3P5-6

Theoretical analysis of retention distribution of bubble-surrounded cells with tempo-spatial division emission

時空間分割照射による細胞-微小気泡凝集体の捕捉分布の理論的解析

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1. Introduction

Recently, cellular immunotherapy [1] has been recognized to be a new cancer therapy to reduce side effects as relapse and metastasis inhibitory effect, where the therapeutic cells are injected into the bloodstream. Because of the dispersion of the cells in blood flow, there is a fundamental problem of the limitation of accumulation at the target area. To address this problem, a breakthrough idea has been proposed for *in vivo* delivery, which produces bubble-surrounded cells (BSCs) by attracting lipid bubble [2] as microbubbles to the surface of cells to reduce their density and to be propelled using an acoustic radiation force. We confirmed that BSCs was retained by a single focal point acoustic field under flow condition [3]. However, in order to realize the cell delivery system *in vivo*, it is necessary to ascertain the condition of changing the acoustic field shape since a single focal point is effective only limited area. Further, it is necessary to simulate the retention of BSCs in order to increase the quantitative predictions and experimental results with high reliability of their acquisition. However it was unknown in terms of modeling retention of BSCs by ultrasound. In this study, we introduce a theoretical model of BSCs retention to compare with experimental results.

2. Theory

Fig.1 shows the model of the retention theory of BSCs by acoustic radiation force of ultrasound. Acoustic radiation force F_a is calculated by considering the King formula [4] and Yoshioka Kawashima theory [5]. Further, when the BSCs under fluid is subjected to external force, it is received a reverse force F_d. Calculate the velocity and displacement of the BSCs in each time step 10 μs from the resultant force of F_a and F_d. This calculation is performed in the range of half-width w of the sound waves.

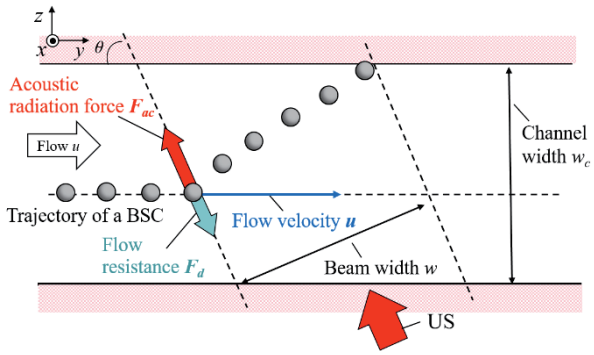

Fig.1 Trajectory of a BSC in flow under ultrasound exposure.

3. Methods

Fig.2 shows the experimental setup to observe the behavior of the BSCs under ultrasound exposure. A 2-dimentional array ultrasound transducer with 128 elements (central frequency of 3 MHz, maximum sound pressure $P \leqq 400$ kPa-pp) was set with elevation angles of θ = 60 deg. Distances between the channel and the transducer are l = 60 mm. By providing a different phase to each element of the transducer, a focal point can be electrically produced in arbitrary position. The method is defined as a tempo-spatial division emission. A thin channel, which was made of poly (vinyl alcohol) (PVA), was had a square cross-section of width 1.0 mm×thick 1.0 mm. The sound wave was started emitting after 30 s of the injection of BSCs suspension 0.5 mL at a flow velocity u = 10 mm/s in the artificial blood vessel. The behavior of the BSCs was recorded using fluorescence

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microscope (Olympus, BXFM) and a digital camera (Olympus, DP74), was measured captured area by using the analysis software.

Next, Fig.3 shows the model of the retention of the acoustic field with multiple focal points. By introducing the tempo-spatial division emission, it is possible to form an acoustic field with pseudo-multiple focal points with the same amount of energy. Therefore it is possible to know the trend of the retention by simulating the trend of the maximum displacement *l*.

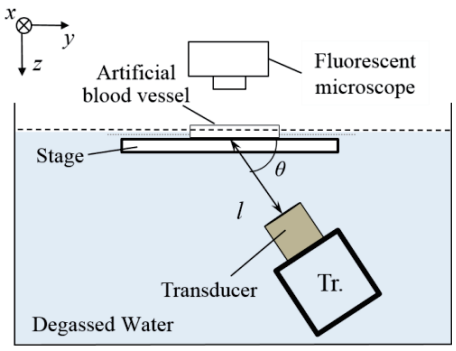

Fig.2 Experimental setup to expose ultrasound to suspension of BSCs in an artificial blood vessel.

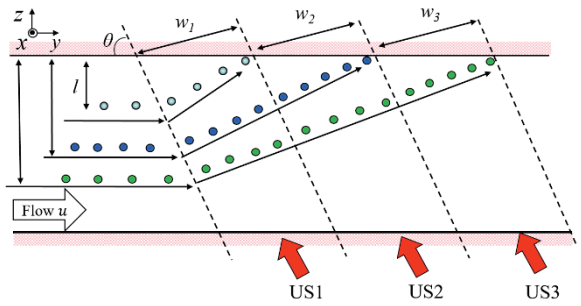

Fig.3 The model of the retention of the acoustic field with multiple focal points.

4. Results

Fig.4 shows the microscopic images, which retained BSCs with maximum sound pressure 400 kPa-pp (exposure time of 30 s). BSCs were retained extensively by forming multiple focal points.

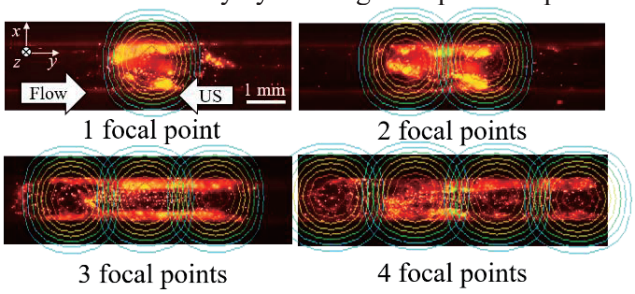

Fig.4 Microscopic image when BSCs were retained.

Fig.5 shows the results of retained area in BSCs versus number of focal points. The transition rate of the focal point in the tempo-spatial division emission was 100 mm/ s.

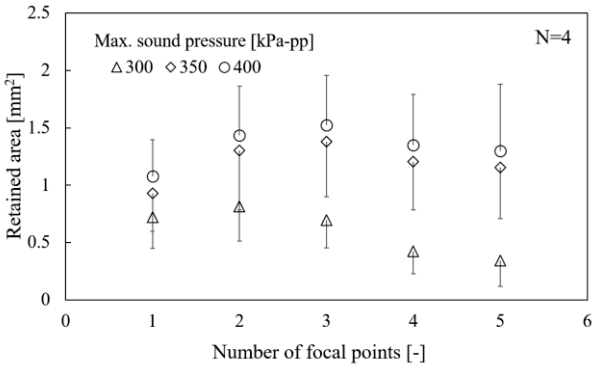

Fig.5 Retained area in BSCs versus number of focal points.

Finally, Fig.6 shows a comparison between the maximum displacement of the simulation and retained area obtained in the experiment. Since the correlation coefficient was 0.778, the correlation was suggested between the retained area and maximum displacement of the wall.

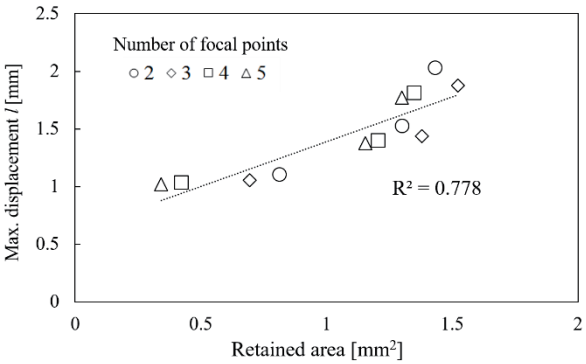

Fig.6 Comparison between the maximum displacement of the simulation and retained area.

5. Conclusion

We have verified retained area in BSCs with various conditions of maximum sound pressure and focal points. It was confirmed that the retained area was the largest in three focal points when the maximum sound pressure was 350 and 400 kPa-pp. We also constructed a theoretical model of the retention of BSCs by acoustic radiation force of the ultrasonic.

References

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