Two-frequency irradiation of the pH-dependent amide proton transfer effect in a clinical scanner:simulation and experiment

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Target Audience: Researchers in CEST and MT Cohorts, Pulse Sequence Developers

Purpose: The amide proton transfer (APT) effect is sensitive to tissue pH changes and has significant potential for describing both pathological acidosis and alkalosis. However, the presence of simultaneous magnetization transfer (MT) effects arising from solid-like macromolecules has posed a significant challenge for *in vivo* quantification of the APT effect. A novel strategy using two-frequency RF irradiation in an 11.7 T NMR spectrometer has previously been shown to isolate the CEST from MT asymmetry in protein samples [1]. In this study, we adapt the technique to a clinical 3T MRI scanner and compare the results acquired from egg white solution to simulation results from a three-pool model.

Method: Simulation: A three-pool model was built to simulate the exchange effect between protons in semisolid proteins (MT pool, 2.34 ppm), amide protons in mobile proteins (APT pool, 8.17 ppm) and bulk water (Water pool, 4.67 ppm). The ratio between the pool sizes was set to 1:1:98. A Gaussian line shape was used to describe the MT pool, whereas a Lorentzian line shape was used for the APT and water pools. The experimentally derived T_1 relaxation rate of cross-linked egg white solution (2020 ms) was used for all three pools. The T_2 of MT and APT pools were assumed to be 100 µs and 10 ms, respectively. The T_2 of the water pool was set to the experimental value of 126 ms. The time-dependent evolution of the imaging signal was calculated by solving the Bloch equations based on a matrix algebra approach [2,3]. The exact pulse profiles in the experiment study were used in the simulation.

Experiments: Three 50 ml tubes of egg white solution were prepared immediately prior to measurement by cross-linking with 25 mM glutaraldehyde (Sigma-Aldrich) for 5 hours to prevent protein degradation, followed by pH adjustment. Z-spectra were obtained on a 3T scanner (Tim Trio, Siemens, Germany) utilizing a FLASH-based sequence [4] (TR, 200 ms; TE, 5 ms; saturation pulse duration, 100 ms; peak saturation pulse amplitude, 1.5µT; reading pulse flip angle, 10°). The Gaussian-shaped saturation pulse was cosine-modulated to enable double-frequency irradiation with a ±5 ppm offset from the central frequency described in Fig 1 and 2.

Results and Discussion:

Simulation: Three schemes were studied in the simulation: pure APT scheme with only APT and water pools included, a pure MT scheme with MT and water pools included, and a scheme with all three pools included. An example simulation for single and double frequency irradiation is illustrated in Fig.1.The APT effect in the three-pool scheme results in the MTR_{asym} peak at 3.5 ppm and 1.5 ppm for single- and double-frequency irradiation, respectively. The MTR_{asym} change in the three schemes with respect to the exchange rate from the APT to water pool is shown in Fig. 3. Compared to the single-frequency irradiation, the double-frequency irradiation setup reduces the MTR_{asym} signal arising from the pure MT scheme (green) by 87.5%. Furthermore, the difference between the MTR_{asym} signal in the three-pool scheme (red) and the pure APT scheme (blue) irradiated by double frequency pulses (17.9 ± 9.0 %, solid line) is smaller than when irradiated by single-frequency pulses (40.0 ± 13.9 %, dashed line). The simulation results indicate double-frequency saturation pulses isolate the APT asymmetry better than single frequency pulses.

Experiments: Fig. 2 shows the experiment data from egg white solution. Similar to the observed MTR_{asym} in the brain, a negative MTR_{asym} is observed in all three egg white samples. The signal dips in double-frequency irradiation experiments (Fig 2) at ±15ppm offset from water pool have been previously reported and are likely excitation sidebands resulting from insufficient sampling of the RF profile by the limited number of pulse steps and truncation error [1]. Although Fig. 4 reveals the linear dependence of MTR_{asym} on pH, the signal improvements of the double frequency irradiation technique determined in the simulations is not realized in the preset data. Additional pulse sequence optimizations and use of more physiologically relevant phantoms that can better tolerate prolonged pH variations would reveal additional differences.

Conclusion: The present study demonstrated the feasibility of double-frequency irradiation for detection of pH-dependent APT effect with partial correction of the MT asymmetry on a clinical scanner; however, quantitative pH imaging using this technique requires more extensive phantom and *in vivo* data.

References: [1] Lee et. al. JMR 2012; [2] Helgstrand et.al JMR 1997; [3] Mueller et. al. JMR submitted; [4] Xu et. al. ISMRM 2012

Fig. 1 Simulation results for single and double frequency irradiation.

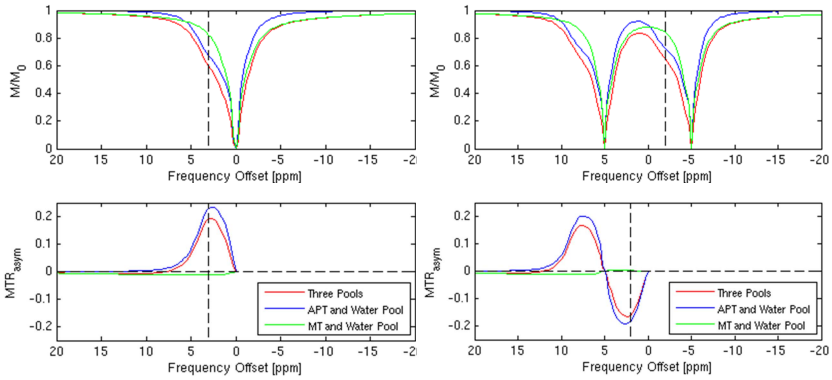

Fig. 2 Experimental data from single and double frequency irradiation of egg white solution at three pH values.

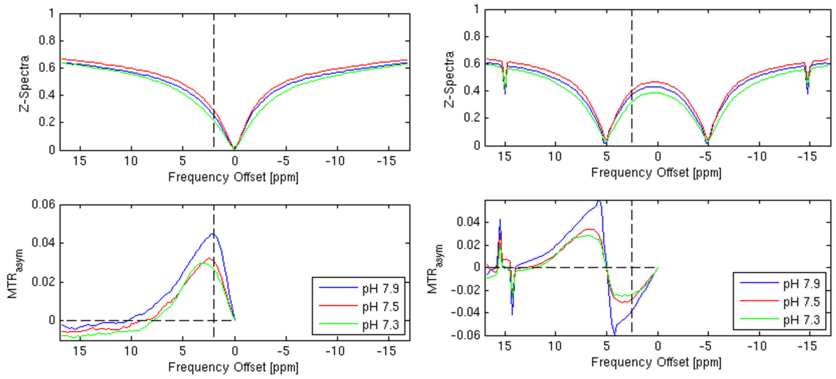

Fig. 3 Simulated dependence of MTR_{asym} on the exchange rate from APT to water pool.

Fig. 4 MTR_{asym} at 3.5 ppm of egg white at varying pH.