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Capturing exchange using periodic radiofrequency irradiation

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ABSTRACT

The dynamics of spin system coupled by chemical exchange between two sites with different chemical shifts during periodic radiofrequency (RF) irradiation was here investigated. When the instantaneous π-flip of effective frequency during the course of frequency sweep was applied, a significant increase of exchange-induced relaxation rate constants was observed for small tip angle of magnetization in the laboratory frame of reference. This increase of the rate constants corresponds to the side bands generated by the periodic irradiation during the RF pulses. The exchange - induced relaxation rate constants depend on the exchange conditions, the RF power and the irradiation period. The described phenomenon promises applications for studying protein dynamics and for generating exchange specific relaxation contrasts in MRI.

1. Introduction

Application of periodic radiofrequency (RF) irradiation to a spin systems coupled by chemical exchange is an unexplored strategy in NMR. Periodic Hamiltonian can influence spin system undergoing anisochronous exchange, i.e., exchange between spins with different chemical shifts, by significantly increasing the relaxation rate constants in correspondence to the side bands generated during the RF pulses. There has been a considerable interest in utilizing periodic irradiation for various purposes in NMR. One example of applying periodic pulses is the Delays Alternating with Notations for Tailored Excitation (DANTE), which is a composite pulse formed by a series of hard pulses with optimized phases producing a wide band excitation with low RF peak power [1]. DANTE pulses have recently been applied for short echo time imaging to produce a high bandwidth excitation with low power and thus take advantage of increased signal to noise ratio when the signal from the side bands generated during periodic irradiation was used for image encoding [2]. Similarly, the idea of sideband excitation has been implemented also for zero echo time imaging (ZTE) [3]. Another example of the applications of periodic irradiation includes the generation of magnetization transfer in MRI by using sidebands produced by the RF pulses [4] and generating adiabatic decoupling sidebands [5].

Conventional continuous wave rotating frame spin lock $T_{1\rho}$ experiment is typically performed without or with one phase shift during an RF pulse applied on/off resonance with the typical pulse duration in the *ms* time scale. However, the influence of periodicity of RF irradiation on exchange-induced relaxation rate constants in the off-resonance $T_{1\rho}$ experiment has not been evaluated so far [6]. In adiabatic $T_{1\rho}$ and $T_{2\rho}$ measurements [7–9], the periodicity of irradiation takes place during the train of adiabatic full passage (AFP) pulses with the phases usually prescribed according to MLEV - 4 [9,10]. Same applies to $T_{1\rho}$ and $T_{2\rho}$ measured using gradient modulated low-power adiabatic pulses [11], and Relaxation Along Fictitious Field in the rotating frame of rank n (RAFFn) [12–15], where the periodic irradiation takes place during rotating frame measurements in the rotating frames of rank 1–5. Conventional magnetization transfer (MT) experiments are conducted using continuous wave technique with relatively low RF power and long pulses used for off-resonance irradiation [16]. In several studies, however, the continuous wave RF pulse is replaced by periodic irradiation to obtain MT weighting. One example is Z-spectroscopy with Alternating-Phase Irradiation (ZAPI) method [17], where periodic sinusoidal modulation of the RF irradiation is applied on-resonance. During ZAPI the sidebands are generated symmetrically to the on-resonance frequency, and the periodicity of RF irradiation could be tuned to generate sidebands which are positioned optimally off-resonance to induce MT.

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In this work, we studied the influence of the periodicity of RF irradiation on exchange - induced relaxation. We calculated relaxation rate constants during periodic irradiation applied to two-pool spin system coupled by equilibrium exchange. We varied tip angle of magnetization, irradiation period, irradiation power, and the fundamental MR parameters of two exchanging sites, and conducted simulations using Bloch-McConnell formalism [12]. The results of our analysis demonstrated that independently of pulse modulation functions of the frequency swept pulses, similar side bands which originate from the refocusing of magnetization were formed. Tuning the irradiation period to the chemical shift differences between exchanging sites allows significantly increasing the exchange-induced relaxation rate constants. As an example, here we analyze relaxation rate constants induced by exchange during the RAFFn family of frequency swept pulses. However, our findings are valid in general for other frequency swept pulses having amplitude and frequency modulation functions different from RAFFn, e.g., RF pulses of the hyperbolic secant family [18], as long as the instantaneous flip of the effective frequency takes place during the course of the RF irradiation, and the tip angle of magnetization from laboratory z axis is small.

2. Theory

2.1. Modulation functions of RAFFn

The modulation functions of the method inducing relaxations in high rotating frames of rank n and entitled Relaxation Along a Fictitious Fields in the rotating frame of rank n (RAFFn) were recently described [12]. Below, we briefly summarize the recently presented detailed description of RAFFn pulse modulation functions. For obtaining time-invariant and equal amplitudes and frequency components in the first rotating frame (n = 1), the amplitude $\omega_1^{(1)}$ and frequency $\Delta\omega^{(1)}$ modulation functions in the first rotating frame of reference are defined as follows:

$$\begin{aligned}\omega_1^{(1)} &= \tan\alpha_1\omega_1^{max}\\ \Delta\omega^{(1)} &= \omega_1^{max},\end{aligned} \tag{1}$$

where ω_1^{max} is the peak RF amplitude in rad/s. The recursive relationship which was used for amplitude and frequency modulation of RAFFn for n > 1 based on *sine/cosine* functions are given by:

$$\begin{aligned}\omega_1^{(n)}(t) &= \Delta\omega^{(n-1)}(t)\sin\left(\int\omega_1^{(n-1)}(t)dt\right)\\ \Delta\omega^{(n)}(t) &= \Delta\omega^{(n-1)}(t)\cos\left(\int\omega_1^{(n-1)}(t)dt\right)\end{aligned} \tag{2}$$

for n = 2, 4, 6, ... and

$$\begin{aligned}\omega_1^{(n)}(t) &= \omega_1^{(n-1)}(t)\sin\left(\int\Delta\omega^{(n-1)}dt\right)\\ \Delta\omega^{(n)}(t) &= \omega_1^{(n-1)}(t)\cos\left(\int\Delta\omega^{(n-1)}dt\right)\end{aligned} \tag{3}$$

for n = 3, 5, 7, ... The pulse duration (T_p) is calculated as $4\pi/(\sqrt{2}\omega_1^{max})$. Each *sine/cosine* pulse consists of four RAFFn pulse elements treated according to a refocusing scheme as was described in [12,14]. The average flip angle during the pulse was estimated by calculating the flip angle of magnetization from the Z axis of the laboratory frame in each pulse point using Bloch equations and averaging the angle over the duration of the pulse.

2.2. Bloch-McConnell formulation of the relaxation during RAFFn

Relaxations during RF irradiation due to the dipolar interactions (like spins) and induced by anisochronous exchange between two pools A and B with different chemical shifts can be described using Bloch-McConnell equations written in the phase-modulated rotating frame [15,19]:

$$\begin{aligned}
\frac{dM_z^A(t)}{dt} &= \frac{M_0^A - M_z^A(t)}{T_{1A}} - k_{ex}^{AB}M_z^A(t) + k_{ex}^{BA}M_z^B(t) + \omega_1\sin(\phi)M_x^A(t)\\
&\quad - \omega_1\cos(\phi)M_y^A(t)\\
\frac{dM_z^B(t)}{dt} &= \frac{M_0^B - M_z^B(t)}{T_{1B}} - k_{ex}^{BA}M_z^B(t) + k_{ex}^{AB}M_z^A(t) + \omega_1\sin(\phi)M_x^B(t)\\
&\quad - \omega_1\cos(\phi)M_y^B(t)\\
\frac{dM_x^A(t)}{dt} &= -\frac{M_x^A(t)}{T_{2A}} - k_{ex}^{AB}M_x^A(t) + k_{ex}^{BA}M_x^B(t) + \Delta_A M_y^A(t) - \omega_1\sin(\phi)M_z^A(t)\\
\frac{dM_x^B(t)}{dt} &= -\frac{M_x^B(t)}{T_{2B}} - k_{ex}^{BA}M_x^B(t) + k_{ex}^{AB}M_x^A(t) + \Delta_B M_y^B(t) - \omega_1\sin(\phi)M_z^B(t)\\
\frac{dM_y^A(t)}{dt} &= -\frac{M_y^A(t)}{T_{2A}} - k_{ex}^{AB}M_y^A(t) + k_{ex}^{BA}M_y^B(t) - \Delta_A M_x^A(t) + \omega_1\cos(\phi)M_z^A(t)\\
\frac{dM_y^B(t)}{dt} &= -\frac{M_y^B(t)}{T_{2B}} - k_{ex}^{BA}M_y^B(t) + k_{ex}^{AB}M_y^A(t) - \Delta_B M_x^B(t) + \omega_1\cos(\phi)M_z^B(t)
\end{aligned} \tag{4}$$

where $\Delta_{A,B}$ are the chemical shifts in rad/s of exchanging groups A and B, respectively ($\delta\omega = |\Delta_A - \Delta_B|$), $k_{ex}^{AB} = P_B/\tau_{ex}$ and $k_{ex}^{BA} = P_A/\tau_{ex}$ are the exchange rate constants for exchanging site populations P_A and P_B, and $T_{1,2,A,B} = 1/R_{1,2,A,B}$ are the relaxation time constants at sites A and B, respectively. The longitudinal R_1 and transverse R_2 free precession relaxation rate constants were calculated considering dipolar interactions between isolated identical spins:

$$R_1 = \frac{3}{10}b^2\left(\frac{\tau_c}{1+\tau_c^2\omega_0^2} + \frac{4\tau_c}{1+4\tau_c^2\omega_0^2}\right), \tag{5}$$

and

$$R_2 = \frac{3}{20}b^2\left(3\tau_c + \frac{5\tau_c}{1+\tau_c^2\omega_0^2} + \frac{2\tau_c}{1+4\tau_c^2\omega_0^2}\right), \tag{6}$$

where τ_c is the rotational correlation time, ω_0 is the Larmor precession frequency, $b = -\mu_0\hbar\gamma^3/(4\pi r^3)$, μ_0 is vacuum permeability, ħ is Planc's constant, γ is gyromagnetic ratio, and r is a hydrodynamic radius, similarly to what was used in [15]. The simulations of the two-site exchange were carried out using full Eq. (3). For all simulations, the calculations were performed with R_1 and R_2 obtained using Eqs. (4) and (5) with $\tau_c = 2\cdot10^{-12}$ s for both sites A and B. The decay of **M** ($\mathbf{M}_0$ = [0 0 1]) during the pulse was estimated by solving partial differential equation (Eq. (3)) using variable step Runge-Kutta numerical method. Simulations were repeated for initially inverted magnetization $\mathbf{M}_0$ = [0 0 –1] including steady state formation. Because RAFFn pulses operate in the positive hemisphere, the application of RAFFn pulse train lead to a formation of the steady state when the magnetization is initially not perturbed [12,14,15]. We have demonstrated that the combined analysis of the SI evolution from positive +z and negative –z axes is essential for the accurate estimation of the relaxation rate constants during RAFFn [14]. This approach was previously described in detail [14], and was shown to facilitate the analysis of the relaxations during RAFFn pulses [12,14,15].

3. Methods

3.1. Bloch-McConnell simulations

All simulations were conducted using full set of two-pool Bloch-McConnell equations Eq. (4). The T_1 and T_2 of the pools were calculated using the model of dipolar interaction between isolated spins using τ_c of $76\cdot10^{-12}$ s in Eqs. (4) and (5). Simulations were