A Combined Diffusion-Perfusion Model for the Analysis of DCE-MRI Data

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Introduction: Many models have been proposed to describe the signal enhancement time course in tissues from images acquired with a dynamic contrast-enhanced MRI (DCE-MRI) protocol.[1-3] A common characteristic of the pharmacokinetic models is that they analyze the transcapillary exchange of a contrast agent (CA) on a voxel by voxel basis. In that approach, exchange of CA takes place between the blood plasma and the extravascular extracellular space. This scheme neglects the diffusion of CA within a tissue. However, CA that has extravasated in a well perfused region may diffuse to a poorly perfused, possibly necrotic, region of a tumor (Fig.1). In this case, neglecting diffusion between voxels can lead to underestimated values of the transcapillary transfer rate (K^{trans} [min^{-1}]) in the well perfused region and overestimation, even to unphysical values, of the extravascular extracellular volume fraction (v_e) in the necrotic region (e.g., $v_e > 1$). We propose a diffusion-perfusion (DP) model where CA diffusion is taken explicitly into account and incorporated into the standard Tofts model[1].

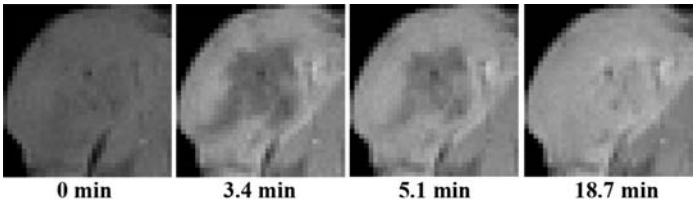

Figure 1: T1-weighted gradient echo images of mouse subcutaneous breast carcinoma. TR/TE: 200/2.4 ms, α: 30°, NA: 4, FOV: 32 x 32 mm^2, data matrix 128 x 128. Images have been zoomed to show the tumor only. A bolus of Gd-DTPA was injected 1 min after the first image.

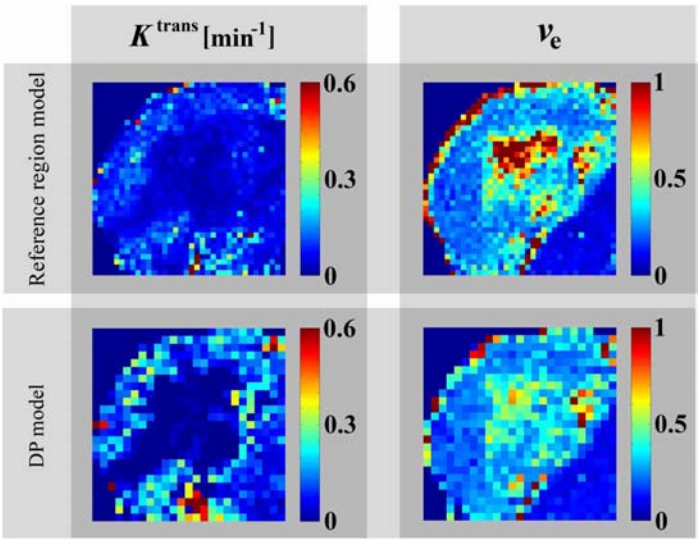

Figure 2: Fitted values of K^{trans} and v_e obtained from the reference region model and from the proposed DP model. Data used with the DP model was downsampled to reduce computation time.

Methods: Adding the diffusion in 2D to the Tofts model[1] for each voxel (i,j) yields:

$$\frac{dC_{i,j}(t)}{dt} = K^{trans}_{i,j}\left(C_p(t) - \frac{C_{i,j}(t)}{v_{e\,i,j}}\right) + \sum_{Interface} D(\vec{r})\,\vec{\nabla}\frac{C_{i,j}(t)}{v_{e\,i,j}}\bigg|_{Interface}\frac{\vec{S}}{V}$$

where $C_p(t)$ is the plasma concentration of CA, D(r) is the diffusion coefficient of the CA within the tissue, $\vec{S}$ is the oriented surface between a voxel (i,j) of volume V and one of its neighbours. Transforming the matrix **C** having a size of m by n into a vector $\bar{\mathbf{C}}$ of length $m*n$ and assuming a small time interval Δt, the solution to the differential equation is approximated by:

$$\bar{\mathbf{C}}(t+\Delta t) = \Delta t\bar{\mathbf{K}}C_p(t)\begin{pmatrix}1\\ \dots \\ 1\end{pmatrix} + \left[\mathbf{1} + \frac{1}{a^2}\Delta t\bar{\mathbf{D}}\bar{\mathbf{V}} - \Delta t\bar{\mathbf{K}}\bar{\mathbf{V}}\right]\bar{\mathbf{C}}(t)$$

where $\bar{\mathbf{K}}, \bar{\mathbf{V}}, \bar{\mathbf{D}}$ are $m\times n$ by $m\times n$ sparse matrices, a^2 is the area of one pixel, and **1** is the $m\times n$ by $m\times n$ identity matrix.

We used a simulated annealing fitting algorithm coded in Matlab™. A stochastic search method is needed to efficiently converge in the very large discrete solution space having countless local minima. The computation was performed on a supercomputer (872 nodes, Intel P4 with 2GB RAM per node). The performance of the proposed model was first tested on simulated data where diffusion of CA was introduced.

Results: In the simulation studies, our results show that the parameters used to generate the simulated data could be recovered reliably when realistic noise (0 – 10% of maximum concentration) was added to the data. The fitting algorithm was found to be insensitive to changes in the initial conditions. We tested our algorithm with experimental DCE-MRI data from mice acquired using the parameters stated on Fig. 1 and the apparent diffusion coefficient (ADC) of water determined from diffusion-weighted spin echo images of the same animals. As a first approximation we hypothesized that the ADC of Gd-DTPA was the same as the measured ADC of water. An arterial input function was derived from a reference region, using the formalism of ref. 3. The top row of Fig. 2 shows the values of K^{trans} and v_e as obtained from the reference region model,[3] which is based on the Tofts model.[1] Unphysical values of v_e are obtained in the center of the tumor, which indicates that a standard two-compartment models may be inadequate in this case. The bottom row shows results from the DP model. Higher K^{trans} values in the well perfused periphery and lower (more realistic) values of v_e in the center are obtained. We chose to use a downsampled dataset to reduce computation time.

Conclusions: Diffusion of CA within a tissue was incorporated in a two-compartment pharmacokinetic model. This DP model was first tested using simulated data. Using real data from a mouse tumor, the DP model yielded more realistic values of v_e in the poorly perfused central region and higher values of K^{trans} in the periphery. This could increase the usefulness of K^{trans} in clinical applications.

References: 1-Tofts PS *et al*., J Magn Reson Imaging *10* 223-32 (1999) **2-**Yankeelov TE *et al*., Magn Reson Med *50* 1151-69 (2003) **3-**Yankeelov TE *et al*., Magn Reson Imaging *23* 519-29 (2005)