Comparison of Pharmacokinetic Models in Quantitative Analysis of T1-Weighted Dynamic Contrast-Enhanced Magnetic Resonance Imaging

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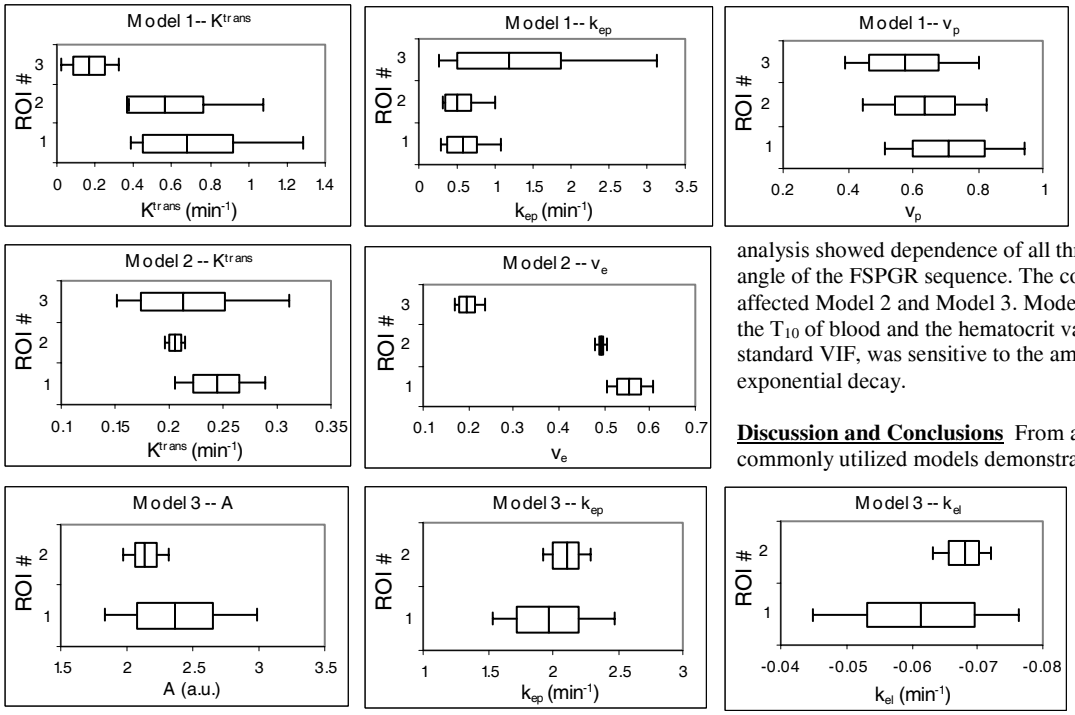
Introduction Several pharmacokinetic models have been proposed and applied in quantitative analysis of dynamic contrast-enhance MRI (DCE-MRI) studies with low-molecular-weight contrast agents. Owing to considerable variations in quantification methodology, different kinetic parameters may be estimated from different models. There is an increasing need for investigating the measurement variability and sensitivity of such pharmacokinetic analysis. In this study, a bootstrap resampling method was used to examine the uncertainty of kinetic parameters estimated from three commonly utilized pharmacokinetic models. The dependence of each modeling parameter on the imaging parameters and other input variables was also studied.

Methods Three two-compartment pharmacokinetic models, which consist of blood plasma space and extravascular-extracellular space, were compared. *Model 1*, the generalized kinetic model (1), computes K^{trans} (transfer constant, min^{-1}), k_{ep} (rate constant, min^{-1}), and v_p (fractional plasma volume). *Model 2*, the model of Tofts and Kermode (2), calculates K^{trans} and v_e (fractional EES volume) by assuming the vascular input function (VIP) is biexponential. *Model 3*, the Brix model (3), assumes that the contrast agent is administered at a constant rate K_{in} (mass/time) and eliminated with first-order kinetics. Contrast enhancement in tissue can be described by: an enhancement constant, A (a.u.), which is proportional to K_{in}, K^{trans}, and other factors; k_{ep}; and an elimination constant, k_{el} (min^{-1}).

A bootstrap method was implemented using IDL to study the variability of the kinetic parameters estimated by each pharmacokinetic model and to provide confidence intervals for these parameters. The bootstrap (4) is a computer-based method in which a set of data is randomly resampled with replacement many times, and statistical estimates are drawn from this data collection. The original data sets used in this study were obtained from a DCE-MRI study of a patient with glioblastoma multiforme, which was performed on a 3.0-T GE Excite MRI system with a phased-array head-coil. A 2-D T_1-weighted fast spoiled gradient echo (FSPGR) sequence was used in the DCE-MRI acquisition (TE/TR=1.4/5.0 ms, α=16°, receiver bandwidth=$\pm$31.25 kHz, FOV=24x24 cm^2, matrix=256x192, slice thickness=6.0 mm, 16 slices without gap, parallel imaging acceleration factor=2, temporal resolution=8.11 sec/phase). A total of 64 phases was acquired before, during, and after an intravenous bolus injection of 0.1 mmol/kg body weight of Gd-DTPA. Precontrast T_1 maps were acquired using the same 2-D FSPGR sequence with multi-low flip angles.

Three regions of interest (ROIs) within the tumor were manually selected: a small uniformly enhanced region (ROI-1); an ROI encompassing the whole tumor (ROI-2) on the same slice as ROI-1; and a small, slightly enhanced region (ROI-3) on an adjacent slice. A representative blood ROI was drawn in the superior sagittal sinus. A random number generator in IDL randomly selected 60% of the pixels in blood and tumor ROIs, with replacement. The VIF (C_p) and tumor contrast concentration curves (C_t) were then calculated from the selected pixels and fitted to each model using a nonlinear least squares fitting routine. This resampling process was repeated and 1000 sets of kinetic parameters were computed for each model. The mean, standard deviation (SD), coefficient of variation (COV), and 95% confidence interval (CI) of each kinetic parameter were obtained.

The sensitivity of the kinetic parameters was studied by varying input variables individually to compute the corresponding kinetic parameters. A linear regression was then performed to fit the percentage change in each kinetic parameter over the percentage change in the input variable. The slope of this linear function was used to estimate the dependence of the modeling parameters on each of the input values.



Results The mean, SD, and 95% CI of the kinetic parameters estimated from all three models are summarized in the figures for tumor ROIs. The boxes show the mean values $\pm$ the SD, while the mean values are represented by the vertical lines within the box. The whiskers indicate the 95% CIs. The sensitivity analysis showed dependence of all three models on T_{10} of tumor and the flip angle of the FSPGR sequence. The contrast agent relaxivity value only affected Model 2 and Model 3. Model 1 showed significant dependence on the T_{10} of blood and the hematocrit value assumed. Model 2, which used a standard VIF, was sensitive to the amplitudes and rate constants of the exponential decay.

Discussion and Conclusions From analyzing a brain tumor study, three commonly utilized models demonstrated different levels of uncertainty in kinetic parameter estimation. Compared with the well-enhanced tumor regions, the poorly enhanced tumor area showed increased parameter variation. The kinetic parameters were found to be dependent on precontrast T_1 values of tumor and blood, the flip angle used in imaging acquisition, and other constants used in modeling. It is, therefore, important to understand the sources of measurement variation in each model in order to develop standardized measurement methods and robust analysis tools.

References **1.** Patlak CS, et al. *J Cereb Blood Flow Metab* 1983;3:1-7. **2.** Tofts PS, Kermode AG. *Magn Reson Med* 1991;17:357-367. **3.** Brix G, *J Comput Assist Tomogr* 1991;15:621-628. **4.** Efron B, Tibshirani RJ. *An introduction to the bootstrap*. New York: Chapman & Hall; 1993.