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Acoustic Holograms for Bilateral Blood-brain Barrier Opening in Mice

Presenter: Sergio Jimenez Gambin

Authors in order: Sergio Jimenez Gambin, *Columbia University*, Antonios N. Pouliopoulos, *Columbia University,* Noe Jimenez, *Universitat Politècnica de València,* José M. Benlloch, *Universitat Politècnica de València*, Elisa Konofagou, *Columbia University*, Francisco Camarena, *Universitat Politècnica de València*

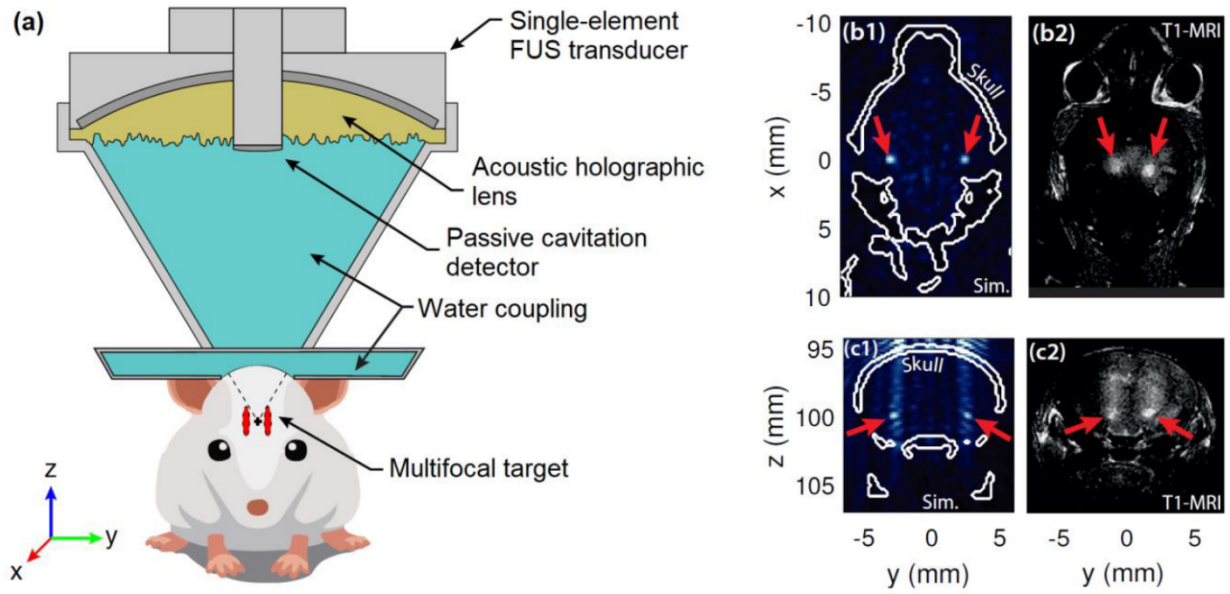
Design and test simple, low-cost acoustic holograms coupled to a single-element FUS transducer for aberration-free, highly-localized, simultaneous, multiple BBB-opening in both brain hemispheres in mice.

Skull geometry and properties were acquired from a micro-CT scan, and target structure from a mouse atlas. The lens was designed from the wavefront generated by the virtual-source target at the design surface using Time-Reversal, and then manufactured by stereolithographic 3D-printing. For in-vivo experiments, 1μl/g Definity microbubbles were injected intravenously and 1.68-MHz 400-kPa-PNP FUS was applied for 2 minutes. Then, 0.2 ml gadolinium tracer was injected intraperitoneally, and BBB opening was assessed using T1-MRI.

T1-MRI showed gadolinium extravasation at two symmetric focal spots separated 3.2±1.0 mm (n=3 mice) compared to 5.3 mm in simulations. In addition, the lens ability to encode time-reversed wavefronts resulted in a focusing performance enhancement, providing quasi-spherical, high-resolution BBB opening locations of 1.0±0.3 mm size for the higher contrast enhancement regions, considerably reduced as compared to the 19.2 mm axial size for the calibration in water. Note that air nuclei trapped within the irregular lens surface may have contributed to the field distortion. Moreover, using the particular micro-CT scan of each treated subject would improve the pressure-field prediction.

This study demonstrates that acoustic holograms are feasible to produce a high-resolution, simultaneous bilateral BBB opening in mice using a single sonication and injection of microbubbles, as well as in different animals using a separate unique micro-CT scan, defining therefore a time- and cost-efficient therapeutic approach for neurological disease treatments.

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CAPTION (10 words):

(a) In-vivo setup scheme. (b1,c1) Simulated pressure-field. (b2,c2) Experimental T1-MRI.