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Transfer Rate Edited experiment for the selective detection of Chemical Exchange via Saturation Transfer (TRE-CEST)

Joshua I. Friedman [a], Ding Xia [b], Ravinder R. Regatte [b], Alexej Jerschow [a,*]

[a] Department of Chemistry, New York University, 100 Washington Square East, New York, NY 10003, USA
[b] Center for Biomedical Imaging, Department of Radiology, New York University Langone Medical Center, New York, NY, USA

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ABSTRACT

Chemical Exchange Saturation Transfer (CEST) magnetic resonance experiments have become valuable tools in magnetic resonance for the detection of low concentration solutes with far greater sensitivity than direct detection methods. Accurate measures of rates of chemical exchange provided by CEST are of particular interest to biomedical imaging communities where variations in chemical exchange can be related to subtle variations in biomarker concentration, temperature and pH within tissues using MRI. Despite their name, however, traditional CEST methods are not truly selective for chemical exchange and instead detect all forms of magnetization transfer including through-space NOE. This ambiguity crowds CEST spectra and greatly complicates subsequent data analysis. We have developed a Transfer Rate Edited CEST experiment (TRE-CEST) that uses two different types of solute labeling in order to selectively amplify signals of rapidly exchanging proton species while simultaneously suppressing 'slower' NOE-dominated magnetization transfer processes. This approach is demonstrated in the context of both NMR and MRI, where it is used to detect the labile amide protons of proteins undergoing chemical exchange (at rates $\geqslant 30\ \mathrm{s}^{-1}$) while simultaneously eliminating signals originating from slower ($\sim 5\ \mathrm{s}^{-1}$) NOE-mediated magnetization transfer processes. TRE-CEST greatly expands the utility of CEST experiments in complex systems, and *in-vivo*, in particular, where it is expected to improve the quantification of chemical exchange and magnetization transfer rates while enabling new forms of imaging contrast.

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1. Introduction

The chemical exchange saturation transfer (CEST) family of magnetic resonance pulse sequences tag protons of a solute molecule with a non-equilibrium nuclear spin magnetization and then detects the subsequent transfer of the labeled magnetization to the bulk water signal [1]. Because the solvent water is typically far more concentrated than any solute, multiple labeling and magnetization transfer events can be cumulatively stored in the water proton pool prior to detection, thereby greatly amplifying the signal of low concentration solute protons. Accurate quantification of magnetization transfer phenomena from CEST data can then be used to probe diverse chemical properties including molecular structure, dynamics, pH, solute concentration gradients, and temperature [2–5].

The precise nature of the magnetization labeling used in a CEST experiment can take on diverse forms including continuous wave (CW) saturation [1], frequency selective excitation dephasing [2], rotational flip angle difference [6] , or frequency labeling [7]. Regardless of the solute labeling method however, CEST experiments utilize a common detection strategy; solute signals are resolved via the labeling-dependent perturbations they induce in the water signal intensity following magnetization transfer. Two physical processes typically mediate the transfer of the labeled magnetization from solutes of interest to bulk water: chemical exchange, where labeled protons physically swap binding partners with the solvent water proton pool, and the through-space NOE interaction where nuclei exchange magnetization via fluctuating dipolar couplings [8].

In many biological samples containing proteins, the intermolecular through-space coupling between water and internal aliphatic or olefinic protons may be very small. In these situations magnetization transfer from non-labile protons is dominated by NOE-relayed CEST effects whereby magnetization is first transferred via intramolecular NOE to labile proton species which then in turn exchange with water [9–11]. We will refer to all signals from non-exchangeable protons detected in CEST experiments as NOE-mediated signals so as to avoid making implicit assumptions about the underlying magnetization transfer process in diverse samples. The through-space NOE transfer step is generally the

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[*] Corresponding author.

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rate-limiting step governing the apparent transfer processes. Additionally, saturation transfer between water and semisolids, where solutes have limited rotational freedom, is commonly referred to using the specific name, MT-effect, despite the fact the same underlying transfer mechanisms are ultimately giving rise to these signals. MT-effect signals are extremely broad, owing to limited rotational averaging that can occur in semisolids.

CEST signals originating from genuine chemical exchange have typically been of greatest interest to the biomedical imaging communities, but signals from NOE transfer have been isolated from biological tissue spectra and could be used to generate diverse new types of imaging contrast [9]. Unfortunately the presence of slower transferring NOE and MT-effect signals commonly complicates the subsequent analysis of CEST data and contaminates the spectral baseline, especially upfield of the water resonance, and often can hamper accurate data extraction [2].

Here, we describe a Transfer Rate Edited CEST (TRE-CEST) experiment that can be selectively tuned to suppress signals arising from experimentally defined ‘slower’-rates of magnetization transfer while greatly amplifying signals of more rapidly exchanging proton species. The TRE-CEST experiment begins with a variable number of identical, discrete Label Transfer Modules (LTMs) that tag solute protons prior to detection of the water signal. The high concentration of water protons (~110 M) coupled with the water’s relatively slow R_1 relaxation rate allows multiple LTMs to cumulatively store a saturation label in the water proton pool prior to detection, thereby greatly amplifying the signal. A frequency-resolved Z-spectrum is then constructed from a series of independent experiments where the response of the water signal is measured as a function of the LTM’s labeling frequency offset.

TRE-CEST accomplishes this transfer rate editing via the interplay between two different magnetization-labeling methods per LTM: A water band-stopped excitation pulse (excitation labeling) and, a frequency selective continuous wave (CW) labeling (saturation labeling). The initial excitation pulse is designed to rapidly equalize the Zeeman energy spin states of all the exchanging proton species in the sample simultaneously by creating single quantum coherence. After all the protons in the sample have been tagged by the excitation labeling step, the longer-duration, frequency encoding CW pulse is then selectively applied to the proton species of interest in order to continuously replace its label as it is transferred to bulk water or lost via other spin relaxation mechanisms. The duration of this continuous wave labeling in consecutive LTMs affects the signals differently depending upon their rate of magnetization transfer with water, and it is this dependence that is exploited by TRE-CEST to selectively suppress signals, and quantitate transfer rates.

2. Theory

A complete description of the TRE-CEST experiment requires solving a multi-pool model of the Bloch equations, but a few simplifying assumptions can be used to help form an intuitive framework for describing the experiment. To build this qualitative description of TRE-CEST we will assume that, (1) the spin-lattice relaxation of labeled protons is negligible during the course of a single LTM, (2) the water proton pool is large enough compared to labile solute proton species so that there is no back transfer of already labeled solvent protons to the solute, (3) steady state conditions are not reached over the time course of the model (an implicit requirement for item (2), and (4) labeling pulses have ideal labeling efficiency. With these assumptions in place, the TRE-CEST experiment can be explained via simple uncorrelated equations that relate the amount of signal generated in a TRE-CEST experiment to the magnetization transfer rate.

Each TRE-CEST LTM contains two different types of spin magnetization labeling, a single excitation labeling pulse followed by a longer duration CW saturation labeling pulse (Fig. 1). Each of these labeling modalities contributes an amount of signal S_{EXT} and $S_{CW,i}$ respectively, from the exchanging proton species to the solvent water proton pool. Phenomenologically, the signals S_{EXT} and $S_{CW,i}$ are the changes in the Z-component magnetization of the water resonance that are caused by saturated spin magnetization from labeled solute protons. We will first consider the signal generated by each of these labeling modalities individually before considering how they work together in the context of a TRE-CEST experiment to selectively suppress signals in a saturation transfer Z-spectra originating from ‘slow’ rates of magnetization transfer.

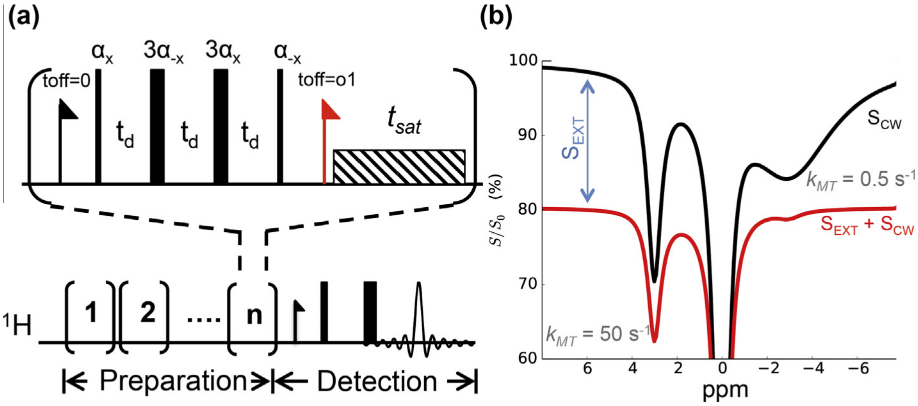

Fig. 1. (a) TRE-CEST pulse sequence with *N* label transfer modules (LTMs) applied prior to detection of the water signal. For MRI experiments, the direct detection is simply replaced by a gradient echo readout element. A detailed insert of the LTM used here is shown at the top. Black flags represent the placement of the transmitter on the center water frequency, while red flags denote moving the carrier to selectively saturate a given proton species. The pulse tip angle is $\alpha = 11.25°$, and the inter-pulse delay is $t_d = 1/(2 \cdot \Delta\omega)$ where $\Delta\omega$ is the frequency offset of the slow exchanging resonance in Hz relative to the spectral center defined by water (see Supplementary Fig. 1). The small, hatched pulse represents a low power frequency selective saturation element. Note the timing diagram is not drawn to scale and t_{sat} is typically much longer than the P1331 pulse element. (b) Bloch simulation of Z-spectra generated by TRE-CEST (red, $\gamma B_1 = 75$ Hz, $t_d = 416$ µs, $n = 10$, $t_{sat} = 100$ ms) and continuous wave saturation CEST (black, $\gamma B_1 = 75$ Hz, $t_{sat} = 1.0$ s). The simulation was performed on a three-spin system, with a 110 M water signal at 0 ppm. The simulated proton resonating at +3 ppm has $k_{MT} = 50$ s^{-1}, $R_2 = 75$ s^{-1}, and $x_s = 0.9\%$ of water. The proton at −3 ppm has $k_{MT} = 0.5$ s^{-1}, $R_2 = 200$ s^{-1}, and $x_s = 36\%$ of water. The baseline of the TRE-CEST spectra is offset by the factor S_{EXT}. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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