Nuclear magnetic relaxation induced by exchange-mediated orientational randomization: Longitudinal relaxation dispersion for spin $I = 1$

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The frequency dependence of the longitudinal relaxation rate, known as the magnetic relaxation dispersion (MRD), can provide a frequency-resolved characterization of molecular motions in complex biological and colloidal samples. But even when spin relaxation is induced by single-molecule (as opposed to collective) dynamics, the interpretation of measured spin relaxation rates is often non-trivial. For molecule (as opposed to collective) dynamics, the interpretation of measured spin relaxation rates is often non-trivial. For complex biological and colloidal samples, the principal challenge is to distinguish contributions to the spin relaxation rate from molecular motions of different kinds and on different time scales.

Motions on different time scales can be resolved, in the frequency domain, by measuring the longitudinal relaxation rate $R_1(\omega_L)$ as a function of the Larmor frequency $\omega_L$, which is determined by the strength of the applied static magnetic field. Using the field-cycling (FC) technique in conjunction with conventional high-field inversion recovery experiments, such magnetic relaxation dispersion (MRD) data can be recorded over five orders of magnitude in frequency.

The spin $I = 1$ $^2$H nuclide plays a particularly important role in this context, because it is coupled to the molecular degrees of freedom by an electric quadrupole interaction that is sufficiently weak to make the spin relaxation time long enough to be measured with the FC technique and, at the same time, sufficiently strong that the (more complicated) effect of multispin magnetic dipole couplings can be ignored.

Prominent among $^2$H MRD applications are studies of water ($D_2O$) in biological systems such as concentrated biopolymer-water systems, living cells, and bacterial spores. Such data provide unique insights about water dynamics in complex systems and also provide access to functionally important protein conformational motions on the rarely accessed time scale $10^{-8}$–$10^{-5}$ s. However, despite the considerable potential of water $^2$H MRD measurements, there is still no general consensus about the relaxation theory required to interpret the data.

Since 1995 our group has argued that the water $^2$H relaxation dispersion from systems containing immobilized proteins is produced by water molecules residing in cavities.
within the protein (and, depending on pH, by labile deuterons in amino acid side-chains). The release of internal water molecules not only mixes the magnetizations associated with internal and external water but actually *induces* the spin relaxation by a process known as exchange-mediated orientational randomization (EMOR). The survival time of the internal water molecule thus becomes the rotational correlation time. Because internal-water survival times are often in the microsecond range, and sometimes longer, the conventional perturbation theory of nuclear spin relaxation is not applicable. We have therefore developed a more general theory, based on the stochastic Liouville equation, which describes relaxation by the EMOR mechanism without the usual restriction to short correlation times. In the original publication, this theory was described in fairly general terms and, although certain extensions of the theory have been used in subsequent experimental MRD studies, a detailed derivation of the full theory or an assessment of the accuracy of its different forms have not been presented. The following is intended to remedy this situation.

In Sec. II, we describe the basic version of the EMOR model. As compared to the original EMOR publication, this presentation is more general and explicit and somewhat more rigorous. In particular, the earlier restriction to an axially symmetric electric field gradient (EFG) tensor is removed. This is a significant generalization because, although the rigid-lattice $^2$H asymmetry parameter $\eta^0$ is small ($\sim 0.1$), even modest internal motions (such as restricted rotation of incompletely immobilized protein molecules) leads to substantially larger values for the rotationally averaged asymmetry parameter $\eta$ that enters the EMOR theory. Moreover, for long correlation times $R_1$ depends more strongly on $\eta$ than in the motional-narrowing regime.

In Sec. III, we present exact results for the integral longitudinal rate $R_1$ as well as approximate results for the relaxation rate $R_0$ that is measured when the longitudinal relaxation is exponential. We compare these results numerically and show that the exponential approximation is highly accurate under most conditions of interest. Special attention is given to the experimentally important dilute regime, where only a small fraction of the observed spins reside in locally anisotropic sites. For this regime, we derive a simple analytical approximation. An analytical result was previously proposed for the special case $\eta = 0$. Here, we present a rigorous derivation of a more general ($\eta \neq 0$) analytical result. Although not quantitatively accurate under all conditions, the analytical result provides conceptual insights. For example, it shows explicitly how, in the ultraslow-motion regime, the apparent correlation time inferred from the dispersion frequency is governed by the pure nuclear quadrupole resonance (NQR) frequencies rather than by molecular motions. The EMOR theory thus rationalizes the observed weak (or absent) temperature dependence of the apparent correlation time. Furthermore, the analytical expression identifies the smallest NQR frequency as the source of the additional low-frequency dispersion that appears in the ultraslow-motion regime when $\eta$ is small. In Sec. III, we also discuss the well-known expression for the longitudinal relaxation rate for a dilute multi-site system, showing explicitly why it is not valid for the EMOR relaxation mechanism except in the trivial fast-exchange limit.

In Sec. IV, we generalize the basic EMOR model in three respects. First, we show how partial averaging of the EFG tensor can be incorporated via the order parameter $S$ and the asymmetry parameter $\eta$. Second, we show how the direct relaxation effect of internal motions adds to the EMOR contribution to $R_1$. Third, we generalize the EMOR model to an arbitrary number of sites with different exchange rates.

In Sec. V, we consider the application of the EMOR model to water $^2$H relaxation in systems with immobilized proteins. Here, we show how the MRD profile is affected by $180^\circ$ water flips and other internal motions. Finally, we compare the performance of the different versions of the EMOR theory by means of fits to synthetic MRD data. Lengthy derivations have been relegated to seven appendixes.

II. EMOR MODEL

A. Spin Hamiltonian

We consider an ensemble of mutually non-interacting $I = 1$ nuclear spins subject to a Zeeman coupling ($Z$) with the external magnetic field $B_0$ and a nuclear quadrupole coupling ($Q$) with the local EFG tensor. The molecular system is spatially heterogeneous and this is modeled by assigning each nucleus to either of two states. In the isotropic (I) state, the quadrupole coupling is averaged to zero by fast unrestricted rotational motions, leaving only the Zeeman coupling. In the anisotropic (A) state, the nuclei experience, in addition to the Zeeman coupling, a (residual) quadrupole coupling. At any time, $N_I$ nuclei reside in the I state while $N_A$ nuclei reside in the A state. The relative equilibrium populations of nuclei in the states are thus $P_A = N_A/(N_A + N_I)$ and $P_I = 1 − P_A$. The A and I state populations are chemically homogeneous, but each A state nucleus is distinguished by the orientation $\Omega$ of its EFG tensor relative to the $B_0$ field. We refer to these distinguishable members of the A state as sites and label them with the index $\alpha = 1, 2, \ldots, N_A$. For notational convenience, we use the site label $\alpha = 0$ to refer to a nucleus in the isotropic state.

The spin Hamiltonians for the two states are

$$H_I = H_Z,$$

$$H_{\alpha\alpha} = H_Z + H_{Q\alpha},$$

The Zeeman Hamiltonian is

$$H_Z = \omega_L I_z,$$

where $\omega_L$ is the static Larmor frequency averaged over all sites. The fluctuating part of $H_Z$, due to exchange among sites with different chemical shifts, has no effect on longitudinal relaxation since $H_Z$ commutes with $I_z$. The quadrupole
Hamiltonian is
\[
\mathcal{H}_{Q\alpha} = \frac{\omega_Q}{3} \sum_{m=-2}^{2} T_m^2 \left\{ \sqrt{6} D_{m,0}^2(\Omega_\alpha) + \eta [D_{m,2}^{2+}(\Omega_\alpha) + D_{m,-2}^{2+}(\Omega_\alpha)] \right\},
\]  
where \( T_m^2 \) is a spherical irreducible spin tensor operator, \( D_{m,\eta}^\alpha(\Omega_\alpha) \) is a Wigner function, and the Euler angles \( \Omega_\alpha \) specify the orientation of the principal frame of the EFG tensor with respect to the lab-fixed frame (with the \( z \) axis along the \( B_0 \) field).\(^{19} \) The quadrupole frequency \( \omega_Q \) and the EFG asymmetry parameter \( \eta \) are taken to be the same in all \( A \) sites (this restriction is removed in Sec. IV), which then differ only in the EFG orientation \( \Omega_\alpha \). The quadrupole frequency in Eq. (2.3) is related to the conventional\(^1 \) quadrupole coupling constant \( \chi \) (in Hz) as
\[
\omega_Q = \frac{3}{2} \pi \chi.
\]  
The eigenvalues of the quadrupole Hamiltonian in Eq. (2.3) are \( E_0 = -2 \omega_Q/3 \) and \( E_{\pm 1} = (1 \pm \eta) \omega_Q/3. \)\(^1 \) The differences of these eigenvalues are the pure NQR frequencies \( \Omega_{Q,0} \equiv E_{+1} - E_{-1} \) and \( \Omega_{Q,\pm} \equiv E_{\pm 1} - E_0. \) For later convenience, we express these NQR frequencies as
\[
\Omega_{Q,m} \equiv c_m \omega_Q,
\]  
with the coefficients
\[
c_0 = \frac{2\eta}{3}; \quad c_{\pm 1} = 1 \pm \frac{\eta}{3}. \quad (2.6)
\]  
The variation of the NQR frequencies with \( \eta \) is shown in Fig. 1.

**B. Exchange kinetics**

In the basic version of the EMOR model, relaxation is induced exclusively by the physical or chemical exchange of nuclei among sites. We thus ignore the effects of local rotational motions in the sites. Specifically, such internal motions are taken to be absent in the \( A \) state and to be infinitely fast in the \( I \) state. In Sec. IV, we generalize the EMOR model to include the two distinct effects of internal motions: (i) a partial orientational averaging of the quadrupole Hamiltonian in Eq. (2.3), and (ii) a direct relaxation contribution. If the internal motion is the same in all \( A \) sites, the first effect can be accounted for simply by interpreting the quadrupole frequency \( \omega_Q \) and the asymmetry parameter \( \eta \) in Eq. (2.3) as motionally averaged quantities. In Sec. IV, we consider the more general case where the extent of motional averaging differs among the \( A \) sites.

We model site exchange as a stationary Markov process, specified by a propagator \( P(t) \) that obeys the operator master equation\(^{20,21} \)
\[
\frac{d}{dt} P(t) = \mathcal{W} P(t),
\]  
with the initial condition \( P(0) = I \). We introduce an orthonormal basis corresponding to the sites \( \alpha = 0, 1, 2, \ldots, N_A \) accessible to the exchanging nucleus. In this site basis, the matrix element  \( \langle \alpha | P(t) | \beta \rangle \) is the conditional probability that the nucleus is in site \( \alpha \) at time \( t \), given that it was in site \( \beta \) initially.

It is convenient to split the exchange superoperator \( \mathcal{W} \) in two parts as
\[
\mathcal{W} = T - \mathcal{K}.
\]  
The \( \beta \to \alpha \) transition probability, that is, the probability per unit time that a nucleus in site \( \beta \) suffers an instantaneous exchange to site \( \alpha \), is given by the matrix element
\[
\langle \alpha | \mathcal{K} | \beta \rangle = \delta_{\alpha\beta} \tau_{\beta}^{-1},
\]  
where \( \tau_\beta \) is the mean survival time in site \( \beta \) and \( \pi_{\alpha\beta} \) is the probability that an exchange from site \( \beta \) leads to site \( \alpha \). To conserve probability, the diagonal part of \( \mathcal{W} \) must be
\[
\langle \alpha | \mathcal{K} | \beta \rangle = \delta_{\alpha\beta} \sum_\gamma \langle \gamma | T | \alpha \rangle = \delta_{\alpha\beta} \tau_\alpha^{-1}. \quad (10.10)
\]  
The principle of microscopic reversibility requires that the transition probabilities obey the detailed balance condition\(^{20,21} \)
\[
\langle \alpha | T | \beta \rangle P_\beta = \langle \beta | T | \alpha \rangle P_\alpha, \quad (11.1)
\]  
where \( P_\alpha \) is the relative population of site \( \alpha \) at equilibrium.

In the EMOR model, \( P_0 \equiv P_1 \) is the population of the isotropic site (or state) and all \( A \) sites have the same population,
\[
P_\alpha = \frac{P_A}{N_A}, \quad (12.2)
\]  
where \( P_A \) is the combined population of all sites in the \( A \) state
\[
P_A = \sum_{\alpha=1}^{N_A} P_\alpha = 1 - P_1. \quad (13.2)
\]  
Furthermore, the EMOR model stipulates that exchange among \( A \) sites always occurs via the \( I \) state. The only nonzero probabilities \( \pi_{\alpha\beta} \) are then \( \pi_{0\alpha} = 1/N_A \) and \( \pi_{\alpha0} = 1 \), where \( \alpha \) is an \( A \) site. Setting \( \beta = 0 \) (the \( I \) site) and summing both sides of Eq. (11.1) over \( \alpha \) while using Eq. (2.9), we obtain the

![FIG. 1. Spin 1 = 1 NQR frequencies \( \Omega_{Q,m} \) versus EFG asymmetry parameter \( \eta \).](image)
equilibrium condition

$$\frac{P_k}{\tau_k} = \sum_{\alpha=1}^{N_A} P_{\alpha} \tau_{\alpha}. \quad (2.14)$$

In the basic version of the EMOR model (to be generalized in Sec. IV C), the mean survival time is the same in all A sites, so we write $\tau_k = \tau_A$. Using this fact and Eq. (2.13), we find that the equilibrium condition (2.14) takes the simple form

$$P_{\Lambda} \tau_k = P_k \tau_{\Lambda}. \quad (2.15)$$

In view of Eqs. (2.13) and (2.15), it is clear that the basic EMOR model is fully specified by two independent parameters, which we choose as $P_{\Lambda}$ and $\tau_{\Lambda}$.

**C. Equation of motion**

In the direct-product space constructed from the nine-dimensional spin-1 Liouville space and the $(N_A + 1)$-dimensional site space, the non-equilibrium spin density operator $\sigma(t)$ (that is, the deviation from the equilibrium spin density operator) evolves according to the stochastic Liouville equation

$$\frac{d}{dt} \sigma(t) = (\mathcal{V} - i \mathcal{L}) \sigma(t). \quad (2.16)$$

The time-independent Liouvillian $\mathcal{L} = \sum_{\alpha} |\alpha\rangle \mathcal{L}_\alpha \langle \alpha|$ is a superoperator in the direct-product space and it is trivially diagonal in the site basis,

$$\langle \alpha | \mathcal{L} | \beta \rangle = \delta_{\alpha\beta} \mathcal{L}_\alpha = \delta_{\alpha\beta} [\mathcal{H}_\alpha, \ldots]. \quad (2.17)$$

The superoperator $\mathcal{L}_\alpha$ acts in spin Liouville space, which we represent by the spherical multipole basis, consisting of irreducible spherical spin tensor operators $T_q^k \equiv |kq\rangle$ of rank $k = 0, 1$ or 2 and quantum order $q = -k, -k+1, \ldots, k-1, k$. The set of 9 such operators constitutes a complete orthonormal basis for a spin-1 nucleus

$$\text{Tr}_S \{T_q^k T_q'^k\} \equiv \langle kq | k'q' \rangle = \delta_{kk'} \delta_{qq'}, \quad (2.18)$$

where the subscript $S$ signifies that the trace operation pertains to the spin degrees of freedom.

The spin observables are related to a reduced spin density operator obtained by averaging over the molecular (M) degrees of freedom as

$$\langle \sigma(t) \rangle \equiv \text{Tr}_M \langle \sigma(t) | P(t \to \infty) \rangle
\begin{align*}
&= \sum_{\alpha=0}^{N_A} \sum_{\beta=0}^{N_A} \langle \alpha | \sigma(t) | \beta \rangle \langle \beta | P(t \to \infty) | \alpha \rangle \\
&= \sum_{\alpha=0}^{N_A} \sum_{\beta=0}^{N_A} \langle \alpha | \sigma(t) | \beta \rangle P_{\beta}. \quad (2.19)
\end{align*}$$

The projections of the reduced spin density operator on the basis operators are the so-called state multipoles

$$\langle \sigma_q^k(t) \rangle \equiv \langle kq | \sigma(t) \rangle. \quad (2.20)$$

Our focus here is on $\langle \sigma_q^k(t) \rangle$, which is proportional to the non-equilibrium longitudinal magnetization $M_z(t) - M_0$.

The Laplace transform

$$\tilde{\sigma}(s) \equiv \int_0^\infty dt \exp(-st) \sigma(t), \quad (2.21)$$

converts Eq. (2.16) to an algebraic equation, with formal solution

$$\tilde{\sigma}(s) = \tilde{U}(s) \sigma(0). \quad (2.22)$$

The resolvent superoperator,

$$\tilde{U}(s) = (s - \mathcal{W} + i \mathcal{L})^{-1}, \quad (2.23)$$

is the Laplace transform of the evolution superoperator $\mathcal{U}(t)$.

We assume that the initial non-equilibrium spin state has been prepared under high-field conditions ($\omega_L \gg \omega_Q$), so that $\langle \alpha | \sigma(0) | \alpha \rangle$ is the same for all sites $\alpha$. This is the case in conventional relaxation experiments using RF pulses as well as in field-cycling relaxation experiments. Averaging Eq. (2.22) over the molecular degrees of freedom, as in Eq. (2.19), we then obtain

$$\langle \tilde{\sigma}(s) \rangle = \langle \tilde{U}(s) \rangle \sigma(0), \quad (2.24)$$

where

$$\langle \tilde{U}(s) \rangle = \sum_{\alpha=0}^{N_A} \tilde{U}_\alpha(s) \quad (2.25)$$

with

$$\tilde{U}_\alpha(s) \equiv \sum_{\beta=0}^{N_A} \langle \alpha | \tilde{U}(s) | \beta \rangle P_{\beta}. \quad (2.26)$$

We now introduce two simplifying assumptions. First, we assume that the number $N_A$ of A sites is sufficiently large that $\Omega_\alpha$ can be treated as a continuous variable $\Omega$ with a distribution function $f(\Omega)$. Second, we assume that this distribution is isotropic, that is,

$$f(\Omega) = \frac{1}{8\pi^2}. \quad (2.27)$$

Because of the rotational invariance implied by Eq. (2.27), any site-averaged superoperator derived from the Liouvillian $\mathcal{L}$, such as the resolvent superoperator $\tilde{U}(s)$, must share the cylindrical symmetry of the $B_0$ field. The Liouville-space Wigner-Eckart theorem then implies that all such superoperators are block-diagonal ($q = q'$) in the multipole representation. For example,

$$\langle kq | \tilde{U}(s) | k'q' \rangle = \delta_{qq'} \langle kq | \tilde{U}(s) | k'q' \rangle \sigma_q^k(0). \quad (2.28)$$

Equations (2.20) and (2.24) yield for the Laplace-transformed state multipoles

$$\langle \tilde{\sigma}_q^k(s) \rangle = \sum_{k'} \sum_{q'} \langle kq | \tilde{U}(s) | k'q' \rangle \sigma_q^k(0)$$

$$= \sum_{k'} (kq \langle \tilde{U}(s) | k'q \rangle) \sigma_q^k(0), \quad (2.29)$$

where Eq. (2.28) was used in the last step. Equation (2.29) shows that, as a consequence of the isotropic distribution in Eq. (2.27), polarizations ($q = 0$) and coherences ($q \neq 0$)
The matrix elements of $\mathcal{L}_Q(\Omega)$ are obtained from Eq. (2.3) and the Liouville space Wigner-Eckart theorem.\textsuperscript{27} For $k' \geq k$,
\[(kq|\mathcal{L}_Q(\Omega)|k'q') = \delta_{k',k+1}(-1)^{k+q'}\left[\frac{k}{3}(k+1)(k+2)(k+4)(2-k)\right]^{1/2} \times \left\{\begin{array}{ccc}
0 & q & q' \\
q & q' - q & -q'
\end{array}\right\}
\times \left\{D_{q-q,0}^{2}(\Omega) + \frac{\eta}{\sqrt{6}}[D_{q-q,2}^{2}(\Omega) + D_{q-q,-2}^{2}(\Omega)]\right\} \omega_0.\]

(2.36)

Since $\mathcal{H}_Q(\Omega)$ is Hermitian, matrix elements with $k' < k$ can be obtained from the symmmetry relation
\[(kq|\mathcal{L}_Q(\Omega)|k'q') = (k'q'|\mathcal{L}_Q(\Omega)|kq)^*.
\]

(2.37)

In general, the matrix elements in Eq. (2.36) depend on all three Euler angles $\Omega = (\alpha, \beta, \gamma)$. The angle $\alpha$ describes a rotation about the $B_0$ field axis and $\beta$ is the angle between the $B_0$ field and the principal EFG axis (defined by the EFG component with the largest magnitude). In the special case of a symmetric EFG tensor, with $\eta = 0$, the matrix elements do not depend on the angle $\gamma$, which describes a rotation about the principal EFG axis.

The explicit matrix representation $\mathbf{M}$ of the superoperator $\mathcal{M}(s = 0, \Omega)$ in the spherical multipole basis can now be obtained from Eqs. (2.33) and (2.35)–(2.37) after evaluating the $3j$ symbols and substituting trigonometric expressions for the Wigner functions in Eq. (2.36). The Zeeman and the quadrupole couplings, respectively, involve the dimensionless quantities
\[L \equiv \omega_0 \tau_\alpha,\]
\[Q \equiv \omega_0 \tau_\beta.\]

(2.38a, b)

The nonzero off-diagonal elements can all be expressed in terms of three quantities
\[a \equiv \frac{iQ}{\sqrt{2}}\left[\cos \beta - \frac{\eta}{3}(\cos \beta \cos 2\gamma + i \sin 2\gamma)\right] \sin \beta \exp(i\alpha),\]
\[b \equiv \frac{iQ}{2}\left\{(\sin^2 \beta + \frac{\eta}{3}(1 + \cos^2 \beta) \cos 2\gamma + i 2 \cos \beta \sin 2\gamma)\right\} \exp(i2\alpha),\]
\[c \equiv \frac{iQ}{2}\{3 \cos^2 \beta - 1 + \eta \sin^2 \beta \cos 2\gamma\}.\]

(2.39a, b, c)

The matrix $\mathbf{M}$ can now be expressed succinctly as
where the basis operators are indicated in the first column and the first row.

III. LONGITUDINAL RELAXATION

A. Integral relaxation rate

We define the integral longitudinal relaxation rate $\hat{R}_1$ of the state multipole $\langle \sigma^0_1(t) \rangle$, proportional to the non-equilibrium longitudinal magnetization, as the inverse of the time integral of the normalized state multipole,\(^{14}\)

$$\hat{R}_1 = \int_0^\infty d\tau \frac{\langle \sigma^0_1(t) \rangle}{\langle \sigma^0_1(0) \rangle} = \frac{1}{10(\langle \sigma^0(0) \rangle)10}. \tag{3.1}$$

where Eq. (3.20) was used in the last step. The supermatrix element in Eq. (3.1) is obtained by setting $s = 0$ in Eq. (2.31), whereby

$$\langle \sigma^0(0) \rangle = \tau_\Lambda \left[ i \mathcal{L}_Z \tau_\Lambda + \frac{P_\Lambda}{P_1} (1 - B) \right]^{-1} \times \left[ P_1 + P_\Lambda \left( 2 \frac{P_\Lambda}{P_1} + i \mathcal{L}_Z \tau_\Lambda \right) \mathcal{B} \right]. \tag{3.2}$$

where, according to Eqs. (2.32) and (2.33), $B \equiv B(0)$ and $\mathcal{M}(\Omega) \equiv \mathcal{M}(0, \Omega)$ are given by

$$B = \frac{1}{8\pi^2} \int_0^{2\pi} d\alpha \int_{-1}^1 d\cos \beta \int_0^{2\pi} d\gamma [\mathcal{M}(\alpha, \beta, \gamma)]^{-1} \tag{3.3}$$

and

$$\mathcal{M}(\alpha, \beta, \gamma) = 1 + i \mathcal{L}_Z \tau_\Lambda + i \mathcal{L}_Q(\alpha, \beta, \gamma) \tau_\Lambda. \tag{3.4}$$

The expression for $\hat{R}_1$ obtained by combining Eqs. (3.1) and (3.2) can be simplified by noting (i) that the spherical multipole supermatrix representation of $\mathcal{B}$ is block-diagonal in $q$ (cf. Eq. (2.28)), (ii) that the $\mathcal{L}_Z$ supermatrix is diagonal with diagonal elements equal to 0 for $q = 0$ (see Eq. (2.35)), and (iii) that the inverse of a block-diagonal matrix is also block-diagonal with the blocks given by the inverses of the corresponding blocks of the original matrix. Using these facts and the normalization condition $P_1 + P_\Lambda = 1$, we obtain the exact result

$$\hat{R}_1 = \frac{P_\Lambda}{\tau_\Lambda} \times \frac{1}{\sum_{k=1}^{2}(1-B)^{-1}|k0|[i\mathcal{L}_1P_1^2 + P_\Lambda(1+P_1)(k0)|B|10]}. \tag{3.5}$$

In general, the non-equilibrium longitudinal magnetization $\langle \sigma^0_1(t) \rangle$ does not decay exponentially. In fact, under certain conditions ($P_\Lambda \approx 1$ and $Q \gtrsim 1$), it exhibits oscillatory (coherent) features as well as decay.\(^{14}\) Nevertheless, the integral longitudinal relaxation rate $\hat{R}_1$ is given exactly by Eq. (3.5) under all conditions. If $\langle \sigma^0_1(t) \rangle$ deviates significantly from a single-exponential decay, the integral relaxation rate does not capture the full information content of $\langle \sigma^0_1(t) \rangle$. But as long as $\hat{R}_1$ can be measured and calculated, it can be used to extract the model parameters from the experimental data. For example, if $\langle \sigma^0_1(t) \rangle$ decays bi-exponentially as

$$\langle \sigma^0_1(t) \rangle = \sigma^0_1(0)c \exp(-R_{1,a}t) + (1 - c) \exp(-R_{1,b}t), \tag{3.6}$$

we can obtain the three parameters $c, R_{1,a}$, and $R_{1,b}$ from a fit of Eq. (3.6). According to Eq. (3.1), the integral relaxation rate can then be obtained as

$$\hat{R}_1 = \left( \frac{c}{R_{1,a}} + \frac{1 - c}{R_{1,b}} \right)^{-1}. \tag{3.7}$$

At the price of some information loss, bi-exponential relaxation data can thus be analyzed with the exact Eq. (3.5). This is useful because simple exact results are not available for the individual rates $R_{1,a}$ and $R_{1,b}$, which, moreover, cannot be uniquely determined by a bi-exponential fit unless they differ substantially in magnitude.

Under certain conditions, $\langle \sigma^0_1(t) \rangle$ decays mono-exponentially. This is so whenever the $q = 0$ block of the supermatrix representation of $\mathcal{B}$ is diagonal, which is the case (for $t \gg \tau_\Lambda$) in the low-field regime, where $L^2 \ll 1 + Q^2$, and in the motional-narrowing regime, where $Q^2 \ll 1 + L^2$. But even outside these regimes, that is, for $L \approx Q \gtrsim 1$, the deviation from exponential decay of $\langle \sigma^0_1(t) \rangle$ is usually too small to be observed experimentally. To a good approximation, we can then neglect the off-diagonal element
levels off for B. Dilute regime

\[ R_\text{P} \approx \frac{\omega}{\tau_A} = 3 \]  

FIG. 2. Dispersion of the exact integral relaxation rate \( \hat{R}_1 \) (red solid curve) and of the exponential approximation \( R_1 \) (blue dots) for \( P_A = 0.1, \tau_A = 3 \mu s, \omega_Q = 10^6 \text{ rad s}^{-1} \), and \( \eta = 0.5 \). The inset shows the relative error of the exponential approximation.

We refer to the range of validity of Eq. (3.8) as the exponential regime. However, even outside this regime, Eq. (3.8) deviations from the exact Eq. (3.5) by only a few percent (Fig. 2). As expected, the maximum error occurs when \( \omega_Q \approx \omega_A \). The error is nearly independent of \( P_A \) and it increases with \( \tau_A \); for \( \eta = 0.5 \) (as in Fig. 2), the error increases (and levels off for \( Q \gg 1 \)) from 0.4% to 6% when \( \tau_A \) increases from 0.3 to 30 \( \mu s \). The error is largest for \( \eta = 0 \), reaching \( \sim 10\% \) for the parameter values of Fig. 2, and it vanishes for \( \eta = 1 \). The small difference between the integral rate \( \hat{R}_1 \) and the approximate rate \( R_1 \) implies that longitudinal relaxation in the EMOR model is very nearly exponential under all conditions. Any deviation from exponential relaxation is likely to escape experimental detection.

B. Dilute regime

Of particular experimental importance is the case where only a small fraction of the nuclei reside in state A, that is, when \( P_A \ll 1 \) and \( P_1 \approx 1 \). In this limiting case, which we refer to as the dilute regime,\(^{14} \) the integral relaxation rate in Eq. (3.5) reduces to

\[ R_1 = \frac{P_A}{\tau_A} \times \frac{1 - (10|\beta|10)}{1 - P_A(1 + P_1)[1 - (10|\beta|10)]}. \]  

(3.8)

where

\[ R_1 = \frac{P_A}{\tau_A} [1 - (10|\beta|10)]. \]  

(3.9)

As seen from Eq. (3.8), the quantity \( R_1 \) in Eq. (3.10) is the exponential approximation to the integral relaxation rate in the dilute regime.

Because \( R_1 \) in Eq. (3.10) depends linearly on the orientationally averaged quantity \( \beta \) in Eq. (3.3), we can regard the observed relaxation rate as an isotropic average of an orientation-dependent rate,

\[ R_1(\beta, \gamma) = \frac{P_A}{\tau_A} \left[ 1 - (10|\beta|10) \right] \frac{K(\beta, \gamma)}{\Delta(\beta, \gamma)}. \]  

(3.10)

The last form, derived in Appendix B of the supplementary material, involves two functions \( K \) and \( \Delta \) that are given explicitly in Appendix C of the supplementary material. The isotropic average in Eq. (3.11) can be restricted to one octant of the unit sphere because \( K \) and \( \Delta \) depend on \( \beta \) via powers of \( \cos^2 \beta \) and on \( \gamma \) via \( \cos (2\gamma) \) and \( \cos (4\gamma) \) (Appendix C of the supplementary material). In the exponential regime, where \( R_1 \) only involves the diagonal element \( (10|\beta|10) \), the dependence on the first Euler angle \( \alpha \) drops out. Therefore, when \( R_1 \) is computed from \( R_1 \) or (3.10), we can set \( \alpha = 0 \) in Eq. (3.28) and (trivially) integrate over \( \alpha \) in Eq. (3.3) before performing the numerical calculation.

In Fig. 3, we compare the integral relaxation rate computed in the dilute approximation Eq. (3.9) with the exact \( \hat{R}_1 \) in Eq. (3.5). For \( P_A = 10^{-2} \) and other parameter values as given in the figure caption, Eq. (3.9) underestimates \( \hat{R}_1 \) by 1.5% at low frequencies. The error depends only weakly on \( \tau_A \) (varying from 0.1% to 2% when \( \tau_A \) increases from 0.3 to 30 \( \mu s \)) and on \( \eta \) (1.2%–1.7%). In applications to crosslinked protein gels \( P_A \) is usually \( < 10^{-3} \), in which case Eq. (3.9) is highly accurate (error < 0.2%).

Within the dilute regime the error incurred by the exponential approximation, that is, Eq. (3.10) versus Eq. (3.9), is similar to the difference between Eqs. (3.8) and (3.5), as shown in Fig. 2.

FIG. 3. Dispersion of the integral relaxation rate \( \hat{R}_1 \) computed exactly (red solid curve) and in the dilute approximation (blue dots) for \( P_A = 10^{-2}, \tau_A = 3 \mu s, \omega_Q = 10^6 \text{ rad s}^{-1} \), and \( \eta = 0.5 \). The inset shows the relative error of the dilute approximation.
C. Analytical approximation

Both the integral relaxation rate $\hat{R}_1$ in Eq. (3.9) and the exponential approximation $R_1$ in Eq. (3.10) must be computed numerically. Even though the computational effort is modest, a closed-form analytical approximation is useful for preliminary data analysis and it also provides conceptual insight. Here, we derive an analytical result for the dilute regime which, like the numerical exponential approximation in Eq. (3.10), is exact in the low-field and motional-narrowing regimes, and, in addition, is a good approximation for $L \approx Q \gtrsim 1$.

In Appendix B of the supplementary material, we show that this approximate result can be expressed on the same form as in the motional-narrowing limit,

$$ R_1 = \frac{1}{3} P_A \sum_{m=-1}^{1} \Omega^2_{Q,m} \left(0.2J_{m1} + 0.8J_{m2}\right), \quad (3.13) $$

but with generalized spectral densities

$$ J_{mn} \equiv \frac{\tau_A}{1 + (\Omega_{Q,m}^2 \tau_A^2) + (n\omega_T \tau_A)^2}, \quad (3.14) $$

with the NQR frequencies $\Omega_{Q,m}$ defined in Eq. (2.5).

In Fig. 4, we compare the analytical $R_1$ expression in Eq. (3.13) with the integral relaxation rate $\hat{R}_1$ in Eq. (3.9), which is virtually exact at $P_A = 10^{-3}$ (Sec. III B). For the parameter values used in Fig. 4, Eq. (3.13) underestimates $\hat{R}_1$ by up to 17%. While Eq. (3.13) provides valuable insight and makes semi-quantitatively correct predictions, it should thus not be used for accurate analysis of experimental data. The error varies from $-1\%$ to $-22\%$ when $\tau_A$ increases from 0.3 to 30 $\mu$s. For $\tau_A = 3 \mu$s, the error varies from $-10\%$ to $-22\%$ when $\eta$ goes from 0 to 1. If Eq. (3.13) is compared with Eq. (3.10), rather than with Eq. (3.9), the discrepancy is somewhat larger since the exponential approximation overestimates $\hat{R}_1$ (Sec. III A).

D. Limiting forms

In the motional-narrowing limit, where $Q^2 \ll 1 + L^2$, Eq. (3.13) reduces to

$$ R_1 = \frac{2}{3} P_A \omega_T^2 \left(1 + \frac{\eta^2}{3}\right) \left[\frac{0.2\tau_A}{1 + (\omega_T \tau_A)^2} + \frac{0.8\tau_A}{1 + (2\omega_T \tau_A)^2}\right], \quad (3.15) $$

and in the low-field regime, where $L^2 \ll 1 + Q^2$, it reduces to

$$ R_1 = \frac{1}{3} P_A \omega_T \sum_{m=-1}^{1} \frac{\Omega^2_{Q,m}}{1 + (\Omega_{Q,m}^2 \tau_A)^2}. \quad (3.16) $$

Although Eq. (3.13) was obtained by invoking approximations (Appendix B of the supplementary material), its limiting forms in Eqs. (3.15) and (3.16) are exact in their respective regimes of validity. In the intersection of these two regimes, known as the extreme-motional-narrowing regime, Eqs. (3.15) and (3.16) both reduce to

$$ R_1 = \frac{2}{3} P_A \omega_T^2 \left(1 + \frac{\eta^2}{3}\right) \tau_A. \quad (3.17) $$

Figure 5 shows, for $Q \equiv \omega_T \tau_A = 3$, how the exact integral relaxation rate $\hat{R}_1$ approaches the low-field limiting form (3.16) for small $L \equiv \omega_T \tau_A$ and the motional-narrowing limiting form (3.15) for large $L$. The defining conditions $L^2 \ll 1 + Q^2$ and $Q^2 \ll 1 + L^2$ for these regimes are only rough (order of magnitude) guides since the dispersion profile involves three quadrupole frequencies, as seen from Eq. (3.13). For $\eta = 0.5$, as in Fig. 5, the largest NQR frequency exceeds the smallest one by a factor 3.5. If the respective regimes are defined by the requirement that the error is less than 1%, then, for the parameter values in Fig. 5, $L < 0.14$ in the low-field regime and $L > 14$ in the motional-narrowing regime.

To a good approximation, the dispersion is centered at $L \approx (1 + Q^2)/3$.
Within the motional-narrowing regime, where Eq. (3.15) applies, $R_1(\omega_L)$ exhibits the well-known maximum as a function of $\tau_A$ (or temperature) at $\tau_A = 0.61\omega_L$ (dashed curves in Fig. 6). Outside the motional-narrowing regime, the zero-frequency relaxation rate $R_1(0)$, given exactly by Eq. (3.16), exhibits a maximum at $\tau_A \approx 1/\omega_Q$ (solid curves in Fig. 6). This behavior is reminiscent of the transition from fast to slow exchange in a two-state exchange model with a sparsely populated high-relaxivity state. However, in the EMOR model the survival time is also the correlation time for the high-relaxivity state so “fast exchange” corresponds to the regime, where $\delta_{m, \pm 1}$ so that Eqs. (2.5), (3.13), and (3.14) yield

$$R_1 = \frac{2}{3} \rho A \omega_Q \left[ \frac{0.2}{1 + (\omega_L \tau_A)^2 + (\omega_L \tau_A)^2} \right] + \frac{0.8}{1 + (\omega_Q \tau_A)^2 + (2\omega_Q \tau_A)^2}. \quad (3.18)$$

This expression, which we have now derived under well-defined approximations (Appendix B of the supplementary material), was previously offered as a conjecture that interpolates between the low-field and motional-narrowing limits. The generalized spectral density function in Eq. (3.14) is still Lorentzian in $\omega_L$, as seen by rearranging it into

$$J_{mm} = \frac{1}{[1 + (\Omega_{Q,m} \tau_A)^2]^{1/2}} \times \frac{\tau_{A,m}}{1 + (\omega_L \tau_A)^2}. \quad (3.19)$$

with the apparent correlation time

$$\tau_{A,m} \equiv \frac{\tau_A}{[1 + (\Omega_{Q,m} \tau_A)^2]^{1/2}}. \quad (3.20)$$

Within the context of the EMOR model, the slow-motion regime is defined as $\Omega_{Q,m} \tau_A \gtrsim 1$. In the ultraslow-motion regime, where $\Omega_{Q,m} \tau_A \gg 1$, Eq. (3.20) shows that the apparent correlation time is simply the inverse NQR frequency, $\tau_A/m$. Hence, the dispersion profile $R_1(\omega_L)$ shifts to lower Larmor frequency, but only until the ultraslow-motion regime is reached, whereafter the profile remains fixed on the $\omega_Q$ axis but decreases in amplitude on further increase of $\tau_A$ (Fig. 6). In the ultraslow-motion regime, the dispersion profile has a characteristic temperature dependence: the amplitude grows with increasing temperature but the shape and position on the $\omega_Q$ axis are invariant. This follows since the NQR frequencies $\Omega_{Q,m}$ are essentially independent of temperature.

Like Eq. (3.13), from which it was derived, Eq. (3.21) is not exact when $\omega_Q \approx \omega_L$. But also the exact (for $P_A \ll 1$) Eq. (3.9) predicts that the dispersion “saturates” with increasing $\tau_A$ (Fig. 7). For $\omega_Q = 10^6$ rad s$^{-1}$, as in Fig. 7, the position and shape of the dispersion profile are essentially fixed by $\omega_Q$ and $\eta$ for $\tau_A > 10\mu$s.

Another feature predicted by Eq. (3.21) is a strong dependence of the dispersion profile on the EFG asymmetry parameter $\eta$. In general, the profile is a superposition of three dispersions with different apparent correlation times, but if $\eta$ is not small these correlation times are similar and the component dispersions cannot be resolved. However, if $\eta$ is close to 0, the NQR frequency $\Omega_{Q,0}$ is much smaller than $\Omega_{Q,-1} \approx \Omega_{Q,+1}$ (Fig. 1) and it then grows rise to a distinct low-frequency dispersion step. As seen in Fig. 8, this feature is also predicted by the exact (for $P_A \ll 1$) Eq. (3.9).

### E. Breakdown of the motional-narrowing approximation

In the motional-narrowing limit, $R_1$ for the dilute regime of the EMOR model is given by Eq. (3.15). Within the context of a two-state exchange model, Eq. (3.15) corresponds to the fast-exchange limit (with no relaxation in the abundant I state;
this restriction is removed in Sec. IV B). In the dilute regime, the multi-state exchange model yields a simple expression for $R_1$ valid over the whole range of exchange rates. For $N_A$ low-population sites, this well-known result takes the form:

$$R_1 = \frac{P_A}{N_A} \sum_{\alpha=1}^{N_A} \frac{1}{\tau_A + 1/R_1(\Omega_\alpha)} = \frac{P_A}{8\pi^2} \int \frac{d\Omega_\alpha}{\tau_A + 1/R_1(\Omega_\alpha)},$$

(3.22)

where we have taken the limit to a continuous isotropic distribution of site orientations $\Omega_\alpha$. In Eq. (3.22), $R_1(\Omega_\alpha)$ is the intrinsic relaxation rate in site $\alpha$ induced by the instantaneous randomization of the EFG orientation $\Omega_\alpha$ upon exchange. In the motional-narrowing limit, this intrinsic rate is given by:

$$R_1(\Omega_\alpha) = \frac{10}{3} \frac{\tau_A}{\omega_Q} \left[ 0.2A_1(\Omega_\alpha) \frac{\tau_A}{1 + \omega_Q \tau_A} + 0.8A_2(\Omega_\alpha) \frac{\tau_A}{1 + 2\omega_Q \tau_A} \right].$$

(3.23)

with the orientation-dependent coefficients:

$$A_0(\Omega_\alpha) = \frac{D_{\sigma 0}^2(\Omega_\alpha)}{\sqrt{6}} + \frac{\eta}{\sqrt{6}} \left[ D_{\sigma 2}^2(\Omega_\alpha) + D_{\pi 2}^2(\Omega_\alpha) \right]^2.$$

(3.24)

If Eq. (3.22) were correct, the more elaborate stochastic Liouville approach used here would not be needed to treat the EMOR model. But Eq. (3.22) is not correct. To appreciate this key point, it must be realized that the mean survival time $\tau_A$ plays a dual role in Eq. (3.22). The explicit dependence of $R_1$ on $\tau_A$ in Eq. (3.22) describes the transfer of longitudinal magnetization among the sites. But $\tau_A$ also enters Eq. (3.22) as the correlation time for the intrinsic relaxation rate $R_1(\Omega_\alpha)$. Because Eq. (3.23) assumes motional narrowing, the approach based on Eq. (3.23) is only valid if $Q^2 \ll 1 + L^2$. This condition is most restrictive at $\omega_Q = 0$, where it requires that $\tau_A \ll 1/\omega_Q$ or $\tau_A \ll 1/R_1(\Omega_\alpha)$. If this condition is not satisfied, a well-defined intrinsic relaxation rate does not exist and Eq. (3.22) cannot be applied. Conversely, under the motional-narrowing conditions where Eq. (3.23) is valid, Eq. (3.22) reduces to the fast-exchange limit, where $R_1 = P_A/R_1(\Omega_\alpha))$. Indeed, after isotropic averaging of $R_1(\Omega_\alpha)$ in Eq. (3.23), we then recover Eq. (3.16).

In contrast to Eq. (3.22), the stochastic Liouville equation (2.16) introduces site exchange (via the exchange superoperator $\mathcal{W}$) in a general way, without restrictions on the magnitude of the survival time $\tau_A$. In the dilute regime, the measured $R_1$ is not in the “slow-motion” regime; as seen from Figs. 3–6 and 8, $1/R_1$ is always much longer than $\tau_A$. The stochastic Liouville approach is needed because the intrinsic relaxation rate (which does not appear explicitly in our treatment) violates the motional-narrowing condition.

For experimental reasons (Sec. V), we are primarily interested in the dilute regime. However, the results in Secs. II D and III A are valid also outside this regime, even in the limit $P_A = 1$. Under such non-dilute conditions, also the directly observed longitudinal relaxation is in the “slow-motion” regime and the evolution function $|\mathcal{U}(t)|$ exhibits coherent features (quadrupolar “precession”) as well as relaxation. Nevertheless, the intrinsic relaxation rate is well-defined also under these conditions and it is rigorously given by the exact Eq. (3.5).

Although the approach based on Eq. (3.22) is non-rigorous and unfit for quantitative analysis of experimental MROD data (Sec. V C), it does make qualitatively correct predictions. To illustrate the quantitative shortcomings of this approach, we consider the zero-frequency relaxation rate $R_1(0)$ in the special case $\eta = 0$, where Eqs. (3.22)–(3.24) yield:

$$R_1 = \frac{P_A}{\tau_A} \left[ 1 - \frac{1}{2\kappa \sqrt{1 + \kappa^2}} \ln \frac{\sqrt{1 + \kappa^2} + \kappa}{\sqrt{1 + \kappa^2} - \kappa} \right].$$

(3.25)

where $\kappa \equiv \omega_Q \tau_A$. In the motional-narrowing regime, $\kappa \ll 1$, this result agrees with Eq. (3.17), as expected. However, in the opposite, ultraslow-motion regime, $\kappa \gg 1$, Eq. (3.25) yields $R_1 = P_A/\tau_A$, which is 50% larger than the exact result obtained from Eq. (3.16).

### IV. GENERALIZED EMOR MODEL

#### A. Partial averaging of quadrupole coupling

Restricted internal motion in A sites has the effect of partially averaging the quadrupole coupling before it is orientationally randomized (averaged to zero) by slower site exchange. If all A sites experience the same internal motion, this effect can be incorporated by reinterpreting the quadrupole frequency $\omega_Q$ and the asymmetry parameter $\eta$ as motionally averaged quantities, distinct from their rigid-lattice counterparts $\omega_Q^0$ and $\eta^0$. The relations between these quantities can be established by a transformation from the principal frame of the motionally average EFG tensor to the principal frame of the rigid-lattice EFG tensor. Let $(\phi, \theta, \psi)$ be the Euler angles that specify this coordinate frame rotation. The motional averaging of the quadrupole frequency is then described by the order parameter:

$$S \equiv \frac{\omega_Q}{\omega_Q^0} = 1 - \frac{3}{2} \sin^2 \theta + \frac{\eta}{2} \sin^2 \theta \cos 2\psi,$$

(4.1)

and the motionally averaged asymmetry parameter is...
If the internal flexibility varies from one site to another, then there will be a distribution of motionally averaged quadrupole frequencies \( \omega_{Q,n} = S_n \omega_Q^0 \) and asymmetry parameters \( \eta_n \) among the sites. Provided that \( S_n \) and \( \eta_n \) are not correlated with the orientation \( \Omega \) of the principal frame of the motionally averaged EFG tensor, the effect of heterogeneous flexibility can be fully described by averaging the superoperator \( \mathcal{B} \) in Eq. (3.3) not only over the orientational distribution \( f(\Omega) \) but also over the distribution \( f(S, \eta) \). If \( \mathcal{B} \) depends linearly on \( \mathcal{B} \), as in the exponential approximation for the dilute regime, we can average \( \mathcal{B} \) directly, in analogy with Eq. (3.11), as

\[
\mathcal{R}_1 = \int dS \int d\eta \ f(S, \eta) \mathcal{R}_1(S, \eta), \tag{4.3}
\]

where \( \mathcal{R}_1(S, \eta) \) is the relaxation rate computed from Eq. (3.10) or (3.13) with \( \omega_Q = S \omega_Q^0 \) and \( \eta \).

**B. Relaxation by internal motions**

Restricted rotational motions in \( \mathcal{A} \) sites are usually much faster than site exchange, that is, the internal-motion correlation time is much shorter than \( \tau_\mathcal{A} \). (This was assumed to be the case also in Sec. IV A.) Furthermore, the internal motions in both \( \mathcal{A} \) and \( \mathcal{I} \) states are usually much faster than the quadrupole frequency \( \omega_Q \) so that the motional-narrowing regime applies. Under these conditions, internal motions can be incorporated in the EMOR model as described in Appendix D of the supplementary material. The effect of internal motions is essentially simple in the exponential approximation for the dilute regime, in which case (see Appendix D of the supplementary material)

\[
\mathcal{R}_1 = P_A R_{1,1}^\text{int} + R_{1,\text{EMOR}} \left( 1 + \rho \right). \tag{4.4}
\]

Here, \( R_{1,1} \) and \( R_{1,1}^\text{int} \) are the direct relaxation contributions from internal motions in states \( \mathcal{I} \) and \( \mathcal{A} \), respectively. Furthermore, \( \rho \equiv R_{1,1}^\text{int} / \tau_\mathcal{A} \) and \( R_{1,\text{EMOR}} \) is given by Eq. (3.10), but with \( Q \) and \( L \) replaced by \( \tilde{Q} \equiv Q/(1 + \rho) \) and \( \tilde{L} \equiv L/(1 + \rho) \), respectively. To obtain Eq. (4.4), we have assumed that the internal motion is the same in all \( \mathcal{A} \) sites and that site exchange is fast compared to any orientation-dependent variation in \( R_{1,\mathcal{A}}^\text{int} \). In Eq. (4.4), \( R_{1,\mathcal{A}}^\text{int} \) thus refers to the orientationally averaged quantity. Typically, \( \rho \ll 1 \) so that Eq. (4.4) reduces to

\[
\mathcal{R}_1 = P_A R_{1,1} + R_{1,\text{EMOR}}. \tag{4.5}
\]

**C. Kinetic heterogeneity**

The basic EMOR model features a single anisotropic state \( \mathcal{A} \), where all sites have the same mean survival time \( \tau_\mathcal{A} \). We now consider the more general case with \( n_A \) anisotropic states, labelled \( \nu = 1, 2, \ldots, n_A \). All \( n_A \) sites belonging to a given state have the same mean survival time \( \tau_\nu \) and \( N_\nu \) is still large enough that we can regard \( \Omega \) as a continuous variable. The total number of anisotropic sites is \( N_A = \sum_\nu N_\nu \), as before. The fraction of all \( \mathcal{A} \) sites that belong to state \( \nu \) is \( x_\nu = N_\nu/N_A \) and the equilibrium population of that state is \( P_\nu = x_\nu P_A \). This extended EMOR model contains \( 2n_A \) independent parameters, which may be chosen as the \( n_A \) survival times \( \tau_\nu \), the \( n_A - 1 \) independent fractions \( x_\nu \) and \( P_A \). The remaining (dependent) parameters follow from the normalization conditions \( P_A + P_1 = 1 \) and \( \sum_\nu x_\nu = 1 \) and from the equilibrium condition

\[
\frac{P_1}{\tau_1} = P_A \sum_{\nu = 1}^{n_A} \frac{x_\nu}{\tau_\nu}, \tag{4.6}
\]

which follows from Eq. (2.14) and generalizes Eq. (2.15).

The treatment of this generalized EMOR model is described in Appendix E of the supplementary material, where we derive explicit results for the dilute regime. The generalization of the integral relaxation rate in Eq. (3.9) is

\[
\mathcal{R}_1 = \left( \frac{P_A}{10(\sum_\nu (x_\nu/\tau_\nu)(1 - B_\nu))^{-1}[10]} \right) \mathcal{R}_1^\text{int}, \tag{4.7}
\]

where \( B_\nu \) is given by Eqs. (3.3) and (3.4) with \( \tau_\nu \) replaced by \( \tau_\mathcal{A} \). In the exponential approximation, this result simplifies to

\[
\mathcal{R}_{1,\nu} = \frac{P_A}{\tau_\nu} \left[ 1 - \left( 10|B_\nu|10 \right) \right]. \tag{4.8}
\]

Thus, \( \mathcal{R}_{1,\nu} \) is calculated in the same way as \( \mathcal{R}_1 \) in the kinetically homogeneous case, either from Eqs. (3.3), (3.4), and (3.10) or from Eqs. (3.13) and (3.14), but with \( \tau_\mathcal{A} \) replaced by \( \tau_\nu \) everywhere. Since the exponential approximation is usually highly accurate (Sec. III A), also the integral relaxation rate may be calculated as a population-weighted average, as in Eq. (4.8), with \( \mathcal{R}_{1,\nu} \) obtained from Eq. (3.9) after replacing \( \tau_\mathcal{A} \) by \( \tau_\nu \).

The structural and energetic origins of kinetic heterogeneity will in general also give rise to heterogeneity in internal motions and in the partial averaging of the quadrupole coupling. All the three generalizations considered in Sec. IV must then be applied together. In the typical case, with internal motions in the fast-exchange regime, we can combine Eqs. (4.3), (4.5), and (4.8) to obtain

\[
\mathcal{R}_1 = P_1 R_{1,1} + P_A \sum_{\nu = 1}^{n_A} x_\nu R_{1,\nu}^\text{int} + \sum_{\nu = 1}^{n_A} x_\nu R_{1,\nu}(S_\nu, \eta_\nu), \tag{4.10}
\]

with \( R_{1,\nu}(S_\nu, \eta_\nu) \) obtained from Eq. (4.9) with the appropriate order parameter \( S_\nu \) and asymmetry parameter \( \eta_\nu \).
V. WATER IN IMMOBILIZED PROTEINS

A. Internal-water exchange from crosslinked proteins

As an application of the spin-1 EMOR model, we consider here a gel made by chemically crosslinking the protein molecules in an aqueous solution.\(^6\) The protein molecules are thus immobilized, being prevented from tumbling by multiple crosslinks to adjacent protein molecules. Each protein molecule contains \(n_A\) internal sites where water molecules reside with occupancy \(\xi_v\) and mean survival time \(\tau_v\). The total internal water occupancy is

\[
\xi_A \equiv \sum_{v=1}^{n_A} \xi_v.
\]  

(5.1)

Then

\[
x_v = \frac{\xi_v}{\xi_A},
\]  

(5.2)

and

\[
P_A = \frac{\xi_A}{N_W},
\]  

(5.3)

where \(N_W\) is the water/protein mole ratio in the gel. If all sites are fully occupied, \(\xi_v = 1\) and \(\xi_A = n_A\). Typically, \(P_A = 10^{-5} - 10^{-3}\). In a macroscopic gel sample, each internal water site is present in a very large number of protein molecules with different orientations sampled from an isotropic distribution as in Eq. (2.27).

We consider the longitudinal relaxation rate \(R_1\) of the water \(^2\)H magnetization measured on a gel sample prepared with \(\text{D}_2\text{O}\). Water molecules interacting with the protein surface have sub-nanosecond correlation times\(^31\) and, together with the unperturbed water molecules further away from the protein surface, constitute the isotropic (I) state in the EMOR model, with relaxation rate \(R_1^I\). The relaxation dispersion is produced by the internal water molecules, which randomize their orientation when they escape from their internal cavities and emerge into the bulk water region where water rotation occurs on a picosecond time scale, very much shorter than the typical survival time of \(10^{-3} - 10^{-5}\) s in an internal site.\(^9\)

The rigid-lattice quadrupole parameters for \(\text{D}_2\text{O}\) ice are \(\omega_Q^0 = 1.06 \times 10^6\) s\(^{-1}\) and \(\eta^0 = 0.11\).\(^{32}\) If the order parameter \(S\) is close to 1, so that \(\omega_Q \approx \omega_Q^0\), an internal water molecule produces a maximum EMOR contribution for a survival time \(\tau_v \approx 1/\omega_Q \approx 1\) \(\mu s\) (Fig. 6). For survival times \(\tau_v \gg 1/\omega_Q \approx 1\) \(\mu s\), the maximum EMOR contribution to \(R_1^I\) is \(P_A/\tau_v\), which may be negligible compared to the internal-motion contribution to \(R_1\) (the first two terms in Eq. (4.10)). Most labile protein deuterons (O–D or N–D) have survival times \(> 100\) \(\mu s\) near neutral pH and therefore do not make significant EMOR contributions.\(^{33}\) Carboxyl deuterons (COOD) can have somewhat shorter survival times and may therefore produce a small EMOR contribution.\(^9\)

B. Internal water motions

Most internal water molecules make 3 or 4 strong hydrogen bonds with the protein. The dominant internal motions are then fast librations that do not contribute significantly to the observed \(R_1\). However, less strongly interacting internal water molecules may undergo slower internal motions of larger amplitude. Of particular interest is the C2 flip, where the water molecule flips \(180^\circ\) about the molecular symmetry (C2) axis.

Assuming, as in Sec. IV B, that the C2 flip is fast compared to site exchange and compared to \(\omega_Q^0\) and that site exchange is fast compared to the orientation-dependent variation in the flip-induced relaxation rate, we show in Appendix F of the supplementary material that the orientationally averaged relaxation rate is

\[
R_{1,A}^{\text{flip}} = \frac{\omega_Q^0}{2} \left( 1 - \eta^0 \right) \sin \theta_{\text{DOD}} \left[ \frac{0.2 \tau_{\text{flip}}}{1 + (\omega_Q \tau_{\text{flip}}/2)^2 + 0.8 \tau_{\text{flip}}^2} \right],
\]  

(5.4)

where \(\theta_{\text{DOD}}\) is the DOD angle in the water molecule and \(\tau_{\text{flip}}\) is the mean lifetime of a flip state (so the flip rate is \(2/\tau_{\text{flip}}\)). As expected, Eq. (5.4) shows that C2 flips do not induce relaxation if \(\theta_{\text{DOD}} = 0\) (no physical motion) or if \(\theta_{\text{DOD}} = 180^\circ\) (since the EFG tensor is invariant under inversion).

For a rigid-lattice asymmetry parameter\(^{32}\) \(\eta^0 = 0.11\) and a DOD angle\(^{34}\) \(\theta_{\text{DOD}} = 106 \pm 5^\circ\), Eq. (5.4) yields \(R_{1,A}^{\text{flip}}(0) = 0.214(\omega_Q^0)^2 \tau_{\text{flip}}\). With \(\omega_Q^0 \approx 10^6\) s\(^{-1}\) and \(\tau_{\text{flip}} \ll 1\) \(\mu s\) (as assumed above), we then have \(R_{1,A}^{\text{flip}}(0) \ll 2 \times 10^5\) s\(^{-1}\). Water C2 flips may thus contribute significantly to the observed \(R_1\) in Eq. (4.5) if \(P_A \gtrsim 10^{-5}\).

In addition to their direct contribution to \(R_1\), water C2 flips can significantly affect the EMOR contribution via the order parameter \(S\) and asymmetry parameter \(\eta\). If the C2 flip is the only internal motion, we obtain from Eqs. (4.1) and (4.2)

\[
S = -\frac{(1 + \eta^0)}{2},
\]  

(5.5)

\[
\eta = -\cos \theta_{\text{DOD}} \left( \frac{3 - \eta^0}{1 + \eta^0} \right).
\]  

(5.6)

For \(\eta^0 = 0.11\), we thus have \(S^2 = 0.31\) and, with \(\theta_{\text{DOD}} = 106 \pm 5^\circ\), \(\eta = 0.7 \pm 0.2\).

Under the conditions stipulated above Eq. (5.4), the direct contribution to \(R_1\) from any internal motion can be calculated from Eqs. (F.1)—(F.3). A ubiquitous internal motion is the fast libration of the O–D bond around its preferred orientation (typically dictated by a hydrogen-bond acceptor). Librational motions are generally too fast to make a significant direct contribution and their effect on the EMOR contribution via \(S\) and \(\eta\) is described by Eqs. (4.1) and (4.2). If the motion is axially symmetric (so that the Euler angle \(\phi\) is uniformly distributed), then Eq. (4.2) shows that \(\eta = 0\).

When the EMOR model is applied to internal water molecules in crosslinked proteins, there are two kinds of internal motion: (i) motion of the internal water molecule relative to the protein, and (ii) motion of the protein relative to a lab-fixed frame. The second type of internal motion is present because the protein molecules are never completely immobilized by crosslinking. The limited protein reorientation that is possible in a gel network may be modeled as a restricted rotational diffusion process in a local potential of mean torque determined by the number of crosslinks, their
positions and their flexibility. We shall not attempt to model this complex motion, but we simply note that it is expected to occur on a nanosecond time scale and will then not interfere with the relaxation dispersion produced by the slower internal-water exchange.\(^3\) To analyze the EMOR contribution, we then only need to recognize that restricted protein rotation affects \(S\) and \(\eta\) according to Eqs. (4.1) and (4.2). In general, this effect will be different for each internal water site and even for the two deuteron of a given internal water molecule (unless it undergoes fast C\(_2\) flips). As an example, consider a protein molecule that can rotate freely about a crosslink but only in a restricted angular range \(-\phi_0 \leq \phi \leq \phi_0\). For this axial sector model, further discussed in Appendix G of the supplementary material, Fig. 9 shows how \(S\) and \(\eta\) depend on the angle \(\theta_0\) between the O–D bond and the rotation axis (the crosslink). For simplicity, we have set \(\phi_0 = 0\) here. Then, as expected, rotation about the O–D bond (\(\theta_0 = 0\)) has no effect. In contrast, rotation about an axis roughly orthogonal to the O–D bond can increase the asymmetry parameter considerably. Therefore, unless it can be established that the protein is completely immobilized, the parameters \(S\) and \(\eta\) cannot be attributed to water motion within the protein.

**C. Performance test**

To illustrate how the EMOR model is used to analyze MRD data and to examine the effect of different approximations on the accuracy of the fitted model parameters, we use a synthetic data set comprising 50 \(R_1\) values in the range 1 kHz–10 MHz computed with the aid of the EMOR model and including 1% random noise. In addition to a dominant isotropic site, the model comprises two classes of anisotropic sites (internal water molecules). The first of these has a mean survival time \((\tau_1 = 100\) ns) in the motional-narrowing regime. The second class contains 3 internal water molecules \((\xi_2 = 3)\) with a mean survival time \((\tau_2 = 4\) \(\mu\)s) in the slow-motion regime. The additional two parameters for the slow site are given in Table I. The second parameter for the fast site is the composite quantity \(\xi_1S_{1,iso}^2 = 1\), where the “isotropic” order parameter is defined as \(S_{iso} = S(1 + \eta/3)^{1/2}\).

With \(N_W = 10000\) water molecules per protein molecule, we have \(P_A = 4 \times 10^{-4} \ll 1\). We are thus in the dilute regime and \(R_1\) is obtained virtually exactly from Eqs. (3.9), (3.15), and (4.5) as

\[
R_1 = R_{1,1} + \frac{2}{3} \xi_2 \xi_1 S_{1,iso}^2 \frac{N_W}{\nu} \left[ \frac{0.2 \tau_1}{1 + (\omega L \tau_1)^2} + \frac{0.8 \tau_1}{1 + (2\omega L \tau_1)^2} \right] + \frac{\xi_2}{N_W \tau_2} \left(10 \mu(1 - B)^{-1})^{10}\right),
\]

with \(B = B(\omega L, \omega L; \xi_2, \tau_2, \tau_2)\) given by Eq. (3.3). The isotropic site includes bulk water, with relaxation rate \(R_{bulk} = 2.34 s^{-1}\) (for D\(_2\)O at 298 K), as well as dynamically perturbed water molecules interacting with the protein surface. We therefore express the first term in Eq. (5.7) as \(R_{1,1} = R_{bulk}(1 + \nu_{dyn}/N_W)\), where the fitted parameter is the so-called dynamic hydration number \(\nu_{dyn}\), determined by the number of water molecules in the hydration layer and their dynamic perturbation factor (the relative slowing-down of hydration water rotation).\(^16\) Finally, the rigid-lattice \(^2\)H quadrupole frequency in D\(_2\)O is \(\omega L = 8.7 \times 10^8\) rad s\(^{-1}\).\(^16\)

In Table I, the first row contains the parameter values used in Eq. (5.7) to compute the data in Fig. 10, while the following rows show the parameter values resulting from nonlinear least-squares fits to these data using different target functions. The fits employed a trust-region-reflective algorithm with all parameters constrained to their physically admissible ranges (0 – 1 for \(S\) and \(\eta\), \(\geq 0\) for all other parameters). Fitting the exact dilute-regime version of the EMOR model (based on Eq. (3.9)), which was also used to generate the data, yields parameter values within one standard deviation of the true values. The relatively large standard deviations (and covariance) for \(\xi_2\) and \(\tau_2\) reflect the fact that we are approaching the ultraslow-motion limit, where \(R_1\) only depends on the ratio of these parameters (see Eq. (3.21)).

<table>
<thead>
<tr>
<th>Table I. Results of EMOR model fits to synthetic MRD data with 1% random error.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit model</td>
</tr>
<tr>
<td>Input(^b)</td>
</tr>
<tr>
<td>Eq. (3.9)(^c)</td>
</tr>
<tr>
<td>Eq. (3.10)(^c)</td>
</tr>
<tr>
<td>Eq. (3.13)(^c)</td>
</tr>
<tr>
<td>Eq. (3.22)(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Parameter uncertainty (1 standard deviation) in last digit(s) within parentheses.

\(^b\)Parameter values used to generate synthetic data using Eq. (3.9).

\(^c\)Equation used for the slow EMOR contribution.
If the last term in Eq. (5.7) is evaluated in the exponential approximation, Eq. (3.10), we find that the parameters are systematically shifted from the true values (by more than one standard deviation for $S_2$). Using the analytical approximation, Eq. (3.13), most parameters differ even more from the true values and the uncertainty in $\xi_2$ and $\tau_2$ increases. Finally, the motional-narrowing approximation, Eq. (3.22), cannot determine $S_2$ or $\eta_2$ and the values obtained for $\xi_2$ and $\tau_2$ are nearly a factor 2 too small (with a large uncertainty for $\tau_2$).

The fit results in Table I reflect the combined effect of random measurement error and a target function that deviates from the true function. To isolate the latter, systematic effect, we also performed fits to error-free data generated by Eq. (5.7). The results of these fits are collected in Table II. As expected, all model versions yield values close to the true ones for the first 3 parameters. However, the 4 parameters describing the slow-motion site are systematically misestimated by the approximate model versions. Based on these and similar results for other data sets, we recommend using the exact version of the EMOR theory for quantitative analysis of MRD data with $R_1$ accuracy of $\sim 1\%$ (as is typical for field-cycling measurements) or better.

VI. CONCLUSIONS

In the foregoing, we have presented a comprehensive and general theoretical account of longitudinal relaxation in the laboratory frame, induced by EMOR of the residual anisotropic electric quadrupole coupling of a spin-1 nucleus. The model considered here, featuring an isotropic state (without residual quadrupole coupling) and an isotropic distribution of anisotropic sites, is sufficiently realistic to be directly applicable for quantitative analysis of MRD data acquired by field-cycling experiments on a variety of complex molecular systems. Notably, the EMOR model quantitatively describes water (D$_2$O) $^2$H relaxation by exchange of internal water molecules and/or labile macromolecular deuterons in aqueous gel-like systems of chemically cross-linked or otherwise immobilized proteins or other macromolecules.

In general, the longitudinal magnetization in the EMOR model approaches equilibrium in a complicated non-exponential manner. Nevertheless, the integral relaxation rate, which can be measured, is given exactly by Eq. (3.5) under all conditions and it can therefore be used to determine the model parameters. In the experimentally important dilute regime ($P_A \ll 1$), the decay of the longitudinal magnetization is single-exponential to within experimental accuracy. The integral relaxation rate, which can be calculated exactly in a relatively simple way, can then be compared directly with the longitudinal relaxation rate obtained from an exponential fit to the experimental magnetization decay.

Although the general theoretical framework of the EMOR model was described in 1996,$^{14}$ the present work provides the first rigorous derivation of the explicit expressions required for quantitative analysis of spin-1 MRD profiles. The most important new results are as follows:

1. An exact expression, Eq. (3.5), for the integral longitudinal relaxation rate, valid without restrictions on the model parameters $\omega_L$, $\omega_Q$, $\tau_A$, $\eta$, and $P_A$.
2. A corresponding exact expression, Eq. (3.9), for the integral longitudinal relaxation rate in the experimentally important dilute regime ($P_A \ll 1$).
3. A simple analytical expression, Eqs. (3.13) and (3.14), for $R_1$ in the dilute regime, which, although approximate, offers conceptual insights, such as an understanding of the “saturation” behavior of the MRD profile in the ultraslow-motion regime, Eq. (3.21).
4. Further generalizations of the EMOR model, apart from allowing the EFG tensor to be biaxial ($\eta \neq 1$), incorporating the direct and indirect effects of internal motions (with specific treatment of water $180^\circ$ flips) and kinetic heterogeneity.
5. A description of how the EMOR model is applied to analyze water $^2$H MRD data from immobilized proteins, including an assessment of the effect of approximations in the theory on the extracted model parameters.

### Table II. Results of EMOR model fits to exact synthetic MRD data.

<table>
<thead>
<tr>
<th>Fit model</th>
<th>$10^{-4} \times \nu_{dyn}$</th>
<th>$\xi_1^2$</th>
<th>$\tau_1$ (ns)</th>
<th>$\xi_2$</th>
<th>$S_2$</th>
<th>$\eta_2$</th>
<th>$\tau_2$ (µs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input$^a$</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>3</td>
<td>0.8</td>
<td>0.2</td>
<td>4</td>
</tr>
<tr>
<td>Eq. (3.10)$^b$</td>
<td>1.003</td>
<td>1.010</td>
<td>103</td>
<td>2.2</td>
<td>0.729</td>
<td>0.43</td>
<td>2.8</td>
</tr>
<tr>
<td>Eq. (3.13)$^b$</td>
<td>0.991</td>
<td>0.976</td>
<td>92</td>
<td>3.9</td>
<td>0.904</td>
<td>0.11</td>
<td>5.2</td>
</tr>
<tr>
<td>Eq. (3.22)$^b$</td>
<td>1.002</td>
<td>0.992</td>
<td>100</td>
<td>1.6</td>
<td>0.741</td>
<td>1.00</td>
<td>2.3</td>
</tr>
</tbody>
</table>

$^a$Parameter values used to generate synthetic data using Eq. (3.9).

$^b$Equation used for the slow EMOR contribution.
This work was financially supported by the Swedish Research Council.


See supplementary material at http://dx.doi.org/10.1063/1.4739297 for further details on the formal solution of the EMOR model (Appendix A); the approximate analytical solution for the dilute regime (Appendix B); the determinant and minors of the \( M \) matrix (Appendix C); incorporation of internal motions in the EMOR model (Appendix D); incorporation of kinetic heterogeneity in the EMOR model (Appendix E); relaxation by water 180° flips (Appendix F); and motional averaging in the axial sector model (Appendix G).

18. See supplementary material at http://dx.doi.org/10.1063/1.4739297 for further details on the formal solution of the EMOR model (Appendix A); the approximate analytical solution for the dilute regime (Appendix B); the determinant and minors of the \( M \) matrix (Appendix C); incorporation of internal motions in the EMOR model (Appendix D); incorporation of kinetic heterogeneity in the EMOR model (Appendix E); relaxation by water 180° flips (Appendix F); and motional averaging in the axial sector model (Appendix G).
Supporting Material

Nuclear magnetic relaxation induced by exchange-mediated orientational randomization.

Longitudinal relaxation dispersion for spin $I = 1$.

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APPENDIX A: FORMAL SOLUTION

To obtain an exact formal expression for $\langle \tilde{U}(s) \rangle$, we start by using Eq. (2.8) to rewrite the resolvent superoperator in Eq. (2.23) as

$$\tilde{U}(s) = \tilde{U}_0(s + \mathcal{K}) + \tilde{U}_0(s + \mathcal{K}) T \tilde{U}(s),$$  \hspace{1cm} (A.1)

where

$$\tilde{U}_0(s) \equiv (s + i \mathcal{L})^{-1}. \hspace{1cm} (A.2)$$

Substituting $\tilde{U}(s)$ from Eq. (A.1) in the matrix element of Eq. (2.26) and noting that, by virtue of Eqs. (2.10) and (2.17), $\tilde{U}_0(s + \mathcal{K})$ is diagonal in the site basis, we obtain

$$\tilde{U}_\alpha(s) = \langle \alpha | \tilde{U}_0(s + \mathcal{K}) | \alpha \rangle \left[ P_\alpha + \sum_{\beta=0}^{N_A} \langle \alpha | T | \beta \rangle \tilde{U}_\beta(s) \right]. \hspace{1cm} (A.3)$$

We now rewrite Eq. (2.25) as

$$\langle \tilde{U}(s) \rangle = \tilde{U}_A(s) + \tilde{U}_I(s), \hspace{1cm} (A.4)$$

where

$$\tilde{U}_A(s) = \sum_{\alpha=1}^{N_A} \tilde{U}_\alpha(s). \hspace{1cm} (A.5)$$

Summing Eq. (A.3) over the A sites and making use of Eq. (2.9), we find

$$\tilde{U}_A(s) = \tau_A \mathcal{B}_A(s) \left[ P_A + \frac{1}{\tau_1} \tilde{U}_I(s) \right], \hspace{1cm} (A.6)$$
where we have defined the superoperators

$$B_A(s) \equiv \frac{1}{N_A \tau_A} \sum_{\alpha=1}^{N_A} \langle \alpha | \tilde{U}_0(s + K) | \alpha \rangle = \frac{1}{8 \pi^2} \int d\Omega [M(s, \Omega)]^{-1} , \quad (A.7)$$

and

$$M(s, \Omega) \equiv 1 + s \tau_A + i \mathcal{L}_Z \tau_A + i \mathcal{L}_Q(\Omega) \tau_A . \quad (A.8)$$

To obtain these results, we have also used Eqs. (2.1b), (2.10), (2.17), (2.27) and (A.2). In a similar way, we obtain

$$\tilde{U}_I(s) = \tau_I B_I(s) \left[ P_I + \frac{1}{\tau_A} \tilde{U}_A(s) \right] , \quad (A.9)$$

where

$$B_I(s) \equiv \frac{1}{\tau_I} \langle 0 | \tilde{U}_0(s + K) | 0 \rangle = (1 + s \tau_I + i \mathcal{L}_Z \tau_I)^{-1} . \quad (A.10)$$

Combining Eqs. (A.6) and (A.9), we obtain

$$\tilde{U}_A(s) = \tau_A \left[ 1 - B_A(s) B_I(s) \right]^{-1} B_A(s) \left[ P_A + P_I B_I(s) \right] , \quad (A.11a)$$

$$\tilde{U}_I(s) = \tau_I \left[ 1 - B_I(s) B_A(s) \right]^{-1} B_I(s) \left[ P_I + P_A B_A(s) \right] . \quad (A.11b)$$

Because of the isotropic site distribution, $B_A$ is block-diagonal ($q = q'$) in the multipole basis (cf. Eq. (2.28)), while $B_I$ is diagonal with $q$-blocks proportional to the identity matrix. Consequently, the superoperators $B_I$ and $B_A$ commute. Using this property and Eq. (2.15) and combining Eqs. (A.4), (A.10) and (A.11), we obtain the exact result in Eq. (2.31).
APPENDIX B: ANALYTICAL APPROXIMATION

By using Eq. (3.3) and the superoperator identity $1 - \mathcal{M}^{-1} = (\mathcal{M} - 1) \mathcal{M}^{-1}$, we can express Eq. (3.10) as

$$R_1 = \frac{P_A}{\tau_A} \sum_{k=1}^{2} \sum_{q=-k}^{k} \left\langle (10| (\mathcal{M} - 1)| kq) (kq | \mathcal{M}^{-1} | 10) \right\rangle,$$  \hspace{1cm} (B.1)

where the angular brackets indicate the isotropic average in Eq. (3.3).

From the structure of the $\mathbf{M}$ supermatrix in Eq. (2.40) it is clear that only the 4 terms with $k = 2$ and $q = \pm 1$, $\pm 2$ contribute to the sum in Eq. (B.1). Noting that

$$(2q | \mathcal{M}^{-1} | 10) = (-1)^q (2 - q | \mathcal{M}^{-1} | 10)^*$$

and that

$$(2 - q | \mathcal{M}^{-1} | 10) = -(10 | \Delta | 2 - q)/\Delta,$$

where $\Delta = \det \mathbf{M}$ is the real-valued determinant of $\mathbf{M}$ and the minor $(10 | \Delta | 2 - q)$ is the determinant of the matrix obtained be deleting row $(10 | \Delta)$ and column $(2 - q)$ from $\mathbf{M}$, we can cast Eq. (B.1) in the form

$$R_1 = P_A \omega_Q^2 \tau_A \left\langle \frac{K}{\Delta} \right\rangle,$$  \hspace{1cm} (B.2)

where we have extracted a factor $Q^2$ and defined the real-valued quantity

$$K \equiv -\frac{2}{Q^2} \text{Re} \left[ a (10 | \Delta | 2 - 1) + \sqrt{2} b (10 | \Delta | 2 - 2) \right],$$  \hspace{1cm} (B.3)

with $a$ and $b$ given by Eq. (2.39). As shown in Appendix C, the quantities $\Delta$ and $K$ are polynomials in $L^n Q^m$ with $n, m = 0, 2, 4$ or 6 and with coefficients that depend on the angles $\beta$ and $\gamma$, but not on $\alpha$. Substituting these expressions into Eq. 4
(B.2) and integrating over the angles, we reproduce the result obtained more directly from Eq. (3.10) by numerical inversion of the $M$ matrix in Eq. (2.40) followed by numerical integration over the Euler angles. At least for $\eta = 0$, Eq. (B.2) actually yields a closed-form analytical result, but it is lengthy and does not provide any insight.

Our aim here is not the exact evaluation of $R_1$. Rather, we seek an analytical expression for $R_1$ that reduces to the known exact results in the low-field and motional-narrowing regimes and that is sufficiently accurate to be quantitatively useful for any values of $L$ and $Q$. To reproduce those limits exactly, we must retain all pure terms in $\Delta$ and $K$, that is, terms containing $L^n$ and $Q^m$. Because these two regimes encompass the entire $L-Q$ plane except for a diagonal band where $L \approx Q \gtrsim 1$, mixed terms containing $L^nQ^m$ with $n, m \geq 2$, which vanish in the two limits, should be relatively unimportant also when $L \approx Q \gtrsim 1$. We therefore derive the approximate expression for $R_1$ by discarding all such mixed terms in the full expressions for $\Delta$ and $K$ given in Appendix C. These truncated expressions are then rearranged (without further approximations) into forms that directly reduce to the known results in the low-field and motional-narrowing limits.

The truncated determinant is expressed as

$$\Delta(L, Q) = \Delta_L(L) + \Delta_Q(Q) - 1,$$

(B.4)
where $\Delta_Q(Q) = 1$ in the motional-narrowing regime and $\Delta_L(L) = 1$ in the low-field regime. These parts are given by

$$\Delta_L(L) = (1 + L^2)^2 (1 + 4 L^2), \quad \text{(B.5)}$$

$$\Delta_Q(Q) = (1 + c_1^2 Q^2) (1 + c_0^2 Q^2) (1 + c_1^2 Q^2), \quad \text{(B.6)}$$

with the coefficients $c_m$ as in Eq. (2.6). Since $\Delta(L, Q)$ does not depend on the Euler angles, we only need to average $K$ in Eq. (B.2).

The truncated $K$ polynomial depends on the angles $\beta$ and $\gamma$ (see Appendix C). Integrating over these angles, we obtain after some algebra

$$\langle K \rangle = \frac{\Delta}{15} \sum_{m=-1}^{1} c_m^2 (j_{1m} + 4j_{2m}), \quad \text{(B.7)}$$

with

$$j_{nm} \equiv \frac{1}{\Delta} \left[ \frac{\Delta_L}{1 + n^2 L^2} + \frac{\Delta_Q}{1 + c_m^2 Q^2} - 1 \right]. \quad \text{(B.8)}$$

This expression can be rearranged into

$$j_{nm} = \frac{1}{1 + \Gamma_{nm}}, \quad \text{(B.9)}$$

with

$$\Gamma_{nm} = n^2 L^2 + c_m^2 Q^2 + \mathcal{O}(L^2 Q^2). \quad \text{(B.10)}$$

To be consistent with the preceding treatment, we discard the last mixed term, of order $L^2 Q^2$. Finally, combining Eqs. (B.2), (B.7), (B.9) and (B.10), we obtain the desired analytical expression for $R_1$ given in Eqs. (3.13) and (3.14).
APPENDIX C: DETERMINANT OF M MATRIX

Here we present explicit expressions for the determinant, $\Delta = \det M$, of the matrix in Eq. (2.40) and for the quantity $K$ obtained from the minors of this matrix according to Eq. (B.3). We decompose these quantities as

$$\Delta(\beta, \gamma) = \Delta_0(\beta) + \Delta_{10}(\beta) + \Delta_{12}(\beta) \cos(2\gamma) + \Delta_{14}(\beta) \cos(4\gamma), \quad (C.1a)$$

$$K(\beta, \gamma) = K_0(\beta) + K_{10}(\beta) + K_{12}(\beta) \cos(2\gamma) + K_{14}(\beta) \cos(4\gamma). \quad (C.1b)$$

In the special case $\eta = 0$, only the first term in each expression survives. These are

$$\Delta_0(\beta) = (1 + L^2)^2 (1 + 4L^2) + (1 + Q^2)^2 - 1 \quad \text{ (C.2)}$$

and

$$K_0(\beta) = [(1 + L^2)^2 + Q^2] \sin^2 \beta + L^2 [3(1 + L^2) + 4Q^2] \cos^2 \beta \sin^2 \beta. \quad \text{ (C.3)}$$

Furthermore,

$$\Delta_{10}(\beta) = \frac{2}{3} \eta^2 Q^2 \left[ 1 + 3L^2 - \frac{1}{4} L^4 + \left(1 + \frac{\eta^2}{6}\right) Q^2 + \frac{2}{3} \left(1 - \frac{\eta^2}{9}\right)^2 Q^4 \right]$$

$$+ \frac{10}{3} \left(1 + \frac{\eta^2}{15}\right) L^2 Q^2 + \frac{3}{2} L^2 (3L^2 - 4Q^2) \cos^2 \beta \sin^2 \beta - \frac{9}{4} L^4 \cos^4 \beta, \quad \text{ (C.4a)}$$

$$\Delta_{20}(\beta) = 6 \eta L^2 Q^2 \left\{ L^2 + \frac{2}{9} (1 - \eta^2) Q^2 \right\} \sin^2 \beta - 3L^2 \cos^2 \beta \sin^2 \beta \quad \text{ (C.4b)}$$

$$\Delta_{40}(\beta) = -\frac{3}{2} \eta^2 L^4 Q^2 \sin^4 \beta, \quad \text{ (C.4c)}$$
and

\[ K_{10}(\beta) = \frac{\eta^2}{18} \left( (1 + L^2) (2 + 5 L^2) + 4 \left( 1 + \frac{5 \eta^2}{18} \right) Q^2 \right. \]
\[ + 8 \left( 1 - \frac{\eta^2}{9} \right)^2 Q^4 + 12 \left( 1 + \frac{\eta^2}{27} \right) L^2 Q^2 \]
\[ + \left[ 6 (1 + L^2)^2 + 12 \left( 1 + \frac{\eta^2}{18} \right) Q^2 + \frac{8}{3} \eta^2 L^2 Q^2 \right] \cos^2 \beta \]
\[ - L^2 \left[ 3 (1 + L^2) + 28 \left( 1 + \frac{\eta^2}{21} \right) Q^2 \right] \cos^4 \beta \left\{ \cos^2 \beta \right\}, \]  \hspace{1cm} (C.5a)

\[ K_{20}(\beta) = \frac{2}{3} \eta \left\{ \left[ (1 + L^2) (1 + 4 L^2) + \frac{4}{9} \eta^2 Q^2 + 6 \left( 1 + \frac{5 \eta^2}{27} \right) L^2 Q^2 \right] \sin^2 \beta \right. \]
\[ + L^2 \left[ 3 (1 + L^2) + 4 \left( 1 + \frac{\eta^2}{3} \right) Q^2 \right] (\cos^4 \beta - 1) \right\}, \]  \hspace{1cm} (C.5b)

\[ K_{40}(\beta) = -\frac{1}{6} \eta^2 L^2 \left[ 1 + L^2 + \frac{4}{3} \left( 1 + \frac{\eta^2}{3} \right) Q^2 \right] \sin^4 \beta. \]  \hspace{1cm} (C.5c)
APPENDIX D: INTERNAL MOTIONS

Internal motions are usually much faster than the quadrupole frequency $\omega_Q$, so that the motional-narrowing regime applies. In addition, restricted rotational motions in A sites are usually much faster than site exchange. Under these conditions, internal motions can be incorporated by adding a relaxation term to the stochastic Liouville equation (2.16):

$$\frac{d}{dt} \sigma(t) = (\mathcal{W} - i \mathcal{L} - \mathcal{R}^{\text{int}}) \sigma(t).$$

(D.1)

Like the Liouvillian $\mathcal{L}$, the internal-motion relaxation superoperator $\mathcal{R}^{\text{int}}$ is diagonal in the site basis,

$$\langle \alpha | \mathcal{R}^{\text{int}} | \beta \rangle = \delta_{\alpha\beta} \mathcal{R}^{\text{int}}_{\alpha}.$$

(D.2)

We assume that all A sites have the same internal motion. The derivation of Eqs. (A.11) then remains valid, except that a term $\mathcal{R}^{\text{int}}_I \tau_I$ or $\mathcal{R}^{\text{int}}_A \tau_A$ must be added to the superoperator $\mathcal{M}$ in Eq. (2.33). For spin $I = 1$, the supermatrix $(kq | \mathcal{R}^{\text{int}}_\alpha | k'q') = \delta_{kk'} \delta_{qq'} (kq | \mathcal{R}^{\text{int}}_\alpha | kq)$ is fully diagonal, but the diagonal elements depend on $k$ even in the extreme-motional-narrowing regime. As a result, the superoperators $\mathcal{B}_A$ and $\mathcal{B}_I$ no longer commute. However, as discussed in Sec. III A, the dynamical coupling of the state multipoles $\langle \sigma_1^I(t) \rangle$ and $\langle \sigma_2^I(t) \rangle$ is weak so the $q = 0$ block of $\mathcal{B}_A$ is nearly diagonal. It is therefore an excellent approximation to regard $\mathcal{B}_A$ and $\mathcal{B}_I$ as commuting superoperators also in the presence of internal motions.
As in the absence of internal motions, we obtain (without further approximations) a result for the integral relaxation rate $\hat{R}_1$ that differs from Eq. (3.5) only in that $1 - B$ is replaced by $1 - B' + R_{\text{int}}^I \tau_1$ in the first factor in the denominator and $P_A(1 - P_I)(k_0 |B| 10)$ is replaced by $P_A(1 + P_I + P_A R_{k,I} \tau_1)(k_0 |B'| 10)$ in the second factor. Here, we have defined

\[
R_{k,I} \equiv \langle k_0 | R_{I}^{\text{int}} | k_0 \rangle , \quad (D.3)
\]

\[
B' \equiv \langle (M + R_{A}^{\text{int}} \tau_A)^{-1} \rangle , \quad (D.4)
\]

with $M$ given by Eq. (3.4).

In the dilute regime ($P_A \ll 1$), the generalized version of Eq. (3.9) contains $1 - B' + R_{I}^{\text{int}} \tau_1$ in place of $1 - B$. However, since we have already invoked the exponential approximation (neglecting the dynamical coupling between $\langle \sigma_0^I(t) \rangle$ and $\langle \sigma_0^2(t) \rangle$), the appropriate dilute-regime result is Eq. (3.10), which now reads

\[
R_1 = \frac{P_A}{\tau_A} \left[ (10 |(1 - B' + R_{I}^{\text{int}} \tau_1)| 10) \right] \]

\[
= P_I R_{1,I} + \frac{P_A}{\tau_A} \left[ 1 - (10 |B'| 10) \right] , \quad (D.5)
\]

where we have also used Eq. (2.13).

In general, $R_{I}^{\text{int}}$ in Eq. (D.4) depends on the site orientation $\Omega$. To proceed without specifying a detailed model for the internal motion, we make a pre-averaging approximation where the supermatrix elements of $R_{A}^{\text{int}}$ are orientationally averaged.
before performing the inversion in Eq. (D.4). Pre-averaging is fully justified if, as is typically the case, site exchange is fast compared to the $\Omega$-dependent variation of $R_{1,A}^{\text{int}}$. Furthermore, we neglect the $k$ dependence of these elements. After these approximations, Eqs. (3.4) and (D.4) yield

$$B' = \frac{1}{(1 + \rho)} \left\langle \left[ 1 + i \tilde{L}_Z \tau_A + i \tilde{L}_Q \tau_A \right]^{-1} \right\rangle,$$

(D.6)

where $\rho \equiv R_{1,A}^{\text{int}} \tau_A$ and

$$R_{1,A}^{\text{int}} \equiv \left\langle \langle 10 | R_{1,A}^{\text{int}}(\Omega) | 10 \rangle \right\rangle.$$

(D.7)

The tilde in Eq. (D.6) signifies that the Liouvillians have been divided by $1 + \rho$. Combination of Eqs. (D.5), (D.6) and (3.10) now yields

$$R_1 = P_1 R_{1,1} + \frac{P_A R_{1,A}^{\text{int}}}{1 + R_{1,A}^{\text{int}} \tau_A} + \frac{\tilde{R}_{1,\text{EMOR}}}{1 + R_{1,A}^{\text{int}} \tau_A},$$

(D.8)

where $\tilde{R}_{1,\text{EMOR}}$ is given by Eq. (3.10), but with $Q$ and $L$ replaced by $\tilde{Q} \equiv Q/(1 + \rho)$ and $\tilde{L} \equiv L/(1 + \rho)$, respectively. In the analytical approximation, $\tilde{R}_{1,\text{EMOR}}$ is still given by Eq. (3.13), but with the generalized spectral densities in Eq. (3.14) replaced by

$$\tilde{J}_{mn} = \frac{\tau_A}{1 + (R_{1,A}^{\text{int}} \tau_A)^2 + (\Omega Q_m \tau_A)^2 + (n \omega_L \tau_A)^2}.$$

(D.9)

Given that the internal motion is in the motional-narrowing regime, we must have $\rho \lesssim \omega_Q^2 \tau_{\text{int}} \tau_A = Q \omega_Q \tau_{\text{int}} \ll Q$, where $\tau_{\text{int}}$ is the internal-motion correlation.
Since the internal motion was taken to be much faster than the exchange, so that \( \tau_{\text{int}} \ll \tau_A \), we also have \( \rho \lesssim \omega_Q^2 \tau_{\text{int}} \tau_A = Q^2 \tau_{\text{int}} / \tau_A \ll Q^2 \). In most cases, \( \tau_{\text{int}} \) will be several orders of magnitude shorter than \( \tau_A \), so that \( \rho \ll 1 \) even if \( Q > 1 \).

Then Eq. (D.8) reduces to

\[
R_1 = P_1 R_{1,1} + P_A R_{1,A}^{\text{int}} + R_{1,\text{EMOR}}. \tag{D.10}
\]
APPENDIX E: KINETIC HETEROGENEITY

Here we consider a generalized EMOR model with \( n_A \) anisotropic states, labelled \( \nu = 1, 2, \ldots, n_A \). All \( N_\nu \) sites belonging to a given state have the same mean survival time \( \tau_\nu \). The fraction of all A sites that belong to state \( \nu \) is \( x_\nu = N_\nu / N_A \) and the equilibrium population of that state is \( P_\nu = x_\nu P_A \).

The detailed balance condition (2.11) remains valid and the only nonzero transition probabilities are

\[
\langle 0 | T | \alpha_\nu \rangle = \frac{1}{\tau_\nu} , \tag{E.1a}
\]

\[
\langle \alpha_\nu | T | 0 \rangle = \frac{P_A}{N_A P_I} \frac{1}{\tau_\nu} , \tag{E.1b}
\]

where \( \alpha_\nu \) denotes an A site in state \( \nu \).

The site-averaged resolvent superoperator in Eq. (2.25) is now written as a sum of contributions from the \( n_A + 1 \) states,

\[
\langle \tilde{U}(s) \rangle = \sum_{\nu=1}^{n_A} x_\nu \tilde{U}_\nu(s) + \tilde{U}_I(s) . \tag{E.2}
\]

Proceeding as in Appendix A, we obtain

\[
\tilde{U}_\nu(s) = \tau_\nu B_\nu(s) \left[ P_A + \frac{P_A}{P_I \tau_\nu} \tilde{U}_I(s) \right] , \tag{E.3}
\]

\[
\tilde{U}_I(s) = \tau_I B_I(s) \left[ P_I + \sum_{\nu=1}^{n_A} \frac{1}{\tau_\nu} \tilde{U}_\nu(s) \right] , \tag{E.4}
\]

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with $B_I(s)$ given by Eq. (A.10) and

$$B_\nu(s) \equiv \frac{1}{N_\nu \tau_{\nu}} \sum_{\alpha_\nu=1}^{N_\nu} \langle \alpha_\nu | \tilde{U}_0(s + K_{\nu}) | \alpha_\nu \rangle = \frac{1}{8 \pi^2} \int d\Omega \frac{1}{|\mathcal{M}_\nu(s, \Omega)|^2}.$$  

(E.5)

$$\mathcal{M}_\nu(s, \Omega) \equiv 1 + s \tau_{\nu} + i \mathcal{L}_Z \tau_{\nu} + i \mathcal{L}_Q(\Omega) \tau_{\nu}.$$  

(E.6)

Substituting $\tilde{U}_\nu(s)$ from Eq. (E.3) into Eq. (E.4) and solving for $\tilde{U}_I(s)$, we obtain

$$\tilde{U}_I(s) = \tau_I \left[ 1 - B_I(s) \mathcal{B}_A(s) \right]^{-1} B_I(s) \left[ P_I + P_A \sum_{\nu=1}^{n_A} x_{\nu} B_{\nu}(s) \right],$$  

(E.7)

with

$$\mathcal{B}_A(s) \equiv \sum_{\nu=1}^{n_A} \frac{x_{\nu}}{\tau_{\nu}} B_{\nu}(s) \bigg/ \sum_{\nu=1}^{n_A} \frac{x_{\nu}}{\tau_{\nu}}.$$  

(E.8)

Rather than pursuing the general case, we focus on the dilute regime, where

$$\langle \tilde{U}(s) \rangle \approx \tilde{U}_I(s) \approx \tau_I \left[ B_I^{-1}(s) - \mathcal{B}_A(s) \right]^{-1}.$$  

(E.9)

Using Eqs. (A.10), (4.6) (with $P_1 = 1$) and (E.8), we can write Eq. (E.9) as

$$\langle \tilde{U}(s) \rangle = \left\{ s + i \mathcal{L}_Z + P_A \sum_{\nu=1}^{n_A} \frac{x_{\nu}}{\tau_{\nu}} \left[ 1 - B_{\nu}(s) \right] \right\}^{-1}.$$  

(E.10)

Combining this result with Eq. (3.1), we obtain the result given in the main text, Eq. (4.7), for the integral relaxation rate in the dilute regime.
APPENDIX F: WATER 180° FLIPS

Here we derive the the $^2$H relaxation rate due to 180° flips of a D$_2$O molecule about the molecular symmetry ($C_2$) axis. If the $C_2$ flips are fast compared to site exchange and compared to the rigid-lattice quadrupole frequency $\omega_Q^0$, then their effect can be incorporated in the EMOR model as described in Sec. IV B and the flip-induced relaxation rate can be calculated with the conventional motional-narrowing theory, according to which

$$R_{1A} = \frac{2}{3} (\omega_Q^0)^2 \left[ 0.2 J_1(\omega_L) + 0.8 J_2(2\omega_L) \right].$$ (F.1)

The spectral density functions are given by

$$J_n(\omega) = \int_0^{\infty} d\tau \cos(\omega \tau) G_{nn}(\tau),$$ (F.2)

with the time correlation functions (TCFs)

$$G_{nn}(\tau) = 5 \langle [V_n^L(0) - \langle V_n^L \rangle]^* [V_n^L(\tau) - \langle V_n^L \rangle] \rangle.$$ (F.3)

Here, $V_n^L$ is the $n^{th}$ spherical component of the EFG tensor in the lab-fixed frame (L), normalized by the component $V_0^F$ in the instantaneous (rigid-lattice) principal frame (F).

The EFG components are first transformed from the L frame to the flip-averaged
principal EFG frame $D$ according to

$$V_n^L = \sum_p D_{np}^2(\Omega) V_p^D ,$$

where the sum runs from $p = -2$ to $p = 2$. Combination of Eqs. (F.3) and (F.4) yields

$$G_{nn}(\tau) = 5 \sum_p \sum_{p'} D_{np}^2(\Omega) D_{np'}^2(\Omega) G_{pp'}^D(\tau) ,$$

where

$$G_{pp'}^D(\tau) = \langle [V_p^D(0) - \langle V_p^D \rangle]^* [V_{p'}^D(\tau) - \langle V_{p'}^D \rangle] \rangle .$$

The internal-motion relaxation rate $R_{1,A}$ thus depends on the site orientation, specified by the Euler angles $\Omega$. However, if exchange among sites with different orientations is fast compared to the $\Omega$-dependent variation of $R_{1,A}$, then the EMOR theory only involves the orientationally averaged relaxation rate

$$\bar{R}_{1,A} \equiv \int d\Omega f(\Omega) R_{1,A}(\Omega) = \frac{1}{8 \pi^2} \int d\Omega R_{1,A}(\Omega) ,$$

where we have inserted the isotropic $\Omega$ distribution from Eq. (??). In contrast to the case of freely tumbling proteins, where $J_1(\omega) \equiv J_2(\omega)$, Eq. (F.1) involves two distinct spectral density functions. However, when the spectral density function is isotropically averaged as in Eq. (F.7) the dependence on the projection index $n$ disappears. (The subscript will therefore be omitted in the following.) Formally,
this is demonstrated by making use of the orthogonality of the Wigner functions,

\[ \frac{1}{8 \pi^2} \int d\Omega \, D_{np}^2(\Omega) \, D_{np'}^2(\Omega) = \delta_{pp'} \frac{1}{5}. \] (F.8)

After isotropic averaging, Eq. (F.5) thus yields

\[ \bar{G}(\tau) = \sum_p G_{pp}^D(\tau). \] (F.9)

For \( \theta_{DOD} < 109.47^\circ \), the \( z_D \) axis (associated with the largest flip-averaged principal EFG component) is normal to the molecular plane, while the \( x_D \) axis (the smallest principal component) is along the \( C_2 \) symmetry axis. It is more convenient to describe the flip motion in a frame (denoted by \( M \)) that reflects the symmetry of the motion, rather than the symmetry of the EFG tensor (as the \( D \) frame does). We therefore transform the EFG components from the \( D \) frame to the \( M \) frame with the \( z_M \) axis along the \( C_2 \) symmetry axis and the \( x_M \) axis normal to the molecular plane. The Euler angles for this transformation are \( \Omega_{DM} = (0, \pi/2, \pi) \). Thus,

\[ V_p^D = \sum_q D_{pq}^2(\Omega_{DM}) \, V_q^M = \sum_q (-1)^q d_{pq}^2(\pi/2) \, V_q^M. \] (F.10)

Combining Eqs. (F.6), (F.9) and (F.10) and making use of the identity

\[ \sum_p d_{pq}^2(\pi/2) \, d_{pq}^2(\pi/2) = \sum_p d_{qp}^2(-\pi/2) \, d_{pq}^2(\pi/2) = d_{qq}^2(0) = \delta_{qq'}, \] (F.11)

we obtain

\[ \bar{G}(\tau) = \sum_q G_{qq}^M(\tau), \] (F.12)
with
\[
G_{qq}^M(\tau) = \langle [V_q^M(0) - \langle V_q^M \rangle]^* [V_q^M(\tau) - \langle V_q^M \rangle] \rangle . \tag{F.13}
\]

Finally, we transform the EFG components from the M frame to the principal frame (F) of the instantaneous (rigid-lattice) \(^2\)H EFG tensor, with the \(z_F\) axis along the O–D bond and the \(x_F\) axis in the molecular plane and pointing towards the positive \(z_M\) axis. The Euler angles for this transformation are \(\Omega_{MF} = (\phi, \theta_{DOD}/2, \pi)\), where \(\theta_{DOD}\) is the DOD angle of the water molecule and \(\phi = \pi/2\) or \(3\pi/2\) for the two flip states. Thus,
\[
V_q^M = \sum_r D^*_{qr} (\Omega_{MF}) V_r^F = K_q \exp(i q \phi) , \tag{F.14}
\]

\[
K_q \equiv \sum_r (-1)^r \, d^2_{qr} (\theta_{DOD}/2) V_r^F . \tag{F.15}
\]

Combination of Eqs. (F.12) – (F.14) yields
\[
\tilde{G}(\tau) = \sum_q |K_q|^2 g_q(\tau) , \tag{F.16}
\]

with the reduced TCF
\[
g_q(\tau) \equiv \langle [\exp(-i q \phi_0) - \langle \exp(-i q \phi_0) \rangle] [\exp(i q \phi) - \langle \exp(i q \phi) \rangle] \rangle
\]
\[
= \langle \exp[i q (\phi - \phi_0)] \rangle - |\langle \exp(i q \phi) \rangle|^2 . \tag{F.17}
\]

The second term is
\[
|\langle \exp(i q \phi) \rangle|^2 = \frac{1}{4} |\exp(i q \pi/2) + \exp(i 3 q \pi/2)|^2
\]
\[
= \frac{1}{2} \left[1 + (-1)^q\right] = \delta_{q,\text{even}} . \tag{F.18}
\]
Modeling the flip motion as a symmetric two-state Poisson process, the first term in Eq. (F.17) is evaluated as

\[
\langle \exp[iq(\phi - \phi_0)] \rangle = \sum_{S_0} P(S_0) \sum_{S} P(S, \tau|S_0) \exp\{iq(\phi(S) - \phi(S_0))\}
\]

\[
= \frac{1}{2} \left\{ [P(A, \tau|A) + P(B, \tau|B)] + (-1)^q [P(A, \tau|B) + P(B, \tau|A)] \right\},
\]

where A and B denotes the two flip states. The flip propagators are

\[
P(A, \tau|A) = P(B, \tau|B) = \frac{1}{2} [1 + \exp(-2\tau/\tau_{\text{flip}})],
\]

\[
P(A, \tau|B) = P(B, \tau|A) = \frac{1}{2} [1 - \exp(-2\tau/\tau_{\text{flip}})],
\]

where \(\tau_{\text{flip}}\) is the mean lifetime of a flip state. Inserting these expressions into Eq. (F.19), we obtain

\[
\langle \exp[iq(\phi - \phi_0)] \rangle = \delta_{q,\text{even}} + \delta_{q,\text{odd}} \exp(-2\tau/\tau_{\text{flip}}).
\]

Then we combine Eqs. (F.17), (F.18) and (F.21), to obtain

\[
g_q(\tau) = \delta_{q,odd} \exp(-2\tau/\tau_{\text{flip}}),
\]

which is substituted into Eq. (F.16), yielding

\[
\bar{G}(\tau) = (|K_{-1}|^2 + |K_1|^2) \exp(-2\tau/\tau_{\text{flip}}).
\]

The prefactor is evaluated with the aid of Eq. (F.15) and the normalized EFG components \(V_0^F = 1, V_{\pm 1}^F = 0\) and \(V_{\pm 2}^F = \eta^0/\sqrt{6}\). Using also explicit trigonometric expressions for the reduced Wigner functions, we obtain the final result for the
isotropically averaged flip TCF

\[ \tilde{G}(\tau) = \frac{3}{4} \left( 1 - \frac{\eta^0}{3} \right)^2 \sin^2 \theta_{\text{DOD}} \exp(-2 \tau/\tau_{\text{flip}}). \]  

(F.24)

Combination of Eqs. (F.1), (F.2) and (F.24) yields Eq. (5.4) in the main text.
APPENDIX G: AXIAL SECTOR MODEL

When the orientation of the principal frame for the motionally averaged EFG tensor is known, we can obtain $S$ and $\eta$ from Eqs. (4.1) and (4.2). When this is not the case, it is convenient to average the EFG components in a frame (here denoted by G) that reflects any symmetry of the motion but is not necessarily a principal frame. The averaged EFG tensor is then diagonalized.

In the axial sector model considered in the main text, the protein molecule rotates freely about an axis ($z_G$) but only in a restricted angular range $-\phi_0 \leq \phi \leq \phi_0$. The orientation of the rotation axis with respect to the principal frame (F) of the instantaneous (rigid-lattice) EFG tensor is specified by the angles $\theta_0$ and $\gamma_0$. Then

$$\langle V_n^G \rangle = \sum_p \langle D_{np}^2(\Omega_{GF}) \rangle V_p^F = \sin(n\phi_0) \sum_p d_{np}^2(\theta_0) \exp(ip\gamma_0) V_p^F.$$  \hspace{1cm} (G.1)

For simplicity, we assume that the EFG tensor is axially symmetric in the F frame ($\eta^0 = 0$), so that only the $p = 0$ term in Eq. (G.1) survives. Then

$$\langle V_0^G \rangle = \frac{1}{2} (3 \cos^2\theta_0 - 1),$$  \hspace{1cm} (G.2a)

$$\langle V_{\pm 1}^G \rangle = \mp \frac{\sqrt{6}}{2} \sin\theta_0 \cos\theta_0 \sin\phi_0,$$  \hspace{1cm} (G.2b)

$$\langle V_{\pm 2}^G \rangle = \frac{\sqrt{6}}{4} \sin^2\theta_0 \sin(2\phi_0).$$  \hspace{1cm} (G.2c)
where all components are normalized by $V_0^F$. Converting to Cartesian components,

\[
\langle V_{xx}^G \rangle = \frac{1}{\sqrt{6}} \left[ \frac{3}{2} \sin^2 \theta_0 (1 + \text{sinc} 2\phi_0) - 1 \right], \quad \text{(G.3a)}
\]

\[
\langle V_{yy}^G \rangle = \frac{1}{\sqrt{6}} \left[ \frac{3}{2} \sin^2 \theta_0 (1 - \text{sinc} 2\phi_0) - 1 \right], \quad \text{(G.3b)}
\]

\[
\langle V_{zz}^G \rangle = \frac{2}{\sqrt{6}} \left[ 1 - \frac{3}{2} \sin^2 \theta_0 \right], \quad \text{(G.3c)}
\]

\[
\langle V_{xy}^G \rangle = \langle V_{yx}^G \rangle = 0, \quad \text{(G.3d)}
\]

\[
\langle V_{xz}^G \rangle = \langle V_{zx}^G \rangle = \frac{\sqrt{6}}{2} \sin \theta_0 \cos \theta_0 \text{sinc} \phi_0, \quad \text{(G.3e)}
\]

\[
\langle V_{yz}^G \rangle = \langle V_{zy}^G \rangle = 0. \quad \text{(G.3f)}
\]

Evidently, the G frame is not a principal frame for the averaged EFG tensor. This EFG tensor is then (numerically) diagonalized and the principal axes are assigned so that

\[
| \langle V_{zz}^D \rangle | \geq | \langle V_{yy}^D \rangle | \geq | \langle V_{xx}^D \rangle |. \quad \text{(G.4)}
\]

Finally, $S$ and $\eta$ are obtained from the relations (assuming $V_0^F \equiv 1$)

\[
S = \langle V_0^D \rangle = \frac{\sqrt{6}}{2} \langle V_{zz}^D \rangle, \quad \text{(G.5)}
\]

\[
\eta = \frac{\sqrt{6}}{\langle V_0^D \rangle} \left( \langle V_{xx}^D \rangle - \langle V_{yy}^D \rangle \right) / \langle V_{zz}^D \rangle. \quad \text{(G.6)}
\]