Parameter Influence in Dynamic-Contrast-Enhanced MRI Analyses

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Introduction: Extremely informative (Dynamic-Contrast-Enhanced) DCE-MRI has been adopted widely for clinical applications. Pharmacokinetic modeling of these data is becoming increasingly popular. Here, simulations based on Gradient Recalled Echo (GRE) data acquisition and a three site water exchange model (1) for pharmacokinetic interpretation are used to investigate parameter influence (2) in DCE-MRI analyses. It is shown that the speed of contrast reagent (CR) extravasation plays the most important role in determining the nature and degree of parameter influence, while the MRI pulse sequence parameter values also have an effect.

Method: The matrix form of the three-site-two-exchange (3S2X) equations (1) was used for all simulations. GRE sequence parameters employed are: TR/FA: 5 ms/15°. The pre-contrast T_1 value for each site was set equal to 1.6 s. This way, parameter sensitivity can be better addressed without distractions from pre-CR T_1 differences, which can be obtained prior to DCE. Average compartmental water lifetime (τ) values were fixed at 0.3 s. When desired, constraint to the 3S2X fast-exchange-limit (FXL) condition is achieved by setting each τ to 0.001 s. With pre-CR T_1 values all equal, both exchange systems are truly in their FXL conditions before CR arrival, even with 0.3 s τ values.

Results: Six K^{trans} (volume CR transfer constant) magnitudes ($10^{-6} - 10^{-1}$ min^{-1}) were used to define different CR extravasation rate regimes. The arterial input function (AIF) was derived from averaging five individually measured AIFs from human femoral arteries. For numerical use, this AIF (plasma [CR] time-course, **Fig. 1a**, circles) was then fitted with a linear function for the uptake phase and a biexponential function for the washout phase (**Fig. 1a**, solid curve). Parameter influence is evaluated by monitoring the DCE-MRI signal intensity change caused by a 20% change in a specific parameter (2) while holding all others constant. **Fig. 1b** shows a 3S2X example for $K^{trans} = 0.04$ min^{-1}. The solid curve defines the reference DCE-MRI time-course. The four other time-courses result from 20% changes in each of: K^{trans}, τ_i (average intracellular water lifetime), v_b (blood volume fraction), and v_e (extravascular extracellular volume fraction). The reference values of v_b and v_e are 0.02 and 0.12, respectively.

Fig 1a.

Fig 1b. time courses
- ■ : K^{trans}
- ● : τ_i
- -- : v_b
- • : v_e

Parameter influence ("strength") is defined by comparing the square root of the difference between the reference time-course and that introduced by a 20% change in a specific parameter (a univariate approach for local sensitivity estimates). The relative differences, normalized within each individual K^{trans} regime, ($10^{-4} - 10^{-1}$ min^{-1}), are summarized in **Figure 2** for both FXL-constrained (FXL-c) and 3S2X analyses. Panels a, b, c summarize relative FXL-c parameter influence changes for DCE acquisition windows of 5, 10, and 15 min, respectively. Panels d, e, f show the corresponding results from the 3S2X analyses. It is clear that the most influential parameter is different in different K^{trans} regimes. v_e sensitivity generally decreases with decreasing K^{trans}, while v_b becomes the most influential parameter when K^{trans} is smaller than 10^{-3}. K^{trans} is the most influential parameter when CR extravasation has K^{trans} on the order of 0.01 - 0.1 min^{-1}, most relevant to cancer applications. For DCE-MRI analysis without consideration of disproportionate compartmental signal T_2^*-quenching (3, 4), the water lifetime parameters become noticeably sensitive only at large K^{trans} for τ_i and very small K^{trans} for τ_b (average capillary water lifetime). In fact, τ_b becomes the 2nd most influential parameter when K^{trans} is less than 10^{-4} min^{-1} (not shown). With almost no extravasation, K^{trans} sensitivity approaches zero for these acquisition windows.

Discussion: Parameter influence analyses provides significant insight for DCE data modeling. The CR extravasation rate regime is the most important consideration for data modeling. DCE-MRI sequence parameters will also affect parameter influence. When disproportionate compartmental quenching is evident (3,4) [it is likely always present to some extent], water exchange parameters can become much more influential - even with these GRE sequences which are conventionally considered to be exchange-insensitive.

Reference: **1.** Li, Rooney, Springer, *Magn Reson Med*. **54**:1351-9 (2005) [Erratum, **55**:1217 (2006)]. **2.** Hamby, *Health Physics*. **68**: 195-204 (1995). **3.** Li, Huang, Morris, Tudorica, Seshan, Rooney, Tagge, Wang, Xu, Springer, *PNAS* **105:** 17937-42 (2008). **4.** Li, Priest, Siddiqui, Beer, Garzotto, Woodward, Rooney, and Springer, *Proc. Int Soc Magn Reson Med*. **17**: 4221 (2009).
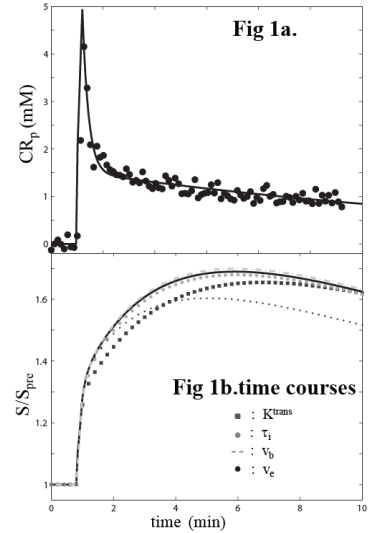
Figure 2.

Legend:
- ■ : K^{trans}
- ■ : v_e
- ■ : v_b
- ■ : τ_i
- □ : τ_b