High frequency image-based flow detection

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Abstract. Tumour angiogenesis refers to neovascular development on a microvascular scale and is an early indicator of cancer. Prototype high frequency pulsed Doppler systems using 50 MHz transducers have been reported to detect microvascular flow in vessels 0.02 mm to 0.5 mm in diameter at superficial depths of 0.5 mm. Detecting flow in microvasculature at deeper depths requires lower frequency transducers with a resulting tradeoff in spatial resolution. Using a 22 MHz transducer, we demonstrate a speckle decorrelation technique to detect in vitro flow in soft tubing of 0.5 mm diameter at a depth of 2 cm. This image-based decorrelation technique is capable of detecting flow in significantly narrower diameters down to 0.125 mm by decreasing the region of interest.

1. Introduction
Medical ultrasound has found widespread clinical application for non-invasive patient evaluation and diagnosis. Compared to other medical imaging modalities such as X-ray computed tomography (CT), magnetic resonance imaging (MRI), and X-ray angiography, ultrasound is non-invasive, relatively portable and does not expose the patient to ionising radiation. In addition to imaging soft tissue structures, it is widely used for the functional assessment of coronary and vascular haemodynamics.

The range of blood vessel diameters in the human body spans four orders of magnitude from the great vessels of the aorta, arteries and veins, to the very smallest capillaries of the microcirculation. Microcirculation, or microvasculature, refers to the hierarchical network of arterioles, venules and capillaries in the body. The diameter of the largest vessel, the ascending aorta, is 20 mm to 30 mm, whereas microvessel diameters are on the order of 1 mm to less than 0.01 mm [1]. Blood flow is pulsatile in arteries and veins, but becomes steady in the smallest arterioles, venules and capillaries.

In addition to established clinical applications for arterial and venous blood flow measurement, ultrasound shows promise for the early detection of malignant cancerous tumours. The potential for tumour detection is based on the physiological principle of tumour angiogenesis. Angiogenesis refers to the growth of a new local blood supply for a given region of cells. This circulatory development is normal when it occurs in growing children and foetal development; menstruation and pregnancy; wound healing; and athletic endurance training.

Angiogenesis is undesirable when a tumour develops its own blood supply. It is one of the early changes that differentiates normal from cancerous tissue. Tumour angiogenesis is structurally more
chaotic than the organised patterns of normal angiogenesis and is a key factor for tumour growth and metastasis. Angiogenesis is a prerequisite for the growth of tumours larger than 2 mm$^2$ in cross-sectional area, as this is the fundamental limit for growth by perfusion alone. It is also principally implicated in the metastasis of tumours as new tumour blood vessels provide a pathway for infiltration of the cancer throughout the body [2].

These emerging new applications capitalise on developments in higher frequency probes and greater system bandwidth. Higher frequency transducers (generally >10 MHz) provide better resolution obtained at the expense of decreasing tissue penetration. Though this is a fundamental physical constraint due to attenuation effects, higher frequency ultrasound systems are well-suited to investigation of extremely small structures located at superficial depths.

Several studies have demonstrated the feasibility of imaging the microcirculation of tumours in skin melanomas [3] and depending on breast lesion depth, as a complement to X-ray mammography [4]. Christopher et al. [5] reported blood flow detection in the microcirculation with high-frequency 50 MHz pulsed Doppler. Their system operated over a frequency range of 1 to 200 MHz, employing a focused poly-vinylidene fluoride (PVDF) transducer optimally tuned for a centre frequency of 50 MHz. For the given $f_{no}$ of 2.2, the system exhibited a -6 dB lateral resolution cell width of 70 µm, axial resolution of 54 µm and a depth-of-focus of 900 µm. The Doppler capabilities of the system were complemented by a duplex scanning mode for simultaneous B-mode imaging.

This high frequency Doppler system detected in vitro string and capillary flow phantom velocities equivalent to capillary and arteriole velocities. It successfully measured a string phantom velocity of 0.5 mm/s, as well as a 100 µm diameter capillary flow phantom velocity of 7.4 mm/s, with reported velocity resolution of 30 to 300 µm/s. These in vitro measurements showed that blood velocities of ‘less than 5 mm/s’ encountered in arterioles and venules with vessel diameters of 20 to 35 µm could also be measured at a penetration depth of 100 µm. Blood flow was also qualitatively detected in the vessels of a human hand 500 µm in diameter. These results showed that high frequency pulsed Doppler velocity detection was feasible, constrained by parameters related to the penetration depth, required resolution for vessel diameter in question, and appropriate velocity range.

2. Background
Conventional ultrasound scanners estimate blood velocity using continuous wave Doppler or pulsed Doppler techniques. The two primary Doppler techniques detect the axial component of fluid flow. In continuous wave (CW) Doppler, velocities are calculated based on the Doppler frequency shift of scatterers in blood. In pulsed Doppler, the time shift of signals at a specified range gate is measured to calculate scatterer velocity. Alternative image-based flow detection methods such as decorrelation are based on the principle that scatterer displacement causes measurable changes in the statistics of image speckle from the B-mode resolution cell.

2.1 Doppler techniques
In continuous wave Doppler ultrasound, a sinusoidal ultrasound beam is transmitted axially toward the region of interest. The return signal is sampled and summed over all scatterers. The resulting Doppler shift frequency is proportional to the axial blood velocity. The velocity estimate must be corrected to account for the angle between the ultrasound beam axis and the direction of blood flow. Continuous wave Doppler systems are simpler to implement than pulsed Doppler systems, but suffer the disadvantage of a large insonified volume. This results in coarse localisation and unavoidable ambiguity when attempting to distinguish velocities in vessels in close proximity.

Pulsed Doppler techniques overcome this measurement ambiguity by using a time shift estimate of scatterers in a precise insonified volume. A rapid sequence of transducer pulses is used to interrogate at a known depth (range gate) to determine localised scatterer velocity. The maximum detectable velocity is limited by pulse repetition frequency, which is in turn limited by depth in tissue. The relationship between pulse repetition frequency and depth in tissue arises because the backscatter signal must be received from the deepest depth of insonification before the next pulse is emitted.
Despite their ubiquity, Doppler methods have several fundamental shortcomings. Continuous wave Doppler suffers from a large insonified volume, and even the smallest pulsed Doppler range gate is formed from a sample volume larger than the B-mode resolution cell of image-based techniques. Angle dependence and one-dimensional measurement are limitations of both Doppler techniques. Doppler measurements in commercial ultrasound systems require \( a \ priori \) knowledge of the angle between transducer and insonified vessel. Doppler methods only quantify the axial flow component and are unable to quantify the lateral or transverse flow component. (A 90° probe orientation incorrectly detects no flow.) However, as many blood vessels of interest are parallel to the skin and hence orthogonal to the transducer, it is clear that techniques capable of quantifying the lateral or transverse flow component are necessary.

2.2 Decorrelation methods

Every pixel in a B-scan ultrasound image is formed from backscattered echoes of a three-dimensional volume in space referred to as the resolution cell. The statistical changes in the echo envelope intensity are related to the motion of scatterers through the ultrasound resolution cell. Scatterer displacement is calibrated against the change in the Pearson correlation coefficient \( \rho \). Increasing scatterer displacement is reflected by decreasing correlation coefficient, signifying greater decorrelation.

Li [6] demonstrated speckle decorrelation methods to determine elevational scan plane motion for freehand 3-D ultrasound. Prager et al. [7] presented a theoretical model for this result that leads to equation (1) under the assumption of a Gaussian resolution cell profile. Their objective was to eliminate the extrinsic position sensor in freehand 3-D ultrasound systems by estimating elevational scan plane motion. Prager et al. relied on the fact that the resolution cells between successive scans overlap and are statistically related. If the probe is stationary and used to scan a flowing fluid, then the sub-resolution scatterers moving through the resolution cell will change over time. When this time interval is sufficiently short, and hence scatterer motion is small, some of the scatterers in the fluid will still remain in the resolution cell, as illustrated in Figure 1.

\[
\rho = \exp \left( -\frac{d^2}{2\sigma^2} \right) \tag{1}
\]

Here \( \rho \) is the Pearson correlation coefficient; \( d \) is the distance the fluid moved in the time interval \( t_1 \) to \( t_2 \); and \( \sigma \) is standard deviation of the width of the resolution cell in the direction of motion.

If there is no fluid motion, then the scatterers of resolutions cells in temporal succession will be stationary and hence completely correlated. Since scatterer displacement is a function of time,
calibrating the rate of decorrelation for a given sample volume produces a velocity estimate. With the transducer mounted in a transverse orientation, fluid flow through the vessel cross-section is detected. State-of-the-art blood velocity estimation methods such as decorrelation overcome many of the disadvantages of conventional Doppler systems. For a given frequency, the B-scan resolution cell is smaller than the pulsed Doppler sample volume. The decorrelation-based technique is sensitive to motion in any direction, and is particularly well-suited to detecting the transverse perpendicular flow component that is impossible with Doppler techniques.

3. Experiments
Ultrasound is constrained by the trade off between spatial resolution and penetration depth. Higher frequency transducers deliver higher resolution images and smaller resolution cell volumes, but lower frequency transducers penetrate deeper into tissue. With this constraint in mind, it would be desirable to detect blood flow in very small blood vessels using a transducer of lower frequency.

We performed in vitro experiments to test whether it was possible to detect the flow of blood mimicking fluid (BMF) in 0.5 mm diameter soft plastic tubing. BMF was prepared according to Ramarine et al. [8] and pumped through a flow phantom using a peristaltic pump as shown in Figure 2(a). The average flow rate was 0.03 ml/s as measured by timed collection, equating to an average linear velocity of 16 cm/s.

Radio frequency ultrasound data was directly acquired using a modified Diasus ultrasound machine (Dynamic Imaging) with a 10-22 MHz linear array probe as in Figure 2(b). After time gain compensation, the RF data was digitised using a 14-bit Gage analogue-to-digital converter, clocked synchronously at 66.7 MHz with the internal clock driving the ultrasound machine timing sequence. RF data was acquired at 53 frames per second. The RF data was used to obtain echo envelope intensity information for B-scan windows of 488 by 260 pixels. Envelope detection and compression were performed in software to avoid non-linear mappings generally introduced in the standard signal processing of commercial ultrasound machines. Three data sets of flowing BMF were acquired along with three data sets where there was no flow in the phantom circuit. One hundred frames were analysed from each data set, and the results were produced from a total of 600 data frames.

Figure 3 presents a B-scan of the transverse vessel cross-section at a depth of 2 cm. The bright patches represent the top and sides of the tube walls, but the bottom of the tube was not visible. The lumen of the tube can be seen as the dark patch in the middle. The interframe correlation of echo envelope intensities was computed for three different patch sizes. The patch sizes were 20 by 5 pixels, 10 by 5 pixels, and 5 by 5 pixels; representing regions of interest (ROI) of 0.5 mm, 0.25 mm and 0.125 mm, respectively.
4. Results
The experimental results showed that the lumen of flowing and non-flowing scans was identifiable by statistically significant differences in the correlation coefficient. In particular, the standard deviations of the interframe correlation coefficients for the vessel lumen and vessel wall were significantly different in flowing and non-flowing scans. Decorrelation caused by moving fluid was reflected in a lower mean correlation coefficient and significantly greater standard deviation in the lumen of flowing versus non-flowing scans. The mean correlation coefficient for vessel wall was very close to unity, as expected, for a stationary structure.

The correlation statistics for all patch sizes are presented in Table 1. Figure 4 presents the results for scans with and without flow for a 20 x 5 patch. For flowing lumen, the mean correlation coefficient was 0.9488 compared to 0.9721 for lumen with no flow. The standard deviation for flowing scans was 0.0663 versus 0.0205 for scans with no flow. There was virtually no speckle decorrelation and a minute standard deviation of less than 0.003 in vessel wall.

The absolute value of the correlation coefficient was well-suited for distinguishing tubing wall from the surrounding water in the acquisition tank of the flow phantom. The region surrounding the tubing was statistically uncorrelated with mean correlation coefficients less than 0.05 in all cases.

Patch sizes of 10 x 5 pixels and 5 x 5 pixels representing lumen widths of 0.25 mm and 0.125 mm, respectively, were also analysed. The results for both the 10 x 5 patch and 5 x 5 patch are presented in Table 1. The 5 x 5 patch was tested to determine the limit of resolution with regard to minimum lumen diameter. These results verified that the variance of the correlation coefficient was able to distinguish flowing and non-flowing lumen in widths narrower than the physical 0.5 mm bore of the original tubing.

5. Discussion and Conclusions
The experimental results for all tubing sizes indicated that the standard deviation of the correlation coefficients of interframe echo envelope intensity was the most reliable statistic for flow detection.
There was significant overlap in the mean absolute values of the correlation coefficients themselves, making them unsuitable for discriminating flow. The surrounding water in the acquisition tank was completely uncorrelated to the lumen and tubing walls.

From Table 1, it is evident that for all patch sizes, standard deviation of lumen during fluid flow was greater than standard deviation for no flow. Furthermore, the standard deviation of the tubing wall was consistently much less than for flowing and non-flowing lumen. The 10 x 5 and 5 x 5 patch sizes corresponded to theoretical lumen widths of 0.25 mm and 0.125 mm, respectively.

The decorrelation technique is viable within a freehand three-dimensional ultrasound system such as Stradx [9]. For a frame rate of 50 Hz, the variance of interframe correlation depicted in Figure 4 suggests that a 20 to 30 frame sequence would be adequate to detect flow in lumen. The probe would be held stationary for approximately 0.5 seconds to ensure statistically reliable flow detection, then moved transversely along the vessel in question to reveal its three-dimensional geometry. In vitro flow was pulsatile, but in vivo we would expect steady flow in microvasculature. Consequently, mean correlation may adequately detect flow, thereby allowing for a shorter measurement interval and a less cumbersome scanning protocol.

We recall that 50 MHz pulsed Doppler was reported to detect flow in vessels of 0.02 mm to 0.5 mm in diameter at a depth of 0.1 mm. We have shown that decorrelation of the echo envelope intensity can be used to detect in vitro flow in tubing of 0.5 mm diameter. Further measurements on smaller patches indicated that this technique may be extended to detect flow in significantly smaller vessels at depths of 1 cm to 2 cm.

6. References

[1] Jensen J A 1996 Estimation of Blood Velocity using Ultrasound: a Signal Processing Approach (Cambridge: Cambridge Univ. Press)
[2] Forsberg F 2002 IEEE 2002 Proc. of the NE Conf. BioMed. Ultrasound imaging of angiogenesis 1 291 – 2
[3] Christopher D A , Burns P N, Starkosk B G and Foster S F 1997 Ultrasound Med Biol. A high-frequency pulsed-wave Doppler ultrasound system for detection and imaging of blood flow in the microcirculation 23 997 – 1015
[4] Taylor K J, Merrit C and Piccoli C 2002 Ultrasound Med Biol. Ultrasound as a complement to mammography and breast examination to characterize breast masses 28 19 – 26
[5] Christopher D A, Goertz D E and Yu J L 2000 Ultrasound Med Biol. High-frequency color flow imaging of the microcirculation 26 63 – 71
[6] Li M 1995 United States Patent 5582173 System and method for 3D medical imaging using 2D scan data Application 529778
[7] Prager R W, Gee A H, Treece G M, Cash C J C and Berman L 2003 Ultrasound Med Biol. Sensorless freehand 3-D ultrasound using regression of the echo intensity 29 437–46
[8] Rammarine K V, Nassiri D K and Hoskins P R 1998 Ultrasound Med Biol. Validation of a new blood mimicking fluid for use in Doppler flow test objects 24 451 – 59
[9] Gee A H, Prager R W, Treece G M and Berman L 2003 Pattern Recognition Letters Engineering a freehand 3-D ultrasound system 24 757 – 77

| Vessel Feature | Flow n = 300 frames | No Flow n = 300 frames | Wall n = 300 frames |
|----------------|---------------------|------------------------|-------------------|
|                | σ                   | σ                      | σ                 |
| Patch 20 x 5   | 0.066               | 0.021                  | 0.003             |
| Patch 10 x 5   | 0.43                | 0.015                  | 0.002             |
| Patch 5 x 5    | 0.096               | 0.017                  | 0.002             |