Evaluation of the Effect of Intra-voxel Contrast Agent Diffusion on Quantitative DCE-MRI

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Target Audience: Those interested in quantitative analysis of DCE-MRI data.

PURPOSE The standard approach to evaluating dynamic contrast enhanced (DCE) MRI data is to fit the signal intensity (SI) time course from a voxel or region of interest (ROI) with the Tofts model (1). This allows for estimation of K^{trans} and v_e, which report on perfusion/permeability and the extravascular extracellular volume fraction (v_e), respectively. However, the standard model assumes instantaneous distribution of the contrast agent (CA), which is frequently not the case as in (for example) the heterogeneous vascular density found in tumors. In this case, diffusion of the CA will lead to a spatial and temporal distribution of the CA within the voxel that will affect the local CA concentration and resulting voxel SI, a situation that the standard model cannot appropriately characterize. This work aims to investigate the effect of CA diffusion within the extravascular extracellular space on DCE-MRI signals and the extracted kinetic parameters.

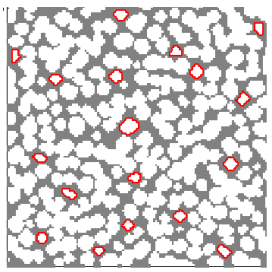

Figure 1. A representative voxel-sized domain.

METHODS We utilize a 2D slice from a 3D phantom consisting of packed cellular ellipsoids to generate the voxel-sized domain (250 um^2) shown in **Figure 1**. The domain consists of the extravascular intracellular space (v_{eis}, white space), vascular space (v_p, red outline), and the extravascular extracellular space (v_e, gray space) into which the CA can diffuse. The voxel utilized in these simulations has a v_e of 0.38. The v_e space of the domain was meshed using triangular elements, and a finite element model (FEM) was devised for the domain which utilized the standard diffusion equation (Eq. [1]), and a variation of the standard Tofts model at the vessel boundaries (Eq. [2]):

$$dC_t/dt = D\nabla^2 C_t \qquad [1] \qquad dC_t/dn = P(C_p - C_t) \qquad [2]$$

where C_t is the concentration of the CA in the v_e, D is the diffusion coefficient, and P is the permeability factor at the vessel boundary. This system allows CA to enter the domain at the vessel boundaries, and then distribute throughout the v_e dependent on the assigned diffusion coefficient (D). Values of D were defined from 5e^{-5} to 3.5e^{-4} mm^2/s, appropriate for the diffusion coefficient of gadolinium chelates in tissue (2,3). The system was then run forward in time for 5 minutes, using a previously measured arterial input function (AIF, 4) as the input. At each time point, the CA concentration distribution was used to calculate the elementally based signal intensity (SI) using the standard gradient echo equation. The calculations were performed assuming an S_0 of 1, $TE << T_2^*$, TR of 0.1 s, T_{10} of 2s, and a flip angle of 25°. For each D the time-to-peak and percent difference in the K^{trans} and v_e from the standard model fit is compared to the fit for the highest diffusion coefficient. Measuring error from the highest D was chosen since the standard model assumes instantaneous mixing of the CA, which is more closely approximated as D is increased; thus, the errors presented are quite conservative.

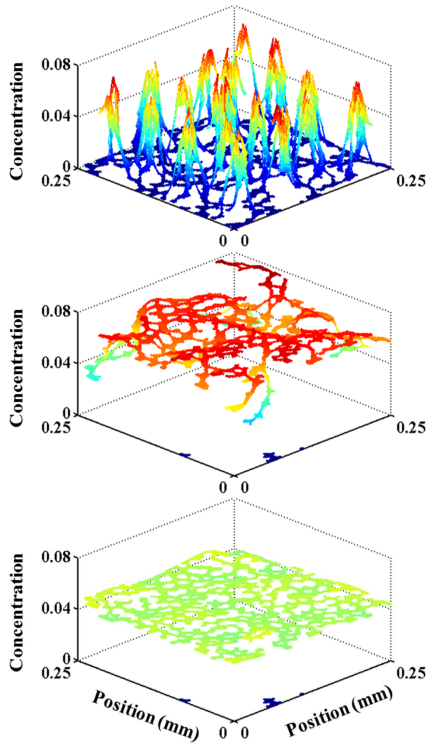

Figure 2. Representative CA concentration distribution at three times (0.36, 1.2, and 4.4 min) during the simulation. Note the inhomogeneity of the distribution.

RESULTS Representative results from the simulations are shown in **Figure 2** and **Table 1**. **Figure 2** shows the concentration distribution within the voxel shown in **Figure 1** for D=6e^{-5} mm^2/s at three time points (0.36, 1.2, and 4.4 min) during the simulation. Based on **Figure 2**, it is (intuitively) clear that as v_e increases, the concentration distribution will be more heterogeneous (for a fixed v_p) thereby increasing the difference in voxel SI. **Table 1** shows that the estimates for K^{trans} and v_e are affected by D, with a more exaggerated effect on K^{trans}.

Table 1. Time to peak and % fit error for D.

D (mm^2/s)	Time to peak (s)	% Fit Difference K^{trans}	% Fit Difference v_e
5e^{-5}	79.9	-45.1	-1.60
6e^{-5}	79.9	-40.6	-1.11
7.5e^{-5}	78.3	-35.0	-0.69
1e^{-4}	67.6	-27.6	-0.35
2.5e^{-4}	59.9	-6.3	-0.01
3.5e^{-4}	58.4	-	-

DISCUSSION In the range of D identified for gadolinium chelates in tissue, CA concentration distribution will have an effect on voxel SI, which will subsequently affect parameterization *via* the standard model. In results not shown, this effect is further magnified in the case of 1) a voxel with poor perfusion and hence a lower v_p, and 2) in cases of slower temporal resolution.

CONCLUSION The work presented here provides simulation-based evidence that passive, intra-voxel CA diffusion can adversely affect the accuracy of estimates of kinetic parameters when the standard DCE-MRI model is used.

REFERENCES (1) Tofts et al. *J Magn Reson Imaging* 1999;10:223-32, (2) Koh et al. MRM, 2013, 69:269-76, (3)Gordon et al. *Biotechnol and Bioeng* 1999; 65(4):459-67, (4) Loveless et al. MRM 2012; 67(1): 226-36.

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