1P5-3

Development of focus controlling method with tFUS aided by numerical simulation for non-invasive brain therapy

非侵襲脳疾患治療に向けたシミュレーション援用による集束超音波焦点制御手法の開発

Yohei Kobayashi[1†], Takashi Azuma[1], Kazuya Shimizu[1], Masashi Koizumi[2], Tomomichi Oya[2], Ryo Suzuki[3], Kazuo Maruyama[3], Kazuhiko Seki[2], Shu Takagi[1]
([1]The Univ. of Tokyo; [2] NCNP; [3]Teikyo Univ.)
小林洋平 [1†]，東　隆 [1]，清水和弥 [1] ,小泉昌司 [2]，大屋知徹 [2]，鈴木亮 [3]，丸山一雄 [3]，関和彦 [3]，高木周 [1]([1] 東大院工, [2] 国立精神神経医療研究センター, [3] 帝京大薬)

1. Introduction

tFUS (transcranial focused ultrasound) has a great potential for non-invasive therapy for brain disease. The purpose of this research is to apply tFUS with microbubble for BBB (Blood Brain Barier) opening and neuromodulation. BBB opening is the technique to enhance the permeability of BBB for efficient drug delivery[1)]. On the other hand, neuromodulation is mechanical stimulation of the neuron induced by ultrasound for some treatment purpose. In this research we focus on the stimulation of red nucleus which exists in deep area of brain and is said to be effective against rehabilitation from cerebral infarction[2)]. For the both therapies the combination with microbubble is expected to increase the therapeutic effects, which improve safety of these therapies[3, 4)]. In this research to further investigate these therapies and the effect of microbubble the experiment on the macaque monkey which is closer to the human is performed. Major issue concerning application of tFUS for brain therapy is focus quality due to the reflection and refraction through the skull. Thus for conducting the experiment with monkey we develop the focal controlling method with array transducer aided by numerical simulation of ultrasound propagation utilizing CT data of monkey.

2. The simulation of ultrasound propagation

The simulation of ultrasound propagation through the skull is conducted by HIFU simulator[5)] based on a FDTD (Finite Differential Time Domain) method developed in Riken. It employs the equation for conservation of mass (Eq.1) and of momentum (Eq.2) for the basic equation.

$$\frac{1}{\rho_m c_{sm}^2}\frac{\partial \rho}{\partial t} + \nabla \cdot \boldsymbol{u} = 0 \qquad (1)$$

$$\rho_m \frac{\partial \boldsymbol{u}}{\partial t} = -\nabla p + \nabla \cdot \left\{ \zeta_{vm} tr(\boldsymbol{e})\boldsymbol{I} + 2\mu_{vm}\left(\boldsymbol{e} - \frac{1}{3}tr(\boldsymbol{e})\boldsymbol{I}\right)\right\} \qquad (2)$$

where ρ_m and c_{sm} is density and velocity of longitudinal wave respectively. **e** is the deformation tensor, ζ_{vm} is bulk viscosity and μ_{vm} is shear viscosity. For representing non-linearity of ultrasound Tait's equation (Eq.3) is employed as the state of equation.

$$\rho = \rho_0 \left(\frac{p + A}{p_0 + A}\right)^{\frac{1}{\gamma}} \qquad (3)$$

where ρ_0 and p_0 is density and pressure of background. A and γ are the constant.
In order to model the monkey's skull Hounsfield unit of CT images was translated to the volume fraction of bone. The density and sound speed of each voxel were average calculated by the volume of fraction inside the all unit voxel. The grid size of simulation was smaller than of original CT data. So the grid size was converted by the cubic spline interpolation.
In order to decide the distribution of phase for precise focal targeting inside the skull two methods were considered in this research. The first method is calculation of propagation time from a target point to the each element of array transducer and decide the phase to correct it. The second method is TR (Time Reversal) method[6)] which is performed by the simulation. The steps of TR are as follows. At first the sound source was set at a target point in the simulation model and the ultrasound emitted from it and propagated to the array transducer through the skull. Next the phase was decided to maximize cross-correlation against the center element from the corrected waveform of each Ch. It considered not only propagation time difference but also the multiple refraction due to the skull. In the present study the controllability of focus was investigated using these two methods to develop real tFUS system for the future experiment with monkey.

3. Result

Fig.1 is the numerical set up and shows the model made by CT of monkey and 64ch array transducer whose radius is 60 mm, f number is 1 and frequency is 500 kHz. The size of numerical domain was $80\,mm \times 80\,mm \times 160\,mm$ with a resolution of

$800 \times 800 \times 1600$ Cartesian meshes.

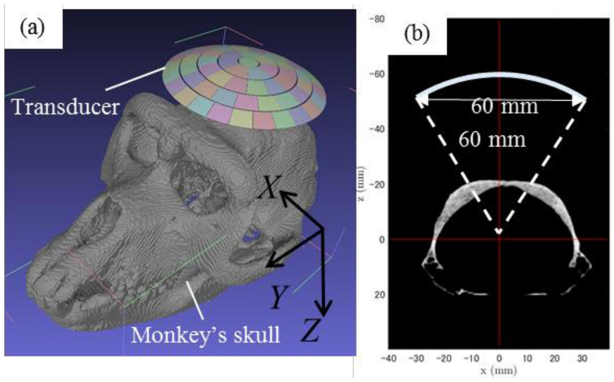

Fig.1 Simulation setup of ultrasound propagation form transducer through the monkey's skull.
(a) Skull model and 64ch array transducer. (b) Cross section of *xz* plane.

Fig.2 is the simulation result showing pressure field by phase controlling to (0, 0, 0) and (-10 mm, 0, 0). The distributions of phase were decided by only propagation time difference (a) and by TR (b). In the both target (b) shows the better focuses than (a), which means TR can correct the multiple refraction due to the skull as well as the propagation time difference.

4. Discussion

Simulation results show that TR with 64ch array transducer works effectively in the case of 500 kHz. But TR takes over 4 hour by the simulation in this case while calculation of propagation time difference takes only few minutes. Fig.2 (a) shows that the distribution of phase decided by only propagation time difference is also available for focal targeting. Short calculation time enables us to move target point quickly during the experiment on the monkey with monitoring the position of generated focal point by CT image utilizing a constant media. Therefore before developing real tFUS system for the experiment with monkey, we plan to further investigate range of focal movement and controllability by the simulation. And to validate the simulation result the experiment using the skull model is also conducted using hydrophone scanning. Finally based on these data we are going to conduct the BBB opening or neuromodulation on the macaque monkey.

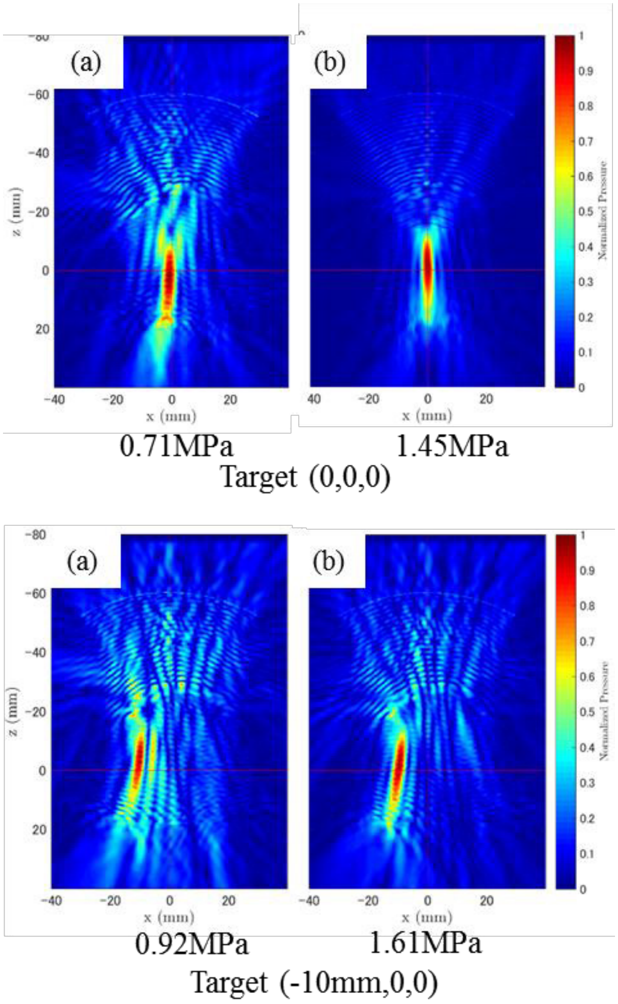

Fig.2 Pressure field on the *xz* plane for the simulation with phase control. The value below each figure is maximum pressure.

Acknowledgment
This work was supported by AMED fund.

References

1. A. Burgess, K. Hynynen: *Expert Rev. Neurother.*, **15**, p.477 (2015).
2. A. Ishida, T. Umeda and T. Isa: *Ultrasound Med. Biol.*, **42**, p.1512 (2016).
3. P Chu, Y. Pei: Sci. Rep., **5**, 1547(2015).
4. K. Martin, P. Dayton: *Wiley Interdiscip. Rev. : Nanomed. Nanobiotechnol.* **5**, p.329 (2013).
5. K.Okita, Y. Matsumoto: *Int. J. Numer. Meth. Fluids*, **65**, p.43 (2010).
6. Fink M., Montaldo G., and Tanter M, S *Rep. Prog. Phys.*, **63**, p.1993 (2000).

kobayashi@fel.t.u-tokyo.ac.jp