Enhanced numerical method for the design of 3D-printed holographic acoustic lenses for aberration correction of single-element transcranial focused ultrasound

Marcelino Ferri[a], José M. Bravo[a], Javier Redondo[b], Juan V. Sánchez-Pérez[a]

a) Centro de Tecnologías Físicas. Universidad Politécnica de Valencia.

Camino de Vera S/N. 46020. Valencia. Spain

b) Instituto para la Gestión Integrada de las zonas Costeras. Universidad Politécnica de Valencia.

Carretera Nazaret-Oliva S/N. 46730. Grao de Gandia. Valencia. Spain

Corresponding author: Marcelino Ferri. mferri@fis.upv.es 0034 963877000 (75245)

Abstract

The correction of transcranial focused ultrasound aberrations is a relevant issue for enhancing various non-invasive medical treatments. The emission through multi-element phased arrays has been the most widely accepted method to improve focusing in recent years; however the number and size of transducers represent a bottleneck that limits the focusing accuracy of the technique. To face this limitations a new disruptive technology, based on 3D printed acoustic lenses, has recently been proposed. As the submillimetre precision of the latest generation of 3D printers has proven to overcome the spatial limitations of phased arrays, a new challenge is to improve the accuracy of the numerical simulations required to design this type of ultrasound lenses. In this study we present and evaluate two improvements in the numerical model applied in previous works for the design of 3D lenses; which consist, first, in allowing the propagation of shear waves in the skull by means of its simulation as an isotropic solid and, second, in the introduction of the absorption in the set of equations that describes the dynamics of the wave in both fluid and solid media. The results obtained in the numerical simulations evidence that the inclusion of both s-waves and absorption significantly improves focusing.

Keywords: 3D printed lenses, focused ultrasound, transcranial ultrasound, single-element transducer, transcranial therapy.

Introduction

Since the first successful ablation of animal brain tissue transcranially using a single transducer by Fry and Goss (1980), the utility of focused ultrasound (FUS) applied to the brain through the intact skull has been demonstrated in many clinical implementations. Treatment of neurological infirmities such as Parkinson's disease (Magara et al 2014), Alzheimer's disease (Meng et al. 2017) or brain tumors (Coluccia et al. 2018, McDannold et al 2010) can be enhanced by this technique (Jolesz and McDannold 2014). The administration of FUS allows a transient and local opening of the blood-brain barrier (BBB) (Hynynen et al 2001, Choi et al 2007) improving the delivery of pharmacological substances such as monoclonal antibodies (Meng et al. 2017), anticancer therapeutic drugs (Kinoshita et al 2006), neurotrophic factors (Baseri et al 2012), therapeutic antibodies (Raymond et al 2008), adeno-associated virus (Alonso et al 2013, Wang et al 2015), and neural stem cells (Burgess et al 2011). Furthermore, High-Intensity Focused Ultrasound (HIFU) can thermally ablate brain tumours (Coluccia et al 2014). Brain ablation can reduce activity of hyper-excitable neurons in such cases as chronic neuropathic pain (Martin et al 2009) and essential tremors (Chang et al 2015, Elias et al 2013).

The success of these medical treatments is highly related with the precision of ultrasound focusing. Maximizing the quality of the focus remains a challenging topic due to the great aberrations induced by some physical characteristics of the skull, such as its elastic heterogeneity, variable thickness, high ultrasound absorption and big acoustic impedance ratio relative to brain. First approaches to reduce aberrations included the sonication after craniotomy (Guthkelch et al. 1991) resulting in an invasive technique with limited potential. Less aggressive techniques include the application of FUS without aberrations correction, radiating from the more regular areas of the skull (Marquet et al. 2012). In recent years, two main lines of research for aberrations correction can be highlighted, (i) the emission by multi-element phased arrays (Tanter et al. 1998, Clement et al. 2000, Hughes et al. 2017) and (ii) the modulation of the acoustic signals radiated by single element transducers (Kamimura et al. 2015). This second technique has been shown to be successful mainly in reducing the energy concentration in stationary waves and secondary foci, but does not seem so suitable for the correction of aberrations in the main focus. Therefore the most accepted line is the first one, which consists on actively shaping the wavefront to correct bone-induced aberrations through the use of a multi-element transducer array whose phase could be adjusted individually. The adjustment of the phase must be done by inverse propagation, measured or simulated, from target to transducer. Initially phase patterns were assessed by physically placing a reference transducer inside the brain at target location (Thomas and Fink 1996, Tanter et al. 1996); several years after, the technique became absolutely non-invasive when it was proven that acceptable phase patterns could be obtained by numerical simulation (Sun and Hynynen 1998, Aubry et al 2003, Clement and Hynynen 2002). The quality of simulations is directly related to the precise knowledge of the physical properties in each voxel of the digital model of brain and skull. Experiments conducted to derive, at each voxel, the acoustic properties from radiological variables obtained from medical imaging techniques, such as computed tomographies (CT) (Marsac et al. 2017) or magnetic resonances (Wintermark et al. 2014, Miller et al. 2015) are highly desirable, but are out of the scope of this paper.

Two remarkable technological limitations are affecting the aberration correction by multi-element phased arrays, (i) the accuracy in the knowledge of the acoustic properties inferred by medical imaging and (ii) the size and number of singular elements that can be implemented in the phased arrays. To face this second limitation a new approach has been recently proposed by Ferri et al (2017) and Maimbourg et al. (2018), consisting on shaping the wavefront by means of high transparency 3D printed refractive ultrasound lenses. Acoustic field control by passive elements such as refractive lens or metamaterials has been successfully proved even at audible frequencies (Li et al 2015, Xie et al. 2016, Melde et al 2016, Brown et al 2017). The work published by Maimbourg et al. (2018) demonstrates that the spatial resolution, associated with the voxel size achieved by the latest generation of 3D printers, improves dramatically the space resolution of phased arrays, leading to better focusing. Thus, instead of racing to create arrays with an ever increasing number of elements, the acoustic lens approach can be considered as a promising technology by allowing submillimetre phase correction over a large surface with limited cost. Compared to the multi-element arrays technique, the use of a single element lens is a compact, affordable and low cost solution. Such an approach would further reduce the amount of equipment and skills required on site at each therapeutic center.

Limitations in the manufacture of 3D lenses are low due to the submillimetre accuracy of the printers; therefore the main front of the problem to be faced consists of increasing the quality of the numerical approach. Thus, in this work we propose and evaluate two improvements to the model developed by Maimbourg et al (2018), which consist of (i) the introduction of the phenomenon of brain and cranial absorption in the set of equations and (ii) the simulation of the skull as an isotropic solid allowing the simultaneous propagation of shear and pressure waves.

Materials and Methods

Computerized tomographies of human skulls. Physical parameters

Numerical simulations were conducted on an in-vivo computerized tomography (CT) of a human head (freely available for scientific purposes at the repository cancerimagingarchive.net). The in-plane spatial resolution of the slices is 0.49mm and interslice spacing of 0.63mm. For each voxel, a single value of the radiodensity in Hounsfield units is provided. To obtain a denser cubic simulation grid, a 3D linear interpolation of the parallelepiped mesh is performed with a spatial step, h=0.244mm. Excitation frequency applied in simulations is 760kHz; thus we have a ratio $\lambda/h>8$ at the slowest medium (given the wave speed of the water) that is an acceptable error condition (Lomax et al, 2013)

In order to apply the elastodynamic damped equations in isotropic solids, a set of four independent parameters must be known at each voxel. This set may be, for instance, density in equilibrium ρ, p-wave speed c, attenuation coefficient α, and shear modulus G. The two first parameters, given its accepted linear dependence with radiodensity in Hounsfield units (HU), are obtained by means of the expressions (Maimbourg et al. 2018)

$$c(x,y,z) = c_{water} + \left(c_{bone} - c_{water}\right)\frac{HU(x,y,z) - HU_{\min}}{HU_{\max} - HU_{\min}} \quad (1)$$

$$\rho(x,y,z) = \rho_{water} + \left(\rho_{bone} - \rho_{water}\right)\frac{HU(x,y,z) - HU_{\min}}{HU_{\max} - HU_{\min}} \quad (2)$$

where ρ_{water} and c_{water} are the density and p-wave speed of water at 21ºC, and ρ_{bone} and c_{bone} are respectively the density and p-wave speed of cortical bone at that temperature. Voxels displaying values beneath 0 HU or above 2400 HU were set respectively to 0 HU and 2400 HU that are respectively the expected values for water and cortical bone (Marsac et al. 2017). Densities and p-wave speed values are in accordance with Connor et al. (2002), Connor and Hynynen (2004), Pichardo et al. (2011) and Maimbourg et al. (2018). For cortical bone and for water we have considered, respectively

$$c_{bone} = 3100 m/s,\quad \rho_{bone} = 1900 kg/m^3,\quad c_{water} = 1485 m/s,\quad \rho_{water} = 10^3 kg/m^3.$$

For the optimal performance of the proposed model it would be desirable to know the four input magnitudes as point functions. However, although the dependence of radiodensity on the density and p-wave velocity has been investigated, its relation with the attenuation coefficient and the shear modulus has not been studied in depth. Therefore, we have applied a different approach for the attenuation coefficient and the shear modulus, consisting on the use of average values for each domain. For the attenuation coefficients at 760kHz we will consider α_{brain}=2Np/m, and α_{skull}=60Np/m. These values are coincident with the smallest ones found in bibliography (Pichardo et al. (2011), Clement et al. (2004), Pinton et al. (2011)) in order to potentiate the extrapolation of the results. Thus, improvements found in real cases are expected to be better than that obtained in the evaluation described here.

In the case of the shear modulus in solid domain, its dependence on radiodensity is assumed. We propose here to obtain it from its known relation with the p-wave modulus, M, and the Poisson's ratio, ν

$$G = \frac{M(1-2\nu)}{2(1-\nu)} \tag{3}$$

Where p-wave modulus is derived from radiodensity (Equation 7), and Poisson's ratio is imposed constant for the skull with a value ν_{skull}=0.316 to achieve a constant relation between p-wave and s-wave speeds, c_p/c_s=27/14, as proposed by Hughes et al. (2016).

Governing equations and numerical model

An elastodynamic linear FDTD centered model has been completely developed by the authors in Matlab scripting code (The MathWorks, Inc. Massachusetts. USA). A nonlinear model hasn't been considered because, with the amplitudes used for BBB opening, typically about 100kPa in the inner skull surface (Clement and Hynynen 2002, Konofagou et al 2012), the presence of relevant nonlinearities would eventually appear exclusively in the close vicinities of the focus, not been able to cause significant displacements or aberrations (Clement and Hynynen 2002). Governing equations implemented for both fluid and isotropic solid media, are

$$\frac{\partial \tau_{ij}}{\partial t} = (M - 2G)\delta_{ij}\left(\nabla \vec{u}\right) + G\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right) \qquad (4)$$

$$\rho \frac{\partial u_i}{\partial t} + \sigma \cdot u_i = \sum_j \frac{\partial \tau_{ij}}{\partial x_j} \qquad (5)$$

where τ_{ij} are the components of the stress tensor, δ_{ij} is the Kronecker delta, u is the velocity, ρ is the density in equilibrium, G and M are respectively the shear and the p-wave moduli, and σ is an artificial absorption parameter causing a perfectly exponential space dependent attenuation in isotropic media. Dependence between the attenuation coefficient α, in Nepers per meter, and the absorption σ, for both solid and fluid can be expressed as

$$\sigma = \rho\sqrt{\left(\omega + \frac{2c^2\alpha^2}{\omega}\right)^2 - \omega^2}\ , \qquad (6)$$

where ω is the angular frequency and c the p-wave speed at the media.

Constitutive and dynamic expressions (Eq, 4 and 5) applied at the whole computational domain are valid for both fluid and elastic media. At solid media, axial stresses τ_{ii} may differ and tangential stresses τ_{ij} are not null. On the other hand, at liquid media -where shear modulus G is zero- the tangential stresses are also zero and the three axial stresses at each point take the same value, equivalent to the pressure at the fluid with opposite sign. The parameter M of the set of equations represents the p-wave modulus at the solid but also the bulk modulus at fluid; both being obtained at any point of the skull and brain from the sound speed and the average density derived from the computerized tomographies, as follows

$$M = \rho c^2 \qquad (7)$$

Simulations are performed in time reversal, to register the phase pattern required to generate the acoustic lens, and in time forward to evaluate the focusing quality. In both cases excitation signal consists of a single frequency continuous burst enveloped by a half Hanning window during the first n

cycles. To facilitate the phase registration and the calculation of the focusing indicators described below, excitation pressure is implemented in complex form

$$\tau_{11} = \tau_{22} = \tau_{33} = -p_o \sin^2\left(\frac{\omega}{4n}\min\left(t, \frac{2n\pi}{\omega}\right)\right)\left(\cos(\omega t) + j\sin(\omega t)\right) \quad (8)$$

where the length of the half Hanning defined is n=10 cycles, and the time step Δt is computed based on a 0.3 Courant–Friedrichs–Lewy (CFL) condition at the cortical bone. In the following, we will use the notation $\overline{p}$ for the complex acoustic pressure in the liquid media; therefore, in liquid $-\overline{p} = \tau_{11} = \tau_{22} = \tau_{33}$.

Phase shift registration

The lens shape is derived from the phase pattern registered at its position. In our implementation all oscillating variables are simulated in complex form so the phase information is included directly at any point of the mesh, the use of complex variables increases the computational cost but reduces the numerical manipulation of the data, not being necessary to perform any transform to obtain amplitude or phase at any point at any instant. A time reversal propagation of a single frequency wave emitted at the target point is performed to register the phase pattern at the transducer position; but properly the phase pattern is registered at a Cartesian discretized spherical surface concentrical to the transducer that is separated a distance equal to the maximum accepted lens thickness (Fig. 1b-f). Once achieved the stationary state a few periods after the wave reaches the target, the numerically computed phase shift between a reference point and any other point of the computational domain remains remarkably constant. Phase is then 2D-unwrapped using the Goldstein's branch cut method (Ghiglia and Pritt, 1998) to avoid abrupt phase jumps. To control the thickness of the 3D printed lens, we propose to limit the maximum acceptable phase to a given value, multiple of 2π. Therefore the phase must be rewrapped inside the accepted interval. For the aims of this work we have limited the phase to the interval [0, 2π).

Numerical design of corrective lens

Once the registered phase has been unwrapped and rewrapped into the defined interval, the thickness of the lens, $e(\theta,\varphi)$, associated to each measuring point is obtained by a linear interpolation from the phase $\beta(\theta,\varphi)$, as follows

$$e(\theta,\varphi)=\frac{\beta(\theta,\varphi)-\beta o}{2\pi}\frac{\lambda_{lens}\lambda_{water}}{\lambda_{lens}-\lambda_{water}} \quad (9)$$

Where λ_{lens}, λ_{water} are the wavelengths of the p-waves associated respectively with the lens and the surrounding media (generally water), and β_{o} is an initial phase optimized to reduce the presence of abrupt phase changes in the central part of the lens. The thickness of 3D printed lens is computed after interpolating the Cartesian domain registered phases in the closest points of a mesh defined in spherical coordinates centered in the target point. If 3D lenses are implemented in simulations, their shape is expressed in the Cartesian domain by again linear interpolation.

The 3D printer ink employed and the maximum phase shift of the lenses accepted are two relevant open points of discussion, complex enough to be matter of future works. In fact, the ideal solution would be an extremely thin lens with a continuously variable profile made of a highly refractive material, but once we take into account that simulations are performed on a finitely discretized mesh obtaining then staggered profiles, lens thickness tending to zero would lead to spatial relative errors tending to infinite. Therefore the theoretically best option is not good in practical, so we shall search for compromise solutions where the best material and lens thickness will be directly related with the size of the numerical mesh.

For the physical printing of the 3D lens we propose that the external surface of the lens shall be a perfectly spherical curve adapted to the curvature of the applied focused ultrasound transducer, and its internal surface shall be rough so that its thickness -measured in radial direction- follows the registered phase pattern. The material used for ultrasonic lenses should be homogeneous, isotropic, with low absorption, and should have -in relation to water- a reasonable refractive behaviour and low reflection. In practical cases the speed of sound in lenses should be about twice as fast as in water, because larger ratios would lead to thinner lenses that must be printed in 3D with higher precision, and smaller ratios would produce thicker lenses that would not be useful in practical cases. Among the great diversity of plastics available on the market, we propose polylactic acid (PLA) for direct 3D printing of acoustic lenses. This material, with adequate acoustic properties, is cheap and has extended use in 3D printing, so the technical and economical threshold is reasonable. At today's state of the art the process of 3D printing moulds to be filled with the most adequate material (Maimbourg et al 2018) seems more feasible than the direct 3D printing of the lens, where some kind of anisotropy is inherent; but we consider that direct printing of the lens may become a competitive option in near future due to 3D printing is a booming technological sector. Furthermore, the more accurate the design of the physical lens the more similarities between the focusing quality found by ***theoretical gold standard emission*** and by ***complete simulations*** (defined below). So simulations carried with PLA lenses can be a realistic estimation of the aberration correction in practical cases

The acoustic characterization of PLA has been performed by means of propagation and resonance experiments conducted on several samples of 3D printed cylinders, and the results have been checked against the existing bibliography regarding physical properties of 3D printer inks. The values taken for the four physical magnitudes required to properly model the behaviour of a solid in the proposed model (Farah et al. 2016) are c_{PLA}=2167m/s, ρ_{PLA}=1252kg·m^{-3}, α_{PLA}=10Np/m and ν=0.36, which lead to a specific acoustic impedance value (z_{PLA}=2.7Mrayl), not very different from that of water, favouring the transmission of ultrasounds through the lens. For the purposes of this study, the precision in the measurements of the parameters can be considered acceptable since we are going to do an exclusively numerical study. However, if the technique evaluated here were to be widely applied, more experiments would have to be carried out to accurately obtain the acoustic characteristics of 3D-printable plastics.

Simulation models

In the following, the model developed by us will be denoted as "Time Reversal with Absorption" (TRA). To check its performance against the method suggested by Maimbourg et al. (2018), two more models will be simulated: one considering s-waves but without absorption, which will be called here "Time Reversal Undamped" (TRU), and other with absorption but modelling the skull as a fluid that we will call "Time Reversal with Absorption modelled as Fluid"(TRAF). The exclusion of s-waves and absorption are easily achieved cancelling respectively the shear modulus, G, in equation 4 or the absorption parameter, σ, in equation 5. Time forward simulations required to evaluate the focusing quality are developed with the complete equations for the three methods, i.e., considering absorption and s-waves. These simulations are performed by two procedures (i) *theoretical gold standard emission* and (ii) *complete simulation.*

In the ***theoretical gold standard emission*** we consider that each emitting voxel acts as a point source affected by the phase patterns registered in the time reversal simulation. These emitting voxels are sited at the surface where the phase pattern has been registered, i.e. separated from the transducer position a distance equal to maximum lens thickness. Amplitude is considered uniform at the emission surface.

In the ***complete simulation*** the emission is simulated from the position of the spherical transducer with uniform initial phase and amplitude, but the numerical medium is modified by adding the Cartesian model of the acoustic lens placed in the correct position. In addition, a backing with conical symmetry is attached to the lens with the same acoustic properties of the lens itself. Backing is placed to prevent numerical noise in the emission.

Evaluation of the methods by numerical simulation

As aforementioned, the main goal of this work is to evaluate if the introduction of the absorption phenomenon and the s-waves in the equations for the time reversal simulation (TRA model) allows manufacturing 3D lenses that are able to correct the skull aberration and to focus the beam better than previous models. For a better evaluation of the effect of each modification, we have developed the aforementioned models TRU and TRAF each one differing to the proposed TRA by a single physical phenomenon.

The focusing efficiency of a ***complete simulation*** will depend on the quality of the equations and discretization, but also on many decisions related exclusively with the lens design as stated before. Then, in order to reduce uncontrolled elements that can mask the improvements associated exclusively with modifications of the set of equations, we will develop our systematic study considering the focusing capability achieved by the ***theoretical gold standard emission*** procedure. Therefore the accuracy of the focusing of the aberrated-corrected focal spots performed by both proposed (TRA) and previous (TRU, TRAF) methods will be evaluated for the ***theoretical gold standard emission*** in five different configurations, called Point_1 to Point_5 (Fig. 1). Transducer-target distances range between 45.8mm and 107.3mm and transducer-target pairs are intentionally placed crossing irregular and non-symmetrical points of the skull to increase the aberration of the beams to be corrected. The five configurations (Fig. 1) have been defined from the available CT scan. To develop our study we have simulated the emission from a single element focused transducer with a radius of curvature of 59mm and a diameter of aperture of 67mm, similar to that analysed by Maimbourg et al. (2018). A frequency of 760kHz has been selected since higher frequencies would precise longest computational times due to the spatial resolution required and would lead to an increase in absorption. Therefore, improvements associated with the inclusion of absorption will be even greater at higher frequencies.

Focusing capability is evaluated by means of several quantitative indicators related with the position, shape, orientation, size and overlapping of the focus. To evaluate overlapping, the knowledge of a reference beam is required; therefore we will perform time forward simulations in a uniform media from a spherical source. The media consists in water without interposed skull and the source is a focused spherical transducer centered at the target point, with a radius equivalent to the distance transducer-focus and an aperture equal to lens aperture. This simulation is used to define the volume, V_{ref}, position, and shape of the ideal beam and as an indicative of the algorithm's numerical precision.

Additionally, we have performed at Point_4 and Point_2, the *complete simulation* of the emission with 3D interposed lenses by the three methods TRA, TRU and TRAF. The evaluation of the focusing quality for both *theoretical gold standard emission* and *complete simulation* is made attending to the indicators defined below.

Focusing indicators

To assess the quality of each focal spot we will evaluate its (i) positional deviation, (ii) radius of gyration, (iii) orientation, (iv) volume and (v) energetic overlapping with the ideal focus. Each one of these properties is associated with a quantitative indicator defined in this section. Numerical parametrization of the beam has been performed for both -3dB and -6dB beam volumes by the five evaluated parameters. These indicators are in concordance with previous works where performance of 3D holographic ultrasonic lenses is evaluated (Maimbourg et al. 2018).

(i) Positional deviation: Position of the acoustic focus is represented by the barycentric coordinates of the module of the squared complex pressure within the -3dB (or -6dB) focal area

$$\vec{r}_F = \frac{\int_{-3dB} \vec{r}\left|\overline{p}^2\right| dV}{\int_{-3dB} \left|\overline{p}^2\right| dV} \quad \text{discretized as (for first coordinate)} \quad x_F = \frac{\sum_{-3dB} x\left|\overline{p}^2\right|}{\sum_{-3dB}\left|\overline{p}^2\right|} \tag{10}$$

The longitudinal and transverse deviations of the focus (z, R) from the target point, $\vec{r}_o$, are obtained as

$$z = \left(\vec{r}_F - \vec{r}_o\right)\cdot \vec{u}_{TO} \ , \qquad R = \sqrt{\left(\vec{r}_F - \vec{r}_o\right)^2 - z^2} \tag{11}$$

With $\vec{u}_{TO}$ being the unit vector in the direction and sense transducer-target

(ii) Radius of gyration: The shape of the focus is evaluated by the radius of gyration of the module of the squared complex pressure within the -3dB (or -6dB) focal area. This parameter is obtained respect to the barycentric point, k, and respect an axis parallel to the direction transducer target, passing through the barycentric point, k_R.

$$k = \sqrt{\frac{\int_{-3dB} \left(\vec{r} - \vec{r}_F\right)^2 \left|\overline{p}^2\right| dV}{\int_{-3dB} \left|\overline{p}^2\right| dV}} \tag{12}$$

$$k_R = \sqrt{\frac{\int_{-3dB} \left(\left(\vec{r} - \vec{r}_F\right)^2 - \left(\left(\vec{r} - \vec{r}_F\right)\cdot \vec{u}_{TO}\right)^2\right)\cdot \left|\overline{p}^2\right| dV}{\int_{-3dB} \left|\overline{p}^2\right| dV}} \tag{13}$$

being $\vec{r}_F$ the barycentre as defined by Equation 10 and $\vec{u}_{TO}$ the aforementioned unit vector

(iii) Orientation: To obtain the orientation, φ, we have computed, at the barycentre, the inertia tensor of the module of the squared complex pressure at the -3dB spot (or -6dB). Then the direction of the beam is defined as the direction of the eigenvector associated with the smallest eigenvalue of the tensor.

(iv) Volume: It is obtained, for both -3db and -6dB focal regions, without spatial interpolation, i.e., voxels surrounding the target point with a squared pressure amplitude bigger than one half of the maximum (-3dB) are considered, and the rest are excluded (Fig. 2c-d).

(v) Energetic Overlapping: Denoted as I_i(%), is obtained computing the percentage of the energy of a particular beam that reaches the reference beam

$$I_i(\%) = \frac{\int_{Vref} \left|\overline{p}^2\right| dV}{\int_{Vi} \left|\overline{p}^2\right| dV} 100 \qquad \text{discretized as} \qquad I_i(\%) = \frac{\sum_{Vref} \left|\overline{p}^2\right|}{\sum_{Vi} \left|\overline{p}^2\right|} 100 \tag{14}$$

Where V_{ref} and V_{i} are the volume of the -3dB (or -6dB) focal region computed respectively for the reference and for the aberrated-corrected scans. To compute this indicator, the squared pressure amplitude is forced to be zero out of the -3dB focal region.

Results

In this section we present the results of the quantitative indicators for the five configurations evaluated by ***theoretical gold standard emission*** and of the configurations Point_2 and Point_4 evaluated by ***complete simulation***.

Theoretical gold standard emission

Positional deviation of the focus: The longitudinal and transverse focal point deviations (z and R respectively), for the -3 dB and -6 dB beams, are shown in Tables 1 and 2 and in Figures 3a and 3b for the aberrated-corrected simulations and for the reference beam. The reference beam deviations are presented as an approximation of the numerical error of the entire time-reverse-time-forward simulation process.

The transverse deviations obtained for the -3dB beams are relatively small compared to the emitted wavelength ($\lambda_{\mathrm{water}} \approx$ 2mm at 760kHz) and to the size of the voxel in the five configurations evaluated and for the three methods (TRA, TRU and TRAF). In all five configurations, the TRA method achieves better accuracy for transverse positioning, showing an average transverse positional deviation 0.07mm lower than the TRU method and 0.08mm lower than the TRAF method. These values are both more than twice the mean transverse deviation of the reference beam (0.03mm) that represents a rough estimate of the numerical error. In the case of -6dB focal points, no clear differences are obtained between the TRA and TRU methods whereas the average difference between TRA and TRAF is 1.7mm favourable to TRA.

From the results obtained, it can be seen that the measured longitudinal deviations show certain dependence on the distance transducer-target. This may be related to (i) the numerical error, (ii) the analytical asymmetry (bigger at larger distances) of the ideal beam in longitudinal direction, and (iii) a lower focusing capability related to the smaller solid angle of the lens subtended from the focal point. On the other hand, there are no remarkable differences between the longitudinal deviations achieved by both TRA and TRU methods. Regarding the differences between methods TRA and TRAF, the -3dB beam and -6dB beams are respectively 1.35mm and 1.55mm more deviated in average with TRAF.

Radius of gyration: The appropriate beam shape, considered as the similitude with the shape of the reference beam, is evaluated using the transverse, k_R, and total, k, radii of gyration of the -3dB and -6dB focal beams. Both the transverse and total radii of gyration at the -3dB focal beams simulated by the TRA, TRU and TRAF methods have certain similarities with those of the reference beam. Particularly the TRA values are generally smaller, more similar to the reference and with a more regular trend compared to TRU, as can be seen in Figure 3c for the transverse radius of gyration, and in Figure 3d for the total radius of gyration. Regarding the TRAF method the transversal and total radius of gyrations obtained are slightly bigger than those obtained by TRA and TRU, in all cases.

When -6dB focal points are evaluated, the aberrations of both methods are greater. Therefore, the trends and values of the calculated radii of gyration are in worst accordance with the ideals and, consequently, there are no clear differences between the TRA and TRU methods, as one can see in Table 2. TRAF method shows again the worst results, being respectively the transverse and total radius of gyration 18% and 17% greater than TRA values in average.

Orientation: Figure 3e shows that the -3dB beams obtained by the TRA method are better oriented than the TRU and TRAF beams for the five cases evaluated. The improvements in orientation provided by the TRA method are slightly more noticeable at the outermost points. The average improvement in orientation between the TRA and TRU methods is 0.8°, and between the TRA and TRAF methods is 1.3°. The numerical error, estimated as the average orientation of the reference beam is approximately 0.3°. In the -6dB beams, larger aberrations are found, with values as large as 46º for TRA, 32º for TRAF, and 19º for the TRU beam, as shown in Table 2.

Focal volume: The -3dB beam focal volumes (Fig. 3f) obtained by the TRA and TRU methods show a reasonable similarity with the reference beams, being TRAF beams slightly larger and more irregular. When target points are close to the transducer there are no noticeable differences between the TRA, TRU and TRAF methods, but at the farthest target points the TRA method provides smaller foci with a size more similar to that of the reference. The average values of the sizes calculated by the TRA method ($28mm^3$) are smaller than those obtained by TRU ($32mm^3$) and TRAF ($38mm^3$) methods.

As with other indicators, the advantage of the TRA method over TRU for this indicator is less significant for -6dB beams than for -3dB beams, as shown in Table 2. In fact, the average volumes are $123mm^3$ for TRA and $126m\ m^3$ for TRU. However, the TRAF beams are notably larger with an average volume of $166mm^3$.

Energetic overlapping: In the -3dB beams (Fig. 3g) we can see that the average overlapping is 74% for the TRA method and 71% for the TRU method. In the three evaluated configurations where the target points are closer to the transducer there are no notable differences between the TRA and TRU methods, but in Point_4 and Point_5 the overlaps achieved by the TRA method are significantly greater than those obtained by the TRU method. TRAF method follows roughly the same pattern, i.e. the differences in overlapping relative to TRA increase with distance. Average value of overlapping with TRAF is 58%, and its individual values are worst than TRA at the five points evaluated.

When -6 dB beams are evaluated (Table 2), the average overlaps are then 64.4% for TRA, 63.8% for TRU and 47.9% for TRAF.

Complete simulation

In this section we present the quantitative focusing indicators of the ***complete simulation*** performed at Point_2 and Point_4. These points have been chosen as representative of cases in which the aberrations induced by the skull are relevant but physically resolvable, unlike other points such as Point_3 (Fig. 1d) in which there are physical limitations related to some incident angles that are impossible to be solved by a lens with the established aperture. (Fig. 4c and Fig. 5c-d illustrate respectively a transversal section of the 3D computational domain and two coronal sections of the energy distribution during the complete simulation at Point_4. The shape of the designed lens and the thickness distributions can be seen in Fig 4a-b. Fig, 6 illustrates similar cross section for Point_2)

The focusing indicators of the aberrated-corrected focal spots are shown at Tables 3 and 4. As expected, at Point_4, all the values are worse than those obtained by the ***theoretical gold standard emission,*** but the TRA method still outperforms TRU and TRAF. In fact, when the -3dB beam of ***complete simulation*** is evaluated we can see that TRA method leads to a smaller positional deviation, a smaller beam volume, a more accurate orientation, a more appropriate shape (radius of gyration) and a greater energetic overlapping than TRU and TRAF. Particularly, an overlapping for TRA method 20% greater than TRU and 36% greater than TRAF must be pointed out. Focusing indicators at Point_2 show better values for TRA than for TRU at both -3dB and -6db beams for all indicators with the exception of transversal deviation of the -3dB beam. It is remarkable, for the TRA method, the small differences found between the focusing indicators obtained with ***theoretical gold standard emission*** and with ***complete simulation***; being overlapping for -3dB beam even 2.3% greater in ***complete simulation***. The comparison between TRA and TRAF shows that, without any exception, focusing indicators are better at TRA. Particularly relevant is the difference in overlapping with a difference larger than 25% between both methods at -3dB and -6dB beams. An energetic sagital cross section of Point_2 for TRA, TRU and TRAF (Fig 6) shows clearly the better focusing achieved by TRA.

Discussion

Numerical parameterization of the focusing has been performed for both -3dB and -6dB beams with an emission frequency of 760kHz. As expected, larger aberrations are found in the -6dB beams leading to orientations, positions and shapes of the focal point more different from the reference beam than those at -3dB. These aberrations occur regardless of the numerical method (TRA, TRU or TRAF) applied to record phase patterns.

Inclusion of the absorption

When we evaluate the effect of the inclusion of the absorption, by comparing the focusing indicators of TRA and TRU methods, we appreciate that the focusing indicators of the -6dB beams calculated with the TRA method are slightly better on average than those of the TRU method, but the difference between the two methods is more noticeable in the -3dB beam case.

The evaluation of the -3dB beam shows several evidences to be pointed out. Energetic overlapping –which is the most direct parameter to qualify the focusing- is remarkably better with the TRA method (Fig. 3g) in three of the five transducer-target pairs evaluated. TRA method shows dominance over larger distances, but both methods are almost equivalent for short distances. This makes sense because the aberrations created by the skull deflect the rays, but some distance is needed to obtain, from a particular angular deflection, a large transverse positional deviation. In this sense, the outermost points are of greater interest to this study and the fact that it is in the outermost points where TRA shows better behaviour than TRU is an important evidence that the TRA method is definitely better in a general comparison.

It can be also appreciated that, in the case of the TRA method, overlapping shows a rough trend to increase as the transducer-target distance increases, which may seem counterintuitive, as a larger solid angle of the transducer is known to improve focusing. But since the beam volume increases parabolically with the distance transducer-target, at longer distances we have larger focal spots, so a small positional deviation does not significantly affect the overlapping. Conversely, the same transverse deviation at closer points -where ideal beams as small as 5,239mm^3 have been found- can lead to bad overlaps.

Note that in the Point_3 we found a greater overlapping with the TRU method, but this is not related to a better focusing but to a paradoxical result in the size of the beam found, notably smaller than the reference method. In fact, the ideal beam volume is V=17.47 mm^3, while the TRU beam volume is V=9.809 mm^3. This same particularity can be seen in the radius of gyration -both transversal and total- whose values are lower in the TRU beam than in the reference one (Table 1). Therefore, the large percentage of energy of the aberrated-corrected TRU beam contained in the reference beam is associated with the larger size of the second and not with a large similarity between the two focal spots. The transverse deviation at point_3 is smaller in TRA method (R=0.074mm) than in TRU (R=0.094mm), which reinforces the stated hypothesis that the large overlapping is not representative of a better focusing in this case. The longitudinal deviation in this particular paradoxical case is smaller in TRU method, but as already mentioned, this parameter is not as decisive as the transverse deviation. The orientation of the TRA beam in this pair is also better than that of the TRU beam, reinforcing the stated hypothesis: In this case a better overlapping does not represent a better focusing but simply an unexpectedly small, poorly focused and poorly oriented beam. Figures 5a and 5b represent the aberrated-corrected energy distributions in Point_1 and Point_3 respectively.

The rest of the indicators evaluated can be divided into two groups depending on whether they show dependence on the distance transducer-target or not. Theoretically, the transverse positional deviation and the orientation do not depend on the distance, whereas the radius of gyration and the volume do. On the other hand, a slight dependence on distance has been found for the longitudinal deviation (Fig. 3a). This is because the beam is not symmetrical and this asymmetry results in a longitudinal positional deviation of the barycentre depending on the size of the focus, and therefore on the distance.

The obtained results for both the transverse positional deviation and the orientation at -3dB (Fig. 3b and 3e) show that both indicators (i) have better results in TRA than in TRU in the five positions and (ii) increase roughly with distance. This increase is due to the inaccuracy of the aberration-correction, since the greater the distance to the target, the greater the angular and spatial effect of the aberration and the smaller the correction capability of the lens since the solid angle of focus is smaller. In addition, the difference between TRA and TRU methods increases roughly with distance, showing that the more critical the situation, the greater the improvement achieved by the TRA method. The statistical significance of TRA improvements over TRU for these parameters has not been studied in depth, but it should be noted that these improvements are greater than the values found for the reference beam, which are a rough reference about numerical uncertainty.

Regarding the parameters dependent on distance, volume and radius of gyration, we can see (Fig. 3) that (i) the trends of these parameters obtained by TRA are closer to the respective ideal trends than those obtained by TRU; (ii) the trends obtained by TRA are more continuous than those obtained by TRU, and (iii) the values of both indicators associated with TRA are on average smaller than those associated with TRU, indicating a greater energy concentration in TRA, except for the paradoxical Point_3.

Although the number of data acquired is not sufficient for a statistically significant study of the improvement achieved by TRA with respect to TRU, we can conclude that the TRA method is generally more accurate for all indicators and at all points, except the paradoxical third point. In addition, in the present study we have sonicated the skull from complicated angles and positions. In particular, the poor results obtained in Point_3 are due to the analytical impossibility of a perfect focusing, and not to inaccuracies in the model.

<u>Inclusion of s-waves in the skull</u>

When evaluating the inclusion of s-waves, comparing the focusing indicators of the TRA and TRAF methods summarized in Tables 1 and 2, several evidences can be appreciated. First, all the focusing indicators, for both -3dB an -6dB beams, in the five situations evaluated here, have been improved by the s-wave inclusion, excepting for the longitudinal deviation at Point_3 and the transverse deviation at Point_4 evaluated for the -3dB beam and the orientation of the -6dB beam at Point_3. A second evidence, associated with the inclusion of s-waves, is that the improvements are better indicated by the focusing indicators of the -6dB beam than by the indicators of the -3dB beam. This result could be associated with the fact that a larger primary focus area is more likely to include energy from any eventual aberrated secondary foci associated with the propagation of s-waves.

Sumarising, TRAF method leads to results clearly worst than TRA, and even notably worst than TRU, for all indicators and transducer-target pairs, at both the -3dB and -6dB beams. Therefore, the inclusion of s-waves leads to notable improvements in aberration correction, more noticeable even than the improvement achieved by the inclusion of the absorption. A fine quantification of the average improvement in aberration correction associated to s-waves would require an exhaustive study of many situations, being the presented results for guidance only. It is well-know that oblique incidences empower the formation of s-waves. Therefore, as some incidences evaluated in this work are more oblique than those applied at clinical cases, the results found in more practical cases could be less conclusive.

<u>Complete simulations</u>

Regarding the ***complete simulations*** carried out at Point_2 and Point_4 with TRA, TRU and TRAF methods, it is worth highlighting certain aspects concerning to both the design of the 3D lens and the values of the focusing indicators obtained. No systematic lens optimization has been performed in this work, as the design of the 3D lens from a recorded phase pattern is an open issue. Simply, a suitable common material (PLA) has been selected and its maximum thickness has been defined associated to a 2π phase shift. As far as the focus indicators of the Point_4 are concerned, the -3dB overlapping achieved by the TRA method in the ***complete simulation*** (58.85%) is comparable to that obtained by the TRU and TRAF methods in the ***theoretical gold standard***, with respective values of 63.01% and 59.36%. This fact suggests that the whole process of designing the lens from a registered pattern contributes to the errors in a way comparable to the error associated with the exclusion of the absorption or the s-waves at the equations. This appreciation with a single indicator is merely indicative, but justifies the aim of this work to improve the physical description of the simulated phenomenon in order to enhance the medical success of the technique.

At Point_2, the results summarized in Table 4 show that the inclusion of both phenomena (absorption and s-waves) is positive for the majority of indicators, both in -3dB and -6dB beams. As in the theoretical gold standard emission, the inclusion of the s-waves improves the focusing quality clearly more than the inclusion of the absorption.

The comparison of the data from Point_2 at Tables 1 and 4 shows an evidence that must be pointed out: in this case, for the TRA method, the ***complete simulation*** drives to better -3dB overlapping than the ***theoretical gold standard emission***. This fact, which doesn't happen in Point_4, can be justified because the lens is able to modify amplitude in addition to phase. Modification of amplitude in this particular case generates a positive effect in focusing. This positive effect appears because the profile of the lens in Point_2 is smooth so its effect is close to the ideal paraxial approach assumed when defining the lens profile attending to the phase pattern. However, in Point_4, where the profile has abrupt edges and rapid variations, paraxial approach in not so acceptable and focusing capability of the real lens is diminished.

In conclusion, a rough global analysis of the Tables 1 to 4 indicates that the inclusion of s-waves improves the focusing indicators mainly at the -6dB focus, and the inclusion of absorption majorly improves the -3dB focus. Therefore, the introduction of both absorption and s-waves helps correcting aberrations in both the near and middle distances to the target point. The submillimetre improvements achieved may seem arguable, as the application of the technique in medical treatments depends on many other factors beyond the numerical simulation that may lead to larger imprecision, such as (i) the quality and homogeneity of the 3D printing process (ii) the precise use of stereotactic frames (Marquet et al 2009) to position the lens or (iii) the proper MRI monitoring during clinical sonications (Lipsman et al 2013). However, our contribution represents a step forward towards the excellence in the application of the technique.

Finally, although the relevance of taking absorption and S-waves into account has been evidenced, there is always some bias inherent in a numerical simulation study. In fact, if amplitude modulation were included in the *theoretical gold standard emission*, we would be performing some kind of symmetrical time-reverse time-forward simulation where many possible errors of the model would be masked. Therefore, for a better confirmation of the relevance of the refined model in practical cases, it is necessary to carry out further experimental validation. In any case, the symmetry in the simulations that could lead to biased results has been partially broken since (i) in the *theoretical gold standard emission* we have not modulated the amplitude and (ii) in the *complete simulation*, time-reversal is performed without the lens and backing that are introduced in time-forward.

Conclusions

The main objective of this work is to numerically demonstrate that the correction of skull-induced ultrasound aberrations by a specific acoustic lens adapted to a single element transducer can be significantly enhanced by modifying the numerical simulation required for lens design. Two particular improvements are introduced in the set of equations applied for the time reversal propagation from target to transducer: (i) the implementation of absorption and (ii) the simulation of the skull as a solid allowing the simultaneous propagation of p-waves and s-waves. Our numerical simulations in five different situations taken from a human skull CT demonstrated that, compared to previously published methods, aberration correction is improved, obtaining better positioned, better oriented focal beams with a shape and size more similar to the reference beam, and with larger energy overlapping in the target area. The improvement associated with the inclusion of s-waves has been found greater than that associated with absorption in the evaluated cases.

Although the principle of acoustic lenses has been known for a long time, the correction of aberrations by 3D-printed acoustic lenses in the context of transcranial ultrasounds has not been proposed until recently. Spatial resolution provided by state of art 3D printers allows for a more accurate focusing than that achieved by multi-element phased arrays which typically present an effective radiation surface much larger than the simulation voxel. Therefore, improvements achieved through the use of more precise physics in the numerical simulation required to design the lenses, which could be masked if multi-element arrays are used, can enhance the focusing quality when 3D printed lenses are applied.

Future developments will decide whether 3D printed lenses or multi-element arrays are the most suitable technique for each particular application. A clear advantage of 3D printed lenses is that the spatial resolution of the emitted phase pattern is somehow unlimited, whereas phased arrays offer the possibility of a precise amplitude control, more difficult to achieve by means of 3D printed lenses. Therefore, considering the characteristics but also the economic and technical thresholds of both clinical techniques, the application of the 3D printed lens is a reasonable alternative that constitutes an open and challenging line of research.

Acknowledgments

This work was partially supported by the Spanish “Ministerio de Economia y Competitividad” under the project TEC2015-68076-R. The authors would like to thank José Sepúlveda, director of *Asociación I2CV*, for his important input and scientific support.

References

Alonso A, Reinz E, Leuchs B, Kleinschmidt J, Fatar M, Geers B, Lentacker I, Hennerici MG, Smedt SC, Meairs S. Focal delivery of AAV2/1-transgenes into the rat brain by localized ultrasound-induced BBB opening. Mol Ther-Nucleic Acids 2013;2:e73

Aubry JF, Tanter M, Pernot M, Thomas JL, Fink M. Experimental demonstration of noninvasive transskull adaptive focusing based on prior computed tomography scans. J Acoust Soc Am 2003;113:84-93

Baseri B, Choi JJ, Deffieux T, Samiotaki G, Tung YS, Olumolade O, Small SA, Morrison B, Konofagou EE. Activation of signaling pathways following localized delivery of systemically administered neurotrophic factors across the blood-brain barrier using focused ultrasound and microbubbles. Phys Med Biol 2012;57:N65–81

Brown MD, Nikitichev DI, Treeby BE, Cox BT, Generating arbitrary ultrasound fields with tailored optoacoustic surface profiles: Appl. Phys. Lett. 2017;110:094102

Burgess A, Ayala-Grosso CA, Ganguly M, Jordao JF, Aubert I, Hynynen K. Targeted delivery of neural stem cells to the brain using MRI-guided focused ultrasound to disrupt the blood-brain barrier. PLoS One 2011;6:e27877

Chang J W, Min BK, Kim BS, Chang WS, Lee YH. Neurophysiologic correlates of sonication treatment in patients with essential tremor. Ultrasound Med Biol 2015;41:124-31

Choi JJ, Pernot M, Small SA, Konofagou EE. Noninvasive, transcranial and localized opening of the blood-brain barrier using focused ultrasound in mice. Ultrasound Med Biol 2007;33:95-104

Clement GT, White PJ, Hynynen K. Investigation of a large-area phased array for focused ultrasound surgery through the skull. Phys Med Biol 2000;45:1071-83

Clement GT, Hynynen K. A non-invasive method for focusing ultrasound through the human skull. Physics in Medicine & Biology 2002;47(8):1219-36

Clement GT, White PJ, Hynynen K. Enhanced ultrasound transmission through the human skull using shear mode conversion. J Acoust Soc Am 2004;115(3):1356-64.

Coluccia D, Fandino J, Schwyzer L, O'Gorman R, Remonda L, Anon J, Martin E, Werner B. First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound. J Therapeutic Ultrasound 2014;2:1–7

Coluccia D, Figueiredo CA, Wu MY, Riemenschneider AN, Diaz R, Luck A, Smith C, Das S, Ackerley C, O'Reilly M, Hynynen K, Rutka JT. Enhancing glioblastoma treatment using cisplatin-gold-nanoparticle conjugates and targeted delivery with magnetic resonance-guided focused ultrasound. Nanomed-Nanotechnol Biol Med 2018;14:1137-48

Connor CW, Clement GT, Hynynen K. A unified model for the speed of sound in cranial bone based on genetic algorithm optimization. Phys Med Biol 2002; 47:3925-44

Connor CW, Hynynen K. Patterns of thermal deposition in the skull during transcranial focused ultrasound surgery. IEEE Trans Biomed Eng 2004;51:1693–708

Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, Frysinger RC, Sperling SA, Wylie S, Monteith SJ, Druzgal J, Shah BB, Harrison M, Wintermark M. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2013;369:640-48

Farah S, Anderson DG, Langer R. Physical and mechanical properties of PLA, and their functions in widespread applications - A comprehensive review. Adv Drug Deliv Rev 2016;107:367-92

Ferri M, Bravo JM, Sánchez JV, Redondo FJ, Peiró MP, Castiñeira S. Empleo de lentes holográficas elaboradas por impresión 3D para la corrección de aberraciones de ultrasonidos focalizados con aplicaciones médicas. Tecniacústica 2017;48:1313-20

Fry FJ, Goss SA. Further studies of the transkull transmission of an intense focused ultrasonic beam: lesion production at 500 kHz. Ultrasound Med Biol 1980;6:33-35

Ghiglia DC, Pritt MD. Two-dimensional Phase Unwrapping: Theory, Algorithms, and Software. New York: Wiley, 1998.

Guthkelch AN, Carter LP, Cassady JR, Hynynen K, Iacono RP, Johnson PC, Obbens EA, Roemer RB, Seeger JF, Shimm DS, Stea B. Treatment of malignant brain tumors with focussed ultrasound hyperthermia and radiation (Results of a phase I trial) . J Neuro-Oncol 1991;10:271–284.

Hughes A, Huang Y, Pulkkinen A, Schwartz ML, Lozano AM, Hynynen K. A numerical study on the oblique focus in MR-guided transcranial focused ultrasound. Phys Med Biol 2016;61(22):8025-43.

Hughes A, Hynynen K. Design of patient-specific focused ultrasound arrays for non-invasive brain therapy with increased trans-skull transmission and steering range. Phys Med Biol 2017;62:L9-L19

Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. Radiology 2001;220:640-46

Jolesz FA, McDannold NJ. Magnetic Resonance–Guided Focused Ultrasound, A New Technology for Clinical Neurosciences. Neurol Clin 2014;32(1):253-69

Kamimura HAS, Wang S, Wu SY, Karakatsani ME, Acosta C, O Carneiro AA, Konofagou EE. Chirp and random-based coded ultrasonic excitation for localized blood-brain barrier opening. Phys Med Biol 2015;60:7695–7712

Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption. Proc Natl Acad Sci USA 2006;103:11719-23

Konofagou EE, Tung YS, Choi J, Deffieux T, Baseri B, Vlachosa F. Ultrasound-Induced Blood-Brain Barrier Opening. Curr Pharm Biotechnol 2012;13(7):1332–1345.

Li Y, Jiang X, Liang B, Cheng Jc, Zhang L. Metascreen-Based Acoustic Passive Phased Array. Phys Rev Appl 2015;4:024003

Lipsman N, Schwartz ML, Huang Y, Lee L, Sankar T, Chapman M, Hynynen K, Lozano AM, MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. Neurology 2013;12(5):462-8

Lomax H, Pulliam TH, Zingg DW, Fundamentals of Computational Fluid Dynamics. New York: Springer, 2013

Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D. First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. Journal of Therapeutic Ultrasound 2014;2:11

Maimbourg G, Houdouin A, Deffieux T, Tanter M, Aubry JF. 3D-printed adaptive acoustic lens as a disruptive technology for transcranial ultrasound therapy using single-element transducers. Phys Med Biol 2018;63:025026

Marquet F, Pernot M, F Aubry JF, Montaldo G, Marsac L, Tanter M, Fink M, .Non-invasive transcranial ultrasound therapy based on a 3D CT scan: protocol validation and in vitro results. Phys. Med. Biol 2009; 54: 2597–613

Marquet F, Tung YS, Teichert T, Ferrera VP, Konofagou EE. Feasibility study of a single-element transcranial focused ultrasound system for bloodbrain barrier opening. AIP Conference Proceedings 2012;1481:233-38.

Marsac L, Chauvet D, La Greca R, Boch AL, Chaumoitre K, Tanter M, Aubry JF. Ex vivo optimization of a heterogeneous speed of sound model of the human skull for non-invasive transcranial focused ultrasound at 1 MHz. Int J Hyperth 2017;33:635-45

Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. Ann Neurol 2009;66:858-61

McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial Magnetic Resonance Imaging-Guided Focused Ultrasound Surgery of Brain Tumors: Initial Findings in 3 Patients. Neurosurgery 2010;66(2):323-32

Melde K, Mark AG, Qiu T, Fischer P. Holograms for Acoustics. Nature 2016;537:518-22

Meng Y, Volpini Matthew, Black S; Lozano AM, Hynynen K, Lipsman N. Focused Ultrasound as a Novel Strategy for Alzheimer Disease Therapeutics, Ann Neurol 2017;81(5):611-617

Miller GW, Eames M, Snell J, Aubry JF. Ultrashort echo-time MRI versus CT for skull aberration correction in MR-guided transcranial focused ultrasound: In vitro comparison on human calvaria. Med Phys 2015;42:2223-33

Pichardo S, Sin VW, Hynynen K. Multi-frequency characterization of the speed of sound and attenuation coefficient for longitudinal transmission of freshly excised human skulls. Phys Med Biol 2011;56:219-50

Pinton G, Aubry JF, Bossy E, Muller M, Pernot M, Tanter M. Attenuation, scattering, and absorption of ultrasound in the skull bone. Med Phys 2012;39(1):299-307

Sun J, Hynynen K. Focusing of therapeutic ultrasound through a human skull: a numerical study. J Acoust Soc Am 1998;104:1705–15

Tanter M, Thomas JL, Fink M. Focusing through skull with time reversal mirrors. Application to hyperthermia. Proc IEEE Ultrasonics Symp 1996;1 and 2:1289-93

Tanter M, Thomas JL, Fink M. Focusing and steering through absorbing and aberrating layers: Application to ultrasonic propagation through the skull. J Acoust Soc Am 1998;103:2403–10.

Thomas JL, Fink MA. Ultrasonic beam focusing through tissue inhomogeneities with a time reversal mirror: application to transskull therapy. IEEE Trans Ultrason Ferroelectr Freq Control 1996;43:1122-29

Wang S, Olumolade OO, Sun T, Samiotaki G, Konofagou EE. Noninvasive, neuron-specific gene therapy can be facilitated by focused ultrasound and recombinant adeno-associated virus. Genetics Ther 2015;22:104-10

Wintermark M, Tustison NJ, Elias WJ, Patrie JT, Xin W, Demartini N, Eames M, Sumer S, Lau B, Cupino A, Snell J, Hananel A, Kassell A, Aubry JF. T1-weighted MRI as a substitute to CT for refocusing planning in MR-guided focused Ultrasound. Phys Med Biol 2014;59:3599-614

Xie Y, Shen C, Wang W, Li J, Suo D, Popa BI, Jing Y, Cummer SA. Acoustic Holographic Rendering with Two-dimensional Metamaterial-based Passive Phased Array. Sci Rep 2016;6:35437

			Point_1	Point_2	Point_3	Point_4	Point_5
Focus distance	(mm)		45.8	59.4	64.0	86.2	107.3
Positional deviation (mm)	TRU	(R, z)	0.105, -0.201	0.090,0.6943	0.094, 0.080	0.319, 4.872	0.331, 10.783
	TRA	(R, z)	0.076, -0.165	0.077, 0.466	0.074, 0.101	0.160, 4.071	0.169, 10.863
	TRAF	(R, z)	0.141,-0.271	0.134,1.1224	0.086, 0.097	0.093, 6.552	0.476, 14.391
	Water		0.009, 0.103	0.031, 0.359	0.008,0.047	0.043, 1.367	0.041, 1.932
Radius of gyration (mm)	TRU	(k_R, k)	0.476, 1.515	0.558, 2.207	0.527, 1.552	0.972, 4.095	1.010, 4.749
	TRA	(k_R, k)	0.524, 1.608	0.554, 2.186	0.562, 1.896	0.759, 3.310	0.938, 4.665
	TRAF	(k_R, k)	0.545, 1.691	0.579,2.321	0.584, 2.011	0.979, 3.841	1.026, 4.914
	Water		0.398, 1.301	0.495, 1.894	0.558, 2.351	0.678, 3.709	0.908, 4.862
Orientation (º)	TRU	φ	2.181	1.809	4.194	3.883	3.9107
	TRA	φ	1.873	1.644	1.934	3.208	3.3452
	TRAF		2.422	2.138	3.785	6.036	4.309
	Water		0.107	0.863	0.041	0.2175	0.164
Volume (mm^3)	TRU	V	7.8589	16.693	9.809	57.807	68.8402
	TRA	V	8.270	16.736	14.306	44.272	60.1662
	TRAF	V	9.104	18.381	15.74	78.861	70.1938
	Water	V_{ref}	5.239	11.410	17.47	42.336	63.6829
Overlapping	TRU	$I(\%)$	69.37	70.86	84.77	63.01	69.12
	TRA	$I(\%)$	66.59	72.54	79.35	74.24	81.17
	TRAF	$I(\%)$	63.19	65.02	71.66	29.36	62.94

Table 1 .- Focusing indicators (-3dB) of the aberrated-corrected scans. Theoretical gold standard emission

			Point_1	Point_2	Point_3	Point_4	Point_5
Focus distance	(mm)		45.8	59.4	64.0	86.2	107.3
Positional deviation (mm)	TRU	(R, z)	0.084, -0.206	0.316, 1.675	1.415, -0.434	0.685, 5.925	0.653, 9.622
	TRA	(R, z)	0.009, -0.008	0.155, 1.112	1.855, 0.612	0.415, 5.800	0.547, 9.745
	TRAF	(R, z)	0.174, -0.317	0.837, 2.307	6.886,1.174	1.241, 7.209	1.975, 14.03
	Water		0.004, -0.005	0.045, 0.213	0.015, 0.143	0.054, 1.856	0.049, 4.551
Radius of gyration (mm)	TRU	(k_R, k)	0.679, 2.154	1.349, 3.783	3.719, 3.939	1.417, 5.129	1.532, 6.789
	TRA	(k_R, k)	0.752, 2.374	1.031, 3.348	4.282, 5.624	1.365, 5.092	1.581, 6.757
	TRAF	(k_R, k)	0.921,3.093	1.487, 4.434	5.018, 6.852	1.479, 5.427	2.032, 8.431
	Water		0.533, 1.741	0.673, 2.568	0.749, 2.827	0.925, 4.534	1.151, 6.293
Orientation (º)	TRU	φ	2.8438	11.078	19.0564	2.608	5.007
	TRA	φ	2.5016	6.671	46.653	1.399	5.913
	TRAF	φ	4.089	12.58	32.83	2.627	7.382
	Water		0.0801	0.0716	0.037	1.156	0.8326
Volume (mm^3)	TRU	V	23.7515	57.341	75.594	189.953	288.163
	TRA	V	26.9076	51.388	86.215	168.181	282.458
	TRAF	V	37.9346	75.038	113.5	212.517	342.172
	Water	V_{ref}	14.3789	32.934	53.717	109.515	221.652
Overlapping	TRU	$I(\%)$	69.15	68.72	60.84	59.82	60.76
	TRA	$I(\%)$	63.07	75.21	54.57	65.88	63.428
	TRAF	$I(\%)$	51.58	55.65	46.76	42.51	50.62

Table 2 .- Focusing indicators (-6dB) of the aberrated-corrected scans. Theoretical gold standard emission

Point_4		-3Db			-6dB		
		TRU	TRA	TRAF	TRU	TRA	TRAF
Positional deviation (mm)	*R* *z*	0.928, 7.705	0.298, 6.266	1.4011, 8.7776	1.112, 7.765	0.719, 7.755	1.3236, 8.0171
Radius of gyration (mm)	k_R *k*	1.337, 4.351	1.243, 4.102	1.3778, 3.9671	1.825, 4.768	1.983, 4.889	1.7225, 5.5642
Orientation (º)	φ	7.597	1.4538	8.5841	3.6300	1.1628	4.1098
Volume (mm^3)	*V*	75.95	46.601	84.076	230.8927	199.7917	236.58
Overlapping	*I(%)*	38.72	58.85	22.97	42.23	48.27	33.76

Table 3.- Focusing indicators of aberrated-corrected scans, at Point_4. Complete simulation.

Point_2		-3Db			-6dB		
		TRU	TRA	TRAF	TRU	TRA	TRAF
Positional deviation (mm)	*R* *z*	0.035 1.159	0.058 0.822	0.570 0.976	0.9029 3.1774	0.4338 1.8016	1.2172 2.8530
Radius of gyration (mm)	k_R *k*	0.551 2.235	0.539 2.212	0.804 2.896	1.6708 4.3803	1.3012 3.7609	1.6787 4.4974
Orientation (º)	φ	2.0137	2.2294	6.5801	13.952	10.837	14.2635
Volume (mm^3)	*V*	16.038	15.921	22.878	73.681	53.469	85.1676
Overlapping	*I(%)*	72.40	74.88	47.19	55.26	72.37	45.39

Table 4.- Focusing indicators of aberrated-corrected scans, at Point_2. Complete simulation.

Figure captions

Figure 1. a) Sagital cross sections of the whole computational domain and of the integration domains of configurations Point_1(white) Point_2 (yellow) and Point_3 (orange) b-d) Sagital cross sections of computational domain at configurations Point_1 to Point_3 respectively. e-f) Transversal cross sections of computational domain at configurations Point_4 and Point_5. In figures b to f the internal and external concentric curves represent respectively position of phase pattern and position of transducer, being their separation the maximum thickness of the lens.

Figure 2. Sagital cross section of -6dB focal spots of the aberrated beams at point_2 obtained (a) without any lens, (b) with phase corrected by TRU and (c) by TRA.

Figure 3. Focusing indicators (-3dB) of the reference focal spot and aberrated-phase-corrected focal spots

Figure 4. Details of 3D lens for Point_4: a) Visions of the 3D printing STL file; b) colour map representation of the lens thickness developed respectively by TRA and TRU methods; c) transversal section of computational domain. Colour represents p-wave speed. Lens and backing (green), water and brain (blue) and skull (variable)

Figure 5. a-b) Sagital cross sections of the stationary energy distribution simulated by ***theoretical gold standard emission*** at configurations Point_1 and Point_3 at the fluid media. c-d) Coronal cross sections at different planes of the stationary energy distribution simulated by ***complete simulation*** at configuration Point_4 at the fluid media (lens and skull modelled as solids).

1

Figure 6. a-c) Details of 3D lens for Point_2 obtained by TRA: (a) sagital and (b) transversal sections of computational domain. Colour represents p-wave speed. Lens and backing (green), water and brain (blue) and skull (variable). c) Vision of the 3D printing STL file. d-f) Sagital cross sections of the stationary energy distribution simulated by ***complete simulation*** at configurations Point_2 at the fluid media, (d) TRAF (e) TRU (f) TRA.