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\(^4\). 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 \(R_{ip} (\sim 1/T_{1p})\), 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\(^2\), \(R_{ip}\) can be expressed as

\[
R_{ip} = R_1 \cos^2 \theta + (R_2 + R_{ip}) \sin \theta \sum \delta, \quad \text{where} \quad R_2 = p_k \delta \frac{k_b \delta^2}{(\delta - \Omega)^2 + (\omega_0 + k_b \delta)^2}.
\]

\(\Omega\) is the frequency offset from the water, \(\omega_0\), is the Rabi frequency \(\gamma \cdot B_1\), \(p_k\) is the relative concentration of the labile proton, \(k\) and \(\delta\) 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. \(\theta = \arctan(\omega_0 / \Omega)\) is the angle between \(B_{1p}\) 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 \(B_{1p}\) (and consequently “locked”) (Fig. 1C), and recovers by the same \(R_{ip}\) to the same steady state (dashed arrows). The magnetization can be expressed as\(^3\):

\[
SLR_\Omega (\Omega) = M_\Omega (\Omega) = \frac{\cos \theta}{R_{ip}} \left[ 1 - e^{-\frac{T_{1p}}{R_1}} \right], \quad \text{where} \quad M_\Omega = R_1 \cos \theta / R_{ip}.
\]

and SLR- and SLR- represent the normalized images acquired for SL and without and with the inversion preparation, respectively. The difference of SLR- and SLR- cancels the \(M_\Omega\) term and yields a mono-exponential function of \(R_{ip}\):

\[
SLR_{\Omega,\text{mag}} (\Omega) = \frac{SLR_\Omega (\Omega) - SLR_{\Omega,\text{SS}} (\Omega)}{2 - e^{-\frac{T_{1p}}{R_1}}}, \quad \text{(3)}
\]

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

\[
R_{\text{mag, asym}} (\delta) = \frac{1}{T_{SLR}} \ln \left[ \frac{SLR_{\Omega,\text{mag}} (-\delta) - SLR_{\Omega,\text{mag}} (\delta)}{SLR_{\Omega,\text{mag}} (-\delta) + SLR_{\Omega,\text{mag}} (\delta)} \right] \frac{\rho_k}{\rho_0} k \delta \Omega \sum \delta \Omega \sum \delta k \delta \Omega \sum \delta.
\]

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

\[
M_{\Omega,SS} = SLR_{\Omega,\text{mag}} \left[ 1 - \frac{1}{\rho_k} \right] \left[ 1 - e^{-\frac{T_{1p}}{R_1}} \right]. \quad \text{(5)}
\]

**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 dissolved in phosphate buffered saline (PBS) and titrated to \(pH = 7.0\) and 8.4, and (2) 50 mM mIns samples at \(pH = 7.0\) 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 \(\Omega = 1\) and -1 ppm with \(\omega_0 = 160\) Hz and twenty TSL values from 0 to 1.5 s. For Creatine samples, images were acquired at \(\Omega = 1.9\) and -1.9 ppm with \(\omega_0 = 100\) 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 \(\Omega = 1\) ppm and -1 ppm, from a sample with 50mM mIns in 2% agar. With normal SL, accurate determination of \(R_{ip}\) from SLR- data using Eq. (2) requires data points to reach or approach the steady state. The logarithm of \(SLR_{\Omega,\text{mag}}\) vs. TSL plot (shown in Eq. (3)) shows two mono-exponential decay lines (Fig. 2B), therefore, the calculation of \(R_{ip}\) becomes easy and can be determined at much shorter TSL values. The difference in \(R_{ip}\) obtained at \(\Omega = 1\) ppm and -1 ppm is directly related to \(R_{ip}\) 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 steady state, \(M_{\Omega,SS}\), 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 \(SLR_{\Omega,\text{mag}} = (SLR_{\Omega,\text{mag}} - SLR_{\Omega,\text{SS}}) / SLR_{\Omega,\text{SS}}\) is also \(R_1\) and \(R_2\) dependent (Fig. 2F). In contrast, the dependence on \(R_1\) and \(R_2\) is removed in the \(R_{\text{mag, asym}}\) 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\(^6\). 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\(^1\). These changes will only give a coefficient of less than 1 in Eq. (3) but \(SLR_{\text{ITIP}}\) is still a mono-exponential function of \(R_{ip}\) 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.

**References**