Quantitative Analysis of DCE-MRI Data without an Arterial Input Function

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INTRODUCTION Dynamic contrast enhanced MRI (DCE-MRI) may be used to assess tumor perfusion, microvascular vessel wall permeability, and extravascular extracellular volume fraction (1). Analysis of DCE-MRI data is based on indicator dilution theory (2) and requires knowledge of the concentration of the contrast reagent in the blood plasma, $[CR_p]$, the so-called arterial input function (AIF). The AIF is typically measured in one of three ways (in both humans and animals): 1) from blood samples obtained during the imaging process (3); 2) by assuming the AIF is similar for all subjects (4,5); 3) by measuring signal intensity changes in a major vessel and using signal intensity changes in phantoms doped with varying levels of [CR] to compute the AIF (6). Disadvantages of these approaches include their invasive nature, poor temporal resolution, and ambiguity concerning the samples' actual acquisition time (method 1); inter- and intra-subject AIF variation which can introduce errors up to 30% in both AIF characterization and the subsequent pharmacokinetic analysis (method 2) (7); and the requirement that a large vessel devoid of partial volume or flow effects is available in the FOV (method 3) (8). We present here a general method, derived from the PET literature (9), that relies on finding a well-characterized reference region (RR) from which to "calibrate" the tissue of interest (TOI) curve shape.

THEORY **Figure 1** displays a simple two-compartment model in which CR diffuses from the blood plasma to the RR and the TOI. The differential equations that describe this system are given as Equations [1] and [2]:

$$(d/dt)[CR_{RR}](t) = K^{trans,RR}\bullet[CR_p](t) - K^{trans,RR}/v_{e,RR}\bullet[CR_{RR}](t) \quad [1];$$

$$(d/dt)[CR_{TOI}](t) = K^{trans,TOI}\bullet[CR_p](t) - K^{trans,TOI}/v_{e.TOI}\bullet[CR_{TOI}](t), \quad [2]$$

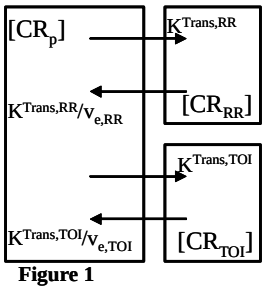


Figure 1

where $[CR_{RR}]$ and $[CR_{TOI}]$ are the concentrations of CR in the RR and the TOI, respectively, $K^{trans,RR}$ and $K^{trans,TOI}$ are the CR extravasation rate constants for the RR and TOI, respectively, and $v_{e,RR}$ and $v_{e,TOI}$ are the extravascular extracellular spaces for the RR and TOI, respectively. From Eqs. [1] and [2], a relationship between $[CR_{TOI}]$ and $[CR_{RR}]$ can be derived that is independent of $[CR_p]$:

$$[CR_{TOI}](T) = R\bullet[CR_{RR}](T) + R\bullet[(K^{trans,RR}/v_{e,RR}) - (K^{trans,TOI}/v_{e,TOI})]\bullet\int_0^T [CR_{RR}](t)\cdot\exp(-K^{Trans,TOI}/v_{e,TOI})\cdot(T-t))dt\,, \quad [3]$$

where $R = K^{trans,TOI}/K^{trans,RR}$. [CR] is not measured directly in a DCE-MRI experiment, so a calibration to the measured longitudinal relaxation rate constant, R_1 ($\equiv 1/T_1$), is required. For example, the fast exchange limit approximation (10) can be assumed: $R_1 = r_1\bullet(v_e/f_w)\bullet[CR] + R_{10}$ [4], where r_1 is CR longitudinal relaxivity, f_w is the water fraction that is CR accessible, and R_{10} is R_1 before contrast administration. Substitution of Eq. [3] into the left hand side of Eq. [4], solving Eq. [4] for [CR] and substituting into the right hand side of Eq. [3] yields an operational equation that can be employed in a curve fitting routine if $R_{1,TOI}$ and $R_{1,RR}$ can be measured.

EXPERIMENTAL A male mouse with an implanted intracerebral glioblastoma tumor was imaged using a Varian 7.0 T scanner equipped with a 38 mm quadrature birdcage coil. A variable flip angle gradient echo approach was employed to produce a R_{10} map.The DCE-MRI protocol employed a standard T_1-weighted, GRE sequence to obtain 21 serial images of each of three coronal oriented planes in 18 min of imaging. The parameters were: TR = 50 ms, TE = 4.1 ms, flip angle = 30°, FOV = $(20\text{ mm})^2$, slice thickness = 1.0 mm, matrix = 128^2, nex = 8. A bolus of 0.3 mmol/kg Magnevist was delivered within 30 s *via* a tail vein catheter. A 20 pixel TOI from the tumor center (**Figure 2**) was selected for analysis. Fifteen pixels in the masseter (jaw) muscle were selected as the RR.

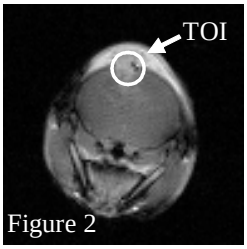
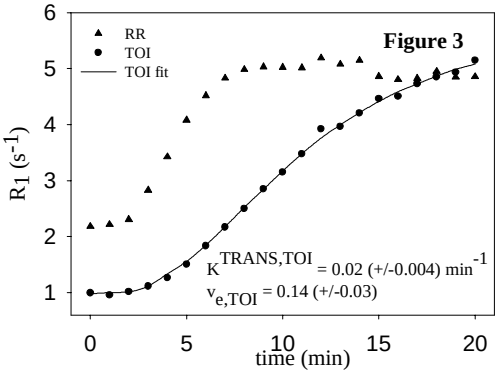


Figure 2



RESULTS Given R_{10}, MR signal intensity time courses were converted to R_1 time courses in the manner of (11). The RR and TOI time courses are the solid triangles and circles, respectively, in **Figure 3**. R_{10} for the TOI was 1.6 s^{-1} and reasonable muscles values of $K^{trans,RR}$ = 0.08 min^{-1} and $v_{e,RR}$ 0.1 min^{-1} were assigned to the RR (10). $K^{Trans,TOI}$ and $v_{e,TOI}$ were adjustable parameters in fitting the TOI data to Eqs. [3] and [4] (solid line in Fig. 3). Excellent agreement between the fit and the experimental data was obtained, returning the brain tumor parameters of $K^{trans,TOI}$ = 0.02 (+/- 0.004) min^{-1} and $v_{e,TOI}$ = 0.14 (+/-0.03). Standard deviations were determined *via* standard Monte Carlo simulations.

DISCUSSION We have presented a simple method by which DCE-MRI data can be quantitatively analyzed for extravasation transfer constant, K^{trans}, and extravascular extracellular space, v_e, without knowledge of the arterial input function. The assumptions inherent in the method are those common to all compartmental models (1). The method is fast (preliminary results indicate that the method can analyze an entire 128^2 DCE-MRI data set in less than five minutes), easily applied and straightforward in implementation, thereby making it useful in, for example, experiments to measure tumor kinetics before and after treatment. We are currently investigating the errors resulting from incorrect assignment of RR parameter values. Preliminary results indicate that $K^{trans,RR}$ and $v_{e,RR}$ values must both be off by at least 20% to introduce significant errors in $K^{trans,TOI}$ and $v_{e,TOI}$.

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