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A Theoretical Framework to Model DSC-MRI Data Acquired in the Presence of Contrast Agent Extravasation

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Abstract

Dynamic susceptibility contrast (DSC) MRI methods rely on the compartmentalization of the contrast agent such that a susceptibility gradient can be induced between the contrast-containing compartment and adjacent spaces, such as between intravascular and extravascular spaces. When there is a disruption of the blood brain barrier, as is frequently the case with brain tumors, contrast agent leaks out of the vasculature, resulting in additional T_1 , T_2 , and T_2^* relaxation effects in the extravascular space, thereby affecting the signal intensity time course and reducing the reliability of the computed hemodynamic parameters. In this study, a theoretical model describing these dynamic intra- and extravascular T_1 , T_2 , and T_2^* relaxation interactions is proposed. The applicability of using the proposed model to investigate the influence of relevant MRI pulse sequence (e.g., echo time, flip angle), physical (e.g., susceptibility calibration factors, pre-contrast relaxation rates) and physiological parameters (e.g., permeability, blood flow, compartmental volume fractions) on DSC-MRI signal time curves is demonstrated. Such a model could yield important insights into the biophysical basis of contrast agent extravasation induced effects on measured DSC-MRI signals and provide a means to investigate pulse sequence optimization and appropriate data analysis methods for the extraction of physiologically relevant imaging metrics.

Keywords

dynamic susceptibility contrast; MRI; tumor permeability; tumor blood flow

Introduction

Dynamic contrast enhanced magnetic resonance imaging (MRI) involves the serial acquisition of MR images of a tissue of interest (e.g., a tumor) before and after an intravenous injection of a contrast agent (CA). As the CA enters into the tissue under investigation, the T_1 , T_2 , and

T_2^* values of tissue water decrease to an extent that is determined by the concentration of the agent and the native tissue properties. Studies that exploit changes in T_1 are usually termed dynamic contrast enhanced MRI (DCE-MRI; reviewed in, e.g., (Yankeelov and Gore, 2007)), while those relying on T_2 and T_2^* changes are termed dynamic susceptibility contrast MRI (DSC-MRI; reviewed in, e.g., (Ostergaard, 2005)). By considering a set of images acquired before, during, and after a CA infusion, the signal intensity time course for a region of interest (ROI) or individual voxels can be related to changes in CA concentration. By fitting the DCE- or DSC-MRI data to an appropriate pharmacokinetic model, physiological parameters can then be extracted. In the case of DCE-MRI, parameters that relate to tissue perfusion and microvascular vessel wall permeability (denoted by the parameter K^{trans}) and extracellular volume fraction (denoted by v_e) may be estimated and have been shown to be sensitive to tumor growth and treatment response (see, e.g., (Tofts and Kermode, 1991; Gossmann *et al.*, 2002; Yankeelov *et al.*, 2007)). In DSC-MRI studies, parameters relating to cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) can be extracted in the intact brain (Aronen *et al.*, 1993; Aronen *et al.*, 1994). DSC-MRI derived brain tumor blood volume and blood flow data have demonstrated a correlation with tumor grade (Donahue *et al.*, 2000; Aronen *et al.*, 1994; Schmainda *et al.*, 2004; Hakyemez *et al.*, 2005) and treatment response (Fuss *et al.*, 2001; Weber *et al.*, 2004; Lee *et al.*, 2005).

DSC-MRI methods rely on the compartmentalization of the CA such that a susceptibility gradient can be induced between the contrast-containing compartment and adjacent spaces, such as between intravascular and extravascular spaces. A potential difficulty with DSC-MRI methods to study tumors results from the fact that currently only small molecular weight Gadolinium based agents are available for clinical use. In normal brain tissue, in which the blood-brain-barrier (BBB) is intact, the passage of a bolus of such an agent through the tissue induces susceptibility gradients that result in signal reduction. However, when there is a disruption of the BBB, as is frequently the case with brain tumors, CA leaks out of the vasculature, resulting in additional relaxation effects in the extravascular space and modulating the effective transverse relaxivity, thereby affecting the signal intensity time course. With commonly used DSC-MRI acquisition and analysis methods, CA leakage has been shown to lead to unreliable estimates of tumor blood volume and blood flow (Donahue *et al.*, 2000; Bruening *et al.*, 1996; Quarles *et al.*, 2005).

The most commonly reported relaxation effect on the extravascular extracellular water (EES) is a decrease in the T_1 of extravascular water. It is well known that such effects occur during and following the first pass of the CA through the vasculature and result in a substantial increase of the MRI signal above the pre-contrast baseline (Donahue *et al.*, 2000; Bruening *et al.*, 1996; Quarles *et al.*, 2005). Numerous techniques have been proposed to reduce or eliminate T_1 leakage effects including loading doses of CA prior to the bolus injection, using low flip angles, longer echo times, dual echo pulse sequences, baseline subtraction, and model-based permeability compensation methods (Weisskoff *et al.*, 1994; Heiland *et al.*, 1999; Vonken *et al.*, 1999; Quarles *et al.*, 2005; Uematsu *et al.*, 2001). A preload of CA is given to reduce tissue T_1 such that subsequent T_1 changes are minimized. The preload approach is only partially successful at reducing EES T_1 effects and the resulting DSC signals are still partially contaminated, requiring the application of model-based correction methods and/or more complex fitting of the resulting signal time courses. As an alternative to using a preload of CA, low flip angles, longer echo times and dual echo pulse sequences are increasingly being used, resulting in enhanced sensitization to extravascular T_2 and/or T_2^* effects that occur as the CA traverses the EES. Unlike the T_1 effects which increase the signal intensity and lead to underestimation of tumor CBV, the T_2^* effects decrease the signal intensity and likely result in an overestimation of the tumor CBV. This has necessitated the development of further post-

processing algorithms to model and correct for EES T_2^* leakage effects prior to the computation of CBV and CBF (Uematsu *et al.*, 2000; Johnson *et al.*, 2004).

To the best of our knowledge, a theoretical study or model of these competing intra- and extravascular T_1 , T_2 , and T_2^* relaxation interactions has not been reported. Such a model could yield important insights into the biophysical basis of CA extravasation induced effects on measured DSC-MRI signals and provide a means to investigate pulse sequence optimization and appropriate data analysis methods for the extraction of physiologically relevant imaging metrics. Therefore we attempt to develop a theoretical framework that describes DSC-MRI signals and then use this model to investigate which physical and biological tissue characteristics in brain and brain tumors most determine the CA leakage effects typically observed in clinical studies.

Theory

DSC-MRI techniques typically employ gradient echo (GE) pulse sequences. The MRI signal from such a sequence, before contrast injection (S_{pre}), can be written as:

$$S_{pre} = \frac{S_o \left(1 - e^{-TR/T_{10}}\right) e^{-TE/T_{20}^*} \cdot \sin(\alpha)}{1 - e^{-TR/T_{10}} \cdot \cos(\alpha)}, \quad (1)$$

where S_o is a constant describing the scanner gain and proton density, TR is the repetition time, TE is the echo time, α is the flip angle, and T_{10} and T_{20}^* are the pre-contrast longitudinal and transverse relaxation times of tissue water. Following contrast injection the signal as a function of time can be expressed as:

$$S(t) = \frac{S_o \left(1 - e^{-TR/T_1(t)}\right) e^{-TE/T_2^*(t)} \cdot \sin(\alpha)}{1 - e^{-TR/T_1(t)} \cos(\alpha)}, \quad (2)$$

where $T_1(t)$ and $T_2^*(t)$ are tissue longitudinal and transverse relaxation times, respectively, shortened by the CA.

The CA induced changes in the longitudinal relaxation time are dependent upon the dipolar interactions of the paramagnetic ions with the protons of water molecules. If we let C_e , v_e , C_i , v_i , C_p , v_p denote the CA concentrations and fractional volume fractions of the extravascular extracellular space (EES), intracellular space (EIS) and blood plasma, respectively, then the following relationship holds for the longitudinal relaxation rate ($R_1(t) \equiv 1/T_1(t)$), assuming water exchange between the compartments is fast (Donahue *et al.*, 1997; Landis *et al.*, 2000):

$$\begin{aligned} R_1(t) &= r_1 C_t(t) + R_{10} \\ \text{or} \\ R_1(t) &= r_1 \left[v_e C_e(t) + v_p C_p(t) + v_i C_i(t) \right] + R_{10}, \end{aligned} \quad (3)$$

where r_1 is the CA T_1 relaxivity and $C_t(t)$ is the tissue CA concentration and is taken to be the weighted average of the concentrations in the EES, plasma space, and the EIS. We assume that CA does not internalize within cells such that $C_i(t)$ is equal to zero for the duration of a typical DSC-MRI study and that the T_1 relaxivity, r_1 , is constant throughout the tissue milieu.

The tissue transverse relaxation rate is not only dependent on the microscopic interactions between the CA and water molecule protons but also upon magnetic field gradients between intravoxel tissue structures (e.g., between vessels and cells) with differing susceptibilities (termed a “mesoscopic” effect) and upon larger-sized static magnetic fields introduced by physical characteristics such as shimming imperfections and sample shape (termed a “macroscopic” effect) (Kiselev, 2005). During the course of a DSC-MRI study only the microscopic and mesoscopic effects dynamically alter the measured signal. The change in the tissue transverse relaxation rate following CA injection, $R_2^*(t)$, where $R_2^* \equiv 1/T_2^*$, can then be expressed as the sum of the contributions from the microscopic (*micro*) and mesoscopic (*meso*) effects:

$$R_2^*(t) = R_2^{\text{micro}}(t) + R_2^{\text{meso}}(t) + R_{20}^*, \quad (4)$$

where R_{20}^* is the pre-contrast relaxation rate ($(1/T_{20}^*)$). Assuming fast water exchange, the contribution of the microscopic interactions to the transverse relaxation rate can be expressed as:

$$R_2^{\text{micro}}(t) = r_2 \left[v_e C_e(t) + v_p C_p(t) + v_i C_i(t) \right], \quad (5)$$

where r_2 is the CA T_2 relaxivity. As indicated above we assume that CA remains extracellular such that $C_i(t)$ is zero over the duration of a typical DSC-MRI study and that r_2 is fixed throughout the tissue milieu.

In normal brain tissue with an intact blood brain barrier the contribution of the mesoscopic effects, $R_2^{\text{meso}}(t)$, to the tissue transverse relaxation rate following CA injection depends on the strength and spatial extent of the susceptibility induced field gradients surrounding blood vessels. The magnetic field distortions arising from the compartmentalization of CA within the vasculature depend on the concentration of the CA and a susceptibility calibration factor, k , that is related to field strength and vessel geometry (Rosen *et al.*, 1990). For typical choices of pulse sequence, the change in the transverse relaxation rate has been shown to vary linearly with agent concentration (Kennan *et al.*, 1994). As such, the CA induced change in the $R_2^{\text{meso}}(t)$ for normal brain tissue can be expressed as:

$$R_2^{\text{meso}}(t) = k C_t(t). \quad (6)$$

Extravasated CA will also create field distortions, which contribute to $R_2^{\text{meso}}(t)$, but for the same concentration of CA, its effect on the tissue T_2^* will be altered since the CA is compartmentalized within the EES and not solely the vasculature. Field gradients created by CA within the EES could influence both intravascular and extravascular intracellular water. As with intravascular CA, the influence of this additional susceptibility effect on the measured transverse relaxation rate depends on the underlying geometry of the EES. There are no geometrical models to describe the extravasated CA induced magnetic field gradients or their interaction with gradients created by CA within the vasculature, so our approach is to develop an analytical linear model that relates the change in the transverse relaxation rate to the susceptibility field gradients that can occur between the blood, EES and EIS.

Four assumptions are followed in the development of the model. First, we assume that the tissue mesoscopic relaxation rate is equal to the weighted sum of the R_2^{meso} for each of the three

compartments (blood plasma: R_{2p}^{meso} ; EES: R_{2e}^{meso} ; and EIS: R_{2i}^{meso}). The weightings are the respective compartmental volume fractions v_p , v_e and v_i . Thus, the tissue mesoscopic relaxation rate change can be expressed as:

$$R_2^{meso}(t) = v_p R_{2p}^{meso}(t) + v_e R_{2e}^{meso}(t) + v_i R_{2i}^{meso}(t). \quad (7)$$

Second, the change in an individual compartment's mesoscopic relaxation rate (e.g. R_{2i}^{meso}) is described as the weighted sum of the susceptibility effects created from the other two compartments. The weightings reflect the geometry of the compartments, and are expressed as susceptibility calibration factors. For example, the intracellular relaxation rate change, R_{2i}^{meso} , is influenced by the susceptibility gradients induced by CA compartmentalized within the blood plasma and the EES and the associated calibration factors are denoted k_{pi} and k_{ei} , respectively. The “ pi ” and “ ei ” notation is used to express the effect of CA within the blood plasma on the EIS and the effect of CA within the EES on the EIS, respectively.

Third, the magnitude of the induced susceptibility field gradient in any compartment A due to CA in any compartment B (say, the effect of CA within blood vessels on the EIS), is directly proportional to the product of B 's volume fraction (in this case, v_p) and the susceptibility difference between the two compartments. Fourth, the susceptibility difference is assumed to be proportional to the absolute value of the CA concentration difference between the two compartments. For example, combining assumptions three and four indicate that the magnitude of these effects in compartment i from field inhomogeneities due to compartment p is proportional to $v_p |C_p - C_i|$. If we combine assumptions two, three and four the three compartments' mesoscopic relaxation rates can be expressed as:

$$R_{2p}^{meso}(t) = k_{ep} v_e |C_e(t) - C_p(t)| + k_{ip} v_i |C_i(t) - C_p(t)| \quad (8a)$$

$$R_{2e}^{meso}(t) = k_{pe} v_p |C_p(t) - C_e(t)| + k_{ie} v_i |C_i(t) - C_e(t)| \quad (8b)$$

$$R_{2i}^{meso}(t) = k_{pi} v_p |C_p(t) - C_i(t)| + k_{ei} v_e |C_e(t) - C_i(t)|. \quad (8c)$$

Equations [8a] - [8c] can then be substituted into Eq. [7] and the tissue mesoscopic relaxation rate can be expressed as:

$$R_2^{meso} = (k_{ep} + k_{pe}) v_p v_e |C_e(t) - C_p(t)| + (k_{ip} + k_{pi}) v_p v_i |C_i(t) - C_p(t)| + (k_{ie} + k_{ei}) v_i v_e |C_i(t) - C_e(t)| \quad (9)$$

For simplification, the sums of the susceptibility calibration factors in the order that they appear in Eq. [9] will be termed K_{pe} , K_{pi} and K_e , respectively. We will also assume that $K_{pe} \cong K_{pi}$ which is reasonable considering that water within the EES and the EIS adjacent to blood vessels should experience the same field gradients as primarily determined by the local vascular geometry. This calibration factor will be termed K_p hereafter. Finally, as indicated above we assume CA does not enter the EIS such that $C_i(t) = 0$. The resulting tissue mesoscopic relaxation rate can then be expressed as:

$$R_2^{meso}(t) = K_p v_p (v_e |C_p(t) - C_e(t)| + v_i C_p(t)) + k_e v_e v_i C_e(t). \quad (10)$$

To ensure the model's biophysical relevancy it is useful to consider the two extremes ($C_e = 0$ and $C_p = 0$). When $C_e = 0$, Eq. [10] reduces to:

$$R_2^{meso}(t) = K_p v_p C_p(t) (v_e + v_i), \quad (11)$$

which is consistent with the commonly used notion for the change in the transverse relaxation rate in normal brain tissue, $\Delta R_2^* = k_p v_p C_p(t)$ or $\Delta R_2^* = k_p C_t(t)$, given that $v_e + v_i \approx 1$. When $C_p = 0$ Eq. [10] reduces to:

$$R_2^{meso}(t) = v_e C_e(t) (K_p v_p + k_e v_i), \quad (12)$$

which indicates, as expected, that the mesoscopic relaxation rate depends on the CA within the EES and the differences in susceptibility between the EES and the other two compartments.

By substituting Eqs. [10] and [5] into Eq. [4], the change in the tissue transverse relaxation rate, which accounts for the dynamic microscopic and mesoscopic effects following CA injection, can be written as:

$$R_2^*(t) = r_2 \left[v_e C_e(t) + v_p C_p(t) \right] + K_p v_p (v_e |C_p(t) - C_e(t)| + v_i C_p(t)) + K_e v_e v_i C_e(t) + R_{20}^* \quad (13)$$

Finally, Eqs. [13] and [3] can be substituted into Eq. [2] to yield an expression for the gradient echo DSC-MRI signal intensity that accounts for changes in the intra- and extra-vascular T_1 and T_2 relaxation times due to the microscopic interaction of CA with tissue water as well as any potential magnetic field gradients created by the compartmentalization of CA within the vascular and extravascular extracellular spaces:

$$S(t) = S_o \left[1 - \exp \left(-TR \cdot \left(r_1 \left[v_e C_e(t) + v_p C_p(t) \right] + R_{10} \right) \right) \right] \times \exp \left(-TE \cdot \left(r_2 \left[v_e C_e(t) + v_p C_p(t) \right] + K_p v_p \left[v_e |C_p(t) - C_e(t)| + v_i C_p(t) \right] + K_e v_e v_i C_e(t) + R_{20}^* \right) \right) \sin(\alpha) \div \left[1 - \exp \left(-TR \cdot \left(r_1 \left[v_e C_e(t) + v_p C_p(t) \right] + R_{10} \right) \right) \cos(\alpha) \right] \quad (14)$$

By selecting the appropriate pulse sequence and physiological parameters, Eq. [14] can be used to generate DSC-MRI data that are similar to those obtained in human brain tumors.

Methods

Simulations were used to investigate the influence of physiological, physical, and pulse sequence parameters on DSC-MRI signal time courses. Generally the simulations consisted of: (1) selection of relevant input physiological and pulse sequence parameters, (2) construction of the arterial input function (AIF), blood plasma and EES concentration time curves and (3) generation of DSC-MRI signals and ΔR_2^* time curves with and without CA leakage effects.

Input Parameters

Pulse sequence parameters were chosen to mirror those found in commonly used DSC-MRI echo planar imaging protocols. As most studies seek to minimize EES T_1 effects using low flip angles, longer echo times, or preloads of CA, the following sequence parameters (flip angle / echo time) were selected for the simulations: $30^\circ / 50$ ms, $60^\circ / 50$ ms and $90^\circ / 30$ ms. For the 90° flip angle approach the effects of a CA preload were included as described below. A dual echo pulse sequence was also simulated since such data can be used to remove T contributions from the computed ΔR_2^* time curves (Vonken *et al.*, 1999). A one second repetition time was used for all the simulations.

The tumor physical and physiological parameters (T_{10} , T_{20}^* , CBF , CBV , the permeability and surface area product, PS and v_e) were selected from values measured in previous MRI (at 1.5 T), PET, and CT studies and are detailed in each study below. The T_1 and T_2 relaxivity of the CA, r_1 and r_2 , were set at 3.9 and 5.3 $\text{mM}^{-1}\cdot\text{sec}^{-1}$, respectively [appropriate for gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) at 1.5 T] (Pintaske *et al.*, 2006). In most DSC-MRI simulation studies, the susceptibility calibration factor, K_p is chosen to generate a 40% peak signal drop at a CBF of 60 ml/100 g/min and CBV of 4%, corresponding to values typically found in human gray matter (Wu *et al.*, 2003). Given the tortuosity of the tumor vascular network, a range of K_p values is likely to be more realistic for the simulations. In a previous experimental study in a 9L gliosarcoma rat tumor model K_p was found to be 0.55 times less than that found in normal contralateral gray matter (Pathak *et al.*, 2003). Since this suggests that increased vascular tortuosity decreases K_p , values for this parameter were arbitrarily chosen to range between 0.35 to 0.75 times that used for normal gray matter. The geometry or architecture of the EES could also be considered highly tortuous, more so than the tumor vasculature, and as such we assume for these simulations that its susceptibility calibration factor, K_e , would likely be lower than K_p . Specifically, K_e was selected to range between 0.25 to 0.75 times the values used for K_p .

Simulated Tissue Signal Time Courses

Concentration time curves were constructed at one second intervals and a total simulated time of five minutes for pulse sequences using no preload and 16 minutes for the 90° flip angle sequence with a preload (which includes 60 seconds of baseline prior to the preload injection, 10 minutes between the start of the preload injection and the second injection and five minutes following the second injection), giving a total of 960 time points. The AIF concentration curves were generated using:

$$C_a(t) = A \left(t/t_p^2 \right) e^{-t/t_p} + B \left(1 - e^{-C \cdot t/t_p} \right), \quad (14)$$

where $A = 200$ M·sec, $B = 1.75$ M, $C = 1$ and $t_p = 2$ sec (Simpson *et al.*, 1999). For the preload injection the AIF curve was scaled to yield a peak concentration of 6.0 mM (Evelhoch, 1999; Conturo *et al.*, 2005) and for all DSC-MRI signals the AIF was computed as twice the preload dose. This computation inherently implies that the DSC-MRI injection rate was twice that of the preload such that the total injection time remains the same. The blood volume fraction and blood plasma CA concentration product, $v_p C_p(t)$, were computed by convolving the AIF with an exponential residue function, $R(t) = \exp(-t / MTT)$, where MTT is the mean transit time:

$$v_p \cdot C_p(t) = \frac{\rho}{k_H} \cdot CBF \cdot \int_0^t C_a(\tau) \cdot R(t - \tau) d\tau, \quad (15)$$

where r is the density of brain tissue and k_H accounts for the hematocrit difference between capillaries and large vessels.

To describe the dynamic extravasation of CA we used the Kety-Tofts model where the concentration of CA in the EES can be expressed as (Tofts *et al.*, 1999):

$$v_e \cdot C_e(t) = K^{trans} \int_0^t C_a(\tau) \cdot \exp\left(-\left(K^{trans}/v_e\right)(t-\tau)\right) d\tau, \quad (16)$$

where $K^{trans} = E \cdot CBF \cdot \rho \cdot (1-k_H)$ and E , the extraction, is $E = 1 - \exp[-PS / CBF(1-k_H)]$ which describes the condition where CA uptake is limited by both blood flow and permeability (Tofts *et al.*, 1999). For the preload study the total EES CA concentration, following the second injection, was computed as the sum of the residual CA concentration and the subsequent CA concentration entering the tissue as a result of the second injection. The tissue T_1 and T_2^* at the time of the second injection were computed using Eqs. [3] and [13].

The concentration time curves were converted to DSC-MRI signal time courses using Eq. [14]. Finally, ΔR_2^* time curves were computed for each DSC-MRI signal using the standard equation:

$$\Delta R_2^*(t) = \frac{-1}{TE} \ln\left(\frac{S(t)}{S(0)}\right), \quad (17)$$

while the dual echo ΔR_2^* time curves were created using the following expression:

$$\Delta R_2^*(t) = \frac{1}{(TE2 - TE1)} \ln\left(\frac{S_{TE1}(t)/S_{TE1}(0)}{S_{TE2}(t)/S_{TE2}(0)}\right), \quad (18)$$

where $S(0)$ is the pre-contrast signal baseline and S_{TE1} and S_{TE2} are the signals derived from Eq. [14] using the first and second echo times, respectively.

To demonstrate the utility of the proposed model, three sets of simulations were performed. First, the individual and combined contributions of the microscopic and mesoscopic relaxation effects on the computed ΔR_2^* time curves are compared (figure 1). Next, DSC-MRI signals for the four pulse sequences are computed for a constant set of physical parameters (K_p , K_e , T_{10} , T_{20}^*) while varying the physiological parameters, PS and v_e (figures 2 and 3). Finally, similar signals were computed for a constant set of physiological parameters while varying each of the physical parameters, K_p , K_e and T_{10} separately (figures 4 - 6).

Results

The influence of the microscopic and mesoscopic CA effects on the computed DSC-MRI ΔR_2^* time courses for a given set of physiological and physical parameters is illustrated in Figure 1. The “Actual” label indicates that the ΔR_2^* time courses were computed without the effects of CA extravasation ($C_e(t) = 0$). The $\Delta R_{1-micro}$ and $\Delta R_{1,2-micro}$ labels indicate that only CA-induced microscopic T_1 and T_2 relaxation changes were included in the ΔR_2^* computations, while $\Delta R_{1,2-full}$ indicates that both microscopic and mesoscopic effects were considered. For these time series the pre-contrast T_1 , pre-contrast T_2^* , CBF , CBV , and v_e are equal to 1.5 sec, 0.05 sec, 80 ml / 100 g / min, 8 ml / 100 g, and 0.25, respectively. The susceptibility calibration factor, K_p , is 0.55 times that normally used for simulating grey matter DSC-MRI time courses and K_e is 35% of K_p . When only T_1 microscopic effects ($\Delta R_{1-micro}$) are considered, the

computed ΔR_2^* time course for a 30° flip angle and 50 ms echo time underestimates the actual one (Fig. 1a). The inclusion of T_2 microscopic effects ($\Delta R_{1,2-micro}$) reduces the degree of this underestimation; an effect observed for all the pulse sequences evaluated. When both microscopic and mesoscopic effects are included ($\Delta R_{1,2-full}$) the resulting $\Delta R_2^*(t)$ overestimates the actual one starting near the peak CA concentration and continuing throughout the simulated time course indicating increased sensitivity to T_2 and T_2^* leakage effects. When only microscopic effects are considered the computed $\Delta R_2^*(t)$ time course for sequence parameters that are more sensitive to T_1 effect (e.g., $\alpha/TE = 60^\circ/50$ ms (figure 1(b)) or $\alpha/TE = 90^\circ/35$ ms (figure 1(c))), always underestimate the actual ΔR_2^* time courses. For the set of parameters in this simulation, the inclusion of mesoscopic effects, which compete with the T_1 leakage effects, only partially improves the underestimation of the ΔR_2^* times courses for these two sequences. For the dual echo approach, which eliminates any T_1 contribution, the inclusion of the T_2 microscopic effects yields a $\Delta R_2^*(t)$ only slightly higher than the actual one while the full model results in its substantial overestimation (figure 1(d)). For all pulse sequences, the microscopic and mesoscopic leakage effects alter the intrinsic shapes (beyond a simple scaling transformation) of the ΔR_2^* time courses, an affect most apparent in the larger mesoscopic effects seen in figure 1. Such shape alterations will likely reduce the reliability of computing CBF and CBV from these ΔR_2^* time courses.

Figure 2 illustrates the influence of vascular permeability (PS) on ΔR_2^* time courses computed using the full model (including mesoscopic and microscopic effects) for the four DSC-MRI pulse sequence parameters used in Figure 1 and a constant set of physical and physiological parameters. The PS ranges from 2 to 60 ml / 100 g / min while CBF and CBV are 60 ml / 100 g / min and 4 ml / 100 g, respectively. In general, when intravascular CA concentration is high (prior to the time when a steady-state level is reached) increasing PS increases the computed ΔR_2^* time course. Similar to the results for figure 1, the $\alpha/TE = 30^\circ/50$ ms and the dual echo DSC-MRI methods substantially overestimate the actual ΔR_2^* time course for all but the lowest of PS values (figure 2(a) and 2(d)) due to their enhanced sensitivity to T_2 and T_2^* leakage effects. With no T_1 sensitivity the dual echo approach yields the greatest degree of overestimation. Conversely, the $\alpha/TE = 60^\circ/50$ ms and the $\alpha/TE = 90^\circ/35$ ms with a preload methods underestimate the actual ΔR_2^* time course for all PS values (figure 2(b) and (c)). In general, the 90° flip angle/35 ms echo time method produces the greatest underestimation of the actual ΔR_2^* time courses due to its considerable T_1 sensitivity.

Figure 3 illustrates the results when v_e is varied (from 0.15 to 0.275) and all other parameters are held constant (CBF and CBV are 60 ml / 100 g / min and 4 ml / 100 g, respectively). Contrast agent leakage results in the $\alpha/TE = 30^\circ/50$ ms (figure 3(a)) and the dual echo (figure 3(d)) methods again overestimating the actual ΔR_2^* time course, while the $\alpha/TE = 60^\circ/50$ ms and the $\alpha/TE = 90^\circ/35$ ms methods underestimated the true time course. However, each methods' sensitivity to varying v_e is markedly less than that observed for PS (figure 2) and is most apparent as the CA concentration in the extravascular space increases (towards the end of the time series). For the set of parameters used in this simulation the $\alpha/TE = 60^\circ/50$ ms method is practically insensitive to varying v_e .

Figure 4 depicts the ΔR_2^* time courses for a range of K_p values (between 0.35 to 0.75 times that used for normal gray matter) while holding all other parameters constant (PS , CBF , CBV are 30 ml / 100 g / min, 60 ml / 100 g / min and 8 ml / 100 g, respectively). For comparison, the "Reference" ΔR_2^* time curve is computed for the case when there is no contrast agent leakage and K_p is set equal to 0.55 times that used for gray matter. When contrast agent leakage effects are considered the ΔR_2^* time courses, for all four DSC-MRI methods, vary substantially as

K_p is varied. Increasing K_p increases each method's sensitivity to T_2 and T_2^* leakage effects, while decreasing K_p increases their sensitivity to the T_1 effects (except for the dual echo approach).

The ΔR_2^* time courses are more sensitive to varying K_e values (between 0.25 to 0.75 times that of K_p used for tumor vessels) as illustrated in figure 5, where PS , CBF , CBV are 30 ml / 100 g / min, 60 ml / 100 g / min and 8 ml / 100 g, respectively. In general increasing K_e values increases the computed ΔR_2^* time courses. Similar to the results above the dual echo method's ΔR_2^* time courses overestimate the actual one while those for the $\alpha/TE = 30^\circ/50$ ms approach are slightly less overestimated (figure 5(a) and 5(d)). Interestingly, the $\alpha/TE = 60^\circ/50$ ms and the $\alpha/TE = 90^\circ/35$ ms with a preload methods yield curves that underestimate the actual ΔR_2^* curve for low K_e values and overestimate it for higher values but in a time dependent manner (figure 5(b) and (c)). For example, for the second to highest K_e value the $\alpha/TE = 60^\circ/50$ ms method slightly underestimates the ΔR_2^* values near the peak of the curve but overestimates the ΔR_2^* values when the actual curve approaches a steady-state baseline. Such an effect likely results from a balancing of the leakage induced T_1 and T_2^* effects.

The ΔR_2^* time courses are also depend upon pre-contrast T_1 values as depicted in Figure 6, where T_{10} varies between 1 to 2 seconds and PS , CBF , CBV are 30 ml / 100 g / min, 60 ml / 100 g / min and 8 ml / 100 g, respectively. With its reduced sensitivity to T_1 effects the $\alpha/TE = 30^\circ/50$ ms approach overestimates the actual ΔR_2^* time course (figure 6(a)). The degree of overestimation increases as the pre-contrast T_1 decreases. In general, for all sequences except the dual echo approach the sensitivity to T_1 leakage effects is reduced as the pre-contrast T_1 decreases since the relative magnitude of these effects are reduced. Similar to the results for K_e , the $\alpha/TE = 60^\circ/50$ ms and the $\alpha/TE = 90^\circ/35$ ms with a preload methods yield ΔR_2^* time courses that both underestimate and overestimate the actual curves depending upon the time and the pre-contrast T_1 . Such an observation is consistent with reduced T_1 and increased T_2 sensitivity. As expected, the dual echo approach shows no sensitivity to T_1 (figure 6(d)) but because of the contrast agent induced T_2 and T_2^* leakage effects the resulting ΔR_2^* time course overestimates the actual one.

Discussion

In this report we have presented a theoretical model to describe the effects of CA extravasation on signal variations in common DSC-MRI pulse sequences. Using this model, simulations were used to assess the influence of relevant MRI pulse sequence and physiological parameters on derived ΔR_2^* time curves. Given the lack of consensus on the appropriate DSC-MRI protocol for application to brain tumor patients the goals of this study were to improve upon the DSC-MRI community's basic comprehension of potential leakage effects and provide a resource to evaluate the sensitivity of pulse sequences to these effects.

Despite the inclusion of the primary phenomena that will likely contribute to the altered transverse relaxation rates (namely, that as contrast agent flows through blood vessels it will leak into the EES), we acknowledge that the proposed analytical model is inherently limited in describing this complex physical process. Even in the absence of contrast agent leakage, non-analytical numerical methods are required to simulate susceptibility-based contrast for arbitrary blood vessel geometries (Pathak *et al.*, 2008). Furthermore, the commonly used spherical and cylinder-based models are likely inadequate to describe the susceptibility induced field perturbations surrounding cells. As an initial step to modeling this phenomenon we sought to first identify the primary physical and physiological factors that contribute to the field perturbations within a voxel. In the absence of contrast agent leakage the factors typically

considered are the concentration of the CA within the blood, the blood volume fraction and a calibration factor that accounts for geometrical differences between the blood vessels. Using this as a starting point the model was then modified to incorporate the multiple compartments that are influenced by the extravasation of the contrast agent.

The first assumption used in modeling the mesoscopic contribution to the transverse relaxation rate is straightforward and typical of compartmental models, where the tissue mesoscopic relaxation rate is a weighted sum of the rates in the individual compartments. The second assumption, the change in an individual compartment's mesoscopic relaxation rate is described as the weighted sum of the susceptibility effects created from the other two compartments, implies that the net field perturbation within a compartment is the linear superposition of the field perturbations created by the surrounding compartments. This is a reasonable first approximation, but its applicability may decrease for exceptionally high vascular density and/or EES CA concentrations, which is similar to conditions where numerous perturbers are in close proximity and the resulting field interactions are more complex. The third assumption, that for a particular compartment of interest the magnitude of the induced susceptibility field gradient between itself and an adjacent compartment is directly proportional to the product of the second compartment's volume fraction and the susceptibility difference between the two compartments, is likely to be more accurate when the volume fraction of the second compartment is much less than the compartment of interest. For example if the blood volume fraction is doubled its effect on the EIS should also double since $v_p \ll v_i$. This linearity could decrease as the volume fractions of the two compartments become more similar. Even with these potential limitations, to a first approximation, the proposed model should reasonably yield DSC-MRI signals characteristic of those measured clinically and provide a means to investigate the sensitivity of pulse sequences to the physical and physiological factors that alter such signals when CA extravasation occurs.

In the derivation of the T_1 and T_2^* relaxation rates water exchange between the three compartments was assumed to be fast, a common assumption used for most DSC-MRI studies. However, the validity of this assumption warrants further investigation considering the well-established influence of water exchange on DCE-MRI studies (Donahue *et al.*, 1997). Given the dynamic and sizable T_1 and T_2^* relaxation rate changes in multiple tissue compartments following contrast agent administration it is possible that the water exchange rate in comparison to the relaxation rate changes could vary between the slow, intermediate and fast regimes. For the purposes of this study, assuming either slow exchange or, ideally, making no assumptions about exchange (numerically solving the Bloch equations modified with exchange terms) requires assuming values for the six susceptibility calibration factors shown in Eq. [8]. As no such data exists regarding the magnitude of most of these factors we believed that such assumptions would have likely introduced greater error than the fast exchange approximation.

A few studies have proposed methods to correct for EES T_2 and T_2^* leakage effects but none, to our knowledge, have described (or modeled) the origins of this phenomenon such as the proposed model herein. Based on the existing clinical data it is not clear whether the microscopic contrast agent effects account for all of the observed leakage effects or if mesoscopic effects also contribute. For sequences that attempt to minimize microscopic T_1 effects, such as the low flip angle or dual echo methods, the T_2 microscopic effects only marginally alter the computed ΔR_2^* time course as figure 1 illustrates. However, data from two previous DSC-MRI studies in glioblastoma patients using such sequences found that the time course remained substantially elevated following the peak enhancement and showed decay kinetics typical of a contrast agent washing in and out of the extravascular space (Vonken *et al.*, 2000; Johnson *et al.*, 2004). Taken together, these results indicate that extravascular mesoscopic effects can substantially contribute to the T_2^* leakage effects observed in DSC-MRI

signals in brain tumors. It is also important to note that the combination of the microscopic and mesoscopic effects introduced substantial dynamic alterations to the DSC-MRI time series, which will likely reduce the reliability of any derived hemodynamic parameters.

The preliminary evaluation of the four pulse sequences reported in this study is not intended to be a comprehensive assessment of their sensitivity to CA extravasation, but to demonstrate the utility of the proposed model to investigate these effects. For figures 2 - 6 only one parameter was varied at a time, but given the number of physiological and physical parameters available there is a wide range of possibilities that could be explored. With the goal of improving CBF and CBV measurements in brain tumors it would also be relevant to compare the model input parameters to those derived from the computed DSC-MRI signals exhibiting leakage effects, with and without post-processing correction methods, as a means to assess their accuracy. However, even in the limited conditions simulated in this study some trends are apparent. The dual echo and low flip angle methods' ΔR_2^* time courses computed in this study systematically overestimate the actual ones due to their limited T_1 sensitivity and enhanced sensitivity to mesoscopic T_2^* leakage effects. The use of such curves, when uncorrected for leakage, to compute CBV would clearly result in its overestimation. The $\alpha/TE = 60^\circ/50$ ms and the $\alpha/TE = 90^\circ/35$ ms with a preload methods yield ΔR_2^* time courses that were more heterogeneous over the range of parameters included in this study due their sensitivity to T_1 and T_2^* . The observation that the ΔR_2^* time courses for these two methods could underestimate or overestimate the actual ones has important implications for the derivation of hemodynamic and permeability parameters using models that do not account for the opposing EES T_1 and T_2^* leakage effects. It is interesting to note that the reported success of the preload for high flip angle pulse sequences is not only a result of its capability to saturate the EES T_1 , but also that it increases the sensitivity to EES T_2^* leakage effects which shifts the computed ΔR_2^* time courses towards higher values and closer to the actual curves. These findings suggest that it may be possible to reduce the effects of contrast agent leakage on DSC-MRI signals by selecting a pulse sequence, and an appropriate preload concentration, with a "balanced" sensitivity to the EES T_1 and T_2^* leakage effects such that the net contribution to the MRI signal is minimal. Further studies are needed to verify this possibility.

It is well known that the vascular susceptibility calibration factor, K_p , varies between normal and tumor tissue especially in regions with abnormal vascular architecture and morphology (Pathak *et al.*, 2003; Kiselev, 2001; Gore and Majumdar, 1990). Pathak *et al* have previously reported that the tumor vascular calibration factor is about half that found in normal tissue (Pathak *et al.*, 2003). Given the tortuosity of the tumor vascular network this factor is likely to be spatially heterogeneous as well. As demonstrated above this calibration factor also influences the sensitivity of DSC-MRI pulse sequences to leakage effects. As this parameter is decreased the sensitivity of all the pulse sequences evaluated in this study to leakage effects were increased and vice-versa. Interestingly a lowered tumor susceptibility calibration factor predisposes DSC-MRI studies in tumors to enhanced sensitivity to T_1 leakage effects. This suggests that for a given permeability value, DSC-MRI studies in tissue with normal vascular architecture would be influenced to a lesser degree by leakage effects than in tissue with abnormal vascular architecture. The proposed extravascular extracellular susceptibility calibration factor, K_e , will likely vary across tissue as well since it is dependent upon CA distribution within a voxel, which is known to be heterogeneous across tumor tissue. In this study as K_e is increased all the pulse sequences were found to have enhanced sensitivity to EES T_2^* leakage effects. The physiological factors that determine K_e are unknown but it could potentially depend upon cell density, the spatial distribution of cells within a voxel or other properties of the extracellular matrix (e.g., quantity and composition of the extracellular matrix) and its estimation could provide a new marker to characterize tumor tissue.

The observation that the EES T_2 and T_2^* leakage effects compete with one another has important implications for post-processing based leakage correction methods and the attempts to estimate permeability (or K^{trans}) using DSC-MRI studies. Most post-processing methods require the estimation of a “leakage factor” that accounts for the underestimation of the ΔR_2^* time course for heavily T_1 weighted sequences (Donahue *et al.*, 2000; Quarles *et al.*, 2005) or its overestimation for sequences utilizing sequence parameters more weighted to T_2^* effects (Uematsu *et al.*, 2000; Johnson *et al.*, 2004). Therefore the leakage factor is considered to be negative in one case and positive in the other depending on the method’s terminology. For the pulse sequence parameters evaluated in this study it is clear that this leakage factor could be either positive or negative dependent upon the underlying physical and physiological characteristics of the tissue. For the low flip angle DSC-MRI signals several models have been proposed that describe the kinetics of the CA through the vascular and extravascular space (Johnson *et al.*, 2004; Law *et al.*, 2004). Since such methods typically consider only T_2^* induced signal changes, any estimate of K^{trans} will likely be confounded by T_1 -induced leakage effects (whether they are apparent or not in the ΔR_2^* time courses) and the pre-contrast tissue T_1 . The only approach that could alleviate this T_1 dependency is the dual echo approach which showed a PS -dependent overestimation of the actual ΔR_2^* time courses due to T_2^* leakage effects. However, a heterogeneous EES susceptibility calibration factor, K_e , could potentially confound estimates of K^{trans} using the dual echo or any other common DSC-MRI approach. Taken together these results indicate that the estimation of K^{trans} using DSC-MRI is likely unreliable until the EES T_1 and T_2^* contributions to the ΔR_2^* time courses can be quantified separately.

In conclusion, we have proposed a simple model to describe the effects of CA extravasation on DSC-MRI signals that enables the assessment of a pulse sequence’s sensitivity to these effects. The model and its assumptions need to be experimentally verified by comparison to clinically comparable data and to cellular and perfusion phantoms with known CA concentrations in the intra- and extra-vascular compartments. A useful extension of this model would be to develop improved methods to separate, quantify and correct for the T_1 and T_2^* leakage effects on clinically measured ΔR_2^* time courses so that tumor CBF and CBV can be reliably measured. As higher fields become increasingly utilized for patient studies, leakage effects will only become more prominent since T_2^* effects are enhanced and tissue T_1 increases with field strength emphasizing the need for further theoretical consideration and pulse sequence development. As the biophysical basis of the DSC-MRI signal in brain tumors is more clearly understood it has great potential to enhance the characterization of the tumor microenvironment including its vasculature architecture, morphology, function and perhaps even features of the extravascular space.

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References

- Aronen HJ, Cohen MS, Belliveau JW, Fordham JA, Rosen BR. Ultrafast imaging of brain tumors. *Top. Magn. Reson. Imaging* 1993;5:14–24. [PubMed: 8416685]
- Aronen HJ, Gazit IE, Louis DN, Buchbinder BR, Pardo FS, Weisskoff RM, Harsh GR, Cosgrove GR, Halpern EF, Hochberg FH. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. *Radiology* 1994;191:41–51. [PubMed: 8134596]
- Bruening R, Kwong KK, Vevea MJ, Hochberg FH, Cher L, Harsh G R t, Niemi PT, Weisskoff RM, Rosen BR. Echo-planar MR determination of relative cerebral blood volume in human brain tumors: T1 versus T2 weighting. *American Journal of Neuroradiology* 1996;17:831–40. [PubMed: 8733954]

- Conturo TE, Akbudak E, Kotys MS, Chen ML, Chun SJ, Hsu RM, Sweeney CC, Markham J. Arterial input functions for dynamic susceptibility contrast MRI: requirements and signal options. *J. Magn. Reson. Imaging* 2005;22:697–703. [PubMed: 16261571]
- Donahue KM, Krouwer HG, Rand SD, Pathak AP, Marszalkowski CS, Censky SC, Prost RW. Utility of simultaneously acquired gradient-echo and spin-echo cerebral blood volume and morphology maps in brain tumor patients. *Magn. Reson. Med* 2000;43:845–53. [PubMed: 10861879]
- Donahue KM, Weisskoff RM, Burstein D. Water diffusion and exchange as they influence contrast enhancement. *J. Magn. Reson. Imaging* 1997;7:102–10. [PubMed: 9039599]
- Evelhoch JL. Key factors in the acquisition of contrast kinetic data for oncology. *J. Magn. Reson. Imaging* 1999;10:254–9. [PubMed: 10508284]
- Fuss M, Wenz F, Essig M, Muentner M, Debus J, Herman TS, Wannenmacher M. Tumor angiogenesis of low-grade astrocytomas measured by dynamic susceptibility contrast-enhanced MRI (DSC-MRI) is predictive of local tumor control after radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys* 2001;51:478–82. [PubMed: 11567824]
- Gore JC, Majumdar S. Measurement of tissue blood flow using intravascular relaxation agents and magnetic resonance imaging. *Magn. Reson. Med* 1990;14:242–8. [PubMed: 2189053]
- Gossmann A, Helbich TH, Kuriyama N, Ostrowitzki S, Roberts TP, Shames DM, van Bruggen N, Wendland MF, Israel MA, Brasch RC. Dynamic contrast-enhanced magnetic resonance imaging as a surrogate marker of tumor response to anti-angiogenic therapy in a xenograft model of glioblastoma multiforme. *J. Magn. Reson. Imaging* 2002;15:233–40. [PubMed: 11891967]
- Hakyemez B, Erdogan C, Ercan I, Ergin N, Uysal S, Atahan S. High-grade and low-grade gliomas: differentiation by using perfusion MR imaging. *Clin. Radiol* 2005;60:493–502. [PubMed: 15767107]
- Heiland S, Benner T, Debus J, Rempp K, Reith W, Sartor K. Simultaneous assessment of cerebral hemodynamics and contrast agent uptake in lesions with disrupted blood-brain-barrier. *Magn. Reson. Imaging* 1999;17:21–7. [PubMed: 9888395]
- Johnson G, Wetzel SG, Cha S, Babb J, Tofts PS. Measuring blood volume and vascular transfer constant from dynamic, T(2)*-weighted contrast-enhanced MRI. *Magn. Reson. Med* 2004;51:961–8. [PubMed: 15122678]
- Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissues. *Magn. Reson. Med* 1994;31:9–21. [PubMed: 8121277]
- Kiselev VG. On the theoretical basis of perfusion measurements by dynamic susceptibility contrast MRI. *Magn. Reson. Med* 2001;46:1113–22. [PubMed: 11746577]
- Kiselev VG. Transverse relaxation effect of MRI contrast agents: a crucial issue for quantitative measurements of cerebral perfusion. *J. Magn. Reson. Imaging* 2005;22:693–6. [PubMed: 16261568]
- Landis CS, Li X, Telang FW, Coderre JA, Micca PL, Rooney WD, Latour LL, Vetek G, Palyka I, Springer CS Jr. Determination of the MRI contrast agent concentration time course in vivo following bolus injection: effect of equilibrium transcytolemmal water exchange. *Magn. Reson. Med* 2000;44:563–74. [PubMed: 11025512]
- Law M, Meltzer DE, Wetzel SG, Yang S, Knopp EA, Golfinos J, Johnson G. Conventional MR imaging with simultaneous measurements of cerebral blood volume and vascular permeability in ganglioglioma. *Magn. Reson. Imaging* 2004;22:599–606. [PubMed: 15172052]
- Lee MC, Cha S, Chang SM, Nelson SJ. Dynamic susceptibility contrast perfusion imaging of radiation effects in normal-appearing brain tissue: changes in the first-pass and recirculation phases. *J. Magn. Reson. Imaging* 2005;21:683–93. [PubMed: 15906330]
- Ostergaard L. Principles of cerebral perfusion imaging by bolus tracking. *J. Magn. Reson. Imaging* 2005;22:710–7. [PubMed: 16261573]
- Pathak AP, Rand SD, Schmainda KM. The effect of brain tumor angiogenesis on the in vivo relationship between the gradient-echo relaxation rate change ($\Delta R2^*$) and contrast agent (MION) dose. *J. Magn. Reson. Imaging* 2003;18:397–403. [PubMed: 14508775]
- Pathak AP, Ward BD, Schmainda KM. A novel technique for modeling susceptibility-based contrast mechanisms for arbitrary microvascular geometries: the finite perturber method. *Neuroimage* 2008;40:1130–43. [PubMed: 18308587]
- Pintaske J, Martirosian P, Graf H, Erb G, Lodemann KP, Claussen CD, Schick F. Relaxivity of Gadopentetate Dimeglumine (Magnevist), Gadobutrol (Gadovist), and Gadobenate Dimeglumine

- (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. *Invest. Radiol* 2006;41:213–21. [PubMed: 16481903]
- Quarles CC, Ward BD, Schmainda KM. Improving the reliability of obtaining tumor hemodynamic parameters in the presence of contrast agent extravasation. *Magn. Reson. Med* 2005;53:1307–16. [PubMed: 15906288]
- Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents *Magn. Reson. Med* 1990;14:249–65.
- Schmainda KM, Rand SD, Joseph AM, Lund R, Ward BD, Pathak AP, Ulmer JL, Badruddoja MA, Krouwer HG. Characterization of a first-pass gradient-echo spin-echo method to predict brain tumor grade and angiogenesis. *AJNR. Am. J. Neuroradiol* 2004;25:1524–32. [PubMed: 15502131]
- Simpson NE, He Z, Evelhoch JL. Deuterium NMR tissue perfusion measurements using the tracer uptake approach: I. Optimization of methods. *Magn. Reson. Med* 1999;42:42–52. [PubMed: 10398949]
- Tofts P, Kermode A. Measurement of blood-brain barrier defect by magnetic resonance imaging and gadolinium-DTPA in patients with multiple sclerosis and brain tumors. *Magn. Reson. Med* 1991;17:357–67. [PubMed: 2062210]
- Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. *J. Magn. Reson. Imaging* 1999;10:223–32. [PubMed: 10508281]
- Uematsu H, Maeda M, Sadato N, Matsuda T, Ishimori Y, Koshimoto Y, Kimura H, Yamada H, Kawamura Y, Yonekura Y, Itoh H. Blood volume of gliomas determined by double-echo dynamic perfusion-weighted MR imaging: a preliminary study. *Ajnr: American Journal of Neuroradiology* 2001;22:1915–9. [PubMed: 11733325]
- Uematsu H, Maeda M, Sadato N, Matsuda T, Ishimori Y, Koshimoto Y, Yamada H, Kimura H, Kawamura Y, Matsuda T, Hayashi N, Yonekura Y, Ishii Y. Vascular permeability: quantitative measurement with double-echo dynamic MR imaging--theory and clinical application. *Radiology* 2000;214:912–7. [PubMed: 10715068]
- Vonken EJ, van Osch MJ, Bakker CJ, Viergever MA. Measurement of cerebral perfusion with dual-echo multi-slice quantitative dynamic susceptibility contrast MRI. *J. Magn. Reson. Imaging* 1999;10:109–17. [PubMed: 10441012]
- Vonken EP, van Osch MJ, Bakker CJ, Viergever MA. Simultaneous quantitative cerebral perfusion and Gd-DTPA extravasation measurement with dual-echo dynamic susceptibility contrast MRI. *Magn. Reson. Med* 2000;43:820–7. [PubMed: 10861876]
- Weber MA, Thilman C, Lichy MP, Gunther M, Delorme S, Zuna I, Bongers A, Schad LR, Debus J, Kauczor HU, Essig M, Schlemmer HP. Assessment of irradiated brain metastases by means of arterial spin-labeling and dynamic susceptibility-weighted contrast-enhanced perfusion MRI: initial results. *Invest. Radiol* 2004;39:277–87. [PubMed: 15087722]
- Weisskoff, RM.; Boxerman, JL.; Sorensen, AG.; Kulke, S.; T, C.; Rosen, BR. Simultaneous blood volume and permeability mapping using a single Gd-based contrast injection; *Proc. Int. Soc. Mag. Reson. Med.*; San Francisco, CA. 1994; p. 279
- Wu O, Ostergaard L, Koroshetz WJ, Schwamm LH, O'Donnell J, Schaefer PW, Rosen BR, Weisskoff RM, Sorensen AG. Effects of tracer arrival time on flow estimates in MR perfusion-weighted imaging. *Magn. Reson. Med* 2003;50:856–64. [PubMed: 14523973]
- Yankeelov TE, Gore JC. Dynamic contrast enhanced magnetic resonance imaging in oncology. *Curr Med Imaging Rev* 2007;3:91–107. [PubMed: 19829742]
- Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, Meszoely I, Mayer IA, Herman CR, McManus K, Price RR, Gore JC. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. *Magn. Reson. Imaging* 2007;25:1–13. [PubMed: 17222711]

Figure 1.

Panels (a)-(d) depict simulated ΔR_2^* time courses for four typical DSC-MRI pulse sequence methods computed with no extravasation effects (Actual) and using microscopic T_1 leakage effects ($\Delta R_{1-micro}$), microscopic T_1 and T_2 leakage effects ($\Delta R_{1,2-micro}$) and both microscopic and mesoscopic effects ($\Delta R_{1,2-full}$). The sequence parameters used in the computation were: flip angle / echo time (ms) = (a) $30^\circ / 50$, (b) $60^\circ / 50$, (c) $90^\circ / 35$ with a CA preload and (d) a dual echo sequence with 20 and 50 ms echo times. When only T_1 microscopic effects are considered the computed ΔR_2^* time courses for all sequences underestimate the actual one, except for the dual echo approach. The inclusion of T_2 microscopic effects reduces the degree of this underestimation for the single echo methods but leads to a slight overestimation for the dual echo method. When both microscopic and mesoscopic effects are included the resulting ΔR_2^* time curves for the $30^\circ / 50$ and dual echo methods overestimate the actual one, due to

their higher sensitivity to T_2^* effects, while the $60^\circ / 50$ and $90 / 35$ with a CA preload still underestimate the actual one but to a lesser degree, because they are sensitive to both T_1 and T_2^* effects.

Figure 2.

Panels (a)-(d) depict simulated ΔR_2^* time courses for four typical DSC-MRI pulse sequence methods for a range of permeability surface area product (PS) values. The sequence parameters used in the computation were: flip angle / echo time (ms) = (a) $30^\circ / 50$, (b) $60^\circ / 50$, (c) $90^\circ / 35$ with a CA preload and (d) a dual echo sequence with 20 and 50 ms echo times. When intravascular CA concentration is high increasing PS increases the computed ΔR_2^* time course for all pulse sequences. The $30^\circ/50$ and the dual echo DSC-MRI methods substantially overestimate the actual ΔR_2^* time course for all but the lowest of PS values due to their enhanced sensitivity to T_2^* leakage effects. Conversely, the $60^\circ/50$ ms echo time and the $90^\circ/35$ with a CA preload methods underestimate the actual ΔR_2^* time course for all PS values due to their partial T_1 sensitivity.

Figure 3.

Panels (a)–(d) depict simulated ΔR_2^* time courses for four typical DSC-MRI pulse sequence methods for a range of EES volume fraction (v_e) values. The sequence parameters used in the computation were: flip angle / echo time (ms) = (a) $30^\circ / 50$, (b) $60^\circ / 50$, (c) $90^\circ / 35$ with a CA preload and (d) a dual echo sequence with 20 and 50 ms echo times. The $30^\circ/50$ and the dual echo methods overestimate the actual ΔR_2^* time course for all values of v_e , while the $60^\circ/50$ and the $90^\circ/35$ with a CA preload methods underestimate the true time course. Each method's sensitivity to varying v_e is most apparent as the CA concentration in the extravascular space increases (towards the end of the time series).

Figure 4.

Panels (a)-(d) depict simulated ΔR_2^* time courses for four typical DSC-MRI pulse sequence methods for a range vascular susceptibility calibration factor (K_p) values. The sequence parameters used in the computation were: flip angle / echo time (ms) = (a) $30^\circ / 50$, (b) $60^\circ / 50$, (c) $90^\circ / 35$ with a CA preload and (d) a dual echo sequence with 20 and 50 ms echo times. The “Reference” ΔR_2^* time curve is computed for the case when there is no contrast agent leakage and K_p is set equal to 0.55 times that used for gray matter. The ΔR_2^* time courses for all four DSC-MRI methods vary substantially as K_p is varied when contrast agent leakage effects are simulated. Increasing K_p increases each method’s sensitivity to T_2 and T_2^* leakage effects, while decreasing K_p increases their sensitivity to the T_1 effects (except for the dual echo approach).

Figure 5.

Panels (a)-(d) depict simulated ΔR_2^* time courses for four typical DSC-MRI pulse sequence methods for a range of EES susceptibility calibration factor (K_e) values. The sequence parameters used in the computation were: flip angle / echo time (ms) = (a) $30^\circ / 50$, (b) $60^\circ / 50$, (c) $90^\circ / 35$ with a CA preload and (d) a dual echo sequence with 20 and 50 ms echo times. For all pulse sequences increasing K_e increases the computed ΔR_2^* time courses. The dual echo method's ΔR_2^* time courses overestimate the actual one while those for the $30^\circ / 50$ approach are slightly less overestimated. The $60^\circ / 50$ and the $90^\circ / 35$ with a CA preload methods yield curves that underestimate the actual ΔR_2^* curve for low K_e values and overestimate it for higher values but in a manner that depends on the concentration of the agent in the intra and

extravascular spaces. Such an effect likely results from the sensitivity of these methods to the competing T_1 and T_2^* leakage effects.

Figure 6.

Panels (a)-(d) depict simulated ΔR_2^* time courses for four typical DSC-MRI pulse sequence methods for a range pre-contrast T_1 values. The sequence parameters used in the computation were: flip angle / echo time (ms) = (a) $30^\circ / 50$, (b) $60^\circ / 50$, (c) $90^\circ / 35$ with a CA preload and (d) a dual echo sequence with 20 and 50 ms echo times. For all sequences except the dual echo approach the sensitivity to T_1 leakage effects is reduced as the pre-contrast T_1 decreases. The $30^\circ/50$ approach overestimates the actual ΔR_2^* time course due to its reduced sensitivity to T_1 effects. The $60^\circ/50$ and the $90^\circ/35$ with a CA preload methods yield ΔR_2^* time courses that both underestimate and overestimate the actual curves depending upon the time and the pre-contrast T_1 .