Intercompartmental Water Exchange Effects in DCE MRI

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Abstract: In Dynamic Contrast Enhanced (DCE) MRI results, the relative importance of the major equilibrium water exchange systems [transendothelial (te), and transcytolemmal (tc)] depends principally on the magnitude of the pseudo first-order rate constant for contrast reagent (CR) extravasation, K^{trans}. Here, simulations are used to clearly show this.

Introduction: Evaluating equilibrium water exchange effects in DCE MRI is very important. Modeling these will depend on the CR pharmacokinetics, the data acquisition technique, and the biological system. Here exchange effects are investigated for a largely intravascular CR using a linear three-site (blood, interstitial, and intracellular) water exchange (3SX) DCE MRI theory [1]. Though inter-compartmental water exchanges are always extant in biological systems, the kinetics of CR extravasation will often make the MR effects of one exchange system dominant.

Methods: All programs were written in Matlab (Mathworks, Natick, MA) and performed on a PC running Windows XP. The normalized T_1-weighted signal intensity [S/S_0] time-course for the first-pass of a monomeric Gd(III) CR through normal brain tissue was simulated. The arterial input function used was that appropriate for the brain following injection of ~0.2 mmol/kg CR in ~20 s [2]. The time-course was discretized, and scattered with random Gaussian noise (zero mean, standard deviation of 5% CNR or ~2% SNR). All fixed parameter values were similar to those in [1]. Unless otherwise specified, values for K^{trans} of 5 x 10^{-5} min^{-1}, v_b (blood volume fraction) of 0.032, τ_b (reciprocal of the unidirectional rate constant for water extravasation) of 0.5 s, and τ_i (mean lifetime of intracellular water molecules) of 1.1 s were used. Fittings of Monte Carlo simulated data (1000 runs each) were used to examine water exchange effects.

Results: **Figure 1** shows a test of the fitting subroutine accuracy and precision. A simulated signal time-course is shown in the inset and a fitted curve is shown in solid line. The initial hyperfine BALD (Blood Agent Dependent Level) peak at 1-2 minutes [3] is quite evident. 1000 fittings of the data from the first 33 minutes were tested with different initial guess values of the two parameters varied, K^{trans} and v_b. (τ_b fixed at 0.5 s) Each gray cross and each filled diamond represents an initial guess and a fitting-returned value, respectively. The two standard deviation (2SD) ellipse of the fittings is shown, and the direction of its axis reflects a positive correlation (r = 0.61) between K^{trans} and v_b. The position of the "true" values, the center of the large blue dashed cross, is well centered within the ellipse.

To characterize te water exchange effects, simulated data like those in the Fig. 1 inset were fitted with fixed τ_b values quite different from that (0.5 s) used to generate the data. **Figure 2a** shows the effect. Again, the position of the "true" K^{trans} and v_b is indicated by the center of the large blue dashed cross. If τ_b is set at a smaller value (0.1 s), the 2SD ellipse is the lower one. If it is set at a larger value (2.5 s), the 2SD ellipse is the upper one. The fitted parameters also show a much higher positive correlation (r > 0.9) in these cases, which indicates stronger parameter interdependence. This indicates that, for very small K^{trans} values such as for the normal brain, te water exchange is a very important factor in DCE MRI modeling that may not be neglected. It certainly may not be ignored as in models that implicitly set τ_b at zero (the fast exchange limit [FXL]) or at infinity (the slow exchange limit).

Another way to characterize te water exchange effects is to make τ_b a variable fitting parameter. **Figure 3** shows this, again for a very small K^{trans} value (5 x 10^{-5} min^{-1}). Now, the fitting cluster must be shown in the 3D parametric space. The 2SD ellipse from these three-parameter fittings is projected onto the K^{trans}, v_b plane in black. The 2SD K^{trans}, v_b ellipse from the Fig. 1 two-parameter fittings is reproduced in blue. The trade-off in going from two-parameter fittings to three-parameter fittings is poorer precision, as expected.

The very slow CR extravasation in the normal brain will almost assure that the equilibrium transcytolemmal water exchange system will remain in the FXL [1]. This is demonstrated in Fig. 2b by setting the fixed τ_i value at a smaller (0.1 s) or larger (3.5 s) value than that (1.1 s) used to generate the data. The two 2SD ellipses almost completely overlap, and also enclose the "true" value blue cross. This confirms that, for very small K^{trans} values, equilibrium tc water exchange will not become a dominant factor in DCE MRI modeling.

However, this won't hold true for even very moderate CR extravasation. **Figure 4** illustrates a simulation similar to that in Fig. 2b, only with a somewhat larger K^{trans} value; 2 x 10^{-3} min^{-1}, instead of 5 x 10^{-5} min^{-1}. Now, a smaller τ_i value (0.1 s) leads to the upper 2SD ellipse (with gray dots) while a larger τ_i value (3.5 s) leads to the lower 2SD ellipse (with green dots). It is clearly shown that, when K^{trans} increases, transcytolemmal water exchange begins to have its impact on the DCE MRI modeling. Neglect of this exchange will lead to inaccurate data interpretation. The departure of fitted results from a small, well-defined 2SD ellipse is also a strong indication of a potentially biased model.

Discussion: These two coupled, sequential water exchange processes have large effects on DCE MRI modeling. The progress of CR pharmacokinetics can make water exchange kinetics appear to transiently slow and then speed back up [1]. Simulations here demonstrate new ways to understand the effects of biological system water exchanges.

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References: **1**. Li, Rooney, Springer, (a) *Proc. Int. Soc. Magn. Reson. Med.* **12**:145 (2004). (b) *Magn. Reson. Med.* **54**:1351-1359 (2005). **2.** Yankeelov, Rooney, Huang, Dyke, Li, Tudorica, Lee, *NMR Biomed.* **18**:173-185 (2005). **3.** Rooney, Li, Telang, Taylor, Coyle, Springer, *Proc. Int. Soc. Magn. Reson. Med.* **12**:1390 (2004).