DOUBLE-ANGLE AMIDE PROTON TRANSFER IMAGING: A NEW CHEMICAL EXCHANGE SATURATION TRANSFER (CEST) CONTRAST

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Introduction: Amide proton transfer (APT) imaging, a type of chemical exchange saturation transfer (CEST) method, has shown promise in imaging endogenous protein and peptide content and pH. In conventional APT experiments, CEST contrast is created by subtracting a label scan (with RF irradiation at the amide resonance 3.5 ppm from the water resonance) from a reference scan (with RF irradiation -3.5 ppm from the water resonance) in order to remove spillover and macromolecular magnetization transfer effects [1]. However, this conventional analysis is sensitive to confounding contributions from magnetic field (B_0) inhomogeneities and, more problematically, inherently asymmetric macromolecular resonances. In addition, the lipid resonance at -3.5 ppm complicates the interpretation of the reference scan and decreases the resulting contrast. In this study, we introduce a new CEST contrast that avoids these issues by creating label and reference scans based on varying the irradiation pulse nutation angle (π and 2π radians) instead of the frequency offset (3.5 and -3.5 ppm). Hence, this new approach is best described as chemical exchange *rotation* transfer (CERT).

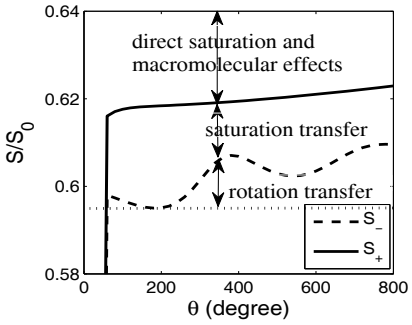

Fig. 1 Simulated signal S_- and S_+ *vs* θ

Theory: Pulsed-CEST imaging is composed of oscillation and saturation effects [2], as can be seen in Fig. 1. S_- is the signal when irradiating at the amide resonance and S_+ is the reference scan when irradiating on the opposite side of the water resonance. Simulations in Fig. 1 indicate that S_- varies with irradiation flip angle (θ), while S_+ is largely independent of θ (for $\theta > 50°$) when $B_{avg\ power}$ is kept constant and the adiabatic condition is satisfied. ($B_{avg\ power}$ is the square root of the mean square applied irradiation.) The oscillation of S_- is caused by the rotation of the solute spin system. The flat plot of S_+ is caused by the saturation of water and macromolecules. The difference between S_+ and S_- is due to roughly equal parts transfer of solute saturation and rotation, and the conventional CEST metric MTR_{asym} combines these effects:

$$MTR_{asym} = (S_+ - S_-)/S_0 \qquad (1)$$

The new CEST metric MTR_{double} isolates the rotation contribution, avoids acquisitions at multiple frequencies, and hence avoids the above listed artifacts.

$$MTR_{double} = (S_-(2\pi) - S_-(\pi))/S_0\big|_{B_{avgpower}} \qquad (2)$$

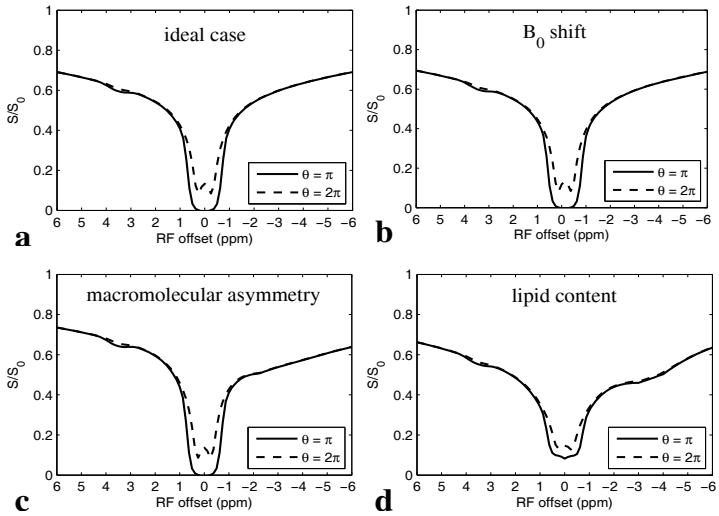

Fig. 2: Simulated z-spectrum for four cases.

Methods: Simulations were performed with a multi-pool model (amide solute pool, lipid pool, macromolecular pool, and water pool), which contains thirteen coupled Bloch equations. *In vivo* rat brain pulsed-CEST experiments (with θ equal π and 2π) were acquired with $B_{avg\ power}$ of 1.6 μT on a 9.4 T Varian animal system.

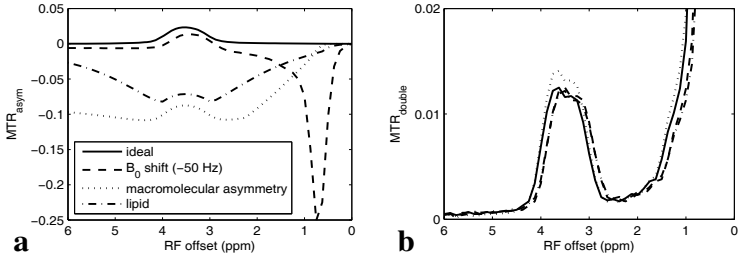

Fig. 3: Simulated MTR_{asym} (a) and MTR_{double} (b) for 4 cases.

Results: Fig. 2 give the simulated z-spectra of pulsed-CEST imaging with θ of π and 2π under four conditions. Fig. 3 plots the corresponding MTR_{asym} (a) and MTR_{double} (b). Note the key result that the MTR_{double} is relatively robust, while conventional MTR_{asym} varies considerably. Hence, MTR_{double} is much more likely to give a measure of amide content and exchange under all conditions. Fig. 4a gives the experimental results for rat brain (gray matter) with the pulsed-CEST sequence. Note the separation between the $\theta = \pi$ and 2π lines in fig. 4a (see arrow), corresponding to amide exchange rotation effects. Also note that this separation is not affected by the signal on the opposite side of water, and hence avoids macromolecular asymmetry and lipid effects. MTR_{double} and MTR_{asym} are plotted in 4b. Note the peak at 3.5 ppm (see arrow) is clear in MTR_{double}, but not in MTR_{asym}, where macromolecular asymmetry and lipid content overwhelm the amide peak.

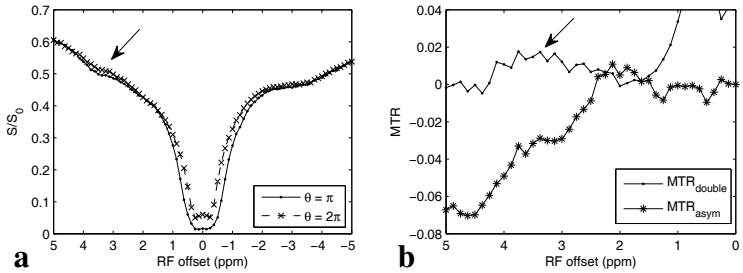

Fig. 4: Z-spectrum (a) and MTR_{double} (b) on rat brain.

References:

[1] Zhou, J. et al., Progr NMR Spectrosc 48, 109 (2006)

[2] Zu, Z. et al., *Magn. Reson. Med.* 66, 1100 (2011)

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