Flow Heterogeneity as a Potential Biomarker of Vascular Normalisation in Tumour Studies

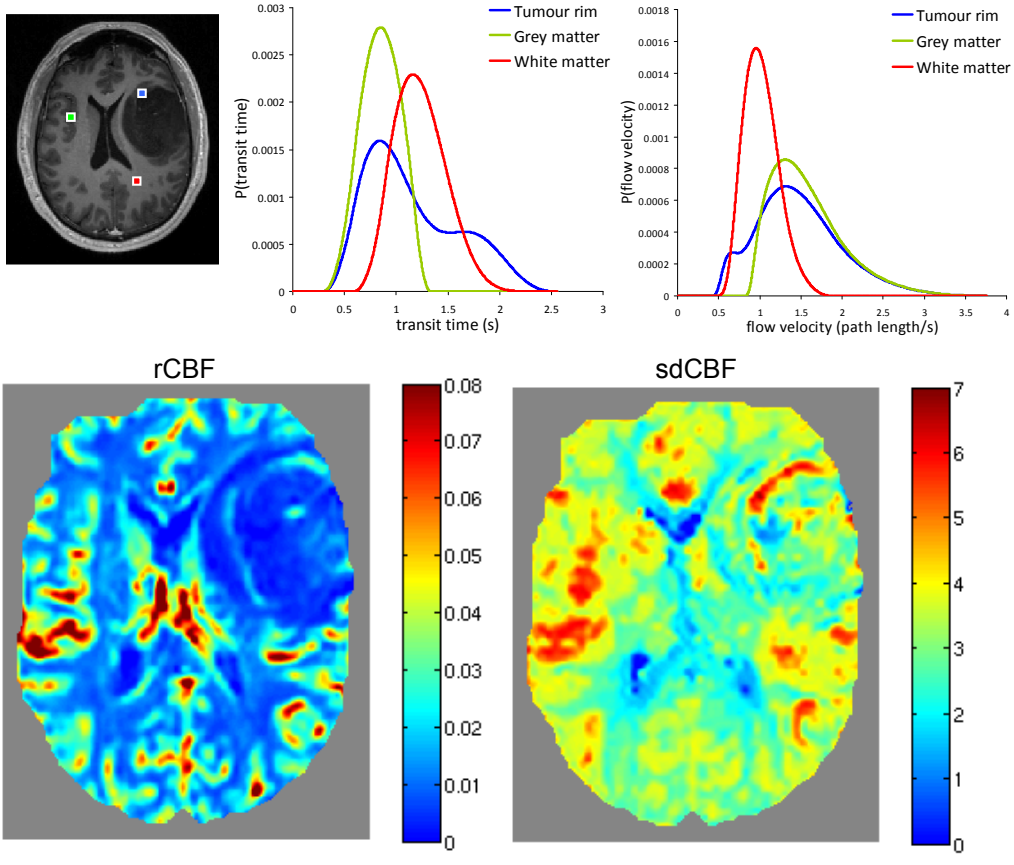
J. D. Dickson[1], R. E. Ansorge[1], and S. Price[2]
[1]Department of Physics, Cambridge University, Cambridge, Cambridgeshire, United Kingdom, [2]Medical School, Cambridge University

Introduction: Recent research has shown that the success of anti-angiogenic treatment can be due to a process known as vascular normalisation. It is thought that by returning the structure and function of the tumour vasculature to that of healthy tissue, the efficacy of conventional therapies can be improved [1,2]. The need to track the effectiveness of anti-angiogenic treatment has therefore created a demand for effective biomarkers of vascular normalisation. One proposed biomarker is the radii of vessels present [3], however vessel size imaging requires intravenous injection of Iron Oxide contrast agents. We propose that effective information on normalisation of vascular morphology may be attainable using only Gadolinium-based tracers by measuring intravoxel heterogeneity in flow rate.

Methods: Seven patients were examined according to our standard perfusion protocol on a Siemens Trio 3T scanner. The pulse sequence was T_2^* weighted GE EPI with: TR = 1.5 s, and TE = 30 ms. There were 90 images acquired with 19 slices per volume, each of 5 mm thickness and 1.5 mm spacing. The in-plane resolution was 2 x 2 mm in a 192 x 192 x 123 mm field-of-view. Imaging started 20 seconds before intravenous injection of Gadoteridol contrast medium. Informed consent was received from all patients and the study was approved by the local ethics committee.

In order to assess the heterogeneity of CBF in a voxel, we took a similar approach to Østergaard *et al* [4], who introduced flow heterogeneity for stroke analysis. The distribution of transit times can be found by taking the time derivative of the residue function, $h(t) = -dR/dt$ (the amount of contrast leaving the voxel at a time *t* after the arrival of an infinitesimally short bolus). This distribution can then be transformed into a distribution of relative flow rates to find the intravoxel flow heterogeneity. Our method differed from that in [4] in three ways. We used Tikhonov regularised Singular Value Decomposition (SVD) rather than standard SVD for deconvolution to minimise unphysical oscillations in the solution. Also we found dR/dt by fitting *R(t)* with a b-spline that could be differentiated directly, rather than the two nearest neighbours. Finally, in order to take a more quantitative measure of flow heterogeneity, we mapped the standard deviation of the flow rate distribution (sdCBF) rather than the significance of the difference between tissue of interest and reference regions.

Results: Transit time and flow velocity distributions for single voxels of tumour, white and grey matter are shown in Fig 1. White matter displays a symmetrical distribution of flow velocities, however the grey matter distribution is heavily skewed and the tumour distribution is more complex. In three patients we observed increased sdCBF in regions of tumour that typically exhibited lower values of absolute CBF.



Conclusion: Variation in flow heterogeneity across tumours can be detected using Dynamic Susceptibility Contrast MRI. Measuring levels of flow heterogeneity during anti-angiogenic treatment will allow the importance of normal flow distributions in cancer therapy to be investigated and potentially generate a new biomarker of vascular normalisation.

References: [1] Sorensen *et al*, Cancer Research, 2009; 69(13): 5296–5300. [2] Jain *et a,* Science. 2005; 307(5706):58-62. [3] Batchelor *et al,* Cancer Cell, 2007; 11, 83–95. [4] Ostergaard *et al*, JCBFM, 1999, 19: 690–699.