Research Article

Multispin Cross-Correlated Transverse Dipolar NMR Relaxation in Solution

Erik R. P. Zuiderweg

1Institute for Molecules and Materials, Radboud University, 6525 XZ, Nijmegen, Netherlands
2Department of Biological Chemistry, University of Michigan, Ann Arbor, MI 41109, USA

Correspondence should be addressed to Erik R. P. Zuiderweg; zuiderwe@umich.edu

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In this paper, we want to consider what would be involved in calculating the $R_2$ relaxation of amide protons in a protein caused by dipolar interactions with nearby protons, for which there are many. NMR textbooks give analytical equations and sometimes derivations for solution NMR relaxation due to dipolar interactions between two spins. There are also closed equations for dipolar interactions between three spins, which include relaxation interference, also known as cross-correlated cross-relaxation. We here derive an expression for interference between four spins. For larger systems, such as amide protons in a protein, we develop a local-field methodology, from which solution relaxation interference can be computed for a basically limitless number of interacting spins.

1. Introduction

Several researchers have been interested in investigating whether proton-proton dipolar interaction in proteins can be utilized to obtain structural [1, 2] or dynamical information [3]. Here, we want to consider what would be involved in calculating the $R_2$ relaxation of amide protons in a protein caused by dipolar interactions with other protons and, ultimately, compare those with experiment [4]. NMR textbooks give closed equations and sometimes derivations for solution NMR relaxation due to dipole-dipole relaxation between two spins and for chemical shift anisotropy (CSA) relaxation. There are also closed equations for relaxation due to interactions between three dipoles [5] and two dipoles and the CSA [6]. In these cases, relaxation interference, also known as cross-correlated cross-relaxation, has been taken into account. Dipolar-dipolar relaxation interference has been described very early in the history of NMR [7, 8] and has been exploited to achieve line narrowing [9] and structural information [1, 2]. CSA-dipolar cross-correlated relaxation is at the core of the line narrowing in the TROSY experiment [10].

Here, we derive an analytical expression for dipolar interference between four spins. For larger systems, such as amide protons in a protein, we develop a local-field methodology, from which solution relaxation interference can be computed for a basically limitless number of interacting spins.

2. Theory

Let us start by considering the $R_2$ relaxation of spin $I$ in a rigid molecule with three protons, S-I-Q, subject to fluctuating dipolar interactions IS and IQ. We assume here that I, S, and Q have different chemical shifts and are thus similar, but “unlike.” The first step is to add the relaxation rates due to the IS and IQ dipolar interactions, as given by equation (A.24) of the Appendix.
\[ R_2^{t\text{otal}} = R_2^{\text{IS}} + R_2^{\text{IQ}}, \]  
\[ R_2^{f\text{otal}} = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{\gamma H H \hbar}{r_{\text{IS}}} \right)^2 + \left( \frac{\gamma H H \hbar}{r_{\text{IQ}}} \right)^2 \left\{ 5f(0) + 9f(\omega_H) + 6f(2\omega_H) \right\}. \]

However, in a rigid molecule, the stochastic fluctuations of the IS and IQ dipolar interactions are 100% correlated and relaxation interference occurs. Relaxation interference is also called cross-correlated cross-relaxation or cross-correlated relaxation.

Interference between two dipolar mechanisms can be qualitatively understood from Figure 1. Here, we consider a linear three-spin system with spin I in the center and spins S and Q equidistant from I.

In this case, there are two relaxation rates for spin I, one for molecule A, where the dipolar fields of S and Q at the location I cancel independent of orientation with respect to the magnetic field, and another for molecule B, where the dipoles reinforce each other and fluctuate strongly depending on orientation. This is expressed as

\[ R_2^{\text{total}} = R_2^{\text{IS}} + R_2^{\text{IQ}} \pm R_2^{\text{SCC-IQ}}. \]

Of course, the dipoles flip by \( R_1 \) processes. For macromolecules, \( R_1 \) rates are much slower than \( R_2 \) rates. Thus, for \( R_2 \) cross-correlations, one may assume that orientations of the dipoles remain set during the typical \( R_2 \) relaxation time.

If the different dipolar permutations also give rise to different resonances, by either scalar or residual static dipolar coupling, one observes four NMR lines for I. The two outer lines have equal linewidths, and the two inner lines also have equal, but different, linewidths. Which set will be the broader one depends on the molecular geometry and the sign of the (scalar) coupling. If no such coupling exists, one will observe a superposition of a broader and narrower line for I.

In order to obtain quantitative values for the dipolar-dipolar cross-correlation, one starts with expanding the double commutator master equation for \( R_2 \) relaxation, as shown in equation (A.16) of the Appendix. We mostly follow a formalism as introduced by [5, 11].

For two \( R_2 \) relaxation mechanisms IS and IQ, modulated by the same motions, the relaxation master equation is

\[ \frac{d\langle I_z \rangle}{dt} = -\frac{1}{2} \sum_{m=-2}^{m=+2} \left\{ \langle [I_z, T_{\text{m}S} + T_{\text{m}Q}], T_{\text{m}S} + T_{\text{m}Q} \rangle \right\} j_m \omega_m, \]

where \( T_{\text{m}S} \) are the tensor operators of the perturbing Hamiltonian, which for dipolar interaction between spins I and S are given by

\[ T_0 = 2I_z S_z - \frac{1}{2} (I_z S_+ + I_+ S_z), \]
\[ T_{+1} = \frac{\sqrt{3}}{2} (I_z S_z + I_+ S_+). \]

Figure 1: Pictorial representation of dipolar cross-correlation in a linear S-I-Q system. The dipolar fields of S and Q at the location of I for A, independent of orientation with respect to the magnetic field (vertical). In B, the dipolar fields of S and Q reinforce each other at the location of I and modulate strongly as a function of molecular orientation.

\[ T_{+2} = \frac{\sqrt{3}}{2} (I_z S_z), \]

with similar equations for \( T_{\text{m}Q} \). \( j_m \omega_m \) are the spectral densities of the molecular motion at the frequencies of the bilinear spin operators including magnitude terms.

In the expansion, the “diagonal” terms such as

\[ \sum_{m=-2}^{m=+2} \left\{ \langle [I_z, T_{\text{m}S}], T_{\text{m}S} \rangle \right\} j_m \omega_m, \]
\[ \sum_{m=-2}^{m=+2} \left\{ \langle [I_z, T_{\text{m}Q}], T_{\text{m}Q} \rangle \right\} j_m \omega_m, \]

and their complex conjugates will give rise to the auto-correlation rates \( R_2^{\text{IS}} \) and \( R_2^{\text{IQ}} \), as shown in equation (A.22) of the Appendix.

In the cross terms,

\[ \sum_{m=-2}^{m=+2} \left\{ \langle [I_z, T_{\text{m}S}], T_{\text{m}Q} \rangle \right\} J_{m_{\text{cc}}} \omega_m, \]
\[ \sum_{m=-2}^{m=+2} \left\{ \langle [I_z, T_{\text{m}Q}], T_{\text{m}S} \rangle \right\} J_{m_{\text{cc}}} \omega_m, \]

and their complex conjugates, only spin operators with exactly the same precession frequency will be relevant, i.e., only the pair \( (I_z S_0, I_z Q_0) \) and the four terms \( I_z S_0, I_z Q_0, I_z S_0, I_z Q_0 \), and \( I_z Q_0 \).

We obtain the following equation from equations (6a) and (6b):

\[ \frac{d\langle I_z \rangle}{dt} = \langle 4[I_z, I_z S], I_z Q_0] \rangle j_0^{\text{cc}}(0) \]
\[ + \frac{3}{2} \langle [I_z, I_z S], I_z Q_0] \rangle j_1^{\text{cc}}(\omega_1), \]
where the $\frac{1}{2}$ term is dropped because there are two equivalent cross terms, as given in equations (7a) and (7b). The cross-correlation spectral densities are
\[
J_{m\omega_{m}}^{\text{cc}} = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{r_{1S}}{r_{IS}^2} \right) \left( \frac{r_{1Q}}{r_{IQ}^2} \right) P_2(\theta_{IS-1Q}) J(\omega_{m}),
\]
(9)
with, for isotropic motion,
\[
J(\omega_{m}) = \frac{2}{5} \frac{r_{c}}{1 + \omega_{m}^2 r_{c}^2}, \tag{10}
\]
where the $P_2(\theta_{IS-1Q}) = 1/2 (3 \cos^2(\theta_{IS-1Q}) - 1)$ term originates from transforming the IQ dipolar vector into the IS frame or vice versa and using the addition theorem of spherical harmonics. Here, $\theta_{IS-1Q}$ is the angle between vectors IS and IQ and $r_{c}$ is the (rotational) correlation time.

In contrast to the $R_2$ autocorrelation, the double commutators drive cross-relaxation
\[
\frac{d}{dt} \begin{pmatrix} (I_+, 4I_S, S_z, Q_z) \\ (I_-, 4I_S, S_z, Q_z) \end{pmatrix} = \begin{bmatrix} R_2^{\text{IS}} + R_2^{\text{IQ}} + R_2^{\text{CC}} & 0 \\ R_2^{\text{IS}} + R_2^{\text{IQ}} - R_2^{\text{CC}} & 0 \end{bmatrix} \begin{pmatrix} (I_+, 4I_S, S_z, Q_z) \\ (I_-, 4I_S, S_z, Q_z) \end{pmatrix},
\]
(13)
with
\[
R_2^{\text{CC}} = \frac{1}{4} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{r_{1S}}{r_{IS}^2} \right) \left( \frac{r_{1Q}}{r_{IQ}^2} \right) P_2(\theta_{IS-1Q}) J(0) + 3J(\omega_{I}). \tag{14}
\]

The total $R_2$ relaxation for proton $i$, as stated before in equation (3), is then given by
\[
R_2^{\text{total}} = R_2^{\text{IS}} + R_2^{\text{IQ}} \pm R_2^{\text{IS-1Q}}. \tag{15}
\]

One notices that $^1H$ IS-autorelaxation contains a $5J(0)$ term (equation (2)), while the dipolar cross-correlation has a $4J(0)$ term (equation (14)). The extra $J(0)$ in autorelaxation is due to the fact that $J(0)$ and $J(\omega_{I} - \omega_{c})$ are for two protons similar enough for the spectral densities to add (see Appendix), but $(\omega_{I} - \omega_{c})$ and $(\omega_{c} - \omega_{s})$ are different enough for the spin operators to diphase and not cross-correlate. Thus, there will not be a complete cancelation of relaxation, as suggested in the situation of Figure 1. It can still happen, if the differences in distances IS and IQ would make up for the 4/5 term.

If one cannot make the approximation that $R_2^{\text{IP}}$ and $R_2^{\text{AP}}$ are equal, the rates become
\[
R_2^{\text{total}} = \frac{1}{2} R_2^{\text{IP}} + \frac{1}{2} R_2^{\text{AP}} \pm \sqrt{\frac{R_2^{\text{IP}} \times R_2^{\text{IP}}}{4} - \frac{R_2^{\text{IP}} \times R_2^{\text{AP}}}{4} + \frac{R_2^{\text{AP}} \times R_2^{\text{AP}}}{4} + \frac{R_2^{\text{IS-1Q}} \times R_2^{\text{IS-1Q}}}{4}}. \tag{16}
\]

Let us now extend this formalism to a 4-spin system, with a central spin $I$ and 3 other spins $S$, $Q$, and $P$ in its vicinity.

From the master equation, we arrive at three cross terms:
leading to terms such as $4I_s S_z Q_x$, $4I_s S_z P_z$, and $4I_s P_z Q_z$, driven by the rates

$$R_{2I}^{S-Q} = \frac{1}{4} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{\gamma I^2 h}{r_{1S}^3} \right) \left( \frac{\gamma I^2 h}{r_{1Q}^3} \right) \cdot P_2 \cos(\theta_{1S-Q}) \{4f(0) + 3f(\omega_j)\},$$

$$R_{2I}^{S-P} = \frac{1}{4} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{\gamma I^2 h}{r_{1S}^3} \right) \left( \frac{\gamma I^2 h}{r_{1P}^3} \right) \cdot P_2 \cos(\theta_{1S-P}) \{4f(0) + 3f(\omega_j)\},$$

$$R_{2I}^{Q-I} = \frac{1}{4} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{\gamma I^2 h}{r_{1Q}^3} \right) \left( \frac{\gamma I^2 h}{r_{1P}^3} \right) \cdot P_2 \cos(\theta_{1Q-I}) \{4f(0) + 3f(\omega_j)\}. $$

This appears to lead to eight different relaxation rates ($R_{2I}^{S} + R_{2I}^{SQ} + R_{2I}^{QP} + R_{2I}^{SP}$). However, that cannot be right; adding one more dipole $P$ to the S-I-Q situation should just give rise to two more rates, four in total. So, one should not stop here and construct the full relaxation matrix.

Also, one must take cross-relaxation between the different four-spin terms into account (here only showing some $f(0)$ terms),

$$\frac{d(4I_s S_z Q_j)}{dt} = \langle 4[4I_s S_z Q_i, I_s S_z, J_{i,j}] \rangle = \langle 4I_s' Q_j P_i \rangle,$$

$$\frac{d(4I_s S_z P_j)}{dt} = \langle 4[4I_s S_z Q_i, I_s Q_i, J_{i,j}] \rangle = \langle 4I_s' S_z P_i \rangle,$$

$$\frac{d(4I_s S_z Q_j)}{dt} = \langle 4[4I_s S_z P_i, I_s Q_i, J_{i,j}] \rangle = \langle 4I_s' S_z Q_i \rangle,$$

and three reverse processes.

The differential equations in matrix form will now become

$$\frac{d}{dt} \begin{pmatrix} I_+ \\ 4I_s S_z Q_z \\ 4I_s S_z P_z \\ 4I_s P_z Q_z \end{pmatrix} = \begin{pmatrix} R_{2I} & R_{2I}^{SQ} & R_{2I}^{QP} & R_{2I}^{SP} \\ R_{2I}^{SQ} & R_{2I} & R_{2I}^{SP} & R_{2I}^{QP} \\ R_{2I}^{QP} & R_{2I}^{SP} & R_{2I} & R_{2I}^{SP} \\ R_{2I}^{SP} & R_{2I}^{QP} & R_{2I}^{SP} & R_{2I} \end{pmatrix} \begin{pmatrix} I_+ \\ 4I_s S_z Q_z \\ 4I_s S_z P_z \\ 4I_s P_z Q_z \end{pmatrix}. $$

We must take another approach. To arrive at an estimation for the effects in a multiproton spin system, we will start from a "solid-state NMR" point of view. We calculate $B_{loc}^{j}$: the net local magnetic field at center proton $i$ due to the $M$ surrounding protons $j$ [12] for a certain orientation of the molecule in the external magnetic field:

$$B_{loc}^{j} = \frac{\mu_0}{4\pi} \sum_{j=1}^{M} \sum_{ij} \mathcal{D} \left( \frac{\gamma I^2 h}{r_{ij}^3} \right) P_2(\cos \theta_{ij}).$$

Here, $\theta_{ij}$ is the angle between the internuclear vector $ij$ and the magnetic field direction $\Omega$ in the molecular frame. $\mathcal{D}$ represents a particular distribution of the signs of the $z$-components of the dipoles $j$. If one varies the magnetic
field direction according to a sphere distribution and adds the results, one obtains the powder pattern for that particular distribution D. Subsequently, one coadds all powder patterns for different values of D and normalizes to arrive at the “cross-correlated” dipolar powder pattern for the 1HN under consideration.

It is the time dependence of B_{loc} as caused by molecular motion, that drives the solution NMR dipolar relaxation. The R_2 relaxation is then obtained as the second moment of the (cross-correlated) powder pattern [12]:

$$R_{2i}^{\text{solution}} = 4\tau_c \sum_{\Omega} (B_{\text{loc}(i)} - B_{\text{loc}(i)\downarrow})^2,$$

(22)

where the brackets indicate average overall orientations. In practice, we permute only the signs of the eight closest protons (256 different distributions D) and treat the spins further out with a single random distribution where spins up and down are on average equal. So, each distribution then gives rise to an individual resonance for i with its own R_2 rate. The sum of all of those creates the inhomogeneous sum-line for resonance i.

3. Verification

We verified the algorithm with a three-atom arrangement (see Table 1) with results in Figure 2. In this figure, the green points were calculated from equations (14) and (15) for dipolar-dipolar cross-correlation, while the drawn black line was calculated using the “solid-state” approach. The results are identical. In red is a relaxation curve calculated from the straight addition of R_2 (IS) and R_2 (IQ) (see equation (1)). It is clear that the cross-correlation cannot be neglected, except when one considers the first part of the curve. Fitting a single exponential against a complete cross-correlated relaxation curve (dashed line) yields an erroneous rate. In red is a relaxation curve calculated from the straight addition of R_2 (IS) and R_2 (IQ) (equation (1)). A (isotropic) rotational correlation time τ_c of 10 ns was used in all calculations.

However, how far down a relaxation curve can go varies from proton to proton environment. Judging from Figure 2(b), one should limit the recording of T_{1rho} relaxation curves to values larger than 0.8xT_{1rho}, where T_{1rho} is the initial value of the decay curve.

4. Description of the Codes

The computer program requires as input a “protonated” PDB file, the radius of the sphere of protons around the amide protons one is interested in, the rotational correlation time, and the spectrometer frequency. Basically, the program consists of four nested loops: amides, protons around amides, permutation of dipole signs of these surrounding protons, and rotation of the magnetic field vector in the molecular frame.

A set of 10 nested loops permutes the dipolar signs of the closest 10 hydrogens (1024 distributions). The more remote hydrogens in the sphere (if any) have their dipolar signs assigned according to a 50% random chance. The local dipolar field at a certain 1HN due to the surrounding protons in a certain permutation D of surrounding dipoles is calculated according to equation (20). Here, the program takes the differences between “like” and “unlike” spins (see Appendix) into account. Then, the program calculates, according to equation (22), the R_2 relaxation rate due to that permutation, by rotating the external field.
direction (the $z$-axis) through the molecular frame using an isotropic spherical distribution (5000 orientations) (http://corysimon.github.io/articles/uniformdistn-on-sphere/).

The relaxation rate for that permutation $D$ is then used to compute a $R_2$ relaxation curve. The computed $R_2$ relaxation curves for all different permutations $D$ are then added to obtain the complete $R_2$ relaxation curve, as shown in Figures 2 and 3.

The program is written in Fortran 90 and contains no references to outside libraries. The source code is available from the author.

**Appendix**

This appendix presents a refresher on dipolar $R_2$ relaxation, mostly following the formalism, as developed by Goldman [11] and further extended by [13], to help follow the algebra in the main body of the paper.

When the density operator $\sigma$ is subject to both a time-independent (eigen) Hamiltonian $\mathcal{H}_0$ and a time-dependent perturbing dipolar Hamiltonian $\mathcal{H}_1(t)$, its evolution, in units of $\hbar$, is given by

$$
\frac{d}{dt} \sigma(t) = -i[\mathcal{H}_0 + \mathcal{H}_1(t), \sigma(t)].
$$

(A.1)

Transforming to the rotating frame of the time-independent Hamiltonian, one obtains

$$
\frac{d}{dt} \tilde{\sigma}(t) = -i[\tilde{\mathcal{H}}_1(t), \tilde{\sigma}(t)],
$$

(A.2)

with the time-dependent Hamiltonian also transformed to the rotating frame. One keeps in mind that this equation describes an ensemble average. First, one imposes on equation (A.2) that the density operator cannot evolve ("relax") when it was not perturbed in the first place (e.g., by a r.f. pulse). Thus, one makes the substitution

$$
\frac{d}{dt} \tilde{\sigma}(t) = -i[\tilde{\mathcal{H}}_1(t), \tilde{\sigma}(0) - \tilde{\sigma}_{eq}],
$$

(A.3)

where $\tilde{\sigma}_{eq}$ is the density operator at equilibrium, which is not evolving under $\mathcal{H}_0$ (i.e., the usual "high temperature approximation with $\tilde{\sigma}_{eq} \sim I_\tau$).

One uses the Hausdorff expansion to integrate equation (A.3):

$$
\tilde{\sigma}(t) = \tilde{\sigma}(0) - i \int_0^t \left[ \tilde{\mathcal{H}}_1(t'), \tilde{\sigma}(0) - \tilde{\sigma}_{eq} \right] dt' - \int_0^t \int_0^{t'} \left[ \tilde{\mathcal{H}}_1(t'), \tilde{\mathcal{H}}_1(t''), \tilde{\sigma}(0) - \tilde{\sigma}_{eq} \right] dt'' dt'' + \ldots.
$$

(A.4)

Since the dipolar Hamiltonian has zero average in solution, the second term in equation (A.4) vanishes. The fourth and higher-order terms also vanish because the perturbing Hamiltonian causes only small changes of the density operator, allowing the expansion to converge rapidly. One thus obtains the formal relaxation equation:

$$
\tilde{\sigma}(t) = \tilde{\sigma}(0) - i \int_0^t \left[ \tilde{\mathcal{H}}_1(t'), \tilde{\mathcal{H}}_1(t''), \tilde{\sigma}(0) - \tilde{\sigma}_{eq} \right] dt' dt''.
$$

(A.5)

The perturbing Hamiltonian fluctuates not only by the fluctuating dipole-dipole interactions between spins $I$ caused by random molecular motion captured in the terms $E^{DD}_m(t)$ but also by frequencies of the spin operators $I$, $S$, and $I,S$ (al, $\omega S$, al$-\omega S$, etc.).

It can be abbreviated as

$$
\tilde{E}^{DD}_{IS}(t) = \sum_{m=2}^{n=2} E^{DD}_m(t) T_{mIS}.
$$

(A.6)

$T_{mIS}$ are the tensor operators of the perturbing Hamiltonian, which for dipolar interaction between spins $I$ and $S$ are given by
\[ T_0 = 2I_zS_z - \frac{1}{2}(I_zS_- + I_zS_+), \quad (A.7a) \]
\[ T_{k+1} = \sqrt{\frac{3}{2}}(I_zS_+), \quad (A.7b) \]
\[ T_{k+2} = \sqrt{\frac{3}{2}}(I_zS_+). \quad (A.7c) \]

On expanding, this becomes

\[
\begin{align*}
\mathcal{P}^{DD}_{IS}(t) &= +2F_0^{IS}(t)(I_zS_- - \frac{1}{2}F_0^{IS}(t)(I_zS_+ + I_zS_-)e^{(\omega_0 - \omega) t} \\
&+ \sqrt{\frac{3}{2}} F_1^{IS}(t)(I_zS_+)e^{(\omega_0)t} - \sqrt{\frac{3}{2}} F_1^{IS}(t)(I_zS_-)e^{(\omega_0)t} \\
&+ \sqrt{\frac{3}{2}} F_1^{IS}(t)(I_zS_+)e^{(\omega_0)t} - \sqrt{\frac{3}{2}} F_1^{IS}(t)(I_zS_-)e^{(\omega_0)t} \\
&+ \sqrt{\frac{3}{2}} F_2^{IS}(t)(I_zS_+)e^{(\omega_0+\omega)t} + \sqrt{\frac{3}{2}} F_2^{IS}(t)(I_zS_-)e^{(\omega_0+\omega)t},
\end{align*}
\]

(\ref{A.8})

with

\[
F_0^{IS}(t) = -\frac{\mu_0}{4\pi} \left( \frac{\gamma_1\gamma_2\hbar}{r_{IS}^3} \right) \frac{3 \cos^2 \theta(t) - 1}{2} = F_0^{IS*}(t),
\]

(A.9a)

\[
F_{\pm 1}^{IS}(t) = \pm \left( \frac{\mu_0}{4\pi} \right) \left( \frac{\gamma_1\gamma_2\hbar}{r_{IS}^3} \right) \frac{3}{2} \sin \theta(t) \cos \theta(t) e^{i\eta(t)} = -F_{\mp 1}^{IS*}(t),
\]

(A.9b)

\[
F_{\mp 2}^{IS}(t) = \left( \frac{\mu_0}{4\pi} \right) \left( \frac{\gamma_1\gamma_2\hbar}{r_{IS}^3} \right) \frac{3}{8} \sin^2 \theta(t) e^{i2\eta(t)} = F_{\mp 2}^{IS*}(t).
\]

(A.9c)

Here, \( \mu_0 \) is the permittivity of vacuum, \( h \) is the Planck’s constant divided by \( 2\pi \), \( \gamma \)'s are the gyromagnetic ratios, and \( r_{IS} \) is the distance between the dipoles. The angles \( \theta(t) \) and \( \phi(t) \) are fluctuating polar angles between the IS vector and the direction of the external magnetic field.

In terms of equations (A.6), (A.7a), (A.7b), and (A.7c), equation (A.5) now becomes

\[
\bar{\sigma}(t) - \bar{\sigma}(0) = \sum_{m,n=-2}^{m,n=2} \left[ T_n \left[ T_n^*, \left( \bar{\sigma}(0) - \bar{\sigma}_0 \right) \right] \right] \times \int_0^t \int_0^t F_m^{IS}(t') F_n^{IS*}(t'') e^{i(\omega_0 t' - \omega_0 t'')} dt'' dt'.
\]

(A.10)

\[
\int \omega^2 = \frac{2}{5} \frac{\tau_c}{1 + \omega^2 \tau_c^2}.
\]

(A.12)

From the 25 terms in equation (A.10), only the ones with equal frequencies \( e^{i(\omega_0 t' - \omega_0 t'')} \) contribute. This is called the Redfield kite, named after the author of one of the earliest papers on NMR relaxation [14]. It suffices to just take the five diagonal terms into account and drop the second summation. One arrives at the “master equation” of relaxation [11].
\[
\frac{d\langle \bar{\sigma} \rangle}{dt} = \frac{1}{2} \sum_{m=-2}^{m+2} \left[ T_{m\text{IS}}^\dagger \left[ \sigma_m^\dagger \left( \bar{\sigma}(0) - \bar{\sigma}_\text{EQ} \right) \right] \right] j_m, \quad (A.13)
\]

with
\[
j_m = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{g_1 g_2 \hbar}{r_{\text{IS}}} \right)^2 I(\omega_m)
\]
\[
= \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{g_1 g_2 \hbar}{r_{\text{IS}}} \right)^2 \frac{2 \tau_c}{5 (1 + \omega_m^2 \tau_c^2)}.
\]

Now, we are finally ready to derive the \( R_2 \) relaxation rate for \( \langle I_+ \rangle \). We start by setting the equilibrium term to zero:
\[
\frac{d\langle I_+ \rangle}{dt} = -\frac{1}{2} \sum_{m=-2}^{m+2} \left\{ \langle [Q, T_{m\text{IS}}], T_{m\text{IS}}^\dagger \rangle \langle [Q, T_{m\text{IS}}], T_{m\text{IS}}^\dagger \rangle_{\text{eq}} \right\} j_m.
\]
\[
\frac{d\langle I_+ \rangle}{dt} = -\frac{1}{2} \left\{ A + B + B' + C + C' + D + D' + E + E' \right\},
\]
with the terms
\[
A = 4 \langle [I_+, I_z S_z], I_z S_z \rangle j_0 (0) = \langle I_+ \rangle j_0 (0),
\]
\[
B = +\frac{1}{4} \langle [I_+, I_z S_+], I_- S_- \rangle j_0 (\omega_t - \omega_s) = 0,
\]
\[
B' = +\frac{1}{4} \langle [I_+, I_+ S_+], I_- S_- \rangle j_0 (\omega_t - \omega_s) = \frac{1}{4} \langle I_+ \rangle j_0 (\omega_t - \omega_s),
\]
\[
C = +\frac{3}{2} \langle [I_+, I_z S_z], I_- S_+ \rangle j_1 (\omega_t) = 0,
\]
\[
C' = +\frac{3}{2} \langle [I_+, I_+ S_z], I_- S_- \rangle j_1 (\omega_t) = \frac{3}{4} \langle I_+ \rangle j_1 (\omega_t),
\]
\[
D = +\frac{3}{2} \langle [I_+, I_z S_+], I_z S_- \rangle j_1 (\omega_s) = \frac{3}{4} \langle I_+ \rangle j_1 (\omega_s),
\]
\[
D' = +\frac{3}{2} \langle [I_+, I_+ S_+], I_z S_- \rangle j_1 (\omega_s) = \frac{3}{4} \langle I_+ \rangle j_1 (\omega_s),
\]
\[
E = +\frac{3}{2} \langle [I_+, I_z S_+], I_+ S_- \rangle j_2 (\omega_t + \omega_s) = 0,
\]
\[
E' = +\frac{3}{2} \langle [I_+, I_+ S_+], I_+ S_- \rangle j_2 (\omega_t + \omega_s) = \frac{3}{2} \langle I_+ \rangle j_2 (\omega_t + \omega_s).
\]
For the expansion of the commutators, one uses

\[ [I_x, I_y] = -I_z, [I_x, I_z] = I_y, [I_y, I_z] = 2I_x, \quad (A.20a) \]

and the product rules

\[ I_x I_x = \frac{1}{4} E; I_x I_y = \frac{1}{2} E + I_z; I_y I_x = \frac{1}{2} E - I_z, \quad (A.20b) \]

\[ I_y I_z = -I_x I_x = \frac{1}{2} I_z, I_z I_x = -I_y I_z = -\frac{1}{2} I_x, \quad (A.20c) \]

with \( E \) being the unit matrix.

One finds that all double commutators in equation (A.19) result in terms linear in \( I_z \), yielding an uncoupled differential equation

\[ -\frac{d\langle I_y \rangle}{dt} = R_z^I \langle I_y \rangle, \quad (A.21) \]

with

\[ R_z^I = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_I \gamma_H \hbar}{r_{IS}^2} \left( 4J(0) + 3J(\omega_I) + 6(\omega_S) \right) + J(\omega_I - \omega_S) + 6J(\omega_I + \omega_S). \quad (A.22) \]

For two protons with different chemical shifts, one makes the substitutions

\[ J(\omega_I - \omega_S) \equiv J(0); J(\omega_S) \equiv J(\omega_I) \equiv J(\omega_H), \quad (A.23) \]

which yields

\[ R_z^I = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_H \gamma_H \hbar}{r_{IS}^2} \left( 5J(0) + 9J(\omega_H) + 6(2\omega_H) \right). \quad (A.24) \]

This is called the “unlike” proton-proton dipolar relaxation equation.

In the case of two protons \( I \) and \( I' \) with identical chemical shifts, or when the chemical shifts are forced to be equal during a spin lock, the cross terms between different coherence orders in the dipolar Hamiltonian cannot be neglected.

In particular, two cross terms between the single quantum terms \( C \) and \( D \) of equation (A.19) enter in the relaxation master equation, giving rise to cross-relaxation to the other spin:

\[ [I_x I_x, I_y I_x] = 2I_z I_x I_y I_x = \frac{1}{2} [I_z I'_x, I'_x] = \frac{1}{2} I'_x, \quad (A.25) \]

Similarly, the frequencies of \( J(0) \) and zero-quantum terms in this case are precisely equal, so that two cross terms between terms \( A \) and \( B \) of equation (A.17) will occur as well:

\[ -[I_x, I_x I_x, I_y I_x] = I_x I_x I_y I_x = \frac{1}{2} I_x. \quad (A.26) \]

Capturing both transfers into one equation yields

\[ -\frac{d\langle I_y \rangle}{dt} = \frac{1}{2} \left( j_0(0) + \frac{3}{2} J(\omega_H) \right) \langle I_y \rangle \equiv \sigma_{ROE} \langle I_y \rangle, \quad (A.27) \]

\[ \sigma_{ROE} = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_I \gamma_H \hbar}{r_{IS}^2} \left( 4J(0) + 6(\omega_I) \right). \quad (A.28) \]

The cross-relaxation rate in equation (A.28) is called the rotating frame Overhauser effect and was first discovered and quantified by [15] using the name “camel-spin.”

Since the \( I \) and \( I' \) chemical shifts are identical, one may add equation (A.28) to equation (A.24) to obtain

\[ R_z^I = \frac{1}{8} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_H \gamma_H \hbar}{r_{IS}^2} \left( 9J(0) + 15J(\omega_H) + 6(2\omega_H) \right). \quad (A.29) \]

This equation holds two protons with identical chemical shifts, or spinlocked. It is called the “like” spin relaxation equation. This has led to confusion. A better nomenclature would be to call this the identical spin relaxation equation.

Data Availability

No experimental data were used in this work.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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