Transfer Rate Edited Experiment for the Selective Detection of Chemical Exchange

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Target Audience: Researchers interested in chemical exchange saturation transfer (CEST) and magnetization transfer (MT) MRI methodology in general

Purpose: Chemical exchange and the through-space nuclear Overhauser effects (NOE) are two important mechanisms responsible for polarization exchange between nuclear spin systems. In chemical exchange, protons physically swap binding partners while carrying their spin states with them. In NOE, the dipolar interactions between nuclear spins cause the polarization exchange without the actual swaps of protons. The polarization transfer due to NOE can be pronounced in biological tissues, such as brain white matter [1] and cartilage [2], which can interfere with the quantification of CEST. In this study, we propose a Transfer Rate Edited CEST (TRE-CEST) experiment that can simplify CEST spectra and data analysis by selectively suppressing signals arising from polarization transfers with slower transfer rates, such as NOE-mediated exchange, while preserving the signals of more rapid polarization transfers.

Theory and Method: The TRE-CEST experiment begins with label transfer modules (LTMs) followed by a detect phase for the water signal. Each LTM makes use of two kinds of magnetic labeling methods as showed in Fig. 1a. The first labeling method is a rapid frequency-selective excitation by the binomial P1331 pulse [3], during which protons resonating within its bandwidth will be tagged but the polarization transfers may not be significant. The other is a much longer continuous wave (CW) saturation pulse continuously saturating proton species at the selected saturation offset, during which the corresponding frequency-selective CEST signal can be accumulated. The total magnetization transfer ratio (MTR) at certain resonance offset $\Delta\omega$ generated by a single LTM can be described as the sum of individual MTRs imparted by the P1331 and CW saturation pulses: $MTR = MTR_{P1331} + MTR_{CW}$. Assuming that the water proton pool is large enough compared to labile solute proton species, that the water's T_1 relaxation is negligible during a LTM, and that the protons tagged by the P1331 pulse completely transfer their polarizations during the CW saturation pulse, then the following relations can be deduced: $MTR_{P1331} \propto \sum \sin^2(\pi \cdot \Delta\omega_i \cdot t_d) \cdot x_i$ and $MTR_{CW} \propto x_s \cdot k_{ex} \cdot t_{sat} \cdot (\gamma B_1)^2 / [(\gamma B_1)^2 + k_{ex}^2]$, where MTR_{P1331} reflects the additive contributions from all proton species in the sample undergoing polarization transfers, $\Delta\omega_i$ is the frequency offset of protons x_i, and t_d is the delay between pulses in the P1331; MTR_{CW} is only tagging protons at a certain resonance offset $\Delta\omega$, k_{ex} is the exchange rate to the water protons, and x_s is the fraction of protons that carry the magnetic tag. MTR_{CW} grows linearly with the product $k_{ex} \cdot t_{sat}$, while MTR_{P1331} has no dependency on k_{ex}. When exchange rate very slow, the contribution through MTR_{CW} become smaller such that $MTR \approx MTR_{P1331}$, as shown in Fig.1b. We implemented the TRE-CEST experiment on a 7T whole body MRI system (Siemens, Germany) using a Tx/Rx 28-channel knee coil (QED, Cleveland OH), a 2D slice selective GRE single-shot sequence was. CEST and TRE-CEST are both preformed, a previously used CW pulse (B1=58 Hz, t_{sat}=100 ms, n=10 cycles) [4] with offsets range from -8.5 to 8.5 ppm ^{1}H was implemented for both, for the P1331 pulse the td=559us. A raw egg was imaged using following parameters: FOV=125x125mm^2, matrix size=128x128, slice thickness=5mm, FA=15°, TR/ TE=12/3.5ms. Variations in the B_0 are corrected using WASSR [4].

Results and Discussion: The behavior of the pulse sequence for a series of exchange rates is shown in Fig. 2. These are based on the Bloch-McConnell Equations. It is clearly seen that signals arising from slow exchange rates decay rapidly with an increasing number of LTMs. This is verified using 12% BSA in a 9.4T vertical scanner. Fig.3 shows in raw egg while the CW-CEST experiment produces about ~5% MTR contrast in the 3 to 4 ppm, which is dominated by NOE-mediated transfer, TRE-CEST effectively eliminates these NOE contributions, thus greatly simplifying the spectra, while preserving the amide proton signals that undergo chemical exchange mediated transfer with water. One can think of the TRE-CEST sequence as follows: the band-stop excitation leads to the saturation of all signals other than water. If the exchange rate is fast, the signals recover quickly enough to be tagged in the conventional manner by CW irradiation. Slowly-exchanging pools, however, remain saturated throughout and are hence suppressed. Since NOE effects typically occur on a small time scale, one can suppress NOE effects while keeping faster CEST effects intact.

Conclusion: We have demonstrated a method for the elimination of NOE contributions in CEST measurements via an exchange-rate filter. The method is shown to work with BSA samples and raw egg sample. This methodology may be useful to authenticate NOE effects in vivo on the one hand, and to measure CEST effects free from NOE contributions on the other.

References: [1] Jones CK et al. Neuroimage 2013;77:114-24.. [2] Lee JS et al. Scientific Reports 2013 3(1707) [3] Friedman JI et al. J Am Chem Soc. 2010;132(6):1813-5. [4] Lee JS et al. NeuroImage 95 (2014) 22–28.

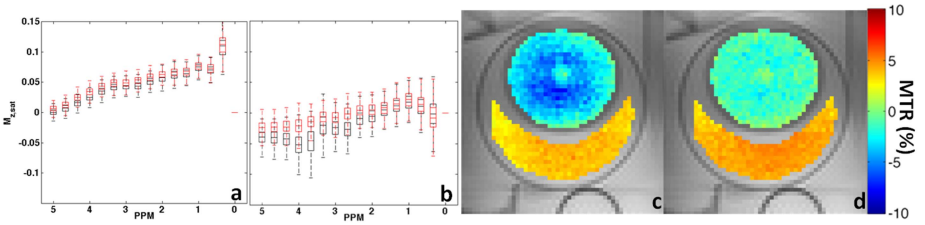

Fig. 3: MT asymmetry curves of **a)** egg white and **b)** egg yolk, black used CW-CEST and red used TRE-CEST. MT contrast from 3 to 4 ppm in both egg white and yolk in **c)** CW-CEST and **d)** TRE-CEST clear shows TRE-CEST eliminated NOE of egg yolk (MTR from negative to around zero) while the APT from egg white is preserved.

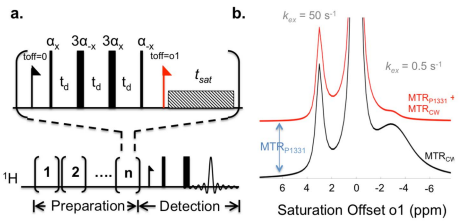

Fig. 1: a) TRE-CEST pulse sequence with *n* label transfer modules (LTMs) applied prior to detection of water signal. A detailed LTM is shown at top. Black flags represent placement on the center water frequency, while red flags denote moving the carrier to certain offset. The pulse tip angle is α=11.25°, and the inter-pulse delay is $t_d = 1/(2\cdot\Delta\omega)$ where $\Delta\omega$ is the frequency offset relative to the spectral center. The small, hatched pulse represents a low power frequency selective saturation element. b) Bloch simulation of Z-spectra generated by TRE-CEST (red, γB_1=75Hz, t_d=416 us, *n*=10, t_{sat}=100 ms) and continuous wave saturation CEST (black, γB_1=75Hz, t_{sat}=1.0s). The baseline of TRE-CEST spectra has a baseline offset relative to traditional CEST spectra by MTR_{p1331}, which is the approximate amplitude of the slow exchanging peak(s)

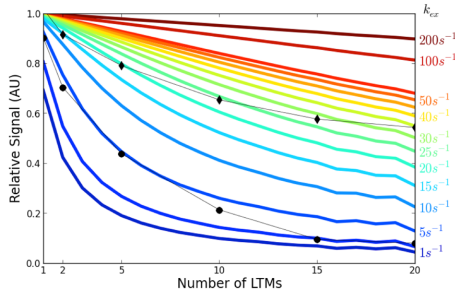

Fig. 2: Bloch-Mcconnell simulation of expected TRE-CEST signal relative to CEST. Data were plotted as a function of n, the number of LTMs, used to supply a cumulative 1.0s of CW labeling with 75.0 Hz B1 field. Contour lines representing the response of TRE-CEST to various rates of polarization transfer (colors) are simulated. Notice that TRE-CEST signals approach the same sensitivity as traditional CEST for the fastest exchanging protons. Black diamonds and circles correspond to experimental data of fast and slow exchange protons from 12% (w/v) bovine serum album (BSA) collected using both CW-CEST and TRE-CEST in a 9.4T vertical bore scanner.