Minimally invasive targeted drug delivery in the brain enhanced by closed-loop focused ultrasound control

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Background

Despite the advantages over conventional invasive approaches, effective minimally-invasive drug delivery in the brain remains a major challenge

- Blood-brain barrier (BBB) limits the drug penetration in the brain
- Improvements in drug penetration is possible by "opening" the BBB using combination of :
  - ✓ Low-intensity focused ultrasound (FUS)
  - ✓ Ultrasound contrast agents called "microbubbles" (MBs)
- During FUS-MB enhanced BBB opening, we can monitor microbubble dynamics by recording their acoustic emissions (AE)

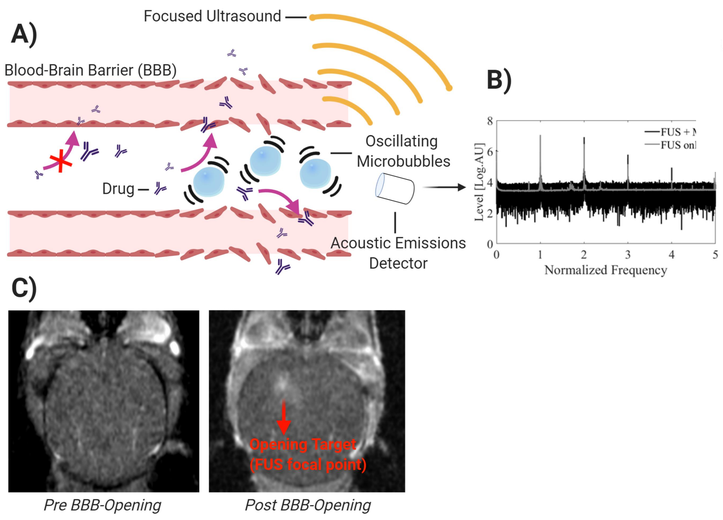

Figure 1. A) Combination of FUS and MB provides a physical method to spatially and temporally modulate the BBB permeability and improves the delivery of a range of therapeutic agents in the brain. **B)** Acoustic emission (AE) detection makes it possible to monitor MB dynamics. **C)** Contrast-enhanced MR Image of rodent brain before and after BBB-opening. **Brighter spot on the brain indicates higher contrast agent penetration and thus higher BBB permeability**

Our aim is to establish closed-loop methods to control the BBB-opening under MB-FUS, for effective minimally-invasive drug delivery

Methods

Ultrasound-guided focused ultrasound system implemented with closed-loop acoustic emission controller

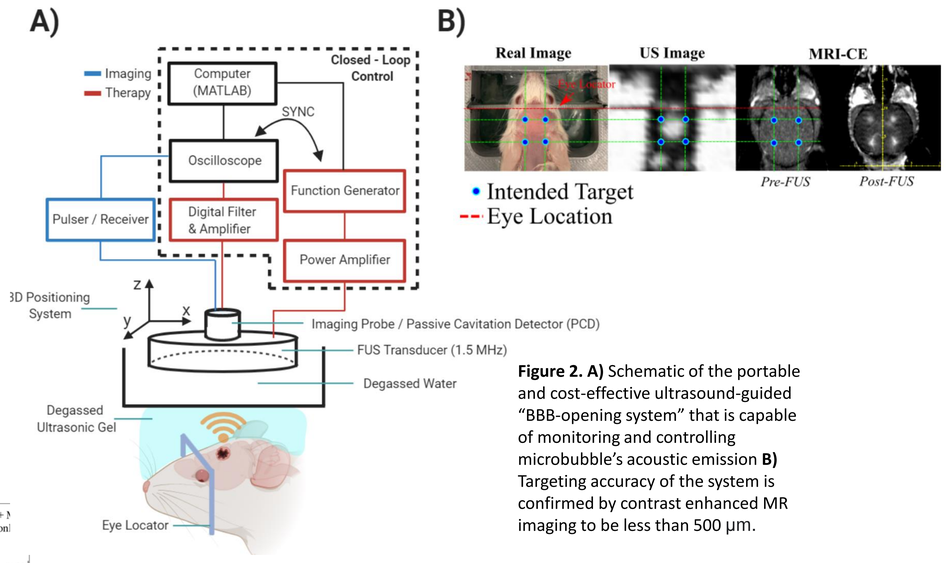

Figure 2. A) Schematic of the portable and cost-effective ultrasound-guided "BBB-opening system" that is capable of monitoring and controlling microbubble's acoustic emission **B)** Targeting accuracy of the system is confirmed by contrast enhanced MR imaging to be less than 500 μm.

Training the controller for microbubble dynamics control

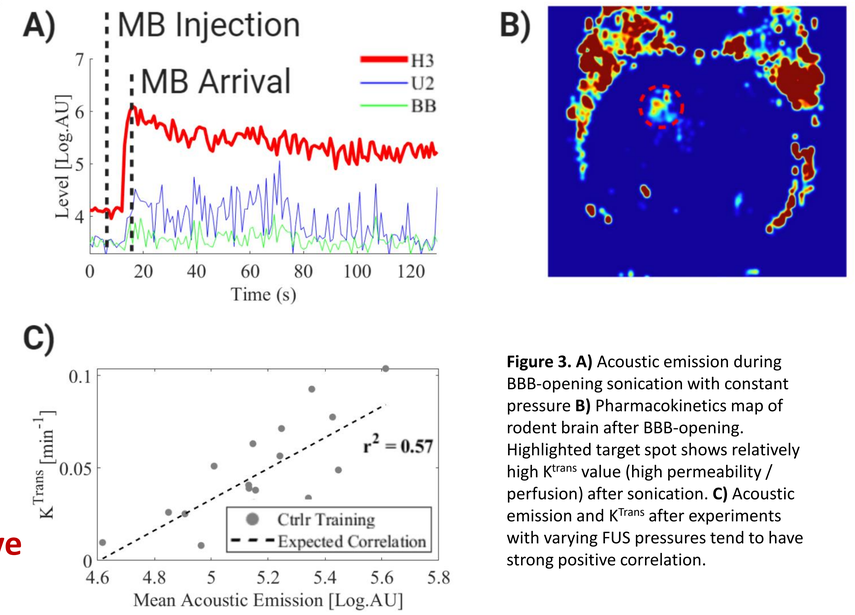

Figure 3. A) Acoustic emission during BBB-opening sonication with constant pressure **B)** Pharmacokinetics map of rodent brain after BBB-opening. Highlighted target spot shows relatively high K^{trans} value (high permeability / perfusion) after sonication. **C)** Acoustic emission and K^{Trans} after experiments with varying FUS pressures tend to have strong positive correlation.

Results

Controller-implemented BBB-opening

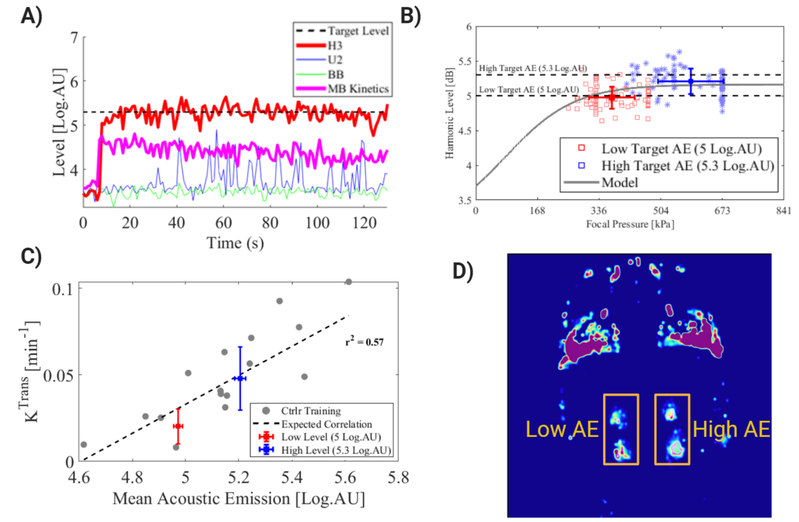

Figure 4. A) Acoustic emission after implementing controller. Targeted acoustic emission was 5.3 Log.AU for given figure when the achieved level was 5.21 ± 0.18 Log.AU, giving 98.2% accuracy and 3.5% of tolerance with rise time of less than 3 seconds. **B)** Applied focal pressure during controlled sonication as a function of acoustic emission. Higher target level had ± 90 kPa of pressure volatility, while lower target level had ± 60 kPa of pressure volatility, indicating that higher target AE level introduces more instability than lower target AE level. **C, D)** Resulting K^{Trans} values after controlled BBB-opening highlighted in red and blue in addition to Fig.3C. Controlled BBB-Opening using acoustic emissions produced reproducible and accurate K^{Trans} values.

Conclusions & Future Works

Controlled BBB-opening is completely "tunable."

- Out methodology shows that it is possible to monitor and locally control the cerebrovascular microbubble dynamics
- This capability not only allows to modulate the level of drug delivered in the brain, but also makes this minimally-invasive technology completely "**tunable**."
- Following the proof-of-concept experiments, this system will be scaled to clinical level to accelerate the clinical translation of this technology against a range of brain diseases, including **Alzheimer's** and **brain cancer**.

Acknowledgements

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