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Fast Super Resolution Ultrasound Imaging using the Erythrocytes

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ABSTRACT

Super resolution (SR) imaging is currently conducted using fragile ultrasound contrast agents. This precludes using the full acoustic pressure range, and the distribution of bubbles has to be sparse for them to be isolated for SR imaging. Images have to be acquired over minutes to accumulate enough positions for visualizing the vasculature. A new method for SUper Resolution imaging using the Erythrocytes (SURE) as targets is introduced, which makes it possible to maximize the emitted pressure for good signal-to-noise ratios. The abundant number of erythrocyte targets make acquisition fast, and the SURE images can be acquired in seconds. A Verasonics Vantage 256 scanner was used in combination with a GE L8-18iD linear array probe operated at 10 MHz for a wavelength of 150 μm. A 12 emissions synthetic aperture ultrasound sequence was employed to scan the kidney of a Sprague-Dawley rat for 24 seconds to visualize its vasculature. An ex vivo micro-CT image using the contrast agent Microfil was also acquired at a voxel size of 22.6 μm for validating the SURE images. The SURE image revealed vessels with a size down to 29 μm, five times smaller than the ultrasound wavelength, and the dense grid of vessels in the full kidney was reliably shown for scan times between 1 to 24 seconds. Visually the SURE images revealed the same vasculature as the micro-CT images. SURE images are acquired in seconds rather than minutes without contrast injection for easy clinical use, and they can be measured at full regulatory levels for pressure, intensity, and probe temperature.

1. INTRODUCTION

The resolution limit in ultrasound imaging is given by the diffraction limit, which is $\lambda/2 = c/2f_0$, where λ is the wavelength, c the speed of sound, and f_0 is the transducer center frequency. Traditional ultrasound imaging can therefore not separate objects closer than half a wavelength. This limit has been broken by super resolution imaging (SRI). Current SRI is based on injecting gas-filled microbubbles and tracking the scattered signal from the bubbles[1–6] yielding images with very high resolution beyond the resolution imposed by the diffraction limit of ultrasound. The bubble density must be sparse in SRI to enable tracking of individual bubbles to create a vascular flow image from the accumulated tracks. This necessitates a long acquisition time from 30 seconds to several minutes to allow enough bubbles to pass through the entire circulation and to obtain reliable vessel images. This is a substantial problem, as the image resolution is in the micrometer range. Therefore, the probe and patient have to be co-registered with micrometer precision, which can be difficult due to both voluntary and involuntary movements from e.g. bowels, respiration, and heart beating during the minutes of acquisition. Another problem is the fragile ultrasound contrast agents, which burst if exposed to a large acoustic pressure.

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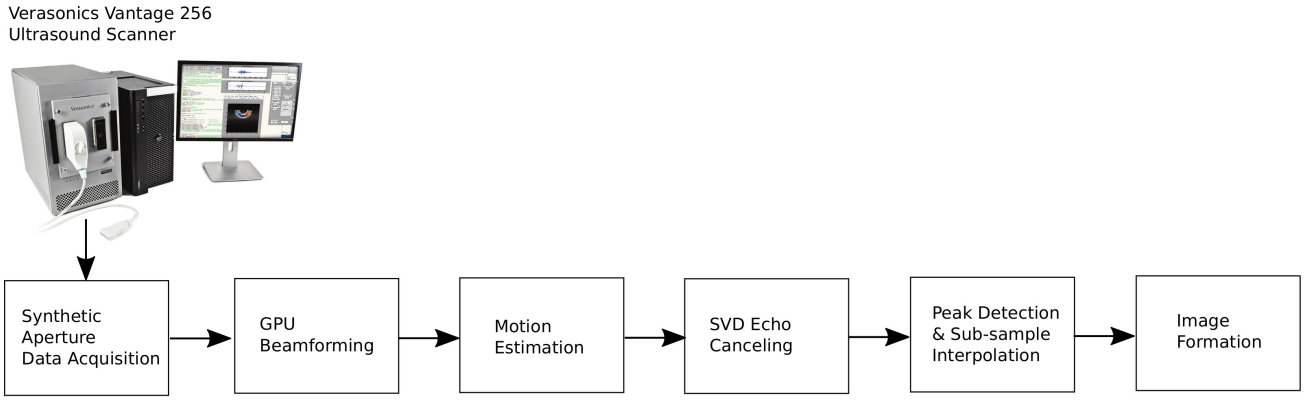

Figure 1. Illustration of the processing stages in the SURE pipeline. From left to right the processing is: Data acquisition using a 12 emissions synthetic aperture ultrasound sequence using a Verasonics Vantage 256 scanner and a GE L8-18iD linear "hockey stick" array. GPU beamforming creates the image, which is then used for motion estimation. The aligned images are SVD processed to remove stationary tissue, and peaks in the envelope image are detected. Accumulating all the peaks yields the SURE image.

The mechanical index (MI) of the sequence should therefore be restricted to 0.05 to 0.2, well below current FDA limits of 1.9. Such low emitted pressures will degrade signal-to-noise ratio and penetration depth.

These problems can be solved, if the use of contrast agents can be avoided. This paper uses the erythrocytes as targets, thus, enabling super resolution imaging with erythrocytes (SURE). As the erythrocytes are responsible for transportation of oxygen, they are abundant in the circulation with roughly 5 million cells per mm^3, and they perfuse any living tissue. They can also withstand the acoustic pressure of clinical ultrasound scanners, and therefore the full MI range can be employed.

2. METHOD

A super-resolved image of the circulation is attained by acquiring ultrasound data using a synthetic aperture (SA) ultrasound sequence implemented on a Verasonics research scanner. The method is to use the speckle pattern of the moving blood. For a single scatterer inside the vessel, the peak position of the point spread function (PSF) will be inside the vessel, if the PSF is symmetric around it's center axis. A collection of scatterers inside the vessel will have a complex appearance, but the peak position will on-average reside within the vessel, if all scatteres are within the vessel. It is therefore important to remove the tissue signal and preserve signals from flow.

In vivo tissue will be moving due to respiration, muscle contraction, and the beating heart. This is taken into account by compensating for tissue motion, and removing the tissue signals gives the erythrocyte signal. The local peaks in the remaining image are then detected, and showing all the peak positions yields a super resolution image of the vasculature, which is the approach applied in this study.

3. MEASUREMENT SETUP

The ultrasound data were acquired using a Verasonics Vantage 256 research scanner (Verasonics, Inc., Kirkland, WA, USA) connected to a 168 channel GE L8-18iD (GE HealthCare, USA) linear array probe. The probe has a wavelength pitch of 150 μm and was used at a frequency of 10 MHz. A synthetic aperture ultrasound sequence with 12 virtual sources (VS) evenly spread out over the aperture was employed.[7] Each VS had a transmit F-number of -0.7 with the transmit focus placed at a depth of -3.36 mm behind the transducer surface and used 32 elements for the de-focused emissions. Data were sampled at a frequency of 62.5 MHz/14 bits for a duration of 24 seconds with a pulse repetition frequency of 5 kHz resulting in a high-resolution image frame rate of 416.7

Hz. The data were stored in local RAM inside the PC and transferred to disk. A computer cluster was later used for processing.

A Sprague-Dawley rat was used as the animal model, and its exposed left kidney was ultrasound scanned. Afterwards, an ex vivo micro-CT scan with the intravascular contrast agent Microfil (MV122, Flow Tech Inc., Carver, MA) was acquired on the kidney to yield a vascular reference image for comparison and validation.

4. PROCESSING PIPELINE

The acquired data were processed using the SURE pipeline shown in Fig. 1, where each box describes a processing stage. All processing was conducted in Matlab 2019b (MathWorks, Massachusetts, USA) with processing modules developed specifically for SURE imaging. The stored data was beamformed using the GPU code presented by Stuart et al.[8] with an axial sampling density of $\lambda/16$ and a lateral density of $\lambda/4$, where λ is the emitted ultrasound wavelength of 150 μm. The motion was then estimated using speckle tracking[9] across the image, and the motion field was employed to align all frames to a reference frame as described by Taghavi et al.[10] The tissue removal or echo canceling was performed using singular value decomposition (SVD)[11] for 400 frames at a time. The first 24 singular values were discarded to remove tissue, and values above 160 were set to zero to reduce noise. The envelope signal was then used to find peaks in the image for indicating position inside the vasculature, and interpolation was employed to increase resolution. The SURE image was finally formed by accumulating all the peak positions and smooth the result by a Gaussian low pass filter with a standard deviation of 7 μm axially and 15 μm laterally.

5. RESULTS

An example of a SURE image of the left kidney of a Sprague-Dawley rat is shown in Fig. 2 together with the corresponding B-mode image. The scan was conducted over 24 s for acquiring 10,000 images. The pipeline detected 41,574,604 peaks in total for a mean detection of 4,157 peaks/image. The image shows the normal anatomic B-mode image. The SURE image displays the very high density of vessels throughout the kidney.

Fig. 3 shows the corresponding micro-CT image of the kidney. A maximum intensity projection has been taken over 20 adjacent slices to mimic the elevation focus of the ultrasound probe. The SURE image is shown on the left, the micro-CT image is in the middle, and finally on the right is the merged SURE and micro-CT images. A fair correspondence can be seen between the vessel structures, but it is also apparent that the contrast has solidified before filling the whole kidney, and this might have give rise to some distortion and shape changes.

The SURE images are generated by accumulating a number of peak detections and can be made for different time intervals. This is shown in Fig. 4 on the left for 0.2 seconds of data acquisition. The image is smoothed with a Gaussian kernel with a standard deviation of 50 μm in the lateral direction and 30 μm in the axial direction to make an improved display. All the major vessels in the vasculature can be seen. The images after 1 second or 5 seconds are shown on the right. Here the Gaussian kernel had standard deviations of 20 and 10μm. An improvement is seen in the image when going form 0.2 to 1 seconds and a further slight improvement is seen when using 5 seconds of data. It is, however, possible to obtain a visualization of vessels with sizes below the diffraction limit even at 0.2 seconds, making it possible to have a real time orientation during scanning, if the whole processing pipeline can be implemented for real time processing.

A zoom of the SURE image for the central region of the kidney is shown in Fig. 5 on the left. The white line indicates the placement of the density profile shown on the right image, which intersects four small vessels. It can be seen that the four vessels are clearly delineated, and they are all smaller than a wavelength.

The Fourier ring correlation (FRC) method is used for estimating resolution, where data from two images are correlated, and the resolution is determined from the correlation.[12,13] Data for the SURE image is split in two, and two images are made for the first 12 seconds of data and the second image is for the remaining 12 seconds. The FRC is then calculated and smoothed with a low pass filter to reduce noise. Bit-based information threshold curves areused for the resolution threshold level as described by Heel and Schatz.[14] The resolution determined by FRC is 29.1 μm for the half bit threshold, which corresponds to one fifth of the emitted wavelength.

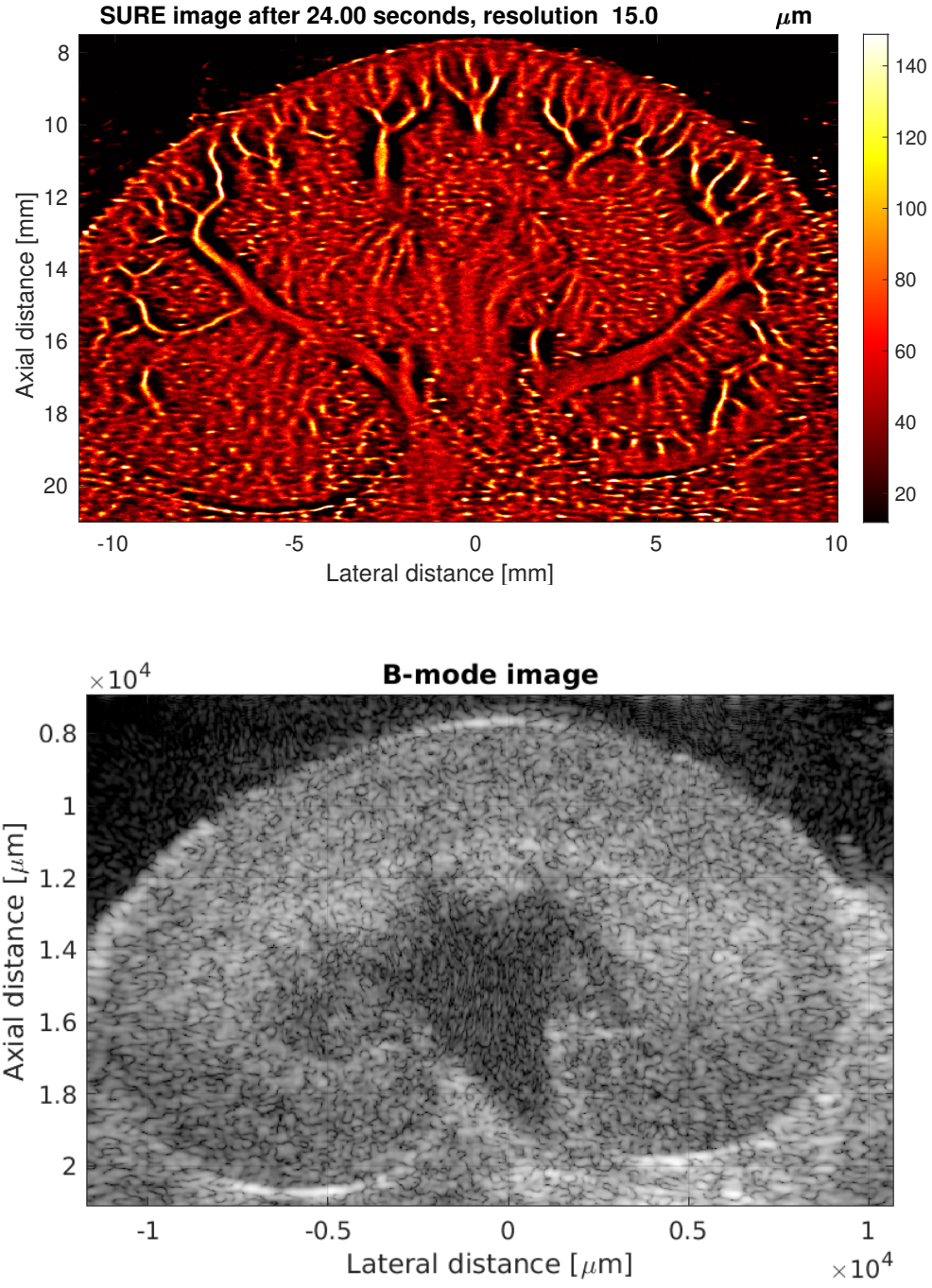

Figure 2. SURE image of rat kidney after 24 seconds acquisition (top) and corresponding B-mode image (bottom). The color in the SURE image shows the number of detections in a pixel.

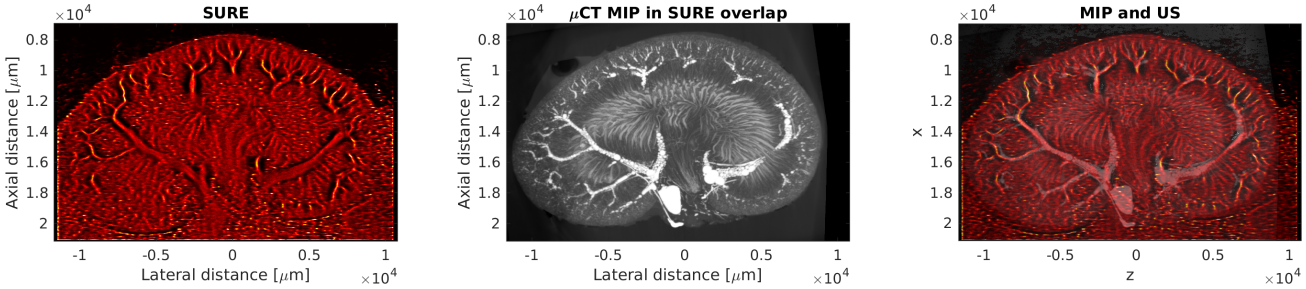

Figure 3. SURE image compared with micro-CT image using maximumum intensity projection for the same slice in the 3-D data set. The left image shows the SURE image, the middle is the micro-CT image and the two are merged on the right.

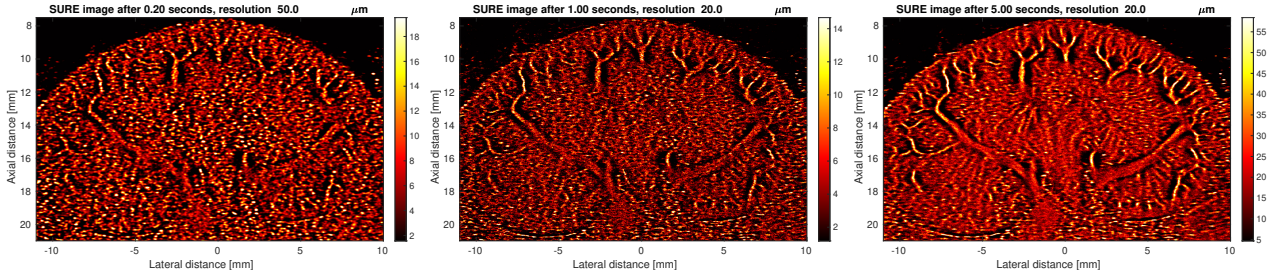

Figure 4. SURE images after 0.2, 1 and 5 seconds of data acquisition.

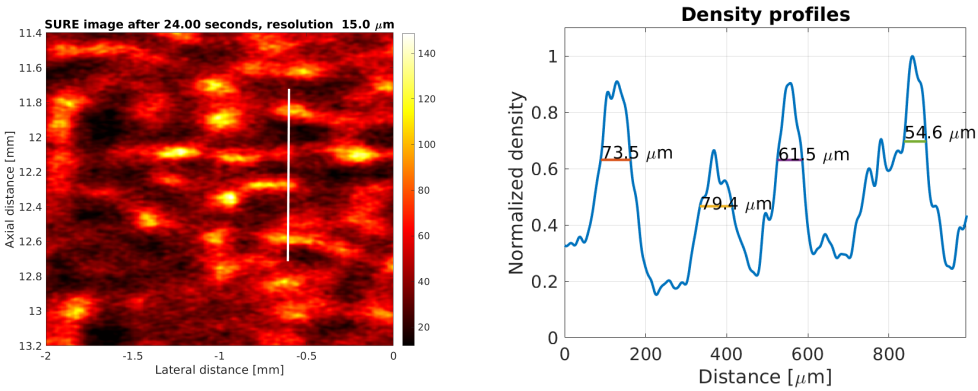

Figure 5. Zoom of the central region of the SURE image showing four small vessels.

6. CONCLUSION

The results show that super resolution imaging using erythrocytes as targets is possible. SURE imaging can reveal small vascular structures of the rat kidney down to vessel sizes of 29 μm. The imaging relies purely on the scattering from erythrocytes, and no patient preparation or contrast agent injection is needed, making this technique fully non-invasive. Therefore, SURE imaging can be used on any patient, where conventional ultrasound is applicable. The method can be used with the full FDA range for MI, probe temperature, and intensity available for normal, clinical ultrasound. Synthetic aperture imaging is used, and the data is acquired within seconds. Reasonable images of the vasculature are obtained in 0.2 seconds, making it possible to have a live view of 5 Hz while scanning a patient. Extending the time to 5 seconds gives an improved view of the smaller vessels. The fast imaging significantly reduces motion artifacts and SURE has the potential for microvascular imaging in patients despite body movements and pulsations from respiration and the beating heart.

7. ACKNOWLEDGMENT

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