A modified deconvolution method to quantify brain tumour haemodynamic parameters in the presence of contrast agent extravasation.

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Target audience: Clinicians and research scientists interested in MR perfusion (DSC-MR) imaging for brain tumours.

Purpose: Dynamic susceptibility contrast (DSC) MRI is increasingly used for imaging brain tumours, due to its ability to measure important haemodynamic parameters such as cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT). In theory, deconvolution of the tracer concentration time curve (CTC) by the arterial input function (AIF) should provide the residue function R(t), representing the microvascular retention of the contrast agent (CA) within a voxel; differences in R(t)-shapes over different brain areas providing information about haemodynamic variation. However in brain tumour tissue parameter estimation is challenging due to CA extravasation. The aim of this work was to apply a previously developed control point interpolation (CPI) deconvolution method[1] to the case of leaky vessels and use this to investigate variation in cerebral haemodynamics derived from DSC-MRI in the presence of CA leakage.

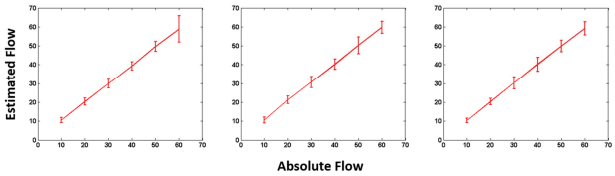

Fig. 1-Estimated CBF plotted against simulated values (SNR=20, CBV=4%) for simulations modelling (a) T2-extravasation, (b) no-extravasation and (c) T1-extravasation effects.*

Methods: CPI represents R(t) by a number of control points whose values are determined by fitting of the predicted DSC signal to the data; the full R(t) being determined by piecewise cubic spline interpolation. However, in the presence of CA leakage a further (primarily T1 related) contribution to the DSC signal arises from CA in the extra vascular space. This was modelled by the calculation of an extravascular function assuming two-compartment kinetics. The intra- and extravascular CTCs were obtained by convolving the intra- and extravascular R(t) with the AIF scaled by CBF and a leakage parameter (LP), respectively. The leakage corrected signal is generated using a CTC to signal conversion equation that accounts for T1 and T2*-relaxivity changes:

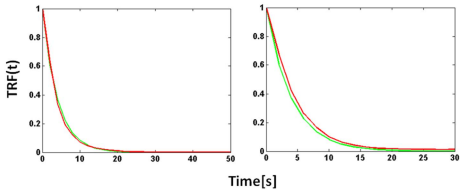

Fig.2 R(t) estimated with mCPI (red) against true residue function (green) for simulations modelling T2 and T1- extravasations (SNR=20, CBV=4%, CBF=60ml/100g/min, LP(T2*)=-0.0001, LP(T1)=00001).*

$$S(t) = S_0 . e^{-(k.CTC_{intra}.TE)} . \frac{(1-e^{-R1.TR}).\sin\theta}{1-e^{-R1.TR}.\cos\theta} \quad ; \quad R_1 = R_{10} + r_1 . CTC_{extra} \; ; \quad r_1 = 4.5 s^{-1} mM^{-1}$$

where LP, in a similar manner to Boxerman et al[2], can take negative (T2* effects dominate) or positive (T1 effects dominate) values. Simulations were performed with S_0=100, TR=2s, θ=FA=60º, TE=0.03s, R_{10}=0.81s^{-1}, CBV=4%, CBF values were varied from 10 to 60ml/100g/min in increments of 10ml/100g/min and LP values from -10^{-4} to $+10^{-4}$ in increments of 10^{-5}. Zero mean Gaussian noise was added to the signal curves to simulate typical DSC-MRI signal curves with a baseline SNR of 20. A total of 50 simulations were run for each combination of CBV, CBF and LP. Coefficients of determination (R^2) were determined to evaluate the signal as well as the R(t) fitting performance for the modified CPI (mCPI) method. Clinical data from two patients with confirmed high-grade glioma were acquired on GE 3.0T MR 750 Discovery using an Institutional Review Board approved protocol with gradient-echo EPI: TR/TE=2s/30ms, FA=60º, 128x128x22 matrix, 1.7x1.7x7mm^3 voxels for Patient 1 and 1.7x1.7x5mm^3 voxels for Patient 2. An intravenous bolus injection of 0.075mmol/kg Gd (Gadovist) was performed. The DSC images were processed and analysed with mCPI. The distribution of transit times (TTD) for passage of blood through the vasculature was calculated from the derivative of R(t) and it was characterised by its standard deviation: the capillary transit time heterogeneity (CTH)[3].

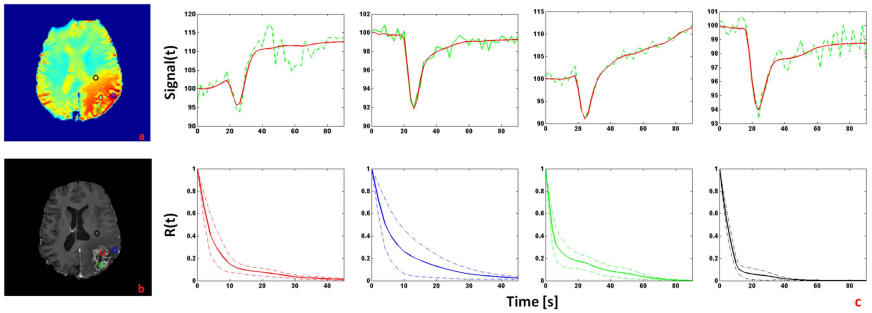

Fig.3-DSC-MRI baseline (a), T1WI (b), signal fitting and extracted residue functions for 4 different ROIs across the tumour (c).

Results: In simulations, mCPI demonstrated both a good signal fitting performance (as given by R^2 values of 0.982±0.03 and 0.977±0.04 for T2* and T1 extravasation effects) and the ability to correctly estimate true CBF (Fig.1). Fig.2 depicts the estimated against true residue function (TRF) with mCPI yielding R(t) in good agreement with TRF, as shown by a R^2 of 0.977±0.09 and 0.944±0.16 for T2* and T1 extravasation effects, respectively. Signal fitting results along with R(t) for four different ROIs (region of interest of 6 voxels) obtained with mCPI for Patient 2 are given in Fig.3.c. The mCPI method demonstrates an accurate fitting for all four ROIs. ROIs I and III demonstrate an overshoot of the pre-contrast baseline, typical for T1 leakage effect. ROIs II and IV appear to be an example of T2*-extravasation effect, believed to be caused by a reduction in the intra-extravascular gradient. R(t) estimated for each ROI depict different trends. E.g. ROI II demonstrates a continuous, close to an exponential decrease. As a contrast, ROI IV contains both a rapid (until t=11s) and a slow component. ROIs I and III yielded higher mean values for CBF [ml/100g/min] (6.38±2.88 and 5.89±4.98) followed by ROI II and IV (2.94±1.11 and 2.71±0.47). Also for CTH [s] ROIs I and III had a higher mean value (20.01±7.85 and 28.64±6.26) when compared with ROIs II and IV (16.11±3.82 and 16.28±4.10).

Discussion: Simulation results demonstrate that the mCPI method was not only able to fit the DSC-MRI signal in the presence of leakage but also to accurately estimate the haemodynamic parameters included in this study. In addition, different R(t)-shapes extracted from different voxels permitted assessment of flow heterogeneity within and around the tumour. The similar CTH values obtained for ROIs II and IV could represent typical flow characteristics of the peritumoral edema, with ROI IV possessing a more heterogeneous capillary TTD assessed by its R(t) shape and its slightly higher CTH value. Elevated CTH is believed to be associated with reduced oxygen extraction factor (OEF)[3], which is linked to hypoxia, known as the initial step of angiogenesis. Based on that, the higher CTH value found for ROI III could be a feature of hypoxic cells present in a dormant rim around the tumour's necrotic core (ROI I).

Conclusion: We have proposed a new deconvolution method which offers a means of obtaining brain tumour haemodynamics perfusion related parameters in the presence of CA leakage. The effectiveness of this method, first tested in simulations, was demonstrated based on clinical cases where different tumour regions presented different residue function shapes.

References: [1] Mehndiratta et al, NeuroImage 2013; [2] Boxerman et al, AJNR Am J Neuroradiol 2006; [3] Ostergaard et al, Cancer Research 2013.