Optimal Overlapping Protocol and Robustness Assessment of Blood-Brain Barrier Opening in Humans Using a Single-Element Focused Ultrasound Transducer

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INTRODUCTION

Background

Microbubble-enhanced focused ultrasound is a non-invasive technique to achieve the blood-brain barrier opening (BBBO), which allows the therapeutic drugs to be effectively delivered in the central nervous system (CNS) for the treatment of neurodegenerative diseases, such as Alzheimer's and Parkinson's.
Conventional procedures generate a small focal area in comparison with the size of the targeted structure, which only allows the BBBO to open where the ultrasound energy is located.

Our proposal

Control transcranial targeting of the whole left hippocampus using single element source:

(1) To develop a protocol to cover the whole brain structure, divided into N equal-size parts and independently targeted using a single-element transducer at 500 kHz.

(2) To implement a semi-adaptive algorithm to find the optimal transducer position that maximizes the overlapped volume for each of the sub-divisions.

(3) To test the robustness of the positioning transducer-skull system.

MATERIALS AND METHODS

Model equations

Simulations are based on a *k*-space pseudo-spectral method (k-Wave Matlab toolbox). The system of coupled first-order partial differential equations is:

$$\frac{\partial \rho}{\partial t} = -\rho_0 \nabla \cdot \mathbf{u} - \mathbf{u} \cdot \nabla \rho_0, \qquad \text{(mass conservation)}$$

$$\frac{\partial \mathbf{u}}{\partial t} = -\frac{1}{\rho_0} \nabla p, \qquad \text{(momentum conservation)}$$

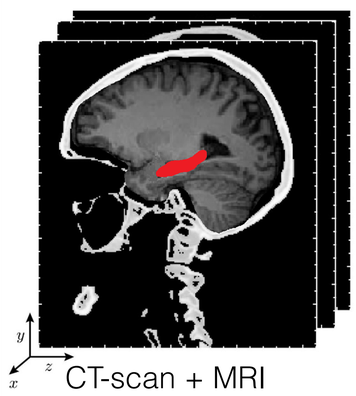
$$p = c_0^2 \left(\rho + \mathbf{d} \cdot \nabla \rho_0 - \mathrm{L}\rho\right), \qquad \text{(state equation)}$$

where $\mathbf{d}$ is the acoustic particle displacement and L is a general loss factor that includes frequency power-law absorption and dispersion as given by

$$\alpha(\omega) = \alpha_0 \omega^{\gamma} \qquad \text{(absorption)}$$

Medium properties

The properties of the skull and the location of soft tissues were extracted from CT-scans and MRI.



CT-scan + MRI

Skull

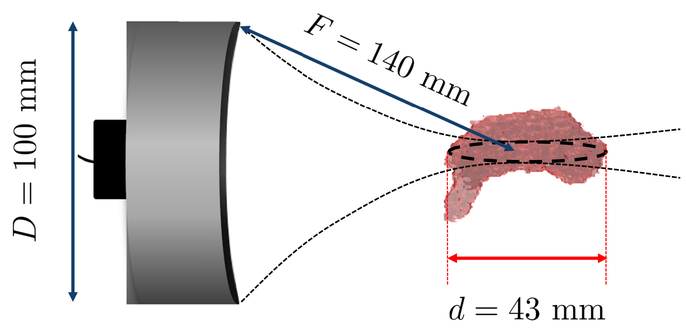
(1) Geometry
(2) Heterogeneous sound speed
(3) Heterogeneous density
(4) Homogeneous absorption

Brain

(1) Geometry of left hippocampus (colored)
(2) Homogeneous sound speed, density and absorption

Transducer design

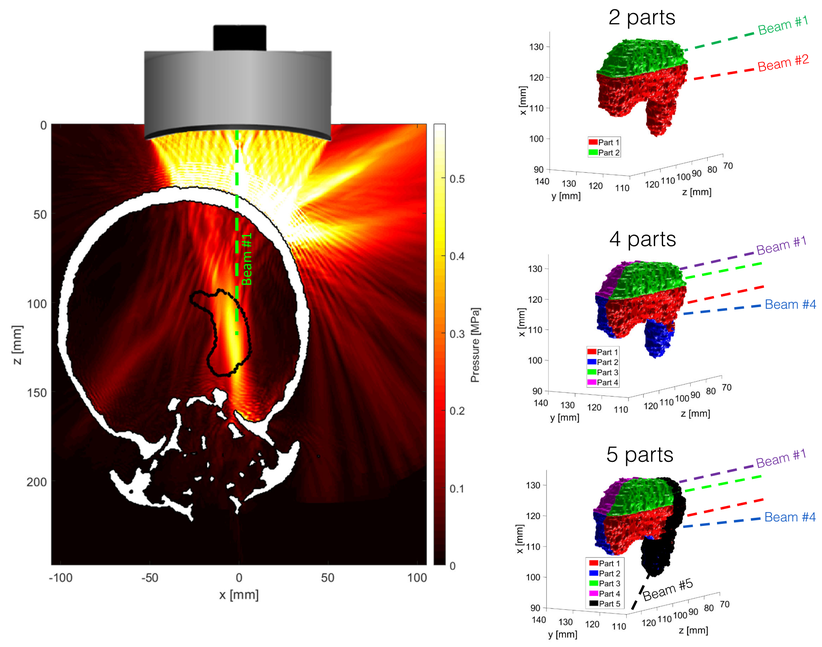
A single-element bowl transducer working at 500 kHz. It was designed to produce a focal area that roughly matches the dimensions of the target.



MATERIALS AND METHODS (cont.)

Protocol

Division of the left hippocampus into 2, 4 and 5 equal-sized parts. The transducer is located propagating towards the orientation axis of each structure. Finally, each part is independently targeted using the semi-adaptive algorithm.



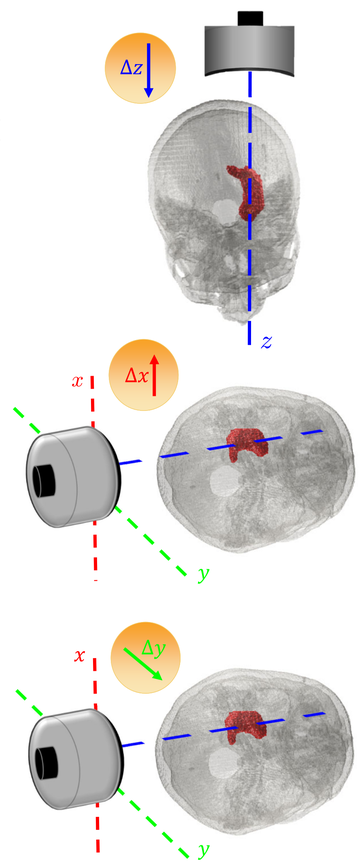
Semi-adaptive algorithm

The transducer is pointing towards the orientation of the organ. It is then moved from a reference position through the axial direction to find the maximum overlapped volume. Transversal movement is finally applied to maximize the covered volume.

Step 1
Movements of ±1 or ±2 mm in Z axis to find the maximum overlapped volume.

Step 2
Movements of ±1 mm in both transversal axes, independently, to find the most dependent one on the overlapped volume.

Step 3
Movements of ±1 mm in the transverse axis.

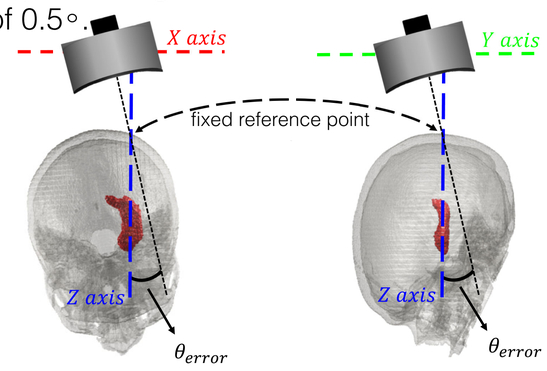


System Robustness

For submillimetric control of the focusing beam, the position deviation of the generated focus is analyzed when a linear or angular positioning error in the transducer is committed.

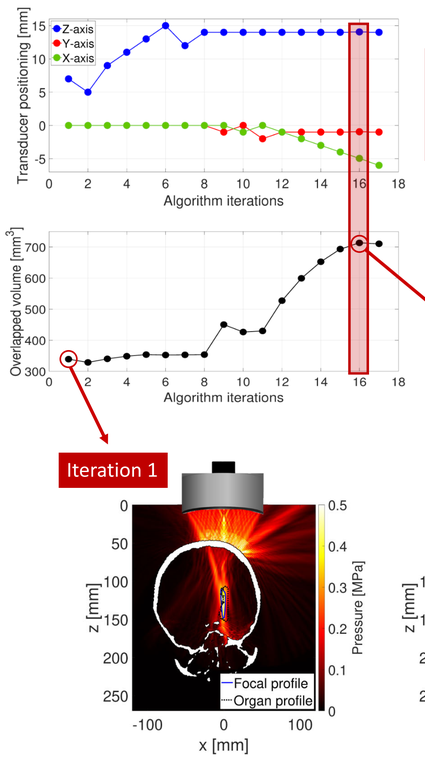
Case 1
Linear positioning error committed error in the three axes moving the transducer from -3 to 3 mm in steps of 0.5 mm.

Case 2
Angular positioning error committed error from -3 to 3◦ in steps of 0.5◦.



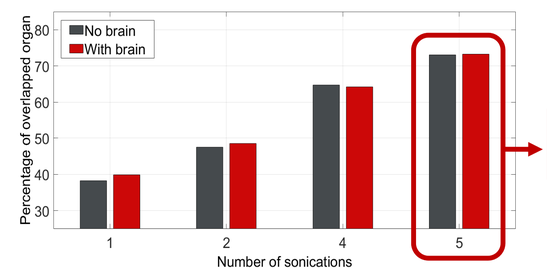
RESULTS

Semi-adaptive algorithm



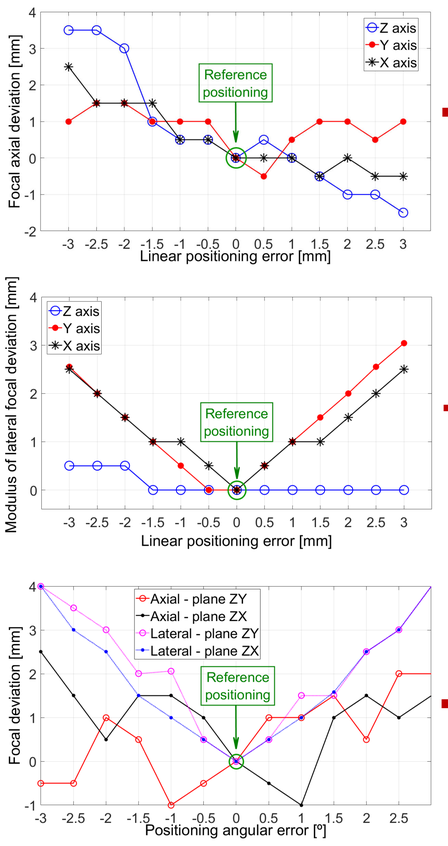
- Increase of 2 times overlapped volume.
- Computation time:
  - ✓ Targeting 1 part → 5 hours
  - ✓ Targeting 5 parts → 4 days

Optimal overlapping



- Overlapped volume:
  - ✓ 1 position → 40%
  - ✓ 5 positions → 73%

System robustness



- Submillimetric control when committed error:
  - ✓ Linear ≤ 1 mm
  - ✓ Angular ≤ 0.5◦

CONCLUSIONS

(1) Feasibility of using a single-element focused transducer working at 500 kHz for BBBO in humans.

(2) The semi-adaptive algorithm and proposed protocol allow up to 73% of overlapping of the left hippocampus.

(3) The submillimetric control of the focal area is achieved if the positioning committed error is also submillimetric and the incidence angle is smaller than 0.5 degrees

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