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Multiscale Modeling of transcranial focused ultrasoundneurostimulation and experimental validation: initial results

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OBJECTIVES Burst-mode focused ultrasound (FUS) exposure combined with microbubbles (MBs) has been shown to induce temporal and local blood-brain barrier (BBB) opening. Contrast-enhanced imaging is now served an indicator to postoperatively confirm the occurrence of BBB opening. Developing a transmit/receive dualmode FUS apparatus has the potential to observe focal position and fulfill implementation of real-time monitoring of the occurrence of BBB opening. This study aims to disclose our recent development in using a self-designed multiple-channel transmit/receive system allow to perform passive cavitation analysis as well as to reconstruct focal beam distribution *via* passive imaging reconstruction.
METHODS Homemade 256-channel ultrasound phased array driving system was employed to drive a 256-channel FUS transducer to deliver focal transmit energy (fundamental frequency = 500 KHz, diameter = 120 mm, curvature = 100 mm). The transmit pulse was designed to be 0.006 ms of burst length, 2 Hz of pulse repeated frequency (PRF) and 3.56 MPa negative pressure output. Received circuits with the channel number ranging from 16-64 were employed to perform RF signal receiving. During the in-vitro experiments, either a strong needle reflector or microbubble (MB) tube was positioned with the flowed MBs concentrations been controlled, the multiple channel RF signals were received in parallel with the human skull were inserted. Passive cavitation detection was implemented, and passive imaging was reconstructed with the developed phase-corrected passive beamformed algorithm.
RESULTS We demonstrate the feasibility in using this self-designed multiple-channel system to serve as a platform to be operated at dual transmit/receive mode (Fig. 1). Multiple channels of RF data can be received in parallel to reconstruct the passive imaging. The system now can support up to 64-parallel channel receiving for the following signal analysis and passive imaging formation. Point-spread function (PSF) imaging can be reconstructed singly using 16-channel receiving, whereas higher channel provide superior SNR of imaging. The system also demonstrates the capability of the focal passive cavitation detection to real-time trace cavitation activity specifically originating from the focal point. We also demonstrated that the implementation of a filtered phase-correction processing been applied into the PSF reconstruction algorithm can successfully identify the focal ultrasound deposition when penetrating through the skull.
CONCLUSIONS We demonstrated the feasibility of the capability in using a self-built multiple-channel ultrasound transmit/receive system to perform passive imagingand real-time focal PCD. The system and architecture has the potential to be developed to real-time monitor the process of microbubble-facilitated FUS BBB opening process.

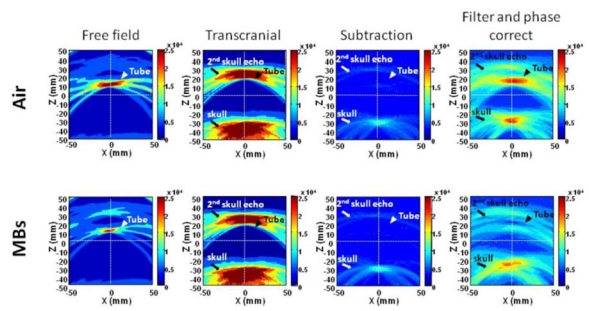

Fig. 1 (abstract P38). Passive imaging reconstruction: upper row shows the tube was filled with air, and lower row shows tube was filled with MBs

P39

Multiscale Modeling of transcranial focused ultrasound neurostimulation and experimental validation: initial results

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OBJECTIVES Low intensity focused ultrasound (LIFU) has the demonstrated ability of non-invasively stimulating neural activity. This is of high value for therapeutic (stimulation, neuroprosthetics, etc.) and diagnostic (preoperative mapping, etc.) purposes. A multiscale simulation platform for image-based and personalized modeling of transcranial LIFU stimulation should be developed to allow mechanistic studies, hypothesis formulation and testing, device development, and, ultimately, personalized treatment planning, safety, and efficacy assessment. Experimental validation is crucial to establish confidence in and explore the limitations of the modeling.
METHODS The Sim4Life computational life sciences has been extended to: 1) Support full-wave acoustic simulation of transcranial sonication: For that purpose, new functionality to consider CT image-based skull inhomogeneity information (density, speed-of-sound, and attenuation maps) and partly compensate for related focus aberration and defocusing with multi-element transducer steering optimization has been implemented. 2) Allow for neuronal dynamics modeling: The NEURON library for compartmental neuronal dynamics modeling supporting detailed neuromorphology and channel dynamics has been integrated and parallelized simulations featuring large numbers of neurons and neural networks can now be performed. 3) Generate personalized, functionalized head models: Patient image data can be used to generate anatomical geometries by segmentation and/or morphing of presegmented models. CT image data informs on inhomogeneity, DTI image-data can be used for fiber tracking to generate neuronal axon models, and Python tools facilitate the anatomo-physiologically correct placement of cortical pyramidal neuron and deep brain stimulation relevant neurons (STN, GPi, IC). 4) Coupled acoustic and neuronal dynamics modeling: The Plaksin-Shoham-Kimmel (PSK) model of membrane-cavitation induced neurostimulation has been implemented and adapted for future use in combination with the compartmental cell models. Furthermore, coupled electromagnetic neuronal modeling is also supported. An experimental setup involving an acoustic transducer sonicating through a rat skull has been constructed. MicroCT image data has been acquired and the 3D pressure distribution inside the skull has been measured using computer controlled hydrophone scanning.
RESULTS The acoustic solver has been extensively validated previously against numerical and experimental data in homogeneous setups and setups with homogeneous obstacles. The new experimental data allows for the first time successful validation of a setup involving inhomogeneous media using the previously presented Gamma method for uncertainty assessment-based, objective comparison of 3D pressure distributions (Fig. 1).The neuron functionalized anatomical head models have been partly validated by comparing modeling of transcranial electric/magnetic and deep brain stimulation with experimental data from literature.The PSK-model could be simplified without significant impact on the results, thus enabling its integration into 3D, extended, morphological cell models. For that purpose, the previously bidirectional coupling of the electrophysiological and cavitation mechanics parts has been broken up and further separation allows to pre-compute costly parts of the model, accelerating the modeling by more than one order of magnitude.
CONCLUSIONS A multi-scale framework for the computational investigation of LIFU neuro-stimulation is being developed. It features image-based acoustic propagation modeling (including support for bone inhomogeneity) and focusing functionality, patient-specific functionalized anatomical model generation with realistic neuron placement, integrated neuronal dynamics simulation, and a coupled model of LIFU-induced neurostimulation that is currently still limited to 0D neuron models, but has been prepared for the future modeling of 3D-extended, morphologically-detailed physiological neuron models. Important parts of the platform (acoustic and neuronal simulations, functionalized models) could be successfully validated against new and existing experimental data.The presented progress is an important step towards the goal of allowing mechanistic studies, hypothesis formulation and testing, device development, and, ultimately, personalized treatment planning, safety, and efficacy assessment.

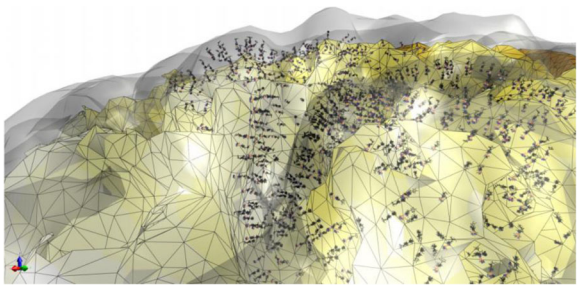

Fig. 1 (abstract P39). Cortex subregion of a human model with anatomically positioned pyramidal neurons and visualized transmembrane voltage activity

P40

SPIO-PEI-pDNA complex loaded microbubbles for ultrasound-based gene therapy in brain

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OBJECTIVES Recently, gene therapy has attracted much attention especially in neurodegenerative diseases. Currently, gene delivery within central nerves system mainly relies on invasive intracerebral injection or viral vectors to circumvent the obstacle of blood-brain barrier. Non-viral gene delivery *via* systematic transvascularroute is an attractive alternative since it is non-invasive. However, a high-yield and targeted gene delivery platform is still lacking. In order to improve the efficiency of gene delivery, this study proposed an ultrasonic sensing vector for gene delivery into brain through polyethylenimine (PEI)-superparamagnetic iron oxide (SPIO)-pDNAloaded microbubbles (PSp-MBs). Cooperating with ultrasound exposure, PSp-MBs could transport the PSp nanoparticles into the desired brain region by acoustic MBs cavitation activity. The rate of gene transfection would be enhanced by the modification of PEI onto PSp nanoparticles. In addition, by an externally applied magnetic field, magnetic targeting (MT) can further increase the deposition of PSp at the targeted location, enhancing the gene delivery.
METHODS The PSPIO was consisted of PEI molecular and SPIO nanoparticles (diameter: 10 nm) *via* ligand exchange. The PSPIO were then conjugated with pDNA and loaded onto the lipid surface of MBs by electrostatic force. PSPIO-pDNA (luciferase plasmid) modulated onto the MBs was confirmed by Prussian blue staining and propidium iodide staining. The size, concentration and PSPIO payload were measured by multisizer and plate reader, respectively. C6 glioma cell and Sprague-Dawleyrats (N = 4) were used in this study. The gene transfection efficiency and BBB opening region resulted from PSp-MBs with ultrasound (frequency = 1 MHz, energy = 0.1-0.5MPa, cycle = 5000, PRF = 1 Hz, sonication time = 60 s) were evaluated by bioluminescence imaging and Evans blue staining, individually. The MT process was performed by a 0.48 Tesla external magnet.
RESULTS Figure 1A shows the fabricated PSp-MBs. The co-localization of the PSp nanoparticles in the bright field images and the fluorescent image indicated a good conjunction of PSPIO-pDNA and MBs (as arrows). The mean size and concentration of PSp-MBs were 1.5 m and (5-10) × 109 bubbles/mL, respectively. The payload ofPSPIO and pDNA onto MBs were 134.5 g and 17.1 g, individually. Figure 1B shows that PSp-MBs with ultrasound could achieve gene transfection and the expression of gene could be further enhanced by MT process. We also confirmed that the PSp-MBs could perform successful BBB opening without bioeffects by the trigger ofultrasound with an acoustic pressure of 0.3 MPa (Fig. 1C).
CONCLUSIONS The MBs have fairly payloads of PSPIO-pDNA. We demonstrated that PSp-MBs with ultrasound can perform locally gene delivery and open BBB concurrently. In addition, the efficiency of gene delivery could be further enhanced by MT process. Future works include quantifying and tracking of distribution of gene delivery and Parkinson's disease rats *via* magnetic resonance imaging.

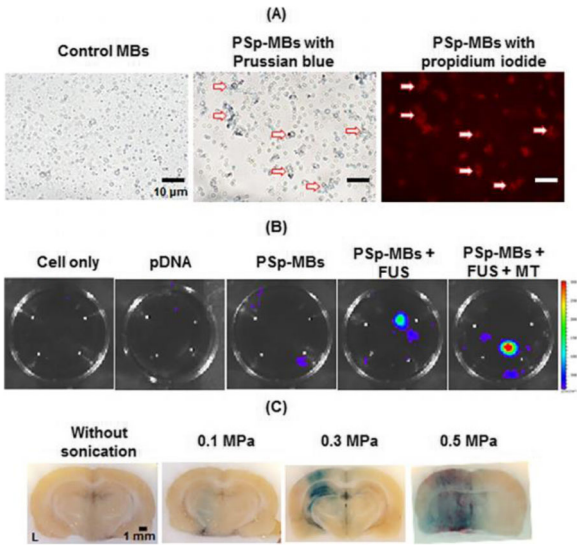

Fig. 1 (abstract P40). (A) Microscope images of the PSpMBs with Prussian Blue and propidium iodide staining. The colocalization of the PSp nanoparticles in the Prussian Blue and propidium iodide staining indicated a good conjunction of PSPIOpDNA and MBs. (B) Gene transfection efficency of PSpMBs with different conditions, suggesting that PSpMBs with ultrasound could achieve gene transfection. (C) BBB disruption of PSpMBs cooperating with FUS by different parameters

P41

Numerical study of bubble area evolution during acoustic droplet vaporization enhanced HIFU treatment

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OBJECTIVES Acoustic Droplet Vaporization (ADV) has the potential to shorten treatment time of high intensity focused ultrasound (HIFU) while minimizing thepossible effects of microbubbles along the propagation path. Distribution of the bubbles formed from the