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Two-Dimensional Microbubble Manipulation by Mechanically Controlled Ultrasound Focus

超音波焦点位置の制御による
マイクロバブルの二次元マニピュレーション

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1. Introduction

Microbubbles (MBs) are widely used as contrast agents in ultrasound diagnostic imaging due to its eminent responsiveness to several MHz band, which is generally used in clinical ultrasound applications. In recent years, researchers are trying to apply MBs not only to ultrasound contrast agent but also ultrasound drug delivery system (DDS), intended for visualization of dose and high accuracy medication to the affected part [1]. For clinical application of MB-DDS, techniques that accumulating MBs selectively on target point and releasing drugs carried by MBs should be established.

Typical MB-DDS techniques adopt ligand – receptor linking as accumulation method of MBs, which is specific binding between a ligand body and a receptor body [2]. After accumulation of MBs, focused ultrasound irradiation is perfomed to cause cavitation to releasing drugs, but ultrasound irradiation may cause moving accumulated MBs away from the target point because ultrasound intensity can be much bigger than ligand – receptor linking strength, resulting in lower effeciency of targeting drug delivery. To maximizing efficiency of MB-DDS, it is crucial to develop contactless manipulation method to accumulate MBs without depending on regand – receptor linking.

The purpose of this study is to investigate acoustic manipulation of MBs using focused ultrasound by moving the focus of ultrasound mechanically, and to find the key to control MBs.

2. Materials and Methods

A schematic view of the experimental setup is shown in **Fig. 1**.

2.1. Preparation of MBs

In this study, we used MBs called Sonazoid® (Daiichi-Sankyo), Perfluorobutane (PFB: C_4H_{10}) gas coated with phospholipids. Sonazoid was diluted with distilled water according to the attached protocol, then diluted Sonazoid solution 5-50 times with distilled water.

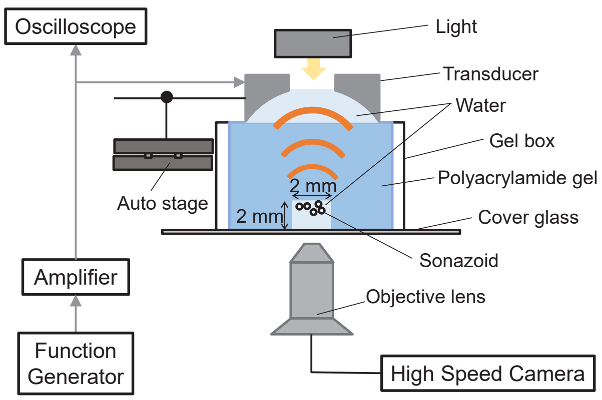

Fig. 1 Experimental setup

2.2. Experimental setup for ultrasound exposure

Bubbles in the ultrasound wave field are subjected to the primary Bjerknes force which is an acoustic radiation force represented by product of MBs' volume and gradient of acoustic pressure [3]. From the relation between the focused ultrasound's frequency and MBs' resonant frequency, small MBs which have higher resonant frequency can be trapped at the antinode or focus of the focused ultrasound field.

MBs were trapped by focused ultrasound (2.04 and 5.46 MHz center frequency, CW), which were irradiated with a function generator (WF1974, NF Corp.), amplified with a wave amplifier (2100L, Electronics & Innovation), and concave transducer (PZT ceramics, both Diameter and focus length: 40 mm). Amplified input was monitored with an oscilloscope (WaveSurfer 24Xs-A, Teledyne LeCroy). Time-lapse behaviors of MBs were observed with a high speed camera (MotionPro X3, IDT), coupled with an inverted microscope (TE2000-E, Nikon). Transducer was controlled with an auto stage (KXG06030-F, Suruga Seiki).

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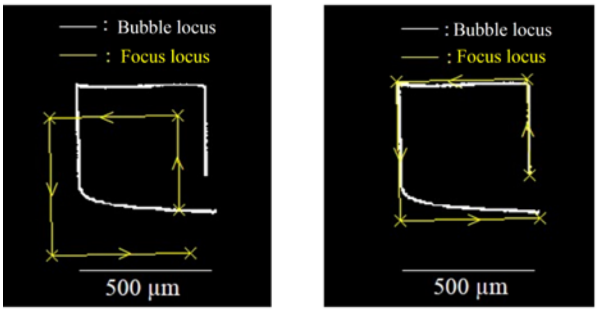
3. Results

Fig. 2 shows preliminary manipulation result of MBs using focused ultrasound with a center frequency of 2.04 MHz and peak negative pressure of 5.9 kPa. Yellow and white lines represent the locus of focal point of ultrasound and the bubble locus, respectively. Fig. 2 (a) shows the absolute locus relations between focal locus and bubble locus, while Fig. 2 (b) shows relative locus of focal locus and bubble locus. When comparing absolute locus of bubble locus and focal locus, bubble locus shifted to upper right in 50 μm (Fig. 2 (a)), while relative loci were nearly corresponded (Fig. 2 (b)).

Fig. 3 shows precise manipulation result of MBs using focused ultrasound with a center frequency of 5.46 MHz and peak negative pressure of 7.6 kPa. Yellow and white lines represent the locus of focal point of ultrasound and the bubble locus, respectively. **Fig. 4** shows trapped MBs at the focus of the focused ultrasound in Fig. 3. MBs were moved in an arc on the first and last straight path, while they moved in almost straight line on the second straight path (Fig. 3). Trapped MBs at the focus of focused ultrasound was 3 MBs (Fig. 4), and MBs' cluster was moved along the locus of the focus with rotation.



(a) Absolute locus (b) Relative locus

Fig. 2 The square locus manipulation of bubble and focus. Ultrasound frequency = 2.04 MHz, peak negative pressure = 5.9 kPa.

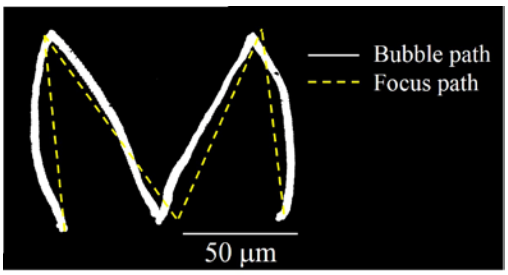


Fig. 3 The "M" shape locus manipulation of bubble and focus. Ultrasound frequency = 5.46 MHz, peak negative pressure = 7.6 kPa.

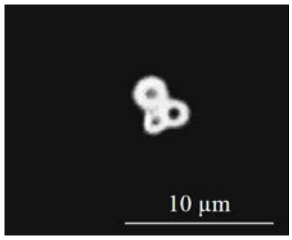


Fig. 4 MBs cluster trapped at the focal point

4. Discussion

From the square shape and "M" shape manipulation experiment, MBs can be manipulated in two-dimensional plane by moving the focus of ultrasound mechanically, forming bubble cluster. The difference between the locus of focus and that of bubble cluster was assumed that was caused by refraction of the ultrasound beam at the interface between water and gel and secondary Bjerknes force from peripheral MBs.

Taking into account the order difference between the locus of the focus and the beam width (**Fig. 5**), the locus shift was sufficiently less (≃ 1/10) than ultrasound resolution. Therefore, this method can manipulate MBs accurately.

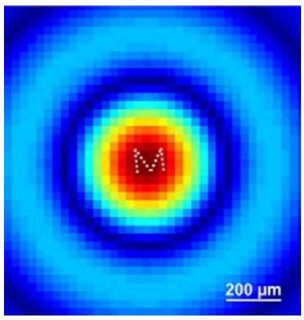


Fig. 5 Comparison of manipulated path and focal point width.

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