1Pb5-13

Behavior simulation of bubble-surrounded cells in flow under exposure of traveling wave

進行波音場中の流路における細胞–微小気泡凝集体の挙動シミュレーション

Shinnosuke Araki[1†‡], Ryota Akutsu[1], Takumi Chikaarashi[1], Daiki Omata[2], Ryo Suzuki[2], and Kohji Masuda[1] ([1]Graduate School of Bio-Application and Systems Engineering Tokyo Univ. of Agriculture and Technology; [2]Faculty of Pharma-science, Teikyo Univ.)

荒木信乃介[1†‡]，阿久津亮太[1]，近嵐匠[1]，小俣大樹[2]，鈴木亮[2]，桝田晃司[1]

([1]東京農工大学大学院生物システム応用科学府, [2]帝京大学薬学部)

1. Introduction

Recently, cellular immunotherapy has been recognized to be a new cancer therapy to reduce side effects as relapse and metastasis inhibitory effects, 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, we have proposed a method for *in vivo* delivery, which produces bubble surrounded cells (BSCs) by attracting microbubbles to the surface of cells to reduce their density and to be propelled using an acoustic radiation force. Then we experimentally confirmed that BSCs in flow can be retained on a vessel wall under various ultrasound emission conditions [1,2] including a multi-foci acoustic field, which showed the possibility of effectively retaining BSCs. However, it is necessary to simulate the retention of BSCs to increase the quantitative predictions and experimental results with high reliability of their acquisition. In our previous research [3], we constructed a two-dimensional simulation, which was insufficient to reproduce the behavior the BSCs in flow. In this study, we propose to simulate the dynamic control of BSCs in a three-dimensional space and compare it with experimental results.

2. Method

Fig.1 shows a theoretical model of BSCs in flow retained on vessel wall under exposure of travelling ultrasound. In this simulation, acoustic radiation force acting on the microbubbles attached to cells is calculated using time-averaged product of microbubble volume and acoustic pressure gradient [4]. First, the time variation of microbubble radius was derived using Rayleigh-Plesset equation [5,6,7]. Next, acoustic radiation force on a BSC was calculated with the time average of volume of attached microbubbles by taking spatial distribution of sound pressure, viscosity coefficient representing

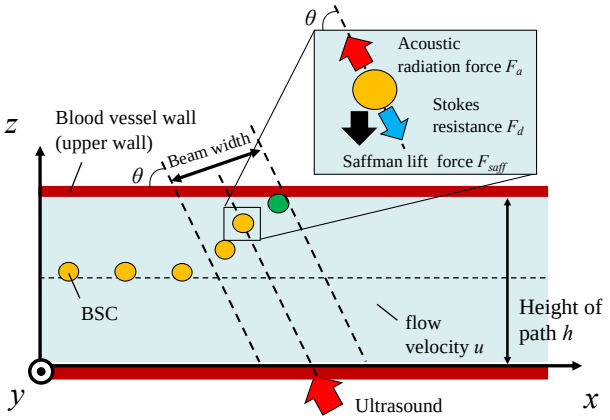


Fig.1 Trajectory of a BSC in flow under ultrasound exposure.

the surface condition of microbubbles, and the density of microbubbles into account. The position of a BSC was periodically plotted in three-dimensional space to elucidate its trajectory concerning the composition of acoustic force and drag force caused by the fluid. Finally, the BSC is regarded to reach to the upper wall of blood vessel, where the drag force is not effective, to retain on the wall.

In our preceding research [3], because the retention efficiency was experimentally evaluated by the brightness, which was converted from the luminescence captured by a fluorescence microscope, there was a nonlinearity between the luminescence

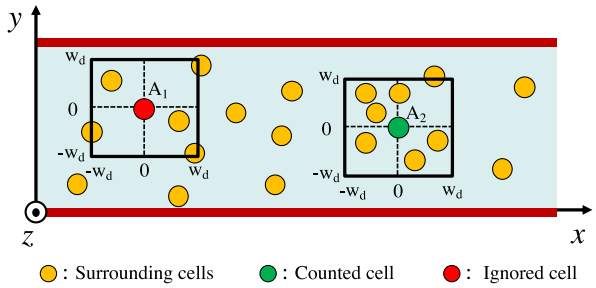


Fig.2 Application of a density threshold D_{th} with examples of ignored cell (A_1) and counted cell (A_2).

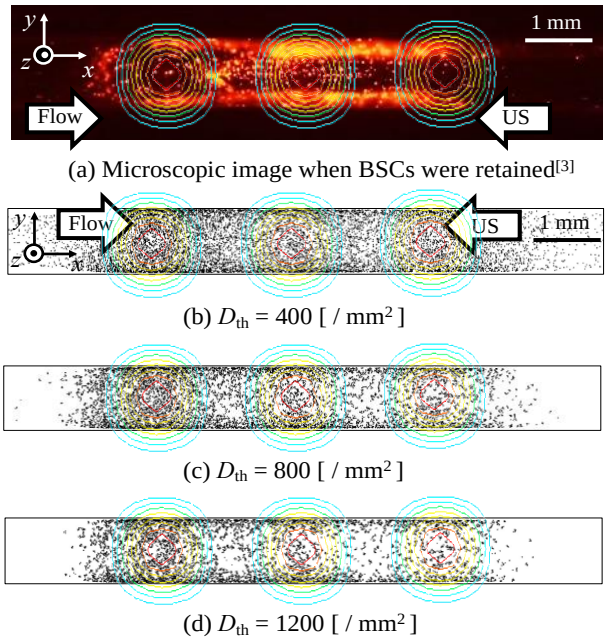
E-mail: ultrason@cc.tuat.ac.jp

and the amount of BSCs. Therefore, we have established a brightness threshold B_{th}, where the brightness less than B_{th} is ignored as background in the experimental results. Also, a density threshold D_{th} is established to eliminate less density of BSCs in the simulation results. **Fig.2** shows the schematic of retained BSCs on the wall in the simulation, which indicates a dispersed density of BSCs, where A_i (i = 1,2⋯) is a region of interest by centering an arbitrary BSC to apply the procedure of threshold D_{th}. In Fig.2, when the parameters were set to D_{th} = 1600 /mm^2 and w_d = 0.05 mm for example, A_2 is counted but A_1 is ignored.

3. Results

We compared the simulation results with the experimental one under the same ultrasound conditions. **Fig.3(a)** shows the microscopic images, which retained BSCs with maximum sound pressure 400 kPa-pp and number of focal points 3 (exposure time of 30s) [3], as a typical experimental result. Three color contours represent the distribution of sound pressure. **Fig.3(b), (c) and (d)** show the simulation results with various D_{th}, where black dots represent the retained BSCs. According to the value D_{th} was increased, although the retained BSCs were decreased, it is confirmed that more BSCs were retained nearer the focal points.

Fig.4 shows the comparison of retention area of BSCs between the simulation and experimental results in the above conditions. The simulation and experimental results were indicated as lines and dots, respectively. In the simulation results, when D_{th} is lower than 400/mm^2, the retained area increased in proportion to the number of focal points. However, the maximum retained area was shown with 3 focal points when D_{th} is higher than 400 /mm^2, which corresponds to the experimental results. Despite the standard deviation was not small, when D_{th} is 800 /mm^2 and B_{th} = 70, we obtained a satisfied correlation between the simulation and experimental results.



(a) Microscopic image when BSCs were retained[3]

(b) D_{th} = 400 [/ mm^2]

(c) D_{th} = 800 [/ mm^2]

(d) D_{th} = 1200 [/ mm^2]

Fig. 3 Comparison between (a) experimental and (b, c, d) simulation results with different values of D_{th}.

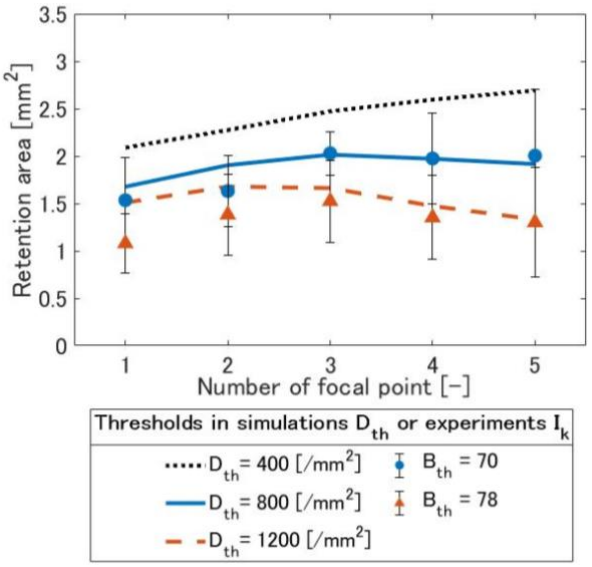


Fig.4 Comparison of retention area of BSCs between the simulation and experimental results according to number of focal points, and thresholds D_{th} and B_{th}.

4. Conclusion

We constructed a 3D theoretical model of the retention of BSCs by acoustic radiation force. We calculated the retention area of BSCs at different focal numbers and compared it with the experimental results. In this simulation we prospected the reliability of reproduction from experimental results. We are going to examine with further parameters to enhance the accuracy of this simulation.

References

1. K.Masuda, et al, Proc. of IEEE Int'l Ultrasonics Symp., 2018
2. R.Oitate, et al, Jpn. J. Appl. Phys., Vol.57, 07LF10, 2018
3. T.Otsuka, et al, USE, 2019
4. T.G.Leighton. The acoustic bubble, 1997
5. M.Overvelde et al. UMB Vol.36, pp.2080– 2092, 2010
6. P.Marmottant et al. JASA, Vol.118, pp.3499-505, 2005
7. T.Segers et al. Soft Matter, Vol.14, pp9550-9561, 2018