Wide variations in cellular-interstitial water exchange rates are within the experimental uncertainty of AIF variations in their effect on uptake curve shapes for DCE-MRI Modelling

M. R. Orton[1], D. J. Collins[1], and M. O. Leach[1]
[1]CR-UK and EPSRC Cancer Imaging Centre, Institute of Cancer Research, Sutton, Surrey, United Kingdom

Introduction Accurate quantification of DCE-MRI data involves the modelling or measurement of three processes; 1) the delivery of contrast to the tissues, typically described by an arterial input function (AIF), 2) the transfer of contrast between the vascular compartment and other tissue compartments, 3) the generation of an MR signal from the tissues of interest. Although there is still debate surrounding appropriate contrast transfer models, we concentrate here on the effects that water exchange can have in relation to variations in the AIF and the MR signal generation process on the tissue uptake curves that are measured in a DCE-MRI examination. Simulations are used to show that for a specific but representative scenario, only small changes in the AIF curve shape are needed to fully account for changes in the tissue uptake curves caused by a very wide range of cellular-interstitial water exchange rates [1,2]. From these we conclude that the AIF and the MR signal model are strongly coupled, indicating that very accurate characteristaion of the AIF is needed to have confidence in in-vivo estimates of cellular-interstitial water exchange rate constants.

Methods Curves were simulated using an AIF described in [3] that is specified by 8 parameters – the middle left panel in the figure shows this curve. The Kety model was used to model transfer of contrast from the vascular to the extra-vascular extra-cellular space (EES) using the following parameters, K^{trans} = 0.05, v_e = 0.14, which are appropriate for muscle tissue [4]. The full two-site exchange model given by equations 1, 2, 3 and 9 of ref. [4] were used to simulate a number of curves for a dynamic gradient-echo imaging experiment with a range of intra-cellular water residence times, t_i. The intra- and extra-cellular relaxation rates were both T_1 = 1060 ms, TR = 3.4 ms and for simplicity S_0 = 1 (amplitude scaling term, including proton density, receiver gain etc.). The left-hand column of panels in the figure use a flip-angle of 30^o, the right-hand column uses 10^o. The top two panels show signal curves generated for a wide range of water residence times and the limits at t_i = 0 (fast exchange) and $t_i = \infty$ (no exchange) are highlighted.

With perfect knowledge of the AIF curve (or equivalently its parameters), these signal curves can in principle be fitted with the model, giving estimates of t_i, v_e and K^{trans} (for simplicity we assume that S_0 and T_1 are known.). This process relies on the fact that the curves have different shapes for different water residence times. We wish to assess whether these changes in the signal curve shape can also be (approximately) generated by using the standard fast-exchange assumption, thus fixing t_i = 0, and instead adjusting the AIF curve, K^{trans} and v_e to fit the signal curves.

Therefore each of the signal curves in the top two panels were least-squares fitted by adjusting K^{trans}, v_e and the 8 AIF parameters with t_i = 0, and with TR, S_0, T_1 and the flip-angles set to their true values.

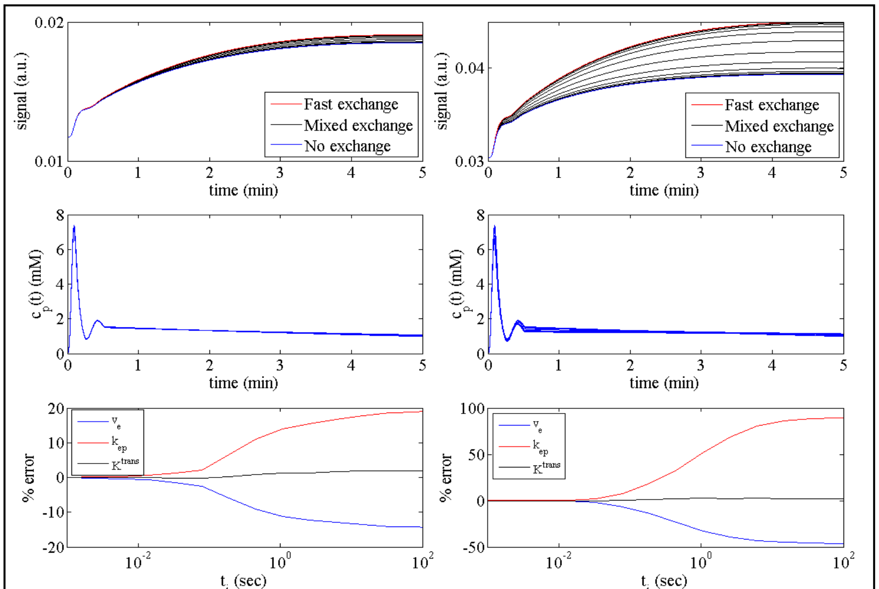

Figure showing simulation results. Left column has FA = 30^o, right column has FA = 10^o. Top row is signal curves from dynamic gradient-echo with various t_i values. Middle row are fitted AIF curves. Bottom row is errors between simulated and fitted transfer parameters.

Results In each case the maximum difference between the "true" signal curve and the fitted curve was less than 0.15%, i.e. they were virtually indistinguishable. The second row of panels shows the AIF curves that are generated from fitting all the signal curves – the mean and maximum differences between the largest and smallest values of these curves are 0.05 and 0.3 mM respectively for the left panel and 0.2 and 1.1 mM for the right panel. The third row of panels show the percentage error between the true and estimated K^{trans}, v_e and k_{ep} (= K^{trans}/v_e) as a function of the water residence time used to simulate the signal curves.

Discussion and Conclusions For the 30^o simulation (left-hand panels) the main conclusion confirms results in [2,4], i.e. that using a high flip-angle decreases the sensitivity of the acquisition to t_i, in that the signal curves are very similar, and the errors on K^{trans} etc. are modest. Higher flip-angles are therefore recommended in practice. Another view of this sensitivity is given by the variability in the AIFs estimated with the fast-exchange assumption – to be able to have any chance of estimating t_i the AIF must be known with greater accuracy than the variability indicated in the middle panel (around 0.05 - 0.3 mM), which is unlikely to be the case in practice for this example. For the 10^o simulation (right-hand panels) the signal curves are now more sensitive to t_i, which in principle is beneficial as these changes may enable t_i to be estimated with reasonable accuracy. However, the corresponding AIF curves indicate that exactly the same shape changes in the signal curves can be produced with rather small changes to the AIF. In practice errors in the AIF are likely to be of similar or larger order than the variability in this figure (0.2 - 1.1 mM) and so it will not be possible to unambiguously interpret these shape changes as being due to water exchange effects. These simulations do not consider the effect of noise in the signal curves and the need to estimate S_0 and T_1; in practice detection and estimation of water exchange effects will therefore be even more challenging than the examples shown here. It should be noted that the apparent insensitivity of the K^{trans} estimates to t_i is not a general property, and is contingent on the particular parameters used in this simulation. To extend this work it would be informative to investigate how these effects vary with different tissue properties, in particular K^{trans}, v_e, T_1 and t_i, and with different AIF shapes. Nevertheless, given that this simulation is typical of a real DCE-MRI system, the inability to extract information on water exchange rates in a single case is sufficient to show that this acquisition set-up should not be used for this purpose. This simulation therefore provides additional support to the suggestion that accurate measurement of the AIF is essential, and that with currently available acquisition protocols, efforts should be made to minimise sensitivity to water exchange effects, e.g. for gradient-echo based DCE-MRI acquisitions high flip-angles should be used.

Acknowledgements We acknowledge the support received for the CRUK and EPSRC Cancer Imaging Centre in association with the MRC and Department of Health (England) grant C1060/A10334 and also NHS funding to the NIHR Biomedical Research Centre. Thanks to Prof. David Buckley for a number of helpful comments and suggestions that have improved this submission.

[1] Yankeelov TE, et., al., *Magn Reson Med* 2003; **50**(6):1151-1169.
[2] Donahue KM, et., al., *Magn Reson Med* 1996; **36**(6):858-867.
[3] Orton MR, et., al., *Proc. Intl. Soc. Mag. Reson. Med.* 16 (2010), 1709.
[4] Buckley D, et. al., *Magn Reson Med.* 2008; **60**(5):1011-1019.