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Experimental study to produce multiple focal points of acoustic field for active path selection of microbubbles through multi-bifurcation

多分岐流路における微小気泡の経路選択制御のための複数焦点形成法の検討

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1. Introduction

Microbubbles are known to form aggregates when they are put into an ultrasound field because secondary Bjerknes force, which acts attractive or repulsive between neighboring bubbles, is produced by local condition of oscillation. The applications of this phenomenon are reported to sonoporation [1] and capillary embolization [2]. We have previously reported our attempt to propel microbubbles in flow [3,4] by a primary Bjerknes force, which is a physical phenomenon where an acoustic wave pushes an obstacle along its direction of propagation. We have elucidated the conditions of ultrasound and flow velocity for active path selection of aggregates of bubbles in an artificial blood vessel [5]. However, the shape of the blood vessel was Y-form therefore too simple to be considered *in vivo*. It is unpractical to use multiple transducers to produce the same number of focal points because single element transducer cannot produce more than two focal points. In this study, we introduced a complex artificial blood vessel according to a capillary model and a 2D array transducer to produce multiple focal points for active control of microbubbles in flow.

2. Theory

Assuming the shape of the aggregates of bubbles is spherical, a primary Bjerknes force [3] acts to propel an aggregate in the direction of acoustic propagation as per the following equation,

$$F_{ac} = \pi r^2 Y_p P , \qquad (1)$$

where P is the mean energy density of the incident wave, Y_p is a dimensionless factor called the radiation force function that depends on the scattering and absorption properties of the bubbles, and r is the equivalent radius of the aggregate of bubbles.

When the aggregates of bubbles are placed in flow, a driving force of flow affects an aggregate. Then, the aggregate should receive a resultant force consit of the primary Bjerknes force and the driving force of flow. **Fig.1** shows the force direction of the aggregate receiving. If the primary Bjerknes force is greater than the driving force of flow, at smaller value of angle θ in **Fig.1**, an aggregate should be transferred against the flow.

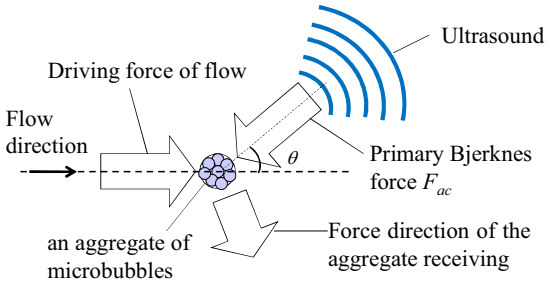

Fig.1 Primary Bjerknes force to propel an aggregate of microbubbles in flow

3. Experiment

We used the F-04E microbubble [3], which has a shell made of poly (vinyl chloride) and an average diameter of 4 μm. We selected only those microbubbles with a diameter less than 20 μm.

Fig.2 shows the position configuration between transducers and the artificial blood vessel. We have prepared artificial blood vessels according to a capillary model, which were made of poly (vinyl alcohol) (PVA) by grayscale lithography method, with the cross-section diameter between 0.5 to 2 mm. The blood vessel was placed in the bottom of a water tank, which was filled with water.

We set two transducers T_{ag} and T_{in}, which positions were adjusted by *xyz*-stage with 0.1 mm precision, to induce stream of bubbles to Path A. T_{ag} was to form aggregates of bubbles, which included a concave ceramic disc to emit focused wave of ultrasound with the central frequency of 7 MHz,

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and the element diameter was 12 mm. The other hand, T_{in} was to induct the aggregates to Path A, which was a 2D array transducer including air-backed 64 PZT elements with the aperture of 23.9 x 23.9 mm^2, the size of each element of 2.9 x 2.9 mm^2, and the pitch of the elements of 3.0 mm, respectively. The driven frequency was 3 MHz. The axis of transducer T_{in} was set at θ = 45 deg from the axis of T_{ag}. Both transducers were positioned at the distance of 60 mm from the observation area.

We used an optical microscope (Omron KH-7700) to observe four paths originating from consecutive two bifurcations.

We set two focal points by T_{in} at P0 located on the first bifurcation of the blood vessel and P1 located on 3 mm upper stream from the second bifurcation connected to Path A and B. Then, we prepared two types of acoustic fields of T_{in}. **Fig.3** shows the sound pressure distribution along *x*-axis from a view point of T_{in}, which was measured at the distance of 53 mm from the surface of T_{in}. Two acoustic fields, which the main beam width was about 2 mm, were targeted at P0 and P1. In **Fig.3**(b), the main beam was seem to be measured lower because of directional characteristics of hydrophone.

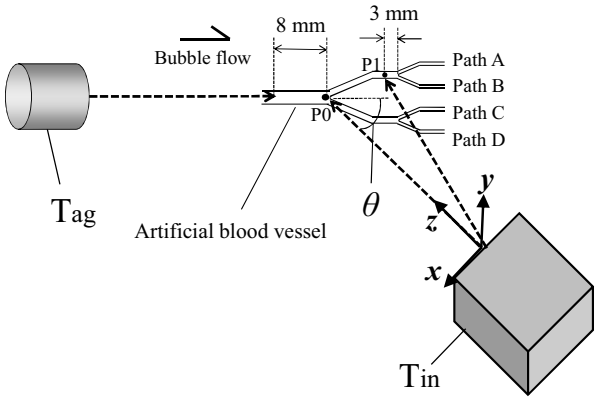

Fig.2. Position configuration between transducers and the artificial blood vessel

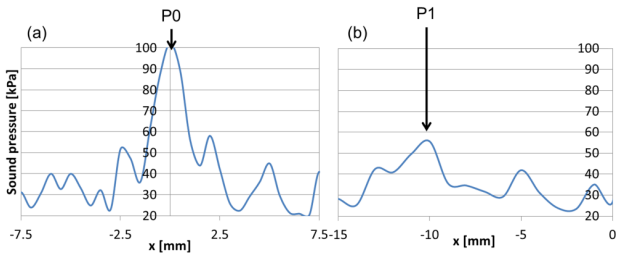

Fig.3. Sound pressure distribution along x-axis from a view point of T_{in}, targeted at P0 (y = 0) (a), at P1 (y = -4) (b)

4. Results

Fig.4 shows the microscopic image of the bifurcation upon emission of sinusoidal ultrasound with T_{ag} maximum sound pressure of 400 kPa, and T_{in} of 100 kPa with 3 MHz and a flow velocity of 20 mm/s. In **Fig.4**(a), when ultrasound was emitted from T_{ag}, we confirmed streaming of aggregates of microbubbles entered to Path B and C, mainly. In **Fig.4**(b) Additional ultrasound to P0 from T_{in}, clearly path selection to Path A was confirmed. In **Fig.4**(c), switched pattern of acoustic field to P1, the aggregates also entered to Path A.

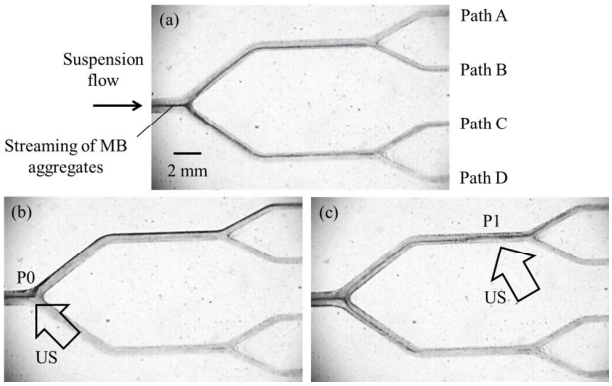

Fig.4 Microscopic images of the bifurcation with T_{ag} emission (a), with T_{ag}+T_{in} to P0 (b), with T_{ag}+T_{in} to P1 (c)

5. Conclusion

In this study, we realized active control of microbubbles in an artificial blood vessel according to capillary model with multiple focal points of ultrasound. We confirmed that bubbles entering the desired path with both focal points. For further analysis, the precise conditions necessary to realize active path switching of bubbles alternately should be elucidated. In the next step, we are going to measure quantitatively for precise evaluation. Also we are going to apply to *in vivo* experiment.

Acknowledgment

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