ASSESSMENT OF UNCERTAINTY IN THE ESTIMATION OF PHARMACOKINETIC MODEL PARAMETERS FOR DCE-MRI DATA ANALYSIS

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Introduction: Pharmacokinetic model analysis has been used as a means to quantitatively analyze dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) data [1]. The estimation of the model parameters is often performed by minimizing the difference between the measurement data and the model fit. However, due to the presence of local minima in noisy measurement data, the parameter estimation can be extremely sensitive to initial guess [2,3], which can become worse as the number of parameters increases. Recently pharmacokinetic models with inter-compartmental water exchange effects, such as the shutter speed model (SSM) [4] and SSM2 [5], have been introduced. However, it has not been shown how reliably the parameter estimation can be done with such models with additional parameters for water exchange. Hence, in this study, we investigated the influence of initial values and noise level on estimation of SSM2 model parameters with the numerically generated MRI data.

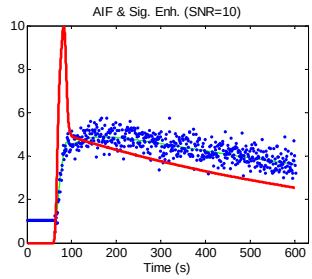

Figure 1: Assumed AIF (red), simulated tissue signal (green), and the signal with noise (blue).

Materials and Methods: The concentration of contrast agent in each compartment was simulated using an assumed arterial input function (AIF) shown in Fig.1 and the BTEX model (NSR, University of Washington) for three tissue compartments; vascular (*b*), extracellular-extravascular (EE) (*e*), and intracellular (*i*) compartments. The nominal tissue parameters for simulation were V_b = 0.06ml/g, V_e = 0.15 ml/g, V_i = 0.79 ml/g, PS = 0.34 ml/(g.min) and F_p=1.2ml/(g.min). The relaxivity (r_1) of the contrast agent was assumed to be 3.8 $mM^{-1}s^{-1}$. 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. [5]. Figure 1 shows an example of the simulated data. Rician noise was added to the simulated data to investigate the influence of noise at signal-to-noise ratio (SNR) of 10 and 20. SSM2 model parameters are K^{trans} (transfer constant), V_e (EE volume fraction), V_b (vascular volume fraction), τ_b (vascular water lifetime), and τ_i (intracellular mean water life time. We assessed two optimization techniques: Simplex method [6] and statistic region contraction (SRC) method [7]. Simplex method was used to find the local minima with different numbers of initial random guesses, such as 10, 50, 100, and 200. The result with the minimum difference between the model and data or the median was selected as the best estimation result for a given set of initial points. This process was repeated 100 times to measure the uncertainty in the estimated parameters depending on the number of initial points. For SRC method, 10,000 random initial points were generated across the parameter ranges. Best 100 (1%) points with minimal cost function value were selected to construct the initial parameter range for the next iteration. Totally 9 iterations were performed. The optimal estimation was extracted from the last iteration by selecting the median value of the 100 points with minimal cost function value.

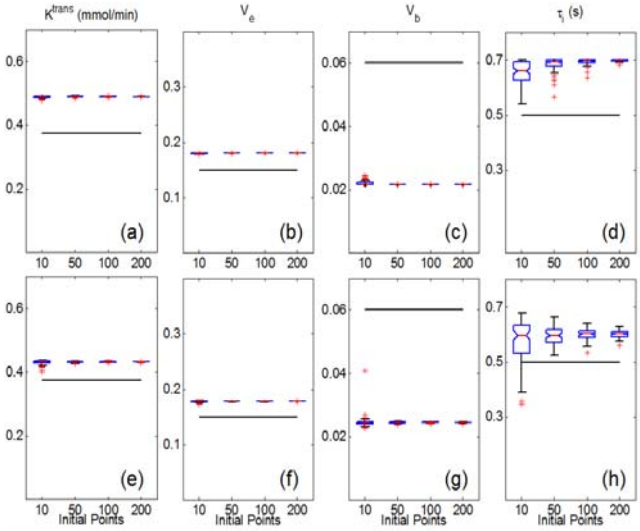

Figure 2: Simplex estimation results depending on the number of initial points (SNR=20). The box plot shows the range of results from 100 repeats. The plots in top row are from using the results with the minimum cost function value, where as those in the bottom row are from using the results with the median cost function value.

Results and Discussion: Figure 2 shows a representative example of Simplex estimation result when SNR = 20. In both cases of using the minimum (top row) or median (bottom row) values, estimation of K^{trans}, V_e and V_b values was remarkably precise even with 10 initial points. However, the accuracy of their estimations was not as good and did not improve by increasing the number of initial points. The observed limit in the accuracy can be partly attributed to the inherent difference between SSM2 and BTEX models, particularly in their assumption for vascular transient response. In contrast, the precision in τ_i estimation improved substantially by using a larger number of initial points. Overall, selecting the results with the median cost function value gave better accuracy than using those of the minimum.

Simulation data were also generated with 5 different K^{trans} values at two noise levels: SNR = 10 and 20. We used both Simplex and SRC methods with the median value scheme. The results are summarized in Figure 3. For K^{trans} and V_e, both Simplex and SRC methods provided similar results for SNR = 20. SRC method was less affected by noise level increase. The estimation of V_b became difficult as K^{trans} increases, as expected, in addition to the inherent difference between SSM2 and BTEX models. Fig.3d shows that estimation of τ_i was most affected by noise and requires good SNR. Similar observation was made with other simulation data with different values of the other model parameters (not shown).

Due to lack of gold standard to measure pharmacokinetic model parameters in practice, it is often left unknown how accurately these model parameters represent the tissue microenvironment. The present study demonstrates that numerical simulation studies can be used to assess the accuracy and precision in the model parameter estimation.

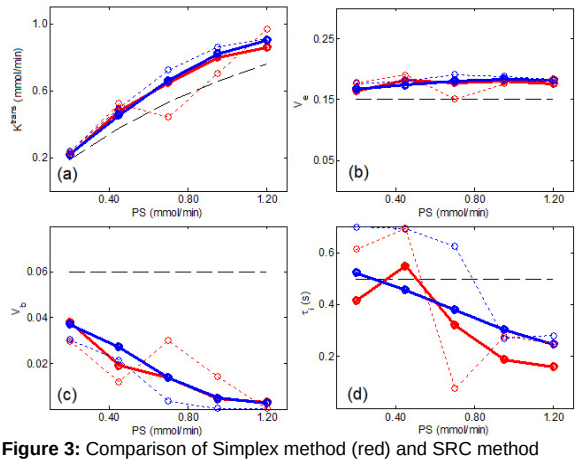

Figure 3: Comparison of Simplex method (red) and SRC method (blue) with SNR = 20 (full lines) and SNR = 10 (dotted lines).

Reference: [1] Tofts PS et al. *JMRI* 1999;10:223-232; [2] Henderson E et al. *JMRI* 2000;12:991-1003; [3] Buckley D. *MRM* 2002;47:601-606; [4] Landis CS et al. *MRM* 1999;42:467-478; [5] Li X et al. *MRM* 2005;54:1351-1359; [6] Nelder and Mead. Comput J 1965;7:308-313; [7]. Berger M.F. et al., *IEEE Trans. Sig. Pro.* 1991;39:11:2377-2386.