

# Passive cavitation mapping during blood-brain barrier opening is facilitated by treating with ultrasonic pulses of inverse polarity

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## Background, Motivation and Objective (645 characters)

Focused ultrasound (FUS) in conjunction with pre-formed circulating microbubbles (MB) is being tested for a wide range of therapeutic applications such as non-invasive and reversible opening of the blood-brain barrier (BBB). An advantage of MB-based therapies is the ability to monitor their evolution by mapping the cavitation activity within the targeted area. However, thick skull and tissues limit our ability to detect low-amplitude MB activity, especially in clinical BBB opening applications. Linear echoes dominate the received signal when the therapeutic and passive imaging frequencies overlap. Here, we employ pulse inversion (PI) to improve the passive cavitation mapping during BBB opening by suppressing linear echoes within the FUS path.

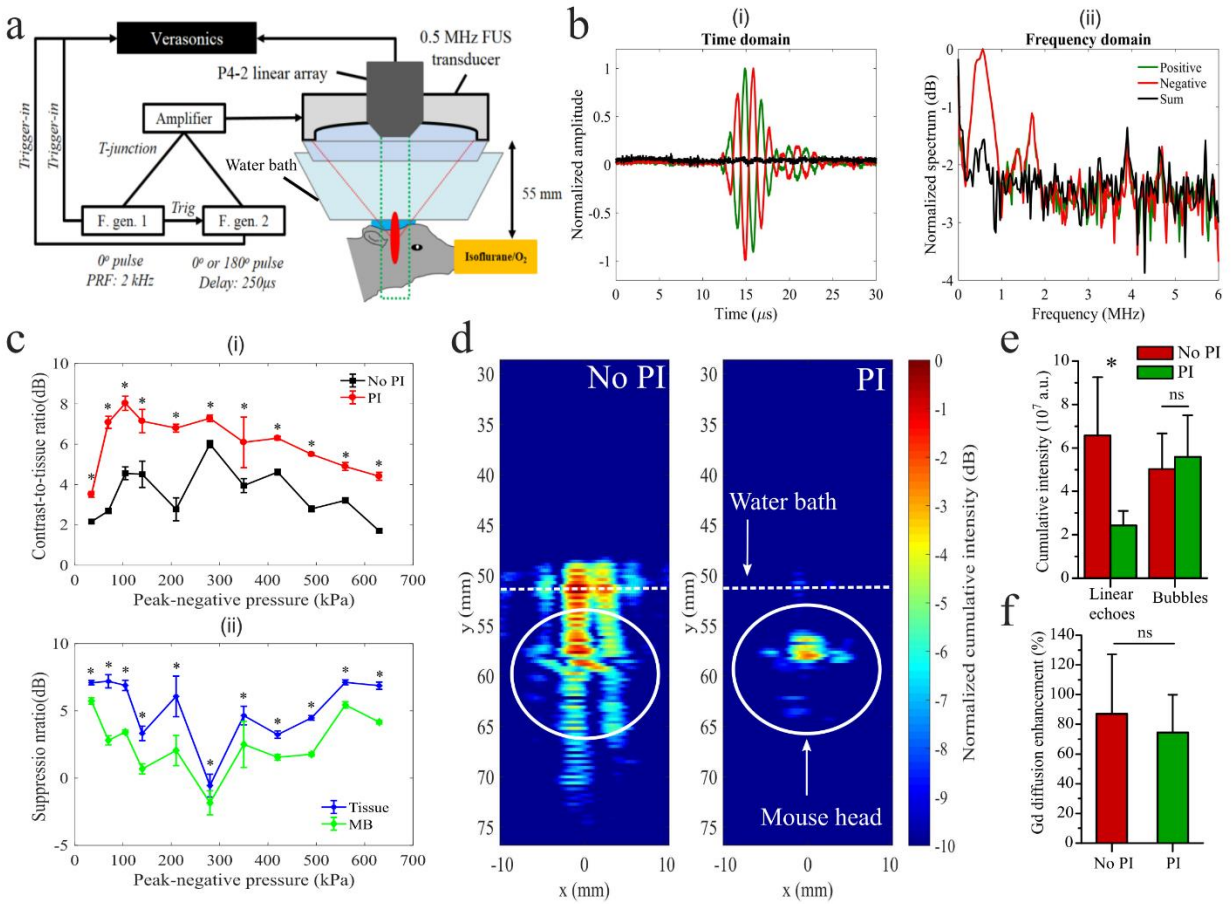
## Statement of contribution/Methods (602 characters)

FUS with PI was achieved by synchronizing the emission of inverse short pulses (pulse length: 2-3 cycles, PRF: 4 kHz, peak-negative pressure: 35-630 kPa) through a focused 0.5-MHz FUS transducer driven by two function generators (fig. 1a). An ATL P4-2 linear array passively captured acoustic signals in synchrony with FUS emission, using absolute time-of-flight information. We tested the PI sequence in a 10% w/v gelatin phantom filled with 0.5% w/v Si particles. Polydisperse lipid-based MB (concentration:  $2 \times 10^6$  MB/ml = 1x clinical dose) flowed through a 5-mm channel (flow speed: 1 mm/s) and exposed to FUS pulses of inverse polarity. FUS with PI was also tested *in vivo* to monitor BBB opening in a mouse model.

## Results/Discussion (749 characters)

Summation of the inverse FUS pulses in free field led to a 15 dB cancellation of the time-domain signal (fig. 1b-i), mainly due to the suppression of the fundamental frequency and 3<sup>rd</sup> harmonic (fig. 1b-ii). PI increased the contrast-to-tissue ratio in the phantom by up to 5.5 dB compared to no PI (fig. 1c-i), due to the enhanced tissue signal suppression compared to the MB signal (fig. 1c-ii). Linear echoes were cancelled *in vivo* (figs. 1d and 1e), facilitating detection of MB activity during BBB opening. Both therapeutic schemes resulted in efficient BBB opening *in vivo*, with no significant difference in the delivery of gadolinium into the brain parenchyma (figure 1f). In conclusion, FUS with PI facilitates the passive mapping of weak MB signals both in a phantom and *in vivo* and can be applied in clinical BBB opening to suppress reflections from the thick human skull and brain tissue.

Character count: 1996/2000



**Figure 1:** a) Experimental setup for BBB opening using PI and passive cavitation mapping. b) FUS pulses of positive (green) and negative (red) polarity were consecutively emitted through the 0.5 MHz FUS transducer. Summation of their waveforms led to a total reduction of 15 dB in the detected time-domain signal. This reduction was due to the suppression of the fundamental frequency and odd harmonics generated by the therapeutic transducer. c) Contrast-to-tissue ratio (CTR) in a tissue-mimicking phantom was significantly higher with PI, when compared to pulses of same polarity, throughout the acoustic pressures (top). Improved CTRs originated from the higher suppression ratio of tissue signal compared to MB signal (bottom). d) Passive cavitation mapping *in vivo* without (left) and with (right) PI. e) Linear echoes from the water bath, skull and tissues were successfully suppressed with PI. In contrast, MB signal was not significantly different *in vivo* (n=5). f) Gd delivery into the brain parenchyma was equivalent between the two therapeutic paradigms (n=5). \*: p<0.05, ns: not significant.