SofTMech Work Package WP6 Progress Report

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July 2021

6.1 Multiscale Solid Tumour Modelling.

The latest research in this area has concentrated on two key aspects of cancer progression: diagnosis/prognosis and metastatic spread. Both have been studied by means of our numerical Perfusion-Tissue-Interactions platform (*numPTI*) – diagnosis/prognosis using novel contrast-enhanced ultrasound (CEUS) models of microbubble transport, and metastatic spread through the coupling of an adaptive angiogenesis methodology to a cellular-scale tissue model.

For the first time, developments have allowed us to compare ground truth (GT) perfusion-related data from the microcirculation with those emerging from established ultrasound simulation tools to help provide an assessment of the accuracy and utility of current imaging protocols. To this end, microbubble (MB) infusions have been tracked as they pass through vascular beds at different angiogenic states and containing a variety of tumour occlusions (Figure WP6.1) – multiscale analysis of corresponding time-signal intensity data has provided valuable insights into how best to interpret ultrasound data for cancer staging and the evaluation of treatment efficacy.

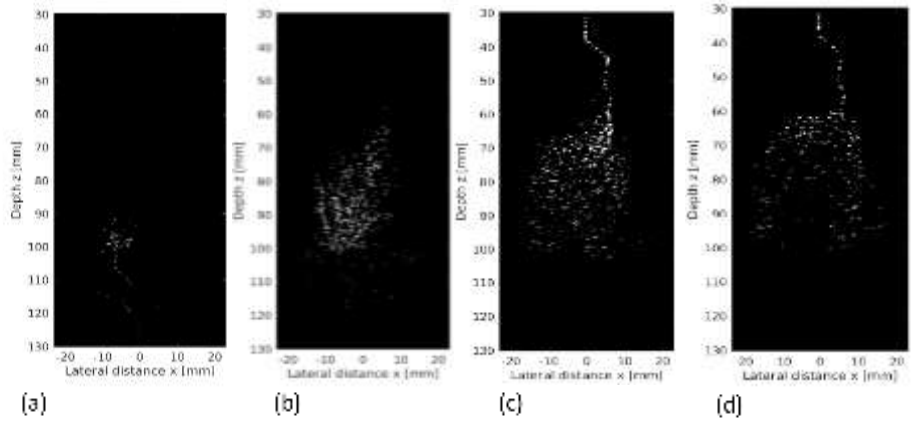

Figure WP6.1: snapshots of MB bolus flow through network(c at a)t=5sec, b) t=10sec, c) t=15 sec, and d) t=25

In addition to the ultrasound studies, work has continued on modelling metastatic spread. New parent vessel networks have been implemented into *numPTI* that allow for the initiation of angiogenic sprout tips throughout a realistic tissue domain. Tumour fragments can be tracked as they enter the nascent vasculature from a developing tumour – when coupled with the St. Andrews cell-based tumour model, we will be able to follow micro-metastases as they leave the primary tumour site and re-emerge as metastatic foci in downstream organs.

Specific outcomes from WP6 include the following:

6.1 We have investigated the use of minimum variance Beamformer (BF) methods, in combination with image analysis, to ascertain whether they are able to provide additional diagnostic benefits and deliver diagnostic data at lower cost [1]. This study showed that the use of adaptive BFs provides improved microbubble localisation for critical separations between 100μm and 1000μm. For lateral distances greater than 1000μm, the use of adaptive BF does not provide any additional benefits in the process of MB localisations because the MBs are already well separated without significant overlap of point spread functions. For lateral distances lower than 100μm the use of adaptive BF does not provide additional benefits because the overlap is so high that there is only one detection for paired events.

6.2 We have used our modelling platform to predict the degree to which an obstruction affects the flow distribution in a micro vessel system and investigated whether Contrast Enhanced Ultrasound Imaging and indicator dilution models would be able to detect these changes. CEUS quantification relies on the spatio-temporal evolution of MBs in the blood stream following their intravenous injection. The MB echoes are registered as intensities that change with time in a specific region of interest and are related to the blood flow dynamics in the region as well as the upstream circulation.

There are two categories of perfusion quantification models: (i) wash-in models of constant infusion used with the destruction-reperfusion method, and (ii) transient MB concentration measurements after bolus injection. The constant infusion method makes use of the fact that MBs can be selectively destroyed by high amplitude ultrasound, allowing cycles of wash-in and destruction to be repeated multiple times and for the wash in behaviour to be modelled and analysed. A realistic vascular bed was realised by constructing a homogeneous capillary plexus and then running the adaptive capillary subroutines available in *numPTI* (Figure WP6.2). We have confirmed our initial hypothesis that an obstruction, even at a capillary level, can have a significant impact in neighbouring areas of the bed and that such abnormalities can be detected using CEUS (Figure WP6.3) [3]. The controlled environment of the vascular model has also allowed us to compare and evaluate of a number of different image processing approaches [3].

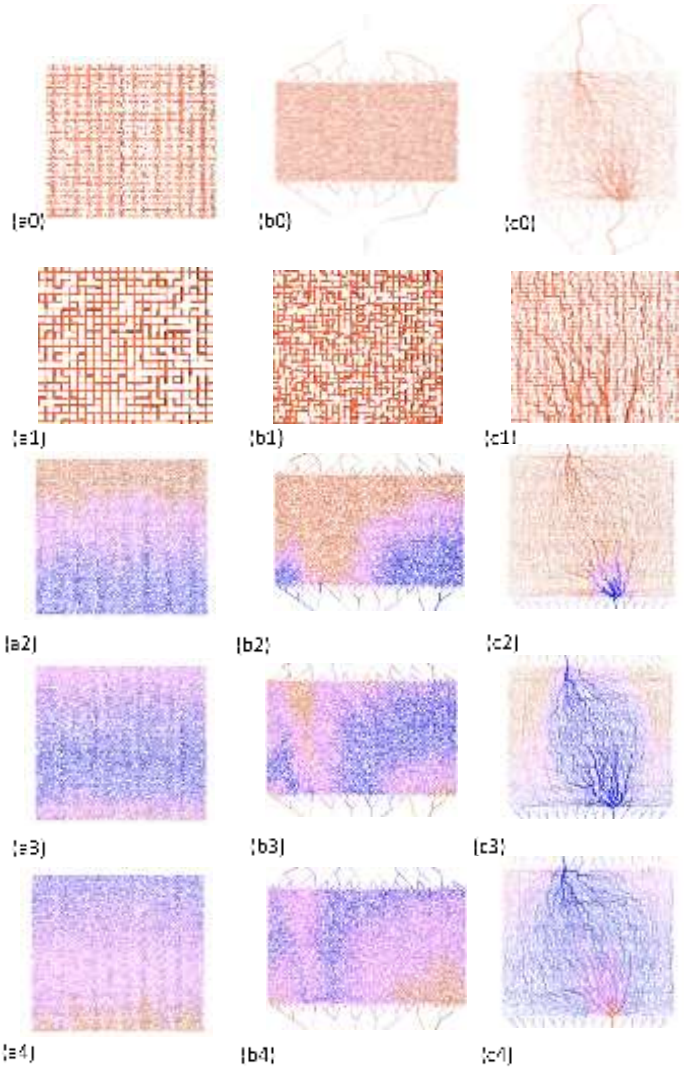

Figure W26.2 Network design evolution, network properties, and tracer flow (blue) in each network. a) Regular lattice network, b) regular lattice network with a 25% distortion of the lattice and introduction of one inlet and one outlet, c) resulting network after the process of adaptation has been applied on (b), a1, b1, and c1) zoomed areas of networks (a), (b), (c) respectively. In b1 the 25% distortion is visible. a2, a3, a4) flow profile of network (a) at t=25, b2, b3, b4) flow profile of network (b) at t=25 c2,c3,c4) flow profile of network (c) at t=25

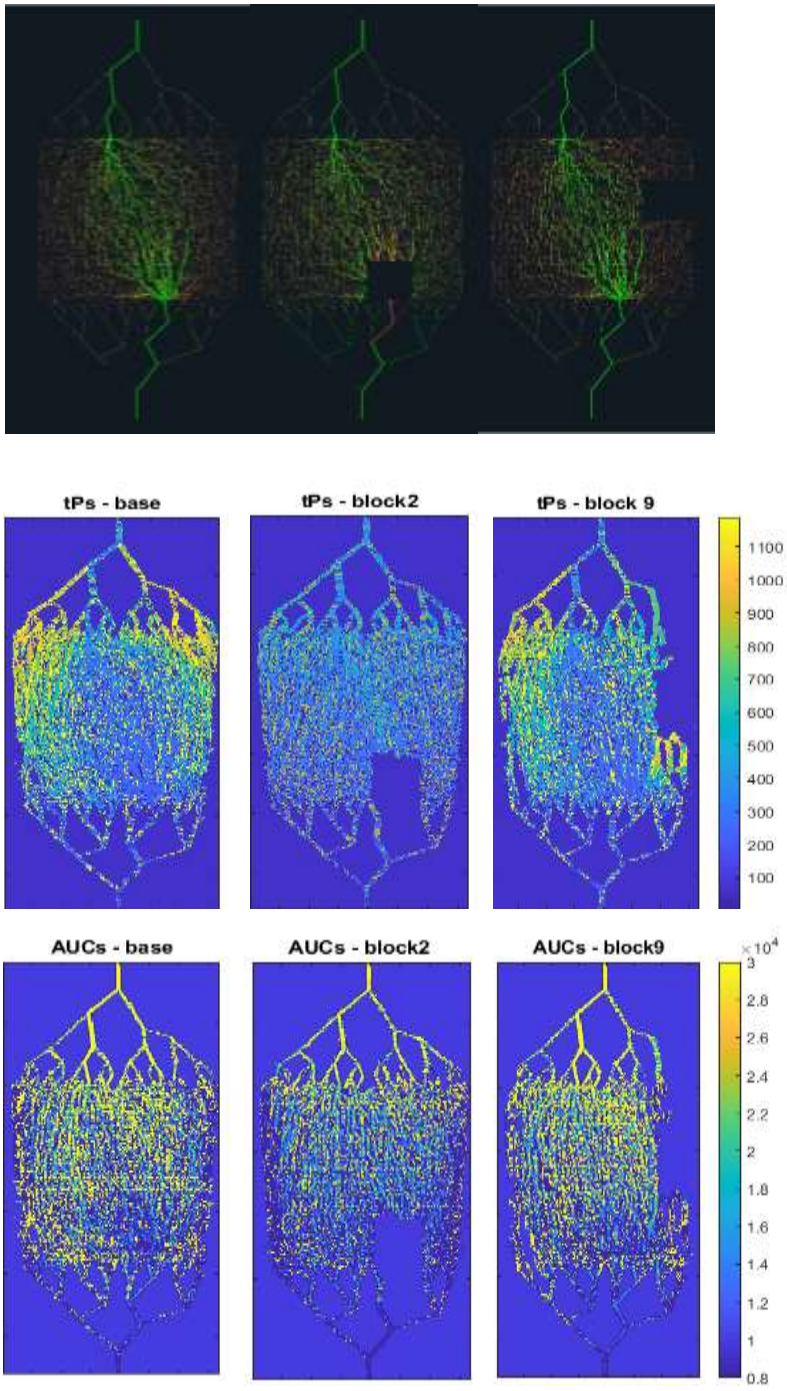

Figure W96.3: a) Maps of ground truth flow distribution corresponding to full network and 2 occluded networks (for which flow probs are shown in green). b) Parametric maps of Time to Peak (tp) and Area Under Curve (AUC) for the same networks.

6.3 By comparing ground truth (GT) data from *numPTI* with Time Intensity Curves (TICs) and parametric maps derived from particle tracking software, we have been able to assess the impact of tumour stage and tumour vascularity on the detection capabilities of CEUS with each method and suggest new measurement protocols. The relative utility of a number of derived imaging parameters, including the classical Area under the Curve (AUC), Mean Transit Time

(MTT), peak Intensity (Ip), and super resolution parameters have been studied and evaluated (Figures WP6.4 and WP6.5). We have demonstrated that SRI parametric mapping reveals useful information on tumour vascularisation for tumours up to 1.5mm in diameter in a vascularised region that would normally be considered poorly vascularised. Tumours with necrotic cores are easier to locate on the maps by identifying: gaps in track maps, increased track density around the tumour, and increased speed at the tumour periphery. In terms of image processing, the SRI algorithm has successfully detected pathologically-compromised tissue in situations that could not be identified through conventional Time Intensity Curve analysis.

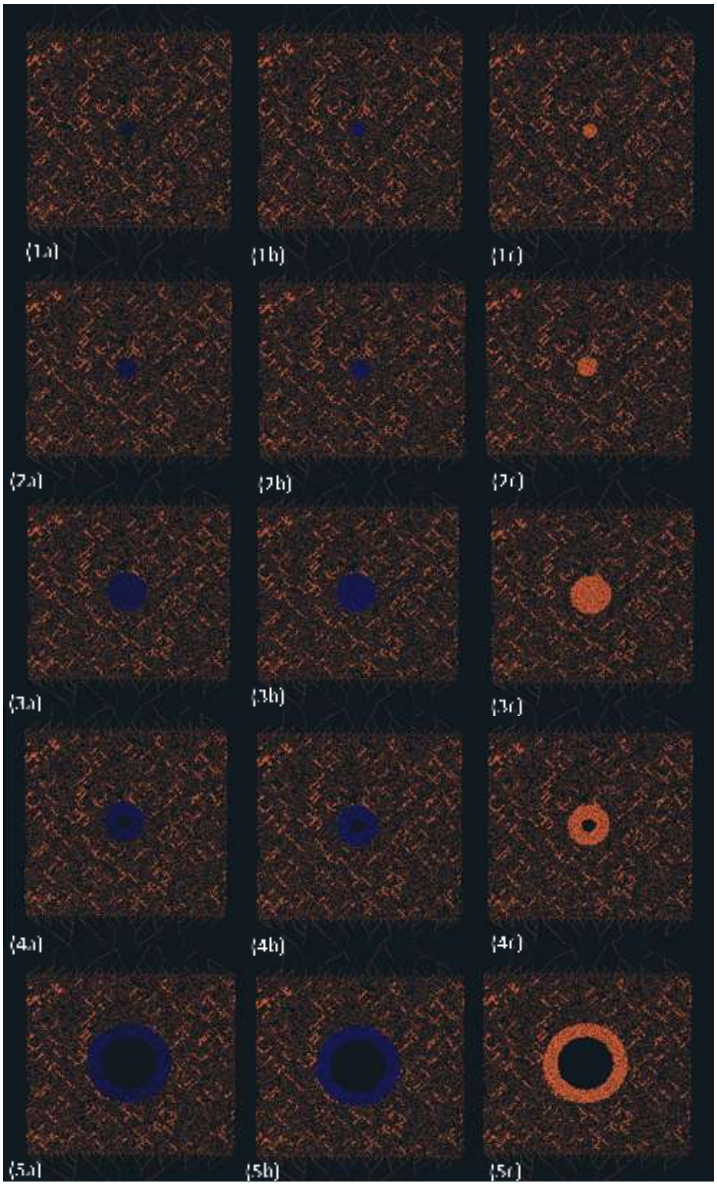

Figure: WP6.4: Different tumour stages placed at the centre of an identical 'base' network. Stages 1-5 indicate tumour stage. Subcategories (a), (b), (c) at each tumour stage are an indicator of the tumour maturity and account for the variability of tumours: (a) are base cases, (b) have increased connectivity of angiogenic capillaries, (c) angiogenic capillaries have increased connectivity and tortuosity.

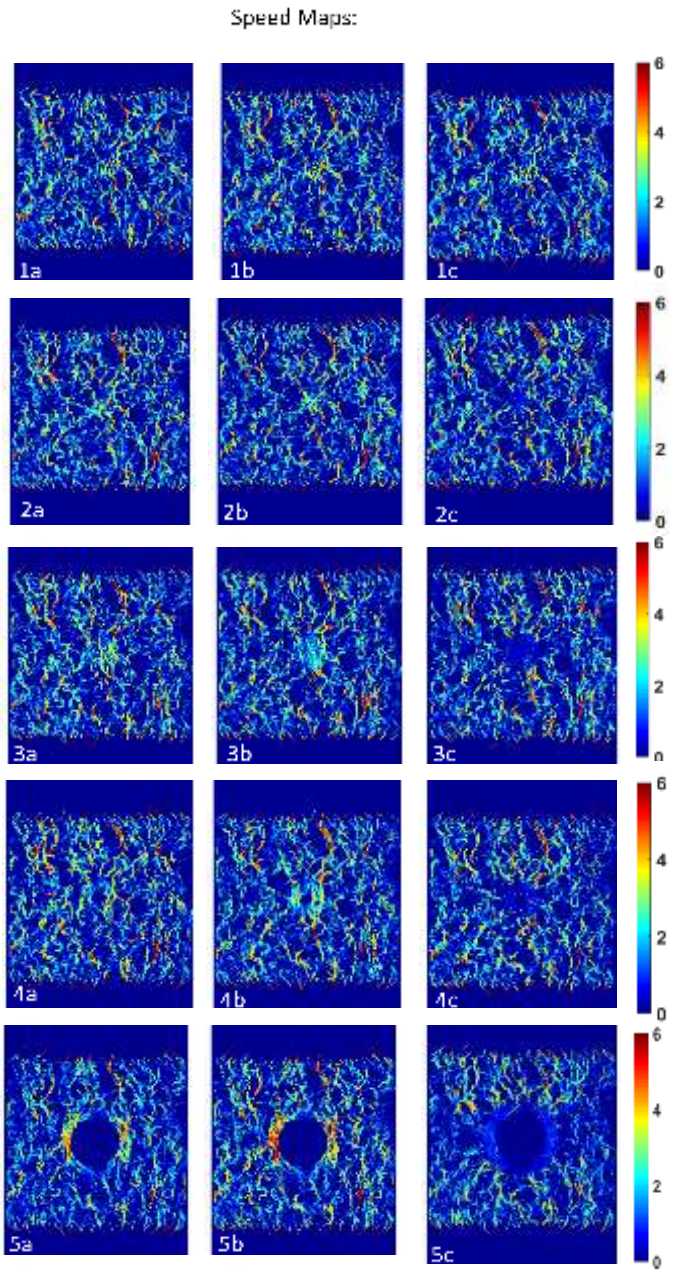

Figure WP6.5. Speed maps for all tumour stages. The colour scales are chosen in way that is the best depiciton of the undelying netowrk

[1] Kanoulas et al, (2019). Super-Resolution Contrast-Enhanced Ultrasound Methodology for the Identification of In Vivo Vascular Dynamics in 2D. *Investigative Radiology*, 54, 1

[2] Voulgaridou et al (2020), An Organ Flow Model for Developing Vascular Characterization Using Contrast Enhanced Ultrasound (CEUS) Imaging, *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020, pp. 1-3, doi: 10.1109/IUS46767.2020.9251467.

[3] Voulgaridou et al (2020), Improved microbubble (MB) Localisation Using Particle Detecting algorithm: Evaluation of Algorithm Performance for Different Beamforming Methods, 2020 IEEE International Ultrasonics Symposium (IUS), Las Vegas, NV, USA, 2020, pp. 1-4, doi: 10.1109/IUS46767.2020.9251433.