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Optical scattering measurement of microbubble cloud dynamics in ultrasound
超音波中の微小気泡群ダイナミクスの光散乱計測

Takashi Miwa[†], Yoshiki Yamakoshi and Tomoharu Mashiyama (Gunma Univ.)
三輪空司[†]，山越芳樹，増山知東 (群馬大・工)

1. Introduction

In order to realize Drug Delivery Systems (DDS), targeting techniques of payloads to a diseased area and drug delivery techniques through cell membrane are key technologies. Ultrasonic aided-DDS (UADDS) technology has possibilities to improve efficacy of DDS. In UADDS, a pumping ultrasonic wave manipulates microbubble including drug. Also a high intensity ultrasonic wave injects the drug in the microbubbles into cell. But, these mechanisms have not been understood yet.

Generally, it is difficult to manipulate individual microbubbles in microbubble cloud for UADDS. However, a microbubble irradiated by an ultrasonic wave oscillates and re-radiates the secondary ultrasonic wave including higher order harmonics. Here, it generates the secondary Bjerknes force which acts as attractive and repulsive force between microbubbles and changes the microbubble cloud into microbubble aggregations aligned with the separation of the wavelength. Thus, we have focused on techniques not to individually manipulate but to control microbubbles as cloud by using the secondary Bjerknes force[1,2)].

To optimize the ultrasonic wave sequences, the dynamics observation of microbubble cloud is required. A direct observation with a high-speed camera[3)] or a light scattering measurement with a photo-multiplier tube detector[4)] has been applied to the dynamics observation. However, the objective of these researches is to investigate dynamics of an individual microbubble. Since the dynamics in aggregation process of a large number of microbubbles is very complicated, we have to quantitatively evaluate a few parameters which statistically represent the dynamics in growing process into microbubble aggregations. Thus, this report presents an evaluation method of microbubble cloud dynamics using a light scattering measurement system with a line sensor.

2. Principle of light scattering measurement

Figure 1 shows a scattering model of aggregated microbubbles. N microbubble aggregations are aligned along the x axis with the interval of x_B. We assume that the microbubbles be uniformly distributed from $-\Delta x_B$ to Δx_B in each microbubble aggregation. The intensity of scattering light far away from the microbubbles significantly depends on the scattering direction due to interference among the scattering light from the N microbubble aggregations. Generally, the specular direction θ_0 corresponding to the 0th order scattering light has maximum intensity. Also local maxima appear at the direction θ_n, in which difference of the path length between the neighboring microbubble aggregations is n times larger than the wavelength. The intensity $I_R(n)$ corresponding to the nth order scattering light is shown with a constant K by

$$I_R(n) = KN^2 \mathrm{sinc}^2\left(2\pi n \frac{\Delta x_B}{x_B}\right). \qquad (1)$$

So, θ_n and $\Delta x_B / x_B$ can be estimated from peak interval and amplitude of intensity distribution on the line sensor, respectively. Here, x_B is given by

$$x_B = n\lambda / (\cos\theta_n - \cos\theta_i) \qquad (2)$$

In $\Delta x_B / x_B << 1$, $I_R(n)$ gets smaller as Δx_B gets larger. Therefore, we can evaluate Δx_B as a statistical index of growth of microbubble cloud.

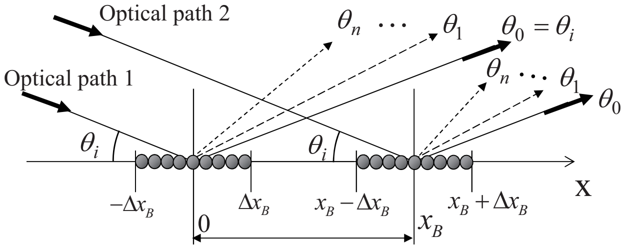

Fig.1 Scattering model of aggregated microbubbles

3. Experimental set-up

We construct a light scattering measurement system as shown in **Fig.2**. 90mW He-Ne laser light (λ=642nm) is introduced into distilled water through an optical window and illuminates on a microbubble flow cell, which has the width and thickness of 1cm and 1mm, respectively and which is wrapped with a polyvinylidene film. Microbubble (Levovist, Bayer Health care) is induced into the flow path in the cell by a rotary pump. The

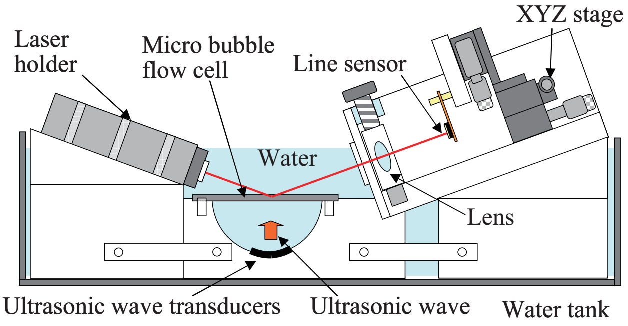

Fig.2 Constructed light scattering measurement system

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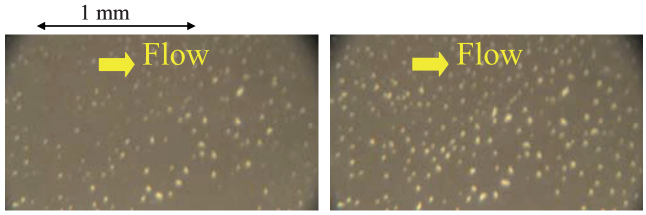
miwa@el.gunma-u.ac.jp

concentration and flow velocity of 22mg/ml and 0.55mm/s, respectively. Two ultrasonic transducers with a focus at the center of the flow path are used to aggregate the micro- bubbles. Through a lens, the scattering light from the microbubbles is focused on a 1-D line sensor with 128 pixels and 63.5μm pitch. This system can evaluate the directivity of the scattering light for infinite distance. From characteristics of the Fraunhofer diffraction, the intensity distribution on the line sensor is equivalent to the Fourier transformation of distribution of the microbubble aggregations. Although, the line sensor can be driven from 5kHz to 8MHz, we select the clock speed of 20kHz due to improvement of SNR.

4. Measurement results

Fig.3 shows microbubble aggregations trapped on the upper film, taken with a video camera. Figure (a) and (b) are at the elapsed time of 5s and 10s after radiating the pumping ultrasonic wave (*t*=0), respectively. The frequency and the sound pressure are 2.5MHz and 100kPa, respectively. The separation between microbubble aggregations is observed to be narrower than the wavelength (600μm). This means that the higher order harmonics for the pumping wave contribute to form such the distribution. Moreover, it is observed that the microbubble cloud grows and aligns in 5s.

Fig.4 shows difference of light intensity on the line sensor from *t*=0. The vertical lines show the 1st and 2nd scattering light predicted by the geometry of the measurement system, assuming that the separation between the microbubble aggregations be 75μm which corresponds to the 8th order harmonics of the fundamental wave. The broken and solid lines are data taken at *t*=1s and 5s, respectively. Since the 0th order scattering light is significantly strong, intensity variation between -700 and 700μm is neglected. We can observe significant spatial variation at (A), (B) and (C). **Fig.5** shows time variation of the intensity at these points. The intensity gradually varies with much larger amplitude than the noise level. This variation can be caused by the growth of microbubble clouds. The time variation at the ±1st order scattering light has little repeatability as the result of 5 trials. This implies that microbubble dynamics in growth has randomness because the dynamics strongly depends on the initial distribution of microbubbles. The same phenomena are also observed in numerical simulations of microbubble dynamics.



(a) 5[s] (b) 10[s]

Fig. 3 Aggregated microbubbles trapped on the upper film. (Frequency: 2.5MHz, Sound pressure: 100kPa)

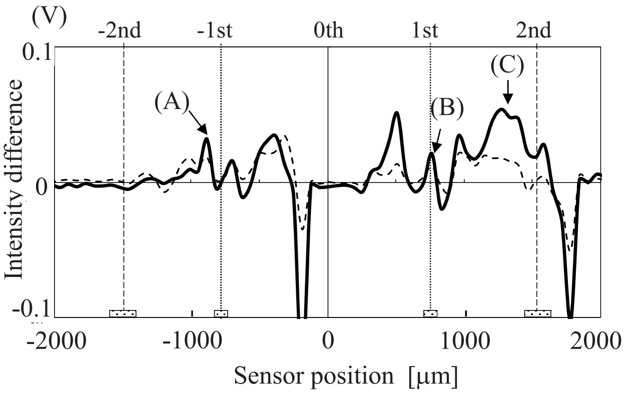


Fig.4 Example of spatial distribution of light intensity. The intensity relative to that at *t*=0 is shown.

5. Conclusion

In order to extract a few parameters which represent the dynamics in growth of microbubble clouds, a light scattering theory is applied, aiming at alignment of microbubble aggregations in ultrasound. We observed the deviation of scattering intensity, which seems to be caused by variation of the higher order scattering light. This implies that dynamics information in growth of microbubble clouds can be obtained with a developed system.

Acknowledgment
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References

1. Y. Yamakoshi and T. Miwa :Jpn. J. Appl. Phys. **47** (2008) 4127.
2. Y. Yamakoshi and T. Miwa :Jpn. J. Appl. Phys. **48** (2008) July.
3. N.Kudo, K.Okada and K.Yamamoto :2003 IEEE Ultrasonic Symp.(2003) 1507.
4. J. F. Guan and T. J. Matula :2004 IEEE Ultrasonic Symp. (2004), 218.

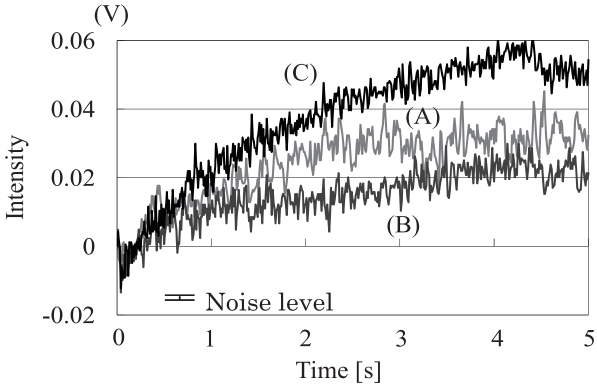

Fig.5 Example of time variation of light intensity at the sensor positions shown in Fig.4.