In vivo small animal super-resolution imaging through the human skull

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Background, Motivation and Objective: Human transcranial super-resolution has the potential to image the brain's vasculature with resolution below the diffraction limit. In previous work [1] we showed that transcranial super-resolution using focused ultrasound can be feasible even without correcting for aberration. In this work, we are using the same focused super-resolution approach to image the vasculature of *in vivo* rat tumors, kidneys, and tail, through a human skull, as models of tissue vasculature.

Statement of Contribution/Methods: A series of *in vivo* experiments were performed on adult rats which were imaged through the parietal window of a human skull specimen using a conventional 2.5 MHz phased array (Fig 1A). The skull specimen was secured with respect to the transducer to pre-calculate a phase correction. This correction was then applied to custom focused super-resolution imaging sequences which acquired a total of 96000 frames to populate a super-resolution image. The tail vein was accessed using a custom catheter. A microbubble solution of a concentration of $8 \cdot 10^7$ bubbles/mL was infused constantly in the rat's bloodstream by means of an infusion pump. The flow rate was set at 75 μL/min in agreement with previous *ex vivo* experiments. The tail was positioned at a depth of 8.6 cm. Similarly, the human skull specimen was placed above the rat's abdomen after corrections had been pre-calculated, and a total area of 2 cm laterally was imaged. For the rat abdominal experiments, the bubble concentration infused was calibrated to $2 \cdot 10^9$ bubbles/mL, which produces an approximate steady-state concentration in the order of 10^6 bubbles/mL in the bloodstream, at a flow rate of 30 μL/min.

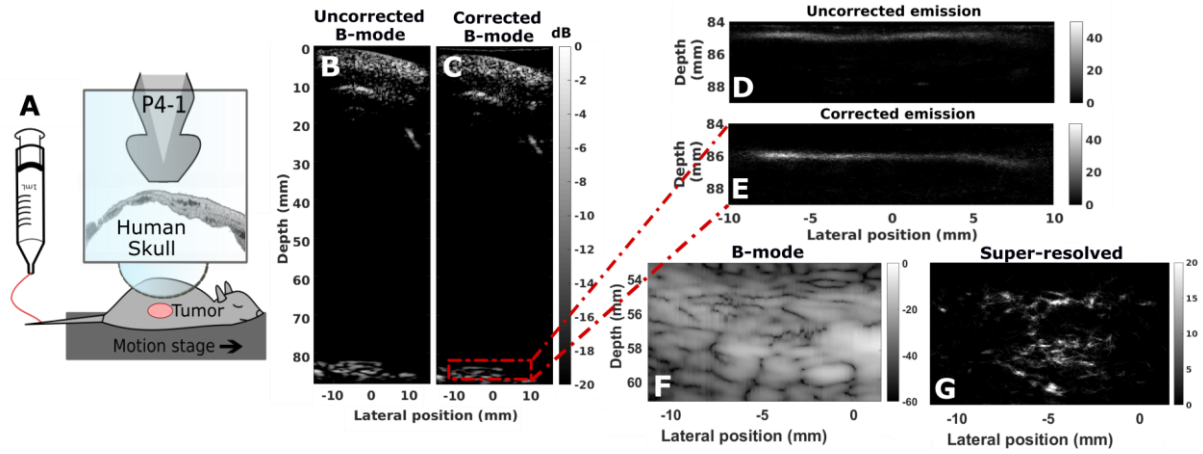

Figure 1: (A) Experimental setup. (B) B-mode images of an uncorrected and (C) a corrected emission of the rat tail and (D),(E) the equivalent super-resolved images. (F) B-mode image of the abdominal rat experiment and (G) super-resolved image for the same region. Super-resolved scale bars are in bubble counts, B-mode in dB.

Results/Discussion: Both corrected and uncorrected emissions through the skull successfully super-resolved the rat tail vein (Fig.1D and E). The application of the correction improved the shape and increased bubble detection sensitivity by a factor of 1.25. The sum of bubbles as a function of axial position estimated the size of the vessel at 250μm for both emissions. In the rat abdominal imaging case, bubbles were detected in the periphery of the kidney, as well as in a few branching structures, as shown in Fig. 1G. The conventional B-mode images in all cases, shown in Figs.1B, C and F, cannot resolve the target structures. The sizes of the detected vascularized structures of the kidney ranged from 200-500 μm.

[1] D. E. Soulioti, D. Espíndola, P. A. Dayton and G. Pinton, "Human Transcranial Super Resolution Imaging", 2018 IEEE International Ultrasonics Symposium (IUS), Kobe, 2018, pp. 1-4.