DSC-MRI simulations: what is the correct model for the in vivo tissue residue function?

Amit Mehndiratta[1], Fernando Calamante[2], Bradley J MacIntosh[3], David E Crane[3], Stephen J Payne[1], and Michael A Chappell[1]

[1]*Institute of Biomedical Engineering, University of Oxford, Oxford, Oxfordshire, United Kingdom,* [2]*Melbourne Brain Centre - Austin campus, Brain Research Institute, Heidelberg, Victoria, Australia,* [3]*Medical Physics, University of Toronto, Toronto, ON, Canada*

Target audience: Scientists and Clinicians with an interest in perfusion MRI

Introduction: Model free deconvolution is widely used in DSC-MRI analysis despite consistently underestimating cerebral blood flow (CBF) and introducing artifactual oscillations in the resulting residue function solution [1][2]. New methods that address these problems are routinely evaluated using simulations, commonly referred to as 'digital phantoms'. Simulation studies are typically based on an exponential residue function, with additional variants such as the box function being considered as test of the methods in extreme conditions. However, none of these models may represent the true residue function in normal tissue and are likely to be unsuitable to model haemodynamic changes during pathology, such as in ischemia. The recently proposed Control Point Interpolation (CPI) deconvolution approach offers the possibility of accurately extracting monotonically decreasing residue functions within an essentially model free analysis [3]. The purpose of this study was to investigate residue function variation in normal and infarcted tissue obtained using CPI, and approximate these with different simple analytical expressions to examine whether the exponential model is appropriate for use in digital phantoms and, if not, propose a suitable alternative.

Material and Methods: DSC data were acquired from 8 patients (median age: 65yrs [47 – 85 yrs], M:F=5:3) with atherosclerotic diseases under an Institutional Review Board approved protocol. MRI data were acquired on a Siemens 3T Trio scanner with Diffusion Weighted Imaging (DWI) and GRE-DSC: TR/TE=1.5s/30ms, 78 volumes, 128x128x22 matrix, 1.7x1.7x5mm^3 voxels. An intra-venous bolus injection of 0.1 mmol/kg Magnevist® was performed followed by a 20 ml saline flush. DSC images were processed and analysed using the CPI deconvolution method [3]. In the CPI method, the tissue response function was estimated at a subset of points and then cubic spline interpolation was used to generate the complete smooth residue function. Residue function characteristics were evaluated from Regions of Interest (ROI) based on the DWI and the perfusion weighted images. Before ROI selection rigid body image registration was performed between perfusion and DWI images using the FMRIB Linear Image Registration Tool (FLIRT) from the FSL toolbox [4]. ROIs were selected under two criteria: 1) within a DWI lesion (DWI+), (2x2 voxels) and 2) normal perfused regions (normal) in the hemisphere contralateral to the DWI lesion (3x3 voxels). In total 32 ROIs were selected from eight patients in normal category and 18 ROIs in the DWI+ category. The observed residue functions were approximated with analytical residue function expressions using a maximum likelihood technique. The following 4 expressions were used to fit to the residue function: a) Exponential: $y = e^{-\tau \cdot t}$; b) Bi-Exponential: $y = A \cdot e^{-\tau 1 \cdot t} + (1 - A) \cdot e^{-\tau 2 \cdot t}$; c) Lorentzian: $y = (1 + t^2/\tau^2)^{-1}$; and d) Fermi function: $y = \left(1 + e^{-\frac{\mu}{\kappa}}\right) / \left(1 + e^{\frac{t-\mu}{\kappa}}\right)$. The best approximation was judged by the minimum in the root mean squared (RMS) error. Statistical significance ($p<0.05$) for difference in RMS error among models was calculated using a Student paired t-test.

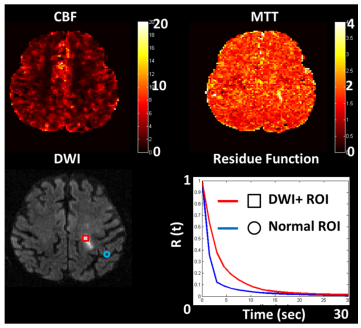

Figure 1: CBF, MTT and DWI image of a representative patient with two ROIs selected in normal (blue) and infarcted (red) tissue. Residue functions observed from ROIs are also shown with slower decay in infarcted tissue ROI.

Table 1: Median (min-max) values of parameters observed for four analytical models investigated while fitting clinical data.

Normal Contralateral Tissue	**Bi-Exponential**	A = 0.97 (0.93-0.99) τ_1= 0.68 (0.43-0.85) τ_2= 0.05 (0.02-0.64)
	Exponential	τ= 0.63 (0.40-0.78)
	Lorentzian	τ= 1.13 (0.91-1.73)
	Fermi	μ= -1.33 (-136 - 0.12) κ= 1.37 (0.85-2.44)
Diffusion Positive Infarcted Tissue	**Bi-Exponential**	A = 0.87 (0.17-0.98) τ_1= 0.24 (0.07-0.59) τ_2= 0.038 (0.005-0.22)
	Exponential	τ= 0.21 (0.07-0.55)
	Lorentzian	τ= 3.31 (1.31-9.96)
	Fermi	μ= -43.5 (-389- 11.48) κ= 4.12 (1.44-11.86)

Results: Smooth monotonically decreasing residue functions were observed with CPI deconvolution method for perfusion analysis of the clinical data. Qualitative differences in the residue function shape were observed for the two ROIs, whereby the DWI+ ROI showed a slower decay (Fig 1). Figure 1 also shows a representative case with CBF and MTT maps, and two selected ROIs (one in diffusion positive infarcted region (red) and other (blue) in normal region). Figure 2 shows the RMS error calculated for analytical residue function approximations with respect to the clinically observed residue function; smallest RMS error was observed with the bi-exponential model for both normal and diffusion positive tissue (fig.2). For normal tissue both bi-exponential and lorentzian models had significantly lower RMS error ($p<0.05$) compared to exponential and Fermi functions. Figure 3 shows a representative residue function fit, the bi-exponential fit approximated the *in-vivo* observed residue function most precisely. Table 1 illustrates that with bi-exponential function fitting the contribution of fast decay component reduced from 0.97 to 0.87 between normal and diffusion positive tissue. The value of fast decay constant (τ_1) reduced by more than 50% and values of slow decay constant (τ_2) also decreased signifying higher contribution from slow transit times in diffusion positive tissue. MTT could be calculated from the bi-exponential model using $MTT = A \cdot \frac{1}{\tau_1} + (1 - A) \cdot \frac{1}{\tau_2}$. The MTT values of 2.03sec (1.18-5.66) and 7.05sec (1.75- 168) were observed for normal and DWI+ tissue respectively using parameters for bi-exponential model as elaborated in table1.

Discussion: When assessing or optimising deconvolution methods for DSC-MRI perfusion analysis, exponential and box-car residue functions are most commonly used. With CPI deconvolution method it is now possible to investigate deviation in *in-vivo* residue function shape under pathological variations. In this study the clinically observed residue function were fit with four different analytical residue function models in order to determine a reasonable residue function shape for digital phantom studies. We showed that bi-exponential residue function expression fits the *in-vivo* observed residue function more closely with lowest RMS error both in healthy and infarcted tissue.

Conclusion: Bi-exponential residue function serves as a good approximation to healthy and infarcted tissue residue function when constructing digital phantoms for DSC-MRI. **Reference:** [1] L. Østergaard et.al, *MRM*, vol. 36, no. 5, pp. 715–25, Nov. 1996. [2] O. Wu et.al, *MRM*, vol. 50, no. 1, pp. 164–74, Jul. 2003. [3] A. Mehndiratta et.al, *NeuroImage*, Sep. 2012. [4] M. Jenkinson et.al, *NeuroImage*, vol. 17, no. 2, pp. 825–841, Oct. 2002.

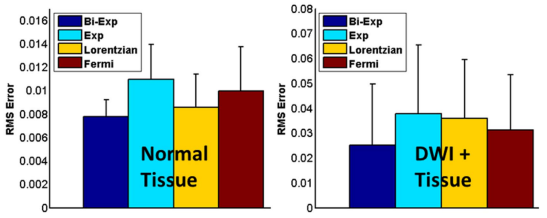

Figure 2: RMS Error in approximating clinically observed residue functions with four analytical functional models. Left: normal tissue, Right: Diffusion positive infarcted tissue.

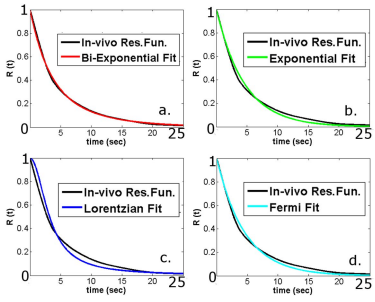

Figure 3: A representative residue function from diffusion positive ROI showing the fitting achieved with four analytical residue functions (a. bi-exponential, b. exponential, c. lorentzian and d. Fermi). The bi-exponential function appears to approximate the *in-vivo* residue function accurately.