Numerical Study of Nonlinear, Transcranial Focused Ultrasound Wave Propagation for Blood-Brain Barrier (BBB) Opening

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BACKGROUND

Objectives

- Aim of the study:

Quantify the importance of nonlinear effects for Focused Ultrasound assisted Blood-Brain Barrier (BBB) Opening techniques.

- ✓ Effective pressure peak position: compression/rarefaction
- ✓ Beam-width
- ✓ Gain

- Methodology

Direct **numerical simulations** of the constitutive equations of non linear acoustics

- ✓ **Developed numerical method based on FDTD**

- **G-FDTD:** Numerical Method Features:

Allows to describe precisely nonlinear acoustics waves in viscous fluids

- ✓ **Nonlinear** (Full wave)
- ✓ **Inhomogeneous** media
- ✓ **No paraxial** approximations
- ✓ **Backscattering**
- ✓ Arbitrary **boundary conditions**
- ✓ Arbitrary **initial conditions**
- ✓ **Time domain** (all frequencies simultaneously, complex waveforms)
- ✓ **2.5D** (extensible to 3D)
- ✓ Absorbent Boundary Conditions (**NL2L-PML**, attenuation up to 50 dB)
- ✓ Compute **pressure**, **density** and vector **velocity** fields

Abstract

- Focused ultrasound techniques for Blood-Brain Barrier opening are emerging for localized and safe brain drug and gene delivery.
- In this work, a transcranial FUS field is computed by a numerical approach entailing nonlinear wave propagation in the time domain in order to determine the non linear behavior of the true focus and including the effects of reflections and resonances.
- A transducer with a curvature radius of 90 mm, and an aperture of 80 mm was simulated at a central frequency of 500 kHz.
- The computational method was a Finite-Difference Time-Domain (FDTD) implemented on nonlinear fluid model over a 2D Axis-symmetric domain.
- The boundary conditions were derived from the apparent density measurements based on a 3D CT scan acquisition performed on a *Macaca mulatta* primate.

Model Equations

- Derived from conservative laws for viscous fluids:

Continuity equation (mass conservation)

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0$$

Motion equation (momentum conservation)

$$\rho\left(\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v}\nabla)\mathbf{v}\right) + \nabla p - \eta \nabla^2 \mathbf{v} - \left(\zeta + \frac{1}{3}\eta\right)\nabla(\nabla \cdot \mathbf{v}) = 0$$

Equation of state

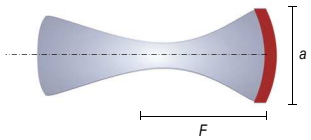
$$p' = c_0^2 \rho' + \frac{c_0^2}{\rho_0}\frac{B}{2A}\rho'^2$$

MATERIALS AND METHODS

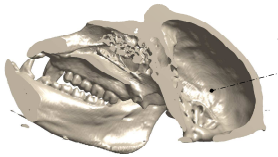
Boundary Conditions

- Transducer design:

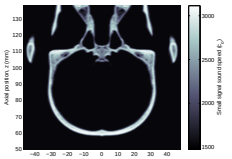
f_0 = 500kHz
F = 90 mm
a = 80 mm
Gain = 18,1
f-number = 1,125



- CT scans: apparent density 3D mapping



- 2.5D mapping
  - ✓ Small signal sound speed (c_0)
  - ✓ Density (ρ_0)
  - ✓ Bone attenuation (α)



Numerical Method G-FDTD

- Finite-Differences Time-Domain (FDTD)
  - ✓ Conservative discretization: **Semi-implicit method**
  - ✓ Solver: **Iterative** method with **"leap frog"** algorithm

- Numerical validation

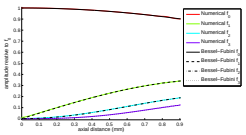
✓ **Linear validation**

Compute focused ultrasound transducer pressure field and compare with analytical solution: (grid = 20 elements/λ)

Effective beam focal: relative error **< 0.24%**
Peak pressure amplitude: relative error **< 0.29%**

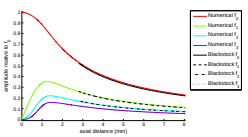
✓ **Nonlinear validation**

Amplitude of the first three harmonics of a plane wave. The axial distance is normalized to the shock formation distance. (grid = 32 elements/λ)



Weak nonlinearities
Bessel-Fubini solution

Relative error **< 1.67 %**



Shock front
Fay-Blackstock solution

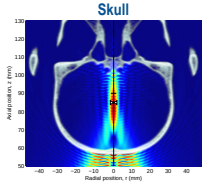
Relative error **< 2.80 %**

RESULTS

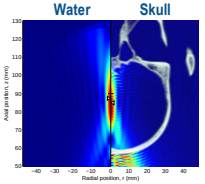
Pressure Fields

A series of simulations were performed in water and inhomogeneous media (primate's skull) in order to quantify the importance of the nonlinearities and the comparison with the effects due to the skull. Simulated linear and non linear pressure fields with and without the skull are presented:

- **LINEAR** simulated pressure fields:

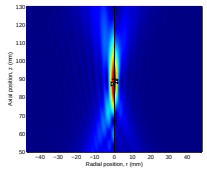


Pressure field in linear regime inside the skull. The focal point is marked by the white triangles

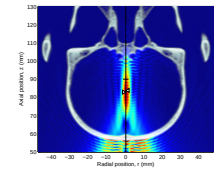


Comparison between the field in water and skull. The focal points are the white triangles

- **NONLINEAR** simulated pressure fields:



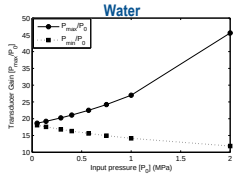
Pressure field in linear and nonlinear regime in water. The focal point is marked by the white triangles

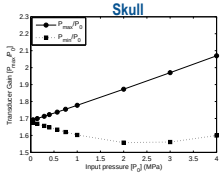


Pressure field in linear and non regime inside the skull. The focal point is marked by the white triangles.

Nonlinear behavior of the Gain

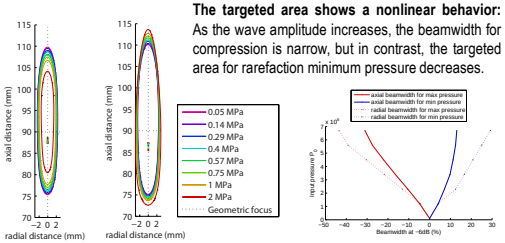
At high pressures, **the effective transducer gain is not constant.** Instead, the gain for the peak compression can augments with the input pressure. On the other hand, rarefaction pressure gain is nearly inversely proportional to the input pressure.





Effective transducer's gain vs. the input pressure: a nonlinear asymmetric behavior is observed

Beamwidth changes

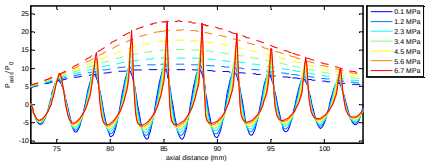


The targeted area shows a nonlinear behavior: As the wave amplitude increases, the beamwidth for compression is narrow, but in contrast, the targeted area for rarefaction minimum pressure decreases.

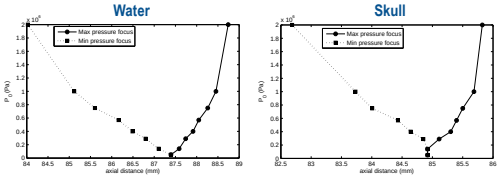
Nonlinear Focal Shift

The *nonlinear focal shift*, i.e. the displacement of the pressure and intensity maxima position of focused acoustic beams under increasing driving voltages, has been studied numerically in water and transcranial propagation.

- Simulated **waves profiles** in the on-axis focal area



- **FOCAL CHANGES** due to nonlinearities:



Compression and rarefaction effective focal point behavior: in skull simulations, a linear shift of **-5,1 mm** and a nonlinear shift of **+1,35 mm** is observed for compression and a nonlinear shift of **-3.37 mm** is observed for rarefaction.

Conclusions

- A numerical method (**G-FDTD**) for ultrasound transcranial simulation in nonlinear regime has been developed and validated with analytical solutions.
- For a BBBD application, the beam proprieties can be affected by the acoustic nonlinearities.
  - ✓ The targeted area, i.e. the **focal position** and the **beamwidth**, and the **gain** for the BBBD varies due to the amplitude of the wave.
  - ✓ This behavior is different for the wave's peak compression maximum and the rarefaction minimum.

Acknowledgments

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