On the role of tissue–blood exchange on the relaxation effect of paramagnetic blood tracers

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INTRODUCTION: In dynamic susceptibility-contrast based (DSC) MRI measurements of brain perfusion, the magnitude signal exhibits a significant transient drop (typically ~30% of the baseline intensity) upon the passage of a bolus of intravascular paramagnetic contrast agent, e.g., lanthanide chelates or large iron oxide particles [1,2]. Since the intravascular volume is only 3–5% of the total brain tissue volume, susceptibility-induced magnetic field inhomogeneities at the mesoscopic scale (~10 μm and above) must largely account for the signal attenuation [2]. Another mesoscopic process contributing to increased spin dephasing in DSC–MRI is diffusion of tissue water into the microvessels across the intact capillary membrane, its transverse magnetisation M then relaxing at a much faster rate mediated by the contrast agent. Thus an *effective extravascular dephased volume*, $\Lambda(t)$, may be defined and compared with the vascular volume. In this abstract a method for calculating $\Lambda(t)$ is presented, numerical estimates are given and practical implications for DSC–MRI are discussed.

THEORY: The mathematical model consists of two non-overlapping regions, i.e., a single cylindrical microvessel with radius a and its surrounding tissue, separated by a membrane with permeability κ [μm ms^{-1}]; cylindrical symmetry is assumed. The magnetisation M undergoes unrestricted diffusion in the tissue and becomes fully relaxed upon traversing the membrane (the relaxation rate $R_2 = \infty$ and $M = 0$ in the microvessel). With these assumptions, the process is described by the diffusion equation in the tissue and the boundary condition at the membrane:

$$\partial_t M = D\nabla^2 M - R_2 M \qquad (1) \qquad \text{and} \qquad D\nabla M\big|_{membrane} = \kappa[M^{tissue} - M^{vessel}]_{membrane} \qquad (2)$$

The boundary condition gives the flux [μm^{-2}ms^{-1}] of transverse magnetisation across the membrane. The method to be described holds for both longitudinal and transverse magnetisation. The substitution $M \to M\cdot\exp(-R_2 t)$ results in $R_2 \to 0$ in (1), thus tissue relaxation needs only be considered at the end of the calculation. To quantify the amount of tissue magnetisation that enters the microvasculature over time, one first calculates Green's function, $G(r, r_0, t - t_0)$, for the ∇^2 operator (1) in the tissue region with the boundary condition (2) [4]. $G(r, r_0, t - t_0)$ gives the magnetisation density for each (r, t) following the placement of a unit magnetisation density at point r_0 at the time t_0. If M is conserved, the integral of G over all tissue points r is unity, whereas if some M is lost due to diffusion across the membrane, the integral of G will be less than unity by the amount of transverse magnetisation that has diffused outwith the tissue. Therefore, the *effective extravascular dephased volume*, $\Lambda(t)$, is defined as the integral of $\Psi(t; r_0, t_0) = 1 - \int G(r, t, r_0, t_0) d^n r$ over all source points r_0, where $n = \{1,2\}$ is the dimension of the vessel cross section. In the one-dimensional (1d) case the exchange occurs across a flat infinite membrane. This case provides valuable insight for the general two-dimensional (2d) case.

RESULTS: Dimensional analysis yields $\Lambda(t) \sim \ell^n \cdot F(a/\ell, t/\tau)$, where $\ell = D\kappa^{-1}$ is the characteristic length (the thickness of a slab across which a steady flux maintains a concentration difference as in (2)) and $\tau = D\kappa^{-2}$ is the characteristic time; F is a function of the normalised time $t/\tau = tD/\ell^2$ and the scale factor $a/\ell = a\kappa/D$. The 1d effective extravascular dephased volume is given by eqn. (3), where $t' = t/\tau$. The asymptotic forms (4) and (5) are discussed next.

$\Lambda_{1D}(t) = \ell\left[2\pi^{-1/2}\sqrt{t'} + \exp(t')\,\mathrm{erfc}\left(\sqrt{t'}\right) - 1\right]$ (3)	$\Lambda_{1D}(t) = \kappa t + O(t^{3/2})$ (4)	$\Lambda_{1D}(t) = (2/\pi)^{1/2}\sqrt{2Dt} - \ell + O(t^{-1/2})$ (5)

In the *permeability-limited regime*, diffusion in the tissue is fast enough that exchange with the blood compartment is limited by the membrane permeability, hence $\Lambda(t)$ must be independent of D. For small permeabilities, the magnetisation M reaches a quasi-stationary state and the flux is approximately constant near the membrane, cf. (1) and (2), hence $\Lambda(t)$ grows linearly with time. The 1d permeability-limited regime is characterised by: $\kappa t \ll (Dt)^{1/2} \ll \ell$; this condition is stated equivalently as $(t/\tau)^{1/2} \ll 1$, which leads to the asymptotic form (4). In the *diffusion-limited regime*, $(t/\tau)^{1/2} \gg 1$ and eqn. (3) results in eqn. (5); $\Lambda(t)$ is now almost independent of κ and grows at a rate slightly smaller than that of free diffusion. An expression for $\Lambda_{2D}(t)$ for the 2d model outlined above has also been obtained; however, reduction to closed form must be considered separately for each exchange regime. Specifically, eqn. (6) holds if $(Dt)^{1/2} < a$ indicating that on this time scale effectively 1d exchange takes place near the membrane. To determine the exchange regime for a typical DSC–MRI experiment, κ is estimated from (7), where PS is the average permeability surface area product per volume of tissue [min^{-1}], ζ is the relative blood volume and $\langle a\rangle$ ($\langle a^2\rangle$) is the mean (mean squared) vessel radius. Eqn. (7) follows from the definition of PS and the 2d model used; it is valid for arbitrary vessel arrangements provided that the individual effective dephased volumes do not overlap. It turns out that the 2d exchange regime is permeability-limited, $(t/\tau)^{1/2} \ll 1$, as justified below. In this case, eqn. (6) simplifies through use of (4) and, on account of (7), finally eqn. (8) is obtained for $\Lambda_{2D}(t)/A$, the ratio of the effective extravascular dephased area to the mean vessel cross-sectional area, in terms of the permeability-surface area product. Eqns. (3) to (6) are in agreement with Monte Carlo simulations.

$\Lambda_{2D}(t) = 2\pi a\cdot\Lambda_{1D}(t)$ (6)	$PS = 2\zeta\kappa\langle a\rangle/\langle a^2\rangle$ (7)	$\Lambda_{2D}(t)/A = 2\kappa t\langle a\rangle/\langle a^2\rangle = PS\, t/\zeta$ (8)

DISCUSSION AND CONCLUSIONS: The exchange regime and the effective extravascular dephased area in the brain are estimated setting $\langle a\rangle = 3.5$ μm, $\zeta = 5\%$ (grey matter), $D = 1.0$ μm^{2}ms^{-1} (apparent diffusion coefficient of water), $t \sim T_E = 50$ ms and $PS = 1.5$ (0.8) min^{-1} for grey (white) matter [3]. From (7), $\kappa \approx 8.8\times10^{-4}$ μm ms^{-1} (grey matter); the resulting 1d normalised time is $T_E\tau^{-1} \approx 3.8\times10^{-5}$, indicative of the 1d permeability-limited regime. The 1d diffusion length $(DT_E)^{1/2} = 7.1$ μm exceeds the average capillary radius, suggesting that the general expression for $\Lambda_{2D}(t)$ should be used. However, since $(DT_E)^{1/2} \sim \langle a\rangle$ and $(T_E/\tau)^{1/2} \ll 1$, eqn. (8) does give an estimate for the 2d effective dephased area: $\Lambda_{2D}/A \approx 2.5\times10^{-2}$. We conclude that in the brain the exchange of tissue magnetisation across the blood–brain barrier is permeability limited and does not contribute significantly to the signal dephasing. Outside the brain, where PS is typically about an order of magnitude higher [3] but $T_E/\tau \ll 1$ still holds, eqn. (8) shows that $\Lambda_{2D}(t)/A$ may indeed be significant, suggestive of an intermediate diffusion- and permeability-limited regime, which is also to be expected in organs with increased blood volume. To conclude, although the present method based on the use of Green's function has been introduced in the context of DSC–MRI, it is applicable to a variety of problems in quantitative perfusion and diffusion MRI. Specifically, our group is currently extending it to ASL perfusion models.

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