Detection of proton chemical exchange between metabolites and water using T1ρ MRI

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Introduction: Much work has been done recently on imaging techniques that utilize chemical exchange of protons to make MR imaging sensitive to concentrations of proteins and their immediate environments[1]. Spin-lattice relaxation in the rotating frame (T1ρ) is an imaging technique which is dependent on the exchange of protons but has yet to be applied to imaging specific metabolites based on their chemical exchange properties[2-4]. In this study, we demonstrated that the $T_{1\rho}$ MRI technique is sensitive to changes in both the concentration and pH of exchangeable protons and can be used to create image contrast and quantify metabolites with exchangeable protons.

Theory: During the spin-lock pulse, the transverse relaxation will relax exponentially with a relaxation rate, $R_{1\rho} = 1/T_{1\rho}$, equal to

$$R_{1\rho} = R_2 + \frac{p_a p_b \delta^2 k}{\omega_1^2 + k^2} \qquad (1)$$

where R_2 is the spin-spin relaxation rate, k is the exchange rate, $p_a = k_b/k$ and $p_b = k_a/k$ are the relative site populations, ω_{eff} is the effective amplitude of the applied rf spin-lock field and δ is the chemical shift difference between the exchange site proton and water[5]. When a low spin-lock amplitude is applied, $k^2 >> \omega_1^2$ and chemical exchange plays a significant role in relaxation. However, when $\omega_1^2 >> k^2$, the chemical exchange effects are minimized. Thus by subtracting $T_{1\rho}$ maps acquired at high and low spin-lock amplitudes, the effect of the chemical exchange can be isolated.

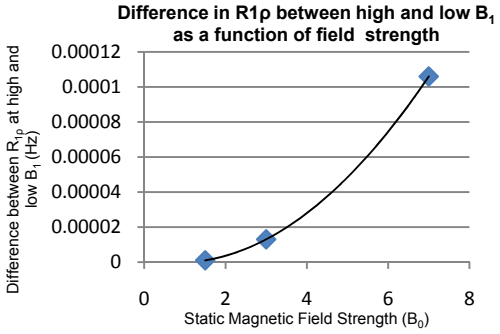

Figure 1: Differences in $R_{1\rho}$ values as a function of static magnetic field strength for a 50 mM GABA sample at a physiological pH (7.4)

Method: Samples of γ-Aminobutyric acid (GABA), which has an amino group ($-NH_2$) capable of exchanging protons with bound water, were prepared at various concentrations and pH. Imaging experiments were performed on 1.5T, 3.0T, and 7.0T whole body scanners using custom coils built for each respective field. Images were acquired using a $T_{1\rho}$ magnetization preparation pulse followed by a TSE readout. The $T_{1\rho}$ magnetization preparation pulse consists of a locking pulse in the rotating frame applied after the magnetization has been flipped from the longitudinal plane to the transverse plane. The spin-lock pulses are phase alternating in order to refocus the effect of an inhomogeneous B1 field[6]. $T_{1\rho}$ maps where constructed for high and low spin-lock amplitudes from images acquired at various spin-lock lengths.

Results and Interpretation: Figure 1 shows the difference in spin-lattice in the rotation frame relaxation rates at high and low spin-lock amplitudes, $\Delta R_{1\rho}$, as a function of static magnetic field. As seen from the plot, there is a quadratic relationship between the difference in $R_{1\rho}$ and static field strength. This is explained by equation (1) which shows that that once the effects of R_2 are removed by subtracting $R_{1\rho}$ values at high and low spin-lock amplitudes, $\Delta R_{1\rho}$ will be proportional to the square of the difference of the chemical exchange sites of the exchanging spins. Since this difference increases linearly with increasing magnetic field, the resulting difference in $R_{1\rho}$ values at high and low spin-lock field will increase quadratically. Due to this relationship, T1ρ offers higher sensitivity at higher fields in probing exchange mediated interactions in nuclear spin systems especially as higher field strength magnets become more widely used clinically.

Along with its favorable relationship to increasing static magnetic field, T1ρ also has several properties which make it attractive for imaging of endogenous and exogenous metabolites with exchangeable protons. Figure 2 shows the linear relationship between $T_{1\rho}$ values and concentration. Due to this linear relationship, $T_{1\rho}$ values could be used to monitor concentration changes in metabolites with exchangeable protons. The effects of pH on $T_{1\rho}$ values are shown in figure 3. Increases in pH will increase the exchange rate in an exponential fashion. At Low spin-lock amplitudes these changes in exchange rate will result in changes in $T_{1\rho}$ values. As a result, $T_{1\rho}$ will vary as a function of pH as seen in the $T_{1\rho}$ map of various samples at varying pH at a low spin-lock amplitude (figure (3a)). At high spin-lock amplitudes the effect of pH is negligible as the effects of exchange rate are removed. $T_{1\rho}$ values will thus remain constant regardless of pH as shown in the same $T_{1\rho}$ map at a high spin-lock amplitude (figure (3b)). Subtraction of $T_{1\rho}$ maps at high and low spin-lock amplitudes will isolate the effects of exchange and the effects of pH. This demonstrates the potential for tracking pH changes in the environment of metabolites with exchangeable protons.

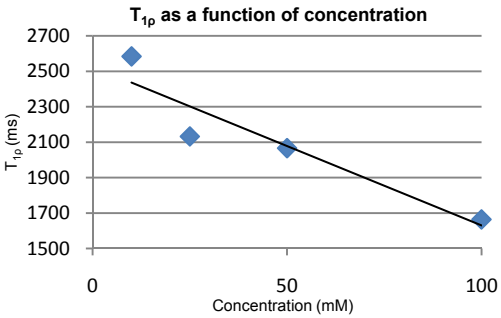

Figure 2: Differences in $T_{1\rho}$ values as a function of concentration for GABA samples at various concentrations at a physiological pH (7.4)

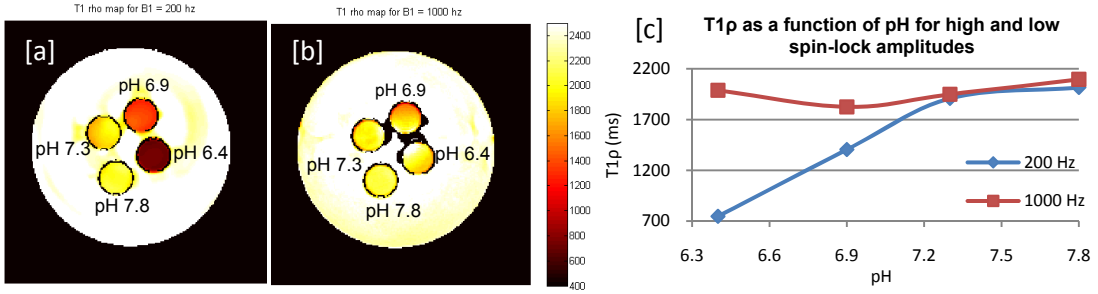

Figure 3: $T_{1\rho}$ maps of 50mM GABA samples at pH 6.4, 6.9, 7.3, and 7.8 respectively at [a] low spin-lock amplitude (200 Hz) and [b] high spin-lock amplitude (1000 Hz). [c] shows a plot of $T_{1\rho}$ values at these high and low spin-lock amplitudes

Conclusion: In this study we demonstrated that $T_{1\rho}$ imaging can be used to create exchange mediated image contrast and quantify metabolites with exchangeable protons. We also showed this method is sensitive to changes in both the concentration and pH of exchangeable protons. Finally we demonstrated that the difference in $R_{1\rho}$ values at high and low spin-lock amplitudes scales quadratically with chemical shift.

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Support: This work was supported by Award Number P41RR002305 from the National Center for Research Resources