Assessment of Kinetic Model Selection, Sampling Rate and Injection Duration on Physiological Parametric Estimation in Dynamic Contrast-Enhanced MRI

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Introduction:

With kinetic modeling, DCE-MRI has the potential of allowing investigators to infer physiological parameters such as perfusion, capillary permeability and blood volume. Accuracy and precision in parameter estimation in terms of model selection [1], temporal sampling and injection duration [2] have been evaluated in the past but separately with simulated vascular input functions (VIF). Using high-temporal resolution VIF measured from healthy human volunteers, we analyzed the effects of different sampling rates and injection protocols on parameters estimated using three common kinetic models under various simulated physiological conditions.

Methods:

Dynamic Contrast-Enhanced MRI: Adult human volunteer subjects (N = 8, ages 23-59 years, weights 70-90 kg) with no known health problems were recruited under an Institutional Review Board-approved protocol. Brain imaging was performed at 3.0 T (Philips Intera; Philips Medical Systems; Andover, MA) using a 6-channel SENSE head coil. DCE-MRI (3D T1-FFE) was obtained once per second for up to 10 minutes. Contrast parameters were: TR 1.82 ms, TE 0.7 ms, α 11º, SENSE 3, NEX 1. Geometric parameters were: FOV 25 cm, MTX 96×68, slice thickness 7 mm, 24 slices. Ten seconds following initiation of the dynamic scan, 0.2 ml/kg Gd-DTPA (Magnevist; Berlex; Montville, NJ) was injected intravenously by constant-rate infusion at one of two rates. Four volunteers were injected rapidly (4 ml/s for 4.0-4.5 s) and four were injected slowly (0.3 ml/s for 60 s). Each injection was immediately followed by 0.9% normal saline flush to clear the intravenous catheter of contrast material.***Generation of Vascular Input Function for Simulation:*** DCE-MRI datasets were analyzed offline on a personal workstation using routines written in Matlab (Mathworks; Natick, MA). Contrast concentration in plasma $c_p(t)$ was determined from signal enhancement of blood by assuming T1 of native blood 1550 ms, T1-relaxivity of Gd-DTPA 3.3 $mM^{-1}s^{-1}$ at 3.0 T. Measurements were obtained from voxels in the superior sagittal sinus or transverse sinus near torcular Herophili to avoid partial volume averaging effects with nonvascular tissue and to avoid errors from flow-related enhancement. Wiener filter was then applied to $c_p(t)$ to suppress imaging noise while preserving peaks and troughs from recirculation. ***Simulation of Tissue Response:*** Simulated data for contrast concentration in tissue $c_t(t)$ were generated from $c_p(t)$ using Model 3 [3]: $c_t(t) = F\int_0^{\tau} c_p(t-\xi)d\xi + K^{trans}\int_{\tau}^{t} c_p(\xi)e^{-K^{trans}(t-\xi-\tau)/v_e}d\xi$, which is the most realistic model assessed in this study. This is not to suggest that the model fully describes true tissue physiology, but it does allow a standard to compare the various models and determine conditions in which certain models may yield erroneous results. Baseline parameter values (K^{trans} = 0.5 min^{-1}, v_e = 0.4, v_p = 0.05, F = 1.2 min^{-1}) were selected based on standard values used by others for simulating breast cancer and meningioma.[1,2] With other parameter values held constant, K^{trans} was varied to simulate low and high-permeability states (0.1 min^{-1} and 1.1 min^{-1}, respectively); F was adjusted to simulate low and high-flow states (0.6 min^{-1} and 2.0 min^{-1}, respectively), and v_p was changed to simulate a high-vascularity state (v_p = 0.15 with F = 3.6 min^{-1} to keep τ = 2.5 s). To limit computational error owing to insufficient temporal resolution, all data were interpolated to 0.1-s temporal resolution using piecewise cubic Hermite polynomials prior to convolution. ***Subsampling:*** After generating 0.1-s high temporal resolution data with the different sets of kinetic parameters, $c_p(t)$ and $c_t(t)$ were resampled at gradually lower temporal resolutions (sampling interval T_s = 1 s, 2.5 s, 5 s, 10 s, 20 s, and 40 s). At each temporal resolution,10 subsampled datasets of $c_p(t)$ and $c_t(t)$ were generated using temporal jitter described by Henderson, *et al.*[2] This was done by first offsetting the high temporal resolution $c_p(t)$ and $c_t(t)$ in time by a fraction (0, 0.1, 0.2, …, 0.9) of T_s prior to resampling at interval T_s starting at t = 0. ***Model Fitting:*** Parameters for Model 1 [4]: $c_t(t) = K^{trans}\int_0^t c_p(\xi)e^{-K^{trans}(t-\xi)/v_e}d\xi$, Model 2 [5]: $c_t(t) = v_p c_p(t) + K^{trans}\int_0^t c_p(\xi)e^{-K^{trans}(t-\xi)/v_e}d\xi$, and Model 3 (above) were estimated from the subsampled $c_p(t)$ and $c_t(t)$ datasets by means of nonlinear least-squares curve fitting. The Nelder-Mead simplex direct search method was implemented to find parameter values that minimized the sum of squared residuals with the constraint that all estimated parameters must be non-negative. For each dataset, 10 trials were attempted with random initial parameter values. If more than one solution was found because of convergence to local minima rather than the global minimum, the solution with the least sum of squared residuals was selected.

Results and Discussion:

Vascular Input Functions for Simulation: Typical plasma contrast concentration curves for fast-injection and slow-injection protocols are shown in Fig. 1a. Graphs of corresponding Fourier transforms (Fig. 1b) demonstrate differences in energy distribution between the two injections. The fast-injection curve has more energy than the slow-injection curve in the high frequency range of 4 rad/min to 100 rad/min, which implies that the use of a fast injection should result in more precise estimates of parameters that are sensitive to high-frequency changes, i.e. v_p, F and τ. However, effects of aliasing would also be more pronounced with a fast injection, especially if the sampling rate is limited. ***Precision in Model Fitting:*** With T_s = 1 s, all three models fitted the simulated data in a reliable manner. The precision of an estimated parameter was determined by the variability of estimated values derived from 10 subsampled datasets implementing temporal jitter. As T_s increased, the variability of all estimated parameters progressively increased at different relative amounts (i.e. Δ relative variability per ΔT_s of F and $\tau > v_p > K^{trans} > v_e$). A model was considered unstable at a critical T_s if at least one of its subsampled dataset trials with temporal jitter yielded a parameter value that was zero or greater than twice its expected value. Fig. 2 shows that Model 3 becomes unstable if T_s approaches τ. For Model 2, the critical T_s for stability decreases with increasing permeability or decreasing flow. In general, use of fast injection results in slightly more precise measures in high permeability or low flow states, whereas slow injection does better in low permeability or high flow states. Except in the case of high permeability with fast injection, Model 1 remains stable even with T_s of 40 s. Fig. 3 shows the relative variability (bars in relative SD) of K^{trans}, which increases in high permeability and low flow states. ***Accuracy in Model Fitting:*** As expected, Model 3 always yielded accurate parameter estimates since it was used to generate the simulated data. Parameter accuracy is model dependent and relatively stable at different sampling rates. Fig. 3 shows Model 1 always overestimates K^{trans} by a factor roughly proportional to v_p. For Model 2, its estimated K^{trans} is always between its true value and that estimated by Model 1 (estimated K^{trans} closer to the true value in low permeability or high flow states). It is interesting to note that the most accurate and precise estimate is the lumped parameter v_e+v_p (relative error ~0, relative SD < 10% even with T_s = 40s), which is steady-state $c_t(t)/c_p(t)$ when contrast has equilibrated in plasma and EES. The next most accurate and precise estimate is $k_{ep} = K^{trans}/v_e$. Since v_p is underestimated with Model 2 (related to PS/F, see Fig. 4) and not even considered by Model 1, this explains the source of K^{trans} overestimation: underestimation of v_p leads to equal overestimation of v_e, which leads to overestimation of K^{trans} that is proportional to k_{ep}.

References:

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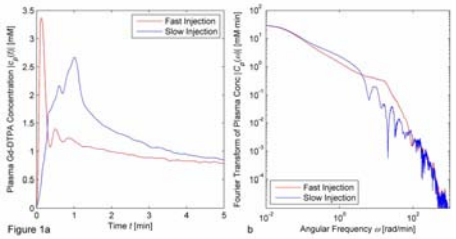

Figure 1a b

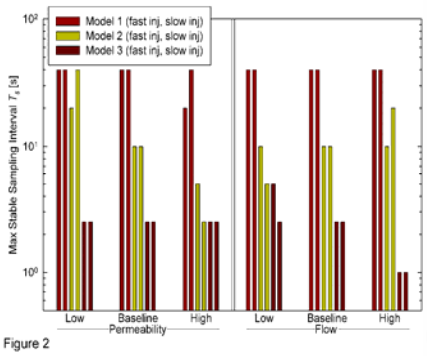

Figure 2

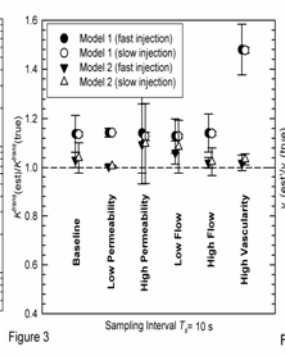

Figure 3

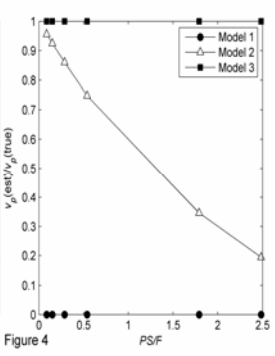

Figure 4