PHARMACOKINETIC MODELING OF DCE-MRI DATA WITH ARTERIAL INPUT FUNCTION

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Introduction: Pharmacokinetic modeling of Dynamic Contrast Enhanced MRI (DCE-MRI) data offers a non-invasive, repeatable approach of investigating physiological and pathological conditions in longitudinal studies [1]. Although the two-compartment pharmacokinetic model [2, 3] generates a good fit to tumor data, its prediction on mono-exponential contrast agent (CA) wash-out from plasma is seldom supported by experiments. In this study, we demonstrate that this inconsistency originates from a model assumption and derive a more realistic model.

Theory: The general solution of the pharmacokinetic equations for a two compartment model (Fig. 1) can be expressed as:

$$\begin{pmatrix} C_p \\ C_e \end{pmatrix} = \frac{K_{in}}{V_p(\lambda_1-\lambda_2)}\left[\begin{pmatrix} \lambda_1+k_{ep} \\ V_p k_{pe}/V_e \end{pmatrix}\frac{e^{-\lambda_1 t'}-1}{-\lambda_1}e^{\lambda_1 t} - \begin{pmatrix} \lambda_2+k_{ep} \\ V_p k_{pe}/V_e \end{pmatrix}\frac{e^{-\lambda_2 t'}-1}{-\lambda_2}e^{\lambda_2 t}\right] \quad (1)$$

Where subscript p stands for the plasma compartment, and e stands for the extravascular extracellular space (EES) compartment. λ_1 and λ_2 are eigenvalues of the parametric matrix. t'=t when $0<t\leq\tau$ and t'=τ when $t>\tau$, where τ is the duration of CA injection. Brix's solution [2] can be shown to be a reduced form of equation (1) under the assumption k_{ep}, $k_{el}>>k_{pe}$. However, this assumption leads to an oversimplification of the model. Inspection of experimentally measured arterial input function (AIF) suggests that CA exchange between compartments is 10-100 times faster than CA wash-out from plasma. So a more realistic model assumption would be k_{ep}, $k_{pe}>>k_{el}$. Under this assumption, it can be derived that $\lambda_1 = -2k_{ep}k_{el} / (k_{ep} + k_{pe})$, $\lambda_2 = -(k_{ep} + k_{pe})$ (Table 1). When an experimentally measured AIF is available, k_{ep} and k_{pe} can be decomposed from λ_2 as follows: First fit the EES compartment equation to the tumor data to get estimations of λ_1 and λ_2, and calculate the exponential terms with those values. Then perform a multiple linear regression on the AIF with respect to the two exponential terms. The ratio of the two coefficients α is an estimate of the quantity $[-(\lambda_1 + k_{ep}) / (\lambda_2 + k_{ep})]$. So the pharmacokinetic parameters can be decomposed as:

$$k_{ep} = \frac{-\lambda_1 - \alpha\lambda_2}{1+\alpha},\quad k_{pe} = -\lambda_2 - k_{ep},\quad k_{el} = -\frac{k_{ep}+k_{pe}}{2k_{ep}}\lambda_1 \quad (2)$$

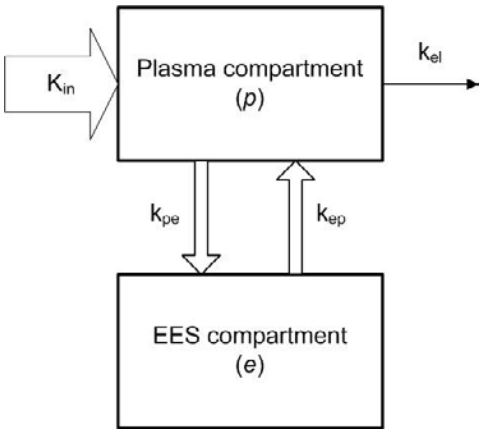

Fig 1. Two compartment model. Experimental data suggests that k_{ep} and k_{pe} are substantially larger than k_{el}.

	Our model	Brix model
Model Assumption	k_{ep}, $k_{pe}>>k_{el}$	k_{ep}, $k_{el}>>k_{pe}$
Eigenvalues	$\lambda_1 = -2k_{ep}k_{el} / (k_{ep} + k_{pe})$ $\lambda_2 = -(k_{ep} + k_{pe})$	$\lambda_1 = -k_{el}$ $\lambda_2 = -k_{ep}$
Prediction on AIF	bi-exponential	mono-exponential

Table 1. Key differences between our model and Brix model

Material and Methods: As a test of our model, we analyzed a data set of 45 Gd chelate enhanced DCE-MRI scans from ten patients with liver metastasis. Both tumor and AIF regions of interest (ROIs) were defined, motion-corrected and verified by experienced radiologists. A randomly picked subset of 30 scans was used to assess the validity of the Brix model, in which a linear function was fitted to the log-transformed decay portion of AIF data. Dependence of the residuals was tested by the Box-Ljung test. Both models were fitted to the data set, and the resulting pharmacokinetic parameters are compared by taking the ratio between our AIF-decomposed k_{ep} and Brix's k_{ep}^B (= $-\lambda_2$) values.

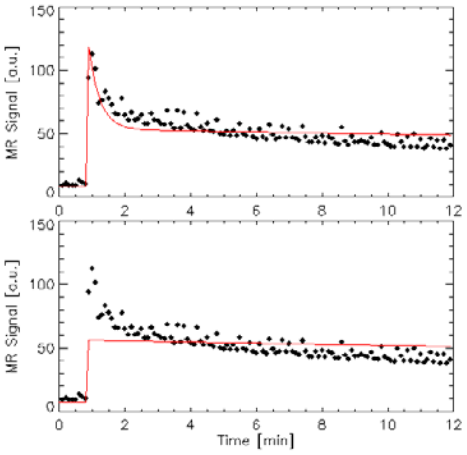

Fig 2. Our model (upper) generates better fit on AIF data than the Brix model (lower).

Results: Box-Ljung test generates small p values ($p<0.05$) in 24 of the 30 data sets tested, suggesting that mono-exponential CA wash-out predicted by the Brix model is a poor description of the observed data. Indeed, our model generates a better fit to the AIF data (Fig 2). Among all 45 observations, the k_{ep}/k_{ep}^B ratio ranges between 4% and 64%, with mean 35%, median 36%, 1st quartile 29%, and 3rd quartile 43%. The observations that the AIF-decomposed k_{ep} only occupies a small portion of k_{ep}^B further supports our statement that k_{pe} should not be simply neglected from the model.

Discussion and Conclusion: The necessity of keeping the k_{pe} term in the model is validated by the Box-Ljung test results, and supported by the k_{ep}/k_{ep}^B data and better fit to AIF function with our model. Thus, k_{ep}^B measured by fitting Brix model to DCE-MRI data is actually a combined effect of both k_{ep} and k_{pe}, which can be decomposed when an experimentally measured AIF is available. Such decomposition helps to generate more accurate, more informative, and more interpretable estimates of pharmacokinetic parameters in DCE-MRI data.

References:

[1] Tofts et. al., *JMRI*, **10**:223-232, 1999; [2] Brix et. al., *J.Computer Assisted Tomography*, **15(4)**:621-628, 1991; [3] Hoffmann et. al., *MRM*, **33**:506-514, 1995