INVESTIGATING 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 Standard analysis of dynamic contrast-enhanced (DCE) MRI data consists of fitting the signal intensity (SI) from a voxel or region of interest (ROI) with the standard Tofts model, allowing for quantification of parameters that estimate tissue vascular characteristics and volume fractions. This model assumes an instantaneous distribution of the contrast agent (CA); however, CA diffusion may play a significant role in regions with heterogeneous perfusion, as would be the case in tumors. In these cases, the standard analysis often results in unphysiological parameter values. This effort investigates the effect of CA distribution due to intra-voxel diffusion on SI and, subsequently, on model parameterization error.

METHODS A finite element model (FEM) of CA diffusion was utilized on a voxel-based domain with a central initial input of CA. The model was run forward such that the amount of CA in the system was fixed, but the distribution within the voxel systematically changed. The resulting sub-voxel distributions were utilized to calculate the concentration of the CA in each element, from which the elemental SI values and hence the total domain SI could be calculated; these values were compared to the SI achieved by uniform concentration distribution, as is assumed in standard analysis. Similarly, a dynamic analysis was performed with varying diffusion coefficients (D) for investigating the relationship between D, temporal resolution, and SI. Again, in the dynamic simulation, a defined amount of CA was introduced at the center of the domain and diffusion allowed to occur. The total SI was calculated at each time step over a specified period of time (i.e., the temporal resolution) for each D so that the dynamic change in SI could be quantified. Finally, to analyze the effect of diffusion on model parameterization, a FEM was devised which coupled the differential form of the standard Tofts model for CA input and the diffusion equation for dispersion of the CA throughout the domain. By inputting K^{trans}, v_e, and D, a forward evaluation of the model resulted in a dynamic tissue concentration curve. The concentration curve was then fit using the standard model, the results of which could be compared to the input parameter values to calculate the parameterization error due to the effects of CA diffusion.

RESULTS **Figure 1** shows the elemental SI values for each of various CA distributions. The distributions include: all CA at the center element, a uniform distribution of CA, and various distributions driven by diffusion (CA Dist #1-3, with increasing values of D which leads to a more uniform distribution of the CA). The total SI for uniformly distributed CA concentration was 2651 (a.u.), and the summed SI for each non-uniform distribution was less than the uniform case (see **Table 1**), thus indicating that distribution of CA within the voxel has an effect on signal intensity. The results from the dynamic simulation are shown in **Figure 2**. The more rapidly the diffusion occurs (see legend), the quicker the total SI approaches the uniform distribution. This is especially interesting in relation to temporal resolution; with an acquisition time of 12 s, a D below ~1e^{-4} mm^2/s has a noticeable effect on the CA distribution and the voxel SI. The results of the parameterization error study (**Figure 3**) showed that with high D, the standard model returns accurate parameter values. However, with decreasing D (and, importantly, over the reported range of the diffusion coefficient of standard CAs [1]), the parameter error increased.

DISCUSSION In the case where there is a non-uniform distribution of the CA within the voxel, the standard model will return inaccurate parameter estimates. Indeed, it is well-known that, in practice, the standard model can yield unphysiological parameter values (e.g., $v_e > 1$), and it has been hypothesized that this error may be due to diffusion of the CA, especially in areas which are poorly perfused [2,3]. Additional data indicates that this problem is exacerbated at imaging voxel sizes (e.g., 220 × 220 μm, 110 × 110 μm) common in DCE-MRI experiments.

CONCLUSION This work provides theoretical evidence that intra-voxel CA distribution, as dictated by CA diffusion, affects the observed SI and hence the estimation of pharmacokinetic parameters.

REFERENCES [1] Koh et al. *MRM*, 2012, epub before print, [2] Pellerin et al. *MRM* 2007;58:1124, [3] Jia et al. *Radiology* 2008;248:901.

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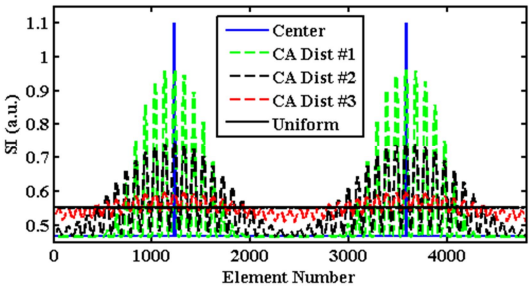

Figure 1. A simulated voxel was divided into ~4800 elements. The SI for each element is shown as a function of CA distribution. Note the differences between the uniform distribution and all other cases.

Table 1. Total SI in the domain for each distribution.

Distribution	Total SI in Domain (a.u)
Center	2244
Dist 1	2465
Dist 2	2597
Dist 3	2647
Uniform	2651

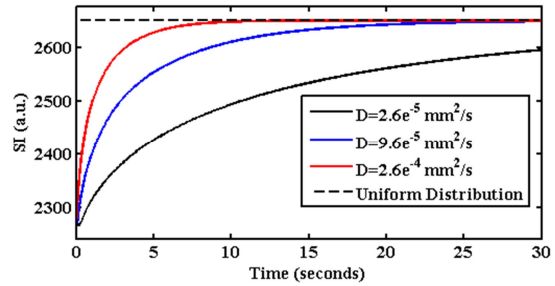

Figure 2. Dynamic domain SI as a function of time.

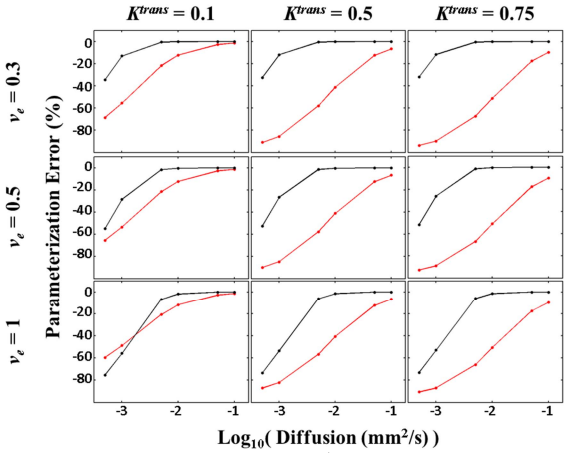

Figure 3. Parameterization error for K^{trans} (red) and v_e (black) as a function of diffusion in a voxel-sized domain (220 × 220 μm). In general, as D increases, the error in K^{trans} and v_e decrease.