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Transcranial propagation with an ultrasonic mono-element focused transducer

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Abstract

Focused Ultrasound is the only truly transient, local and non-invasive technique able to induce safe Blood-Brain Barrier Opening (BBBO), technique used in Parkinson or Alzheimer diseases research. However, the presence of the skull in the path usually affects the focus characteristics (gain, beam width, shape and maxima location). In this work, transcranial acoustic wave propagation generated by a mono-element focused transducer has been modeled using 2D and 3D FDTD methods. Skull structure of the non-human primate under test can be compared in terms of density and sound speed with polymethylmethacrylate (PMMA) films. Then, focus aberration and the phenomena that cause it are characterized, providing a better control of the beam focus using the BBBO technique. Results throw that focal axial displacements are constant with the angle of incidence for PMMA flat films. In normal incidence, a shift of 6 mm is given for axial displacement in the 2D transcranial propagation. Moreover, if the skull geometry under the action of the ultrasonic beam can be compared with the curvature radius of the transducer, displacements should be constant with angle independency, like those seeing in the homogenous flat films with the same thickness.

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Keywords: Blood-Brain Barrier Opening; Focused Ultrasound; Parkinson & Alzheimer diseases; FDTD methods

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1. Introduction

The principal impediment to drug delivery into Central Nervous System (CNS) is to administrate therapeutics molecules (bigger than 400 Dalton) (Deffieux et al., 2010) through endothelial tissue, such as those used in Parkinson or Alzheimer treatments because the Blood-Brain Barrier (BBB) blocks them. In recent years, a new promising technique is hanging up that drawbacks using ultrasound beams, which can disrupt the BBB localized, transiently, non-invasively and in a safe way. On the other hand, transcranial acoustic wave propagation exhibits many inconveniences, such us focal deviations or aberrations that affect to focal quality and beam control over the target area.

In this study, we suggest a 2D/3D numerical method using Finite Difference Time Domain (FDTD) technique in order to facilitate the comprehension of acoustics phenomena that are involved on transcranial propagation like diffraction, refraction, reflection, absorption, etc. Furthermore, an experimental validation of the FDTD model is measured in laboratory. Moreover, results provide an initial aberration estimation before a laboratory experiment, which improves the use of the BBB technique.

2. Materials and Methods

2.1. Boundary Conditions

The BBB opening protocol is recently used in a non-human primate Macaca Mulatta specie, which a formalin-fixed skull is 145 mm long, 85 mm high and 69 mm with a thickness of 2.6 mm ± 0.2 mm (Deffieux et al., 2010). Therapy objective is to sonicate those areas that are directly related with Alzheimer or Parkinson diseases such as Hippocampus, Putamen or Caudate.

The focused ultrasound device used in this research is a mono-element transducer with a curvature radius of 50 mm and aperture radius of 50 mm. Transducer central frequency is 500 kHz, its Fresnel number (on water) is $N_F \;\; 4.2$, and a linear gain of G=13.2. The transducer was assembly in our laboratory, and it let us to measure the ultrasonic field generated and extract from results the effective values of curvature radius, focal distance, beam-width, etc. in order to perform the FDTD method with those realistic values.

2.2. FDTD Method

Skull complexity hinders the microscopic evaluation in transcranial propagation. Thus, the mechanical behaviour of skull can be approximate as a macroscopic system that gives a model to transcranial propagation in heterogeneities tissues in base of local tissue homogeneity. In that way, we model tissue microstructure as macroscopic variations of velocity, density and α coefficient.

Propagation in bone media normally involves longitudinal and transversal waves, and in particular cases, depending on the boundary conditions, it can give rise to surface waves, such as Rayleigh waves. As incident angles on fluid/solid surface smaller than 20º implies that all the energy is transferred to the longitudinal wave, the other ones will be neglected (Deffieux et al., 2010).

Considering a lineal medium with independent frequency absorption, momentum and continuity equations (Kinsler and Frey, 1988) yields

$$\frac{\partial \vec{u}}{\partial t} + \Omega \vec{u} = -\frac{1}{\rho} \nabla P, \tag{1}$$

$$\frac{P}{t} + \Omega P = -\rho c^2 \left(\nabla \vec{u} \right), \tag{2}$$

where $\vec{u}$ (velocity vector), P (pressure), ρ (density), c (sound speed), Ω (attenuation factor). For the numerical resolution the finite difference time domain method has been used. So, partial derivate on constitutive equations are approximate to central finite differences (Schneider, 2010).

2.3. Algorithm Convergence

Establishing the algorithm convergence allows us to evaluate the minimum points per wavelength necessary to obtain a simulation with an acceptable error. As a baseline, we accept a relative error between numerical, analytic and experimental solutions less than 1%. To validate the numerical method, propagation on water has been simulated in an enclosure. In that way, comparing results given by simulation with theoretical solution and by O'Neil equation is warranted for the propagation model convergence.

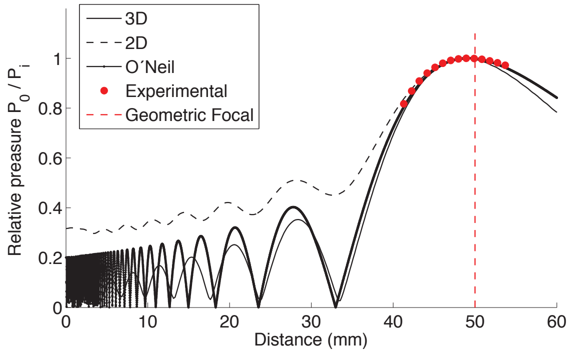

Fig. 1. Comparison of the results obtained from 2D, 3D, experimental and analytic models

It is observed that model solution converges, on focal point, to the theoretical solution proposed by O'Neil on 2D results and for 3D simulations are the same. Out of focal point, the differences between simulated and theoretical results for 2D results are caused because the analytic solution is for a 3D system. Table 1 sums up the analysis of the effective parameters for the transducer.

Table 1. Effective transducer characteristics for each model

	Real	O'Neil	2D	3D
Aperture (mm)	50.0	43.8	40.5	43.0
Curvature radius (mm)	50.0	55.3	52.0	55.0

Thus, we can validate the convergence of the numerical method; as well as focused transducers can be modelled in a 2D coordinate system. However, we cannot confirm that the effects of heterogeneities (skull) are similar between 2D and 3D.

3. Results

Displacements seen on results are characterized from transducer geometric focal given as its curvature radius. In addition, a characteristic effect on these focused transducers is that focal point is delayed around 2 mm from its curvature radius (Yu et al., 2008), distances not evaluated in the results. Figure 2 shows a schema of displacements.

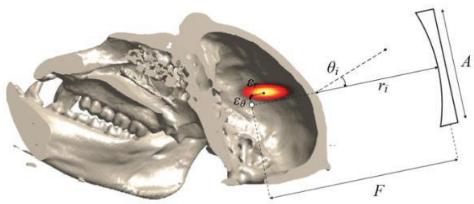

Fig. 2. Scheme characterization of the displacements, where ε_0 and ε_r, are lateral and axial displacement respectively.

To facilitate the comprehension of acoustic phenomena involved on transcranial propagation it has been decided to study homogenous multilayer film cases such as flat polymethylmethacrylate (PMMA) films as representative samples of the monkey skull. Media properties are summarised in table 2.

Table 2. Media properties involved at the model

	Velocity (m/s)	**Density (kg/m^3)**
H_2O (distiled)	1500	1000
Human Skull (Deffieux et al., 2010)	2690	1895
Primate Skull (Deffieux et al., 2010)	2550	1900
PMMA (Christman, 1972)	2746	1180
Magnitude Factor	1.07	1.61

The magnitude factor is the relation between the PMMA and the primate skull properties. The velocity of sound on PMMA layers is similar to the non-human primate's, and the density does not vary overly. Hence, we have decided to use PMMA films to study the transcranial propagation in the case that heterogeneities are neglected.

3.1. PMMA Simulations

Figure 3 sum up the results of focal displacements seeing at the simulations with homogenous PMMA flat films. It can be seen a flat behaviour in all the simulations, as it was seen in our previous work (Iglesias, 2013). Also, it is observed a difference between 2D-3D around 4mm in axial displacements and almost 0 in lateral.

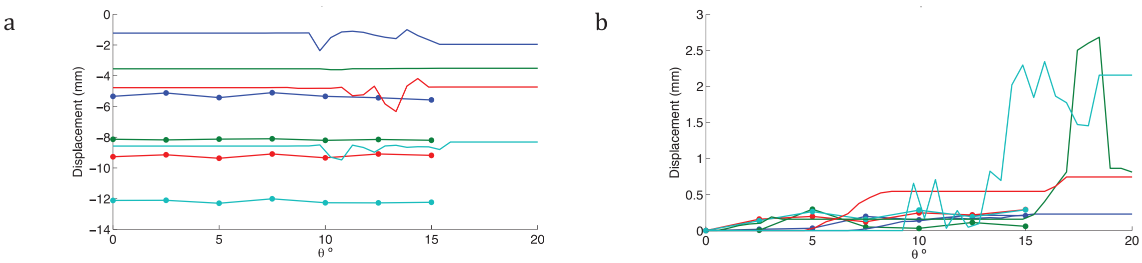

Fig. 3. Results comparison obtained from 2D and 3D simulations in different thicknesses homogenous films.
(a) Axial. (b) Lateral. Simple line (2D), line with marker (3D). λ/4 (blue), λ/2 (green), 3λ/4 (red), λ (cyan)

Figure 3.b, shows lateral displacements that they are below of 0.5 mm. It is worth to mention that the grid step for the FDTD algorithm is in the same order of magnitude (0.122 mm), hence, displacements under that threshold cannot be measured. In the range from 15º to 20º the lateral displacements increase too much. In this case, those results are obtained because the focus is not uniform and the target area has the contribution of a double focus.

Furthermore, shapes of the focus in the target area from 2D and 3D simulations are compared. As we can see in the figure 4, the focus aberration is the same in both simulations, and also the dimensions of both are very similar with a difference between them of 4 mm length and less than 1 mm width.

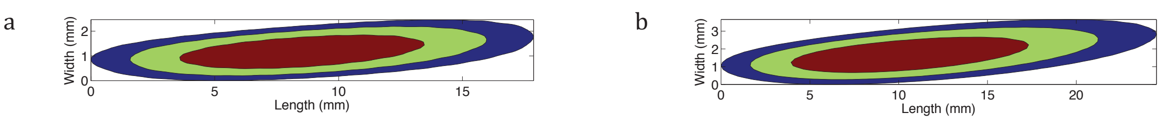

Fig. 4. Focus aberration comparison in the films for an incidence angle of 10º in 2D (a) and 3D (b) models for a layer thickness of 2.7 mm

3.2. Skull Simulations

Finally, Fig. 5 shows simulations including realistic skull boundary conditions for the 2D model.

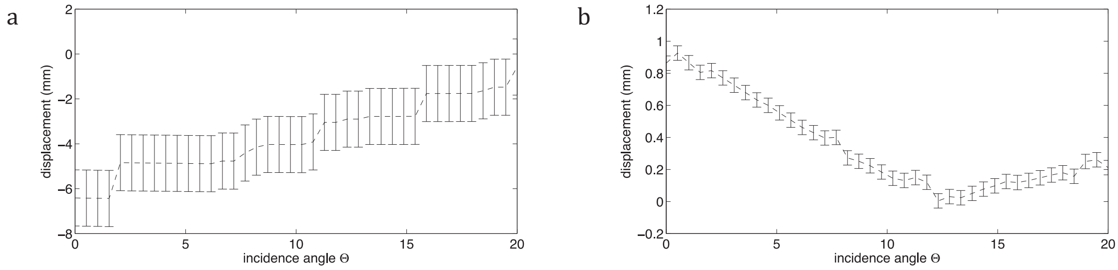

Fig. 5. Axial (a) and lateral (b) displacements obtained from the 2D skull simulation

There is an initial shift of 6 mm from the geometric focal point and a positive linear tendency in axial displacements. Axial displacements from 10º to ~16º are the same as the displacement observed for the λ/2 homogenous film which has the same thickness as the skull layer. For these incidence angles range the transducer curvature radius is similar to the skull curvature in the beam incidence. As a result, the field generated by the transducer sees a flat film. In the case of lateral displacements, from 10º to 20º, the same displacements as in 2D-3D simulations for this layer thickness are observed

4. Conclusions

To summarize, a 2D/3D FDTD model was implemented in this work. Common tendencies between 2D and 3D simulations have been shown. However, we cannot confirm that 3D skull heterogeneities are similar from the 2D. An approximation of the problem is given in this work, and is expected to have around 6 mm of axial shift, in normal incidence, using the BBBO technique with the non-human primate.

It is particularly worth highlighting that the deviations from the focal point are dependent on the layer thickness, reflections and refraction. The minimum axial and lateral focal displacements observed have been obtained for layers with thickness equivalent to λ/4. Therefore, the work frequency of the transducer can be obtained directly from the skull thickness under therapy. However, the most important effect that affects to the larger displacements is the wave refraction, as shown in previous works (Iglesias, 2013).

Moreover, if the transducer curvature radius is similar to that of the skull, the beam present normal incident angle over all of the skull surface. In this situation observed axial and lateral displacements remains constant for those angles. Finally, the back-reflection on the skull and again reflected on the transducer surface lead to an aberration of the focus, in such a way that a double focus appears on the target area.

Acknowledgements

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