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Revisiting dipolar relaxation of a homonuclear spin pair in the presence of a radio frequency field: A tutorial

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ABSTRACT

NMR studies exploit spin relaxation in a multitude of different ways, providing information on molecular structure and dynamics. Calculating the relaxation rates of NMR active nuclei in multi-spin systems is often a prerequisite for the proper analysis of experimental data. For many researchers the calculations appear complex, often involving different basis sets or expressions describing relaxation in different frames. In this tutorial paper we derive expressions for dipolar relaxation of an *I-S* two spin spin-system in the presence of a B_1 radio frequency field, where spins *I* and *S* can be either like or unlike. We consider two different approaches for the derivation of relaxation elements that have been used in the literature, including one where a series of transformations are carried out to the interaction representation of the effective field, comprising B_1 and Zeeman components. A second procedure is based on the well-known Solomon equations. We show that both approaches lead to identical results, in the process presenting a pedagogical description of relaxation theory.

1. Introduction

Solution nuclear magnetic resonance spectroscopy is a powerful technique for characterizing molecular structure and dynamics, exploiting, in many cases, various nuances of spin relaxation. Included in the portfolio of relaxation studies are those that involve application of a B_1 field, often providing unique information. For example, rotating frame Overhauser enhancement spectroscopy (ROESY) [1,2], initially called cross-relaxation appropriate for minimolecules emulated by locked spins (CAMELSPIN) [1], takes advantage of the fact that in the presence of a B_1 field cross-relaxation in the transverse plane occurs between spins, establishing through-space internuclear connectivity in medium-sized molecules where it can be the case that longitudinal cross-relaxation, which forms the basis of nuclear Overhauser effect spectroscopy (NOESY), is not observed. ROESY experiments can be conducted with the B_1 field applied in an off-resonance manner (off-resonance ROESY) so as to suppress Hartmann-Hahn magnetization transfer or to selectively observe the correlated motion of two nuclei by carefully choosing the offset and the B_1 field strength [3–5]. Further, application of a variable strength B_1 field can be used to modulate dephasing of coherences from chemical exchange, providing valuable information about the conformational dynamics of molecules occurring on a micro- to milli-second time-scale. This class of experiments has been extensively utilized to quantitatively characterize functionally-related motions of proteins and nucleic acids [6–9].

To date, a number of publications have presented the theory for spin relaxation in the presence of a B_1 field. Beginning from the quantum mechanical and semi-classical treatment of spin relaxation [10], Jones derived the well-known spin-lattice relaxation time of magnetization aligned along an effective field ($T_{1\rho}$), focusing on two dipolar-coupled identical spins [11]. The calculation was performed via a number of coordinate transformations so that the effects of evolution due to chemical shift and the B_1 field were both ultimately included in the dipolar Hamiltonian that was described in a tilted doubly rotating frame, the so called interaction representation of the effective field. The resulting relaxation equations were then simplified according to the "secular approximation", neglecting rapidly evolving time-dependent terms, as described in detail in Redfield's treatment of relaxation [12,13]. Kuwata and Schleich have considered the case of a pair of unlike, dipolar coupled spins [14], using a formalism similar to that of Jones. In this case where the two interacting spins have different chemical shifts and when the applied B_1 field is not sufficiently strong so as to render the

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effective shift differences negligible, a larger number of components of the Redfield relaxation matrix oscillate rapidly, at rates much larger than the relaxation of the individual coherences, relative to the case for like spins. Such terms do not contribute to the evolution of magnetization. In this sense, the application of a B_1 field can alter the structure of the relaxation matrix, in a manner that depends on the chemical shift differences between interacting spins and on the B_1 field strength. The approach of Jones was subsequently further extended to the calculation of $T_{1\rho}$, and the relaxation time of magnetization perpendicular to the effective field ($T_{2\rho}$), considering a number of different relaxation mechanisms [15], and anisotropic motions [16]. Calculations involving *J*-coupled multi-spin systems [17,18] and of heteronuclear two-spin systems have also being carried out [19,20].

An alternative, equally valid way of calculating spin relaxation in the presence of a B_1 field is one where evolution of the spin system due to relaxation, described by the Solomon equations [21], is separated from evolution due to Zeeman and B_1 fields [12,22–24], in contrast to the method of Jones [11]. This approach holds true for any B_1 field that might reasonably be considered in solution NMR [24], with the final result valid for both like and unlike spins. This, alternative, and less mathematically demanding formalism is commonly used to describe rotating-frame relaxation ($R_{1\rho}$) experiments for identifying and characterizing chemical exchange processes occurring on a microsecond to millisecond timescale [6,25,26]

As the spin gymnastics involved in the two approaches are somewhat different, we were interested in examining each in some detail, using a common formalism, with a pedagogical description of the results. We emphasize that the theoretical framework described here is not novel, and our intent is not to present original research. Rather, the goal of this tutorial paper is to provide an example of how seemingly different spin relaxation formalisms can lead to identical final answers, in the process showing how the secular approximation plays differently into both methods, by considering the example of relaxing spin-pairs in the presence of a weak B_1 field.

2. Results and discussion

In what follows we consider the auto- and cross-relaxation of two dipolar-coupled homonuclear spin ½ particles, denoted as *I* and *S*, in the presence of a B_1 field, with an arbitrary chemical shift difference. This spin-system is well-suited to describe ^{1}H-^{1}H spin relaxation in on-/off-resonance ROESY experiments, for example. For simplicity, we neglect coupling of the spins to a lattice (*i.e.*, the return of magnetization back to its equilibrium position), although this could be easily added in an *ad hoc* manner [12,22–24,27]. In many applications phase cycling of pulses ensures that, in fact, rather than evolving to equilibrium, magnetization relaxes towards zero when the average over the complete phase cycle is considered [28].

2.1. Calculation of relaxation elements via the method of Jones

2.1.1. Coordinate transformations

We first consider a series of coordinate transformations that ultimately place all the chemical shift and B_1 field dependencies in a revised dipolar Hamiltonian [11] which is then used to calculate relaxation rates, with retention of only those terms that are secular. We begin by briefly reviewing the frames that will be used, as summarized in Fig. 1. These include (i) the laboratory frame (x^{lab}, y^{lab}, z^{lab}), where the *z*-axis is pointed along the static B_0 field, (ii) the rotating frame (*x, y, z*) that rotates about the static magnetic field at the Larmor frequency (ω_0) of the two dipolar coupled homonuclear spins (not including their chemical shift offsets), (iii) the tilted frame (*x*′, *y*′, *z*′), generated by tilting the rotating frame about the *y*-axis through an angle θ so that the *z*′-axis is along the effective field given by the vector sum of the (residual) Zeeman and B_1 fields in the rotating frame, the latter applied along the *x*-axis, and, finally, (iv) a tilted doubly rotating frame (*x*″, *y*″, *z*″), corresponding to the interaction representation of the effective field. Note that when the offset frequencies of the two spins are different, the tilt-angle and tilted doubly rotating frame for each spin are distinct, so that separate transformations must be performed for each spin (tilting of *z*′ followed by rotation about *z*″), as illustrated below. We derive expressions for the relaxation matrix components in a basis of cartesian spin operators (I_x, I_y, I_z, S_x, S_y, and S_z), in the final (*x*″, *y*″, *z*″) frame, that is subsequently compared with an approach based on the Solomon equations [21], described in a following section.

Consider a B_1 field of magnitude $2\omega_1$ oscillating at ω_0 along the *x*-axis in the laboratory frame. The Hamiltonian, $\widehat{\mathscr{H}}^{lab}$ in this frame (rad/s) is defined as follows,

$$\widehat{\mathscr{H}}^{lab} = \omega_I I_z^{lab} + \omega_S S_z^{lab} + 2\omega_1 \cos(\omega_0 t)\left(I_x^{lab} + S_x^{lab}\right) + \widehat{\mathscr{H}}_{DD}^{lab}(t) \tag{1}$$

where ω_I and ω_S are the precession frequencies of spins *I* and *S*, and $\widehat{\mathscr{H}}_{DD}^{lab}(t)$ is the time-dependent dipolar Hamiltonian in the laboratory frame [12,29]. Note that each operator term in the laboratory frame is indicated with a superscript "*lab*". The transformation of the dipolar Hamiltonian will be described in the following section (*The dipolar Hamiltonian in the tilted doubly rotating frame*).

The first coordinate transformation involves the rotation of the system at a frequency of ω_0 about the *z*-axis (Fig. 1A). The operative Hamiltonian in this first rotating frame ($\widehat{\mathscr{H}}$) is given by

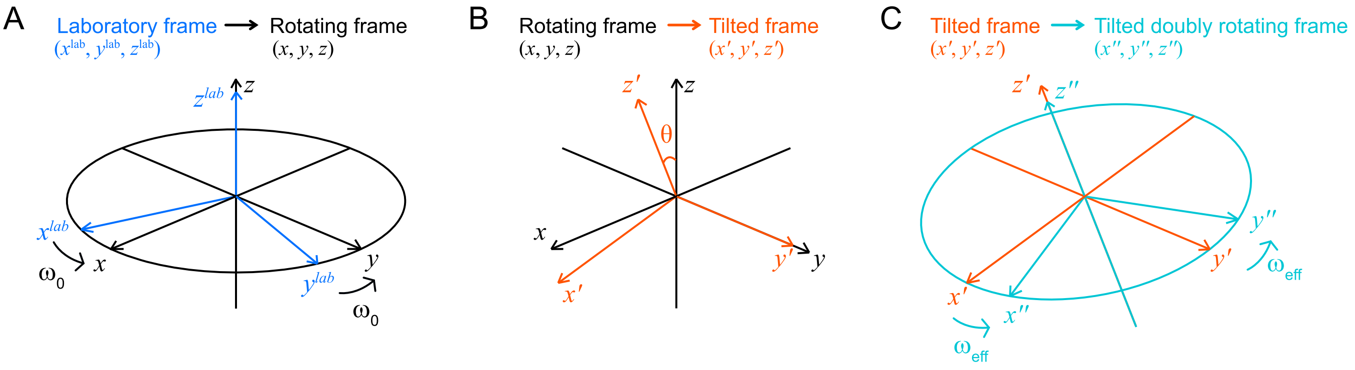

Fig. 1. Coordinate transformations used in this work. (A) Transformation from the laboratory frame (x^{lab}, y^{lab}, z^{lab}) (blue) to the frame (*x, y, z*) rotating about the *z*-axis at a frequency of ω_0 (black). (B) Transformation from the rotating frame (*x, y, z*) (black) to the tilted frame (*x*′, *y*′, *z*′) where the *z*-axis is rotated about the *y*-axis by an angle θ ($\tan\theta = \omega_1/\Omega$, where ω_1 is the B_1 field strength and Ω is the offset frequency, rad/s; the B_1 field is applied along the *x*-axis) (red). (C) Transformation from the tilted frame (*x*′, *y*′, *z*′) (red) to the tilted doubly rotating frame (*x*″, *y*″, *z*″), which rotates about the *z*′-axis at a frequency of ($\omega_{eff} = \sqrt{\omega_1^2 + \Omega^2}$) (turquoise).

$$\begin{aligned}
\widehat{\mathscr{H}} &= \mathbf{U}^{lab}\widehat{\mathscr{H}}^{lab}\mathbf{U}^{lab-1} - i\mathbf{U}^{lab}\frac{d}{dt}\mathbf{U}^{lab-1} \\
&\approx (\omega_I-\omega_0)I_z + (\omega_S-\omega_0)S_z + \omega_1(I_x+S_x) + \widehat{\mathscr{H}}_{DD}(t) \\
&= \Omega_I I_z + \Omega_S S_z + \omega_1(I_x+S_x) + \widehat{\mathscr{H}}_{DD}(t) \\
\mathbf{U}^{lab} &= \exp\left(i\omega_0 I_z^{lab}t\right)\exp\left(i\omega_0 S_z^{lab}t\right)
\end{aligned} \tag{2}$$

where $\mathbf{U}^{lab}$ is the unitary operator that transforms the laboratory frame into the rotating frame, Ω_i $(=\omega_i-\omega_0)$ is the offset frequency of spin i from the carrier placed at the Larmor frequency (ω_0) and $\widehat{\mathscr{H}}_{DD}(t)$ $(=\mathbf{U}^{lab}\widehat{\mathscr{H}}_{DD}^{lab}(t)\mathbf{U}^{lab-1})$ is the dipolar Hamiltonian in the rotating frame. The second term in the first line of Eq. 2 derives from the time-dependence of the unitary operator $\mathbf{U}^{lab}$ [29]. As is routinely done, the B_1 field term oscillating at $2\omega_0$ in the rotating frame, giving rise to the so called Bloch-Siegert shift [30], has been ignored.

In a second transformation the rotating frame is tilted by θ_i about the y-axis, where $\tan\theta_i=\omega_1/\Omega_i$, so that the resulting z'-axis (axes in the tilted frame are denoted with a prime) is parallel to the effective field (Fig. 1B). When the two spins have different chemical shift offsets this transformation is performed as two successive rotations with distinct angles, θ_I and θ_S, about the y-axis (one for each spin), as shown below in the derivation of the effective Hamiltonian in the tilted frame $(\widehat{\mathscr{H}}')$

$$\begin{aligned}
\widehat{\mathscr{H}}' &= \mathbf{U}\widehat{\mathscr{H}}\mathbf{U}^{-1} \\
&= (\omega_1\sin\theta_I + \Omega_I\cos\theta_I)I_z' + (\omega_1\sin\theta_S + \Omega_S\cos\theta_S)S_z' + \widehat{\mathscr{H}}'_{DD}(t) \\
&= \omega_{I,eff}I_z' + \omega_{S,eff}S_z' + \widehat{\mathscr{H}}'_{DD}(t) \\
\mathbf{U} &= \exp\left(i\theta_I I_y\right)\exp\left(i\theta_S S_y\right)
\end{aligned} \tag{3}$$

where $\mathbf{U}$ is the unitary operator that transforms the rotating frame into the tilted frame, $\omega_{i,eff}$ $(=\sqrt{\omega_1^2+\Omega_i^2})$ is the effective frequency of spin i, and $\widehat{\mathscr{H}}'_{DD}(t)(=\mathbf{U}\widehat{\mathscr{H}}'_{DD}(t)\mathbf{U}^{-1})$ is the dipolar Hamiltonian in the tilted frame. Spin angular momentum operators in the rotating (first) frame and those in the tilted (second) frame are related according to

$$\begin{aligned}
I_x &= I_x'\cos\theta_I + I_z'\sin\theta_I \\
I_y &= I_y' \\
I_z &= I_z'\cos\theta_I - I_x'\sin\theta_I \\
S_x &= S_x'\cos\theta_S + S_z'\sin\theta_S \\
S_y &= S_y' \\
S_z &= S_z'\cos\theta_S - S_x'\sin\theta_S
\end{aligned} \tag{4}$$

Finally, one last coordinate transformation is performed to eliminate the time-independent parts of the Hamiltonian (*i.e.*, terms proportional to I_z' and S_z'). This can be accomplished with two successive transformations about the z'-axes with frequencies of $\omega_{I,eff}$ and $\omega_{S,eff}$, similar to the transformations from the laboratory to the rotating frames (Eq. 2) (Fig. 1C). The operative Hamiltonian in the tilted doubly rotating frame $(\widehat{\mathscr{H}}'')$ is given by

$$\begin{aligned}
\widehat{\mathscr{H}}'' &= \mathbf{U}'\widehat{\mathscr{H}}'\mathbf{U}'^{-1} - i\mathbf{U}'\frac{d}{dt}\mathbf{U}'^{-1} \\
&= \widehat{\mathscr{H}}''_{DD}(t) \\
\mathbf{U}' &= \exp\left(i\omega_{I,eff}I_z't\right)\exp\left(i\omega_{S,eff}S_z't\right)
\end{aligned} \tag{5}$$

where $\mathbf{U}'$ is the operative unitary transformation. All of the time-independent terms (Eq. 3) have now been incorporated into the dipolar Hamiltonian in the tilted doubly rotating frame $(\widehat{\mathscr{H}}''_{DD}(t)=\mathbf{U}'\widehat{\mathscr{H}}'_{DD}(t)\mathbf{U}'^{-1})$. It is thus straightforward to calculate the Redfield relaxation matrix in this final frame and then to intuit what the individual relaxation terms mean in terms of the evolution of magnetization (see below).

2.1.2. *The dipolar Hamiltonian in the tilted doubly rotating frame*

Before proceeding further the dipolar Hamiltonian in the tilted doubly rotating frame $(\widehat{\mathscr{H}}''_{DD}(t))$ must be calculated, as described previously [11]. Table S1 lists all of the terms for the dipolar Hamiltonian in the rotating frame, $\widehat{\mathscr{H}}_{DD}(t)$; the subsequent transformations expand the number of terms considerably and place all of the time-dependence of the spin system explicitly in $\widehat{\mathscr{H}}''_{DD}(t)$, as shown in detail below, where we illustrate how these transformations are accomplished. We begin by representing the dipolar Hamiltonian in the laboratory frame using the spin tensor operators A_p^q and the spatial variables $F^q(\beta,\varphi)$ of rank q and order p as follows,

$$\begin{aligned}
\widehat{\mathscr{H}}_{DD}^{lab}(t) &= d_0\sum_{q=-2}^{+2}\sum_p A_p^q F^q(\beta,\varphi) \\
d_0 &= -\sqrt{6}\left(\frac{\mu_0}{4\pi}\right)\frac{\gamma^2\hbar}{r_{IS}^3}
\end{aligned} \tag{6}$$

where β and φ are time-dependent angles defining the orientation of the vector connecting spins I and S in the lab frame, r_{IS} is the distance between the two spins, γ is the gyromagnetic ratio (here assuming $\gamma=\gamma_I=\gamma_S$), $\hbar$ is Planck's constant divided by 2π, and μ_0 is the permeability of free space [12,29]. Thus, Eq. [6] makes it clear that changes in the orientation of the dipole vector with respect to the magnetic field from molecular tumbling or internal dynamics, or fluctuations of the inter-nuclear distance, r_{IS}, give rise to time dependent dipolar fields that produce the relaxation of interest (*i.e.*, modulation of $\widehat{\mathscr{H}}_{DD}^{lab}(t)$). In what follows we consider only isotropic overall motion as the source of the fluctuations. As mentioned above, Table S1 lists the A_p^q and $F^q(\beta,\varphi)$ values that are germane in this case.

$\widehat{\mathscr{H}}_{DD}^{lab}(t)$ is initially transformed to the rotating frame using the unitary rotations defined in Eq. 2

$$\begin{aligned}
\widehat{\mathscr{H}}_{DD}(t) &= \mathbf{U}^{lab}\widehat{\mathscr{H}}_{DD}^{lab}(t)\mathbf{U}^{lab-1} \\
&= d_0\sum_{q=-2}^{+2}\sum_p A_p^q F^q(\beta,\varphi)\exp\left(i\omega_p^q t\right)
\end{aligned} \tag{7}$$

which follows directly from the fact that $[\widehat{\mathscr{H}}_0, A_p^q]=\omega_p^q A_p^q$, where $\widehat{\mathscr{H}}_0$ $(=\omega_0(I_z+S_z))$ is the Hamiltonian used for the transformation into the rotating frame, Eq. 2 [29]. Thus, it follows that the operators A_p^q are eigenstates of the Liouvillian $\widehat{\widehat{\mathscr{H}}}_0$ $(=[\widehat{\mathscr{H}}_0,\ ]$; in what follows we denote superoperators, such as the Liouvillian, with double hats), with eigenvalues (eigenfrequencies) ω_p^q.

The second and the third transformations can be similarly performed using the unitary rotations defined in Eqs. 3 and 5, respectively,

$$\begin{aligned}\widehat{\mathscr{H}}''_{DD}(t) &= \mathbf{U}'\mathbf{U}\widehat{\mathscr{H}}_{DD}(t)\mathbf{U}^{-1}\mathbf{U}'^{-1}\\ &= d_0\sum_{q=-2}^{+2}\sum_{p}A''^{q}_{p}F^{q}(\beta,\varphi)\exp\left(i\omega''^{q}_{p}t\right)\end{aligned}\tag{8}$$

whereby $\widehat{\mathscr{H}}_{DD}(t)$ is successively transformed into the tilted and then tilted doubly rotating frames. The transformation into the tilted frame ($\mathbf{U}$) "spreads out" each spin tensor operator (A_p^q) into multiple terms (for example, starting from $A_p^q \propto I_zS_z$ (q=0, p=0; Table S1) it can be shown that $I_zS_z \rightarrow I'_zS'_z$, $I'^{+}S'_z$, $I'^{-}S'_z$, $I'_zS'^{+}$, $I'_zS'^{-}$, $I'^{+}S'^{+}$, $I'^{+}S'^{-}$, $I'^{-}S'^{+}$, and $I'^{-}S'^{-}$ with coefficients that depend on θ; Table S2), leading to many more coherence orders p for each q. In addition, the final transformation ($\mathbf{U}'$) leads to a net modulation of $\exp(i\omega''^{q}_{p}t)$ and as a consequence, the frequencies for each term comprising $\widehat{\mathscr{H}}''_{DD}(t)$ are now dependent on the effective fields of I and S ($\omega_{I,eff}$ and $\omega_{S,eff}$) that are, in turn, a function of the B_1 field strength (ω_1) and offset frequencies (Ω_I and Ω_S) (Table S2). As discussed below, these frequency terms determine which of the many possible combinations of spin operators in $\widehat{\mathscr{H}}''_{DD}(t)$ give rise to non-zero contributions to relaxation; many of these combinations are irrelevant since they lead to oscillations that average to zero much more rapidly than the decay of the density elements from relaxation.

In summary, Eq. 9 below illustrates how the Liouville-von Neuman equation for the density operator "evolves" with the different coordinate transformations described above, showing that the time-independent part of the Hamiltonian is progressively simplified in the process. This "evolution" has important implications for evaluating the relaxation elements, as discussed below, since the frequencies of evolution of the spin operator components of the relaxation Hamiltonian can change between frames (compare ω_p^q and ω''^{q}_{p} values for A_p^q, Table S1, and A''^{q}_{p}, Table S2).

2.1.3. Calculation of relaxation

Having derived the operative Hamiltonian in the tilted doubly rotating frame it is now possible to calculate the Redfield relaxation matrix components using Eqs. 8 and 10

$$\begin{aligned}\frac{d\sigma''(t)}{dt} &= -\int_0^\infty \overline{[\widehat{\mathscr{H}}''_{DD}(t), [\widehat{\mathscr{H}}''_{DD}(t-\tau), \sigma''(t)]]}\,d\tau\\ &= -\widehat{\widehat{\Gamma}}''\sigma''(t)\end{aligned}\tag{10}$$

where $\widehat{\widehat{\Gamma}}''$ denotes the relaxation superoperator (double prime indicates that the relaxation expressions correspond to those for the tilted doubly rotating frame) and the top bar inside the integral represents an ensemble average [12,13]. Expanding the density matrix in terms of product operators, $\sigma''(t) = \sum_s b''_s(t)B''_s$ [31], where the time dependence associated with the evolution of each of the operators B''_s in the tilted doubly rotating frame is subsumed in $b''_s(t)$, Eq. 10 reduces to

$$\begin{aligned}\frac{db''_r(t)}{dt} &= -\sum_s \frac{\left\langle B''_r\middle| \int_0^\infty \overline{[\widehat{\mathscr{H}}''_{DD}(t), [\widehat{\mathscr{H}}''_{DD}(t-\tau), B''_s]]}\right\rangle d\tau}{\langle B''_r | B''_r\rangle} b''_s(t)\\ &= -\sum_s \widehat{\widehat{\Gamma}}''_{rs} b''_s(t)\end{aligned}\tag{11}$$

with the time-dependence introduced by the coordinate frame transformation of Eq. 8 contained within $\widehat{\mathscr{H}}''_{DD}(t)$. Replacing $\widehat{\mathscr{H}}''_{DD}(t)$ by the relation in Eq. 8, yields

$$\begin{array}{lll} & \text{Evolution of density matrix} & \text{Hamiltonian}\\ \text{Laboratory frame} & \dfrac{d\sigma^{lab}(t)}{dt} = -i[\widehat{\mathscr{H}}^{lab}, \sigma^{lab}(t)] & \widehat{\mathscr{H}}^{lab} = \omega_I I_z^{lab} + \omega_S S_z^{lab} + 2\omega_1\cos(\omega_0 t)(I_x^{lab} + S_x^{lab}) + \widehat{\mathscr{H}}^{lab}_{DD}(t)\\ (x^{lab}, y^{lab}, z^{lab}) & & \\ & \downarrow & \downarrow\\ \text{Rotating frame} & \dfrac{d\sigma(t)}{dt} = -i[\widehat{\mathscr{H}}, \sigma(t)] & \widehat{\mathscr{H}} = \Omega_I I_z + \Omega_S S_z + \omega_1(I_x + S_x) + \widehat{\mathscr{H}}_{DD}(t)\\ (x, y, z) & & (\Omega_I = \omega_I - \omega_0,\ \Omega_S = \omega_S - \omega_0)\\ & \downarrow & \downarrow\\ \text{Tilted frame} & \dfrac{d\sigma'(t)}{dt} = -i[\widehat{\mathscr{H}}', \sigma'(t)] & \widehat{\mathscr{H}}' = \omega_{I,eff} I'_z + \omega_{S,eff} S'_z + \widehat{\mathscr{H}}'_{DD}(t)\\ (x', y', z') & & \left(\omega_{I,eff} = \sqrt{\omega_1^2 + \Omega_I^2},\ \omega_{S,eff} = \sqrt{\omega_1^2 + \Omega_S^2}\right)\\ & \downarrow & \downarrow\\ \text{Tilted doubly rotating frame} & \dfrac{d\sigma''(t)}{dt} = -i[\widehat{\mathscr{H}}'', \sigma''(t)] & \widehat{\mathscr{H}}'' = \widehat{\mathscr{H}}''_{DD}(t)\\ (x'', y'', z'') & & \end{array}\tag{9}$$

$$
\begin{aligned}
\hat{\hat{\Gamma}}''_{rs} &= d_0^2 \sum_{q,q'} \sum_{p,p'} \exp\left(i\left(\omega''^{q}_{p} + \omega''^{q'}_{p'}\right)t\right) \frac{\left\langle B''_r \middle| \left[A''^{q'}_{p'}, \left[A''^{q}_{p}, B''_s\right]\right]\right\rangle}{\left\langle B''_r \middle| B''_r\right\rangle} \int_0^{\infty} \overline{F^{q'}(\Omega(t)) F^{q}(\Omega(t-\tau))} \exp\left(-i\omega^{q}_{p}\tau\right) d\tau \\
&= \frac{d_0^2}{2} \sum_{q,q'} \sum_{p,p'} \exp\left(i\left(\omega''^{q}_{p} + \omega''^{q'}_{p'}\right)t\right) \frac{\left\langle B''_r \middle| \left[A''^{q'}_{p'}, \left[A''^{q}_{p}, B''_s\right]\right]\right\rangle}{\left\langle B''_r \middle| B''_r\right\rangle} \int_{-\infty}^{\infty} \overline{F^{q'}(\Omega(t)) F^{q}(\Omega(t-\tau))} \exp\left(-i\omega^{q}_{p}\tau\right) d\tau \\
&\simeq \frac{d_0^2}{2} \sum_{q} \sum_{p,p'} \delta_{\omega''^{q}_{p}, -\omega''^{-q}_{p'}} \frac{\left\langle B''_r \middle| \left[A''^{-q}_{p'}, \left[A''^{q}_{p}, B''_s\right]\right]\right\rangle}{\left\langle B''_r \middle| B''_r\right\rangle} \int_{-\infty}^{\infty} \overline{F^{-q}(\Omega(t)) F^{q}(\Omega(t-\tau))} \exp\left(-i\omega^{q}_{p}\tau\right) d\tau \\
&= \frac{d_0^2}{2} \sum_{q} \sum_{p,p'} \delta_{\omega''^{q}_{p}, -\omega''^{-q}_{p'}} \frac{\left\langle B''_r \middle| \left[A''^{-q}_{p'}, \left[A''^{q}_{p}, B''_s\right]\right]\right\rangle}{\left\langle B''_r \middle| B''_r\right\rangle} (-1)^q \int_{-\infty}^{\infty} \overline{F^{q*}(\Omega(t)) F^{q}(\Omega(t-\tau))} \exp\left(-i\omega^{q}_{p}\tau\right) d\tau
\end{aligned}
\tag{12}
$$

where $\delta_{\omega''^{q}_{p}, -\omega''^{-q}_{p'}}$ is the Kronecker delta, and the time-dependence of the orientation of the *I-S* inter-nuclear vector in the rotating frame is given by $\Omega(t) = \{\beta(t), \varphi(t)\}$. A factor of 1/2 is introduced in the second line to account for the extension of the integral to cover the range -∞ to ∞ in the spectral density function presented below. Importantly, Eq. 12 indicates that the sum of eigenfrequencies of operators A''^{q}_{p} and $A''^{-q}_{p'}$, $\omega''^{q}_{p} + \omega''^{-q}_{p'}$, determines whether a particular double commutator term contributes to relaxation or not via what is referred to as the secular approximation. When $\omega''^{q}_{p} + \omega''^{-q}_{p'}$ is much larger than the relaxation rates of the operative density elements (typically on the order of 0.1-10^2 s^{-1}), there is no contribution to relaxation because the term in question is rapidly averaged between −1 and 1 over the much slower timescale of relaxation (the term is called *non-secular*). Thus, in the calculation, commutator terms are only considered when $\omega''^{q}_{p} = -\omega''^{-q}_{p'}$ (the terms are called *secular*), enforced by $\delta_{\omega''^{q}_{p}, -\omega''^{-q}_{p'}}$ in lines 3 and 4 of Eq. 12. It is noteworthy that rotations to different coordinate frames, Eq. 9, effectively transfer the chemical shift and B_1 field terms to the dipolar Hamiltonian such that what is secular in one frame can become non-secular in another frame. By means of a trivial example, consider the expression for $\widehat{\mathscr{H}}'_{DD}(t)$ (the dipolar Hamiltonian in the tilted frame), that is given in Table S2 with the modification that $\omega''^{q}_{p} = q\omega_0$ (last column), and all double primes become single primes. Thus, $\omega'^{q}_{p} = -\omega'^{-q}_{p'}$ for each of the nine terms associated with a given value of q and $-q$. In contrast, in the tilted doubly rotating frame a much smaller number of terms satisfy the relation $\omega''^{q}_{p} = -\omega''^{-q}_{p'}$ (*i.e.*, are secular). Of course, as we illustrate below, the net evolution of the density matrix is the same in both frames, considering all terms (both dipolar and non-dipolar) that contribute to the Hamiltonian of the system.

Assuming random Brownian isotropic motion characterized by a rotational correlation time τ_{corr}, $J(\omega)$ depends on the spatial component of $\widehat{\mathscr{H}}''_{DD}(t)$ as follows

$$
\begin{aligned}
J(\omega) &= \mathrm{Re}\left\{ \int_{-\infty}^{\infty} \overline{F^{q*}(\Omega(t)) F^{q}(\Omega(t-\tau))} \exp(-i\omega\tau) d\tau \right\} \\
&= \frac{2}{5} \frac{\tau_{corr}}{1 + \omega^2 \tau_{corr}^2}
\end{aligned}
\tag{13}
$$

where "Re" indicates the real component of the integral [12,29]. As listed in Table S2, each term of $\widehat{\mathscr{H}}''_{DD}(t)$ is associated with a unique frequency, ω''^{q}_{p}, and accordingly, many different $J(\omega''^{q}_{p})$ terms potentially need to be considered when calculating relaxation rates [11,15]. However, for typical ω_1, Ω_I, and Ω_S values considered in solution NMR, it follows that $\omega_0 \gg \omega_{I,eff}, \omega_{S,eff}$, and that $\omega_{I,eff}\tau_{corr}, \omega_{S,eff}\tau_{corr} \ll 1$, and, thus, only three spectral density terms need be considered,

$$
\begin{aligned}
J(0) &= J\left(\pm\omega_{I,eff}\right) = J\left(\pm\omega_{S,eff}\right) = J\left(\pm\left|\omega_{I,eff} \pm \omega_{S,eff}\right|\right) \\
J(\omega_0) &= J\left(\omega_0 \pm \omega_{I,eff}\right) = J\left(\omega_0 \pm \omega_{S,eff}\right) = J\left(\omega_0 \pm \left|\omega_{I,eff} \pm \omega_{S,eff}\right|\right) \\
J(2\omega_0) &= J\left(2\omega_0 \pm \omega_{I,eff}\right) = J\left(2\omega_0 \pm \omega_{S,eff}\right) = J\left(2\omega_0 \pm \left|\omega_{I,eff} \pm \omega_{S,eff}\right|\right)
\end{aligned}
\tag{14}
$$

Although we have indicated the simplest form of $J(\omega)$ in Eq. 13, other spectral density functions that include additional motional parameters, discussed in the context of the model-free formalism [32,33], for example, may be more appropriate.

2.1.4. *Relaxation matrix for like spins*

Using Eqs. 12-14, we are now ready to calculate Redfield relaxation matrices. Here we describe the evolution of the *I-S* spin system using the density matrix expanded in a Cartesian product basis, $\sigma''(t) = [I''_x, I''_y, I''_z, S''_x, S''_y, S''_z]^+$, where + denotes transpose, and the double prime indicates that the coordinate system is the tilted doubly rotating frame. In this section it is assumed that spins *I* and *S* are "like" [12], so that either their chemical shift difference is sufficiently small and/or the applied B_1 field is sufficiently strong, such that their effective frequencies are the same ($\omega_{I,eff} = \omega_{S,eff}$). Thus, a single tilt angle ($\theta = \theta_I = \theta_S$) and offset frequency ($\Omega = \Omega_I = \Omega_S$) is sufficient to describe the system.

In what follows we will express the calculated relaxation rates in terms of those derived in the laboratory frame [4,29],

$$
\begin{aligned}
R_1 &= \frac{1}{4}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma^4 \hbar^2}{r_{IS}^6} \left(J(0) + 3J(\omega_0) + 6J(2\omega_0)\right) \\
R_2 &= \frac{1}{8}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma^4 \hbar^2}{r_{IS}^6} \left(5J(0) + 9J(\omega_0) + 6J(2\omega_0)\right) \\
\sigma_{ROE} &= \frac{1}{4}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma^4 \hbar^2}{r_{IS}^6} \left(2J(0) + 3J(\omega_0)\right) \\
\sigma_{NOE} &= \frac{1}{4}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma^4 \hbar^2}{r_{IS}^6} \left(-J(0) + 6J(2\omega_0)\right)
\end{aligned}
\tag{15}
$$

where R_1 and R_2 are the longitudinal and transverse relaxation rates of dipolar-coupled spins *I* and *S*, and σ_{ROE} and σ_{NOE} are the transverse and longitudinal cross-relaxation rates, respectively. As presented below, each component of the relaxation matrix in the tilted doubly rotating frame can be rewritten in terms of a relatively simple combination of the terms in Eq. 15, providing a more intuitive picture of relaxation. After tedious but straightforward calculations, the Redfield relaxation matrix $\hat{\hat{\Gamma}}''$ describing the evolution of $\sigma''(t) = [I''_x, I''_y, I''_z, S''_x, S''_y, S''_z]^+$ is given by,

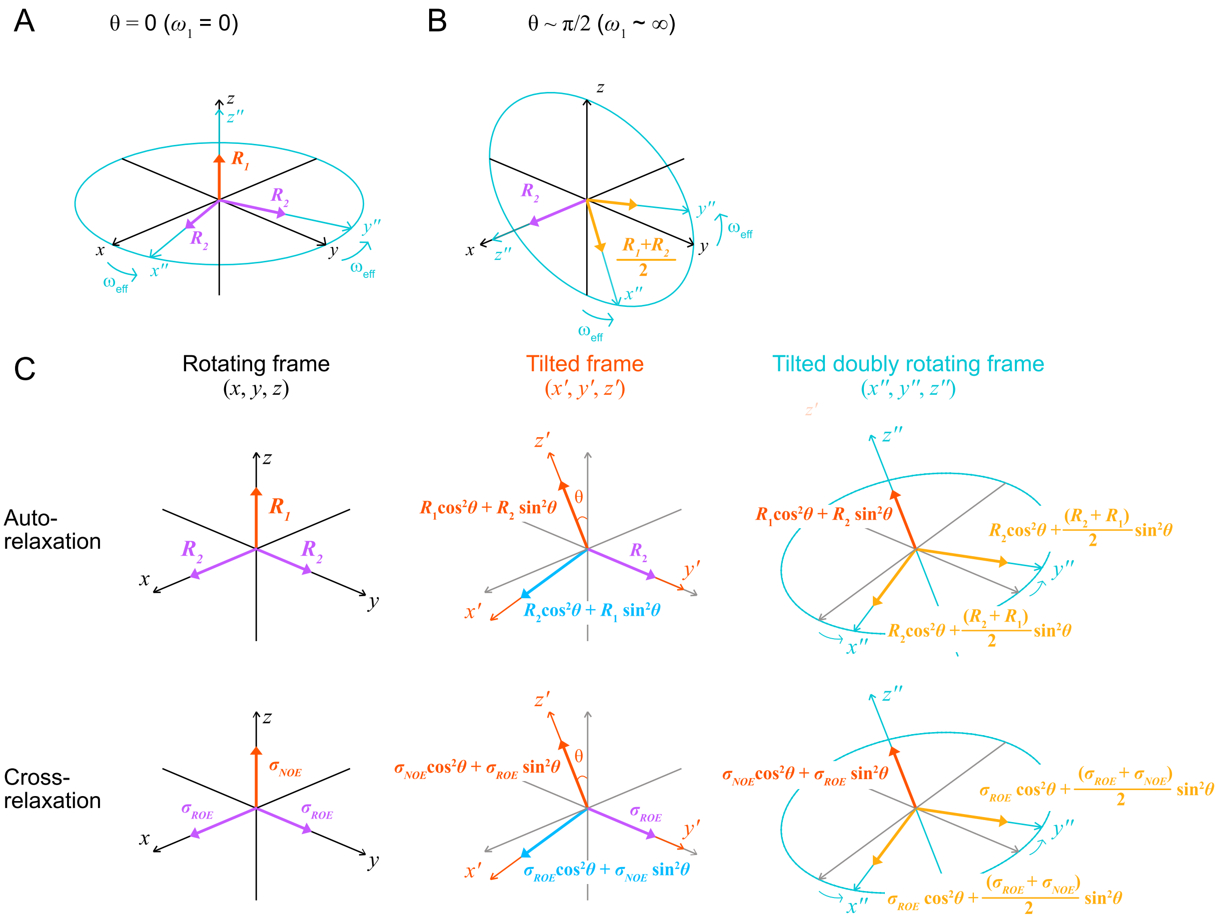

Fig. 2. Relaxation rates of magnetization components parallel to coordinate axes in the rotating frames discussed in the text. (A, B) Superposition of doubly rotating (x'', y'', z'', turquoise) and rotating (x, y, z, black) frames where the z-axis points along the static magnetic field. When $\theta = 0$ ($\omega_1 = 0$, A), the z''-axis of the tilted doubly rotating frame (turquoise) is coincident with the z-axis, and the effective relaxation rates of the x''/y''- and z''-components are R_2 (purple) and R_1 (red), respectively. The effective field frequency (ω_{eff}) is equal to the offset frequency ($\omega_{eff} = \sqrt{\Omega^2 + \omega_1^2} = \Omega$). In the case where $\theta = \pi/2$ ($\omega_1 \to \infty$, B), the z''-axis of the tilted doubly rotating frame (turquoise) is parallel to the x-axis. The effective relaxation rates of the x''/y''- and z''-components are (½($R_1 + R_2$); orange) and R_2 (purple), respectively. The effective field (ω_{eff}) is equal to the B_1 field strength ($\omega_{eff} = \sqrt{\Omega^2 + \omega_1^2} \sim \omega_1$). (C) Effective auto- (top) and cross- (bottom) relaxation rates of each magnetization component, in the rotating (left), titled (middle), and tilted doubly rotating (right) frames, for the intermediate case where $\tan\theta = \omega_1/\Omega$, assuming like spins.

$$\frac{d\sigma''(t)}{dt} = -\hat{\hat{\Gamma}}''\sigma''(t)$$

$$\frac{d}{dt}\begin{bmatrix} I''_x \\ I''_y \\ I''_z \\ S''_x \\ S''_y \\ S''_z \end{bmatrix} = -\begin{bmatrix} R''_{11} & 0 & 0 & R''_{14} & 0 & 0 \\ 0 & R''_{22} & 0 & 0 & R''_{25} & 0 \\ 0 & 0 & R''_{33} & 0 & 0 & R''_{36} \\ R''_{41} & 0 & 0 & R''_{44} & 0 & 0 \\ 0 & R''_{52} & 0 & 0 & R''_{55} & 0 \\ 0 & 0 & R''_{63} & 0 & 0 & R''_{66} \end{bmatrix}\begin{bmatrix} I''_x \\ I''_y \\ I''_z \\ S''_x \\ S''_y \\ S''_z \end{bmatrix} \tag{16}$$

with

$$\begin{aligned} R''_{11} &= R''_{22} = R''_{44} = R''_{55} = R_2\cos^2\theta + \frac{R_2 + R_1}{2}\sin^2\theta \\ R''_{33} &= R''_{66} = R_1\cos^2\theta + R_2\sin^2\theta \\ R''_{14} &= R''_{41} = R''_{25} = R''_{52} = \sigma_{ROE}\cos^2\theta + \frac{\sigma_{ROE} + \sigma_{NOE}}{2}\sin^2\theta \\ R''_{36} &= R''_{63} = \sigma_{NOE}\cos^2\theta + \sigma_{ROE}\sin^2\theta \end{aligned} \tag{17}$$

For identical spins I and S, as considered here, the effective $R_{1\rho}$ rate ($I''_z + S''_z$; relaxation aligned along the z''-axis) is given by $R''_{33} + R''_{36}$ ($= R''_{66} + R''_{63}$), while the effective $R_{2\rho}$ rate ($I''_{x/y} + S''_{x/y}$; relaxation perpendicular to the z''-axis) is equal to $R''_{11} + R''_{14}$ ($= R''_{22} + R''_{25} = R''_{44} + R''_{41} = R''_{55} + R''_{52}$). These rate constants are consistent with those reported by Jones and Blicharski in the limit that $\omega_0 \gg \omega_{I,eff}$, $\omega_{S,eff}$, and $\omega_{I,eff}\tau_{corr}$, $\omega_{S,eff}\tau_{corr} \ll 1$ [11,15], and agree with the well-known expression for the auto-relaxation rate of aligned magnetization (I''_z and S''_z), $R_1\cos^2\theta + R_2\sin^2\theta$ [4,14,34].

It is of interest to consider two limiting cases, $\theta = 0$ (Fig. 2A) and $\theta = \pi/2$ (Fig. 2B). In the first case, the B_1 field strength is 0 ($\omega_1 = 0$), and the relaxation matrix reduces to the Solomon equations [21]. In addition to longitudinal cross-relaxation between $I''_z \leftrightarrow S''_z$, transverse cross-relaxation between $I''_x \leftrightarrow S''_x$ and $I''_y \leftrightarrow S''_y$ is effective, because I and S spins oscillate at the same frequency. In practical cases where $\omega_1 \neq 0$ and B_1 inhomogeneity is a limiting factor, any magnetization component orthogonal to the effective field axis will dephase and hence does not contribute to the resulting signal; the $I''_x \leftrightarrow S''_x$ and $I''_y \leftrightarrow S''_y$ cross-terms will, thus, have no effect. When the B_1 field strength is infinitely strong ($\omega_1 \to \infty$), $\theta \to \pi/2$, the z''-axis coincides with the applied B_1 field and the relaxation rates of the longitudinal (I''_z and S''_z) and transverse (I''_x, I''_y, S''_x, and S''_y) components of magnetization become R_2 and ½($R_1 + R_2$), respectively. Thus, in the tilted doubly rotating frame, $\theta = \pi/2$, the x''-

and y''-axes rapidly rotate about the z''-axis at a frequency of ω_{eff} and have components that oscillate between parallel and perpendicular to the static magnetic field (Fig. 2B). In the general case, where the tilt angle satisfies the relation $\tan\theta = \omega_1/\Omega$, it is straightforward to intuit Eq. 17. Fig. 2C shows the relaxation rates for components of magnetization along the x-, y-, and z-axes of the rotating frame (left), and along the x'-, y'- and z'-axes of the tilted frame (center). Subsequent transformation to tilted doubly rotating frame, that rotates about the z''-axes, leads to averaging of relaxation rates for the transverse components of magnetization along the x'- and y'-axes, as illustrated in Fig. 2C (right).

2.1.5. Relaxation matrix for unlike spins

Calculation of the Redfield relaxation matrix in the case of unlike spins (I and S have distinct chemical shifts, $\Omega_I \neq \Omega_S$) follows directly from Eq. 12. Here we assume that the chemical shift difference between I and S spins is sufficiently large such that the oscillation of spin operators, A''^{q}_{p}, at frequencies proportional to $|\omega_{I,eff} - \omega_{S,eff}|$, is rapid compared to relaxation rates; $\hat{\hat{\Gamma}}''$ elements that contain high frequency oscillations (or for that matter any oscillatory terms) can be discarded by the secular approximation. When this is not the case then the relaxation matrix itself becomes time-dependent; to our knowledge this case is seldom considered and is not further discussed here. As a consequence of the secular approximation, there are fewer non-zero relaxation matrix components for the case of unlike spins relative to the situation for like spins. The Redfield relaxation matrix $\hat{\hat{\Gamma}}''$ describing the evolution of σ'' for unlike spins is,

$$\frac{d}{dt}\begin{bmatrix} I''_x \\ I''_y \\ I''_z \\ S''_x \\ S''_y \\ S''_z \end{bmatrix} = -\begin{bmatrix} R''_{11} & 0 & 0 & 0 & 0 & 0 \\ 0 & R''_{22} & 0 & 0 & 0 & 0 \\ 0 & 0 & R''_{33} & 0 & 0 & R''_{36} \\ 0 & 0 & 0 & R''_{44} & 0 & 0 \\ 0 & 0 & 0 & 0 & R''_{55} & 0 \\ 0 & 0 & R''_{63} & 0 & 0 & R''_{66} \end{bmatrix}\begin{bmatrix} I''_x \\ I''_y \\ I''_z \\ S''_x \\ S''_y \\ S''_z \end{bmatrix} \tag{18}$$

where

$$\begin{aligned} R''_{11} &= R''_{22} = R_2\cos^2\theta_I + \frac{R_2 + R_1}{2}\sin^2\theta_I \\ R''_{33} &= R_1\cos^2\theta_I + R_2\sin^2\theta_I \\ R''_{44} &= R''_{55} = R_2\cos^2\theta_S + \frac{R_2 + R_1}{2}\sin^2\theta_S \\ R''_{66} &= R_1\cos^2\theta_S + R_2\sin^2\theta_S \\ R''_{36} &= R''_{63} = \sigma_{NOE}\cos\theta_I\cos\theta_S + \sigma_{ROE}\sin\theta_I\sin\theta_S \end{aligned} \tag{19}$$

Eq. 19 is similar in many respects to Eq. 17, derived for like-spins, but a number of clear differences emerge. Note that relaxation matrix components depend on both θ_I and θ_S ($\theta_I \neq \theta_S$) for unlike spins and that the transverse cross-relaxation pathways between $I''_x \leftrightarrow S''_x$ and $I''_y \leftrightarrow S''_y$ are not effective, as spins I and S rotate about their z''-axes at different frequencies so that equal amounts of positive and negative magnetization are transferred between the spins [35]. (This is reflected mathematically by the fact that the commutator terms giving rise to transverse cross-relaxation terms in the like spin case now vanish due to the secular approximation). Thus, cross-relaxation occurs only between the aligned components, I''_z and S''_z, with the well-known cross-relaxation rate constant, $\sigma_{NOE}\cos\theta_I\cos\theta_S + \sigma_{ROE}\sin\theta_I\sin\theta_S$ [34].

2.2. Relaxation matrix in the tilted frame as predicted from the Solomon equations

The treatment described above, based initially on the work of Jones [11], is rigorous in the sense that the resulting relaxation expressions hold even in the limit where it is not the case that $\omega_0 \gg \omega_{I,eff}$, $\omega_{S,eff}$, and $\omega_{I,eff}\tau_{corr}$, $\omega_{S,eff}\tau_{corr} \ll 1$, so long as all of the spectral density terms are kept (*i.e.*, Eq. 14 is not used). However, as mentioned above, for all practical cases of interest in solution NMR (or at least all that we can think of), it follows that $\omega_0 \gg \omega_{I,eff}$, $\omega_{S,eff}$, and $\omega_{I,eff}\tau_{corr}$, $\omega_{S,eff}\tau_{corr} \ll 1$. In this limit there is a simpler way of calculating relaxation matrices that has been described in the literature [4,22,23]. Herein, we follow the approach of Desvaux *et al.* [4] with a number of modifications, whereby the relaxation matrix in the tilted doubly rotating frame is obtained by a series of simple manipulations of the Solomon relaxation matrix in the rotating frame [21].

In this case the master equation in the rotating frame ($\sigma(t) = [I_x, I_y, I_z, S_x, S_y, S_z]^+$) can be described as follows

$$\frac{d\sigma(t)}{dt} = \left(-i\hat{\hat{\mathscr{L}}}^{Sol.} - \hat{\hat{\Gamma}}^{Sol.}\right)\sigma(t) \tag{20}$$

where the Liouvillian ($\hat{\hat{\mathscr{L}}}^{Sol.} = [\hat{\mathscr{H}}_0,]$, $\hat{\mathscr{H}}_0 = \Omega_I I_z + \Omega_S S_z + \omega_1(I_x + S_x)$, and [,] denotes a commutator operation) is given by

$$\hat{\hat{\mathscr{L}}}^{Sol.} = i\begin{bmatrix} 0 & -\Omega_I & 0 & 0 & 0 & 0 \\ \Omega_I & 0 & -\omega_1 & 0 & 0 & 0 \\ 0 & \omega_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\Omega_S & 0 \\ 0 & 0 & 0 & \Omega_S & 0 & -\omega_1 \\ 0 & 0 & 0 & 0 & \omega_1 & 0 \end{bmatrix} \tag{21}$$

The relaxation superoperator ($\hat{\hat{\Gamma}}^{Sol.}$) is, in turn, defined by

$$\hat{\hat{\Gamma}}^{Sol.} = \begin{bmatrix} R^{Sol.}_{11} & 0 & 0 & R^{Sol.}_{14} & 0 & 0 \\ 0 & R^{Sol.}_{22} & 0 & 0 & R^{Sol.}_{25} & 0 \\ 0 & 0 & R^{Sol.}_{33} & 0 & 0 & R^{Sol.}_{36} \\ R^{Sol.}_{41} & 0 & 0 & R^{Sol.}_{44} & 0 & 0 \\ 0 & R^{Sol.}_{52} & 0 & 0 & R^{Sol.}_{55} & 0 \\ 0 & 0 & R^{Sol.}_{63} & 0 & 0 & R^{Sol.}_{66} \end{bmatrix} \tag{22}$$

where the matrix components are

$$\begin{aligned} & R^{Sol.}_{11} = R^{Sol.}_{22} = R^{Sol.}_{44} = R^{Sol.}_{55} = R_2 \\ & R^{Sol.}_{33} = R^{Sol.}_{66} = R_1 \\ & R^{Sol.}_{14} = R^{Sol.}_{41} = R^{Sol.}_{25} = R^{Sol.}_{52} = \sigma_{ROE} \\ & R^{Sol.}_{36} = R^{Sol.}_{63} = \sigma_{NOE} \end{aligned} \tag{23}$$

and the superscript "*Sol.*" is added to emphasize that the expression was originally derived by Solomon [21]. Although $\hat{\hat{\Gamma}}^{Sol.}$ is intuitive, and the terms easily "guessed", it can be derived rigorously starting from the expression for $\hat{\mathscr{H}}_{DD}(t)$ (Table S1) and Eqs. 11 and 12, above. Note that the longitudinal and transverse relaxation terms naturally emerge in such a derivation. Eqs. 20-23 can be similarly applied to both like and unlike spins by setting $\Omega_I = \Omega_S$ for like spins. For the case of unlike spins and when $\sin\theta_I\sin\theta_S \sim 0$ transverse cross-relaxation is not effective because $I_{x/y}$ and $S_{x/y}$ precess at different frequencies such that net magnetization cannot be transferred between the spins [35].

In order to compare the relaxation rates obtained in the tilted doubly rotating frame where the secular approximation was enforced (Eq. 16-19), with the corresponding rates in an equivalent frame starting from the Solomon equations (Eq. 20), we first derive the master equation (Eq. 20) in the tilted frame by introducing a rotation matrix, $\hat{\hat{\mathscr{R}}}$, that transforms $\sigma(t)$ to $\sigma'(t) = [I'_x, I'_y, I'_z, S'_x, S'_y, S'_z]^+$. Thus,

$$\sigma'(t) = \hat{\hat{\mathscr{R}}}\sigma(t) \tag{24}$$

where the matrix representation of $\hat{\hat{\mathscr{R}}}$ is given by

$$\widehat{\widehat{\mathscr{R}}} = \begin{bmatrix} \cos\theta_I & 0 & -\sin\theta_I & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ \sin\theta_I & 0 & \cos\theta_I & 0 & 0 & 0 \\ 0 & 0 & 0 & \cos\theta_S & 0 & -\sin\theta_S \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & \sin\theta_S & 0 & \cos\theta_S \end{bmatrix} \tag{25}$$

The inverse rotation $\widehat{\widehat{\mathscr{R}}}^{-1}$ can be obtained by interchanging the signs of θ_I and θ_S in Eq. 25. By taking the time derivative of both sides of Eq. 24, the master equation in the tilted frame can be calculated as follows,

$$\begin{aligned} \frac{d\sigma'(t)}{dt} &= \widehat{\widehat{\mathscr{R}}}\frac{d\sigma(t)}{dt} \\ &= \widehat{\widehat{\mathscr{R}}}\left(-i\widehat{\widehat{\mathscr{L}}}^{Sol.} - \widehat{\widehat{\Gamma}}^{Sol.}\right)\sigma(t) \\ &= \widehat{\widehat{\mathscr{R}}}\left(-i\widehat{\widehat{\mathscr{L}}}^{Sol.} - \widehat{\widehat{\Gamma}}^{Sol.}\right)\widehat{\widehat{\mathscr{R}}}^{-1}\widehat{\widehat{\mathscr{R}}}\sigma(t) \\ &= \left(-i\widehat{\widehat{\mathscr{R}}}\widehat{\widehat{\mathscr{L}}}^{Sol.}\widehat{\widehat{\mathscr{R}}}^{-1} - \widehat{\widehat{\mathscr{R}}}\widehat{\widehat{\Gamma}}^{Sol.}\widehat{\widehat{\mathscr{R}}}^{-1}\right)\sigma'(t) \\ &= \left(-i\widehat{\widehat{\mathscr{L}}}'^{Sol.} - \widehat{\widehat{\Gamma}}'^{Sol.}\right)\sigma'(t) \end{aligned} \tag{26}$$

The Liouvillian in the tilted frame is,

$$\begin{aligned} \widehat{\widehat{\mathscr{L}}}'^{Sol.} &= \widehat{\widehat{\mathscr{R}}}\widehat{\widehat{\mathscr{L}}}^{Sol.}\widehat{\widehat{\mathscr{R}}}^{-1} \\ &= i\begin{bmatrix} 0 & -\omega_{I,eff} & 0 & 0 & 0 & 0 \\ \omega_{I,eff} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\omega_{S,eff} & 0 \\ 0 & 0 & 0 & \omega_{S,eff} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \end{aligned} \tag{27}$$

and the relaxation matrix in the tilted frame is given as

$$\begin{aligned} \widehat{\widehat{\Gamma}}'^{Sol.} &= \widehat{\widehat{\mathscr{R}}}\widehat{\widehat{\Gamma}}^{Sol.}\widehat{\widehat{\mathscr{R}}}^{-1} \\ &= \begin{bmatrix} R'^{Sol.}_{11} & 0 & R'^{Sol.}_{13} & R'^{Sol.}_{14} & 0 & R'^{Sol.}_{16} \\ 0 & R'^{Sol.}_{22} & 0 & 0 & R'^{Sol.}_{25} & 0 \\ R'^{Sol.}_{31} & 0 & R'^{Sol.}_{33} & R'^{Sol.}_{34} & 0 & R'^{Sol.}_{36} \\ R'^{Sol.}_{41} & 0 & R'^{Sol.}_{43} & R'^{Sol.}_{44} & 0 & R'^{Sol.}_{46} \\ 0 & R'^{Sol.}_{52} & 0 & 0 & R'^{Sol.}_{55} & 0 \\ R'^{Sol.}_{61} & 0 & R'^{Sol.}_{63} & R'^{Sol.}_{64} & 0 & R'^{Sol.}_{66} \end{bmatrix} \end{aligned} \tag{28}$$

In Eq. 28 the non-zero matrix components for auto-relaxation are

$$\begin{aligned} R'^{Sol.}_{11} &= R_2\cos^2\theta_I + R_1\sin^2\theta_I \\ R'^{Sol.}_{22} &= R_2 \\ R'^{Sol.}_{33} &= R_1\cos^2\theta_I + R_2\sin^2\theta_I \\ R'^{Sol.}_{44} &= R_2\cos^2\theta_S + R_1\sin^2\theta_S \\ R'^{Sol.}_{55} &= R_2 \\ R'^{Sol.}_{66} &= R_1\cos^2\theta_S + R_2\sin^2\theta_S \end{aligned} \tag{29}$$

and those for cross-relaxation are given by

$$\begin{aligned} R'^{Sol.}_{13} = R'^{Sol.}_{31} &= (R_2 - R_1)\sin\theta_I\cos\theta_I \\ R'^{Sol.}_{14} = R'^{Sol.}_{41} &= \sigma_{ROE}\cos\theta_I\cos\theta_S + \sigma_{NOE}\sin\theta_I\sin\theta_S \\ R'^{Sol.}_{16} = R'^{Sol.}_{61} &= \sigma_{ROE}\cos\theta_I\sin\theta_S - \sigma_{NOE}\sin\theta_I\cos\theta_S \\ R'^{Sol.}_{25} = R'^{Sol.}_{52} &= \sigma_{ROE} \\ R'^{Sol.}_{34} = R'^{Sol.}_{43} &= \sigma_{ROE}\sin\theta_I\cos\theta_S - \sigma_{NOE}\cos\theta_I\sin\theta_S \\ R'^{Sol.}_{36} = R'^{Sol.}_{63} &= \sigma_{ROE}\sin\theta_I\sin\theta_S + \sigma_{NOE}\cos\theta_I\cos\theta_S \\ R'^{Sol.}_{46} = R'^{Sol.}_{64} &= (R_2 - R_1)\sin\theta_S\cos\theta_S \end{aligned} \tag{30}$$

Eqs. 27-30 are identical to the results of Desvaux *et al.* (Eq. 19 in Ref. [4]) and hold for both unlike ($\Omega_I \neq \Omega_S$) and like ($\Omega_I = \Omega_S$) spins.

It is straightforward to show that the time evolution of the density matrices in the tilted frame, derived from the Solomon equations (Eqs. 26-30), and in the tilted doubly rotating frame (Eqs. 16-19) are identical. This can be seen in a qualitative way by noting that the effect of the Liouvillian in Eqs. 26-27 is to rapidly interconvert the x' and y' components of magnetization (*i.e.*, I'_x, I'_y or S'_x, S'_y rapidly rotate about the z'-axis in their respective tilted frames at frequencies of $\omega_{I,eff}$ or $\omega_{S,eff}$, respectively). This leads to an averaging of auto-relaxation rates of spins I and S, for example,

$$\begin{aligned} R'^{Sol.}_{I,ave} &= \frac{1}{2}\left(R'^{Sol.}_{11} + R'^{Sol.}_{22}\right) \\ &= R_2\cos^2\theta_I + \frac{R_2 + R_1}{2}\sin^2\theta_I \\ R'^{Sol.}_{S,ave} &= \frac{1}{2}\left(R'^{Sol.}_{44} + R'^{Sol.}_{55}\right) \\ &= R_2\cos^2\theta_S + \frac{R_2 + R_1}{2}\sin^2\theta_S \end{aligned} \tag{31}$$

so that they become equivalent to those in Eqs. 17 and 19. For both like and unlike spins cross-relaxation between x' and z' components of magnetization ($I'_x \leftrightarrow I'_z$, $I'_x \leftrightarrow S'_z$, $S'_x \leftrightarrow S'_z$, and $S'_x \leftrightarrow I'_z$) can be neglected because I'_x (S'_x) rapidly oscillates about the z' axis so that no net transfer of magnetization to I'_z (S'_z) can occur. Thus, $R'^{Sol.}_{13}$, $R'^{Sol.}_{16}$, $R'^{Sol.}_{31}$, $R'^{Sol.}_{34}$, $R'^{Sol.}_{43}$, $R'^{Sol.}_{46}$, $R'^{Sol.}_{61}$, and $R'^{Sol.}_{64}$ (Eq. 30) can be set to zero. In a similar manner, in the case of unlike spin pairs ($\omega_{I,eff} \neq \omega_{S,eff}$), transverse cross-relaxation between $I'_x \leftrightarrow S'_x$, and $I'_y \leftrightarrow S'_y$ also averages to zero because there is no phase coherence between transverse x' and y' components of I and S magnetization. Therefore, $R'^{Sol.}_{14}$, $R'^{Sol.}_{41}$, $R'^{Sol.}_{25}$, and $R'^{Sol.}_{52}$ can be further discarded in this case. With these "modifications" to the relaxation matrix of Eq. 28, it becomes completely equivalent to the corresponding matrices in Eqs. 17 and 19 for like and unlike spins, respectively. As mentioned above, in practical applications the components perpendicular to the aligned magnetization dephase due to the inhomogeneity of the applied B_1 field without contributing to the observed signal; nevertheless, it is of interest to note that magnetization exchange involving these components can be averaged to zero even in the limit of a perfectly homogenous B_1 field.

An alternative and slightly more mathematical way of showing the equivalence illustrated above is to express Eq 26 in the tilted doubly rotating frame. Here we define the superoperator $\widehat{\widehat{\mathscr{R}}}'(t)$ that transforms $\sigma'(t)$ to $\sigma''(t) = [I''_x,\ I''_y,\ I''_z,\ S''_x,\ S''_y,\ S''_z]^+$,

$$\sigma''(t) = \widehat{\widehat{\mathscr{R}}}'(t)\sigma'(t) \tag{32}$$

and transformation of each product operator, B'_i, by $\widehat{\widehat{\mathscr{R}}}'(t)$ can be defined by

$$\begin{aligned} \widehat{\widehat{\mathscr{R}}}'(t)B'_i &= \exp\left(i\widehat{\mathscr{H}}_{eff}t\right)B'_i\exp\left(-i\widehat{\mathscr{H}}_{eff}t\right) \\ \widehat{\mathscr{H}}_{eff} &= \omega_{I,eff}I'_z + \omega_{S,eff}S'_z \end{aligned} \tag{33}$$

where $\widehat{\mathscr{H}}_{eff}$ is the Hamiltonian of the effective field (see Eq. 5). The explicit matrix representation of $\widehat{\widehat{\mathscr{R}}}'(t)$ is given by

$$\widehat{\widehat{\mathscr{R}}}'(t) = \begin{bmatrix} \cos\omega_{I,eff}t & \sin\omega_{I,eff}t & 0 & 0 & 0 & 0 \\ -\sin\omega_{I,eff}t & \cos\omega_{I,eff}t & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & \cos\omega_{S,eff}t & \sin\omega_{S,eff}t & 0 \\ 0 & 0 & 0 & -\sin\omega_{S,eff}t & \cos\omega_{S,eff}t & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \tag{34}$$

where each matrix component can be obtained from

$$\widehat{\widehat{\mathscr{R}}}'(t)_{rs} = \frac{\langle B_r' | \exp(i\widehat{\mathscr{H}}_{eff}t) B_s' \exp(-i\widehat{\mathscr{H}}_{eff}t) \rangle}{\langle B_r' | B_r' \rangle} \tag{35}$$

By taking the time-derivative of both sides of Eq. 32, we arrive at a master equation in which the Liouvillian part is eliminated, by effectively incorporating it into the relaxation matrix:

$$\begin{aligned} \frac{d\sigma''(t)}{dt} &= \frac{d}{dt}\{\widehat{\widehat{\mathscr{R}}}'(t)\sigma'(t)\} \\ &= \frac{d}{dt}\widehat{\widehat{\mathscr{R}}}'(t)\sigma'(t) + \widehat{\widehat{\mathscr{R}}}'(t)\frac{d\sigma'(t)}{dt} \\ &= \frac{d}{dt}\widehat{\widehat{\mathscr{R}}}'(t)\widehat{\widehat{\mathscr{R}}}'(t)^{-1}\sigma''(t) + \widehat{\widehat{\mathscr{R}}}'(t)\left(-i\widehat{\widehat{\mathscr{L}}}'^{Sol.} - \hat{\hat{\Gamma}}'^{Sol.}\right)\sigma'(t) \\ &= \frac{d}{dt}\widehat{\widehat{\mathscr{R}}}'(t)\widehat{\widehat{\mathscr{R}}}'(t)^{-1}\sigma''(t) + \widehat{\widehat{\mathscr{R}}}'(t)\left(-i\widehat{\widehat{\mathscr{L}}}'^{Sol.} - \hat{\hat{\Gamma}}'^{Sol.}\right)\widehat{\widehat{\mathscr{R}}}'(t)^{-1}\widehat{\widehat{\mathscr{R}}}'(t)\sigma'(t) \\ &= \left(\frac{d}{dt}\widehat{\widehat{\mathscr{R}}}'(t)\widehat{\widehat{\mathscr{R}}}'(t)^{-1} - i\widehat{\widehat{\mathscr{R}}}'(t)\widehat{\widehat{\mathscr{L}}}'^{Sol.}\widehat{\widehat{\mathscr{R}}}'(t)^{-1} - \widehat{\widehat{\mathscr{R}}}'(t)\hat{\hat{\Gamma}}'^{Sol.}\widehat{\widehat{\mathscr{R}}}'(t)^{-1}\right)\sigma''(t) \\ &= -\widehat{\widehat{\mathscr{R}}}'(t)\hat{\hat{\Gamma}}'^{Sol.}\widehat{\widehat{\mathscr{R}}}'(t)^{-1}\sigma''(t) \\ &= -\hat{\hat{\Gamma}}''^{Sol.}\sigma''(t) \end{aligned} \tag{36}$$

In the derivation of Eq. 36, we have used the relation, $\frac{d}{dt}\widehat{\widehat{\mathscr{R}}}'(t)\widehat{\widehat{\mathscr{R}}}'(t)^{-1} - i\widehat{\widehat{\mathscr{R}}}'(t)\widehat{\widehat{\mathscr{L}}}'^{Sol.}\widehat{\widehat{\mathscr{R}}}'(t)^{-1} = 0$ which follows from Eqs. 27 and 34. Thus, the Solomon relaxation matrix in the tilted doubly rotating frame is given by $\hat{\hat{\Gamma}}''^{Sol.}$ $(= \widehat{\widehat{\mathscr{R}}}'(t)\hat{\hat{\Gamma}}'^{Sol.}\widehat{\widehat{\mathscr{R}}}'(t)^{-1})$. Table S3 lists the 36 elements of $\hat{\hat{\Gamma}}''^{Sol.}$ obtained in this way. Assuming that $\omega_{I,eff}, \omega_{S,eff} \gg \hat{\hat{\Gamma}}_{rs}''^{Sol.}$ (equivalent to the secular approximation invoked in Eq. 12) it follows that the only terms contributing to the evolution of $\sigma''(t)$ are those that are time-independent. The expressions in Table S3 then reduce to those for like (Eqs. 16 and 17) and unlike (Eqs. 18 and 19) spins given above.

3. Concluding remarks

We have presented a tutorial describing the calculation of dipolar relaxation for a two spin *I-S* homonuclear spin-system in the presence of a B_1 field. Two different approaches have been taken, including one where a series of transformations was accomplished, ultimately transferring the B_1 field and chemical shift contributions to the dipolar Hamiltonian [11], with the relaxation matrix in this interaction representation of the effective field calculated by enforcing the secular approximation. Alternatively the relaxation evolution of the *I-S* spin system can be described simply from the Solomon Equations [21], as discussed previously [4]. As the equations involved appear, at first glance, to be different, a thoughtful analysis of both approaches is a useful pedagogical exercise in understanding elements of relaxation theory. In the limit where $\omega_0 \gg \omega_{I,eff}$, $\omega_{S,eff}$, and $\omega_{I,eff}\tau_{corr}$, $\omega_{S,eff}\tau_{corr} \ll 1$, which is fulfilled in essentially all applications in solution NMR, identical results are obtained, as demonstrated here. Where the limit above is not fulfilled, calculation of the relaxation elements in the interaction representation of the effective field [11] ensures that the correct frequency components of the spectral densities are obtained.

Declaration of Competing Interest

The authors declare no competing conflicts of interest.

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Supplementary materials

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