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Production of local acoustic radiation force to constrain microcapsules from diffusion in blood vessel

生体内マイクロカプセルの拡散抑制のための局所的音響放射力形成

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1. Introduction

Microcapsules or microbubbles collapse upon exposure to ultrasound near their resonance frequency. The phenomenon has been identified as a basic method for drug delivery [1,2]. Making use of sonoporation [3], the existence of capsules (or bubbles) improves the introduction efficiency to affect the target area. While the lifetime of the microbubbles is several minutes, the microcapsules are thought to be better for use with various types of delivery. However, because of the diffusion of capsules after injection, it is difficult to deliver capsules to desired target area. If the behavior of capsules could be controlled, the introduction efficiency would be enhanced. Then we have ever reported our attempt to propel microcapsules in water owing to an acoustic radiation force [4,5], which is a physical phenomenon where an acoustic wave pushes an obstacle along its direction of propagation. We have elucidated the conditions in sound pressure, flow velocity and diameter of capsules for active path selection of capsules in an artificial blood vessel [6]. Then we have used the diameters of capsules ranged from 65 to 73 µm, which size is not to be applied *in vivo*. Considering that an acoustic radiation force is proportional to the cube of the size of a capsule, we have investigated with plane wave of ultrasound and smaller size of capsules for active path selection.

2. Theory

Assuming spherical capsules or bubbles, an acoustic radiation force [10] acts to propel the capsules in the direction of acoustic propagation as per the following equation,

$$F_{ac} = \frac{4}{3}\pi R_0^{\ 3} A \frac{P^2}{\rho c^2}, \tag{1}$$

where R_0 is the average capsule radius, P is the sound pressure, and r is the density of the medium.

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A is a constant which is derived from ρ and the density of capsules.

When the microcapsules are placed in flow, a capsule should receive a flow resistance F_d. If the acoustic radiation force is greater than the flow resistance, the trajectory of the capsule is curved, as shown in Fig.1.

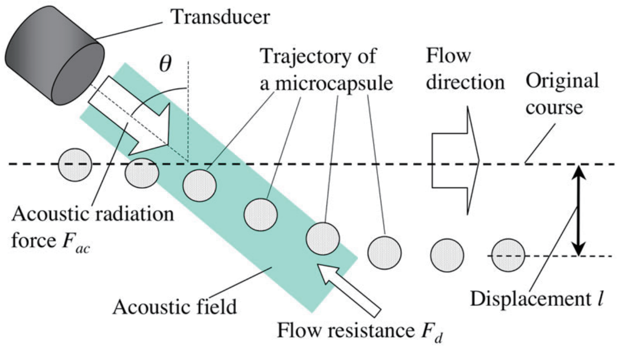

Fig.1. Trajectory of microcapsule in flow under ultrasound emission.

At larger value of angle θ in Fig.1, a capsule passes through the acoustic field for a longer period causing a larger displacement from the original course. In Fig.1, although the shape of the acoustic field is expressed as a square, it is measured before the calculation of theoretical displacement.

3. Experiment

We used the F-04E microcapsule, which has a shell made of polyvinyl chloride (PVC), a specific gravity of 0.0225, and an average diameter of 4 µm. It contains isobutene inside and is stable in room temperature. We selected only those microcapsules with a diameter less than 20 µm. We also have prepared an artificial blood vessel made of polyethylene glycol (PEG), including a Y-form bifurcation with inner diameter of the paths was 2 mm. The blood vessel was placed in the bottom of a water tank, which was filled with water. As shown in Fig.2, the observed area was recorded optically using an inverted microscope (Leica, DMRIB).

In Fig.2, the relationship between focal areas of ultrasound and the bifurcation is shown. The axis of the transducer was set at 40 degrees to the x-axis and θ deg to the z-axis to prevent physical interference between the transducer and the edge of the water tank. The transducer included a flat ceramic disc with a diameter of 25 mm to emit plane wave of ultrasound.

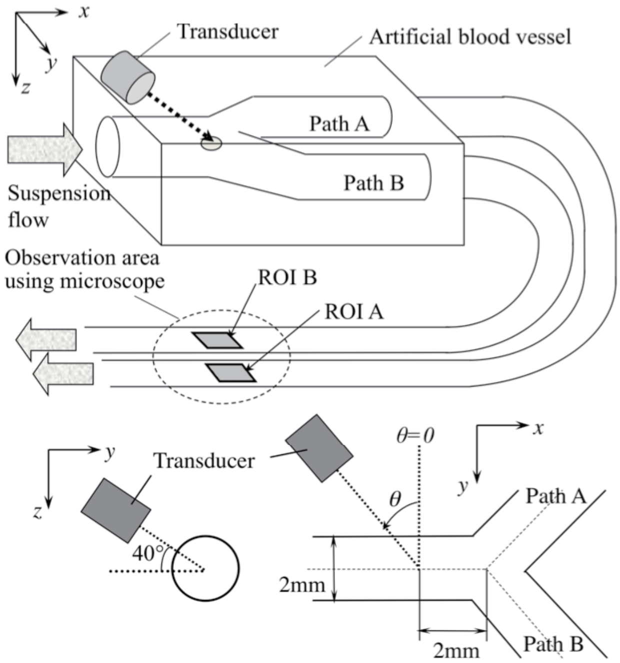

Fig.2. Relationship between focal points of ultrasound and the bifurcation area.

4. Result

When ultrasound was emitted, more capsules entered path B than path A, whereas no significant difference was observed without ultrasound emission. To evaluate the amount of capsules that passed through each path, we extended the two paths using semitransparent tubes and established the observed area, where both paths were observable in a single view. To measure amount of microcapsules, we established two square regions of interest in each path (ROIs A and B) and calculated the average brightness. The brightness of a region decreases depending on the number of capsules present. Thus, we defined the shadow index σ using the following equation to determine the number of capsules in each ROI,

$$\sigma = \left(REF - \sum_{x}\sum_{y} f(x,y) \right) / REF \qquad (2)$$

where f is the brightness of the ROI and REF is the summation of brightness in the absence of capsules in the ROI.

We measured the shadow indices in two ROIs upon emission of sinusoidal ultrasound with a frequency of 0.5 and 2 MHz, and a flow velocity of 5, 10 and 20 mm/s. Fig.3 shows the ratio in shadow index of ROI B to the summation versus the sound pressure at the bifurcation, where θ was fixed as 45 degree. In Fig.3, a ratio more than 50% indicates that more capsules passed through path B than path A. When the frequency is 2MHz, clear capsule selection to path B was confirmed.

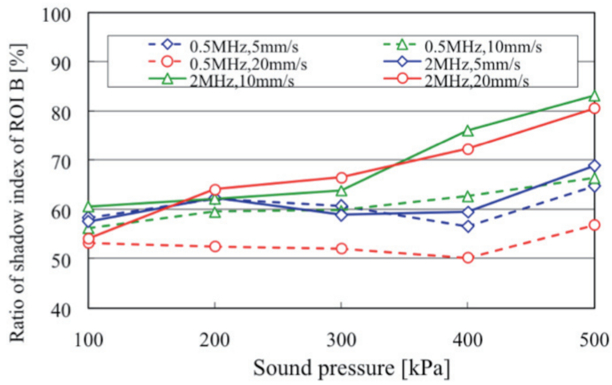

Fig.3. Ratio in shadow index of ROI B to the summation (ROI A and B) with $\theta = 45$ degree.

From the result, using higher sound pressure than 400kPa, 80% of capsules were introduced to a desired path, which result is much progressed than our previous attempt [6] using a focused ultrasound. For active path selection of capsules, higher pressure, higher frequency and plane ultrasound should be required.

5. Conclusion

In this study, we realized active control of microcapsules of micrometer size in an artificial blood vessel. We confirmed that capsules with a diameter less than 20 µm were directed into the desired path. For further analysis, the precise conditions necessary to realize active control of capsules in a complicated shape of blood vessel should be elucidated. Also we are going to apply to *in vivo* experiment.

Acknowledgment

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