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3-dimensional active control of microbubbles and its observation by spatio-temporal control of acoustic field
超音波音場の時空間制御による微小気泡の 3 次元動態制御とその観測

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1. Introduction

Recently efficiency of therapeutic methods using thermal and non-thermal effects of ultrasound in combination with microbubbles are expected. However, because of the dispersion of injected microbubbles in human body, there was a problem of low dose efficiency of microbubbles to affect in the target area. Therefore we have proposed to control microbubbles by acoustic radiation forces in order to increase the local concentration of microbubbles. Active control of microbubbles will reduce the side effect, which caused by unwanted microbubbles, and the amount of drug. In the previous experiments we have investigated the methods for active induction of microbubbles at a bifurcation in artificial blood vessels by forming multiple focal points [1,2] with phase variations [3] using a matrix array transducer. However, we have observed the behavior of microbubbles from the bottom of a water tank as projection images despite the acoustic fileds were in three-dimension. In this paper, we report a new method to control and to observe three-dimensional behavior of microbubbles including two high-speed cameras.

2. Experimental Method

Fig.1 shows the experimental setup to control and to observe three-dimensional behavior of microbubbles in a straight path, which was made of poly(ethylene glycol) monomethacrylate (PEGMA) with the square cross section of 2.0 x 2.0 mm, and was fixedly floated from the bottom of a water tank with filled water. The observation area was focused and adjusted in the center of the path, which is defined as (x_c, y_c, z_c) = (0, 0, 0) in the camera coordinate, by two high-speed cameras (Photron, 1024-PCI) to observe from the side and bottom of the path. We used a matrix array transducer, which has 64 elements with a central frequency of 3 MHz. Then a point on the axis of the transducer, which is defined as (x_{Tr}, y_{Tr}, z_{Tr}) = (0, 0, d) in the transducer coordinate, was relatively adjusted in the camera coordinate with elevation angle θ [deg], azimuth angle φ [deg], and distance d [mm], where the array surface was entirely soaked below water.

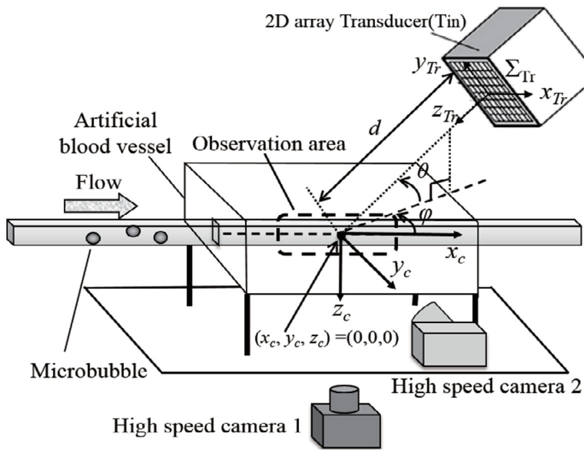

Fig.1 Experimental setup.

Fig.2 shows the evaluation method of local concentration of microbubbles in the path. We have established three regions of interest of A, B, and C to distinguish the presense of microbubbles, where the lengths of X_R, and Y_R were determined by frame rate and flow velocity, and one third of the width in the path, respectively. The amount of microbubbles, which pass through each regions, was calculated using eq. (1), where I_{A0} is initial average brightness in the region A, I_A is average brightness in the region A during the experiment, α is the conversion factor, and σ_A is the occupied area of microbubbles in the region A, respectively. Induction rate to the region A is calculated as ε_A using eq. (2). The similar calculations are applied to other regions [2].

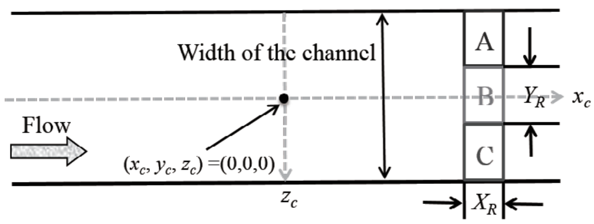

Fig.2 Definition of the regions A, B, and C in the path.

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$$\sigma_A = \alpha \left| I_{A0} - I_A \right| \quad (1)$$

$$\varepsilon_A = \frac{\sigma_A}{\sigma_A + \sigma_B + \sigma_C} \times 100\ [\%] \quad (2)$$

3. Results

First we produce an acoustic field of two focal points with opposite phase [3] in the position of (x_{Tr}, y_{Tr}, z_{Tr}) = (0, 2.5, 60) and (0, -2.5, 60) mm with the maximum sound pressure of 280 kPa-pp in each peak. Fig.3 shows the distribution of sound pressure in the plane of z_{Tr} = 60 mm to apply to the following experiment.

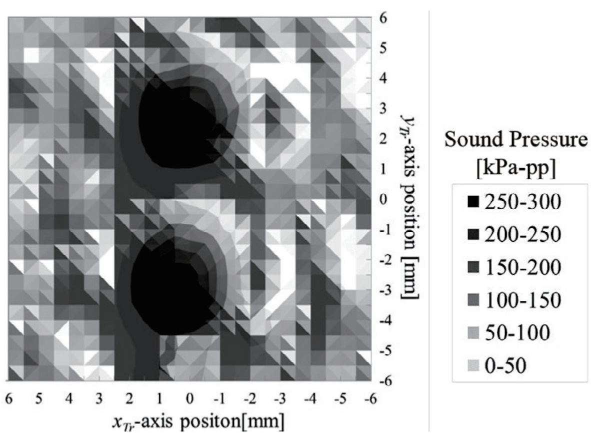

Fig.3 Distribution of sound pressure of two focal points with opposite phase.

We set the transducer with the elevation angle θ = 30 deg, the azimuth angle φ = 45 deg and the distance d = 60 mm in Fig.1 to produce the above-mentioned acoustic field to form two focal points. Fig.4 shows the representative images observed using the camera #2 after 7.5 sec of injection of microbubbles suspension (F-04E, Matsumoto Oil) with concentration of 1.57 μl/ml and a flow velocity of 30 mm/s. In Fig.4 (a), (b), and (c) the position of (x_{Tr}, y_{Tr}, z_{Tr}) = (0, 0, 60) mm were corresponded to (x_c, y_c, z_c) = (0, 0, 1.5), (0, 0, 0), and (0, 0, -1.5) mm, respectively. In these images microbubbles streams were clearly confirmed to concentrate towards each of three regions against gravity.

Fig.5 shows the comparison of the induction rates ε_A, ε_B, and ε_C through above experiments. The horizontal axis indicates the position of the transducer, which corresponds to Fig.4. These results indicate that the active levitation of microbubbles in flow was possible with a significant difference in the induction rates. Thus, by combining our preceding results of active path selection and active induction of microbubbles, three-dimensional active control of microbubbles would be realized.

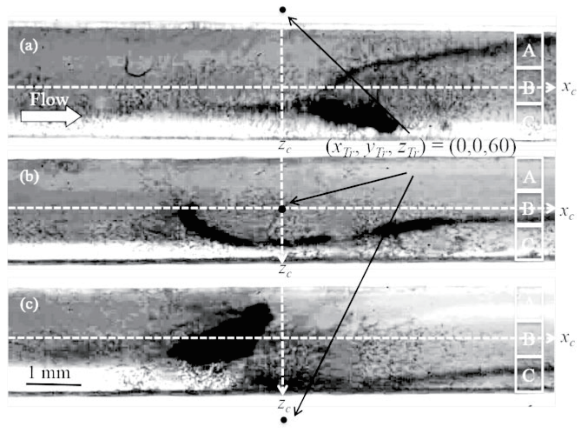

Fig.4 Representative images observed using the camera #2 (side view) after injection of microbubbles suspension with three positions of the transducer.

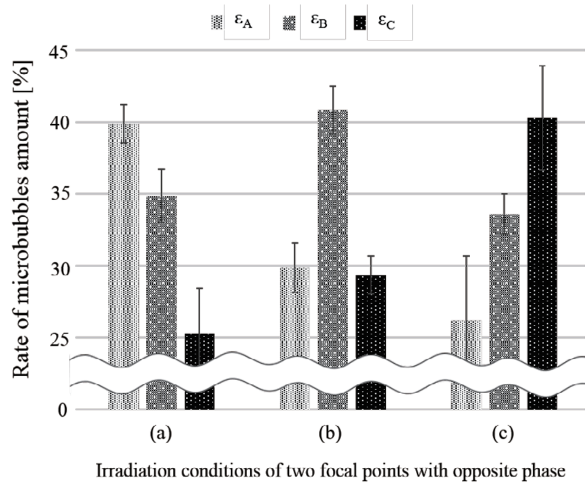

Fig.5 Comparison of the three induction rates in the different positions of the transducer.

4. Conclusions

We have realized an active levitation of microbubbles against gravity and confirmed by using three-dimensional observation system. Forming two focal points with opposite phase, we have succeeded to control microbubbles in the vertical position in an straight path as well as our preceding experiments to control in the horizontal position. By composing three-dimensional acoustic field to fit to the objective blood vessel, we are going to realize three-dimensional active control of microbubbles through multiple bifurcations.

References

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