A Unified Pharmacokinetic Theory for Intravascular and Extracellular CRs

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INTRODUCTION. The kinetics of equilibrium intercompartmental water exchange processes have significant effects on quantitative interpretations of longitudinal ^1H_2O magnetization data from studies in which paramagnetic contrast reagents (CRs) are constrained to only certain compartments (1). This is true for transendothelial exchange in cases where CR is restricted to the blood, at a level that is either in steady-state (2,3) or varying during the first-pass following a bolus injection (4,5), and for transcytolemmal exchange in cases where the CR extravasates into the interstitium (5,6). The most general view (1) reveals a four-site / three-exchange (4S3X) situation: $H_2O_r \leftrightarrow H_2O_p \leftrightarrow H_2O_o \leftrightarrow H_2O_i$, where the subscripts r, p, o, and i represent the erythrocyte cytoplasm, plasma, interstitial ("outside"), and parenchymal cell cytoplasm ("inside") compartments, respectively. The kinetics of the first exchange are sufficiently fast (the mean lifetimes of water molecules in the two blood compartments, τ_r and τ_p, are each ~10 ms) that it can reasonably be assumed to remain in the fast-exchange-limit (FXL) for practical [CR_p] values (7). This leaves us with a three-site / two-exchange (3S2X) situation: $H_2O_b \leftrightarrow H_2O_o \leftrightarrow H_2O_i$, where the subscript b represents the entire blood compartment. This is fortunate because while the 4S3X case is analytically "intractable," the 3S2X situation (termed "linear") has been solved for use in anisochronous spectroscopy experiments (8).

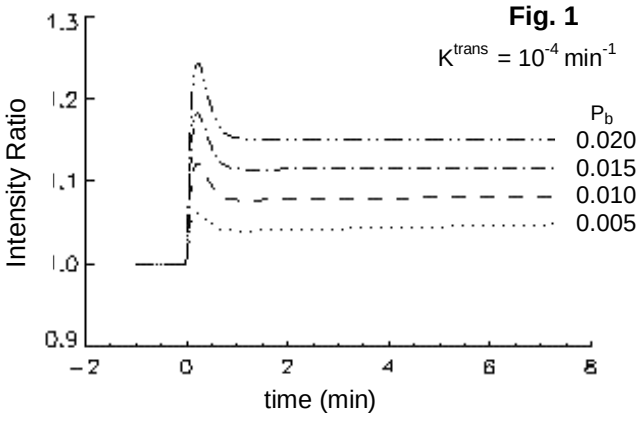
Here, we apply the 3S2X solution to the case of the isochronous compartmental ^1H_2O resonances as CR washes into and out of the blood, with or without consequent extravasation into and intravasation from the interstitium. We show that, in the former case (the normal brain), the transendothelial exchange effect dominates, and transcytolemmal exchange can be neglected, yielding a 2S1X case (4,5). On the other hand, when there is significant CR extravasation, neglect of the transendothelial exchange and indeed of the blood signal, $^1H_2O_b$, - yielding the transcytolemmal 2S1X situation (5,6) – can be invoked with impunity.

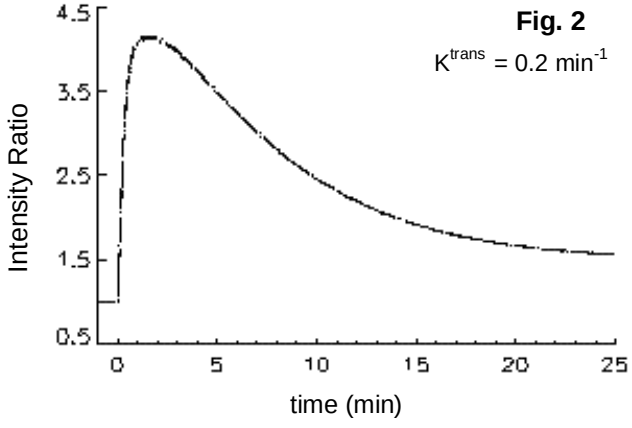
METHODS. We used the Bloch longitudinal ^1H_2O relaxation rate laws appropriately modified for the 3S2X situation [in a matrix format similar to that of Spencer and Fishbein (8)] and combined these with a form of the Kety pharmacokinetic rate law for CR extravasation (5,6). The 3S2X equilibrium McConnell Relationship for this case is: $p_o/\tau_o = (p_b/\tau_b) + [(1 - p_o - p_b)/\tau_i]$, where the p's and τ's represent the water fractions ("populations") and mean lifetimes in the respective compartments. The unified formalism was used to simulate two cases: one in which the CR extravasation is negligible (as in the normal brain), and the other in which it is quite noticeable (as in a malignant breast lesion). In each of these, the simulation calculated the pharmacokinetic time-dependence of the signal intensity (S) measured in a steady-state, T_1-weighted gradient-recalled-echo acquisition with TR = 9 ms, $\alpha = 30^o$, and no signficant T_2 effects. Physiological parameters were held constant at reasonable values: macro- and microvascular hematocrits, 0.5 and 0.3, respectively; tissue volume fraction accessible to mobile aqueous solutes (f_W), 0.8; τ_b = 0.5 s, and τ_i = 1 s. MR parameters were held constant at reasonable values: longitudinal relaxation rate constants [$\equiv T_1^{-1}$] in the absence of CR and exchange for $^1H_2O_b$, 0.7 s^{-1}, $^1H_2O_o$, 0.6 s^{-1}, $^1H_2O_i$, 0.7 s^{-1}; and CR_p and CR_o relaxivities, 3.8 $(mM)^{-1}s^{-1}$.

RESULTS. Figure 1 shows the p_b-dependence of the signal intensity ratio [S/S_{pre}] time-course for the first-pass of a monomeric Gd(III) CR through normal brain tissue. For this, the arterial input function (AIF) used was that appropriate for the brain following injection of ~0.2 mmol/kg CR in ~20 s. The transendothelial CR transfer rate constant, K^{trans}, was set to be negligibly small, and the extravascular, extracellular volume fraction, v_e [$\equiv p_o \bullet f_W$], held at 0.16. There is a peaked response that is mostly completed after one minute. This is caused by the equilibrium transendothelial water exchange process, and has been termed the hyperfine BALD [Blood Agent Level Dependent] response (4,5). It is completely dependent on the p_b value: the magnitudes of which are indicated for the Fig. 1 curves. Such curves are completely insensitive to the τ_i value (5). Here, for a p_b value characteristic of white matter, 0.02, the maximum S increase is ~25%. This effect is easily detectable at higher magnetic fields (4,5). The p_b for grey matter is approximately twice as large.

Figure 2 shows the p_b-independence of the S/S_{pre} time-course for the passage of a monomeric Gd(III) CR through malignant breast tissue. For this, the AIF used was appropriate for that derived from an axillary artery following injection of ~0.1 mmol/kg CR in ~15 s. The value of K^{trans} was set at 0.20 min^{-1} [a conservatively small value for invasive ductal carcinoma], and v_e was held at 0.24 – similar to the Fig. 1 value. Now, there is a very significant temporal change in S – an increase by over 400% - but the p_b-dependence is extremely small: the family of hardly distinguishable curves has the same p_b value range as in Fig. 1. The analysis of such data ignoring the $^1H_2O_b$ signal has been referred to as "BOLERO [BOLus Enhanced Relaxation Overview] (5). In contrast to the first case, the shapes and magnitudes of such curves are highly sensitive to the τ_i value (5).

DISCUSSION. The comprehensive theory presented here covers the range of conditions from exclusively intravascular to highly extravasating CRs. Since it connects the BALD and BOLERO approximations for the former and latter, respectively, it could be called BALDERO (Blood Agent Level Driven Extravasation Relaxation Overview). Analyses using this theory will be necessary for frequently-found intermediate cases, such as in the diseased brain and in normal muscle.





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