Quantifying Intrinsic Susceptibility Variations and Exchange Processes by $T_{1\rho}$ Dispersion in Blood

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Target Audience: Investigators interested in tissue characterization by quantifying effects of intrinsic susceptibility gradients and chemical exchange on MRI signals.

Purpose: Spin-lattice relaxation in the rotating frame ($R_{1\rho}$=1/$T_{1\rho}$) has traditionally been used to investigate slow molecular rotational and translational motions as well as chemical exchange processes,[1,2] especially at high field where exchange processes may dominate other relaxation mechanisms. However, diffusion in the presence of susceptibility induced magnetic field gradients has also been shown to affect $R_{1\rho}$, and the variation of $R_{1\rho}$ with locking field may also provide useful information about the spatial dimensions of magnetic inhomogeneities within tissues.[3] In general, both chemical exchange and relatively slow diffusion processes will significantly affect $R_{1\rho}$ dispersion. We have combined theoretical equations describing the effects of diffusion through internal gradients [3] with chemical exchange [4] to account for both in whole blood as a model system, $R_{1\rho} = R_{1\rho}^{Diff} + R_{1\rho}^{Exch} = \left\{\frac{\gamma^2 g^2 D}{(q^2 D)^2+\omega_1^2}\right\} + \left\{\frac{R_2+R_{1\rho}^{\infty}\omega_1^2/S_\rho^2}{1+\omega_1^2/S_\rho^2}\right\}$. Here, γ is the gyromagnetic ratio, g^2 is the mean squared gradient, D is the self-diffusion coefficient, q is the spatial frequency of susceptibility gradients, ω_1 is the strength of the applied RF field, R_2 is the R_2 contribution from chemical exchange, $R_{1\rho}^{\infty}$ is the R_1 offset at high ω_1, and S_ρ^2 is a fitting parameter based on the chemical exchange rate. Chemical exchange effects will usually contribute independently at higher spin-lock amplitudes than diffusion effects, allowing for their effects to be analyzed separately. Dispersions may be fit to estimate the mean gradient strength and a correlation time ($\tau_c = 1/q^2 D$) that is a measure of the spatial scale of the gradients, and an indirect measure of the mean spatial distribution of inhomogeneities. Tissues may possess significant susceptibility differences due to microvasculature, iron proteins, or other physiologic masses such as amyloid plaques in Alzheimer brain tissue. Here, whole blood was chosen as a model system to demonstrate the feasibility of measuring both effects. The oxygenation of red blood cells (RBC's) governs the mean internal gradient strength, while blood constituents constantly undergo chemical exchange.

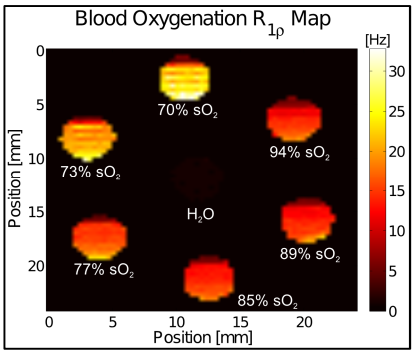

Fig. 1 $R_{1\rho}$ map of oxygenated whole bovine blood with water as a reference in the center. The relaxation rates are higher at the bottom of each sample due to the settling of red blood cells.

Methods: Fresh whole bovine blood in sodium citrate anticoagulant was acquired from Lampire Biological Laboratories, and immediately bubbled with pure oxygen to achieve saturation levels of 70%, 73%, 77%, 85%, 89%, and 94% sO_2. The dispersion of $R_{1\rho}$ was measured with a standard spin-locking pulse sequence at 10 spin-lock amplitudes, each of which was fit using 6 logarithmically spaced locking times from 10-100 ms. $R_{1\rho}$ maps were made on a pixel-by-pixel basis, and dispersions were calculated for each sample by ROI analysis. Dispersions were fit to the double dispersion $R_{1\rho}$ equation above using a weighted least squares algorithm fitting for g^2D, q^2D, R_2, $R_{1\rho}^{\infty}$, and S_ρ^2. Parameters were plotted as a function of sO_2.

Results: The $R_{1\rho}$ map generated with a locking field of 250 Hz is shown in figure 1. This map is a function of both chemical exchange and diffusion through internal gradients, and only the dispersion with locking field can separate the effects. The corresponding $R_{1\rho}$ dispersions with the double dispersion fits are shown in figure 2a. Gradient strengths were not measured directly, but were quantified by fitting for g^2D, which is the plot in figure 2b.

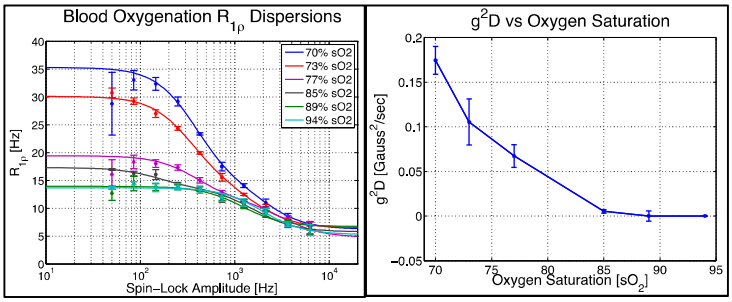

Fig. 2 a) Measured $R_{1\rho}$ dispersions with corresponding double dispersion fits. b) Fitted parameter g^2D plotted as a function of sO_2 decreases due to diminishing susceptibility gradients.

Discussion: The relaxation rate at the bottom of each sample shown in figure 1 is higher than at the top due to the inevitable settling of the RBC's during the scan setup. This visually demonstrates the diffusion effect since the gradients will be larger at the bottom of each sample compared to the top, and that difference in rates is larger for the low levels of saturation. The low locking field $R_{1\rho}$ values decrease with oxygen saturation as the susceptibility gradients diminish, leaving only chemical exchange at high saturations. This is confirmed by the analysis from the plot of g^2D, which shows the gradient dependent parameter going to zero at high sO_2. The spatial frequency parameter q^2D, which estimates the mean spacing of inhomogeneities, stayed relatively stationary and estimated a spatial distribution of ~4 μm between RBC's assuming the diffusion coefficient was 2.5 μm^2/ms. Increasing the oxygen saturation could slightly lower the pH and modify chemical exchange rates, though we did not see a noticeable change in fitted parameters. This effect has potential to be large in vivo, especially in venous blood that has much lower oxygen saturation levels.

Conclusion: Examining $R_{1\rho}$ dispersion in blood as a function of oxygen saturation demonstrates that both diffusion and chemical exchange contributions can be quantified separately. This approach may be adapted to more fully characterize many in vivo systems of interest containing magnetic inhomogeneities, including microvasculature in tissues.

References: [1] Jin et al. Magn Reson Med 65:1448-1460, 2011. [2] Cobb et al. Magn Reson Med 66:1563-1571, 2011. [3] Spear et al. Magn Reson Med, doi 10.1002/mrm.24837. [4] Chopra et al. J Magn Reson 59:361-372, 1984.