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Three-dimensional super-resolution imaging using Sonazoid microbubbles

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1. Introduction

Contrast enhanced ultrasound (CEUS) is an ultrasound imaging technique that selectively delineates vascular regions by visualizing only the nonlinear echoes from microbubbles (MBs) circulating in the blood. Moreover, super-resolution (SR) imaging, a technique that significantly improves the spatial resolution of CEUS images, has been proposed [1, 2]. In SR imaging, isolated MBs within the blood flow are localized and tracked using high-frame-rate CEUS images. Then, the trajectories of the center positions of the MBs are visualized to form SR-CEUS images. This visualization of the trajectories achieves a resolution significantly higher than the point spread function (PSF) of CEUS images. SR imaging can also visualize the velocity of the blood flow from the trajectories.

However, detecting microvasculature with complex structures and evaluating flow velocities from the tomographic (two-dimensional) SR-CEUS images remains difficult. Therefore, the goal of this study is to realize three-dimensional (3D) SR imaging using Sonazoid® MBs. Sonazoid (GE Healthcare) is an ultrasound contrast agent approved in Japan. In this report, diluted Sonazoid MBs in a water tank were observed using a two-dimensional (2D) array probe to validate 3D-SR imaging.

2. Method

2.1. Ultrasound imaging

The 3D ultrasound images were acquired with the 1024-element 2D array probe (8 MHz, Vermon) driven by the research ultrasound system (Vantage 256, Verasonics). The 1024 elements were divided into four sub-apertures. Each sub-aperture has 256 elements, aligned on a 32×8 grid with a pitch of 0.3 mm. Since there are 0.3 mm intervals between the sub-apertures, the area of the 32 × 32 grid full aperture is 9.6 × 10.5 mm. Each sub-aperture received echoes provided by the transmission of each sub-aperture, due to the limitation of the number of channels in the system. In addition, the pulse inversion (PI) method, the transmission and reception of positive and negative inverted pulses, is applied for CEUS. Consequently, 32 sequences of all combinations of 4 sub-apertures and 2 kinds of pulses per frame are required in the system.

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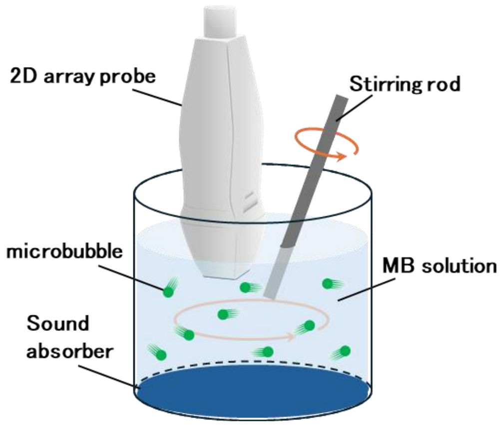

Fig. 1 Experimental setup.

2.2 Experimental setup

The experimental setup in this study is shown in **Fig. 1**. A suspension of MBs was diluted 1,000,000 times in a water tank using thoroughly degassed ultrapure water. The dilution factor was chosen based on the theoretical value of MBs alone (approximately 1 MB / mm^3). The probe was fixed with its aperture positioned just below the surface of the suspension. A very slow near-horizontal vortex flow was created manually using a stirring rod and measurements were taken.

Two cycles of the sinusoidal wave at 4.464 MHz was transmitted as a plane wave. The applied voltage for the transducer elements were set at 8 V. A total of 256 frames (8192 sequences of transmission and reception) were acquired with the pulse-repetition frequency of 4 kHz. The received signals were stored at a sampling frequency of 35.712 MHz. The synthesis of full-aperture echo signals and signal/image processing were performed off-line using MATLAB.

2.3 3D-SR imaging processing

After PI processing to combine two RF signals by positive and negative pulse transmissions, 3D delay-and-sum beamforming was performed to create 3D-CEUS images. For localization, the 3D template matching method was applied. The MB

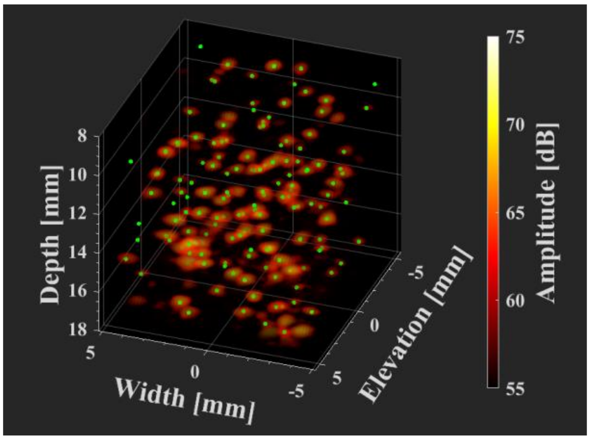

Fig. 2 3D-CEUS image with localized points.

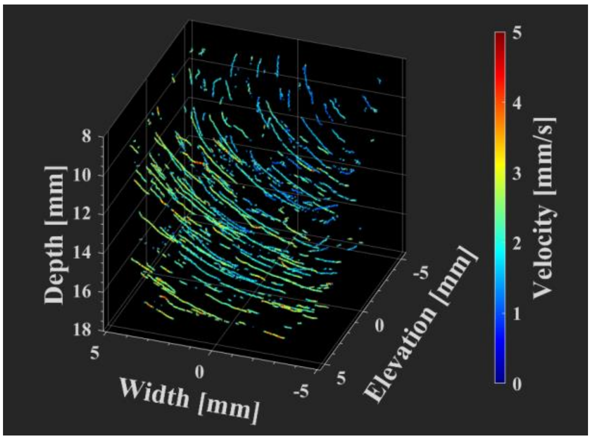

Fig. 3 Super-resolved 3D velocity map.

with an ideal PSF was manually selected from the 3D-CEUS images as a 3D template image. Then, the template image and the 3D-CEUS image were cross-correlated, and the correlation peak above a specified threshold of 0.60 was defined as the center position and localized point of the MBs.

The localized points were stored over all frames to be tracked. Tracking was performed using the Kuhn-Munkres algorithm [3, 4]. The square distance between the localized points of each MBs in frame n and the points in frame n + 1 was calculated, and the pairs of each MBs were determined between consecutive frames so that the total distance was minimized. The maximum distance between MBs in the previous and next frames was 240 µm (30 mm / s). The acquired tracks were then smoothed by moving average using points from the previous and next 5 frames, and tracks of 10 frames or less were rejected.

3. Result and discussion

A 3D-CEUS image with the localized points superimposed as green dots is shown in **Fig. 2**. The localized points were confirmed at the center of each isolated MBs. Then, tracking of all points was

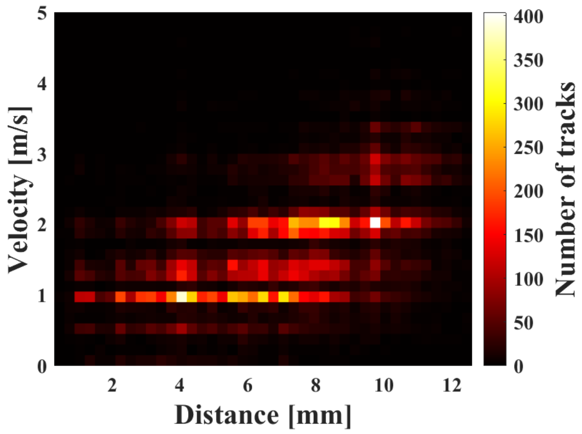

Fig. 4 Velocity distribution.

performed and the trajectories were smoothed. For each track, velocities of the MBs were calculated using the distance traveled between frames to create a super-resolved 3D velocity map, shown in **Fig. 3**. On this map, the trajectories were color-coded based on their velocity values.

To evaluate the velocity distribution, the relationship between the azimuthal distance from the reference point at Width - 4 mm and Elevation - 5 mm and the velocity to each coordinate was investigated **(Fig. 4)**. The reference point was selected as the location near the center of the vortex flow based on Fig. 3. In Fig. 4, MB velocities were distributed in the range of 0 ~ 4 mm/s, and tended to increase with distance. This result and the 3D velocity map suggest that the flow velocity was higher toward the outer side of the vortex flow.

4. Conclusion and future work

In this report, MBs flowing in water were continuously imaged for 3D-SR imaging using Sonazoid. Tracking of the MBs allowed quantitative visualization of the velocity of very slow vortex flow in 3D. In future studies, visualization of actual microchannels by 3D-SR imaging will be performed, and the spatial resolution will be evaluated.

Acknowledgment

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