Quantitative Aspects of Measuring Contrast Reagent Extravasation in the Healthy Human Brain

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Abstract: A sufficiently high magnetic field (≥4T) allows detection of extravasation of the common Gd(III) contrast reagents (CRs) in the normal human brain. [This is not caused by the greater field strength.] We use simulations to investigate aspects of Dynamic-Contrast-Enhanced (DCE) MRI experimental design that allow precise and accurate measurement of this.

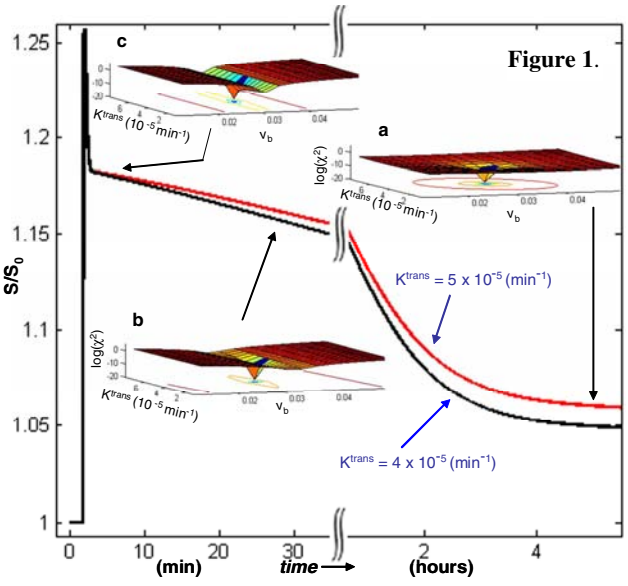
Introduction: Equilibrium compartmental water exchange plays an important role in the interpretation of DCE-MRI results. The introduction of an explicit, linear three-site (blood, interstitial, and intracellular) water exchange (3SX) allows a unified pharmacokinetic theory spanning intravascular and extracellular contrast reagents (CRs) [1]. Starting from the three ^1H_2O magnetizations measured during DCE-MRI, this theory automatically incorporates the effects of these major compartmental water interchanges.

The hyperfine Blood Agent Level Dependent (BALD) effect arises from transendothelial water exchange. It is significant when there is little or no CR extravasation (i.e., intravascular CR), such as in the normal human brain, where the pseudo first-order rate constant measuring extravasation (K^{trans}) is very small for the approved Gd(III) chelates. The initial hyperfine BALD peak in the signal time-course is detectable at magnetic fields of 4T and higher [2], and can be used to determine the blood volume fraction (v_b) and unidirectional rate constant for water extravasation (τ_b^{-1}) assuming $K^{trans} = 0$ [2]. But, also at ≥4T, one can see evidence in the later signal time-course for slow CR extravasation [3].

The unified DCE-MRI model (BALDERO) [1] allows assessment of the feasibility, stability, accuracy and precision of fitting time-course data in order to determine the very small K^{trans} values of the normal brain. The simulations reported here will lead to improved strategies for such DCE-MRI experiments.

Methods: All programs were written in Matlab (Mathworks, Natick, MA) and run on a PC utilizing Windows XP. All DCE MRI pharmacokinetic models have a number of potentially variable parameters (itemized in [1]), and their hierarchy and interactions must be determined. The normalized, T_1-weighted signal intensity ratio [S/S_0] time-course for the first-pass of a monomeric Gd(III) CR through normal brain tissue was simulated as in [1]. The arterial input function used was that appropriate for the brain following injection of ~0.2 mmol/kg CR in ~20 s [4]. Unless otherwise specified, the values for K^{trans} of 5 x 10^{-5} min^{-1}, v_b of 0.032, and τ_b of 0.5 s were used for the simulations. The values of the other fixed variables used were similar to those in [1].

Results: To investigate feasibility, the parametric space resulting from noiseless simulations was examined. A specific input parameter vector [K^{trans}, v_b], was used to simulate a signal time-course labeled S_{true}. Then, other parameter vectors in a range close to the values of the "true" vector were used to produce other signal time-courses, S_{test}. Examples of S_{true} are shown as the two solid curves (red and black, K^{trans} = 5 x 10^{-5} and 4 x 10^{-5} min^{-1}, respectively) in the main portion of **Figure 1**. The time scale is changed at ~ 35 minutes, as indicated. The reduced chi-square statistic, $\chi^2 = \Sigma\,[S_{true}(t) - S_{test}(t)]^2$, was calculated for each S_{test} vs. S_{true} time-course. Inset **a** shows a surface plot of $\log(\chi^2)$ in K^{trans}, v_b space: constant $\log(\chi^2)$ contours are projected onto the K^{trans}, v_b plane. The coordinate pair with the S_{test} parameter vector closest to that of S_{true} exhibits the smallest χ^2 value. Inset **a** reflects acquisition of essentially the entire red time-course (5.6 hr). A well-defined focal minimum like this is desired for a precise and accurate fitting. However, such a long acquisition is quite impractical. For inset **b**, only the first 33.3 min of the red time-course was acquired, but the minimum remains acceptably localized. One cannot truncate the acquisition much further, however. Inset **c** exemplifies an acquisition of only the hyperfine BALD peak, the first 4.2 min. after CR arrival. Its determination of such a small K^{trans} is especially poor, though without affecting the accuracy for v_b.



The effects of acquisition window length with noisy data and discrete data sampling must also be addressed. **Figure 2** shows the relative standard deviations (SD/mean value) of K^{trans} (green) and v_b (black) for different acquisition window lengths. A typical normalized signal time-course is shown in the inset [discretized as filled black circles; with random Gaussian noise (zero mean, standard deviation of 5% CNR; SNR ~50) added], along with a fitted curve. An "adaptive imaging" acquisition [5] was simulated: data sampling was fast during the first approximately four minutes, then dramatically slowed for the remainder of the acquisition window. When the window length is small, the K^{trans} determination accuracy increases with the window at essentially no expense for the v_b determination accuracy, which is quite good. When the acquisition is >35 minutes, however, little improvement is seen even with longer acquisition and more data points. So for this system (K^{trans} = 5x10^{-5} min^{-1}, SNR ~50), practical data acquisition for the determination of K^{trans} can stop at ~40 minutes. Prolonged sampling would not give much more advantage.

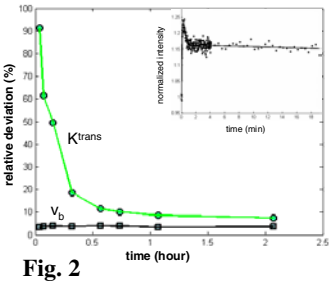


Fig. 2

Figure 3 shows an attempt at testing the accuracy and precision of a fitting subroutine. A simulated signal time-course is generated as described above. 1000 fittings of data from the first 33 minutes are tested with different initial guess values of two fitting parameters, K^{trans} and v_b. Each gray cross and each filled diamond represents an initial guess and a fitting-returned value, respectively. The two standard deviation ellipse of the fittings is shown, and the direction of its axis reflects a positive correlation of 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. The inset shows a typical fitting. The data points are shown as filled circles, and a 3SX fitting as a curve.

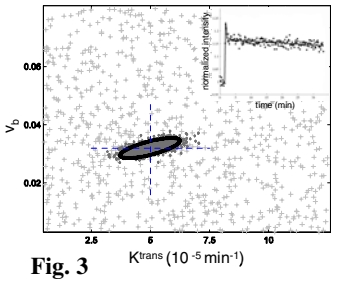


Fig. 3

Discussion: Simulations for determining very small K^{trans} values are presented here. Even though parametric space for noiseless data suggests that a very long acquisition window is required for extremely accurate determination of small K^{trans}, noisy data actually enables a mid-ranged acquisition window that is practical. For the case presented here, an acquisition of ~40 minutes would be sufficient. These results will lead to effective experimental designs for measuring CR leakage into normal human brain.

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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.** Rooney, Li, Telang, Taylor, Coyle, Springer, *Proc. Int. Soc. Magn. Reson. Med.* **12**:1390 (2004). **3.** Rooney, Telang, Springer, *Proc. Int. Soc. Magn. Reson. Med.* **10**:1314 (2002). **4.** Yankeelov, Rooney, Huang, Dyke, Li, Tudorica, Lee, *NMR Biomed.* **18**:173-185 (2005). **5.** Krishnan, Chenevert, *J. Magn. Res. Img.* **20**: 129-137 (2004).