

Multi-Frame Rate Plane Wave Contrast-Enhance Ultrasound Imaging for Tumour Vasculature Imaging and Perfusion Quantification

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Abstract—A multi-frame rate plane wave imaging strategy is developed to simultaneously image tumor vasculature and quantify tumor perfusion. Customised imaging sequences interleaving a short but high frame rate (HFR) plane wave imaging sequence with a long but low frame rate imaging (LFR) sequence were implemented using a programmable ultrasound research platform. The results from a spatio-temporal coherence processing technique of ours demonstrated a significant improvement in the SNR and vasculature contrast when compared with the existing ultrafast Power Doppler (PD) using the same data. Initial perfusion quantification using LFR imaging was also demonstrated. Mean time intensity curve and some parametric measures were generated. Combining both structural and functional perfusion imaging using the multi-frame rate sequences, a better evaluation of the tumour angiogenesis can be assessed.

Keywords—Molecular imaging, microvascular flow and perfusion, CEUS, plane wave imaging, microbubbles contrast agents.

I. INTRODUCTION (HEADING 1)

Tumour angiogenesis is a crucial factor in the progression of cancer [1]. New blood vessels form from the pre-existing vessels as adequate blood supply is required to sustain the tumour growth and allows it to spread. The increased blood supply demand therefore allows the assessment of tumour vasculature by means of perfusion quantification. Besides, the structure of the tumour vasculature is also characterised by its complex and tortuous network of micro vessels. The morphology of the tumour structure therefore enables a unique way to differentiate normal tissue from cancerous tissue.

Contrast enhanced ultrasound (CEUS) imaging has shown exciting potential in imaging angiogenesis and flow dynamics [2], [3]. Microbubble contrast agents significantly enhance the acoustic signals within the vessels thus offering substantial benefits for quantitative flow and perfusion measurements[4], [5].

Recent development of plane wave high frame-rate (HFR) CEUS has offered new opportunities many applications such as vascular flow imaging [6]–[8], elastography [9], cardiac imaging [10], and brain functional imaging [11]. The high temporal resolution from plane wave imaging and the high sensitivity from CEUS can be used not only for imaging fast

moving targets, but also to improve visualisation of the slow blood flow in small vessels such as those associate in the kidney or tumour angiogenesis [12].

In this study, we developed a multi-frame rate plane wave CEUS for better tumour vasculature imaging and perfusion quantification. Both structural and functional imaging were acquired simultaneously to complement the assessment of the tumour angiogenesis. Initial evaluation of such imaging strategy was evaluated *in vivo* on a mouse tumour model.

II. METHODS

A. Tumour model

U2932 lymphoma cells were implanted in the flank of an NOD/SDIC immunocompromised mouse. In-vivo experiment was performed after 4 weeks when the tumour reached adequate size for ultrasound imaging.

B. Microbubbles preparation and administration

Microbubbles was prepared using a mixture of 1,2-dipalmitoyl-snglycero 3-phosphatidylcholine (DPPC), 1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine-polyethyleneglycol-2000 (DPPE-PEG-2000), and 1,2-dipalmitoyl-3-trimethylammonium propane (chloride salt; 16:0 TAP) in molar ratio of 65:5:30 and a total lipid concentrations of 0.75, 1.5 and 3 mg/mL[13].

Given the mouse weight of 25g, maximum of two bolus injections of microbubbles were administrated through a tail vein catheter. For each injection, 50ul micro bubbles diluted to the concentration of 5×10^7 microbubbles/ml, was injected followed by 50ul flush with heparin-PBS before imaging.

C. Multi-frame rate plane wave contrast-enhance ultrasound imaging

A Verasonics research ultrasound platform (Verasonics, Redmond, WA, USA) was programmed to acquire ultrasound images in real-time using a L22-14v probe. A customized plane wave imaging pulse sequence were designed which interleaved multi-frame rate plane wave CEUS to perform perfusion quantification and generate vasculature images with improved

resolution and contrast. A HFR plane wave sequence (1.5s, 600Hz) was inserted at the peak bolus enhancement within a long but low frame rate (LFR) plane wave sequence (180s, 2Hz). For both imaging sequences, fifteen 1-cycle plane wave pulses with angle spanning between -7.5° and 7.5° were transmitted at the centre frequency of 18MHz and the details for the imaging parameters can be found in Table I.

TABLE I. PLANE WAVE IMAGING SETTING

Parameter	Descriptions
<i>Imaging Mode</i>	Plane wave Bmode
<i>Transmit Frequency</i>	18 MHz
<i>Excitation Pulse</i>	1-cycle Gaussian
<i>Compounding Plane Wave</i>	15
<i>Angle range</i>	15° (1° step)
<i>Imaging Depth</i>	2cm
<i>PRF</i>	2.5 kHz
<i>Effective Frame Rate</i>	600Hz (fast), 2Hz (slow)

D. Vasculature image processing and perfusion quantification

Both HFR and LFR were acquired in real-time and transferred to a workstation for post-processing. All RF-data was reconstructed using a custom GPU-beamformer. Spatio-temporal coherence image processing technique was used to generate tumour vasculature images with improved contrast and signal-to-noise (SNR), taking the advantages of large amount of data available from HFR imaging and exploiting the spatio-temporal coherence of the classical Doppler signal [12]. Singular value decomposition (SVD) was also applied to the reconstructed Doppler signals to remove the tissue clutter [14]. Our technique reserved the key processing steps of the Power Doppler (PD), however because the noise is not correlated when taking into account both the spatial and temporal coherence, the noise level is significant reduced.

PD images were also generated using both HFR and LFR data. The former is used for the comparison between PD and our processing technique whereas the latter is used to generate a mask to segment to tumour perfusion region. With the binary mask applied to the clutter-filtered LFR images, the global mean time intensity curve (TIC) was then computed and fitted to a gamma-variate function

$$I(t) = At^{\alpha} e^{-\frac{t}{\beta}}$$

where A, α , β are the controlling parameters of the non-linear least-square curve fitting. By analysing the curve, several parametric measures were extracted. This includes the peak intensity (I_{pk}), time-to-peak intensity (T_{pk}), area under the curve (AUC), wash-in rate (WIR), and wash-out rate (WOR).

III. RESULTS

A. Tumour vasculature imaging

Fig. 1 shows the original Bmode image and the images processed using PD and our coherent-based technique. While clutter filter and PD may help to reveal the major tumour vasculature from the tissue signal, the noise level is still relatively high and comparable to the weak signal coming from the small vessels, and thus impedes the visibility of the small vessels. Besides, the noise power which changes with depth makes it even difficult to separate noise from the weak vessel signal by varying the dynamic range when using PD.

With the same RF-data, an improved vasculature image is generated using our developed technique. Noise level is significant reduced thus enhance the contrast of the tumour vasculature. The smaller vessels, which cannot be distinguished using PD, are clearly visible.

B. Tumour perfusion

To improve the perfusion quantification, clutter filtering and PD were applied to the LFR images. Binary mask was generated to automatically segment the tumour perfusion region from the clutter filtered data. The global mean TIC was then generated as demonstrated in Fig. 2, and the parametric measurements are shown in Table II.

TABLE II. PARAMETRIC PERFUSION QUANTIFICATION

Parameter	Value
I_{pk}	4.1×10^{18}
T_{pk}	39.8s
<i>AUC</i>	79.0
<i>WIR</i>	0.066
<i>WOR</i>	0.030

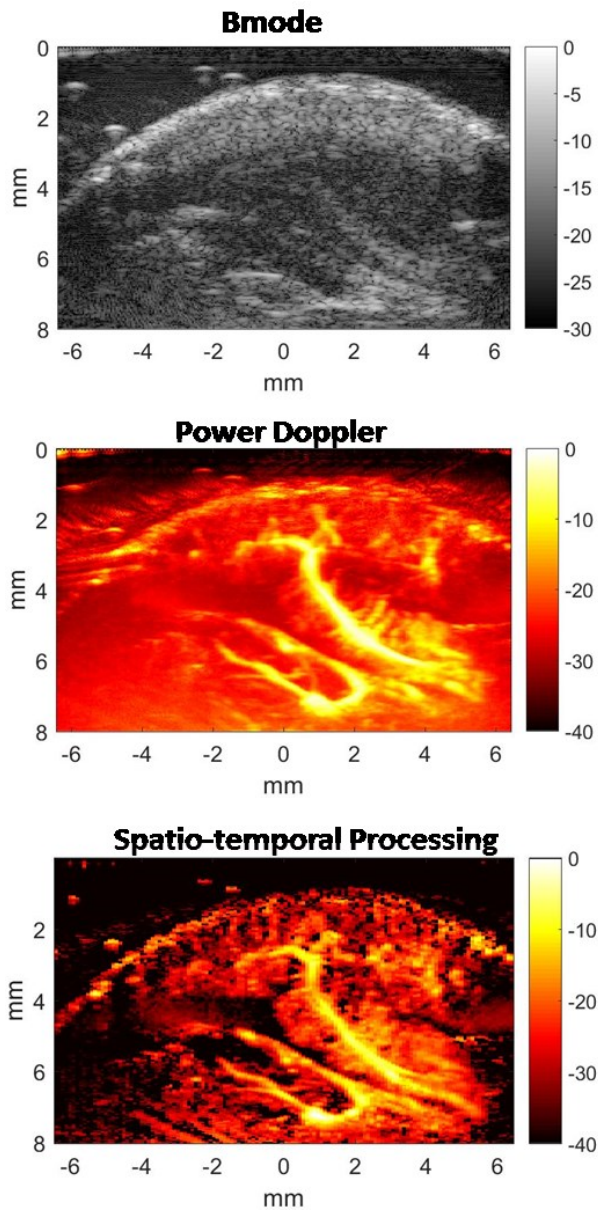


Fig. 1. Original Bmode image and the vascular images generated using Power Doppler and spatio-temporal processing techniques.

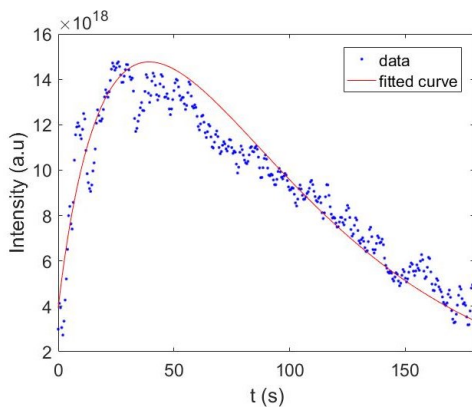


Fig. 2. Mean time-intensity curve (TIC) calculated from the tumour region after the microbubbles bolus injection.

IV. DISCUSSION AND CONCLUSION

A novel imaging strategy combining HFR and LFR imaging is developed for imaging tumour vasculature and quantification of tumour perfusion dynamics in a single data acquisition. Tumour vasculature image generated using a novel spatio-temporal coherence processing technique demonstrated a higher SNR and contrast for imaging tumour vasculature using HFR plane wave imaging when compared to the state-of-the-art ultrafast Power Doppler.

LFR plane wave imaging is important for perfusion quantification. We have demonstrated not only the mean TIC, but also some parametric measures to quantitatively describe the perfusion. Our initial result demonstrated the potential of combining both structural and functional imaging to improve the quantitative assessment of the tumour angiogenesis.

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