Communication

The time-dependence of exchange-induced relaxation during modulated radio frequency pulses

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Abstract

The problem of the relaxation of identical spins 1/2 induced by chemical exchange between spins with different chemical shifts in the presence of time-dependent RF irradiation (in the first rotating frame) is considered for the fast exchange regime. The solution for the time evolution under the chemical exchange Hamiltonian in the tilted doubly rotating frame (TDRF) is presented. Detailed derivation is specified to the case of a two-site chemical exchange system with complete randomization between jumps of the exchanging spins. The derived theory can be applied to describe the modulation of the chemical exchange relaxation rate constants when using a train of adiabatic pulses, such as the hyperbolic secant pulse. Theory presented is valid for quantification of the exchange-induced time-dependent rotating frame longitudinal $T_{1\rho,\mathrm{ex}}$ and transverse $T_{2\rho,\mathrm{ex}}$ relaxations in the fast chemical exchange regime.
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1. Introduction

In the early days in the development of nuclear magnetic resonance, in typical experimental scenarios and their theoretical description, pulse durations (in the microsecond range) were usually so short in comparison to the time scale of temporal delays that the so-called "delta function" approximation was considered valid. By this we mean that the time evolution of the magnetization during the pulses could be ignored. This also entailed the total neglect of relaxation processes during the pulse. In more recent applications, the duration of pulses has increased to the millisecond order of magnitude, and the use of long trains of such pulses is now commonplace [1,2]. This means that current experimental protocols now demand that relaxation during pulses cannot be neglected. With the advent of millisecond pulse durations there also is use of time-dependent pulse parameters such as time-dependent pulse amplitudes and frequency offsets. All of these issues demanded clarification with a suitable theoretical formalism.

Here, it has been found that the introduction of time-dependent relaxation functions can be successfully used to simulate adiabatic pulses of the hyperbolic secant HSn family [2,3]. The concept of time-dependent relaxation functions is not new and had been developed by many investigators from the very beginning of the NMR formalism [4–6]. The necessity of including time-dependence in the relaxation functions here stems from the time-dependence in the first rotating frame (RF) of both the pulse amplitudes and the frequency offsets of adiabatic pulses [1,7]. The need to model the dependence on the pulse parameters of the RF applied necessitates working in the tilted doubly rotating frame (TDRF) [8]. The theory developed here is applicable to the fast exchange regime (FXR) [8]. Although direct experience with this formalism has been restricted to modeling the HSn class of pulses, the general method outlined here can be applied to a wide variety of so-called "shaped pulses" [9,15,16]. The crux of the method is to make the tilt angle of the effective field with respect to the laboratory B_0 field direction as well as

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the angular precession frequency around the time-dependent effective field time-dependent [7]. This time-dependence can be easily included using the Wigner rotation matrices [10] to transform the relevant operators between the various frames.

2. Theory

In this work the formalism originated by Kubo and Tomita [11] and described in detail in [12] was adapted to derive the time-dependent relaxation functions during adiabatic rotation. The theoretical effort is based on the use of a second-order cumulant expansion [12]. We start by stating the cumulant second-order result:

$$I_z^*(t) = \exp\left[\int_0^t -(t-\tau)\langle\langle \text{Tr}[I_z^*, H_{\text{ex}}^*(t-\tau)][H_{\text{ex}}^*(t), I_z^*]\rangle\rangle/\langle I_z^* I_z^*\rangle \, d\tau\right], \tag{1}$$

$$I_+^*(t) = \exp\left[\int_0^t -(t-\tau)\langle\langle \text{Tr}[I_+^*, H_{\text{ex}}^*(t-\tau)][H_{\text{ex}}^*(t), I_-^*]\rangle\rangle/\langle I_+^* I_-^*\rangle \, d\tau\right]. \tag{2}$$

Here, $H_{\text{ex}}^*(t)$ is the Hamiltonian written in the TDRF simulating relaxation governed by a chemical exchange mechanism. Note, that the $I_z^* I_z^*$ term in Eq. (1) divides the argument of the exponential. The $\langle I_+^* I_-^*\rangle$ term in Eq. (2) also divides the argument of the exponential. In Eqs. (1) and (2) the superscript * indicates operators written in the TDRF [8]. The double carets indicate the taking of an ensemble average. For a detailed discussion of these classes of Hamiltonians see the paper by Wennerstrom [13].

The chemical exchange Hamiltonians in terms of Cartesian spin operators are defined as

$$H_{\text{ex}}^*(t) = \delta\omega(t)[(\cos(\alpha(t))I_z^* - \tfrac{1}{2}\sin(\alpha(t))) \times (I_+^* \exp(-i\psi(t)) + I_-^* \exp(i\psi(t)))]. \tag{3}$$

Here, $\delta\omega(t)$ is a stochastic variable that is 1 when the spin is at either chemical site and zero otherwise. A similar equation to Eq. (3) holds for the case where the time argument is $[t-\tau]$.

The time-dependent tilt angle of the effective field to the laboratory B_0 field direction is defined as

$$\alpha(t) = \tan^{-1}\left[\frac{\omega_1(t)}{\Delta\omega(t)}\right], \tag{4}$$

and the magnitude of the effective field is the time-dependent quantity

$$\omega_{\text{eff}}(t) = \sqrt{\omega_1^2(t) + \Delta\omega^2(t)}. \tag{5}$$

Here, $\psi(t)$ is the time-dependent precession angle around the effective field direction

$$\psi(t) = \int_0^t \omega_{\text{eff}}(\varsigma) \, d\varsigma. \tag{6}$$

Here $\omega_1(t)$ is the time-dependent pulse amplitude and $\Delta\omega(t)$ is the time-dependent pulse frequency offset.

To obtain the relaxation functions for the longitudinal magnetization, commutators $[I_z^*, H_{\text{ex}}^*(t-\tau)]$ and $[H_{\text{ex}}^*(t), I_z^*]$ in Eq. (1) should be evaluated. Evaluation of the commutators [14] leads to the following equation:

$$\begin{aligned}[I_z^*, H_{\text{ex}}^*(t-\tau)] &= -\sin(\alpha(t-\tau))/2 \exp(-i\psi(t-\tau))[I_z^* I_+^*] \\ &\quad - \tfrac{1}{2}\sin(\alpha(t-\tau))\exp(-i\psi(t-\tau))[I_z^* I_-^*] \\ &= -\tfrac{1}{2}[\sin(\alpha(t-\tau))\exp(-i\psi(t-\tau))I_+^* \\ &\quad + \sin(\alpha(t-\tau))\exp(-i\psi(t-\tau))I_-^*]. \end{aligned} \tag{7}$$

Similarly, the expression for the $[H_{\text{ex}}^*(t), I_z^*]$ at time t can be derived. Further, the trace of the product of the two commutators was calculated in the following form:

$$\begin{aligned} &\text{Tr}[I_z^*, H_{\text{ex}}^*(t-\tau)][H_{\text{ex}}^*(t), I_z^*]/\langle I_z^* I_z^*\rangle \\ &= \langle\langle \delta\omega(t-\tau)\delta\omega(t)\rangle\rangle \text{Tr}[\tfrac{1}{4}\sin(\alpha(t))\sin(\alpha(t)) \\ &\quad \times \exp(-i(\psi(t-\tau) - \psi(t))I_+^* I_-^* + \tfrac{1}{4}\sin(\alpha(t)) \\ &\quad \times \sin(\alpha(t-\tau))\exp(-i(\psi(t-\tau)) - \psi(t))I_-^* I_+^*). \end{aligned} \tag{8}$$

Because the trigonometric terms are scalar functions of time and the trace acts on the operators only, the quantities $\text{Tr}[I_+^* I_-^*]$ and $\text{Tr}[I_-^* I_+^*]$ should be evaluated.

Using the Cartesian definition of the operators [14], the following relations are valid:

$$\text{Tr}[I_+^* I_-^*] = 1; \quad \text{Tr}[I_-^* I_+^*] = 1. \tag{9}$$

Using known trigonometric relations $(\cos[x]) = 1/2(\exp[ix] + \exp[-ix])$, we obtain

$$\begin{aligned} &\tfrac{1}{4}\sin(\alpha(t)\sin(\alpha(t-\tau))(\exp(-i(\psi(t-\tau) - \psi(t))) \\ &\quad + \exp(+i(\psi(t-\tau) - \psi(t)))) \\ &= \tfrac{1}{2}\sin(\alpha[t]\sin(\alpha[t-\tau])\cos(\psi[t-\tau] - \psi[t]). \end{aligned} \tag{10}$$

Now term "$\langle\langle\delta\omega(t-\tau)\delta\omega(t)\rangle\rangle$" should be considered. For a simple two-site chemical exchange system for identical spins with complete randomization between jumps, this evaluates to $P_A P_B \delta\omega_{\text{av}}^2 \exp[-\tau/\tau_{\text{ex}}]$. Here, P_A and P_B are the populations of the two sites, $\delta\omega_{\text{av}}$ is the average chemical shift of the two species, and τ_{ex} is the mean lifetime of the exchanging species at the two sites. Therefore, returning to Eq. (1) we obtain for the following equation for the argument of the exponential for the longitudinal magnetization, meaning Eq. (11) results

$$\begin{aligned} I_z^*(t) &= \exp\left[\int_0^1 -(t-\tau)\langle\langle \text{Tr}[I_z^*, H_{\text{ex}}^*(t-\tau)][H_{\text{ex}}^*(t), I_z^*]\rangle\rangle/\langle I_z^* I_z^*\rangle\right] d\tau \\ &= \exp\left[-tK\int_0^t \sin[\alpha[t]]\sin[\alpha[t-\tau]]\cos[\psi[t-\tau] - \psi[t]] \right. \\ &\quad \times \exp[-\tau/\tau_{\text{ex}}]d\tau + K\int_0^t \sin\alpha[t]\sin\alpha[t-\tau]\cos[\psi[t-\tau] - \psi[t]] \\ &\quad \left. \times \exp[-\tau/\tau_{\text{ex}}]\tau \, d\tau\right]. \end{aligned} \tag{11}$$

Here, K is equal to $P_A P_B \delta\omega_{\text{av}}^2$.

To find expressions for the transverse magnetization the Trace of the product of commutators in Eq. (2) needs to be evaluated. By a similar treatment to that used for the treat-

ment for the longitudinal magnetization the equations were obtained for the transverse case. The complete system of equations derived are given, with $I_+^*[t]$ indicating the transverse magnetization in the TDRF as acted upon by the chemical exchange relaxation mechanism (i.e., Eq. (2)) and $I_z^*[t]$ (Eq. (1)) is the longitudinal magnetization in the TDRF where the dominant relaxation mechanism is the chemical exchange. The following expressions were obtained:

$$I_+^*[t] = \exp[-tN[t] + L_1[t] + L_2[t]] \exp[-i(tL_0[t] - L_3[t])], \tag{12}$$

$$I_z^*[t] = \exp[-tI_1[t] + I_2[t]]. \tag{13}$$

With the following definitions:

$$N[t] = K \int_0^t \cos\alpha[t] \cos\alpha[t-\tau] \exp[-\tau/\tau_{ex}] d\tau + K/2$$
$$\times \int_0^t \sin\alpha[t] \sin\alpha[t-\tau] \sin(\psi(t-\tau) - \psi(t))]$$
$$\times \exp[-\tau/\tau_{ex}] d\tau, \tag{14}$$

$$L_0[t] = K/2 \int_0^t \sin\alpha[t] \sin\alpha[t-\tau] \sin(\psi(t-\tau) - \psi(t))]$$
$$\times \exp[-\tau/\tau_{ex}] d\tau, \tag{15}$$

$$L_1[t] = K \int_0^t \cos[\alpha[t]] \cos[\alpha[t-\tau]] \exp[-\tau/\tau_{ex}] \tau d\tau, \tag{16}$$

$$L_2[t] = K/2 \int_0^t \sin\alpha[t] \sin\alpha[t-\tau] \cos(\psi(t-\tau) - \psi(t))]$$
$$\times \exp[-\tau/\tau_{ex}] \tau d\tau, \tag{17}$$

$$L_3[t] = K/2 \int_0^t \sin\alpha[t] \sin\alpha[t-\tau] \sin(\psi(t-\tau) - \psi(t))]$$
$$\times \exp[-\tau/\tau_{ex}] \tau d\tau, \tag{18}$$

$$I_1[t] = K \int_0^t \sin\alpha[t] \sin\alpha[t-\tau] \cos(\psi(t-\tau) - \psi(t))]$$
$$\times \exp[-\tau/\tau_{ex}] d\tau, \tag{19}$$

$$I_2[t] = K \int_0^t \sin\alpha[t] \sin\alpha[t-\tau] \cos(\psi(t-\tau) - \psi(t))]$$
$$\times \exp[-\tau/\tau_{ex}] \tau d\tau. \tag{20}$$

It should be noted that Eqs. (20) and (21) can be rewritten as:

$$I_+^*[t] = \exp[-R_{xy}[t]] \exp[-i\phi[t]], \tag{21}$$

$$I_z^*[t] = \exp[-R_z[t]], \tag{22}$$

where $R_{xy}[t] = tN[t] - L_1[t] - L_2[t]$, $\phi[t] = (tL_0[t] - L_3[t])$, $R_z[t] = tI_1[t] - I_2[t]$.

Here, $R_{xy}[t]$ is the relaxation rate function for the transverse magnetization in the TDRF, $\phi[\tau]$ is the phase of the transverse magnetization in the TDRF, and $R_z[t]$ is the relaxation rate function for the longitudinal magnetization in the TDRF. Note that the longitudinal magnetization has no phase modulation, as expected.

The more commonly encountered expressions specific to the case where the rf parameters are constants, for the longitudinal exchange rate constant in the tilted doubly rotating frame, can be obtained from Eqs. (13) and (14) by setting the instantaneous precession frequency in the tilted doubly rotating frame to a constant, and by also making the limits of integration in the expressions to be from zero to infinity. This step follows for any case when the exchange constant is much less than the time t of interest. One must also then set the tilt angle of the magnetization with respect to the laboratory field direction to a constant. The same arguments apply for the transverse exchange rate constant in the tilted doubly rotating frame.

We note that because of the range of values of the limits of integration, the terms in Eqs. (13)–(23) where there is a multiplication by the single τ term will be much smaller than the other integrated quantities so that in some cases these terms may be neglected.

3. Methods

The derived time-dependent relaxation functions during adiabatic rotation can be used to describe the relaxation phenomena during adiabatic pulses through the $\omega_1(t)$ and $\alpha(t)$ time-dependencies. In the frequency modulated frame (in terminology of adiabatic pulses associated with the rotating frame), the amplitude and frequency modulated functions for the HS1 pulse are given by:

$$\omega_1(t) = \omega_1^{max} \text{sech}(\beta(2t/T_p - 1)), \tag{23}$$

and

$$\omega_{RF}(t) - \omega_c = A \tanh(\beta(2t/T_p - 1)), \tag{24}$$

where $t \in [0, T_p]$, β is a truncation factor ($\text{sech}(\beta) = 0.01$), A is the amplitude of the frequency sweep in rad/s, T_p is pulse length, ω_c is carrier frequency (the center frequency in the bandwidth of interest), and ω_1^{max} is the maximum value of $\omega_1(t)$. During this AFP pulse, the vector $\omega_{eff}(t)$ changes its orientation at the instantaneous angular velocity, $d\alpha(t)/dt$.

To calculate the average effective relaxation rate constant $\overline{R}_{2\rho ex}$ during an AFP pulse of length T_p, all of the $R_{2\rho,ex}$ contributions during the pulse must be taken into account and the average relaxation rate is determined by

$$\overline{R}_{2\rho,ex} = \frac{1}{T_p} \int_0^{T_p} R_{2\rho,ex}(t) dt. \tag{25}$$

Numerical calculations were produced using Mathematica (Version 5.0) from Wolfram Research.

4. Results and discussion

Fig. 1 shows three-dimensional plots of the $R_{2\rho,ex}$ dependencies during the HS1 on the exchange correlation time. In Fig. 1 the $R_{2\rho,ex}$ dependencies during the HS4 pulse are presented. The oscillatory behavior of $R_{2\rho,ex}$ increases in the middle of the pulse (Fig. 1). It can be seen that the oscillatory terms having a small contribution to $R_{2\rho,ex}$ during the pulse
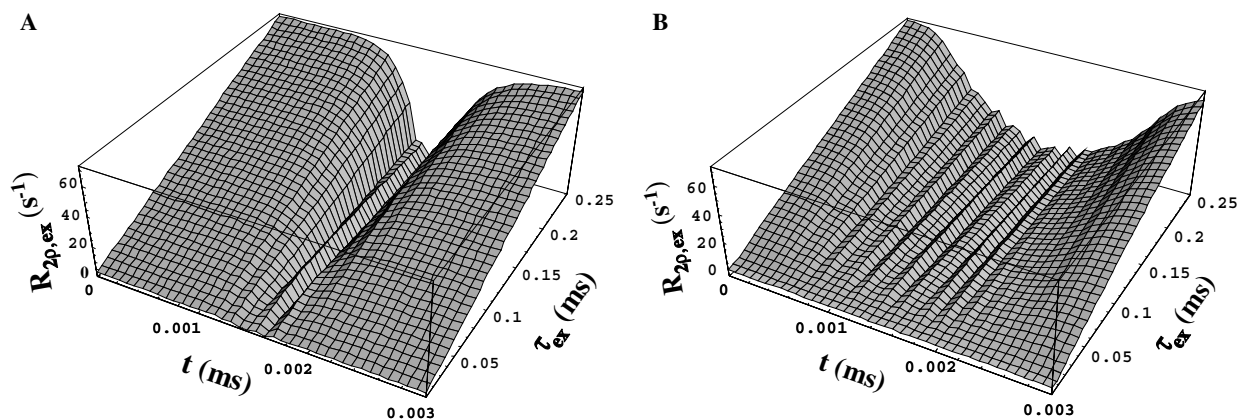
A

B

Fig. 1. (A and B) Calculated transverse relaxation rate functions $R_{2\rho,ex}$ during the HS1 and HS4 pulses, respectively, for the full solution as a function of exchange residence times τ_{ex} and time during the pulse t; $\omega_1^{max}/2\pi = 2.5$ kHz was used.

duration t, and the envelope of $R_{2\rho,ex}$ resembles the amplitude modulation function of the AFP pulse.

The issue of time evolution of the magnetization during time-dependent RF in the first rotating frame has been considered sparingly in the literature [4]. An extant treatment is the use the Redfield super matrix approach [4]. The resulting expressions were thought only amenable to computer calculation without any increase in "physical understanding." In our treatment, which is valid in the fast correlation time regime, the results are highly satisfying. The tilt angle of the effective field vector to the B_0 field is taken as time-dependent as well as the precession frequency around the effective field direction. In addition, the limits of integration for the definition of the spectral density are taken to be time-dependent. This is why we choose to refer to time-dependent rate functions rather than rate constants. When considering the foundational literature on relaxations [4–6], it can be seen that in the most general case the spectral densities are time-dependent. It should be noted that in Eqs. (12) and (13) the oscillatory terms under certain conditions, such as slow and intermediate exchange regimes, may be important for the accurate fitting of the model to data. The results obtained agree with that of Fisher et al. [17] and that of Palmer's group [18] when specialized to a constant rf pulse.

The motivation for the theoretical work presented has been to derive the relaxation functions during adiabatic rotation. Preliminary work in this regard has already appeared in print [2]. Since the formalism developed is quite general, the resulting method of development should be of use for a wide class of "shaped pulses" [9].

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