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Parametric Study of Transcranial Focused Ultrasound Propagation for Blood–Brain Barrier Opening

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Introduction

The main impediment to drug delivery into the central nervous system (CNS) is that the endothelial tissues block the way to the molecules bigger than 500 Dalton, such as many therapeutic molecules used in therapy research for Alzheimer or Parkinson diseases [1]. In recent years, a promising ultrasound technique has been developed in order to perform the Blood-Brain Barrier (BBB) disruption in a localized, transient, noninvasive and safe way [1]. This technique employs a transcranial focused ultrasound beam in conjunction with coated micro-bubbles (ultrasound contrast agents) for disrupt the tight junctions of the endothelium tissue, achieving the therapeutic molecules pass to the capillary bloodstream to the CNS tissues [1]. However, the propagation of acoustic waves through skull bone tissue exhibits serious drawbacks, generating focal aberrations in the focal area that adversely affect the control of the area under therapy. Typical amplitudes to achieve safe opening of the BBB in nonhuman primates was 0.5 MPa at 500 kHz [2]. In this work, a parametric numerical study was developed with the aim of clarify how focal distortion is produced as a function of the incidence of the beam over a real primate skull boundary conditions. The study is extended to nonlinear propagation for determine the magnitude of the nonlinear effects in the focal area.

Material and Methods

The boundary conditions for the computational methods are extracted from a computerized tomography (CT) GE LigthSpeed VCT 64 scanner (GE Medical Systems, Milwaukee, WI) of a *Macaca mulatta* primate skull with a native resolution of 488 μm and slice resolution of 625 μm. Sound speed, density and bone attenuation 3D maps are derived from the normalized CT apparent density scans. The acoustic source was a single element focused transducer with a focal of $F = 90$ mm and an aperture of $A = 80$ mm located Fig. 1. The excitation was a sinusoidal pulse of 50 cycles and central frequency of 500 kHz.

Two models are simulated: first, for linear propagation, a 3D linear acoustic model solved by a standard FDTD method was implemented in order to study the role of the incidence angle θ_i and transducer position (r_i) in the focal aberration parameters: axial shift (ε_r) and transversal shift (ε_θ). The second method

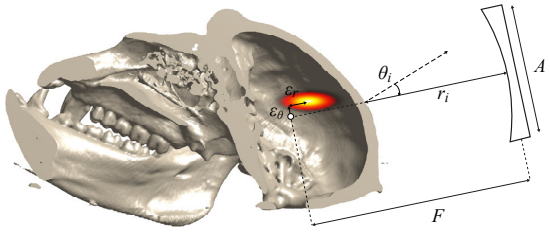


Figure 1: Scheme of the boundary conditions: model cut and isosurface at density value of 1238 kg/m^3, the transducer model position (θ_i, r_i) and focal aberration measurements (ε_θ, ε_r)

includes nonlinear propagation, so a semi-explicit FDTD based numerical scheme is implemented for solving the conservative laws of momentum, mass and the fluid state equation. Due to computational cost an axisymmetric coordinate system is considered for nonlinear propagation: the transducer position was fixed and the parametric study was done varying the amplitude of the excitation (i.e. the pressure at the transducer surface). In both methods the shear elasticity is neglected as the beam incidence angle is below 20^o respect the normal of the skull surface [2].

Results

The results show that the main factor affecting the focal beam properties is the refractive lens effect of the skull. Due to the skull, focal aberrations appears: a shift in the maximum peak location towards the transducer has been detected according to previous experimental results and a small effect in the axial and lateral HWFM has been found. At interest pressures (0.1 MPa to 1 Mpa at the focus), the beam properties are not substantially affected by the acoustic nonlinearities, but small changes were detected in the targeted area, i.e. the focal position, the full width at half maximum, the gain and variations in the sonificated volume. Thus, numerical results show that the peak pressure shifts -5.1 mm from the geometrical focus for small amplitude transcranial propagation. Simulated nonlinear propagation shifts the peak pressure location away from the transducer: shifted focus of +0.5 mm relative to the linear peak location for 0.5 MPa peak pressure and +0.9 mm for 4 MPa. For rarefaction peak pressure location a shift of -2.23 mm has been predicted. A variation of -7.2 % in the sonificated volume covered by the beam has been observed for 0.5 MPa peak pressure. These results evidence that nonlinear propagation effects can slightly affect the ultrasound beam properties. All of these properties grow with the amplitude and frequency of the wave, so it can be specially relevant if higher values of these quantities are required for the therapy or if real brain tissue is considered.

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