

A Markov Model for Relaxation and Exchange in NMR Spectroscopy

Daniel Abergel*

Département de Chimie, Ecole Normale Supérieure, 24, rue Lhomond, 75231 Paris CEDEX 05

Arthur G. Palmer, III*

Department of Biochemistry and Molecular Biophysics, Columbia University, 630 West 168th Street, New York, New York 10032, U.S.A.

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A two-state Markov noise process for lattice fluctuations and chemical exchange dynamics is used to derive a stochastic Liouville equation describing the evolution of the spin-density operator in nuclear magnetic resonance spectroscopy. Relaxation through lattice fluctuations and chemical exchange processes is incorporated into the theory at the same fundamental level, and the results are valid for all time scales provided that lattice fluctuations are much faster than chemical exchange kinetics. Time-scale separation emerges as an essential feature from the lowest-order perturbation expansion of the average resolvent in the Laplace domain.

1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy is a valuable method for the study of dynamical processes in molecules in solution, with particularly powerful applications to biological macromolecules, such as proteins and nucleic acids. Conceptually different tools that depend on the time scales of the dynamical processes involved are used to describe the effects of time-dependent phenomena in NMR spectroscopy. Dynamical processes that occur on the picosecond–nanosecond time scale, for example, molecular rotational diffusion and fast motions of the molecular backbone, stochastically modulate the nuclear spin Hamiltonians, including dipole–dipole, chemical shift anisotropy, and quadrupole interactions. These fast processes lead to relaxation of the spin-density operator toward Boltzmann equilibrium. Relaxation as described in the Redfield theory¹ involves the correlation functions of the lattice, which characterize the local fluctuations of the molecule. Dynamical processes that occur on the microsecond–millisecond time scale, typically larger intramolecular conformational changes or intermolecular chemical reactions, enter the evolution equations through random modulation of the isotropic (rotationally invariant) resonance frequencies of nuclear spins. These slower dynamical processes lead to population exchange and dephasing of transverse coherences and are referred to as chemical exchange in NMR spectroscopy. To describe both picosecond–nanosecond and microsecond–millisecond dynamical processes simultaneously, two fundamentally different approaches have been introduced in the literature. A straightforward way to account for chemical exchange is to superimpose a set of kinetic equations describing transitions (jumps) between sites with different resonance frequencies with the relaxation master equation derived from the Redfield theory (or using the Bloch equations in the simplest case). This approach leads to the McConnell equations.² In this case, relaxation and exchange are treated separately and rely on different levels of description. The two descriptions are combined in a phenomenological

manner. Another approach, developed by Wennerström,³ introduces the exchange process in a formally more fundamental way by using a Hamiltonian for which the Zeeman term and the stochastic properties of the lattice functions are randomly modulated by jumps between sites. This fluctuating Hamiltonian is used in the relaxation master equation⁴ to derive the evolution of the spin-density operator. However, unlike the McConnell approach, which is valid for arbitrary exchange rates, the Wennerström approach requires that exchange is fast on the chemical-shift time scale (*vide infra*).

In this paper, we present a theoretical analysis that describes relaxation and chemical exchange processes on an equal footing. To this aim, the description of the lattice is somewhat simplified and chemical exchange is reduced to the generic two-site exchange model, where the resonance frequency of a nuclear spin undergoes stochastic jumps between two states only.

Redfield relaxation theory is a perturbative theory that involves only two-time lattice correlation functions $\langle f(t)f(t-\tau) \rangle$ and neglects higher-order correlation functions. Any stochastic process is exactly defined by knowledge of all its n –time correlation functions. Therefore, from the Redfield viewpoint and in the absence of further constraints based on physical considerations, different statistical models for the lattice functions are equally acceptable, and the matter of their choice remains an open question. However, the lattice correlation functions involved in magnetic resonance relaxation frequently are assumed to exhibit an exponential time decay.⁴ Hence, to describe spin relaxation, simple models that fulfill this weak constraint can be employed; the discrete Markov two-state noise process may be the simplest such model. One of the main advantages of the two-state noise process is that analytical results can be derived while maintaining a degree of generality comparable to the Redfield–Abragam theory. In this paper, we adopt the two-site jump model for the description of chemical/conformational exchange, which contains the essential features of a spin system driven by a frequency-modulated Hamiltonian. We also use results recently derived within the formalism of the stochastic Liouville equation (SLE)^{5,6} in order to obtain the

* Address correspondence to daniel.abergel@ens.fr, agp6@columbia.edu.

evolution equation of the average spin-density operator and find approximate analytical solutions for the relaxation rate constants in the presence of exchange.

The approach used in this work will be illustrated in the simple example of relaxation induced by a fluctuating field obeying two-state Markov jump statistics. This simple case allows us to derive results for relaxation times R_1 and R_2 , which are similar to those of Andreozzi et al.,⁷ although derived through analytical expressions obtained in the special case of two-state processes instead of using a cumulant expansion of the SLE. The paper is organized as follows: In section 2, results from application of the SLE to a two-state Markov process are reviewed. In section 3, joint two-state processes for exchange and relaxation are presented, and relationships with the single two-state model are specified. In section 4, a lowest-order perturbation expansion of the average resolvent in the Laplace domain is employed to obtain an equation describing evolution of the spin-density operator subject to both relaxation and chemical exchange processes. Finally, in section 5, the special case of a single spin subject to relaxation by a two-state fluctuating magnetic field is explicitly treated.

2. The Stochastic Liouville Equation (SLE) with a Two-State Markov Jump Process: Review of the Theory

The dynamics of a spin system described by a density operator, $\rho(t)$, is completely determined by the associated Liouville equation given by⁸

$$\frac{d}{dt}\rho(t) = -i\mathcal{L}(t)\rho(t) = \mathbf{L}(t)\rho(t) \quad (1)$$

in the superoperator representation,⁹ where $\mathcal{L}(t)$ is the Liouvillian of the spin system and $\mathbf{L}(t) = -i\mathcal{L}(t)$. Random fluctuations of $\mathbf{L}(t)$ are expressed through its dependence on the variable ζ : $\mathcal{L}(t) = \mathcal{L}(\zeta, t)$. In the case of a Markovian jump process between N states, ζ takes the values $\zeta = \zeta_1, \zeta_2, \dots, \zeta_N$ with jump rates γ_{ij} . The master equation for the transition probabilities from state $\zeta = \zeta_1$ to state $\zeta = \zeta_i$ of this stationary Markov process, p_{i1} , is given by¹⁰

$$\frac{d}{dt}P = \mathbf{\Gamma}P \quad (2)$$

where $P = (p_{11}, p_{21}, \dots, p_{N1})^T$ is the vector of the transition probabilities, $\Gamma_{kj} = \gamma_{kj}$, and $\Gamma_{jj} = -\sum_{k \neq j} \gamma_{kj}$. The asymptotic limit for $t \rightarrow \infty$ of this Markov process leads to¹⁰

$$\lim_{t \rightarrow \infty} p_{i1} = p_i \quad (3)$$

where p_i is the equilibrium probability of state i (i.e., the equilibrium population of site i). The right and left eigenvectors of $\mathbf{\Gamma}$ with zero eigenvalue are $|\phi_0\rangle = (p_1, p_2, \dots, p_N)^T$ and $\langle\psi_0| = (1, \dots, 1)$, respectively.

If transitions (jumps) between sites are so fast that the spin system does not evolve during jumps, then the evolution under chemical exchange and the spin system can be combined into the SLE.¹⁰ Because of the discrete nature of ζ , the SLE can be expressed in the direct-product space as

$$\frac{d}{dt}\rho(\zeta, t) = (\mathbf{\Lambda} + \mathbf{\Xi})\rho(\zeta, t) \quad (4)$$

where

$$\rho(\zeta, t) = \begin{pmatrix} \rho(\zeta_1, t) \\ \rho(\zeta_2, t) \\ \vdots \\ \rho(\zeta_N, t) \end{pmatrix} \quad (5)$$

and $\rho(\zeta_i, t)$ is the density operator for the population of spins with $\zeta = \zeta_i$. It is noteworthy that, in the particular case at hand, where the stochastic process is described by Markov jumps, the SLE takes a form similar to the Bloch–McConnell equations² or to an equivalent formulation by Binsch,¹¹ for instance. The operators $\mathbf{\Lambda}$ and $\mathbf{\Xi}$ of eq 4 are defined as

$$\mathbf{\Lambda} = \begin{pmatrix} \mathbf{L}(\zeta_1) & 0 & \dots & 0 \\ 0 & \mathbf{L}(\zeta_2) & \dots & 0 \\ 0 & 0 & \ddots & 0 \\ 0 & 0 & 0 & \mathbf{L}(\zeta_N) \end{pmatrix} = \sum_{i=1, N} \mathbf{P}_i \otimes \mathbf{L}(\zeta_i), \quad (6)$$

$$\mathbf{\Xi} = \mathbf{\Gamma} \otimes \mathbf{1}_{\text{spin}} \quad (7)$$

\mathbf{P}_i is the projector onto the state corresponding to the value $\zeta = \zeta_i$

$$[\mathbf{P}_i]_{mn} = \delta_{im}\delta_{in} \quad (8)$$

and $\mathbf{1}_{\text{spin}}$ is the identity matrix in the Hilbert spin space. In this space, the average $\langle\rho(t)\rangle$ is given by

$$\langle\rho(t)\rangle = [\langle\psi_0| \otimes \mathbf{1}_{\text{spin}}]\rho(\zeta, t) \quad (9)$$

From eq 4, the Laplace transform of $\rho(\zeta, t)$ defined by

$$\rho(\zeta, s) = \int_0^\infty \rho(\zeta, t) e^{-st} dt \quad (10)$$

and is related to the resolvent \mathbf{K}

$$\rho(\zeta, s) = (s - \mathbf{\Lambda} - \mathbf{\Xi})^{-1}\rho(\zeta, 0) = \mathbf{K}\rho(\zeta, 0) \quad (11)$$

Moreover, if the jump process is stationary and the initial condition $\rho(\zeta_i, 0)$ is given by $\rho(\zeta_i, 0) = \rho(0)p_i$, then

$$\langle\rho\rangle(s) = \langle\mathbf{K}\rangle\rho(0) \quad (12)$$

where the average resolvent is given by

$$\langle\mathbf{K}\rangle = [\langle\psi_0| \otimes \mathbf{1}_{\text{spin}}]\mathbf{K}[\langle\phi_0\rangle \otimes \mathbf{1}_{\text{spin}}] \quad (13)$$

Equation 12 demonstrates that the evolution of the average density operator is obtained from an average evolution operator. The solution $\langle\mathbf{K}\rangle$ can be expressed in the form

$$\langle\mathbf{K}\rangle = [s - \mathbf{D}_0(s)]^{-1} \quad (14)$$

so that

$$\langle\rho\rangle(s) = [s - \mathbf{D}_0(s)]^{-1}\rho(0) \quad (15)$$

Expressions for $\mathbf{D}_0(s)$ can be derived in the form of a series expansion,⁵ but for the present purpose, the particular situation of a two-site jump process between sites a and b is of primary interest. In this model, the stochastic variable takes only two values $\zeta = \zeta_{a,b}$. After introducing the change of notation $\gamma_{ab} = \gamma_b$ and $\gamma_{ba} = \gamma_a$, the exchange matrix describing the two-site jump process is

$$\mathbf{\Gamma} = \begin{pmatrix} -\gamma_a & \gamma_b \\ \gamma_a & -\gamma_b \end{pmatrix} \quad (16)$$

the equilibrium population distribution is

$$|\phi_0\rangle = \begin{pmatrix} p_a \\ p_b \end{pmatrix} = \begin{pmatrix} \gamma_b/\gamma \\ \gamma_a/\gamma \end{pmatrix} \quad (17)$$

and $\gamma = \gamma_a + \gamma_b$. A straightforward calculation shows in this special case^{5,6} that $\mathbf{D}_0(s)$ can be written in the closed form

$$\mathbf{D}_0(s) = \bar{\mathbf{L}} + p_a p_b \Delta [\gamma + s - \mathbf{S}]^{-1} \Delta \quad (18)$$

where

$$\begin{aligned} \Delta &= \mathbf{L}(\xi_b) - \mathbf{L}(\xi_a) \\ \bar{\mathbf{L}} &= p_a \mathbf{L}(\xi_a) + p_b \mathbf{L}(\xi_b) \\ \mathbf{S} &= p_b \mathbf{L}(\xi_a) + p_a \mathbf{L}(\xi_b) \end{aligned} \quad (19)$$

To compute decay rate constants, a time-domain approach is more intuitive, although Laplace and time-domain approaches are strictly equivalent. Thus, using eq 18, inverse Laplace transform of eq 15 provides the integro-differential equation obeyed by the average density operator

$$\frac{d}{dt} \langle \rho \rangle(t) = \bar{\mathbf{L}} \langle \rho \rangle(t) + p_a p_b \Delta \int_0^t e^{-(\gamma - \mathbf{S})(t-t')} \Delta \langle \rho \rangle(t') dt' \quad (20)$$

3. A Simplified Jump Model for Relaxation and Chemical Exchange

In the present section, we consider a spin system evolving under a stochastic Hamiltonian in which the random perturbation is caused by two stochastic two-state jump processes $\{\xi, \eta\}$. The Hamiltonian governing the evolution of the system is given in the laboratory frame of reference by

$$H = H_0(\xi) + H_1(\eta) \quad (21)$$

In this representation, the variable ξ accounts for the exchange process and can take the values $\xi = \xi_{a,b}$. For a single spin I

$$H_0(\xi) = \omega(\xi) I_z \quad (22)$$

in which $\omega(\xi)$ is the resonance frequency associated with the variable ξ ; thus, $\omega(\xi_{a,b}) = \omega_{a,b}$. The chemical exchange kinetic rate constant is defined by $k_e = k_a + k_b$, and the equilibrium populations are p_a and p_b for the two-site chemical exchange process. The jump matrix for the transition probabilities $p(\xi, t; \xi_0, t_0)$ of the chemical exchange variable ξ is

$$\mathbf{\Gamma}_e = \begin{pmatrix} -k_a & k_b \\ k_a & -k_b \end{pmatrix} \quad (23)$$

In addition, we assume that relaxation is caused by fluctuations of the local magnetic field $\mathbf{B}_1(\eta)$, which is expressed by the Hamiltonian $H_1(\eta)$

$$H_1(\eta) = \omega_1(\eta)(I_x + I_y) + \Delta(\eta)I_z \quad (24)$$

The stochastic variable η obeys Markovian two-state jump statistics and takes the values $\eta = \eta_{1,2}$ with the transition rate $\gamma(\xi)$. Thus, according to eq 2

$$\mathbf{\Gamma}_r = \frac{\gamma(\xi)}{2} \begin{pmatrix} -1 & 1 \\ 1 & -1 \end{pmatrix} = \gamma(\xi) \mathbf{\Gamma}_{\text{rel}} \quad (25)$$

The dependence of γ upon ξ in eq 25 emphasizes the fact that the relaxation rate constant (or correlation time) may depend

on the conformational state described by the value of the exchange variable ξ . The stationary nuclear spin eigenstates associated with each value of the variable ξ are herein assumed to be equally populated, which amounts to imposing an infinite lattice temperature. This deficiency is corrected by the usual ad hoc introduction of a constant equilibrium density operator $\langle \rho_0 \rangle$ in the evolution equation.^{1,4}

The master equation for the joint process $\{\xi, \eta\}$, which determines the stochastic properties of the fluctuating Hamiltonian, can be expressed in the product space $\{\xi\} \otimes \{\eta\}$ by

$$\frac{d}{dt} p(\xi, \eta, t; \xi_0, \eta_0, t_0) = \Xi p(\xi, \eta, t; \xi_0, \eta_0, t_0) \quad (26)$$

where

$$\Xi = \mathbf{1}_{\text{rel}} \otimes \mathbf{\Gamma}_e + \mathbf{\Gamma}_{\text{rel}} \otimes \begin{bmatrix} \gamma(\xi_a) & 0 \\ 0 & \gamma(\xi_b) \end{bmatrix} \quad (27)$$

Following the approach introduced in section 2, the Liouvillian operator is introduced as

$$\mathcal{L}_{i,\mu} = [H(\eta_i, \xi_\mu)] \quad (28)$$

Therefore, the Liouvillian in the direct space is given by

$$\mathbf{\Lambda} = \sum_{i=1,2;\mu=a,b} \mathbf{P}_i \otimes \mathbf{P}_\mu \otimes \mathcal{L}_{i,\mu} \quad (29)$$

and the evolution operator is

$$\begin{aligned} \mathbf{\Lambda} + \mathbf{\Gamma} &= \sum_{i=1,2;\mu=a,b} \mathbf{P}_i \otimes \mathbf{P}_\mu \otimes \mathcal{L}_{i,\mu} + \\ &\quad \left(\mathbf{1}_{\text{rel}} \otimes \mathbf{\Gamma}_e + \mathbf{\Gamma}_{\text{rel}} \otimes \begin{pmatrix} \gamma(\xi_a) & 0 \\ 0 & \gamma(\xi_b) \end{pmatrix} \right) \otimes \mathbf{1}_{\text{spin}} \\ &= \sum_{i=1,2} \mathbf{P}_i \otimes \left(\sum_{\mu=a,b} \mathbf{P}_\mu \otimes \mathcal{L}_{i,\mu} + \mathbf{\Gamma}_e \otimes \mathbf{1}_{\text{spin}} \right) + \\ &\quad \mathbf{\Gamma}_{\text{rel}} \otimes \begin{pmatrix} \gamma(\xi_a) & 0 \\ 0 & \gamma(\xi_b) \end{pmatrix} \otimes \mathbf{1}_{\text{spin}} \end{aligned} \quad (30)$$

where

$$\mathbf{\Gamma} = \Xi \otimes \mathbf{1}_{\text{spin}} \quad (31)$$

the relationship $\mathbf{1}_{\text{rel}} = \sum_{i=1,2} \mathbf{P}_i$ has been used. By making the simplifying assumption $\gamma(\xi_a) = \gamma(\xi_b) = \gamma$ (i.e., that the relaxation rate constants in both exchange states are equal) and defining the operator \mathbf{L}_i as

$$\mathbf{L}_i = \sum_{\mu=a,b} \mathbf{P}_\mu \otimes \mathcal{L}_{i,\mu} + \mathbf{\Gamma}_e \otimes \mathbf{1}_{\text{spin}} \quad (32)$$

yields

$$\mathbf{\Lambda} + \mathbf{\Gamma} = \sum_{i=1,2} \mathbf{P}_i \otimes \mathbf{L}_i + \gamma \mathbf{\Gamma}_{\text{rel}} \otimes \mathbf{1}_{\text{exch+spin}} \quad (33)$$

in which $\mathbf{1}_{\text{exch+spin}} = \mathbf{1}_{\text{exch}} \otimes \mathbf{1}_{\text{spin}}$. The corresponding SLE is thus

$$\frac{d}{dt} \rho(\xi, \eta; t) = (\mathbf{\Lambda} + \mathbf{\Gamma}) \rho(\xi, \eta; t) \quad (34)$$

As an intermediate step toward solving the SLE, the density operator is marginally averaged with respect to the relaxation

variable η in order to find the evolution equation for the marginally averaged density operator describing the exchange motion $\tilde{\rho}(\xi; t) = \sum_{i=1,2} \rho(\eta, \xi; t)$. The evolution equation in the Laplace domain for a partially averaged density operator is given by the following equation, as seen previously

$$\tilde{\rho}(\xi; s) = \frac{1}{s - \mathbf{D}_0^{\text{rel}}(s)} \quad (35)$$

Using eq 32, the solution of the SLE in the Laplace domain has the form given by eq 18, so that $\mathbf{D}_0^{\text{rel}}(s)$ is written as

$$\mathbf{D}_0^{\text{rel}}(s) = \bar{\mathbf{L}} + \frac{1}{4} \Delta \frac{1}{s + \gamma - \bar{\mathbf{L}}} \Delta \quad (36)$$

with

$$\bar{\mathbf{L}} = \frac{1}{2}(\mathbf{L}_1 + \mathbf{L}_2) \quad (37)$$

$$\Delta = \mathbf{L}_1 - \mathbf{L}_2 = \begin{pmatrix} \Delta_a & 0 \\ 0 & \Delta_b \end{pmatrix} \quad (38)$$

$$\Delta_\mu = \mathcal{J}_{1,\mu} - \mathcal{J}_{2,\mu} \quad (\mu = a, b) \quad (39)$$

The assumption of equal relaxation rate constants in both conformational states is necessary so that the operators in the SLE have a structure which is similar to the ones given in eqs 6 and 7. A closed-form solution can be derived in the manner of eq 36 for the case where $\gamma(a) \neq \gamma(b)$. Although formally similar, the corresponding expression is somewhat more complicated and is not given in the text for sake of clarity.

4. Perturbation Expansion of the Resolvent

The closed-form expression of $\mathbf{D}_0^{\text{rel}}(s)$ is useful only if actual computations of the matrices involved is simplified. We now show that, under circumstances that are encountered in almost all situations of interest in solution NMR spectroscopy, the complexity of the problem can be reduced further. To proceed, the matrix expression giving $\mathbf{D}_0^{\text{rel}}(s)$ must be evaluated. First, new notation is introduced

$$\frac{1}{s + \gamma - \bar{\mathbf{L}}} = \frac{1}{(s + \gamma)\mathbf{1}_{\text{exch}} \otimes \mathbf{1}_{\text{spin}} - \frac{1}{2} \sum_{\mu=a,b} \mathbf{P}_\mu \otimes (\mathcal{J}_{1,\mu} + \mathcal{J}_{2,\mu}) - \mathbf{\Gamma}_e \otimes \mathbf{1}_{\text{spin}}} \quad (40)$$

with

$$\mathbf{V}_0 = (s + \gamma)\mathbf{1}_{\text{exch}} \otimes \mathbf{1}_{\text{spin}} - \frac{1}{2} \sum_{\mu=a,b} \mathbf{P}_\mu \otimes (\mathcal{J}_{1,\mu} + \mathcal{J}_{2,\mu}) \quad (41)$$

and

$$\mathbf{V} = -\mathbf{\Gamma}_e \otimes \mathbf{1}_{\text{spin}} \quad (42)$$

The perturbation expansion of $\mathbf{V}_0 + \mathbf{V}$ is

$$\frac{1}{\mathbf{V}_0 + \mathbf{V}} = \frac{1}{\mathbf{V}_0} + \frac{1}{\mathbf{V}_0} \mathbf{V} \frac{1}{\mathbf{V}_0} + \dots \quad (43)$$

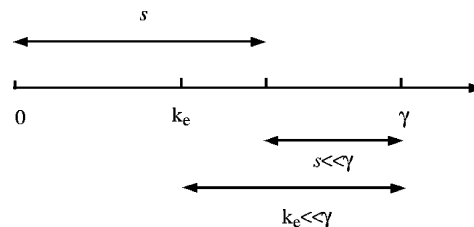


Figure 1. Orders of magnitude of the Laplace variable s , the exchange rate k_e , and the relaxation rate γ .

The jump rate for the exchange processes k_e is assumed to be small compared to other characteristic frequencies of the problem. Therefore, k_e is also small compared to the range of the matrix \mathbf{V}_0 . In this limit, a zeroth-order expansion is sufficient and

$$\frac{1}{\mathbf{V}_0 + \mathbf{V}} \approx \frac{1}{\mathbf{V}_0} \quad (44)$$

with

$$\frac{1}{\mathbf{V}_0} = \begin{pmatrix} \frac{1}{(s + \gamma)\mathbf{1}_{\text{spin}} - \bar{\mathbf{L}}_{0,a}} & 0 \\ 0 & \frac{1}{(s + \gamma)\mathbf{1}_{\text{spin}} - \bar{\mathbf{L}}_{0,b}} \end{pmatrix} \quad (45)$$

Therefore, eq 36 is written as

$$\mathbf{D}_0^{\text{rel}}(s) \approx \mathbf{D}_0^{(0)}(s) = \begin{pmatrix} \bar{\mathbf{L}}_{0,a} + \frac{1}{4} \Delta_a \frac{1}{(s + \gamma)\mathbf{1}_{\text{spin}} - \bar{\mathbf{L}}_{0,a}} \Delta_a & 0 \\ 0 & \bar{\mathbf{L}}_{0,b} + \frac{1}{4} \Delta_b \frac{1}{(s + \gamma)\mathbf{1}_{\text{spin}} - \bar{\mathbf{L}}_{0,b}} \Delta_b \end{pmatrix} + \mathbf{\Gamma}_e \otimes \mathbf{1}_{\text{spin}} \quad (46)$$

with

$$\bar{\mathbf{L}}_{0,\mu} = \frac{1}{2}(\mathcal{J}_{1,\mu} + \mathcal{J}_{2,\mu}) \quad \mu = a, b \quad (47)$$

and Δ_μ and $\bar{\mathbf{L}}_{0,\mu}$ are given by eqs 37 and 47, respectively.

The zeroth-order expansion is valid in the case of complete statistical decorrelation between relaxation and exchange processes, which takes place for large time-scale separations between the correlation times for relaxation and exchange. Thereby, the first part of $\mathbf{D}_0^{(0)}(s)$ on the right-hand side (rhs) of eq 43 has a simple block diagonal structure. Alternatively, when perturbation expansion at the lowest order is not possible, nonzero matrix elements connecting diagonal blocks appear. The rather unusual situation in which γ and k_e have the same order of magnitude has also been studied by other methods.^{12,13}

Furthermore, in the limit of (real) values of s that are small enough with respect to γ ($s \ll \gamma$), the relaxation process may be considered as in the “long time limit” (i.e., $s \rightarrow 0$) and⁵

$$\mathbf{D}_0^{\text{rel}}(s) \approx \mathbf{D}_0^{(0)}(0) \quad (48)$$

This approximation allows values of s (much) larger than k_e and consequently does not imply any constraint on the exchange time scale other than $\gamma \gg k_e$. The various assumptions regarding time-scale separations involving the various characteristic times of the problem are depicted in Figures 1 and 2. With this assumption, eq 35 takes the simpler form

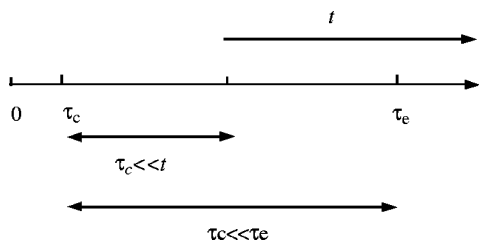


Figure 2. Orders of magnitude of the time t , the exchange time τ_e , and the relaxation correlation time τ_c .

$$\tilde{\rho}(\zeta; s) = \frac{1}{s - \mathbf{D}_0^{(0)}(0)} \quad (49)$$

which is equivalent to the following SLE in the time domain

$$\frac{d}{dt} \tilde{\rho}(\zeta; t) = \mathbf{D}_0^{(0)}(0) \tilde{\rho}(\zeta; t) \quad (50)$$

Equation 50 is therefore the stochastic Liouville equation for a two-state jump process. This is the main result of this paper. The simple model presented in this section allows the derivation of an approximate evolution equation for a spin system undergoing the combined effect of exchange and relaxation that has the same structure as the Bloch–McConnell equations.^{2,14} This result is not unexpected, because the Bloch–McConnell equations are just a particular case of the stochastic Liouville equation for a discrete Markov jump process. However, in the Bloch–McConnell equations, relaxation is treated beforehand and included in the Bloch part, whereas in this work, both relaxation and chemical exchange constitute the stochastic components of the dynamics.

The Bloch–McConnell equations or their quantum mechanical counterpart, in which the Bloch equations are replaced by a master equation for relaxation, are valid for all exchange regimes, provided that $\tau_c \ll \tau_e = 1/k_e$. In practical situations of interest in solution NMR spectroscopy, the characteristic exchange time τ_e is in the microsecond–millisecond range, whereas the correlation time of the lattice, τ_c , is at most in the nanosecond time scale. Therefore, in the McConnell approach, both fluctuating processes may safely be assumed to be statistically decorrelated, because, on average, the relaxation correlation functions have decayed to zero before an exchange jump takes place. In the present work, the effect of time-scale separation between both processes leading to decorrelation is introduced in a consistent manner through the zeroth-order perturbation expansion. This is the key justification for modeling both processes by a composite Markovian process built on a set of two-state processes. This approach takes full advantage of the simple features of the two-state processes when decorrelation is applicable. Thereby, both relaxation and chemical exchange are treated on equal footing. Note in addition that the model presented here is relevant for the description of processes for which τ_c and τ_e are on the same order.

A microscopic description of relaxation that includes spin exchange was developed by Wennerström.³ This approach introduces exchange through a Hamiltonian that is frequency-modulated by jumps of the spin between sites. The Abragam–Redfield theory for relaxation is based on a perturbative solution of the Liouville–Von Neumann equation. The evolution of the density operator in the interaction frame is described by^{4,15}

$$\frac{d}{dt} \rho^*(t) = - \int_0^{+\infty} [\mathcal{H}_1^*(t), [\mathcal{H}_1^*(t - \tau), \rho^*(t)]] d\tau \quad (51)$$

in which $\mathcal{H}_1^*(t)$ is the interaction frame representation of the time-dependent stochastic part of the Hamiltonian

$$\mathcal{H}_1^*(t) = \exp(i\mathcal{H}_0 t) \mathcal{H}_1(t) \exp(-i\mathcal{H}_0 t) \quad (52)$$

$\overline{\mathcal{H}_1(t)} = 0$, and the laboratory frame Hamiltonian is

$$\mathcal{H}(t) = \mathcal{H}_0 + \mathcal{H}_1(t) \quad (53)$$

However, eq 51 is obtained from

$$\frac{d}{dt} \rho^*(t) = - \int_0^t [\mathcal{H}_1^*(t), [\mathcal{H}_1^*(t - \tau), \rho^*(0)]] d\tau \quad (54)$$

in which the upper limit t of the integral is replaced by ∞ , assuming that contributions to the integral from times τ 's exceeding the correlation time, τ_c , are negligible, and $\rho^*(0)$ is replaced by $\rho^*(t)$, assuming that $\rho^*(0)$ and $\rho^*(t)$ differ negligibly over the time scales of interest.

In Wennerström's theory,³ both the lattice fluctuations and frequency jumps are introduced in the master equation for relaxation. This approach is valid insofar as the characteristic exchange time τ_e is both much larger than the correlation time of the lattice functions (which is generally the case in solution NMR spectroscopy) and shorter than the characteristic time during which the density operator varies appreciably. This was implicitly assumed in ref 3, and the latter assumption deserves comment. If the notation introduced by Wennerström is used, the exchange process is described by a random function $f_\mu(t)$, which takes the two values $f_\mu(t) = 1$ if the spin is in the state described by ζ_μ at time t and $f_\mu(t) = 0$ otherwise. The time-independent part of the Hamiltonian is

$$\mathcal{H}_0 = \sum_{\mu} p_{\mu} \omega_{\mu} I_z \quad (55)$$

and the fluctuating part $\mathcal{H}_1(t)$ is given by

$$\mathcal{H}_1(t) = \sum_{\mu} [f_{\mu}(t) - p_{\mu}] \omega_{\mu} I_z + \sum_{\mu, q} f_{\mu}(t) (-1)^q F_{\mu}^{-q}(t) A_p^q \quad (56)$$

where the $F_{\mu}^{-q}(t)$ functions are the lattice functions leading to relaxation, ω_{μ} values are the resonance frequencies, and the p_{μ} values are the equilibrium populations at each site. In ref 3, the corresponding master equation is therefore

$$\begin{aligned} \frac{d}{dt} \rho^*(t) = & - [I_z, [I_z, \rho^*(t)]] \int_0^{\infty} \sum_i [f_i(t) - p_i] \Delta \omega_i \sum_j \langle [f_j(t - \tau) - p_j] \Delta \omega_j \rangle d\tau \\ & - \sum_{p, q} (-1)^q [A_p^q, [A_p^{-q}, \rho^*(t)]] \int_0^{\infty} \sum_{ij} \langle f_i(t) f_j(t - \tau) F_i^q(t) F_j^{-q}(t - \tau) e^{-i\omega_p \tau} \rangle d\tau \end{aligned} \quad (57)$$

However, the correlation time of the fluctuating Hamiltonian $\mathcal{H}_1(t)$ is on the order of τ_e . Therefore, the limit of the integral cannot be extended to infinity in eq 54 for large values of τ_e , that is, for exchange regimes that are outside of the fast exchange limit, because the inequality

$$|\mathcal{H}_1(t)|^2 \tau_e t \ll 1 \quad (58)$$

which is a necessary condition for the Redfield master equation,⁴ does not hold.

5. A Simple Example: Relaxation by a Markovian Two-State Fluctuating Field

One of the key steps in the theory presented in the preceding section is the decorrelation of relaxation and exchange processes expressed by eq 44. This feature enables both aspects to be treated independently and make use of the useful closed-form expressions of eqs 18 and 20. In particular, this provides a simple model for spin relaxation which may lead in favorable cases to analytical solutions for the relaxation rates. To illustrate this point and clarify the virtues of eq 46, we take as an example the problem of a single spin $I = 1/2$ undergoing the combined action of fluctuating random fields and conformational exchange. First, the relaxation equation in each site of the exchange process, given by the blocks of the matrix $\mathbf{D}_0^{(0)}(0)$, must be solved. The Hamiltonian is given by eqs 21–24 in which $\eta = \pm 1$, $\omega_1(\eta) = \eta\omega_1$, and $\Delta(\eta) = \eta\Delta$. For a single spin $I = 1/2$, the problem will be described, without loss of generality, using the magnetization, $\mathbf{M} = [M_+, M_-, M_z]^T = \text{trace}\{\mathbf{I}\rho(t)\}$, in which $\mathbf{I} = [I_+, I_-, I_z]^T$. The evolution equation for the magnetization is

$$\frac{d}{dt}\mathbf{M}(t) = [\mathbf{\Omega}_0 + \mathbf{\Omega}(t)]\mathbf{M}(t) \quad (59)$$

in which the matrices

$$\mathbf{\Omega}_0 = \begin{pmatrix} -i\bar{\omega}_0 & 0 & 0 \\ 0 & i\bar{\omega}_0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad (60)$$

and

$$\mathbf{\Omega}(t) = \begin{pmatrix} -i\eta\Delta & 0 & i\eta\frac{\omega_1}{2} \\ 0 & i\eta\Delta & -i\eta\frac{\omega_1}{2} \\ i\eta\frac{\omega_1}{2} & -i\eta\frac{\omega_1}{2} & 0 \end{pmatrix} \quad (61)$$

have been introduced and $\bar{\omega}_0 = \omega(\mu)$. Utilizing eq 20 gives

$$\frac{d}{dt}\langle\mathbf{M}(t)\rangle = \mathbf{\Omega}_0\langle\mathbf{M}(t)\rangle + \frac{1}{4}\int_0^t \mathbf{D} e^{-\gamma(t-t')} \mathbf{D}\langle\mathbf{M}(t')\rangle dt' \quad (62)$$

where

$$\mathbf{D} = \mathbf{\Omega}_{\eta=+1} - \mathbf{\Omega}_{\eta=-1} \quad (63)$$

In the rotating reference frame, the evolution equation for the magnetization is given as

$$\frac{d}{dt}\mathbf{M}^*(t) = \mathbf{\Omega}^*(t)\mathbf{M}^*(t) \quad (64)$$

where the starred quantities \mathbf{M}^* and $\mathbf{\Omega}^*$ are related to the laboratory frame quantities through the transformations

$$\mathbf{M}^*(t) = e^{-\mathbf{\Omega}_0 t} \mathbf{M}(t) \quad (65)$$

$$\mathbf{\Omega}^*(t) = e^{-\mathbf{\Omega}_0 t} \mathbf{\Omega}(t) e^{\mathbf{\Omega}_0 t} \quad (66)$$

Applying these definitions yields

$$\mathbf{\Omega}^*(t) = \begin{pmatrix} -i\eta\Delta & 0 & i\eta\frac{\omega_1}{2} e^{i\bar{\omega}_0 t} \\ 0 & i\eta\Delta & -i\eta\frac{\omega_1}{2} e^{-i\bar{\omega}_0 t} \\ i\eta\frac{\omega_1}{2} e^{-i\bar{\omega}_0 t} & -i\eta\frac{\omega_1}{2} e^{i\bar{\omega}_0 t} & 0 \end{pmatrix} \quad (67)$$

These definitions allow one to express eq 62 in the rotating frame

$$\begin{aligned}\frac{d}{dt}\langle\mathbf{M}^*(t)\rangle &= \frac{1}{4}\int_0^t \mathbf{D}(t) e^{-\gamma(t-t')} \mathbf{D}(t') \langle\mathbf{M}^*(t')\rangle dt' \\ &= \frac{1}{4}\int_0^t \mathbf{B}(t, t') dt'\end{aligned}\quad (68)$$

where

$$\mathbf{D}(t) = \mathbf{\Omega}_{\eta=+1}^* - \mathbf{\Omega}_{\eta=-1}^* \quad (69)$$

Calculation of $\mathbf{B}(t, t')$ yields

$$\mathbf{B}(t, t') = \begin{pmatrix} \left(-\Delta^2 - \frac{\omega_1^2}{4} e^{i\bar{\omega}_0(t-t')}\right) e^{-\gamma(t-t')} & \frac{\omega_1^2}{4} e^{i\bar{\omega}_0(t+t')} e^{-\gamma(t-t')} & \frac{\omega_1\Delta}{4} e^{i\bar{\omega}_0 t'} e^{-\gamma(t-t')} \\ \frac{\omega_1^2}{4} e^{-i\bar{\omega}_0(t+t')} e^{-\gamma(t-t')} & \left(-\Delta^2 - \frac{\omega_1^2}{4} e^{-i\bar{\omega}_0(t-t')}\right) e^{-\gamma(t-t')} & \frac{\omega_1\Delta}{4} e^{-i\bar{\omega}_0 t'} e^{-\gamma(t-t')} \\ \frac{\omega_1\Delta}{4} e^{-i\bar{\omega}_0 t'} e^{-\gamma(t-t')} & \frac{\omega_1\Delta}{4} e^{i\bar{\omega}_0 t'} e^{-\gamma(t-t')} & -\frac{\omega_1^2}{4} (e^{-i\bar{\omega}_0(t-t')} + e^{i\bar{\omega}_0(t-t')}) e^{-\gamma(t-t')} \end{pmatrix} \quad (70)$$

If t is large enough, that is, $t \gg \omega_0^{-1}$, the rapidly oscillating terms average to zero, and in this adiabatic approximation

$$\begin{cases} \frac{d}{dt}\langle M_{\pm}^{\text{adia}}(t) \rangle = \int_0^t \left(-\Delta^2 - \frac{\omega_1^2}{4} e^{\pm i\bar{\omega}_0(t-t')}\right) e^{-\gamma(t-t')} \langle M_{\pm}^{\text{adia}}(t') \rangle dt' \\ \frac{d}{dt}\langle M_z^{\text{adia}}(t) \rangle = \int_0^t -\frac{\omega_1^2}{4} (e^{-i\bar{\omega}_0(t-t')} + e^{i\bar{\omega}_0(t-t')}) e^{-\gamma(t-t')} \langle M_z^{\text{adia}}(t') \rangle dt' \end{cases} \quad (71)$$

The Laplace transform of eq 71 is

$$\begin{cases} \langle \hat{M}_{\pm}^{\text{adia}} \rangle(s) = \frac{1}{s + \frac{\Delta^2}{s + \gamma} + \frac{\omega_1^2}{4(s + \gamma \mp i\bar{\omega}_0)}} M_{\pm}^{\text{adia}}(0) = \frac{1}{s + D_{\pm}^{\text{adia}}(s)} M_{\pm}^{\text{adia}}(0) \\ \langle \hat{M}_z^{\text{adia}} \rangle(s) = \frac{1}{s + \frac{\omega_1^2}{4} \left(\frac{1}{s + \gamma + i\bar{\omega}_0} + \frac{1}{s + \gamma - i\bar{\omega}_0} \right)} M_z^{\text{adia}}(0) = \frac{1}{s + D_z^{\text{adia}}(s)} M_z^{\text{adia}}(0) \end{cases} \quad (72)$$

Equation 72 is the solution of the Laplace transform of eq 71 in the adiabatic approximation valid for all times. In the present context, the evolution of the magnetization at times which are comparable to the characteristic decay time of the magnetization, but which are much longer than $\tau_c = \gamma^{-1}$, the correlation time of the relaxation process, are of primary interest. Therefore, the “long-term” approximation of eq 72 is obtained by taking the limit $s \rightarrow 0$ in $D_z^{\text{adia}}(s)$ and $D_{\pm}^{\text{adia}}(s)$. The transverse relaxation rate constant is given by the real part of $D_{\pm}^{\text{adia}}(s)$

$$R_2 = \frac{\Delta^2}{\gamma} + \frac{\omega_1^2 \gamma / 4}{\bar{\omega}_0^2 + \gamma^2} = \Delta^2 J(0) + \frac{\omega_1^2}{4} J(\bar{\omega}_0) \quad (73)$$

and the longitudinal relaxation rate constant is given by $D_z^{\text{adia}}(s)$, which is purely real

$$R_1 = \frac{\omega_1^2 \gamma / 2}{\bar{\omega}_0^2 + \gamma^2} = \frac{\omega_1^2}{2} J(\bar{\omega}_0) \quad (74)$$

in which the spectral density function $J(\omega)$ is defined by

$$J(\omega) = \frac{\tau_c}{1 + (\omega\tau_c)^2} \quad (75)$$

These results (eqs 73 and 74) were obtained previously using a second-order cumulant expansion of the stochastic Liouville expansion⁷ instead of the exact solution of eq 68. In both cases, however, the long-time (small s) approximation was used. It may be pointed out that the simple model with $R_2/R_1 = 1/2$ when Δ is zero is the anticipated result for lifetime broadening in a two-level system.

Finally, the imaginary part of $D_{\pm}^{\text{adia}}(s)$ also defines the dynamic frequency shift $\delta\omega_{\pm}$

$$\delta\omega_{\pm} = \pm \frac{\omega_1^2 \bar{\omega}_0}{4(\gamma^2 + \bar{\omega}_0^2)} \quad (76)$$

which may be expressed as

$$\delta\omega_{\pm} = \pm \frac{\omega_1^2}{4} K(\bar{\omega}_0) \quad (77)$$

by defining

$$K(\omega) = \frac{\tau_c^2 \omega}{1 + (\omega \tau_c)^2} \quad (78)$$

$J(\omega)$ and $K(\omega)$ are the real and imaginary parts of the Fourier transform of an exponential correlation function.

6. Conclusion

The analysis of the Markov dichotomous noise process for lattice fluctuations and chemical exchange described here yields the SLE for two-site chemical exchange. Unlike the McConnell equations, relaxation through lattice fluctuations and chemical exchange processes are incorporated into the theory at the same fundamental level. Unlike the approach of Wennerström, the results are valid for all chemical exchange time scales, subject only to the assumption that lattice fluctuations are much faster

than site transitions due to the chemical exchange process. A main conclusion of the derivation is that time-scale separation is a requirement imposed by the lowest-order perturbation expansion of the average resolvent in the Laplace domain.

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