Isolating chemical exchange saturation transfer contrast from magnetization transfer asymmetry under two-frequency rf irradiation

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ABSTRACT

Chemical exchange saturation transfer (CEST), arising from mobile groups, and magnetization transfer (MT) contrast arising from immobile protons, have enjoyed wide popularity recently in MRI applications. It is often difficult to separate genuine CEST signatures from MT effects, which are asymmetric with respect to the water resonance. A two-pool model for magnetization transfer (MT) is established based on Provotorov's theory of saturation, and then extended to the situation of simultaneous two-frequency rf irradiation. Numerical simulations and experimental results demonstrate that two-frequency rf irradiation can flatten out MT asymmetry when both frequency components lie within the spectrum of an MT pool. Based on this result, we propose a strategy to isolate chemical exchange saturation transfer (CEST) contrast from MT asymmetry contrast by using the two-frequency rf irradiation technique.

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1. Introduction

Magnetization transfer (MT) is in general a macroscopic phenomenon in which two distinct pools of nuclear spins exchange their magnetic polarizations. In the field of magnetic resonance imaging (MRI), MT indicates a specific phenomenon: one of the two pools consists of water protons, the amount of which is present in large excess in tissues and organs, and the other consists of protons associated with solid-like macromolecules, between which there can exist either a physical exchange or a magnetization exchange via relaxation pathways such as NOE [1–3].

The term chemical exchange saturation transfer (CEST), is used when MT is caused by chemical exchange, especially between water protons and exchangeable solute protons [4–6]. In tissues and organs, CEST may occur together with MT, which makes the quantitative measurement of CEST difficult. In principle, CEST can be distinguished from conventional MT by its frequency selectivity: CEST generally occurs in a very narrow range of frequencies, which can be selectively irradiated, compared with MT happening over a wide range of frequencies. It is not trivial, however, to separate the two effects if an asymmetry in MT exists. Such cases are very common in tissues [7,8].

In previous work [9,10], it was demonstrated that one can achieve uniform saturation of a strongly-coupled spin system by simultaneously irradiating at two different frequencies that lie within its dipolar coupling-broadened spectral range. If the MT exchange processes occur on a timescale that is slower than the rate of saturation, the two-frequency rf irradiation may uniformly saturate those protons belonging to the macromolecules in tissues and organs. As a result, the magnetization of water protons diminishes through MT exchange processes. Consequently, the MT effect becomes independent of the frequency positions of the saturating rf irradiation. On the other hand, due to the frequency selectivity of CEST agents, two-frequency rf irradiation does not significantly alter CEST dynamics. Therefore, an unencumbered extraction of CEST contrast can be expected.

In this work, we establish a two-pool model for MT based on Provotorov's theory of saturation and extend the model to describe the dynamics under simultaneous two-frequency rf irradiation. Through numerical and experimental studies, we show that two-frequency rf irradiation can make the MT effect uniform and that it is possible to isolate CEST from MT asymmetry effects. Finally, a novel two-frequency CEST scheme is proposed, which will be useful for the quantification of CEST contrast.

2. Two-pool model under two-frequency rf irradiation

Provotorov's thermodynamic theory has been used to describe the dynamics of a strongly coupled spin system under weak rf irradiation [12,13], i.e., when the strength of the rf Hamiltonian is much smaller than the Zeeman and dipolar Hamiltonians. By

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treating the weak rf irradiation as a perturbation, the master equation can be solved by iteration to second order under the assumption that the density operator is described at all times by a quasi-equilibrium form $\rho(t) = (1/2^N)[1 + \beta_S(t)\omega_0 S_z - \beta_d(t)\mathcal{H}_d]$, where β_S and β_d are respectively the Zeeman and dipolar inverse spin temperatures, ω_0 is the resonance frequency, and $\mathcal{H}_d$ is the dipole–dipole interaction Hamiltonian. By introducing the spin and dipolar polarizations $P_S = (2/N)\langle S_z \rangle$ and $P_d = (2/N)(\langle \mathcal{H}_d \rangle / \omega_{loc})$, one can obtain a set of first-order coupled differential equations as follows [11]:

$$\frac{dP_S}{dt} = -W_S\left(P_S - \frac{\Delta}{\omega_{loc}}P_d\right) - \frac{P_S - P_{S,0}}{T_{1,S}}, \tag{1}$$

and

$$\frac{dP_d}{dt} = W_S\frac{\Delta}{\omega_{loc}}\left(P_S - \frac{\Delta}{\omega_{loc}}P_d\right) - \frac{P_d}{T_{1,d}}, \tag{2}$$

where $\langle O \rangle \equiv \text{tr}\{O\rho\}$, $\omega_{loc} \equiv \text{tr}\{\mathcal{H}_d^2\}/\text{tr}\{S_z^2\}$, $\Delta \equiv \omega_0 - \omega$ is the frequency difference between the resonance frequency ω_0 and the frequency ω of the weak rf irradiation, $W_S = \pi\omega_1^2 g_S(\Delta)$, $\omega_1(\ll \omega_{loc})$ is the amplitude of the weak rf irradiation, $g_S(\Delta)$ is the normalized absorption line shape for a spin S, $T_{1,S}$ and $T_{1,d}$ are the spin–lattice relaxation times for the Zeeman and dipolar reservoirs, respectively, and $P_{S,0}$ is the thermal equilibrium polarization. Eqs. (1) and (2) are valid in both the rotating and laboratory frames.

To build a two-pool model for MT, one can add an additional Zeeman polarization P_I without any dipolar reservoirs attached, representing protons in bulk water, for example. Following the same procedure leading to Eq. (1), it is easy to show that the spin polarization follows a kinetic equation

$$\frac{dP_I}{dt} = -WP_I - \frac{P_I - P_{I,0}}{T_{1,I}}. \tag{3}$$

Notice that Eq. (3) is written in the laboratory frame and valid if $\omega_1 \ll \omega_0$ and the changes in P_S and Δ are small on a time scale of the spin–spin relaxation time T_2 or the inverse of the line width. In the rotating frame, the perturbation approach cannot be applied because there is only the rf term in the spin Hamiltonian. In addition, Eq. (3) has been derived without any assumptions about the form of $g(\Delta)$. It is straightforward to check that Eq. (3) gives exactly the same steady state as the Bloch equations with a Lorentzian line shape $g_{Lorentz}(\Delta) = (T_2/\pi)[1 + (\Delta T_2)^2]^{-1}$.

A two-pool model for MT can be established by combining Eqs. (1)–(3) and adding exchange terms. It is customary to assume that the exchange between the two pools is a first-order process. The equations

$$\frac{dP_I}{dt} = -W_I P_I - \frac{P_I - P_{I,0}}{T_{1,I}} + k_{S\to I}P_S - k_{I\to S}P_I, \tag{4}$$

$$\frac{dP_S}{dt} = -W_S\left(P_S - \frac{\Delta}{\omega_{loc}}P_d\right) - \frac{P_S - P_{S,0}}{T_{1,S}} + k_{I\to S}P_I - k_{S\to I}P_S, \tag{5}$$

and

$$\frac{dP_d}{dt} = W_S\frac{\Delta}{\omega_{loc}}\left(P_S - \frac{\Delta}{\omega_{loc}}P_d\right) - \frac{P_d}{T_{1,d}}, \tag{6}$$

can be used to describe MT phenomena. By setting $P_d = 0$, one obtains the relevant expressions for the description of CEST phenomena. Notice that Δ is measured from the resonance of spin I and that the chemical shift of spin S is imbedded in the line shape function $g_S(\Delta)$.

With additional irradiation frequencies, we cannot take recourse of a rotating frame in which the Hamiltonian is time-dependent, so the description of the dynamics becomes more complicated. On the other hand, it was shown that the accomodation of additional weak rf irradiation was rather straightforward in

the laboratory frame [9]. If the difference between irradiation frequencies is much larger than the amplitudes of the rf fields, the cross effect caused by the simultaneous existence of two rf fields can be shown to be negligible, and each frequency contributes to the kinetics in the same way as in Eqs. (1)–(3). Therefore, the kinetic equations for a two-pool model for MT with a dipolar reservoir and under two-frequency rf irradiation will be given by:

$$\frac{dP_I}{dt} = -W_I P_I - W'_I P_I - \frac{P_I - P_{I,0}}{T_{1,I}} + k_{S\to I}P_S - k_{I\to S}P_I, \tag{7}$$

$$\frac{dP_S}{dt} = -W_S\left(P_S - \frac{\Delta}{\omega_{loc}}P_d\right) - W'_S\left(P_S - \frac{\Delta'}{\omega_{loc}}P_d\right) - \frac{P_S - P_{S,0}}{T_{1,S}} + k_{I\to S}P_I - k_{S\to I}P_S, \tag{8}$$

and

$$\frac{dP_d}{dt} = W_S\frac{\Delta}{\omega_{loc}}\left(P_S - \frac{\Delta}{\omega_{loc}}P_d\right) + W'_S\frac{\Delta'}{\omega_{loc}}\left(P_S - \frac{\Delta'}{\omega_{loc}}P_d\right) - \frac{P_d}{T_{1,d}}, \tag{9}$$

where the primed symbols W' and Δ' are the transition rate and the offset for the second rf irradiation at ω'. Likewise, CEST under two-frequency rf irradiation can be described by Eqs. (7) and (8) with $P_d = 0$.

By setting $dP_I/dt = dP_S/dt = dP_d/dt = 0$, Eqs. (7)–(9) give the steady-state solutions $P_{I,\infty}$, $P_{S,\infty}$, and $P_{d,\infty}$:

$$P_{I,\infty} = \frac{(P_{I,0}/T_{1,I})\left[(W_I + W'_I + 1/T_{1,I} + k_{I\to S}) - B\right] + (P_{S,0}/T_{1,S})k_{S\to I}}{A - (W_I + W'_I + 1/T_{1,I} + k_{I\to S})B}, \tag{10}$$

$$P_{S,\infty} = \frac{(P_{I,0}/T_{1,I})k_{I\to S} + (P_{S,0}/T_{1,S})(W_I + W'_I + 1/T_{1,I} + k_{I\to S})}{A - (W_I + W'_I + 1/T_{1,I} + k_{I\to S})B}, \tag{11}$$

and

$$P_{d,\infty} = P_{S,\infty}\frac{B\omega_{loc}}{W_S\Delta + W'_S\Delta'}, \tag{12}$$

where
$A \equiv (W_I + W'_I + 1/T_{1,I} + k_{I\to S})(W_S + W'_S + 1/T_{1,S} + k_{S\to I}) - k_{I\to S}k_{S\to I}$
and $B = (W_S\Delta + W'_S\Delta')^2/(W_S\Delta^2 + W'_S\Delta'^2 + \omega_{loc}^2/T_{1,d})$.

3. Numerical study

Eqs. (4)–(6) can now be solved numerically to check whether they produce a proper two-pool model. Two different examples, specific to MT and CEST, respectively, are investigated, depending on the spectral parameters given to spin S.

The simulation parameters were chosen as follows. The relaxation times for spin I, $T_{1,I} = 5$ s and $T_{2,I} = 1$ s, were set to be similar to those of the water proton NMR signal in the chondroitin sulfate (CS) solution used in the experimental study (Section 4). The same T_1 relaxation time was used for spin S, i.e., $T_{1,S} = T_{1,I}$, because the concentration of spin S was set to be small: the initial and equilibrium polarizations $P_{I,0}$ and $P_{S,0}$ were assumed to be 0.99 and 0.01. Therefore, it may be assumed that the major relaxation mechanism for spin S is due to the fluctuating dipolar field from spin I, which makes the T_1 relaxation times similar. The resonance frequency of spin S was set to be 1500 Hz, which is the frequency offset measured from the resonance frequency of spin I. If the external static magnetic field is 11.74 T, this value of 1500 Hz is close to the chemical shift (3.2 ppm) of amide protons relative to the water signal in cartilage [14,15].

The line shape of spin I was assumed to be Lorentzian. For the CEST case, the line shape of spin S was also set to Lorentzian with $T_{2,S} = 1$ s. The exchange rates $k_{I\to S}$ and $k_{S\to I}$ were set to 1 s^{-1} and 99 s^{-1}, respectively. They are 3–5 times higher than the reported chemical exchange rates of amide protons [5,6], so the CEST effect