

Study of chemical exchange in the intermediate exchange regime: a comparison of spin-locking and CEST techniques

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Introduction: Recently, an indirect MRI detection of hydroxyl protons of small metabolites via the water signal was reported [1]. Selective off-resonance irradiation attenuates the water signal via chemical exchange saturation transfer (CEST) between hydroxyl and water protons. It was found that the magnetisation transfer (MT) asymmetry ratio (MTR_{asym}) depends nonlinearly on hydroxyl-group concentration. Since the spin-lattice relaxation rate in the rotating frame ($R_{1\rho}$) is also known to be sensitive to proton exchange [2], we hypothesized that metabolite proton exchange may also be detectable using an on-resonance spin-locking pulse. The aim of this study was to quantify and analyze $R_{1\rho}$ dispersion over a range of spin-locking (SL) B_1 fields ($\omega_{1,SL}$), for hydroxyl-, amide- and amine-phantoms, and a protein sample. The results were compared to measurements made with CEST off-resonance irradiation.

Materials and Methods: Glucose (Glc), nicotinamide (Nic), glutamate (Glu) and bovin serum albumin (BSA) were dissolved in potassium phosphate buffer and titrated to pH 7.4. All MR experiments were performed at room temperature on a 9.4T/31-cm magnet (Magnex) interfaced to a Unity INOVA console (Varian). A 3.8-cm diameter volume coil (Rapid Biomedical) was used to achieve SL. Following SL, images were acquired with a double spin-echo (SE) EPI sequence. $R_{1\rho}$ dispersion was measured over a range of ten $\omega_{1,SL}$ between 170 and 4000 Hz. Fourteen SL times (TSL) ranging between 0 and 330 ms were used to calculate $R_{1\rho}$ at each $\omega_{1,SL}$ by fitting to a monoexponential signal decay with respect to TSL. Assuming the asymmetric-population limit ($p_{water} \gg p_a$, where a represents exchangeable non-water protons), the exchange related relaxation rate can be expressed as $R_{ex} = p_a \delta^2 k / [(\delta - \omega_{1,rf})^2 + \omega_{1,SL}^2 + k^2]$, where k is the exchange rate, $\omega_{1,rf}$ is the Larmor frequency of the applied rf field and δ is the difference between water and non-water proton frequencies [3]. k and p were estimated assuming δ was 0.6, 3.3, 3.0 and 2.8 ppm for the Glc, Nic, Glu and BSA phantoms, respectively. For CEST measurements, Z-spectra were collected within ± 10 -ppm of the water resonance, with a 4-s presaturation pulse ($B_1 = 170$ Hz) followed by a gradient pulse for dephasing residual transverse magnetization. The CEST magnitude was estimated by calculating $MTR_{asym}(\Delta\omega) = [S(-\Delta\omega) - S(\Delta\omega)] / S_0$, where $\Delta\omega$ is the offset frequency between $\omega_{1,rf}$ and the central water frequency. $S(\Delta\omega)$ and S_0 are the signal intensities at the offset frequency and at a reference offset (200 or 300 ppm), respectively. A repetition time of 18 s was used.

Results and Discussion: In Fig. 1A, $R_{1\rho}$ dispersion is shown for Glc, Nic, Glu (50 mM) and BSA (10 % by weight) phantoms. $R_{1\rho}$ was clearly dependent on $\omega_{1,SL}$. Significant MTR_{asym} was observed for all phantoms (Fig. 1B). Note that due to slow k of the amide-water exchange, the Nic sample showed no significant dispersion (Fig. 1A), but it did have clear off-resonance irradiation contrast (Fig. 1B). Robust fits of R_{ex} to the dispersion data were possible for all samples except Nic. Estimates of p were 0.0093, 0.0014 and 0.0015 for the Glc, Glu and BSA phantoms, respectively. Corresponding estimates of k were 855, 1455 and 1013 s^{-1} , which were likely in the intermediate exchange regime. In Fig. 2A and C, $R_{1\rho}$ dispersion and MTR_{asym} -spectra are shown for 20, 50, 100 and 200 mM Glc phantoms. The $R_{1\rho}$ dispersion increase with Glc concentration over the measured range (Fig. 2B). Fitting to the dispersion data gave a linear increase in p (0.0038, 0.0093, 0.0195 and 0.0390), whereas the k was relatively unaffected (802, 855, 847 and 921 s^{-1}), wrt increasing concentration. Consistent with a previous report [1], an increase in CEST effect wrt concentration was also observed but the MTR_{asym} (and its integral) has a more complicated nonlinear behaviour depending on the measurement offset (Fig. 2D). Moreover, the frequency offset of maximum MTR_{asym} shifts as a function of concentration, probably due to overlapping of hydroxyl proton spectra on both sides of the water frequency ($k_{Glc} > \delta_{Glc}$).

Conclusions: Our results indicate that the metabolites have significant $R_{1\rho}$ dispersion at concentrations in the mM range. The proton exchange model presented in [3] fits the data well and enables k and p quantification by measuring $R_{1\rho}$ wrt $\omega_{1,SL}$. However, it should be noted that the results will vary depending on the properties of the buffer, the pH, the temperature and magnetic field strength. The quantification of CEST effects using MTR_{asym} analysis worked well in slow exchange regime ($k \ll \delta$) [4], but can become problematic for faster exchanges. Our results suggest that SL technique with on-resonance irradiation is not sensitive to very slow exchange, but may be more suited for quantitative study in the intermediate exchange regime ($k \sim \delta$).

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References: [1] van Zijl et al, PNAS 104(11):4359-4364 (2007). [2] Duvvuri et al, PNAS 98(22):12479-12484 (2001). [3] Trott et al. JMR 154:157-160(2002). [4] Zhou et al., MRM 51:945 (2004).

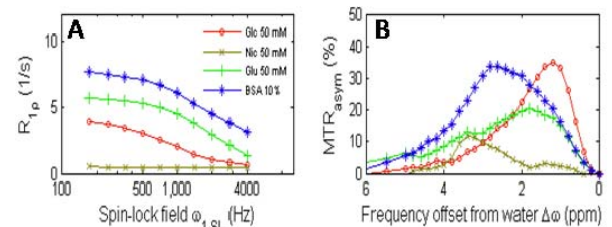


Fig. 1. (A) $R_{1\rho}$ dispersion, and (B) MTR_{asym} -spectra for the hydroxyl-, amine- amide- and BSA-phantoms.

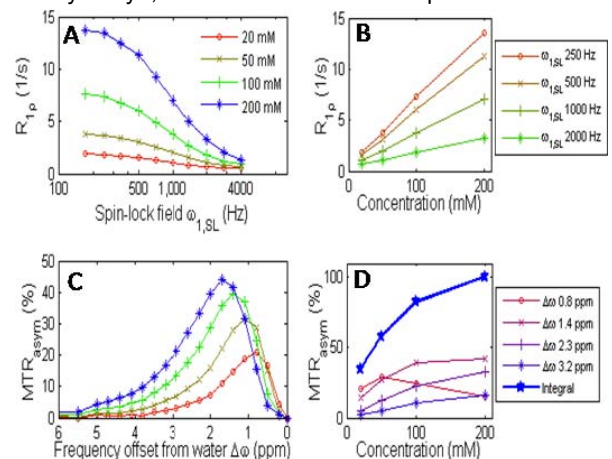


Fig. 2. (A) $R_{1\rho}$ dispersion and (B) $R_{1\rho}$ at selected $\omega_{1,SL}$ dependence on Glc concentration. (C) MTR_{asym} -spectra and (D) MTR_{asym} (and its integral) at selected $\Delta\omega$ as a function of concentration.