

MTR_{ReX} – a new spillover and MT correction method for quantitative pulsed steady-state CEST

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Introduction

Studies of endogenous CEST effects always require isolation of competing effects such as direct water saturation and macromolecular MT. We compare the standard evaluation for pulsed CEST experiments, MTR_{asym} with a new, spillover-corrected normalization called MTR_{ReX}. For verification amine proton exchange of creatine in solutions with different agar concentrations were studied experimentally. We demonstrate that spillover can be corrected properly and also quantitative evaluation of pH and creatine concentration is possible which proves MTR_{ReX} as quantitative CEST-MRI method.

Theory

Since spinlock theory can be applied successfully to CEST^{1,2} we employ the formula for normalized steady-state magnetization after irradiation at label or reference frequency:

$$Z_{lab/ref} = \frac{M_{2w}^{SS}(\Delta\omega/-\Delta\omega)}{M_{2w}^0} = \cos^2 \theta \frac{R_{1w}}{R_{eff} + R_{ex,lab/ref}} \quad (1)$$

where $R_{eff} = R_{1w} \cos^2 \theta + R_{2w} \sin^2 \theta$ is R_{1p} of the water pool (direct saturation) and R_{ex} is the exchange-dependent relaxation rate in the rotating frame, tilted by angle $\theta = \tan^{-1}(\omega_1 / \Delta\omega)$. For simplicity we assume $\cos \theta = 1$ and slow exchange ($R_{ex,ref} = 0$). Asymmetry³ expressed by eq. (1) still contains terms of direct saturation (R_{eff})

$$MTR_{asym} = Z_{ref} - Z_{lab} = \frac{R_{ex} R_{1w}}{R_{eff}(R_{eff} + R_{ex})} \quad (2)$$

whereas MTR_{ReX} contains no spillover terms:

$$MTR_{ReX} = \frac{1}{Z_{lab}} - \frac{1}{Z_{ref}} = \frac{R_{ex}}{R_{1w}} \quad (3)$$

For modeling saturation employing a train of pulses with a certain duty cycle DC we assume $R_{ex}^{pulsed} = DC \cdot R_{ex}$

instead of using an effective cw B_1 equivalent. In the case of full saturation¹ and slow exchange $R_{ex} = k_s \cdot f_s$ we get quantitative access to by the variable we call QUREX (quantification of R_{ex}):

$$QUREX = MTR_{ReX} \cdot R_{1w} / DC = k_s \cdot f_s \quad (5)$$

which employs a R_{1w} map and DC and provides direct access to k_{sw} .

Methods

For variation of spillover and MT, agar was added to a 55.5 mM creatine solution at pH = 6.38. Z-spectra were acquired by saturation using a train of 80 Gaussian shaped pulses with $t_p = 100$ ms and 100ms interpulse delay (DC=50%) at $B_1 = \text{flip angle}/(\gamma t_p) = 0.2\text{--}2 \mu\text{T}$ followed by single-shot TSE imaging (FOV: 220; 1.1x1.1x4 mm³). Z-spectra were B_0 -corrected employing a WASSR⁴ map. By WEX measurements we obtained k_s as a function of pH and T: $k_s(\text{pH}, 19^\circ\text{C}) = 1.4615 \cdot 10^{10 \text{pH}}$ which yields pH as a function of QUREX via $\text{pH}(19^\circ\text{C}) = \log(QUREX / (1.4615 \cdot f_s))$.

Results and Discussion

MTR_{ReX} is less sensitive to spillover and MT effects than MTR_{asym} (Fig.1,2). A large spillover dilution (strong B_1 , high agar conc.) leads to an increased uncertainty of MTR_{ReX} (Fig.2). Using fit results, R_{ex}^{pulsed} could be calculated according to eq. (4) and Ref.[1]. Figure 1 demonstrates that MTR_{ReX} can directly be interpreted using R_{1w} and R_{ex}^{pulsed} and is therefore not just a correction, but easily yields a quantification (QUREX (eq. 5)) also for the pulsed CEST case. Employing the exchange rate from WEX $k_{sw}(\text{pH}=6.38) = 35.08$ Hz an absolute creatine concentration map (Fig. 3, other pH greyed out) was obtained assuming 4 labile protons for the amine group. Using the obtained fraction $f_{s,55\text{mM}} = 0.2\%$ we also got a pH map (Fig. 3, right, other conc. greyed out). Both the concentration and pH map deviate not strongly from expectation even in the solidified solutions. With increased regularity Z-spectra are evaluated not by asymmetry analysis, but by subtracting the fitted direct water saturation^{5,6}. In this case MTR_{ReX} can be used with the modification $Z_{ref} = Z_{fit}$. The normalization MTR_{ReX} is also valid for trains of 180°-pulses.

Conclusion

We propose a new spillover and MT correction method for Z-spectra evaluation which requires no further knowledge of the system. This approach is of special interest for clinical static field strengths and protons resonating near the water peak. This is the case for –OH-CEST effects like gagCEST⁷ or glucoCEST⁸, but also amine exchange of creatine⁹ or glutamate¹⁰ which require high B_1 . For general understanding and analysis of steady-state Z-spectra we postulate that the inverse metric $1/Z$ is useful not just for corrections, but also for quantitative CEST MRI.

References

- Zaiss and Bachert, arXiv:1203.2067 (2012). (accepted by NMRBioMed)
- Jin et al. MRM 65, 1448 (2011).
- Zhou and van Zijl, PNMRS 48, 109–136 (2006).
- Kim et al. MRM 61, 1441–1450 (2009).
- Jin et al., MRM (2012) doi: 10.1002/mrm.24315

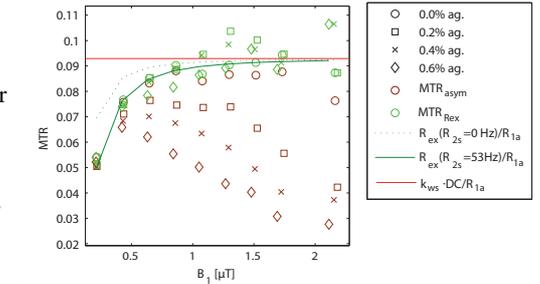


Figure 1: Comparison of MTR normalizations as a function of B_1 and agar conc. Spillover correction of MTR_{ReX} exceeds MTR_{asym}. MTR_{ReX} is within a narrow band and can be interpreted quantitatively by R_{ex}^{pulsed} / R_{1a} (solid green) and in full saturation by $k_{ws} \cdot DC / R_{1a}$ (solid red).

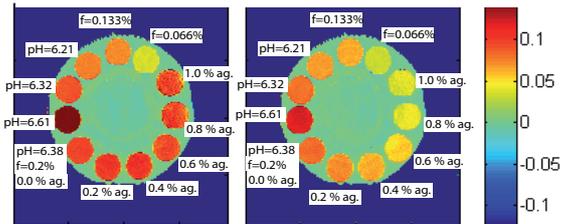


Figure 2: MTR_{ReX} (left) vs. MTR_{asym} (right) of creatine solutions (standard: 55.5mM; pH=6.38), but different agar concentration. In contrast to MTR_{asym}, MTR_{ReX} is hardly affected by the agar concentration. Different pH and concentration values can be distinguished well with both normalizations.

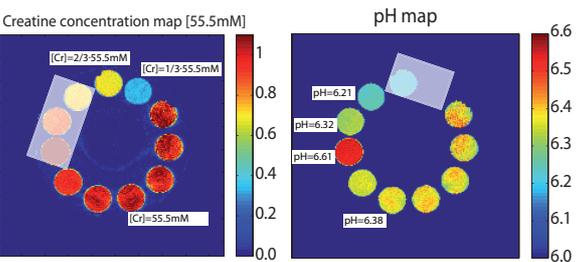


Figure 3: pH map (left) and Cr conc. map (right) from MTR_{ReX} (1.9 ppm, 1 μ T) (Fig 2). pH agrees with the pH-meter values. Concentration is as expected if 4 exchanging protons are assumed. In solutions with agar the noise increases, but estimation of pH and conc. are still valid.

With increased regularity Z-spectra are evaluated not by asymmetry analysis, but by subtracting the fitted direct water saturation^{5,6}. In this case MTR_{ReX} can be used with the modification $Z_{ref} = Z_{fit}$.