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Active induction of microbubbles in flow by time-shared production of two focal points with opposite phase

逆位相 2 焦点音場の時分割形成による流路内微小気泡の能動的誘導

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1. Introduction

To improve the feasibility of local treatment using microbubbles with ultrasound e.g. HIFU therapy or drug delivery, because of the diffusion of *in vivo* microbubbles, we have reported our attempts for active path selection [1] of microbubbles by acoustic radiation forces. Controlling the behavior of the microbubbles physically, the area of side effect caused by unwanted microbubbles would be decreased, which has a possibility to reduce the amount of not only microbubbles but also drug. In the previous experiments we have investigated to control microbubbles by forming multiple focal points of continuous wave using a matrix array transducer [2,3]. However, because those focal points were located to sweep microbubbles along the slope of sound pressure, it was difficult to concentrate microbubbles against the direction of flow. In this paper, we report our experiment of active induction of microbubbles by producing time-shared acoustic field with phase variation.

2. Experimental Method

We prepared the suspension of microbubbles (bubble liposomes), which were produced with poly(ethylene glycol)-modified liposomes and perfluoropropane gas. Those were prepared by a reverse-phase evaporation method [4] with an average diameter of 0.5 μm.

Fig.1 shows the experimental setup. A thin channel, which was made of poly(ethylene glycol) monomethacrylate (PEGMA) with the thickness of 2 mm and the width of 10 mm, 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 chanel by an optical microscope (Omron KH-7700) from the bottom of the tank. The axis of the matrix array transducer [2,3], which central frequency is 1 MHz, was set to cross the center of the observation area with the angle θ = 40 deg, φ = 0 deg and the distance d = 80 mm, where the array surface was entirely soaked below water.

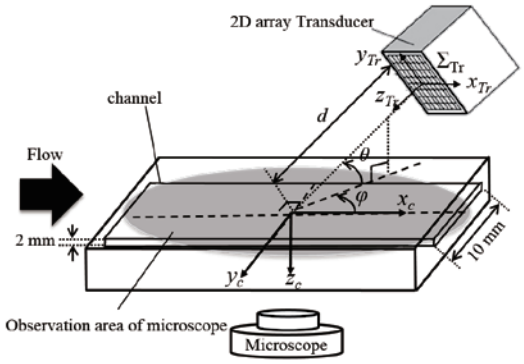

Fig.1 Experimental setup.

To concentrate microbubbles in flow, we have considered to form two focal points, where microbubbles are going to be propelled away from them to form the centerline in the middle of them. Fig.2 shows the measurement results of sound pressure distribution with (a) in-phase and (b) opposite phase, where the distance of two points were 8 mm, the distance from the transducer was 80 mm, and applied voltage to the transducer was 14 V-pp. Though two focal points were merged to form one greater point in Fig.2 (a), the line of absolute sound pressure of 0 kPa was produced in the middle of the two points in Fig.2 (b), where microbubbles are expected to flow along the line.

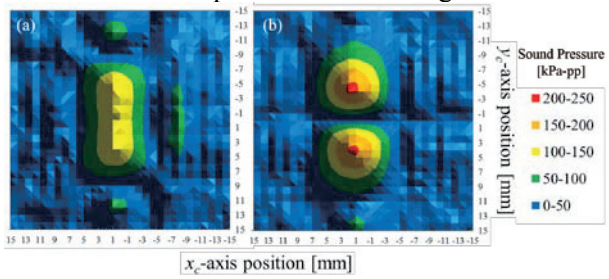

Fig.2 Distributions of sound pressure of (a) in-phase, and (b) opposite phase.

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Fig.3 (a) shows the positions where the pair of the two focal points were produced in the thin channel. To affect acoustic force to microbubbles with wider area without increasing sound energy, the positions of the pairs were changed periodically from P_1 to P_5. The transition was set with 500 ms period and shown in Fig.3 (b), which we defined as the time-shared acoustic field.

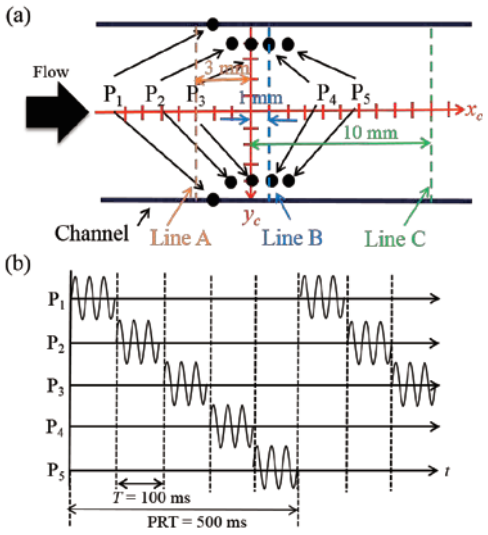

Fig.3 Production of time-shared acoustic field, (a) positions of the pair of two points in the channel, and (b) the transition of ultrasound emission for each pair.

3. Results

Fig.4 shows the images of the observation area after 7.0 s of injection of microbubbles suspension (concentration of 0.05 mg lipid/ml) with a flow velocity of 30 mm/s, where maximum sound pressure was 300 kPa-pp. In Fig.4 (a), with in-phase between the two points, most microbubbles were trapped in the middle of the acoustic field, which indicates that acoustic field with high sound pressure prevented microbubbles to move. On the other hand, with opposite phase between two points as Fig.4 (b), streamline of microbubbles was clearly confirmed in the middle of the pair of two focal points, where most microbubbles already passed through the observation area.

Fig.5 shows the distribution of brightness along the line A (x_c = -3), line B (x_c = 1), and line C (x_c = 10) in Fig. 4, respectively. Here lower brightness indicates more microbubbles in the channel. Using the in-phase acoustic field, most microbubbles cannot reach to the line B. Thus the opposite phase was effective for active induction of microbubbles in the thin channel, which can be applied to various shapes of flow path.

4. Conclusions

We have produced time-shared acoustic fields including the pairs of two focal points with phase variation using a matrix array transducer. We confirmed that microbubbles were induced between the two focal points with opposite phase, which indicates the possibility of active induction of *in vivo* microbubbles.

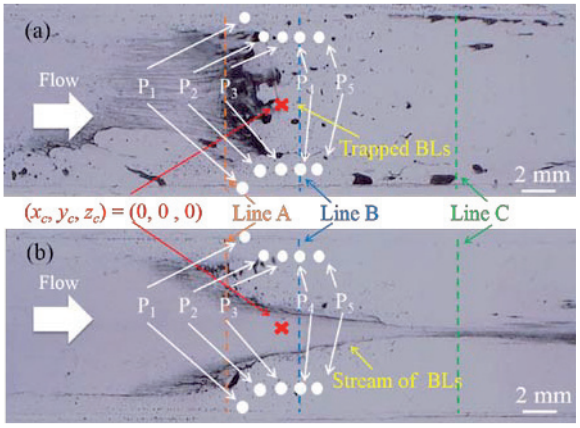

Fig.4 Microscope images with suspension flow of microbubbles under the exposure of time-shared acoustic field with (a) in-phase, and (b) opposite phase.

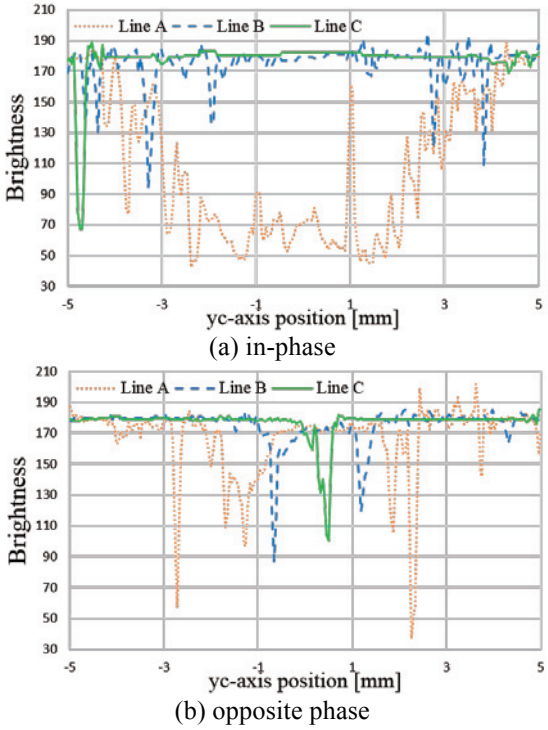

Fig.5 Brightness distribution of lines A to C shown in Fig.4.

References

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