CESTrho: A New Method for Studying Chemical Exchange at Intermediate Exchange Rates

F. Kogan[1,2], H. Hariharan[1], and R. Reddy[1]
[1]CMROI, Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, United States

Introduction: Chemical exchange between protein labile groups and bulk water can make MRI sensitive to information about the concentrations and environments of endogenous proteins. Chemical Exchange Saturation Transfer (CEST), a technique which uses the attenuation of bulk water magnetization through magnetization exchange with saturated labile protons, has become a popular method for measurement of metabolites with exchangeable protons.[1] While CEST is most sensitive to slow proton exchange ($k_{sw} \ll \Delta\omega$ where $\Delta\omega = |\omega_w - \omega_s|$), $T_{1\rho}$ is another technique that depends on chemical exchange which is more sensitive to faster exchange processes ($k_{sw} \geq \Delta\omega$) but is not specific to one chemical exchange site.[2,3] In order to utilize the sensitivity of $T_{1\rho}$ imaging at faster exchange rates while maintaining specificity we designed a pulse sequence that combines a long saturation pulse followed by a $T_{1\rho}$ magnetization preparation. The resulting acquired water signal is specific to the T_1 relaxation effects of CEST contrast as well as the chemical exchange dependent transverse relaxation effects of the $T_{1\rho}$ pulse and should show increased sensitivity along the entire spectrum of exchange rates.

Methods: The CEST proton transfer ratio (PTR) is computed by subtracting the normalized magnetization signal at the exchangeable solute proton frequency, from magnetization at the corresponding reference frequency symmetrically at the opposite side of the water resonance.[4]

$$CEST\ PTR = \frac{M_{sat}(-offset) - M_{sat}(+offset)}{M_O} \quad (1)$$

The $T_{1\rho}$ signal is dependent on the spin-lock amplitude.[5] When the applied spin-lock amplitude is small, chemical exchange plays a significant role in relaxation. However, when the spin-lock amplitude is large, the chemical exchange effects are minimized. In order to isolate the effects of the proton chemical exchange, we define the $T_{1\rho}$ PTR as

$$T_{1\rho}\ \text{PTR} = \frac{M_{\text{High Spin-Lock}} - M_{\text{Low Spin-Lock}}}{M_{\text{High Spin-Lock}}} \quad (2)$$

Combining the two methodologies, we define the CESTrho PTR as the difference in magnetizations resulting from a pulse consisting of a saturation pulse at the exchangeable solute proton frequency followed by a low amplitude spin-lock $T_{1\rho}$ magnetization preparation and a saturation pulse of corresponding reference frequency symmetrically at the opposite side of the water resonance followed by a high amplitude spin-lock $T_{1\rho}$ magnetization preparation, normalized with a nonselective irradiation pulse and high spin-lock $T_{1\rho}$ magnetization preparation

$$CESTrho\ PTR = \frac{M_{-offset+High\ spin-lock} - M_{+offset+Low\ spin-lock}}{M_{50\ ppm\ offset+High\ Spin-lock}} \quad (3)$$

The effects of proton exchange on CEST, $T_{1\rho}$, and CESTrho were simulated by solving the Bloch equations modified for chemical exchange using the ordinary differential equation solver in Matlab. The effects of the proton exchange rate and labile proton concentration on the PTR of each method was studied. A chemical shift of 900 Hz was selected to represent the resonance frequency offset of amine protons observed at 7T. For imaging experiments, samples of monosodium glutamate (Glu), which has an amino group (-NH_2) capable of exchanging protons with bulk water, were imaged on a 7T whole body scanner (Siemens Medical Systems, Erlangen, Germany). Glu phantoms in phosphate-buffered saline (PBS) were created and imaged at varying concentrations (2, 5, 8, 10 and 12 mM) at a pH of 7.0 and varying pH (6.8, 7.0, 7.2) with a 10 mM concentration. CEST, $T_{1\rho}$, and CESTrho PTR maps were computed by fitting images acquired with each magnetization preparation to equations (1), (2), and (3) respectively.

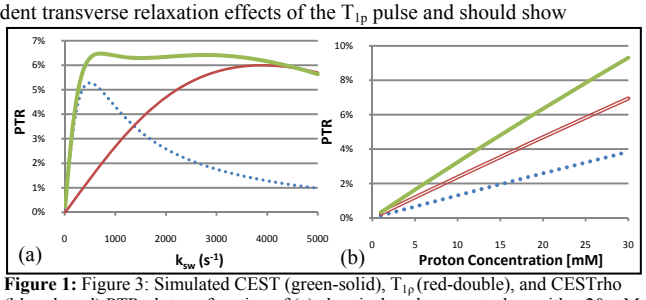

Figure 1: Figure 3: Simulated CEST (green-solid), $T_{1\rho}$ (red-double), and CESTrho (blue-dotted) PTR plots as function of (a) chemical exchange rate, k_{sw}, with a 20 mM proton concentration and (b) labile proton concentration with k_{sw} = 2000 s^{-1}. CEST simulations used a 3 second 80Hz square pulse, the T1ρ simulations used a 300 ms spin lock pulse at low/high amplitudes of 100/1000 Hz respectively, and the CESTrho combined the two magnetization preparations. The model parameters used were $T_{1w} = 2.4\ s, T_{2w} = 70\ ms,\ T_{1s} = 0.6\ s,\ T_{2s} = 0.1s, \Delta\omega = 3.0\ ppm, B_0 = 300\ MHz$

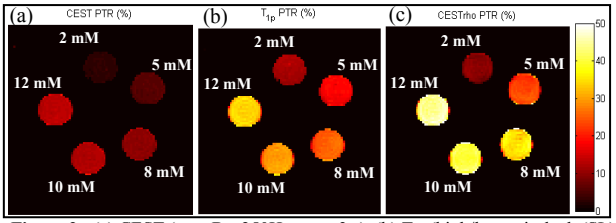

Figure 2: (a) CEST (max B_1=250Hz, t_{sat} = 3 s), (b) $T_{1\rho}$ (high/low spin-lock (SL) of 150Hz/1500Hz, TSL = 600ms), and (c) CESTrho (3s -250Hz Saturation pulse + 600 ms SL) PTR Maps at 7T Glu phantoms of varying concentrations (pH 7.0)

Results and Discussion: Figure 1 shows the relationship between the proton transfer ratios of the three methods as a function of exchange rate, k_{sw} (1a) and labile proton concentration (1b). The CEST method is most sensitive at slower exchange rates while $T_{1\rho}$ was more sensitive at intermediate to fast exchange rates. The CESTrho method had an almost additive effect and was more sensitive to proton exchange across the entire spectrum of exchange rates sampled. More interesting, the CESTrho method was relatively insensitive to changes in chemical exchange rate for exchange rates between 500 s^{-1} and 3500 s^{-1} for the particular parameters used. Under pathological conditions, the pH of diseased tissue can change by up to ±0.3 units, greatly affecting the proton exchange rate. While these changes in pH present a clinical opportunity for CEST and $T_{1\rho}$ imaging, they also confound measurements of concentrations. In the case of changing pH and concentration, determining the source of PTR changes may be difficult. For a particular magnetization preparation scheme, these simulations show that CESTrho can alleviate the confounding effects of changing chemical exchange rates. Figure 1b displays that at the low concentrations sampled; all three methods have a linear dependence on concentration. This simulation demonstrates that all three methods can be exploited to quantitatively measure the distribution and modulation of metabolites with exchangeable protons in vivo. This is especially significant for the CESTrho method, which will be significantly less affected by confounding pathologic changes in pH, temperature, and other factors that can influence exchange rate. It should be noted that the slope of this relationship is contingent on the exchange rate, particularly for CEST and $T_{1\rho}$. Figure 2 shows CEST, $T_{1\rho}$, and CESTrho PTR maps at varying Glu concentration. A linear slope of 1.1%, 2.2%, and 3.3% per mM of Glu solution was observed for the CEST, $T_{1\rho}$ and CESTrho PTR respectively demonstrating the sensitivity of each method to proton exchange at this particular exchange rate of Glu in PBS. The PTR dependence on pH for each imaging method is shown in figure 3. Near physiological pH, the exchange rate of Glu labile protons goes up with increases in pH. Subsequently, CEST PTR contrast decreases with increases in pH while $T_{1\rho}$ PTR contrast has the opposite effect. For the particular magnetization preparation parameters used, the CESTrho PTR contrast does not change with changing pH. This demonstrates that a magnetization preparation scheme can be created for a particular metabolite which is insensitive to the confounding effects of changing pH and temperature. This technique will greatly facilitate accurate measurement of changes in metabolite concentrations in vivo.

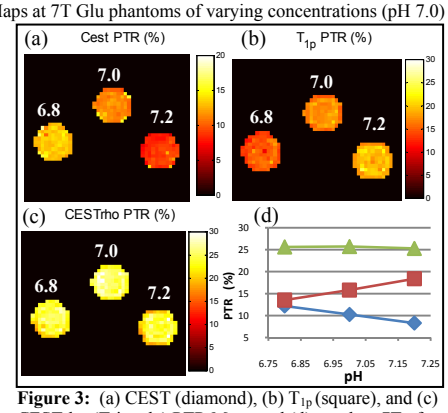

Figure 3: (a) CEST (diamond), (b) $T_{1\rho}$ (square), and (c) CESTrho (Triangle) PTR Maps and (d) graph at 7T of Glu phantoms at varying pH (10 mM)

Conclusion: In this work we developed a new pulse sequence which combines CEST and T1p proton exchange methods. This new CESTrho sequence has higher sensitivity to proton exchange in the slow to intermediate exchange regimes compared to CEST or T1rho, has a linear dependence on proton concentration and can be customized to make it insensitive to changes in pH and or temperature induced exchange rate.

References: [1] Wolff et al. *J. Magn. Reson*. 86(1990): 164–169, [2] Redfield AG. *Phys. Rev*. 98 (1955): 1787, [3] Michaeli et al. *J. Magn. Reson*. 169 (2004), 293–299, [4] Ward et al. *J. Magn. Reson.* 143 (2000): 79–87, [5] Trott et al. *J. Magn. Reson*. 154 (2002):157–160.

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