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Investigation of standing wave formation in a human skull for a clinical prototype of a large-aperture, transcranial MR-guided Focused Ultrasound (MRgFUS) phased array: An experimental and simulation study

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Abstract

Standing wave formation in an *ex vivo* human skull was investigated using a clinical prototype of a 30 cm diameter with 15 cm radius of curvature, low frequency (230 kHz), hemispherical transcranial Magnetic Resonance guided Focused Ultrasound (MRgFUS) phased-array.

Experimental and simulation studies were conducted with changing aperture size and *f*-number configurations of the phased array, and qualitatively and quantitatively examined the acoustic pressure variation at the focus due to standing waves.

The results demonstrated that the nodes and anti-nodes of standing wave produced by the small aperture array were clearly seen at approximately every 3 mm. The effect of the standing wave became more pronounced as the focus was moved closer to skull base. However, a sharp focus was seen for the full array, and there was no such standing wave pattern in the acoustic plane or near the skull base. This study showed that the fluctuation pressure amplitude would be greatly reduced by using a large-scale, hemispherical phased array with a low *f*-number.

Index Terms

Magnetic Resonance guided Focused Ultrasound (MRgFUS); standing wave; transcranial; high intensity focused ultrasound (HIFU)

I. Introduction

Transcranial Magnetic Resonance guided Focused Ultrasound (MRgFUS) has been investigated as a promising noninvasive surgical means for the treatments of various brain

diseases. Previous studies [1–4] have shown that a high intensity focused ultrasound (HIFU) beam can be noninvasively delivered through the skull and focused at deep-seated tissue in the brain for thermal tissue ablation without damaging surrounding tissues. While ultrasound energy is being delivered to a target in the brain, Magnetic Resonance Imaging (MRI) is used to precisely localize the target tissue and allows monitoring of temperature changes with high spatial and temporal resolution during the sonication [5–8]. Numerous research studies have demonstrated the potential applications of MRgFUS beyond brain tissue ablation, such as thrombolysis [9–11], blood-brain barrier (BBB) disruption for the targeted drug delivery [12–16], and potentially neural stimulation [17–19].

The primary obstacle for the use of ultrasound in the brain is the presence of the skull in the path of the ultrasound beam. High attenuation and distortion of the transmitted ultrasound beam by the cranium result in a diffused focus with highly decreased acoustic power as well as bone heating. These issues have been considerably solved with the development of large-aperture hemispherical phased arrays [20–22] which distribute transducer elements over the entire hemispherical surface area of the phased array. Therefore, spreading the ultrasound beam over most of the large surface area of the skull, combined with active skin cooling, substantially reduces cranial heating together with active skin surface cooling [23]. In addition, such a large aperture hemispherical phased array can restore a sharp focus and maximize acoustic energy delivery at target tissue through the skull by correcting the phase and amplitude distortions of the ultrasound beam from each array element induced by heterogeneities in the bone. The phase and amplitude correction is often performed using computer simulations with the individual patient skull properties, such as its shape, thickness and density, deduced from Computed Tomography (CT) images [24–26].

Although one can achieve an excellent focus and desired therapeutic acoustic power level at deep-seated tissue in the brain with the hemispherical phased array, there are still questions about standing wave formation inside the cranium, especially when low frequency ultrasound or long sonications are used. Commonly, standing waves are known to form in a closed space and create stationary pressure maxima or minima at every half wavelength of the acoustic frequency. The pressure amplitude of standing waves at the maxima and minima is highly dependent on the surface geometry from which acoustic waves reflect and reverberate. Such unpredictable pressure variation due to standing waves could cause unexpected bio-effects at locations outside of the focal volume. For example, a recent clinical study of the treatment of stroke reported problematic hemorrhages when an unfocused, small aperture, low frequency ultrasound device was used [9, 13]. These serious complications have been explained to be possibly related to standing waves [27–29]. Thus, there are questions of whether similar remote effects due to the standing wave formation may be induced with the large aperture hemispherical devices with CT driven phase and amplitude correction, especially when low frequencies are used.

In this paper we investigated standing wave formation in an *ex vivo* intact human skull using a clinical prototype of a large scale, low frequency (230 kHz), hemispherical transcranial MRgFUS phased array. Experimental and numerical simulation studies were conducted with changing aperture size and *f*-number configurations of the hemispherical phased array to

qualitatively and quantitatively examine the acoustic pressure variation at a focal point in the skull due to standing waves.

II. MATERIALS AND METHODS

Transcranial MRgFUS system

The study was conducted using a commercial clinical prototype of a low frequency transcranial MRgFUS system (ExAblate 4000, InSightec, Haifa, Israel). The MRgFUS system consists of an MR-compatible, 30 cm diameter, radius of curvature of 15 cm, 1011-element hemispherical ultrasound phased array driven at 230 kHz mounted on an MR patient table (Fig. 1). The number of active transducer elements, aperture size and f -number of the array are electronically adjustable by changing the apodization setting as shown in Table 1. The system was operated with a 3T MR scanner (Signa MR750, GE Healthcare, Milwaukee, WI, USA), which provided MR images of the measurement geometry in the planning stage prior to sonication as well as MR thermometry during sonication.

The focal point could be electrically steered to any location within an effective steering range of approximately $50 \times 50 \times 50 \text{ mm}^3$ around the geometric focus where the volume is defined by 50% of the pressure-squared amplitude peak. To compensate for the wave propagation aberration induced by the skull bone, the treatment planning software used CT scan images of the skull, and corrected the phase and amplitude for each element.

Experimental setup

The overall experimental apparatus is shown in Fig. 2. A $30 \times 20 \times 30 \text{ cm}^3$, Lucite water tank was constructed in-house. The tank was lined with 5 mm thick rubber to minimize the acoustic reflections from the tank walls, and filled with degassed, deionized water (*Resistivity* $> 16 \text{ M}\Omega\text{-cm}$) with dissolved oxygen level below 1 ppm. A 30 cm diameter circular plate was added on the front of the tank and tightly fit to the array to provide leak-free conditions during the experiments.

An *ex vivo*, human skull sample, fixed in 10 % buffered formaldehyde, was degassed prior to the experiments. A $4 \text{ cm} \times 4 \text{ cm}$ hole was made on the sample close to the *Foramen Magnum*, through which a hydrophone was placed for the measurement of pressure fields. The position of the skull was fixed by four adjustable grippers located on the left and right sidewalls of the tank. A $125 \text{ }\mu\text{m}$ diameter planar fibre-optic hydrophone with an active sensor diameter of $10 \text{ }\mu\text{m}$ (Precision Acoustics, Dorchester, UK) was used to measure the pressure fields parallel to the acoustic axis of the array. The hydrophone was affixed to a Velmax 3-D scanning system (Velmax Inc, Broomfield, NY, USA).

Fig. 3 shows an overall schematic diagram of the experimental setup. A Cartesian coordinate system is shown in the diagram. Since the scanning system was not MR compatible, all of the pressure field measurements were conducted outside the MR room. Prior to the pressure field scans, the distance between the skull bone and focal point was measured using the MR images to estimate the maximum scannable area. The hydrophone scans were controlled by a computer, via RS-232, using a program written in LabView (National Instruments, Austin, TX, USA). The radiated pressure field measurements were taken over $20 \times 70 \text{ mm}^2$ in the

YZ-plane with spatial resolution of 1 mm. The measurements were captured on a digital oscilloscope (TDS 3012B, Tektronix, Richardson, TX, USA) and saved on a computer via a GPIB bus.

A 1 ms long burst signal (1 % duty cycle, 10 Hz pulse repetition frequency (PRF)) was fed into the phased array by triggering the driving amplifier using a function generator (AFG3102, Tektronix, Richardson, TX, USA). The 1 ms pulse duration corresponded to a travel distance of approximately 1472 mm ($\sim 230\lambda$, $\lambda \approx 6.4$ mm at 230 kHz), which was long enough to produce multiple reflections inside the skull.

Magnetic Resonance Imaging (MRI)

The initial location of the hydrophone in the skull was prescribed using Single-Shot Fast Spin Echo (SSFSE) sequence in the axial, sagittal and coronal planes (parameters; repetition time/echo time (TR/TE): 2765/49.3 ms, slice thickness: 2 mm, and bandwidth: ± 83.3 kHz). These images were used to locate the hydrophone with respect to the geometric focus of the phased array. They are also used to avoid colliding the hydrophone tip into the skull as well as align a CT image of the skull for phase correction.

Pressure field measurements using a 72- and 1011-element phased array

The standing waves inside the skull were measured using the 72 element (37.5% apodization) and full (100% apodization, 1011 elements) phased arrays. In case of the 72 element phased array, 72 elements were selected from the centre of the array such that they formed an array approximately 10.7 cm in diameter with a 15 cm focal length. The full phased array was 30 cm in diameter and also had a focal length of 15 cm. Each element had the same surface area of 114 mm². Fig. 4 shows the simulated radiating pressure field for both of the arrays focused at the geometric focus in the acoustic and lateral axis, calculated using the Rayleigh-Sommerfield integral [30]. The theoretical full width at half maximum (FWHM) value is 12.6 mm for the 72-element array and 3.8 mm for the full phased arrays (Fig. 4 (a,b)).

Only the ultrasound beams with the incident angle less than the longitudinal wave critical incident angle with respect to the skull were used. The incident angle was estimated using the skull shape and properties deduced from CT image of the skull sample. A total electrical power of 40 W was applied to the active array elements for both the full and 72-element phased arrays.

The fibre-optic hydrophone was located in the skull as shown in the MR images of Fig. 5. We sonicated close to skull base (or a Sphenoid bone) where we could identify standing wave formation due to the reflections and reverberation of propagating acoustic waves. The dashed lines in the image were the contour of the transcranial phased array. Since the accessible window for the hydrophone inside the skull was limited by the 4 cm $\times$ 4 cm hole, we only scanned the half section around the focal point. In our experiments we sonicated at the geometric focus of the array. A Cartesian coordinate system with its origin at the geometric center of the array is shown in Fig. 5(a), where X- and Y-axis are defined to be the radial and lateral directions, respectively. The Z-axis is defined along the acoustic axis of

propagation towards outward of the phased array. The skull was placed at an angle with respect to the phased array such that the beam reflected at the skull base

Numerical Simulation Model

The linear wave equations governing the sound propagation in water and solid media (skull bone) were solved by using a Gauss-Lobatto-Legendre spectral element method [31]. The CT and MR measurements of the skull were used to obtain the geometry and orientation of the skull in the phased array. The temporal pressure and the pressure amplitude were calculated around the geometric focus and skull-base with spatial and temporal resolution of 0.652 mm and 24.6 ns, respectively. A detailed description of the simulation model is presented in Appendix A.

To investigate the effect of the aperture size and f -number of the transducer on the formation of standing waves in the skull, we simulated for eight sonications each at four foci with different configurations of the phased array. The simulated four foci were located at $(-12, -6, 0, 6)$ mm from the geometric focus of the phased array on the acoustical axis (Fig. 6). The geometric focus was located at the same position as the ones used in the experiments. The simulations were conducted by using both full and partial skulls. In the case of the partial skull simulation, we removed the skull base from the full skull, which essentially removed any reflecting waves, as reflected by the skull-base, from the simulations of the partial skull. By comparing the simulations with the full and partial skull, the effect of standing waves as created by the skull-base can be analysed.

The phase aberration for each transducer element at a focus was computed by placing a point sound source at the intended focus and computing the pressure field at the phased array elements as produced by the sound source. In the phasing simulations the partial skull was used. By inverting the phases recorded by each transducer element and using them as the driving phases of the phased array, the focus could be reconstructed. Equal amplitude of each driven phased-array element was used. The phased array was driven by using eight different apodization levels at each focus as shown in Table 1: 12.5, 25.0, 37.5, 50.0, 62.7, 75.0, 87.5 and 100%.

III. RESULTS

The numerical simulation results and experimental measurements were compared for the case when the 72-element or full (1011 element) phased array sonicated at the geometric focus of the array through *ex vivo* human skull (Fig. 7–9). The position and orientation of the skull in the array were the same in the simulation and experimental studies. Fig. 7 shows the simulations of the pressure field in the YZ-plane after standing wave forms in the skull. The active elements, 72-element or full array, are shown in thick solid lines on the outer circle as well as the contour of the skull. The close-up images of the pressure fields near the skull base are shown over an $80 \times 80 \text{ mm}^2$ area in Fig. 7 (b, d). As shown in Fig. 7(a, b), the 72-element array produced a stripe wave pattern in the acoustic plane and near the skull bone. The bright stripes periodically appeared at every 3 mm, approximately half the wavelength ($\lambda/2 \approx 3.2 \text{ mm}$) at 230 kHz. In Fig. 7(a), the amplitude of standing wave was shown to be smaller than the ones between the transducer and skull since sound wave

propagating through the skull is highly reflected and attenuated by the skull bone. However, strong standing waves were shown close to skull base at the focal point. As an f -number of the transducer reduces, the pressure distribution between the transducer and the skull is significantly smaller than at the focus. Compared to the 72-element phased array, a sharp focus was seen at the focus for the full array (Fig. 7(c,d)) and there was no such the stripe pattern seen in the acoustic plane or near the skull base.

Fig. 8 shows the experimental results of the normalized maximum pressure amplitude over an area of $20 \times 70 \text{ mm}^2$ in the YZ plane during a 40 W, 10 Hz PRF with 1% duty cycle burst sonication. Similar to the simulation, the 72-element phased array (Fig. 8 (a)) produced a node and anti-node stripe pattern of the standing wave at approximately every 3 mm, as is characteristic of standing waves. In contrast to this, with the full array (Fig. 8 (b–c)), the stripe pattern was not seen and the array produced a sharp focus at the targeted location. Using CT image-based phase correction for the full hemispherical phased array did not affect the formation of standing waves in the skull.

Fig. 9 shows the comparison of normalized acoustic pressure measurements and simulation results in the acoustic (Z) axis when the 72 and full element phased arrays were focusing at (0, 0, 0). When the standing wave was fully formed in the skull cavity, the pressure field was seriously distorted in the case of the 72-element array (Fig. 9 (a)). The nodes and anti-nodes of the standing wave were clearly shown at every 3 mm in the measurement. The simulation results showed the same periodic maxima and minima in the pressure field amplitude. As shown in Fig. 9(b), the pressure field produced by the full array did not show such significant interference in the waveform. Without the CT image based phase and amplitude correction, approximately 20% lower pressure amplitude was seen at the focus than with phase correction. However, there was no significant focal distortion except for an approximately 8% higher sidelobe amplitude without phase correction.

Fig. 10 shows the simulation of the pressure amplitude distribution for the eight apodization levels when the phased array is focusing at the geometric focus. A standing wave pattern is clearly seen in all the sonications except the one with 100% apodization.

Fig. 11 shows the pressure amplitude in the acoustic axis inside the skull for both simulations with the full skull and the partial skulls for each apodization level. The pressure maxima and minima due to standing waves are decreased as the apodization level increases (decreasing f -number).

Fig. 12 shows the Relative Standing Wave Fluctuation amplitude (RSWF) as a function of apodization and f -number based on the simulation:

$$\text{RSWF}(\%) = \frac{\max(P_{\text{tot}}(z) - P_{\text{inc}}(z))}{\max(P_{\text{inc}}(z))}, \quad (1)$$

where $P_{\text{tot}}(z)$ and $P_{\text{inc}}(z)$ are the pressure amplitude with and without skull-base in place, respectively, and z is a location on the acoustic axis. The RSWF is defined to be the difference in the pressure amplitude of the full skull simulation and the partial skull simulation on the acoustic axis, which essentially results in the amplitude distribution of the

standing waves. By taking the spatial peak of the pressure fluctuation divided by the peak amplitude of the pressure, the relative peak amplitude of the standing wave fluctuations can be found. The results show that increasing the size of the array (or decreasing the f -number) reduces the relative fluctuation of the standing-wave amplitude.

IV. DISCUSSION

This study demonstrated the benefits of using a large-scale, hemispherical phased array in reducing standing wave formation in a human skull. It also showed that the focusing quality of the multi-element array was significantly improved with phase correction. However, the influence of phase correction on the standing wave formation was not intensively investigated in this study. The experiments were conducted using an *ex vivo* human skull and a clinical prototype of a 230 kHz, MRgFUS system with different aperture apodizations: 72-element and full array. Both of the phased arrays were focusing at a location close to the skull base. The absorption and thermal effects of the brain were not investigated in this study.

The simulation and experimental results demonstrated that the nodes and anti-nodes of standing wave produced by the 72-element array were clearly seen at approximately every 3 mm, the half the wavelength at 230 kHz. Moreover, the effect of the standing wave became more pronounced as the pressure measurement was taken closer to the skull base. As shown in Fig. 9 (a), the significant fluctuations in the acoustic pressure amplitude occurred near the skull base. Consequently, such standing wave formation could cause serious problems, such as cavitation or unexpected hot spots.

The consequences of standing wave formation using small aperture transducers were reported in several experimental and clinical studies. Daffertshofer *et al.* [9] reported an unexpected increased rate of cerebral hemorrhages after transcranial thrombolysis treatments at 300 kHz. A 50 mm diameter planar transducer with a 5 % duty cycle and a pulse repetition frequency of 100 Hz was used in their study. Azuma *et al.* [27] demonstrated induction of unintentional cavitation due to standing waves in a section of a *ex vivo* human cranium using a 10 mm diameter single element transducer. Reinhard *et al.* [13] observed unexpected blood-brain barrier disruptions near the border of the skull bone, far from the target volume. Baron *et al.* [29] performed simulation studies using the same experimental parameters used in Reference 9 and 27, including transducer dimension, pulse repetition frequency and pulse length. They showed the possibility of standing wave formation due to the long pulse length. These experimental and clinical studies showed that standing waves could be readily formed by a small transducer with a large f -number and long pulse duration, and that this was highly dependent on the transducer location. They suggested that the unexpected results were related to standing waves due to continuous low frequency sonication.

It was evident in this study that the multiple reflections or reverberations of the propagating ultrasound wave in the skull cavity interfered constructively and destructively with the direct pressure waves from the small aperture phased array. The interferences were mainly generated by the repeated interactions between the wide and long focal pressure wave of the

small aperture array and its reflections and reverberations at skull base. As a result, they formed a complicated pressure field with standing wave components. Compared to a clinical environment, the air outside the head and membrane was replaced by water in this study, both experimentally and numerically. Moreover, standing waves are less likely to occur in a clinical treatment since brain is more absorbing than water. This reduces the amplitude of any reflections from the skull-base when compared to the reflections in water and hence the amplitude of standing wave.

As shown in Fig. 12, the fluctuation amplitude would be greatly reduced by using a transducer of low f -number. This is due to the increased gain of the transducer as f -number is decreased. Increased gain results in rapid decay of the pressure amplitude of the transmitted sound waves after the focus due to the sound waves diverging in wider angles with decreasing f -number. Since the amplitudes beyond the focus are decayed, the amplitudes of the back-reflecting waves (and hence the standing-wave) from the skull base will be reduced. Thus, the fraction of the back-reflecting waves and the focal pressure will reduce.

The variation of the standard deviation of the fluctuation amplitude for different apodization levels show that for the different segments of elements on the phased array the effect of reflecting waves from the skull base is different and geometry dependent as well. The geometrical inhomogeneities of the skull are also the most likely reason why the standing-wave fluctuation increases when shifting from apodization of 25% to 37.5%. For different segments on the phased array corresponding to different apodization levels, the incidence angle of the sound wave as it passes the focus and hits the skull-base varies. For some segments it is possible that this incident angle is close to normal which means that the reflected wave will mostly be directed towards the focus as well. The effect is, however, minimized by using a smaller f -number. The reduction in standing waves will be even further decreased by higher frequencies that can form even sharper focal spots [22, 32]. The possibility for standing wave formation is further decreased at higher frequencies by the increased ultrasound wave attenuation in the brain tissue that suppresses the wave propagation beyond the focal volume. However, this would come at the expense of increased attenuation and distortion by the skull at higher frequencies.

The full array produced a sharp focus at 230 kHz without forming the striped pattern of standing waves. The peak pressure amplitude at the focal point was only 20% higher in the cases with than without CT image based phase and amplitude correction. This supports the suggestion by Yin and Hynynen [33] that the low frequency acoustic waves are minimally distorted while propagating through the skull, and so it may not be necessary to use individual CT based corrections. The focal distortions were further reduced since the hemispherical phased array was highly effective in minimizing the standing waves in the skull cavity due to its sharp focus. In contrast, the 72-element phased array produced most of acoustic energy through a small section of the skull and through a relatively large focus. When a long pulse length was used, localized standing waves could be easily formed if the incident beam and the reflection beam happened to overlap.

V. CONCLUSION

This study demonstrated a method to measure a standing wave field in a skull using a fibre-optic hydrophone and a transcranial MRgFUS system. A large-scale transcranial phased array with a low f -number maximized acoustic energy delivery into a focal spot in the brain, while significantly minimizing the chance of standing wave formation. Our experimental results did not show a significant standing wave formation or secondary hot spots in the skull when a hemispherical array elements was used at 230 kHz. However, standing waves could be readily formed by a small transducer with a large f -number. The same results were qualitatively seen and quantitatively examined with the numerical simulations.

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Appendix A. Simulation Model

The linear wave equations governing the sound propagation in water and solid interface (skull bone) were solved by using a Gauss-Lobatto-Legendre spectral element method [31]. The CT and MR measurements of the skull were used to obtain the geometry and orientation of the skull in the phased array. The temporal pressure and maximum pressure amplitude were calculated around the geometric focus and skull base with temporal and spatial resolution of 0.652 mm and 24.6 ns, respectively.

The linear wave equation governing the propagation of sound in soft-tissue [34] is

$$\frac{1}{\rho c^2} \frac{\partial^2 p}{\partial t^2} = \nabla \cdot \frac{1}{\rho} \nabla p - \frac{2\alpha}{\rho c} \frac{\partial p}{\partial t}, \quad (\text{A1})$$

where ρ is the density, c is the speed of sound, α is the absorption, p is the acoustic pressure and t is time. A wave equation describing the propagation within the bone is [35]

$$\rho \frac{\partial^2 \mathbf{u}}{\partial t^2} = (\mu + \eta \frac{\partial}{\partial t}) \nabla^2 \mathbf{u} + (\lambda + \mu + \xi \frac{\partial}{\partial t} + \frac{\eta}{3} \frac{\partial}{\partial t}) \nabla \nabla \cdot \mathbf{u} \quad (\text{A2})$$

where $\mathbf{u}$ is the particle displacement, λ and μ are the first and second Lamé coefficients, and η and ξ are the first and second viscosities. Equations (A1) and (A2) are coupled on the water-bone interface with continuation of normal particle displacement and stress. The system formed by equations (A1) and (A2) is solved by using Gauss-Lobatto-Legendre Spectral Element Method (GLL-SEM) based on [31, 36].

The weak formulation of equation (1) is found after multiplication by test function v and integrating over the volume Ω and applying the divergence theorem:

$$\partial_t^2 \int_{\Omega} \frac{1}{\rho c^2} p v \, dr + \partial_t \int_{\Omega} \frac{2\alpha}{\rho c^2} p v \, dr + \int_{\Omega} \frac{1}{\rho} (\nabla v) \cdot (\nabla p) \, dr - \int_{\partial\Omega} \frac{1}{\rho} v \nabla p \cdot \mathbf{n} \, dr = 0 \quad (\text{A3})$$

Shorthand notation of the time derivative, ∂_t , is used. $\mathbf{n}$ is the surface normal and $\partial\Omega$ is the boundary of Ω . Weak form of equation (A2) is found by multiplication of vector test function $\mathbf{w}$, integrating over the volume and applying Betti formula [37]

$$\begin{aligned} & \partial_t^2 \int_{\Omega} \rho \mathbf{u} \cdot \mathbf{w} \, dr - \int_{\Omega} (\lambda + (\xi - \frac{2}{3}\eta) \partial_t) (\nabla \cdot \mathbf{u}) (\nabla \cdot \mathbf{w}) \, dr \\ & - \int_{\Omega} \frac{1}{2} (\mu + \eta \partial_t) (\nabla \mathbf{u} + (\nabla \mathbf{u})^T) : (\nabla \mathbf{w} + (\nabla \mathbf{w})^T) + \int_{\partial\Omega} \mathbf{T}^{(n)}(\mathbf{u}) \cdot \mathbf{w} \, dr = 0 \end{aligned} \quad (\text{A4})$$

where notation $\mathbf{A}:\mathbf{B} = \sum_{ij} A_{ij} B_{ij}$ is the tensor product and $\mathbf{T}$ is the traction operator defined as

$$\mathbf{T}^{(n)}(\mathbf{u}) = 2\mu \frac{\partial \mathbf{u}}{\partial \mathbf{n}} + \lambda \mathbf{n} \nabla \cdot \mathbf{u} + \mu \mathbf{n} \times \nabla \times \mathbf{u}, \quad (\text{A5})$$

Equations (A3) and (A4) are coupled via the boundary integrals with transmission conditions for the continuation of particle displacement,

$$\frac{1}{\rho} \mathbf{n} \cdot \nabla p = -\partial_t^2 \mathbf{u} \cdot \mathbf{n}, \quad (\text{A6})$$

and for continuation of normal stress,

$$\mathbf{T}^{(n)}(\mathbf{u}) \cdot \mathbf{n} = -p. \quad (\text{A7})$$

In GLL-SEM the test functions v and w are chosen to be products of 1D Lagrange interpolants derived for Gauss-Lobatto-Legendre (GLL) points [31].

Acoustical field variables p and $\mathbf{u}$ are approximated in each element as the sum of the test functions. Numerical integration of the mass matrices with GLL integration rules results in a diagonal matrix. This makes advancement of the acoustical fields in time computationally light weight, as there will be no matrices to invert. The spatially discretized GLL-SEM can be written as

$$\begin{pmatrix} \mathbf{M}_f & \mathbf{T}_{fs} \\ 0 & \mathbf{M}_s \end{pmatrix} \begin{pmatrix} \partial_t^2 p \\ \partial_t^2 \mathbf{u} \end{pmatrix} + \begin{pmatrix} \mathbf{M}_f^\alpha & 0 \\ 0 & \mathbf{S}_s^\alpha \end{pmatrix} \begin{pmatrix} \partial_t p \\ \partial_t \mathbf{u} \end{pmatrix} + \begin{pmatrix} \mathbf{S}_f & 0 \\ \mathbf{T}_{sf} & \mathbf{S}_s \end{pmatrix} \begin{pmatrix} p \\ \mathbf{u} \end{pmatrix} = 0, \quad (\text{A8})$$

where $\mathbf{M}_f$ and $\mathbf{M}_s$ are the mass matrices of the fluid and solid portions of the computational domain, $\mathbf{M}_f^\alpha$ and $\mathbf{S}_s^\alpha$ are the mass and stiffness matrices for the attenuation terms, $\mathbf{S}_f$ and $\mathbf{S}_s$ are the stiffness matrices of the fluid and solid, respectively, and $\mathbf{T}_{fs}$ and $\mathbf{T}_{sf}$ are the transmission matrices from fluid to solid and solid to fluid, respectively.

Assembly of $\mathbf{M}_f$, $\mathbf{M}_f^\alpha$, $\mathbf{S}_f$ and $\mathbf{T}_{fs}$ proceeds as follows. For each grid-point i the adjacent elements e in the surrounding are inspected. For each fluid element e in the surroundings of i the mass matrix $\mathbf{M}_f$ of the fluid will receive a contribution from the adjacent test functions as

$$\mathbf{M}_f(i, j) \rightarrow \mathbf{M}_f(i, j) + \frac{1}{\rho_e c_e^2} \int_{\Omega_e} v_i(r) v_j(r) dr, \forall j \in \Omega_e^h \quad (\text{A9})$$

where $v_i(r)$ and $v_j(r)$ are the test functions of grid node i and grid nodes j which belong to element e . r in equation (A9) is the integrated position vector, Ω_e is the volume of the element e and Ω_e^h is the set of grid-nodes belonging to element e . Sub index e in the material parameters refers to the element-wise constant material parameters at element e . $\mathbf{M}_f(i, j)$ refers to i th row and j th column of the matrix. Due to the specific numerical integration method used in GLL-SEM method only the diagonal of $\mathbf{M}_f$ and $\mathbf{M}_s$ will have nonzero values. Absorption and stiffness matrices will receive contributions, respectively.

$$\mathbf{M}_f^\alpha(i, j) \rightarrow \mathbf{M}_f^\alpha(i, j) + \frac{2\alpha_e}{\rho_e c_e^2} \int_{\Omega_e} v_i(r) v_j(r) dr, \forall j \in \Omega_e^h \quad (\text{A10})$$

$$\mathbf{S}_f(i, j) \rightarrow \mathbf{S}_f(i, j) + \frac{1}{\rho_e} \int_{\Omega_e} (\nabla v_i(r)) \cdot (\nabla v_j(r)) dr, \forall j \in \Omega_e^h \quad (\text{A11})$$

Matrix $\mathbf{M}_f^\alpha$ is diagonal. The assembly of transmission matrix $\mathbf{T}_{fs}$ is based on the transmission condition,

$$\mathbf{T}_{fs}(i, j') \rightarrow \mathbf{T}_{fs}(i, j') + \int_{\partial\Omega_{e,e'}} \mathbf{w}_{j'}(r) \cdot \mathbf{n} dr, \forall j' \in \Omega_{e,e'}^h \quad (\text{A12})$$

where j' is the grid-node in the solid element e' , $\mathbf{n}$ is the normal of the interface $\Omega_{e,e'}^h$, shared by the elements e and e' . Computation of the integrals is presented in [36]. Assembly of solid matrices proceeds in similar fashion.

The temporal discretization and propagation of the acoustic field parameters is done in two sub-sequential steps. In the first step predictions $p_{k+1}^{\sim}$ and $\tilde{\mathbf{u}}_{k+1}$ of the acoustical fields at the time instance $k+1$ are computed from

$$\frac{1}{\Delta t^2} \begin{pmatrix} \mathbf{M}_f & \mathbf{T}_{fs} \\ 0 & \mathbf{M}_s \end{pmatrix} \begin{pmatrix} \tilde{p}^{k+1} - 2p^k + p^{k-1} \\ \tilde{\mathbf{u}}^{k+1} - 2\mathbf{u}^k + \mathbf{u}^{k-1} \end{pmatrix} + \frac{1}{2\Delta t} \begin{pmatrix} \mathbf{M}_f^\alpha & 0 \\ 0 & \mathbf{S}_s^\alpha \end{pmatrix} \begin{pmatrix} \tilde{p}^{k+1} - p^{k-1} \\ 2(\mathbf{u}^k - \mathbf{u}^{k-1}) \end{pmatrix} + \begin{pmatrix} \mathbf{S}_f & 0 \\ \mathbf{T}_{sf} & \mathbf{S}_s \end{pmatrix} \begin{pmatrix} p^k \\ \mathbf{u}^k \end{pmatrix} = 0 \quad (\text{A13})$$

In the second step the predictions are used to compute the corrected acoustical fields p_{k+1} and $\mathbf{u}_{k+1}$ at time instance $k+1$ from

$$\frac{1}{\Delta t^2} \begin{pmatrix} \mathbf{M}_f & \mathbf{T}_{fs} \\ 0 & \mathbf{M}_s \end{pmatrix} \begin{pmatrix} p^{k+1} - 2p^k + p^{k-1} \\ \mathbf{u}^{k+1} - 2\mathbf{u}^k + \mathbf{u}^{k-1} \end{pmatrix} + \frac{1}{2\Delta t} \begin{pmatrix} \mathbf{M}_f & 0 \\ 0 & \mathbf{S}_s \end{pmatrix} \begin{pmatrix} p^{k+1} - p^{k-1} \\ \tilde{\mathbf{u}}^{k+1} - \tilde{\mathbf{u}}^{k-1} \end{pmatrix} + \begin{pmatrix} \mathbf{S}_f & 0 \\ \mathbf{T}_{sf} & \mathbf{S}_s \end{pmatrix} \begin{pmatrix} p \\ \mathbf{u}^k \end{pmatrix} = 0 \quad (\text{A14})$$

The predictor-corrector method was used because the absorption mechanism in the bone involves mixed temporal and spatial derivatives of the displacement. This results in non-diagonal absorption matrix $\mathbf{S}_s^\alpha$, which in turn would require a matrix inversion to solve the fields if implicit method of time integration were used. Due to the intense memory requirements of assembling all the global matrices of equation (A13) and (A14), the implementation of the model used in this paper was done in a matrix-free way.

The density of the skull was approximated based on the CT-scans [38]. Longitudinal attenuation α_L and sound speed c_L used were interpolated based on the density approximation and the data presented in [38]. As there exist no proper data as a function of density for the shear attenuation and sound speed, the following approximations were used:

$C_s = \frac{1400}{2550} C_L$, $\alpha_s = \frac{90}{85} \alpha_L$. Lamé and viscosity coefficients in equation (A2) are computed based on [39]. The summary of these parameters as a function of a skull density is shown in Fig. 13.

Spatial discretization of $h = 0.652$ mm with temporal discretization of $\Delta t = 24.6$ ns. The discretization corresponds to maximum Courant-Friedrich-Levy (CFL) number of $CFL = 0.15$. CFL is defined as

$$CFL = \frac{\max(c) \Delta t}{\Delta h} \quad (\text{A15})$$

Spatial discretization h corresponds to 10 points per wavelength in water. First degree spectral elements are used and thus the acoustical fields are approximated by piecewise linear basis functions.

Fig. 1.

(a) A picture of a clinical prototype low frequency transcranial MRgFUS system, and schematic diagrams of the hemispherical phased array: (b) 1011 elements (100 % apodization), and (c) 72 element (37.5 % apodization). The apertures size corresponding to the 37.5 % and 100 % apodization settings are 10.7 cm and 30 cm, respectively. The radius of curvature of 15 cm is the same for both apodizations.

Fig. 2.
An experimental apparatus for the pressure measurement in a human skull sample.

Fig. 3.
Schematic diagram of the experimental setup.

Fig. 4.

Simulated radiating pressure field in the lateral and acoustic axis of the 72 element (a, c) and 1011-element (b, d) phased array when the array focused at the geometric focus. The full width at half maximum (FWHM) is 12.6 mm for the 72-element and 3.8 mm for the 1011 element phased arrays, respectively. The focal zone extends from -46.45 mm to 46.21 mm for the 72-element array and from -3.22 mm to 4.27 mm for the full array.

Fig. 5. MR images of a fibre-optic hydrophone and Insightec ExAblate 4000 transcranial phased array in the sagittal (a) and coronal (b) planes. The inset image in (a) shows the location of the focal point with respect to skull base.

Fig. 6.

Schematic diagram of the locations of the simulated four foci. The geometric focus of the phased array is located at the location, ③. The location of sonication points, ①, ②, and ④ are $[-12, -6, 6]$ mm from the geometric focus (③) on the acoustic axis, z .

Fig. 7.

Simulated pressure field through the skull when the phased array focused at (0, 0, 0): (a) 10 cm in diameter, 72-element (apodization: 37.5%) array, f -number: 1.5, and (b) a close-up view of the dotted box shown in (a), (c) 1011-element (apodization 100 %) hemispherical array, f -number: 0.5, and a close-up view of the dotted box shown in (d). Thick solid lines show the profile of the active array elements. (b) and (d) are normalized to their peak values. The horizontal stripe patterns in (b) were shown at every 3 mm, which is approximately the same as a half wavelength at 230 kHz.

Fig. 8.

Normalized maximum pressure amplitude measurements in the YZ plane when the phased array focused at (0, 0, 0): (a) 72-element (apodization: 37.5 %) array, and full (Apodization: 100%) array (b) with or (c) without CT based phase correction. The horizontal stripe patterns in (a) were shown at every 3 mm. The positive Z-axis is an outward of the phased-array toward the skull base.

Fig. 9.

Comparison of the normalized pressure field measurements and simulation results: (a) 72 (apodization: 37.5%) element, and (b) full (apodization: 100%) phased array.

Fig. 10.

Simulation results of sagittal views of the normalized pressure amplitude distribution inside the skull for eight different apodization levels when the focus is located at the geometric focus of the hemispherical phased array: (a) 12.5%, (b) 25.0%, (c) 37.5% (d) 50.0%, (e) 62.5%, (f) 75.0%, (g) 87.5%, and (h) 100% apodization. Each plot shows the normalized pressure amplitude in dB with respect to the maximum amplitude of each case.

Fig 11.

The simulated pressure amplitude on the acoustical axis of the transducer inside the skull when sonicating at the geometric focus of the transducer at different apodization levels. The pressure amplitude at each plot is normalized with the maximum pressure amplitude with 100% apodization. Simulations are shown for both the full skull (thick solid line) as well as the partial skull (thin dashed line). : (a) 12.5%, (b) 25.0%, (c) 37.5 % (d) 50.0%, (e) 62.5 %, (f) 75.0%, (g) 87.5%, and (h) 100% apodization.

Fig. 12.

Relative amplitude of the standing-wave variation as a function of apodization. Shown in the figure is the curve of the average variation of each sonication location with the standard deviations bars. Cross marks show each individual sonication.

Fig. 13.

Acoustic parameters used in the numerical study as a function of a human skull density. ρ is the skull density, C_L and C_S are the longitudinal and shear wave speed in a skull bone, and α_L and α_S are the longitudinal and shear attenuation.

Summary of the phased array configurations for the clinical prototype system. The manufacturer's pre-defined apodization % settings are marked in '●'.

TABLE 1

Apodization settings (%)		Aperture size (cm)	Radius of curvature (cm)	# of array elements	<i>f</i> -number
12.5		3.5	15	8	4
25.0		7.5	15	32	2
37.5	●	10.7	15	72	1.4
50.0	●	15.0	15	138	1
62.7		18.8	15	232	0.8
75.0	●	21.4	15	346	0.7
87.5		25.0	15	522	0.6
100.0	●	30.0	15	1011	0.5