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The Vanishing Shutter-Speed Limit

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Synopsis

Dynamic-contrast-enhanced MRI (DCE-MRI) has been widely used to characterize microvasculature permeability. Recently, it was shown to reveal metabolic activity using the shutter-speed pharmacokinetic paradigm (SSP), in which steady-state intra/extracellular water exchange kinetics was incorporated into DCE-MRI data analysis. Interesting insights into DCE-MRI signals come from modeling the extravascular tissue MR signal. The questions addressed here are, "When can extravascular ^{1}H2O longitudinal magnetization recovery from inversion/saturation still be described by a single-exponential process, and when can the intra/extracellular water exchange kinetics be accurately determined?"

Purpose

Dynamic-contrast-enhanced MRI (DCE-MRI) is a widely used clinical imaging tool.[1] A quantitative DCE-MRI protocol is a pharmacokinetic study. A paramagnetic contrast agent (CA) is injected intravenously and transiently extravasates only to the extracellular tissue spaces, a process described by Kety-Schmitt (KS) pharmacokinetic law (**Figure 1**). Interesting aspects of the analysis of DCE-MRI signals come from modeling the extravascular tissue MR signal. Typically, a tracer pharmacokinetic paradigm (TP) has been used,[2] where longitudinal magnetization, *M*, recovery from inversion/saturation is assumed to be described by an empirical single exponential process with apparent relaxation rate, . However, this ignores an important feature of water compartmentalization, i.e., finite steady-state exchange of intra- and extracellular water molecules.[3]

In 1999, two-site-exchange (2SX) expressions for steady-state intra/extracellular water exchange kinetics (**Figure 1**) were incorporated into DCE-MRI data analysis, via the shutter-speed pharmacokinetic paradigm (SSP).[3] SSP-based analysis not only characterize microvasculature, like TP, but also reveal cellular metabolic activity.[4,5] In SSP models, *M* is described with a bi-exponential function, which could admit two MR signals with different apparent relaxation rate constants. The questions addressed here are the conditions when *M* relaxation can still be described as a single-exponential process and when the intra/extracellular water kinetics can still be accurately determined under SSP.

Methods

To illustrate the effects of varying [CA_o] during DCE-MRI, simulations with the following 2SX parameters (**Figure 1**): f_i = 0.80, R_{1o0} = 0.55 s^{-1}, and r_{1o} = 3.94 $s^{-1}mM^{-1}$. The values were varied from 0 to 3 s^{-1}, with 0.5 s^{-1} steps, and the [CA_o] values were varied from 0 to 6 mM. The simulations were run at two different intrinsic intracellular ^{1}H2O relaxation rate constants: R_{1i} = 0.55 and 2.00 s^{-1}. In all simulations, the small microvascular plasma (and blood) signal was ignored.

The 2SX model describes intra- and extracellular *M* with an empirical bi-exponential function,

$$\frac{M_0 - M(t_1)}{M_0} = (1-\cos\alpha)\left[f'_{sm}e^{-R'_{1sm}t_1} + (1-f'_{sm})e^{-R'_{1lar}t_1}\right] \quad (1)$$

where $M(t_1)$ is the magnetization at recovery time t_1, M_0, at equilibrium, α the effective flip angle of the inversion/saturation pulse, and R'_{1sm} and R'_{1lar} are the small and large apparent relaxation rate constants, respectively, and f'_{sm} is the apparent fractional intensity of the signal with R'_{1sm}. The analytical expressions for Eq. (1) quantities given in terms of physical quantities are described in **Figure 2**.[6]

Results

Figures

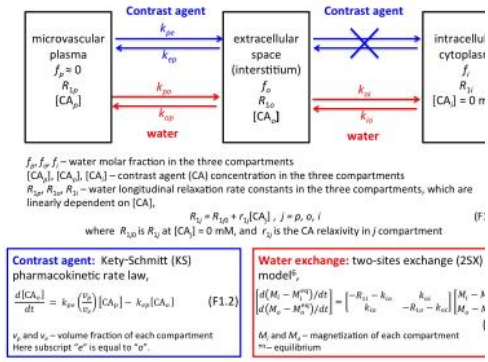

Figure 1. Shutter-Speed Pharmacokinetic Paradigm for DCE-MRI

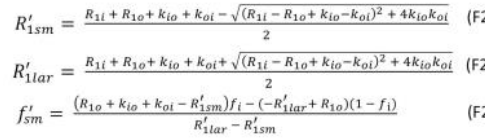

Figure 2. Analytical solution for the 2SX model.

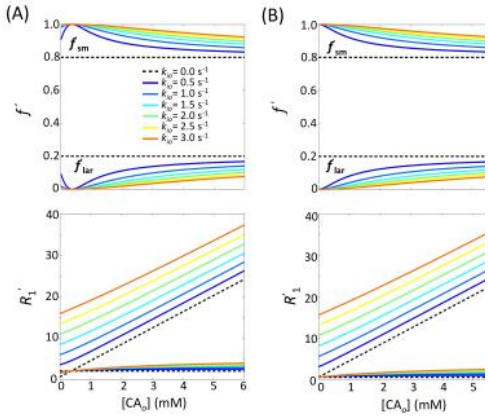

Figure 3. Analytical 2SX solutions of the empirical f'_{sm} and f'_{lar}, the relative apparent fractions of the R'_{1sm} and R'_{1lar} (up), and the apparent relaxation rate constants R'_{1sm} and R'_{1lar} themselves (down) at various [CA_o] and k_{io} values, for $\kappa_1 \equiv |R_{1i} - R_{1o0}|$ = 1.45 s^{-1} (A) and 0 s^{-1} (B).

The analytical 2SX solutions for f'_{sm}, R'_{1sm}, and R'_{1lar} as functions of [CA_o] and k_{io} are illustrated in **Figure 3**. Without any exchange, both f'_{sm} and R'_{1sm} are [CA]-independent (horizontal dashed lines). With exchange, both parameters are strongly dependent on [CA_o] and k_{io} values. For $R_{1i} - R_{1o0} = 0$ s^{-1}, f'_{sm} is equal to 1.0 at [CA_o] = 0 mM for any finite k_{io} value. For $R_{1i} - R_{1o0} = 1.45$ s^{-1}, f'_{sm} approaches 1.0 at [CA_o] = 0.37 mM ($R_{1i} - R_{1o} = 0$ s^{-1}) for any finite k_{io} value. In both cases, the recovery time-course could be well approximated with the single-exponential expression Eq. (1) with R'_1.

Discussions

Figure 3 illustrates important theoretical features of the 2SX model. The abscissa is a measure of the longitudinal shutter-speed ($\kappa_1 \equiv | R_{1i} - R_{1o}|$) for this system.[7] For simulations at $R_{1i} - R_{1o0} = 0$ and 1.45 s^{-1}, f'_{lar} approaches 0 as κ_1 approaches zero. This has been traditionally called the fast-exchange-limit [FXL]. However, the FXL term comes from NMR in chemistry, where reactions can be accelerated or slowed, *i.e.*, k_{io} can be increased or decreased, respectively. **Figure 3** makes clear the f'_{lar} vanishing is independent of the k_{io} value at finite k_{io}. Thus, the FXL label is misleading. It is more descriptive to refer to the left ordinate as the vanishing-shutter-speed-limit [VSSL]. This is important because the TP represents a special case of the SSP – in the limit of a short SS. It has been shown algebraically that as κ_1 vanishes, R'_{1sm} approaches the *f*-weighted R_{1i}, R_{1o} average [$\equiv R'_1$].[8] Any DCE-MRI model within the TP is the special VSSL case of the analogous shutter-speed model.[7,9]

In most practical situations, ($R_{1i} - R_{1o0}$) is small in tissue but > 0 and $[CA_o]_{max}$ rarely exceeds 2 mM.[8,10] In these cases, f'_{lar} is very small, and its signal also likely suffers disproportionate transverse relaxation quenching ($R^*_{2lar} > R^*_{2sm}$).[7] Thus, the component can reasonably be neglected. In this very common regime, the recovery is mono-exponential, but the relaxation rate constant is R'_{1sm} (**Figure 2**), not R'_1 defined in TP model

$R'_1 = r_{1o}[CA_o] + R'_{10}$ (2)

This can be called the vanishing shutter-speed regime [VSSR]. Measurements in blood suggests the VSSR extends to [CA_o] past 20 mM; most likely due to transverse quenching.[8] This is important because k_{io} is only accessible in the VSSR but not the VSSL.

Acknowledgements

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