**Proceedings Paper:**
Nie, L, Harput, S, McLaughlan, JR orcid.org/0000-0001-5795-4372 et al. (3 more authors) (2017) Acoustic microbubble trapping in blood mimicking fluid. In: IEEE International Ultrasonics Symposium. 2017 IEEE International Ultrasonics Symposium (IUS), 06-09 Sep 2017, Washington, DC. IEEE . ISBN 9781538633830

https://doi.org/10.1109/ULTSYM.2017.8092590

# Acoustic Microbubble Trapping in Blood Mimicking Fluid

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***Abstract*—Microbubble (MB) volumetric pulsations can be selectively seeded with external ultrasonic fields. The therapeutic use of this phenomenon encompass mechanical thrombolysis and targeted drug deliveries through sonoporating endothelial cells. However, expected outcomes are still plagued by low bubble concentrations and short circulation time after administration. MBs preferentially flow along the centerline of large vessels which deteriorates biological targeting methodology in the case of vascular disease treatment with MBs.**

**Simultaneous MB imaging and trapping against high flow rates has been recently proposed by instantaneously switching optimized ultrasonic beams. Principles were previously validated by circulating MBs with purified water through a flow phantom. But differences between blood and water call for preliminary investigations with blood mimicking fluid (BMF). This study demonstrated the capability of trapping bubbles in BMF with the acoustic trap but with nearly 40% efficiency reduction over the control in water, being present by the suppressed increase of image brightness.**

## I. Introduction

Sustained or violent MB oscillations have been used to enhance interactions with diseased sites and induce therapeutic bio-effects [1]–[3]. For molecular imaging or treatment of cancers, MBs can be functionalized to specifically seek molecular targets by attaching ligands onto the bubble shell [4]. The efficacy of the biological MB targeting could be pertinent in these scenarios, where flow rates are relatively low. Things are strikingly different in large vessels, where large shear stress as a result of high flows can easily compete with the biological bounding force, and deflect bubbles away from the endothelium [5].

Recent advancements of magnetic particle-doped MBs provide a means to achieve MB targeting through externally applying magnetic fields, but with restricted depth of around 20 mm [6], [7]. The use of acoustic radiation force (ARF) to transport MBs to the distal vascular wall has been appreciated for years, while the translation is still affected by some confounding factors [8]. One of the problems is that the single-element transducer makes the real-time feedback non-intuitive [9]. With a standard linear array, simultaneous MB accumulation and imaging has been presented recently by interleaving fast plane wave and acoustic trap beams [10]. But the existence of particles and high viscosities in blood could impede the MB translation and retention. This study investigated the feasibility of acoustic MB trapping in BMF by setting exposures within limits for ultrasound diagnostic imaging, which is set by the Food and Drug Administration (FDA) and the British Medical Ultrasound Society (BMUS).

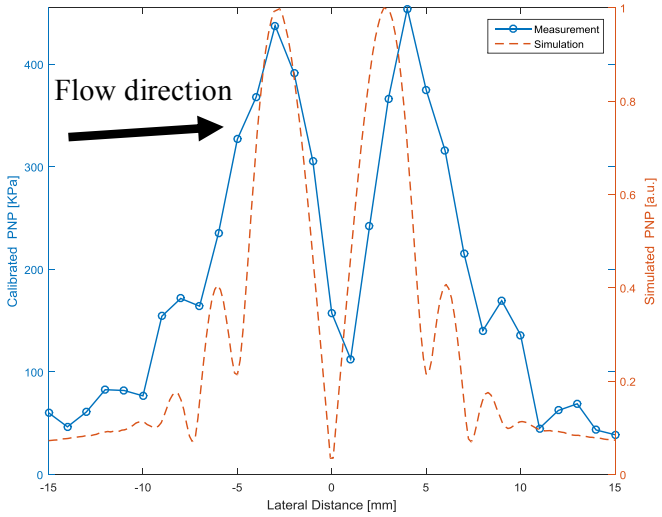


Fig. 1. Simulated acoustic trap beam compared with its counterpart measured in water.

## II. Materials and Methods

### A. Acoustic Trapping and Fast Detection of Contrast Agents

The main driving mechanism behind the acoustic trap is the interaction between acoustic fields and MBs. Drops of pressures within the propagating medium produce radiation forces to push bubbles away from the source [11].

Connected to the Ultrasound Array Research Platform II [12]–[15], a Verasonics L11-4 transducer (Verasonics, Inc., WA, USA) was triggered with a train of pulses to realize MB trapping and fast imaging. For trapping, central 64 elements were divided into two sub-groups symmetrically. These two sub-groups were excited with the same-level voltage at the same time, but excitations for one sub-aperture were reversed with $\pi$ phase shift before relayed to amplifiers. Consequently,

TABLE I
ULTRASOUND PARAMETERS

| Parameter | Acoustic Trap | Single Plane-Wave Imaging |
|---|---|---|
| Number of elements | 64 | 128 |
| Excitation signals | sinusoids (7 MHz) | square pulse (50 ns) |
| Mechanical index (MI) | 0.07 | 0.15 |

traversing the field of view, a low pressure region was engendered because of wave destructive interferences in the middle. Fig. 1 depicts one typical lateral pressure profile at the depth of 30 mm which is in accordance with the vessel depth in experiments. Peak negative pressures (PNPs) were calibrated with a 0.2 mm needle hydrophone (Precision Acoustics, Dorchester, UK) in water. The significant ARF from the inlet beam precluded MBs to enter the trap, and the duty cycle of the this beam was reduced to a half compared to that of the outlet beam. For imaging, all elements of 128 were used to perform fast plane wave imaging to secure the trapping efficiency during excitation switch, and preserve high-resolution ultrasound imaging. Ultrasound parameters adopted in experiments are given in Table I.

### *B. Trapping Experiments*

Definity-like MBs were prepared according to [16] and solutions were diluted to a concentration of $1.6\text{x}10^6$ bubbles/mL. The blood mimicking fluid was produced by suspending Orgasol particles, glycerol, dextran and surfactant into a water base [17]. MB populations were subsequently flown through a wall-less flow phantom [18] with purified water or BMF at a constant flow rate of 28 mL/min. The phantom had a 2.5 mm vessel and assuming a Newtonian fluid, this flow condition resulted in a wall shear rate of 304 $s^{-1}$ that was within the human venous flow range [19].

The timing of pulse trains is elaborated by Fig. 2 for two sets of experiments. Noted that trapping pulses were only interleaved between 100 and 900 ms. A total of 2200 frames were acquired at an imaging rate of 1 kHz. Three regions of interest (ROIs) were chosen as given by Fig. 3(a). The overlaid dashed red line simulates the laterally absolute PNP profile for trapping. Image brightness was used for arbitration of MB trapping effect and the baseline was found with 100 frames without introducing MBs. Image intensities were pre-processed by subtracting the mean value of the baseline and displayed as a function of time with every 100 frames averaged.

## III. Experimental Results

The ARF produced by the steep slopes of the pressure field was used for localized trapping of MBs within the low-pressure trap. Increases of image intensity in the middle ROI was of primary interest and indicative of the trapping effect. When circulated by water, compared with its initial value, the largest brightness gain of 28% was found inside the

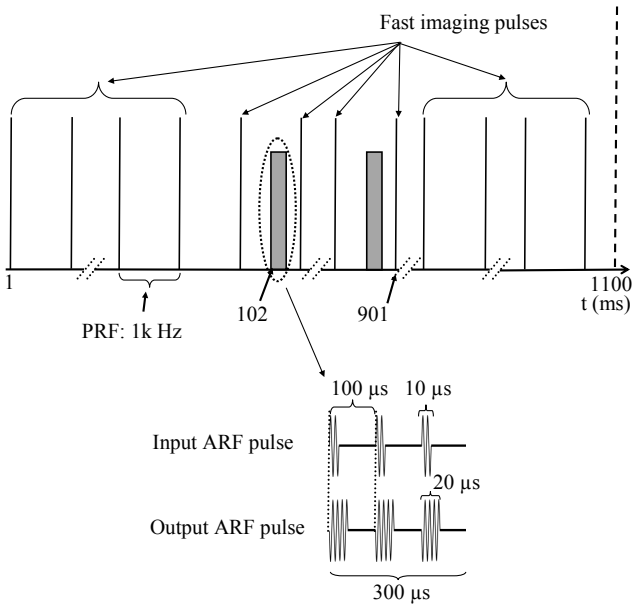


Fig. 2. Timing of emitted pulse sequences in experiments.

middle ROI (Fig. 3(b)). In BMF, MB accumulation was also achieved with an averaged intensity growth of 17%. (Fig. 3(c)). Intensities from the outlet ROI dropped after activating the trapping beam until plateaued with both fluids. Whilst much more obvious climbs were seen by using water after the ARF was off. Finally, relatively small fluctuations were observable in the inlet ROI in Fig. 3(b) and Fig. 3(c).

## IV. Discussions

In comparison to previously reported work [10], where ultrasonic exposures (especially $I_{SPAT}$) are above FDA limits for diagnostic imaging, this study investigated the possibility to halt MB populations in BMF against venous flow rates with moderate acoustic emissions (all in accordance with FDA limits for ultrasound imaging).

The presence of scattering particles and higher viscosity of the BMF makes MBs more resistant to the ARF, delaying the onset of MB accumulation in the middle ROI (Fig. 3). Akin to the delayed response to trapping beams, prolonged intensity increases even after deactivating the acoustic trap is resultant from the ambient resistance exposed by the BMF.

Thanks to the flexibility of the acoustic trap formation, which is wholly dependent on the beam control, the ease of manipulating pressure slopes in the middle makes this tool applicable to a range of flow rates. The price to pay could be increased acoustic outputs especially to trap high-speed flowing MBs in blood.

Compared with the magnetic targeting methodology, a pulse train can be relayed to a single transducer to perform bubble localized delivery and imaging with the acoustic trap. Even further, destructive pulses can be added to burst bubbles and induce therapeutic effects.

Plane waves were employed to produce the acoustic trap in this study. Low pressures can be produced along the central

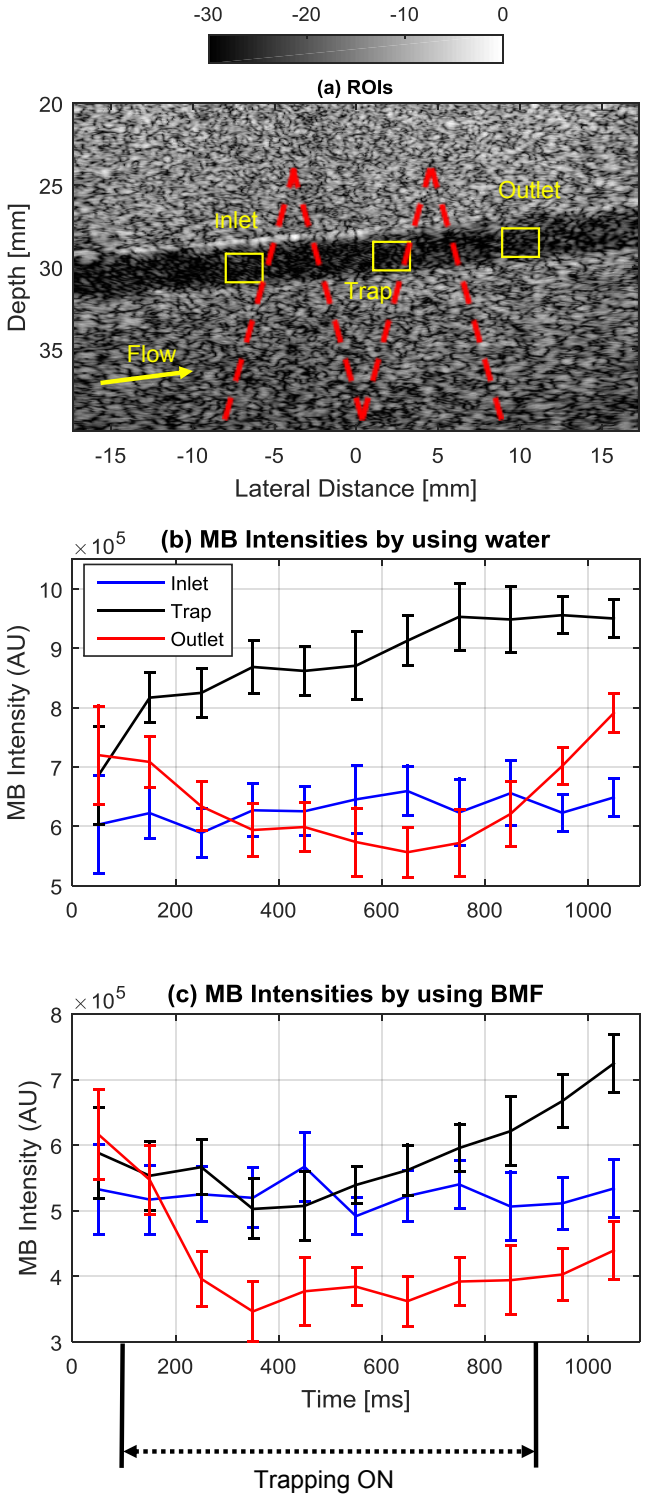


Fig. 3. (a) ROIs. Temporal MB intensity evolutions in water (b) and BMF (c) with identical acoustic trap beams interleaved.

line starting from the shallow depth to deep regions. This removes the need to repeatedly focus at different depths [20]. When targeting deep vessels with the plane-wave based acoustic trap, shallow tissues are subject to higher-level exposures because of the lack of transmission focus and depth-dependent attenuation. Experiments in this study simulate a deep vein scenario, results show that accumulating bubbles with optimized ultrasonic beams is feasible within exposure limits for ultrasound diagnostic imaging.

## V. Conclusions

Acoustic MB trapping in BMF with moderate exposure conditions was achieved but different from the control in water, with delayed response to the ARF beam and relatively suppressed increase of image intensity. The flow rate of 28 mL/min is within the upper band of venous flows. Results indicate that the acoustic trap could benefit thrombolysis in deep veins, where trapped bubbles would act as cavitation nuclei and locally amplify bio-mechanical effects.

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