The implication of assuming a linear relationship between MR signal and contrast agent concentration for evaluating the drug effects for DCE-MRI

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Introduction:

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has the potential for estimating a number of key properties of tumor vasculature. Knowledge of these features could be used to provide indicators of tumor grade and surrogate markers of therapeutic response. Several physiological kinetic models have been proposed to model these signal dynamic curves in order to extract functional parameters that could quantify the tumor vascular environment. For kinetic modeling, the knowledge of the contrast agent (CA) concentration time course is essential for estimating of kinetic parameters. However, for the most used spoiled gradient echo pulse (SPGR) sequence for DCE-MRI, a nonlinear relationship exists between MR signal and CA concentration and T1 information is needed for the conversion between them. When TE is extremely short (1-3 msec) as in the case for most DCE-MRI experiments, it is possible to assume that the signal enhancement is linearly related with CA concentration. The linear assumption is desirable since the T1 information is not always available in a clinical setting. However, the effects of this linear approximation have not been well addressed in DCE-MRI. In this work, we investigate the error incurred in kinetic parameters due to this linear approximation and illustrate its implication in drug efficacy evaluation.

Theory:

The tissue concentration time-course can be calculated from the Toft's model [1].

$$C_t(t) = K^{trans}\int_0 C_p(\tau)\exp\left(-\frac{K^{trans}}{v_e}(t-\tau)\right)d\tau + v_p \cdot C_p(t) \qquad [1]$$

where K^{trans}, v_p, v_e, C_p are the transfer constant, plasma fraction volume and interstitial fraction volume and arterial input function (AIF), respectively. The MR signal can be created from the CA concentration by the following equations [2]:

$$R_1(t) = \frac{1}{T_{10}} + r_1 \cdot C(t)$$

$$S(t) = M_0 \sin(\alpha)\frac{1-\exp(-T_R \cdot R_1)}{1-\cos(\alpha)\cdot\exp(-T_R \cdot R_1)}$$

where $R_1(t)$, T_{10} r_1, M_0, T_{10}, TR, α are relaxation rate, intrinsic relaxation time for the tissue of interest, relaxivity for the contrast agent, proton density, repetition time and flip angle for the SPGR sequence, respectively. The linear approximation CA concentration can be calculated by

$$C_{approx} \propto \frac{S(t)}{S(0)} - 1$$

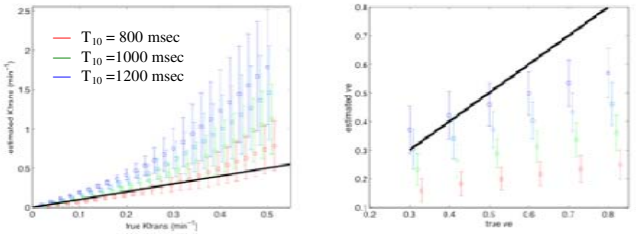

Fig.1 The influence of linear approximation on parameter estimates Ktrans and ve. Three tissue relaxation times are used in the simulation.

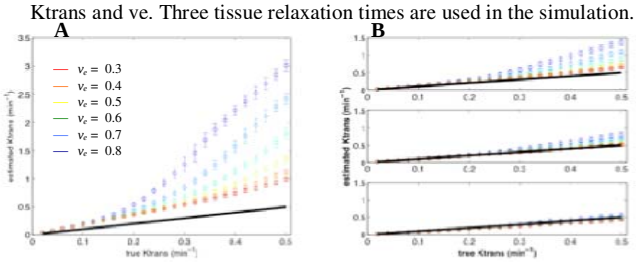

Fig.2 (A) The estimated K^{trans} by linear approximation is compounded by v_e. **(B)** The accuracy of K^{trans} estimation improves as CA injection dose is decreased. The injection does from top to bottom are 0.05, 0.025, 0.0125 (mM/Kg) with injection rate at 3 cc/sec.

Methods:

To generate the tissue concentration time course, an arterial input function was measured experimentally in a patient cohort was used [4]. Toft's two compartment model Eq.[1] was then used to simulate tissue time courses for a range of parameter values: K^{trans} = 0.01-0.5 min-1, v_e = 0.3-0.8, *vp =0.02*. The tissue curves were converted to MR signal where random noise resulting in SNR of 30 was added before the curves were used to calculate the linear approximation of CA concentration. The SNR was defined as the mean of the pre-contrast MR signal divided by the standard deviation (SD) of the noise. Finally the approximated CA concentrations were fitted to Tofts's model Eq.[1] by a Levenberg-Marquardt fitting algorithm. For each simulation, the process was repeated 100 times and the mean value of each parameter estimate was obtained over all combination.

Results:

Fig.1 shows that estimated K^{trans} values by linear approximation are compounded by tissue intrinsic T_1 and tend to over-estimate the true K^{trans} value. v_e estimation is not reliable with the approximation. Fig. 2A showed that the estimated K^{trans} values are indeed v_e dependent. This dependency on v_e explains the big uncertainty in K^{trans} estimation in Fig.1. Fig.2B shows that the accuracy of K^{trans} estimation improves as the injected CA dose is decreased.

Conclusions:

In summary, though it is tempting to assume a linear relationshiop between the signal enhancement and CA concentraion, one has to be cautious for the implication particularly with respect to drug efficacy evaluation since the estimated K^{trans} is v_e and tissue intrinsic T1 dependedent. The linear approximation will also artifically exagerate the drug effect as the degree of overestimation is proportional to the K^{trans} value. Therefore, when evaluating a drug effect, K^{trans} should be interpreted with extremem caution if T_1 information is not available and a linear approximation has to be made.

Reference: [1] Tofts PS, et al. JMRI 1997; 7:91 [2] Jackson A, et al. Br J Radiol 2003;76:153 [3] Parker GJ, et al. MRM 2006; 56:993