Spillover correction for quantification of pulsed-CEST experiments

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Introduction

Amide proton transfer (APT), a sub-type of chemical exchange saturation transfer (CEST), uses the chemical exchange between amide and bulk water protons in cells to create a new contrast in MR imaging [1-2]. Through off-resonant saturation at different frequencies, parameters that depend on the transfer rate can be measured by evaluation of z-spectra. However, the residual direct saturation of the water pool (*spillover*) dilutes the CEST effect and must be avoided or compensated. This was already done for the cw case [3,4]. In this study, we present a correction algorithm which is able to remove *spillover* effects of APT z-spectra achieved by pulsed saturation of trains of Gaussian-shaped pulses with gradient spoiling. Additional, a comparison of pulsed- ($PPTR$) and cw-proton transfer rate (PTR) is given which permits analytical quantification of pulsed CEST experiments.

Theory

The combined model (cm) *spillover* correction [4] for cw irradiation combines the weak-saturation-pulse solutions PTR

$$PTR = \frac{k_{WS}}{R_{1W} + k_{WS}} \cdot \frac{\omega_1^2}{\omega_1^2 + pq + \Delta\omega_S^2 \frac{q}{p}} \quad (1)$$

$$p = R_{2S} + k_{SW} - \frac{k_{SW} k_{WS}}{R_{2W} + k_{WS}} \qquad q = R_{1S} + k_{SW} - \frac{k_{SW} k_{WS}}{R_{1W} + k_{WS}}$$

and the direct water saturation DWS to the complete z-spectrum. Likewise, but inversely, we calculate $PPTR$ on CEST resonance to

$$PPTR_{cm} = \frac{DWS - MTR_{label}}{(2 \cdot DWS - MTR_{label} \cdot DWS - 1)} \quad (2)$$

$$\approx \frac{MTR_{asym}}{(1 - 2 \cdot MTR_{ref} + MTR_{label} \cdot MTR_{ref})} = \frac{MTR_{asym}}{\sigma} \quad (3)$$

which is compared to PTR.

2.2-σ-Gaussian pulses of duration t_p and interpulse delay of t_d were concatenated to pulse trains with varied B_{1cwpe} [5] and flip angle θ, at constant duty-cycle $DC = t_p/(t_p+t_d)$ and saturation time $t_{sat} = n \cdot (t_p+t_d)$.

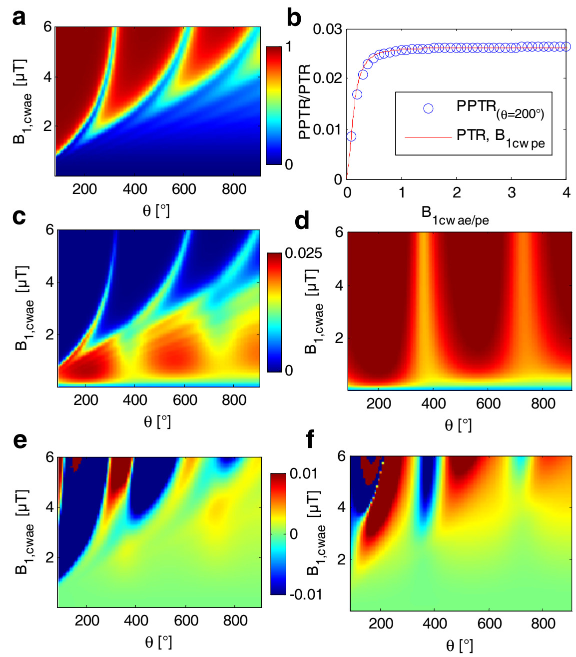

Figure 1: Combination of DWS at 3.5 ppm (**a**) and PPTR at 3.5 ppm (**d**) leads to MTRasym(3.5ppm) (**c**). Deviation from simulated PPTR is shown in (**f**) and with approx. of eq. (3) in (**e**). PPTR and PTR as functions of B_1 (**b**).

Materials & Methods

The time-dependent 2-pool-Bloch-McConnell equations with transfer terms were solved using Matlab 7 (The Mathworks, Natick, MA, USA) by common numerical solutions [6] extended for non-constant ω_1.

For constant $t_{sat} = 3\ s\ (>>T_{1W})$ and $DC = 56\%$, B_{1cwpe} and θ were varied. At $\Delta\omega = \pm 3.5ppm$ maps of $MTR_{label/ref}$, DWS and $PPTR$ (by artificial removing of direct water saturation) were simulated with the parameters of Tab. 1 with spoiling after each pulse ($M_T = 0$). One simulation took ~6 hours. With the same parameters ideal $PTR(3.5\ ppm)$ was calculated by eq. (1).

Table 1: Simulation parameters

Pool	A (water)	B (CEST)
f	1	0.002
T_1	450 ms	1000 ms
T_2	220 ms	15 ms
offset	0 ppm	3.5 ppm
k	0.025Hz	25 Hz

Results & Discussion

Figure **1a** shows $DWS(3.5\ ppm)$ as a function of B_{1cwpe} and θ. Short pulses lead to high direct water saturation which causes low MTR_{asym} (Fig**1c**) for B_1 larger than $1.5\ \mu T$. Compared to simulated $PPTR$ (Fig**1d**) the asymmetry analysis showed general loss of ideal CEST effect. Optimal MTR_{asym} is found at $B_{1cwpe} \approx 0.44 \mu T$ and $\theta \approx 192°$ in agreement with [7,8]. The difference of simulated PPTR and the combined model $PPTR_{cm}$ calculated by eq. (2) is negligible up to B_1 of $1.5 \mu T$ (Figure **1f**). Also the approximation in eq. (3) which only uses label and reference scan for the *spillover* factor σ [3] is able to reproduce $PPTR$ with only a small deviation $(<0.5\%)$ for $B_1 < 1.5 \mu T$. Furthermore, $PPTR$ can be compared to PTR which is an analytic expression as shown in Fig. 1b: It proves that on-resonant $PPTR(\theta \sim 200°)$ is correlated to PTR with B_{1cwpe} which means that the applied *spillover* correction gives analytic access to pulsed chemical exchange saturation transfer experiments and, by QUESP [9] or extrapolation to ideal $PTR_{max} = k_{ws}/(R_{1W}+k_{ws})$, access to the exchange rate. All approaches using MTR_{asym} as a measure for CEST effect should therefore use pulses with $\theta \sim 200°$ and the proposed asymmetry correction of $PPTR_{cm}$. This will reduce significantly errors in quantification due to the influence of *spillover* effects. Encouraged by the cw case, it has still to be proven that conventional MT effects can be corrected by this method like it was successfully done in [4].

Conclusion

APT CEST effects in experiments using pulsed saturation feasible in clinical MRI scanners can be corrected from *spillover* dilution by the combined model correction without further knowledge of the system parameters. The obtained PPTR is correlated to the analytical PTR and therefore allows analytic access to pulsed saturation transfer experiments. The presented spillover correction is also applicable to CEST effects of other exchangeable groups.

References

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