Study on Effect of Water Exchange in Dynamic Contrast Enhanced MRI and Pharmacokinetic Model Analysis

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Introduction:

Dynamic contrast enhanced-MRI (DCE-MRI) of a diffusible tracer has widely been used for diagnosis of cancer and monitoring treatment response. However, extracting physiologically relevant parameters from DCE-MRI data is still a challenging problem since the effect of contrast agent is indirectly measured in proton MRI. It has been reported earlier that the water exchange between the interstitium and intracellular space may not be fast enough to be ignored in NMR experiments [1]. However, cross-validation of such effect in DCE-MRI is not trivial and has not been reported. Hence, the purpose of the current study was to use a numerical simulation to generate DCE-MRI data with water exchange effect and to investigate its effects on the pharmacokinetic model parameters.

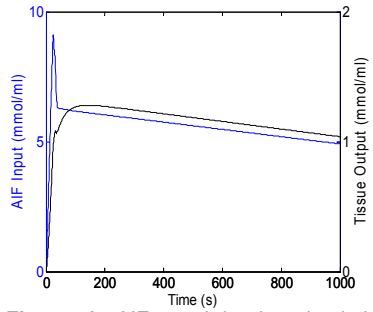

Figure 1. AIF used in the simulation study and an example tissue concentration curve from BTEX.

Materials and Methods:

In this study, it was assumed that the tissue has three compartments; vascular (*p*), extracellular-extravascular (*e*), and intracellular (*i*) compartments. The concentration of contrast agent in each compartment was simulated using the BTEX model (NSR, University of Washington). The relaxivity (r_1) of the contrast agent was assumed to be 3.8 as commonly used for Gd-DTPA. The longitudinal relaxation rate (R_1) of each compartment was estimated based on the linear relationship: $R_1 = r_1[Gd] + R_0$. MRI signal intensity from a spoiled gradient echo sequence was calculated using the three-site two-exchange model presented by Li et al. [2].

Firstly, the effect of water exchange in MRI signal was investigated with a constant concentration of contrast agent and water exchange rates found in literature [2]. Difference in the MRI signal with fast exchange limit (FXL) and that with fast exchange regime (FXR) was calculated for a range of TR and flip angle (α) values. For FXL, the mean intracellular water lifetime (τ_i) and the mean vascular water lifetime (τ_b) were set to 1 us. For FXR, τ_i and τ_b were 0.5 and 0.05 s, respectively. Secondly, the effect of water exchange in DCE-MRI was investigated using an AIF shown in Fig.1. We used two commonly used pharmacokinetic models:

(model-1) $C_t(t) = K^{trans}\int_0^t C_p(t)\exp\left(-K^{trans}(t-u)/V_e\right)du$ and (model-2) $C_t(t) = V_pC_p(t) + K^{trans}\int_0^t C_p(t)\exp\left(-K^{trans}(t-u)/V_e\right)du$

where $C_t(t)$ represents tissue concentration, K^{trans} transfer constant, V_e extravascular-extracellular volume fraction, V_p vascular volume fraction. The models were fitted to the simulated reference using the Simplex algorithm provided in Matlab.

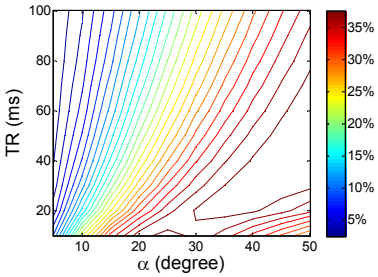

Figure 2. Percent difference between FXL and FXR relative to FXL, depending on TR and α. [Gd]=9mM.

Results and Discussion:

Fig.2 shows a contour plot of the percent difference between FXL and FXR (relative to FXL) plotted as a function of TR and α, when [Gd] = 9mM. The maximum point is about 55%, and the minimum point is about 5%. This shows that the sensitivity of MRI signal to the effect of water exchange can be varied depending on TR and α. Fig.3 shows the accuracy in estimating pharmacokinetic model parameters from the MRI data generated with either FXL or FXR assumption. The first row shows the result of model parameter estimation when only K^{trans} was changed in BTEX. Likewise, the second and third rows show the estimation results when v_e or v_p was changed, respectively. In FXL, it can be observed that model-1 has bigger estimation errors than model-2 as model-1 does not have the vascular compartment. However, in FXR, both model-1 and model-2 fail to estimate the true parameters. The preliminary result shown in this study substantiates the significance of the water exchange effect in estimating pharmacokinetic model parameters. This study will be extended further to assess the pharmacokinetic models including the water exchange effect (1, 2) with the simulated data.

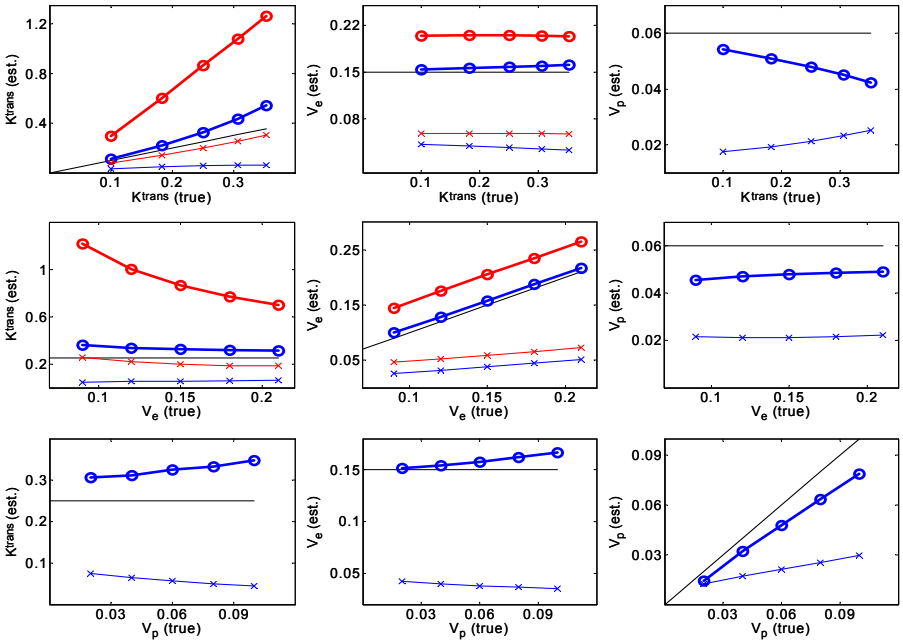

Figure 3. Comparison between estimated and true parameters. Model 1/FXL, solid red lines with circle; Model 1/FXR, dashed red lines with cross; Model 2/FXL, solid blue line with circle; Model 2/FXR, dashed blue line with cross; true value – dashed black lines

Reference: 1. Landis et al., MRM. 42:467-478 (1999). 2. X. Li, et al, MRM. 54:1351–1359 (2005).

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