 2 \sum_{n=1}^N \alpha(f) I_n = \sum_{n=1}^N \alpha_0 (nf_0)^b \frac{p_n^2(x, y, z)}{\rho c} \quad (16)$$

The BHTE was solved using the finite-difference time-domain (FDTD) method with initial and boundary conditions of 37 °C. The thermal dose, an equivalent exposure time at 43 °C ($TD_{43^\circ\text{C}}$), is used to characterize the ablation outcome [23].

$$TD_{43^\circ\text{C}}(t) = \int_0^t R^{43-T(\tau)} d\tau \quad (17)$$

where R is 0.5 for $T \geq 43^\circ\text{C}$ and 0.25 for $T < 43^\circ\text{C}$. The lesion formation requires a thermal dose of a 240-min exposure at 43 °C. The thermal properties of viscera used in the BHTE equation are as follows: $C_t = 3628 \text{ J/kg/}^\circ\text{C}$, $C_b = 3628 \text{ J/kg/}^\circ\text{C}$, $\kappa = 0.465 \text{ W/m/}^\circ\text{C}$, $W_b = 10 \text{ kg/m}^3/\text{s}$, $T_a = 37^\circ\text{C}$.

Phased array

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

$$\frac{j\rho ck}{2\pi} \sum_{n=1}^N u_n \int_S \frac{e^{-jk(r_m - r_n)}}{|r_m - r_n|} dS = p(r_m) \quad (18)$$

where u_n and S are the velocity and surface area of the n -th element, respectively [24]. The equation above can be expressed in matrix form as

$$Hu = p \quad (19)$$

where u is the complex excitation vector of the array elements, $u = [u_1, u_2, \dots, u_n]'$, and the vector p denotes the complex pressure at the control points in the field, $p = [p(r_1), p(r_2), \dots, p(r_n)]'$, and H is the forward propagation operator. When H is full rank, Eq. (19) has the weighted minimum-norm solution as:

$$\hat{u}_w = H^{*t} (HWH^{*t})^{-1} p \quad (20)$$

where H^{*t} is the conjugate transpose of H , $\hat{u}_w$ is the final driving signals, W is an $N \times N$ real positive definite weighting matrix to reduce the dynamic range and improve the efficiency of the driving signals. An iterative weighting algorithm was utilized to achieve the specified power deposition at the control points. Although straightforward, this weighting algorithm can increase the array excitation efficiency to near 100% efficacy in most cases [10]. Furthermore, in order to compensate the refraction occurring at the tissue interface additional weight, ratio of the thickness of each layer to the total one [36] which is determined by backward propagating the acoustic field to the transducer surface [20, 6], is applied to the driving signal. All the simulation ran in MATLAB (R2010b, Mathworks, Natick, MA) on a PC (3.3 GHz Interl(R)-Core(TM) i5-2500 CPU, 4 GB RAM) with Windows 7 32 bits operating system.

HIFU Field Scanning

In order to validate the proposed algorithm, the HIFU field was measured using established protocol [40]. An annular focused HIFU transducer (H102, outer diameter = 69.94 mm, inner diameter = 22 mm, $F = 62.64$ mm, $f = 1.1$ MHz, Sonic Concepts, Woodinville, WA) was mounted at the bottom of a Lucite tank ($L \times W \times H = 20$ cm $\times$ 20 cm $\times$ 35 cm) filled with degassed and deionized water at the room temperature ($O_2 < 4$ mg/L, $T = 25^\circ\text{C}$) and driven by sinusoidal bursts produced by a function generator (AF3021B, Tektronics, Beaverton, OR) together with a power amplifier (BT00250-AlphaA, Tomco Technologies, Adelaide, Australia). To map the acoustic field of HIFU transducer, a needle hydrophone (HNA-0400, Onda, Sunnyvale, CA) was connected to a three-dimensional positioning system (XSlide, Velmex, Bloomfield, NY), which has a minimum step size of 5 μm and a maximum scan range of 200 mm. The picked up signal was first recorded by a digital oscilloscope (Wavesurfer MXs-B, LeCroy, Chestnut Ridge, NY) operated at 500 MHz sampling rate, and then transferred to a PC for off-line analysis. First 3 harmonics of pressure waveform were calculated using FFT. A LabVIEW (National Instruments, Austin, TX) program was written to automatically control the output of the function generator, data acquisition and transfer, and hydrophone scanning. To minimize temperature elevation and cavitation damage to the sensing element, the HIFU transducer was operated in burst mode with a low duty cycle (i.e., 10-20 cycles/burst). Averaging over 100 bursts was used to improve the signal-to-noise ratio of the measured pressure waveforms. The geometric focus was determined by searching for the location of maximum signal strength. For line scan along and transverse to the transducer axis, the range and step size was set as $x = -3$ – 3 mm, $z = -3$ – 3 cm, $\Delta x = 0.2$ mm, $\Delta z = 0.5$ mm, respectively.

Results

Model Validation

To validate the proposed algorithm, harmonics generated by a concave transducer in a two-layer media (3 cm water and 5 cm tissue) were compared with those simulated by using the KZK model [HIFU-Simulator v1.2, Food and Drug Administration (FDA), Silver Spring, MD] [25]. The acoustic properties of water and tissue are listed in Table 1 [5]. The concave transducer has a driving frequency of 2.08 MHz, focal length of 5 cm, an aperture diameter of 1.9 cm, and the acoustic pressure at the transducer surface is 480 kPa. In the simulation, the spatial sampling interval in the transverse plane is 0.238 mm ($\lambda_{\text{water}}/3$), and the dimension of the source plane is 18.24 cm $\times$ 18.24 cm, corresponding to 768 $\times$ 768 grid points. The sampling interval on the axis is 0.356 mm ($\lambda_{\text{water}}/2$) and 0.39 mm ($\lambda_{\text{tissue}}/2$) in the water and tissue layer, respectively. The axial pressure amplitude for the first 5 harmonics simulated by the KZK model (HIFU-Simulator) and by the second order splitting operator using the ASA is shown in Fig. 3. It is found that these two results agree closely in the far field (amplitude of fundamental harmonic: 3.04 MPa vs. 3.16 MPa at the focus located at $z = 4.08$ cm vs. 4.12 cm, respectively) but differ largely in the near field, which may be due to the different approximation of diffraction effects, consideration of refraction at the interface, and the starting position of nonlinear effects. HIFU simulator assumes that the propagation within the concave bowl is linear and nonlinear propagation starts from the aperture of the HIFU transducer. In contrast, **the algorithm used in this study** calculates the nonlinear effects from the bottom plane of the transducer by back-projecting the acoustic pressure at the transducer surface to it. No ripple was found in the far field, which shows good convergence using the Tukey window.

The numerical simulations were further compared with experimental results. The pressure waveforms at the focus were purposely aligned in the time domain to match the peaks for easy comparison (see Fig. 4). Good agreement was found between measured and synthesized waveforms using both numerical models although the KZK model has the largest negative pressure (9.84 MPa vs. 8.62 MPa using 2nd order operator splitting and 8.07 MPa in the measurement, respectively). Furthermore, the distributions of first 3 harmonics along and transverse to the transducer axis measured by the hydrophone were compared with the numerical simulations (see Fig. 5). The 2nd order operator splitting algorithm was found to have a better agreement than the KZK model, especially the locations of pressure nodes and more side lobes in the prefocal region. Overall, the proposed algorithm is an accurate way to simulate the nonlinear wave propagation of HIFU burst. The calculation time of HIFU-Simulator and the proposed algorithm is similar, about 30 min. In order to enhance the calculation accuracy, second-order Runge-Kutta method was used to compute the nonlinearity due to high pressure at the focus while the computation time would increase to about 50 min.

Acoustic field

The acoustic field (the distribution of first 5 harmonics in axial and lateral directions and the pressure waveform at the focus) in water and multiple-layered media produced by the phased-array HIFU transducer with the initial acoustic intensity of 8.33 W/cm² on the transducer surface (about 500 kPa acoustic pressure), which is considered as high input excitation ($p_0 > 0.4$ MPa) [27], was simulated (see Figs. 6 and 7). Peak pressures are summarized in Table 2 for easy comparison. Three cases were considered: geometrical focus (0, 0, 10) cm, transverse focus shifting (1, 0, 10) cm, and four foci in the focal plane (-1, -1, 10) cm, (-1, 1, 10) cm, (1, -1, 10)

cm, (1, 1, 10) cm. The transverse sampling intervals are set as 0.2 mm, and the axial one is $\lambda/4$ in all layers. The computation discretization is $512 \times 512 \times 42$, $512 \times 512 \times 80$, and $512 \times 512 \times 130$ grid in water, fat, and the viscera layer, respectively. The computation on the PC takes about 10 minutes. With the electrical steering on the focus, the peak positive pressure reduces by 11.4% in water (27.05 MPa to 23.97 MPa) and 8.9% in tissue (from 13.54 MPa to 12.33 MPa), respectively, but with less change to the peak negative pressure, 5.2% in water (from 7.33 MPa to 6.95 MPa) and 4.4% in tissue (from 5.23 MPa to 5.0 MPa), respectively. There is no significant change in the lateral distribution of harmonics with shifted focus while the change in the axial direction, especially in the near field, is due to the definition of the axis through points of (1, 0, 10) cm and (1, 0, 0) cm. For the four foci case, the peak positive pressure is almost half of shifted focus (10.09 MPa vs. 23.97 MPa in water and 6.11 MPa vs. 12.33 MPa in tissue, respectively), but the reduction of the peak negative pressure is much less (5.01 MPa vs. 6.95 MPa in water and 3.58 MPa vs. 5.0 MPa in tissue, respectively). Despite weak acoustic pressure for four foci in tissue, the presence of harmonics can still be illustrated clearly and the ratio of the second harmonic at the focal point to the fundamental frequency is more than 0.2.

The distributions of first 3 harmonics in the x - z plane using these three focusing strategies are shown in Fig. 8. It is found that the grating lobes on the axis ($z = 4\text{--}5$ cm) occur mostly at the fundamental harmonics (ratio of pressure at the focus to that in the grating lobe is about 6 dB. Shifting the focus slightly worsens the grating lobe (the pressure ratio of 5.94 dB) while splitting into four foci has a significant influence on it, the pressure ratio of 4.71 dB and much wide area of multiple grating lobes with similar pressure. The corresponding pressure distributions in the x - z plane are shown in Fig. 9. Although the patterns of peak positive and negative pressure distribution are quite similar, there are some discrepancies. First, the beam size of peak negative

pressure is larger than that of peak positive pressure. Because of the acoustic nonlinearity the duration of the positive and negative pulse will decrease and increase, which means shifting towards low and high frequency correspondingly [40]. Second, the grating lobes of negative pressure are more significant than that of positive pressure.

Thermal pattern and lesion size

The thermal fields in both the focal region (xy and xz plane) and prefocal region (xz plane) using the phased-array HIFU transducer immediately after 2 s continuous ablation at an input acoustic intensity of 8.33 W/cm^2 with the three different focusing strategies are shown Fig. 10. The presence of grating lobe in the prefocal region with significant temperature rise (56.3°C , 57.5°C , and 44.1°C , respectively) is found, which may cause unexpected damage. For the four foci case, the presence of interference patterns in both the pre- and post-focal region could be figured out easily (as shown by the arrows in Fig. 10c). Such interference results in broad and complicated patterns of the grating lobe. In addition, the temperature evaluation at the focal point using these three focusing strategies is also compared with each (see Fig. 11). Linear acoustics model, which ignores the nonlinear operator in Eqs. (1) and (9), is also included in the comparison with the same computation volume and the transverse sampling intervals. It shows that the nonlinear acoustic propagation results in higher temperature in the HIFU ablation than that predicted by the linear model (i.e., 98.7°C vs. 86.1°C for geometrically focusing) due to significant differences in the heating deposition rate by the harmonics. Because of the low acoustic pressure in the four foci case, the discrepancy of temperature rises between nonlinear and linear model is quite small (only 1°C). However, the lesion boundary after HIFU ablation is not affected much by the nonlinear effect (see Fig. 12), which owes to the quick dissipation of

nonlinearity away from the focus and low thermal conduction in the soft tissue. The thermal output in the focal region for these three cases is summarized in Table 3. The total lesion volume of four foci is much less than a single focus (47.2 mm^3 vs. 126.6 mm^3 and 103.9 mm^3 for geometric focusing and transverse shifting, respectively). Furthermore, if the peak positive pressure at focus is adjusted to the same value for all focusing strategies, the comparison of thermal fields is listed in Table 4. The maximum temperatures induced by transverse focus shifting and four foci are a little smaller than that at the geometrical focus, and the lesion area and volume produced by transverse focusing shifting are slightly larger, which may be due to the large beam width. However, the maximum temperatures in the prefocal region cannot be neglected ($61 \text{ }^\circ\text{C}$ and $74.3 \text{ }^\circ\text{C}$ for transverse focus shifting and four foci, respectively). It suggests that great attention should be paid when shifting the focus or generation of multiple foci in HIFU ablation in order to avoid the unintended heating in the prefocal region. In addition, transverse focus shifting and generation of four foci requires to increase the input acoustic intensity by 1.15 and 5.0 folds, respectively.

Discussions and Conclusion

Nonlinear acoustics plays a significant role in HIFU ablation, and the use of phased-array is becoming popular for compensation of phase aberration and flexibility of focusing pattern. In this study, a numerical algorithm has been adopted to investigate the pressure distribution and the corresponding thermal pattern of the phased-array HIFU with the geometric or off-axis focus or multiple foci. The second-order operator splitting scheme proposed here has a better agreement with harmonics distribution of HIFU field in the measurement than the KZK model. For pulsed excitation, attenuation was coupled with the half step of diffraction rather than the nonlinear substep [33]. In HIFU ablation, the burst duration is usually on the order of hundred milliseconds, and the transient response at both the starting and termination of excitation is not important. Therefore, a different second-order operator-splitting scheme was used here. The presence of higher harmonics in the waveform spectrum due to acoustic nonlinearity can result in higher heat deposition rate [40]. However, there are much fewer differences between the boundary of lesion simulated by linear and nonlinear models, which is due to low thermal conductivity of soft tissue. **The increase of thermal conductivity in the tissue leads to exponential decrease of the maximum temperature elevation at the focus but significant increase in the focal region [39].** Therefore, the HIFU-induced thermal ablation could be predicted easily and quickly using a simple linear model with promising accuracy. Meanwhile, the absorption of the acoustic wave increases with the frequency. Thus, although the nonlinearity of tissue is higher than that of water, the waveform distortion at the focal point is not significant because of high attenuation. The absorption law was found to have less impact on the prediction of the fundamental frequency than high harmonics and on the transverse distribution than the axial distribution [33]. The shifting of focus and generation of multiple foci pattern will decrease

the nonlinear effect and deposited acoustic energy, leading to the formation of smaller lesions. In addition, this algorithm was also used for the planar phased array HIFU transducer with the similar conclusion (data not shown). Overall, our numerical model can simulate the acoustic and thermal field of HIFU phased array in a high computational accuracy. Optimization of HIFU treatment planning is feasible to enhance the efficacy and safety, but needs further investigation.

The computational efficiency is another reason of using ASA. The computation burden for the ASA is on the order of $N_x N_y N_t \cdot \log_2(N_x N_y N_t / 2)$ where N_t is the number of temporal samples, and solving the nonlinear wave equation in the frequency domain has a complexity of order N^2 where N is the number of harmonics retained. Thus, the computation volume, the transverse and axial plane sampling intervals, and the number of harmonics are key parameters in the simulation and chosen as the tradeoff between accuracy and computation burden. The value of N can be dynamically adjusted according to the waveform distortion [5]. If no shocks are anticipated, 5–10 harmonics can adequately describe a continuous wave field; otherwise, 30–50 harmonics are required. The transverse plane sampling rate should be large enough to describe the significant spatial frequency component, otherwise large wrap-around errors will occur. For unfocused fields, 1~2× the Nyquist rate of the fundamental works very well while 4× the Nyquist rate is used for focused transducer [32]. The axial sampling intervals and N can also vary accordingly in the simulation. At the beginning of the simulation large Δz and small N can be used due to the weak nonlinear effect. As the wave propagates towards the focal region and nonlinear effect becomes significant, finer step size and large N are gradually included. The resultant exponential attenuation across Δz in the focal or far-field region for the highest harmonic should be no smaller than 0.7, which ensures the accuracy of the joint effect of

nonlinearity, attenuation, and diffraction in propagation. If all of these parameters are varied adaptively in the simulation (fixed in this study), the computation time would be reduced. Dynamic data allocation has been applied in three-dimensional acoustic field calculation to effectively implement the nonlinear algorithms with the application of stream data processing and efficient memory organization [31]. The size of k -th echelon is determined as

$$L_k = L_1 \frac{2N - 2k + 1}{2N - 1} \quad (18)$$

where k is the echelon number, N is the overall number of echelons, and L_1 is the size of the first echelon. Subsequently, the resources of memory could be saved by a factor of tens while maintaining the calculation efficiency.

In the practical hyperthermia or ablation, several variations in the physical properties of tissue should also be considered. If the tissue has small variations in the density changes, then a new term $\nabla p \cdot \nabla \rho_0 / \rho_0$ will be introduced to the full wave equation [33]. Small scale variations in other parameters (i.e., nonlinearity, absorption, and dispersion) do not introduce extra terms into the second-order wave equation [33]. The density fluctuation in the transverse direction, $\rho_0(z)$, could be incorporated into the diffraction term as first-order derivatives while that in the axial direction should be included in the operator splitting paradigm as a new ordinary first-order differential equation [33],

$$\frac{\partial p}{\partial z} = \frac{1}{2\rho_0(z)} \frac{\partial \rho_0(z)}{\partial z} p \quad (19)$$

The speed of sound in the tissue is a function of the temperature, increasing with temperature and exhibiting a maximum at around 50 °C in non-fatty tissues but a negative dependence for fatty tissues [4]. Such variation constitutes a localized aberrator, becomes significant as the progress

of HIFU ablation, and causes the self-defocusing of the acoustic beam. The ultrasonic attenuation coefficient of fresh bovine and human soft tissue has asymmetric quasi-parabolic curves with temperature, being convex downward with their minimum at the turning temperature of around 40 °C [4]. Furthermore, all the thermal parameters (specific heat capacity, thermal conductivity and heat diffusivity) of *ex vivo* porcine liver heated from 20 °C to 90 °C had a similar relationship with the temperature [13]. Therefore, more work is required to improve the proposed algorithm for *in vivo* application, compensate the aberrators for perfect and consistent focusing, and predict lesion formation accurately.

Skin burns could be occasionally found during the clinical HIFU treatment and is a concern for HIFU safety [38]. One of the reasons may be the bad acoustic coupling at the wave entry site. Hair in the skin could trap bubbles in the coupling media, degassed and deionized water or ultrasound coupling gel. Using real-time sonography the coupling condition can be checked frequently. When hyperechoes show up, HIFU ablation may be terminated to remove these bubbles. The appearance of grating lobe in the prefocal region of HIFU field is another mechanism, which is inherent to the geometry and frequency of HIFU parameters. The pressure in the grating lobe is much larger than that in the first side lobe which is more than 15 dB less than the pressure at the focus. Splitting focus into multiple ones will further worsen this phenomenon. If each split focus has the similar acoustic pressure as that at the geometrical focal point of the transducer, the large area of grating lobes as shown in Fig. 9 should be considered seriously because of significant temperature rises as listed in Table 4. In this study, it is also found that the negative pressure has more significant grating lobe. If higher than the cavitation threshold, the negative pressure in the grating lobe will induce bubbles, which may shield the propagation of subsequent HIFU bursts towards the focal region and scatter them towards the

transducer. The presence of bubbles in the acoustic field results in enhanced heat deposition and formation of larger lesions [38]. Several approaches have been proposed for reducing the grating lobe, such as elements with unequal center-to-center spacing [10], sparse array with random distribution of elements [12], the use of a wide-band signal (phase modulated by a pseudorandom code) [8], array apodization (unequal element amplitude weighting) [9, 28], and optimized random distributions of unequally size elements [15].

In summary, the proposed algorithm allows the calculation of nonlinear HIFU wave propagation from arbitrary excitation geometry through multiple tissue layers with different focusing strategies in an accurate and efficient way. Despite the popularity of the KZK model used in the HIFU simulation, the axially symmetric source and parabolic approximation limit its application, especially for phased array HIFU. Narrower beam size along and transverse to the transducer axis is predicted by the KZK model than those by the proposed algorithm and measurement, which may be due to the underestimation of diffraction. The resultant thermal field, temperature elevation, and lesion formation, can be used to evaluate the HIFU treatment plan in the practice quantitatively. Shifting and splitting the focus leads to the reduced acoustic pressure and lesion size. In addition, the grating lobe in the prefocal region becomes worsen. Compensation of tissue phase aberration, tracking of target motion due to respiratory, and avoidance of unintended energy accumulation in a vital region by using phased-array HIFU transducer will be further investigated on the basis of this simulation algorithm.

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Declaration of interest

The authors alone are responsible for the content and writing of this paper.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

(a)

(b)

(c)

Figure 6.

(a)

(b)

(c)

Figure 7.

(a)

(b)

Figure 8.

Figure 9.

Figure 10.

Figure 11.

Figure 12.