Chemical exchange sensitive imaging without a long irradiation pulse: irradiation with toggling inversion preparation

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Introduction Chemical exchange (CE) based MRI techniques, such as spin-locking (SL) or chemical exchange saturation transfer (CEST), rely on an irradiation pulse during which the imaging contrast builds up. One outstanding problem is that conventional longitudinal and/or transverse relaxation also occurs during the irradiation; therefore, the measured water signal will be affected by T_1 and T_2 in addition to CE. Because *in vivo* CE contrast is usually small and T_1 and/or T_2 may change significantly in many pathological conditions, it is crucial to separate the T_1 and T_2 effects and get a pure CE contrast. Recently, Sun proposed a ratiometric analysis approach that utilizes a steady state irradiation pulse to normalize the signal and subsequently minimize the T_1 and T_2 effects [1]. One practical issue is that due to hardware and/or specific absorption rate limitations, CE-sensitive image often has to be acquired using a short irradiation pulse, although a long pulse reaching the steady state may give simpler quantification of CE effect and, in many circumstances, result in better imaging contrast. In this work, we propose a new acquisition method which can use a relatively short irradiation pulse (i) to obtain pure CE contrast without T_1 and T_2 effects, and (ii) to obtain steady-state imaging contrast.

Theory During an irradiation pulse in a typical SL experiment (RF1, Fig. 1A), the water magnetization is "locked" by an effective B_1 and relaxes with a rate constant $R_{1\rho}$ (=1/$T_{1\rho}$), the spin-lattice relaxation rate in the rotating frame, to a steady state (Fig. 1B). From a two-site exchange model with asymmetric population approximation [2], $R_{1\rho}$ can be expressed as

$$R_{1\rho} = R_1 \cos^2\theta + (R_2 + R_{ex})\sin^2\theta, \quad \text{where } R_{ex} \approx p_B \cdot k \cdot \delta^2 \cdot \left[(\delta-\Omega)^2 + \omega_1^2 + k^2\right]^{-1} \qquad (1)$$

Ω is the frequency offset from the water, ω_1 is the Rabi frequency (=$\gamma \cdot B_1$), p_B is the relative concentration of the labile proton (much smaller than water), k and δ are the exchange rate and chemical shift between the labile proton and water, and R_1 and R_2 are the longitudinal and transverse relaxation rates of water, respectively. θ = arctan(ω_1/Ω) is the angle between $B_{1,\text{eff}}$ and the Z-axis. If an inversion pulse of water frequency is applied right before the SL module (RF2 in Fig. 1A), then the water magnetization is still collinear with the $B_{1,\text{eff}}$ (and consequently "locked") (Fig. 1C), and recovers by the same $R_{1\rho}$ to the same steady state (dashed arrows). The magnetization can be expressed as [3]:

$$SLR_{\pm}(\Omega) = \frac{M_{\pm}(\Omega)}{M_0} = \pm 1 \times e^{-R_{1\rho}\cdot TSL} + M_{SS} \cdot \left(1 - e^{-R_{1\rho}\cdot TSL}\right), \quad \text{where } M_{SS} = R_1 \cos\theta / R_{1\rho} \qquad (2)$$

and SLR_+ and SLR_- represent the normalized images acquired for SL without and with the inversion preparation, respectively. The difference of SLR_+ and SLR_- cancels the M_{ss} term and yields a mono-exponential function of $R_{1\rho}$:

$$SLR_{ITIP}(\Omega) \equiv \left[SLR_+(\Omega) - SLR_-(\Omega)\right]/2 = e^{-R_{1\rho}\cdot TSL} \qquad (3)$$

The asymmetry in $R_{1\rho}$, *i. e.* $R_{1\rho}(\delta) - R_{1\rho}(-\delta)$, can thus be obtained from Eqs. (3) and (1):

$$R_{1\rho,asym}(\delta) = \frac{1}{TSL} \cdot \ln\frac{SLR_{ITIP}(-\delta)}{SLR_{ITIP}(\delta)} = p_B k \cdot \left\{\left(1 + \frac{k^2}{\omega_1^2}\right)\cdot\left(1 + \frac{\omega_1^2}{\delta^2}\right)\cdot\left(1 + \frac{\omega_1^2 + k^2}{4\delta^2}\right)\right\}^{-1} \qquad (4)$$

Eq. (4) does not contain the R_1 and R_2 terms and allows simplified quantification of chemical exchange parameters. From Eqs. (2) and (4), the steady state signal M_{SS} can also be calculated from:

$$M_{SS} = \left(SLR_+ + SLR_-\right)/\left(1 - SLR_{ITIP}\right) \qquad (5)$$

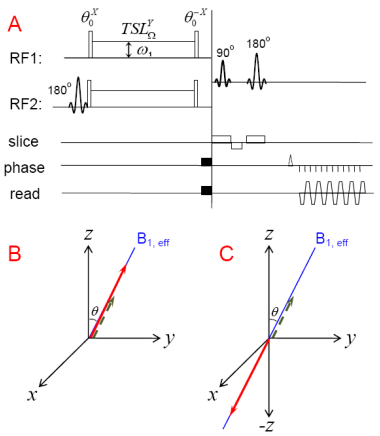

Fig. 1. (A) Pulse sequence for ITIP. (B) With RF1, water magnetization is locked by $B_{1,\text{eff}}$ and decays with $R_{1\rho}$ to a steady state (dashed arrow). (C). With RF2, the magnetization is initially locked at the negative plane but recovers with same $R_{1\rho}$ to the same steady state.

Materials and methods All experiments were performed on a 9.4T Varian MRI system at room temperature. A 3.8-cm diameter volume coil was used for excitation and reception. Three type of phantoms were prepared: (1) 50 mM of myo-Inositol (mIns) were mixed in 2% agar, (2) 50mM Creatine were dissolved in phosphate buffered saline (PBS) and titrated to pH = 7.0 and 8.4, and (3) 50 mM mIns in PBS were added with 0.025mM, 0.05mM, 0.075mM, and 0.1mM $MnCl_2$ to modulate R_1 and R_2. CE sensitive images were acquired using an Irradiation with Toggling Inversion Preparation (ITIP) scheme (Fig. 1A). For all mIns samples, images were acquired at Ω = 1 and -1 ppm with ω_1 = 160 Hz and twenty TSL values from 0 to 1.5 s. For Creatine samples, images were acquired at Ω = 1.9 and -1.9 ppm with ω_1 = 100 Hz and twenty TSL values from 0 to 6 s.

Results and discussions Fig. 2A shows the normalized magnetizations acquired with the ITIP scheme at Ω = 1 ppm and -1 ppm, from a sample with 50mM mIns in 2% agar. With normal SL, accurate determination of $R_{1\rho}$ from SLR_+ data using Eq. (2) requires data points to reach or approach the steady state. The logarithm of SLR_{ITIP} vs. TSL plot (shown in Eq. (3)) shows two mono-exponential decay lines (Fig. 2B), therefore, the calculation of $R_{1\rho}$ becomes easy and can be determined at much shorter TSL values. The difference in $R_{1\rho}$ obtained at Ω = 1 ppm and -1 ppm is directly related to R_{ex} without any R_1 and R_2 contributions. For SL measurement of 50 mM Creatine in PBS, the irradiation steady states for both pH = 7.0 and 8.4 samples are reached at TSL > 5s (solid lines, Fig. 2C). Acquiring SL images by toggling inversion preparation allows calculation of the steady state, M_{ss}, with Eq. (5) from data obtained at much shorter TSL values (almost horizontal red and dark squares, Fig. 2C), *e. g.* ~1 s. For 50 mM mIns samples with 4 $MnCl_2$ concentrations, both R_1 and R_2 increased with the $MnCl_2$ concentration (Fig. 2D and 2E). Consequently, the CE contrast measured with SLR_{asym} (=$SLR_+(-\Omega) - SLR_-(\Omega)$) is also R_1 and R_2 dependent (Fig. 2F). In contrast, the dependence on R_1 and R_2 is removed in the $R_{1\rho,asym}$ map acquired using the ITIP approach (Fig 2G).

For SL with inversion preparation, the magnetization at the lower hemisphere (Fig. 1C) may experience complicated dynamics if radiation damping effect is not negligible [4]. While such an effect is not present in our data, in such a case, the inversion pulse can be replaced by a saturation pulse. Moreover, a perfect SL is not required (Fig. 1) and can even be replaced by a CEST or MT acquisition [5]. These changes will only give a coefficient of less than 1 in Eq. (3) but SLR_{ITIP} is still a mono-exponential function of $R_{1\rho}$, and Eq. (4) will be the same. Due to the use of a short irradiation pulse and its capability to obtain a pure CE contrast and steady state imaging contrast, the proposed ITIP approach can be particularly useful for high field human CE based applications.

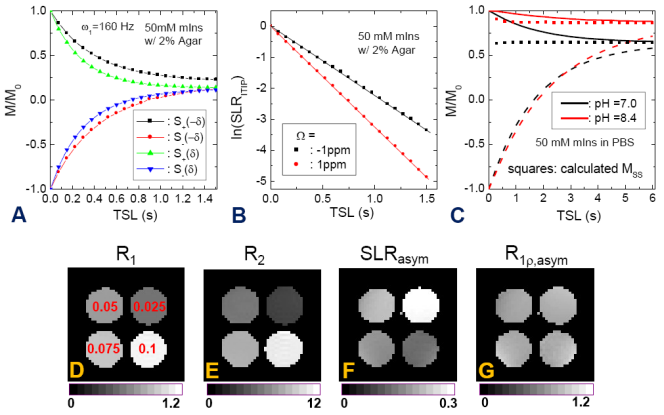

Fig. 2. (A). The magnetizations for SL with and without inversion preparation approach the same steady state. (B). SLR_{ITIP} signal obtained using Eq. (3) decays mono-exponentially vs. TSL. The steady state imaging contrast of 50 mM mIns samples at pH = 7.0 and 8.4 can be obtained with very short TSL using Eq. (5) (C). Despite large differences in R_1 (D), R_2 (E), and SLR_{asym} (F) maps, the $R_{1\rho,asym}$ map (G) appears fairly uniform for 50mM mIns samples with 4 different $MnCl_2$ concentrations (denoted in red,

References: [1]. Sun PZ, MRM (in press) [2]. Trott O et al, JMR (2002). [3]. Jin T et al., NeuroImage (in press). [4]. Warren WS et al, J Chem Phys (1989). [5]. Mangia S et al., MRI (in press).