Chapter 2
Theoretical Principles

In this chapter we shall present a phenomenological description of nuclear spin dynamics, including relaxation, in a magnetic field (i.e., the Bloch equations) as well as a more accurate description using the principles of quantum mechanics (Redfield relaxation theory). We shall then use these concepts to develop analytical models to describe relaxation dispersion experiments and to derive analytical functions that allow one to extract information from the experimental data.

2.1 The Bloch Equations

In this section we shall follow the approach of [1]. The semiclassical vector model developed by Felix Bloch in [2] describes the behavior of an ensemble of noninteracting spin-1/2 nuclei in a static magnetic field but fails in describing more complex systems, where a quantum mechanical approach is required. However, because the basic concepts and terminology are still used in modern NMR, we shall briefly present the Bloch equations.

2.1.1 Equations Describing Spin Dynamics in the Absence of Relaxation

The evolution of the bulk magnetization vector $\mathbf{M}(t)$ in the presence of a magnetic field $\mathbf{B}(t)$ is described by

$$\frac{d\mathbf{M}(t)}{dt} = \mathbf{M}(t) \times \gamma \mathbf{B}(t) \tag{2.1}$$

where γ is the gyromagnetic ratio of the nuclei of interest. Equation 2.1 is valid in the laboratory frame. It is convenient to rewrite it in a frame that rotates with angular velocity ω around the z-axis, defined by the unit vector $\mathbf{k}$:

$$\left[\frac{d\mathbf{M}(t)}{dt}\right]_{rot} = \left[\frac{d\mathbf{M}(t)}{dt}\right]_{lab} + \mathbf{M}(t) \times \omega\mathbf{k}$$
$$= \mathbf{M}(t) \times [\gamma\mathbf{B}(t) + \omega\mathbf{k}]. \tag{2.2}$$

The two equations can be actually written in the same form, provided that $\mathbf{B}(t)$ is replaced by an *effective* field defined as

$$\mathbf{B}_{eff} = \mathbf{B}(t) + \frac{\omega}{\gamma}\mathbf{k}. \tag{2.3}$$

For a static field $|\mathbf{B}(t)| = B_0$, the effective field is zero if ω is chosen to correspond to the *Larmor frequency*

$$\omega_0 = -\gamma B_0, \tag{2.4}$$

and the bulk magnetization appears to be stationary. In other terms, in the absence of other fields the bulk magnetization simply precesses at the Larmor frequency around the magnetic field that defines the z-direction of the laboratory and rotating frames.

The magnetic component of a radio-frequency (*rf*) field that is linearly polarized along the x-axis of the laboratory frame is

$$\mathbf{B}_{rf}(t) = 2B_1 \cos(\omega_{rf}t + \phi)\,\mathbf{i}$$
$$= B_1\{\cos(\omega_{rf}t + \phi)\,\mathbf{i} + \sin(\omega_{rf}t + \phi)\,\mathbf{j}\}$$
$$+ B_1\{\cos(\omega_{rf}t + \phi)\,\mathbf{i} - \sin(\omega_{rf}t + \phi)\,\mathbf{j}\}, \tag{2.5}$$

where B_1 is the amplitude of the applied *rf* field, ω_{rf} its angular (or carrier) frequency, ϕ its phase, and $\mathbf{i}$ and $\mathbf{j}$ are unit vectors defining the x- and y-axes, respectively. In the second equality of the previous equation, we decomposed the linearly polarized *rf* field into two circularly polarized components, with opposite directions of rotation around the z-axis. Only the component rotating in the same sense as the magnetic moment can interact with the nuclear spins. The counter-rotating field produces only a small effect, known as Bloch-Siegert shift, that is proportional to $(B_0/2B_1)^2$, and can be neglected for our purposes. Therefore, one obtains

$$\mathbf{B}_{rf}(t) = B_1\{\cos(\omega_{rf} + \phi)\,\mathbf{i} + \sin(\omega_{rf} + \phi)\,\mathbf{j}\}. \tag{2.6}$$

It is useful then to rewrite Eq. 2.1 in a rotating frame where the *rf* field is time-independent, i.e. a frame that rotates at angular frequency ω_{rf}:

$$\frac{d\mathbf{M}^{rff}(t)}{dt} = \mathbf{M}^{rff}(t) \times \gamma\mathbf{B}^{rff}, \tag{2.7}$$

where the effective field in the *rf* frame is

$$\mathbf{B}^{rff} = B_1\{\cos\phi\,\mathbf{i}^{rff} + \sin\phi\,\mathbf{j}^{rff}\} + \Delta B_0\mathbf{k}^{rff}, \tag{2.8}$$

and

$$\Delta B_0 = -\frac{\Omega}{\gamma}, \tag{2.9}$$

where we used the definition of the offset $\Omega = \omega_0 - \omega_{rf}$. The magnitude of the effective field is

$$B^{rff} = \sqrt{B_1^2 + \Delta B_0^2} = \frac{B_1}{\sin \theta}, \tag{2.10}$$

where θ indicates the angle through which the frame is tilted with respect to z-axis of the laboratory frame:

$$\tan \theta = \frac{B_1}{\Delta B_0} = \frac{\omega_1}{\Omega}. \tag{2.11}$$

In general, we will use this tilted frame in the following discussion, unless otherwise stated. For the sake of clarity, we will use a simplified notation, dropping the superscript *rff*.

2.1.2 Empirical Description of NMR Relaxation

Using the equations of the previous section, the magnetization would evolve around the z-axis freely and forever. This is of course not the case, because the experimental practice shows that the thermal equilibrium is restored after some time. In other words, nuclear spins are subject to relaxation. Bloch [2] proposed to introduce two processes to account for such relaxation. The first mechanism accounts for the return of the population difference across the Zeeman transition to Boltzmann equilibrium, i.e. for the z-component of the magnetization to go back to equilibrium. This process, known as longitudinal or spin-lattice relaxation, can be described by a first-order rate expression:

$$\frac{dM_z(t)}{dt} = R_1 \left[M_0 - M_z(t) \right], \tag{2.12}$$

in which $R_1 = 1/T_1$ is the longitudinal relaxation rate constant and M_0 is the magnitude of the equilibrium magnetization, which lies entirely on the z-axis. According to Eq. 2.12, the longitudinal magnetization returns to equilibrium in an exponential fashion.

Another first-order rate process, known as transverse or spin-spin relaxation, was introduced to model the decay of the transverse magnetization in the transverse plane:

$$\frac{dM_x(t)}{dt} = -R_2 M_x(t),$$
$$\frac{dM_y(t)}{dt} = -R_2 M_y(t), \tag{2.13}$$

where $R_2 = 1/T_2$ is the transverse relaxation rate constant. This second process accounts for the mutual dephasing of the spins in the xy-plane.

The Bloch equations are obtained combining Eqs. 2.1, 2.12 and 2.13:

$$\frac{dM_x(t)}{dt} = \gamma\,[\mathbf{M}(t) \times \mathbf{B}(t)]_x - R_2 M_x(t),$$
$$\frac{dM_y(t)}{dt} = \gamma\,[\mathbf{M}(t) \times \mathbf{B}(t)]_y - R_2 M_y(t), \qquad (2.14)$$
$$\frac{dM_z(t)}{dt} = \gamma\,[\mathbf{M}(t) \times \mathbf{B}(t)]_z - R_1\left[M_z(t) - M_0\right].$$

These equations describe the evolution of the magnetization in a static magnetic field and in the absence of an applied *rf* field. A more general expression can be obtained in a rotating reference frame including the effect of an *rf* pulse (see Eqs. 2.6 and 2.7). In a convenient matrix form, one obtains

$$\frac{d}{dt}\begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix} = \begin{bmatrix} -R_2 & -\Omega & \omega_1 \sin\phi \\ \Omega & -R_2 & -\omega_1 \cos\phi \\ -\omega_1 \sin\phi & \omega_1 \cos\phi & -R_1 \end{bmatrix}\begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix} + R_1 M_0 \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}.$$
$$(2.15)$$

In many cases of practical interest the equation can be simplified even further. For instance, during free precession, that is in the absence of *rf* pulses, $\omega_1 = 0$ and 2.15 simplifies to

$$\frac{d}{dt}\begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix} = \begin{bmatrix} -R_2 & -\Omega & 0 \\ \Omega & -R_2 & 0 \\ 0 & 0 & -R_1 \end{bmatrix}\begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix} + R_1 M_0 \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}. \qquad (2.16)$$

If the pulse is short enough, i.e. its duration $\tau_p \ll T_1, T_2$, it is possible, in a good approximation, to neglect relaxation contributions to the trajectory of the magnetization:

$$\frac{d}{dt}\begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix} = \begin{bmatrix} 0 & -\Omega & \omega_1 \sin\phi \\ \Omega & 0 & -\omega_1 \cos\phi \\ -\omega_1 \sin\phi & \omega_1 \cos\phi & 0 \end{bmatrix}\begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix}. \qquad (2.17)$$

As mentioned earlier, the Bloch equations fail at describing systems of interacting spins. Several extensions to Bloch model to account for such interactions, such as the Solomon Eq. [3], have been proposed. However, to be useful for practical applications, it is necessary to use the semiclassical approach of Bloch, Wangsness and Redfield [4, 5].

2.2 Chemical Exchange Effects

In the absence of scalar coupling interactions, chemical exchange processes are described by an extension of the Bloch equations (see Sect. 2.1). In the case of a first-order chemical reaction or, equivalently, a two-site chemical exchange process, the kinetic rate laws are written in matrix form as

$$\frac{d}{dt}\begin{bmatrix}[A_1](t)\\ [A_2](t)\end{bmatrix}=\begin{bmatrix}-k_1 & k_{-1}\\ k_1 & -k_{-1}\end{bmatrix}\begin{bmatrix}[A_1](t)\\ [A_2](t)\end{bmatrix}, \tag{2.18}$$

in which k_1 (k_{-1}) is the rate constant for the forward (reverse) reaction. In general, in the case of a set of N coupled reactions, one has

$$\frac{d\mathbf{A}(t)}{dt}=\mathbf{K}\mathbf{A}(t), \tag{2.19}$$

in which the elements of the rate matrix $\mathbf{K}$ are given by

$$K_{ij}=k_{ji}, \tag{2.20}$$

$$K_{ii}=-\sum_{\substack{j=1\\ j\neq i}}^{N}k_{ij}. \tag{2.21}$$

Modified Bloch equations, known as McConnell equations, can be derived for such a system:

$$\frac{d\mathbf{M}_{jx}(t)}{dt}=\gamma\left(1-\sigma_j\right)\left[\mathbf{M}_j(t)\times\mathbf{B}(t)\right]_x-R_{2j}M_{jx}(t)+\sum_{k=1}^{N}K_{jk}\mathbf{M}_{kx}(t),$$

$$\frac{d\mathbf{M}_{jy}(t)}{dt}=\gamma\left(1-\sigma_j\right)\left[\mathbf{M}_j(t)\times\mathbf{B}(t)\right]_y-R_{2j}M_{jy}(t)+\sum_{k=1}^{N}K_{jk}\mathbf{M}_{ky}(t),$$

$$\frac{d\mathbf{M}_{jz}(t)}{dt}=\gamma\left(1-\sigma_j\right)\left[\mathbf{M_j}(t)\times\mathbf{B}(t)\right]_z-R_{1j}\left[M_{jz}(t)-M_{j0}\right]+\sum_{k=1}^{N}K_{jk}\mathbf{M}_{kz}(t).$$

$$\tag{2.22}$$

The above equations can be generalized to higher-order reactions by introducing the pseudo-first order rate constants:

$$k_{ij}=\frac{\zeta_{ij}(t)}{[A_i](t)}, \tag{2.23}$$

where $\zeta_{ij}(t)$ is the rate constant for the conversion of the ith species into the jth one.

The McConnell equations can be solved analogously to the Bloch equations. Three different regimes emerge from the set of solutions to these equations:

1. in the case of *slow exchange*, i.e. when the exchange rate is smaller than the chemical shift difference between the two sites, two resonance lines are observed;
2. as the exchange rate increases, the lines broaden and, when the rate is of the order of the chemical shift difference, the lines coalesce (*intermediate exchange* or *coalescence*);
3. if the rate is further increased, the system is in *fast exchange* and a single narrow resonance line is observed at the average of the chemical shifts.

2.3 Bloch-Wangsness-Redfield Theory

In this model, also known as Redfield theory, a quantum mechanical description of the system is derived, while describing the surroundings (i.e., the heat bath or lattice) in a classical way. The main limitation of this approximation is that the energy levels are predicted to be equally populated at equilibrium. Therefore, the theory is formally valid only in the high-temperature limit, which is a very good approximation at room temperature. At finite temperatures, corrections are required to ensure that the correct equilibrium populations are reached. However, these corrections are significant only in the case of very low temperatures. In our discussion, we shall follow the account of [1].

2.3.1 The Master Equation

Let us write the Hamiltonian as a sum of terms that act only on the spin system ($\mathscr{H}_0$) and a stochastic part, $\mathscr{H}_1(t)$, that couples the spin system to the lattice:

$$\mathscr{H}(t) = \mathscr{H}_0 + \mathscr{H}_1(t). \tag{2.24}$$

In the above expression the absence of applied *rf* fields was implicitly assumed, thus $\mathscr{H}_0$ is time-independent. In other words, a time-dependent perturbation $\mathscr{H}_1(t)$ is superimposed onto the main time-independent Hamiltonian $\mathscr{H}_0$.

The corresponding Liouville equation of motion, describing the evolution of the density operator $\sigma(t)$, is

$$\frac{d\sigma(t)}{dt} = -i\left[\mathscr{H}_0 + \mathscr{H}_1(t), \sigma(t)\right] = -i\left\{\hat{L}_0 + \hat{L}_1(t)\right\}\sigma(t), \tag{2.25}$$

in which $\hat{L}(t) = [\mathscr{H}(t)]$, is the commutation superoperator or Liouvillian.

It is convenient to remove the explicit dependence on $\mathcal{H}_0$ by rewriting the density operator in a new reference frame, called the *interaction frame*:

$$\sigma^T(t) = \exp\left(i\hat{L}_0 t\right)\sigma(t) = \exp\left(i\mathcal{H}_0 t\right)\sigma(t)\exp\left(-i\mathcal{H}_0 t\right). \qquad (2.26)$$

Transforming also the stochastic Hamiltonian,

$$\mathcal{H}_1^T(t) = \hat{L}_0 \mathcal{H}_1(t) = \exp\left(i\mathcal{H}_0 t\right)\mathcal{H}_1(t)\exp\left(-i\mathcal{H}_0 t\right), \qquad (2.27)$$

it is possible to rewrite Eq. 2.25 in the interaction frame:

$$\frac{\mathrm{d}\sigma^T(t)}{\mathrm{d}t} = -i\left[\mathcal{H}_1^T(t),\sigma^T(t)\right] = -i\hat{L}_1^T(t)\sigma^T(t). \qquad (2.28)$$

In mathematical terms, the transformation into the interaction frame is isomorphous to the rotating-frame transformation. However, there are some marked differences between the two. Indeed, in the rotating frame the *rf* Hamiltonian is time-independent and the interactions contained in $\mathcal{H}_0$ are retained; on the other hand, in the interaction frame, $\mathcal{H}_0$ is not (explicitly) active, whereas the time dependence of $\mathcal{H}_1^T(t)$ is retained. This means that it is possible to apply both the transformation sequentially.

Several assumptions are required to solve Eq. 2.28:

1. The ensemble average of $\mathcal{H}_1^T(t)$ is zero. Any time-dependent fluctuations that do not vanish upon averaging are to be included in the time-independent Hamiltonian;
2. $\sigma^T(t)$ and $\mathcal{H}_1^T(t)$ are not correlated, thus it is possible to take the ensemble average of the fluctuations of the Hamiltonian and of the quantum states independently;
3. $\tau_c \ll t \ll 1/R$, where τ_c is the correlation time relevant for $\mathcal{H}_1^T(t)$ and R is the relevant relaxation rate constant;
4. in order for the system to relax towards thermal equilibrium, $\sigma^T(t)$ has to be replaced by $\sigma^T(t) - \sigma_0$, in which σ_0 is the density operator at equilibrium. By definition, one has $\sigma_0^T = \sigma_0$.

Using this assumption, the right-hand term in Eq. 2.28 can be replaced by an integral:

$$\frac{\mathrm{d}\sigma^T(t)}{\mathrm{d}t} = -\int_0^\infty \mathrm{d}\tau \overline{[\mathcal{H}_1^T(t),[\mathcal{H}_1^T(t-\tau),\sigma^T(t)-\sigma_0]]}, \qquad (2.29)$$

where the overbar represents the ensemble average. In this equation the third assumption allows the integral to run to infinity; because we assumed that the fluctuations of the Hamiltonian are not correlated with the density matrix, we could calculate the ensemble average over the stochastic Hamiltonians independently from $\sigma^T(t)$.

In order to be able to transform Eq. 2.29 back to the laboratory frame, the stochastic Hamiltonian has to be decomposed as the sum of random functions of spatial variables $F_k^q(t)$ and tensor spin operators $\mathbf{A}_k^q$:

$$\mathscr{H}_1(t) = \sum_{q=-k}^{k} (-1)^q F_k^{-q}(t) \mathbf{A}_k^q.$$

(2.30)

The tensor spin operators are chosen to be spherical tensor operators because of their transformations properties under rotations. For the Hamiltonians of interest in NMR spectroscopy, the rank of the tensor k is one or two. These operators can be further decomposed as a sum of basis operators:

$$\mathbf{A}_k^q = \sum_p \mathbf{A}_{kp}^q,$$

(2.31)

where the components $\mathbf{A}_{kp}^q$ have the following property:

$$\hat{L}_0 \left\{ \mathbf{A}_{kp}^q \right\} = \left[\mathscr{H}_0, \mathbf{A}_{kp}^q \right] = \omega_p^q \mathbf{A}_{kp}^q.$$

(2.32)

In other words, $\mathbf{A}_{kp}^q$ are eigenfunctions of the Hamiltonian commutation superoperator with eigenfrequencies ω_p^q. The index p here is used to distinguish between spin operators with the same order q but different eigenfrequencies. Furthermore, Eq. 2.32 implies the following property:

$$\exp\left(i\hat{L}_0 t\right) \mathbf{A}_{kp}^q = \exp\left(i\mathscr{H}_0 t\right) \mathbf{A}_{kp}^q \exp\left(-i\mathscr{H}_0 t\right) = \exp\left(i\omega_p^q t\right) \mathbf{A}_{kp}^q,$$

(2.33)

which defines also the transformation of $\mathbf{A}_{kp}^q$ in the interaction frame:

$$\mathbf{A}_k^{qT} = \exp\left(i\mathscr{H}_0 t\right) \mathbf{A}_k^q \exp\left(-i\mathscr{H}_0 t\right) = \sum_p \mathbf{A}_{kp}^q \exp\left(i\omega_p^q t\right).$$

(2.34)

Substituting Eqs. 2.30 and 2.34 in Eq. 2.29, one obtains

$$\frac{d\sigma^T(t)}{dt} = -\sum_{q,q'} \sum_{p,p'} (-1)^{q+q'} \exp\left\{ i\left(\omega_p^q + \omega_{p'}^{q'}\right) t \right\} \left[\mathbf{A}_{kp'}^{q'}, \left[\mathbf{A}_{kp}^q, \sigma^T(t) - \sigma_0 \right] \right]$$

$$\times \int_0^\infty \overline{F_k^{-q'}(t) F_k^{-q}(t-\tau)} \exp\left(i\omega_p^q \tau\right) d\tau.$$

(2.35)

If $q' \neq -q$, the two random processes $F_k^{-q'}(t)$ and $F_k^{-q}(t)$ are assumed to be statistically independent, which causes the ensemble average to vanish, unless $q' = -q$. Thus,

$$\frac{d\sigma^T(t)}{dt} = -\sum_{q=-k}^{k} \sum_{p,p'} \exp\left\{i\left(\omega_p^q - \omega_{p'}^q\right)t\right\} \left[\mathbf{A}_{kp'}^{-q}, \left[\mathbf{A}_{kp}^q, \sigma^T(t) - \sigma_0\right]\right]$$

$$\times \int_0^\infty \overline{F_k^q(t) F_k^{-q}(t-\tau)} \exp\left(i\omega_p^q\tau\right)d\tau. \tag{2.36}$$

The equation above can be further simplified by noticing that terms in which $|\omega_p^q - \omega_{p'}^q| \gg 0$ oscillate much faster than the typical time scales of relaxation phenomena, and therefore do not affect the evolution of the density matrix. Furthermore, in the absence of degenerate eigenfrequencies, terms in Eq. 2.36 are not vanishing only if $p = p'$. Therefore,

$$\frac{d\sigma^T(t)}{dt} = -\sum_{q=-k}^{k} \sum_{p} \left[\mathbf{A}_{kp}^{-q}, \left[\mathbf{A}_{kp}^q, \sigma^T(t) - \sigma_0\right]\right] \int_0^\infty \overline{F_k^q(t) F_k^{-q}(t-\tau)} \exp\left(i\omega_p^q\tau\right)d\tau. \tag{2.37}$$

The terms $\overline{F_k^q(t) F_k^{-q}(t-\tau)}$ are known as *correlation functions*. The real part of the integral in Eq. 2.37 is the *power spectral density function* $j^q(\omega)$:

$$j^q(\omega) = 2\operatorname{Re}\left\{\int_0^\infty \overline{F_k^q(t) F_k^{-q}(t-\tau)} \exp\left(i\omega\tau\right)d\tau\right\}$$

$$= \operatorname{Re}\left\{\int_{-\infty}^\infty \overline{F_k^q(t) F_k^{-q}(t-\tau)} \exp\left(i\omega\tau\right)d\tau\right\}$$

$$= \operatorname{Re}\left\{\int_{-\infty}^\infty \overline{F_k^q(t) F_k^{-q}(t+\tau)} \exp\left(i\omega\tau\right)d\tau\right\}. \tag{2.38}$$

The equation above shows that the power spectral density is an even function of τ. Furthermore, it is an even function of ω as well. On the other hand, the imaginary part of the integral in Eq. 2.37,

$$k^q(\omega) = \operatorname{Im}\left\{\int_0^\infty \overline{F_k^q(t) F_k^{-q}(t-\tau)} \exp\left(-i\omega\tau\right)d\tau\right\}$$

$$= \operatorname{Im}\left\{\int_0^\infty \overline{F_k^q(t) F_k^{-q}(t+\tau)} \exp\left(-i\omega\tau\right)d\tau\right\}, \tag{2.39}$$

is an odd function of ω.

In the high-temperature limit, the equilibrium density matrix is proportional to $\mathcal{H}_0$. Thus, using Eq. 2.33, the double commutator $\left[\left[A_{kp}^{-q}, A_{kp}^{q}\right], \sigma_0\right] = 0$. Using this property in Eq. 2.37, one obtains

$$\frac{d\sigma^T (t)}{dt} = -\frac{1}{2} \sum_{q=-k}^{k} \sum_{p} \left[A_{kp}^{-q}, \left[A_{kp}^{q}, \sigma^T (t) - \sigma_0\right]\right] j^q \left(\omega_p^q\right)$$

$$+ i \sum_{q=0}^{k} \sum_{p} \left[\left[A_{kp}^{-q}, A_{kp}^{q}\right], \sigma^T (t)\right] k^q \left(\omega_p^q\right). \tag{2.40}$$

By transforming the above equation back to the laboratory frame, the *Liouville-von Neumann* differential equation for the density equation is obtained:

$$\frac{d\sigma (t)}{dt} = -i [\mathcal{H}_0, \sigma (t)] - i [\Delta, \sigma (t)] - \hat{\Gamma} (\sigma (t) - \sigma_0), \tag{2.41}$$

in which the *relaxation superoperator* is

$$\hat{\Gamma} = \frac{1}{2} \sum_{q=-k}^{k} \sum_{p} \left[A_{kp}^{-q}, \left[A_{kp}^{q}, \quad\right]\right] j^q \left(\omega_p^q\right). \tag{2.42}$$

Δ is the dynamic frequency shift operator that accounts for second-order frequency shifts of the resonance lines, known as dynamic frequency shifts:

$$\Delta = -\sum_{q=0}^{k} \sum_{p} k^q \left(\omega_p^q\right) \left[A_{kp}^{-q}, A_{kp}^{q}\right]. \tag{2.43}$$

This term can be incorporated into the Hamiltonian to obtain the final result, known as *master equation*:

$$\frac{d\sigma (t)}{dt} = -i [\mathcal{H}_0, \sigma (t)] - \hat{\Gamma} (\sigma (t) - \sigma_0). \tag{2.44}$$

In the calculation of relaxation rates it is often convenient to expand Eq. 2.44 in terms of the basis operators used to expand the density operator:

$$\frac{db_r (t)}{dt} = \sum_{s} \{-i\Omega_{rs} b_s (t) - \Gamma_{rs} [b_s (t) - b_{s0}]\}, \tag{2.45}$$

where Ω_{rs} are characteristic frequencies defined as

$$\Omega_{rs} = \frac{\langle \mathbf{B}_r \mid [\mathcal{H}_0, \mathbf{B}_s]\rangle}{\langle \mathbf{B}_r \mid \mathbf{B}_s \rangle}, \tag{2.46}$$

Fig. 2.1 Redfield kite. In the absence of degenerate transitions, only the elements contained in the *solid blocks* can be non-zero, i.e. cross-relaxation is possible between populations, while the coherences relax independently. In the case of degenerate transitions, additional non-zero elements can be found inside the *dashed blocks* between coherences of the same order. *ZQ* zero quantum, *SQ* single quantum, *DQ* double quantum
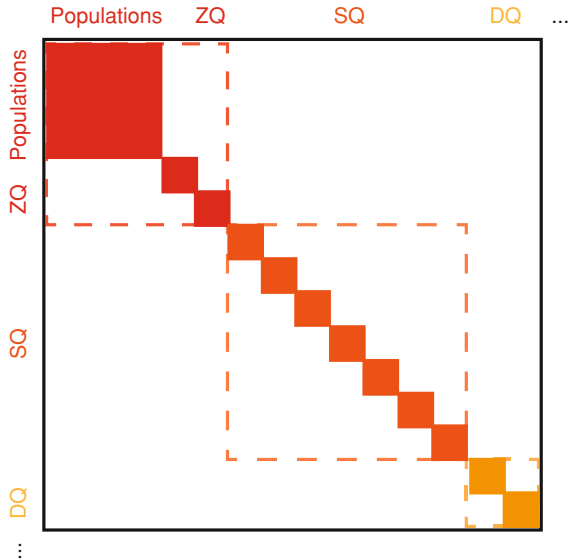
Γ_{rs} are the rate constants for relaxation between the operators $\mathbf{B}_s$ and $\mathbf{B}_r$ (and vice versa, since $\Gamma_{rs} = \Gamma_{sr}$ for normalized basis operators)

$$\Gamma_{rs} = \frac{\langle \mathbf{B}_r \mid \hat{\Gamma} \mathbf{B}_s \rangle}{\langle \mathbf{B}_r \mid \mathbf{B}_r \rangle}$$
$$= \frac{1}{2} \sum_{q=-k}^{k} \sum_{p} \left\{ \frac{\langle \mathbf{B}_r \mid \left[\mathbf{A}_{kp}^{-q}, \left[\mathbf{A}_{kp}^{q}, \mathbf{B}_s \right] \right] \rangle}{\langle \mathbf{B}_r \mid \mathbf{B}_r \rangle} \right\} j^q \left(\omega_p^q \right), \qquad (2.47)$$

and finally $b_r(t)$ results from the application of the relevant projection superoperator onto the density matrix:

$$b_r(t) = \frac{\langle \mathbf{B}_r \mid \sigma(t) \rangle}{\langle \mathbf{B}_r \mid \mathbf{B}_r \rangle}. \qquad (2.48)$$

The diagonal elements Γ_{rr} are *auto*-relaxation rates, while off-diagonal elements Γ_{rs} are *cross*-relaxation rates. Because we assumed that only terms satisfying $q = -q'$ give non-zero contributions to Eq. 2.35, cross-relaxation can occur only between operators with the same coherence order. In addition, because of the secular approximation in Eq. 2.37, cross-relaxation between off-diagonal terms is forbidden in the absence of degenerate transitions. These two features give rise to a characteristic block shape in the relaxation superoperator, known as Redfield kite (see Fig. 2.1).

2.3.2 Interference Between Relaxation Mechanisms

In general there is more than one process that can cause relaxation. In this case, one can generalize Eq. 2.30 to

$$\mathscr{H}_1(t) = \sum_m \sum_{q=-k}^{k} (-1)^q F_{mk}^{-q}(t) \mathbf{A}_{mk}^q,$$

(2.49)

in which the index m runs over all active mechanisms. Using the above equation, a generalization of Eq. 2.47 can be written:

$$\Gamma_{rs} = \frac{1}{2} \sum_m \sum_{q=-k}^{k} \sum_p \left\{ \frac{\left\langle \mathbf{B}_r \mid \left[\mathbf{A}_{mkp}^{-q}, \left[\mathbf{A}_{mkp}^q, \mathbf{B}_s \right] \right] \right\rangle}{\langle \mathbf{B}_r \mid \mathbf{B}_r \rangle} \right\} j^q\left(\omega_p^q\right)$$

$$+ \frac{1}{2} \sum_{\substack{m,n \\ m \neq n}} \sum_{q=-k}^{k} \sum_p \left\{ \frac{\left\langle \mathbf{B}_r \mid \left[\mathbf{A}_{mkp}^{-q}, \left[\mathbf{A}_{nkp}^q, \mathbf{B}_s \right] \right] \right\rangle}{\langle \mathbf{B}_r \mid \mathbf{B}_r \rangle} \right\} j_{mn}^q\left(\omega_p^q\right)$$

$$= \sum_m \Gamma_{rs}^m + \sum_{\substack{m,n \\ m \neq n}} \Gamma_{rs}^{mn},$$

(2.50)

in which the cross-correlated spectral density was used, defined as

$$j_{mn}^q = \text{Re}\left\{ \int_{-\infty}^{\infty} \overline{F_{mk}^q(t) \, F_{nk}^{-q}(t+\tau)} \exp(-i\omega\tau) \, d\tau \right\}.$$

(2.51)

In other words, according to Eq. 2.50, in a spin system where more than one stochastic Hamiltonian is present, we can have relaxation due to only one mechanism, with relaxation rate constant Γ_{rs}^m, and relaxation arising from the interference (or cross-correlation) between different mechanisms, with relaxation rate constant Γ_{rs}^{mn}. The latter is possible only if there is some degree of correlation between the mth and nth mechanisms, i.e., if $F_{mk}^q(t)$ and $F_{nk}^q(t)$ are correlated.

2.3.3 Relaxation in the Rotating Frame

In the presence of an applied *rf* field, a transformation into a rotating frame, where the time dependence of the *rf* Hamiltonian $\mathscr{H}_{rf}(t)$ is removed, has to precede the transformation into the interaction frame. When the Zeeman interaction is the dominant term in $\mathscr{H}_0$, the interaction frame is a doubly rotating tilted frame. Thus, the frequencies used as arguments of the spectral density function should be replaced by $\omega_p^q + \omega_p^{q(rf)}$, where the latter is defined by

$$\sum_{i=1}^{K} \omega_{rf,i} \left[I_{zi}, \mathbf{A}_{kp}^q \right] = \omega_p^{q(rf)} \mathbf{A}_{kp}^{-q}, \tag{2.52}$$

in which $\omega_{rf,i}$ is the frequency of the rotating frame for the ith spin and K is the number of irradiated spins.

However, in most of the cases $\omega_1 \tau_c \ll 1$, where ω_1 is the applied rf amplitude and τ_c is the rotational correlation time of the molecule of interest. Therefore $j^q \left(\omega_p^q + \omega_p^{q(rf)} \right) \approx j^q \left(\omega_p^q \right)$. Using this approximation, it is possible to compute approximate relaxation rate constants by transforming the operators in the tilted frame to the laboratory frame before using Eq. 2.47:

$$\Gamma_{rs}' = \frac{\left\langle \mathbf{U}^{-1} \mathbf{B}_r' \mathbf{U} \mid \hat{\Gamma} \left\{ \mathbf{U}^{-1} \mathbf{B}_s' \mathbf{U} \right\} \right\rangle}{\left\langle \mathbf{B}_r' \mid \mathbf{B}_r' \right\rangle}. \tag{2.53}$$

For instance, if an rf field is applied with x-phase, the transformation is defined as a rotation around the y-axis:

$$\mathbf{U} = \exp \left\{ i \sum_{i=1}^{K} \theta_i I_{yi} \right\}, \tag{2.54}$$

in which $\theta_i = \omega_1 / \Omega_i$ is the tilt angle.

The autorelaxation rate $R_1 (\theta_i)$ or $R_{1\rho}$ is given by

$$R_{1\rho} = R_1 \cos^2 \theta_i + R_2 \sin^2 \theta_i. \tag{2.55}$$

Operators that do not commute with the Hamiltonian in the rotating frame decay rapidly as a consequence of rf inhomogeneities: therefore, if a continuous-wave field is applied, only operators which do not evolve in the rotating frame have to be considered, i.e. longitudinal operators and zero-quantum coherences. If the rf field is phase- or amplitude-modulated in order to suppress the effect of offsets and rf inhomogeneities, more quantum states have to be considered and the effective average rate constant has to be obtained by averaging the instantaneous rate constant over the trajectory followed by the operator under the influence of the rotating-frame Hamiltonian (see Sects. 2.4 and 2.5).

2.3.4 Spectral Density Functions

As shown by Hubbard [6], in the high-temperature limit, the description of the relaxation properties of the system requires only one spectral density function, because the following identity holds:

Table 2.1 Spatial functions for relaxation mechanisms

Interaction	$c(t)$
Dipolar	$-\sqrt{6}\,(\mu_0/4\pi)\,\hbar\gamma_I\gamma_S r_{IS}\,(t)^{-3}$
CSA	$\Delta\sigma\,\gamma_I B_0/\sqrt{3}$
Quadrupolar	$e^2 qQ/[4\hbar I\,(2I-1)]$

An axially symmetric chemical shift tensor is assumed, with $\sigma_{zz} = \sigma_\parallel$, $\sigma_{xx} = \sigma_{yy} = \sigma_\perp$ and $\Delta\sigma = \sigma_\parallel - \sigma_\perp$. The electric field gradient tensor is assumed to be axially symmetric, with principal values $V_{zz} = eq$ and $V_{xx} = V_{yy}$. Q is the nuclear quadrupole moment and e is the electron charge

$$j^q(\omega) = (-1)^q j^0(\omega) \equiv (-1)^q j(\omega).\tag{2.56}$$

Tensor operators of rank 2 can be used to describe the relaxation mechanisms of interest. The random functions $F_2^0(t)$ in Eq. 2.39 can be factored as

$$F_2^0(t) = c_0(0)\,Y_2^0\,[\Omega(t)].\tag{2.57}$$

Therefore, the spectral density function can be written as

$$j(\omega) = \mathrm{Re}\left\{\int_{-\infty}^{\infty} \overline{c_0(t)\,c_0(t+\tau)\,Y_2^0[\Omega(t)]\,Y_2^0[\Omega(t+\tau)]}\exp\left(-i\omega\tau\right)\mathrm{d}\tau\right\}$$

$$= \mathrm{Re}\left\{\int_{-\infty}^{\infty} C(\tau)\exp\left(-i\omega\tau\right)\mathrm{d}\tau\right\},\tag{2.58}$$

with the stochastic correlation function:

$$C(\tau) = \overline{c_0(t)\,c_0(t+\tau)\,Y_2^0[\Omega(t)]\,Y_2^0[\Omega(t+\tau)]}.\tag{2.59}$$

In the above equations, $c_0(t)$ is a function of physical constants and spatial variables (see Table 2.1), $Y_2^0[\Omega(t)]$ is a modified second-order spherical harmonic function (see Table 2.2) of the polar angles in the laboratory frame $\Omega(t)$. The polar angles are used to define the orientation in the laboratory frame of a vector that points in the principal direction for the interaction. The most important feature of spectral density functions is that, as the molecules tumble in solution, the oscillating magnetic fields that cause relaxation are not distributed in a homogeneous way over all frequencies. The power spectral density function can be used to measure the probability of motions with frequency between ω and $\omega + \mathrm{d}\omega$.

For a rigid spherical molecule, the spatial function is time-independent (i.e., $c(t) = c_0$), and therefore $J(\omega) = d_{00}J(\omega)$, in which $d_{00} = c_0^2$. The orientational spectral density function used here is defined as

Table 2.2 Modified second-order spherical harmonics

q	Y_2^q
0	$\left(3\cos^2\theta - 1\right)/2$
1	$-\sqrt{3/2}\sin\theta\cos\theta e^{i\phi}$
2	$\sqrt{3/8}\sin^2\theta e^{i2\phi}$

$$J(\omega) = \mathrm{Re}\left\{ \int_{-\infty}^{\infty} C_{00}^2(\tau)\exp(-i\omega\tau)\,\mathrm{d}\tau \right\}, \qquad (2.60)$$

in which the orientational correlation function

$$C_{00}^2(\tau) = \overline{Y_2^0\left[\Omega(t)\right] Y_2^0\left[\Omega(t+\tau)\right]} \qquad (2.61)$$

was used. For instance, in the case of isotropic rotational diffusion of a rigid rotor, the orientational correlation function is

$$C_{00}^2(\tau) = \frac{1}{5}e^{-\tau/\tau_c}, \qquad (2.62)$$

in which τ_c is the correlation time, which depends on the size of the molecule, the viscosity of the solution, and the temperature. The corresponding spectral density function is

$$J(\omega) = \frac{2}{5}\frac{\tau_c}{\left(1+\omega^2\tau_c^2\right)}. \qquad (2.63)$$

The functional form in Eq. 2.63 is a Lorentzian. Therefore, because the value of a Lorentzian is almost constant for $\omega^2\tau_c^2 < 1$, if the molecular motion is rapid enough to satisfy $\omega_p^{(q)2}\tau_c^2 \ll 1$ (i.e., τ_c is short enough), $J\left(\omega_p^q\right) \approx J(0)$ is a good approximation. We shall refer to this limit as *extreme narrowing* regime. On the contrary, if the motion is very slow, i.e. $\omega_p^{(q)2}\tau_c^2 \gg 1$, then $J\left(\omega_p^q\right) \propto \omega_p^{(q)-2}\tau_c$, a limit known as *spin diffusion* (or slow tumbling) regime.

Both overall rotational Brownian motions and relative motions of nuclei in a molecular reference frame contribute to the modulation of local magnetic fields. In the case of isotropic rotational diffusion, to a very good approximation, the total correlation function can be factored as

$$C(\tau) = C_O(\tau)C_I(\tau), \qquad (2.64)$$

in which the correlation function for overall motions $C_O(\tau)$ is given by Eqs. 2.61 and 2.62, whereas the correlation function for internal motions has to be computed directly from Eq. 2.59 assuming a model of intramolecular motions.

Table 2.3 Tensor operators for the dipolar interaction

q	p	A_{2p}^q	ω_p
0	0	$\left(2/\sqrt{6}\right) I_z S_z$	0
0	1	$-1/\left(2\sqrt{6}\right) I^+ S^-$	$\omega_I - \omega_S$
1	0	$-\left(1/2\right) I_z S^+$	ω_S
1	1	$-\left(1/2\right) I^+ S_z$	ω_I
2	0	$\left(1/2\right) I^+ S^+$	$\omega_I + \omega_S$

2.3.5 Relaxation Mechanisms

In the following, we will limit ourselves to intramolecular dipolar, anisotropic chemical shift, quadrupolar and scalar coupling interactions. Intramolecular paramagnetic relaxation can be described by the same Hamiltonian as dipolar interactions, the only difference being that the interaction is between the nucleus and an unpaired electron. All other relaxation mechanisms are of no practical interest in the case of biomolecules. In particular, for spin-1/2 nuclei in diamagnetic biological molecules, the dipolar and the anisotropic chemical shift mechanisms are by far the dominant mechanisms.

2.3.5.1 Dipolar Relaxation

In the case of intramolecular dipolar relaxation for a an IS spin system, the terms $\mathbf{A}_{2p}^q$ are given in Table 2.3. The relaxation rate constants can be calculated using Eq. 2.47 and are given in Table 2.4. It is worth pointing out that R_1 has a maximum for $\omega_0 \tau_c = 1$, whereas R_2 increases monotonically with τ_c.

If the two spins are weakly coupled, the longitudinal relaxation is unaffected by the scalar interaction because both I_z and S_z commute with the scalar coupling Hamiltonian. The expressions in Table 2.4 are therefore still valid.

As far as the transverse relaxation is concerned, the in-phase I^+ (S^+) term evolves into the anti-phase operator $2I^+ S_z$ $(2I_z S_+)$ under the effect of the scalar interaction. If the evolution is faster than the relaxation processes, an average relaxation constant is measured because the magnetization is rapidly exchanging between in-phase and anti-phase terms.

2.3.5.2 Chemical Shift Anisotropy and Quadrupolar Relaxation

Local fields that lie at the origin of chemical shifts are in general anisotropic. Therefore, the chemical shift is best described as a tensor. The reorientation of this tensor with respect to the laboratory frame induces a time-varying magnetic field on the nucleus and, consequently, relaxation. The chemical-shift anisotropy (CSA) relaxation is significant for ^{13}C, ^{15}N and ^{31}P, while it is negligible for protons, and it has a quadratic dependence on the strength of the static magnetic field.

Table 2.4 Relaxation rate constants for *IS* dipolar interaction

Coherence level	Operator	Relaxation rate constant
Populations	I_z	$(d_{00}/4) \{J(\omega_I - \omega_S) + 3J(\omega_I) + 6J(\omega_I + \omega_S)\}$
	S_z	$(d_{00}/4) \{J(\omega_I - \omega_S) + 3J(\omega_I) + 6J(\omega_I + \omega_S)\}$
	$I_z \leftrightarrow S_z$	$(d_{00}/4) \{-J(\omega_I - \omega_S) + 6J(\omega_I + \omega_S)\}$
0	$2I_z S_z$	$(3d_{00}/4) \{J(\omega_I) + J(\omega_S)\}$
	ZQ_x, ZQ_y	$(d_{00}/8) \{2J(\omega_I - \omega_S) + 3J(\omega_I) + 3J(\omega_S)\}$
± 1	I^+, I^-	$(d_{00}/8) \{4J(0) + J(\omega_I - \omega_S) + 3J(\omega_I) + 6J(\omega_S) + 6J(\omega_I + \omega_S)\}$
	S^+, S^-	$(d_{00}/8) \{4J(0) + J(\omega_I - \omega_S) + 3J(\omega_S) + 6J(\omega_I) + 6J(\omega_I + \omega_S)\}$
	$2I^+S_z, 2I^-S_z$	$(d_{00}/8) \{4J(0) + J(\omega_I - \omega_S) + 3J(\omega_I) + 6J(\omega_I + \omega_S)\}$
	$2I_z S^+, 2I_z S^-$	$(d_{00}/8) \{4J(0) + J(\omega_I - \omega_S) + 3J(\omega_S) + 6J(\omega_I + \omega_S)\}$
± 2	DQ_x, DQ_y	$(d_{00}/8) \{3J(\omega_I) + 3J(\omega_S) + 12J(\omega_I + \omega_S)\}$

$d_{00} = (\mu_0/4\pi)^2 \hbar^2 \gamma_I^2 \gamma_S^2 r_{IS}^{-6}$

Table 2.5 Tensor operators for the CSA interaction

q	p	A_{2p}^q	ω_p
0	0	$\left(2/\sqrt{6}\right) I_z$	0
1	0	$-(1/2) I^+$	ω_I

Table 2.6 Tensor operators for the quadrupolar interaction

q	p	A_{2p}^q	ω_p
0	0	$\left(1/2\sqrt{6}\right) \left[4I_z^2 - I^+I^- - I^-I^+\right]$	0
1	0	$-(1/2) \left[I_z I^+ + I^+ I_z\right]$	ω_I
2	0	$(1/2) I^+ I^+$	$2\omega_I$

Nuclei with $I > 1/2$ also have a nuclear electric quadrupole moment, which is a measure of how much the nuclear charge distribution departs from a spherical one. A relaxation pathway is provided by the interaction of the quadrupole moment with local oscillating electric field gradients, generated by the electrons.

The terms $\mathbf{A}_{2p}^q$ for the CSA and quadrupolar interactions are given in Tables 2.5 and 2.6, respectively. Longitudinal and transverse relaxation rate constants are given in Table 2.7, where axially symmetrical CSA and quadrupolar tensors were assumed for a spin-1 nucleus.

2.3.5.3 Scalar Relaxation

In the presence of a scalar interaction, the local magnetic field experienced by spin S (e.g., a nitrogen-15) depends on the value of the J-coupling constant with spin I (e.g., a proton). The magnetic field is time-dependent in the following two scenarios:

1. the value of the J-coupling constant is time-dependent (*scalar relaxation of the first kind*). This can happen in the case of transitions of the spin system between environments where the coupling constant assumes different values;

Table 2.7 CSA and quadrupolar relaxation rate constants

Rate constant	CSA	Quadrupolar
R_1	$d_{00}J(\omega_I)$	$3d_{00}\{J(\omega_I) + 2J(2\omega_I)\}$
R_2	$(d_{00}/6)\{4J(0) + 3J(\omega_I)\}$	$(3d_{00}/2)\{3J(0) + 5J(\omega_I) + 2J(2\omega_I)\}$

CSA $d_{00} = (\sigma_\parallel - \sigma_\perp)^2 \omega_I^2/3$

Quadrupolar $d_{00} = [e^2qQ/(4\hbar)]^2$

2. the state of spin I varies very rapidly (*scalar relaxation of the second kind*). This is the case if the nucleus relaxes rapidly or if it is involved in fast chemical exchange.

Expressions for contributions to relaxation rate constants from scalar relaxation are given by [7]:

$$R_1^{sc} = \frac{2A^2}{3}S(S+1)\frac{\tau_2}{1 + (\omega_I - \omega_S)^2 \tau_2^2}; \tag{2.65}$$

$$R_2^{sc} = \frac{A^2}{3}S(S+1)\left[\frac{\tau_2}{1 + (\omega_I - \omega_S)^2 \tau_2^2} + \tau_1\right]. \tag{2.66}$$

For scalar relaxation of the first kind, $A = 2\pi (p_1p_2)^{1/2} (J_1 - J_2)$, in which J_1 and J_2 are the scalar coupling constants, p_1 and p_2 the populations of the two sites, and $\tau_1 = \tau_2 = \tau_e$ is the exchange time constant. In the case of relaxation of the second kind, $A = 2\pi J_{IS}$ and τ_1 and τ_2 are the spin-lattice and spin-spin relaxation time constants for spin S.

2.4 Average Hamiltonian Theory

In the following section, we will adopt the approach of [8].

The principle on which Average Hamiltonian Theory (AHT) rests is that, in the case of a periodic time-dependent Hamiltonian, it is possible, under suitable conditions, to describe the evolution of the spin system with good accuracy considering the average effect of the Hamiltonian over a cycle of its oscillations [9]. For a time-independent system, the evolution operator can be written in an exponential form. Therefore, in the time-dependent case, for the Schrödinger equation

$$\frac{d\sigma(t)}{dt} = -i\mathscr{H}(t)\sigma(t), \tag{2.67}$$

a solution expressed in an exponential form is postulated, given by

$$\sigma(t) = e^{-iH(t)}\sigma(0), \tag{2.68}$$

in which $H(t)$ is a continuous function of time, that is not to be confused with the Hamiltonian $\mathscr{H}(t)$.[1] As proposed by Magnus [10], $H(t)$ can be written as a series expansion:

$$H(t) = H^{(0)}(t) + H^{(1)}(t) + H^{(2)}(t) + \cdots. \tag{2.69}$$

For reference, the first two terms are

$$H^{(0)}(t) = \int_0^t \mathscr{H}(t_1)\, dt_1, \tag{2.70}$$

$$H^{(1)}(t) = -\frac{i}{2} \int_0^t \int_0^{t_2} [\mathscr{H}(t_2), \mathscr{H}(t_1)]\, dt_1 dt_2. \tag{2.71}$$

In the case of a periodic Hamiltonian, i.e., $\mathscr{H}(t) = \mathscr{H}(t + \tau)$, one can compute the integrals over one cycle and extend them to arbitrary durations by setting

$$\sigma(N\tau) = \left[e^{-iH(\tau)}\right]^N \sigma(0). \tag{2.72}$$

In the literature, the terms of the expansion of $H(\tau)$ are divided by τ to yield a time-independent effective Hamiltonian. The average Hamiltonian is given by the zeroth-order term

$$\overline{H}^{(0)} = \frac{H^{(0)}(\tau)}{\tau}, \tag{2.73}$$

whereas the first-order correction to $\overline{H}^{(0)}$ is given by

$$\overline{H}^{(1)} = \frac{H^{(1)}(\tau)}{\tau}, \tag{2.74}$$

and so on for higher-order terms.

Although a considerable simplification in the calculations is achieved, one drawback of AHT is that the system can only be observed "stroboscopically" at integer multiples of the period, i.e., at $t = N\tau$. A second, possibly more serious, limitation is that the series in Eq. 2.69 must converge. A rough criterion is developed as follows. $H^{(n)}(t)$ contains n-fold products of $\mathscr{H}(t)$ and each integration introduces a term proportional to τ. Therefore, the nth-order term is roughly proportional to $\left(\langle\mathscr{H}^2\rangle^{1/2}\tau\right)^n$. Hence, the series should converge for $\langle\mathscr{H}^2\rangle^{1/2}\tau < 1$. Although often useful, this criterion is not rigorous and can provide misleading results.

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[1] Magnus [10] shows that, rigorously speaking, $H(t)$ *always* exists for t close to zero, but may not be a solution valid for the entire domain of the function. Indeed, some restrictions must be placed on $\mathscr{H}(t)$ for $H(t)$ to be well defined for all t. The reader is referred to the original work of Magnus for a discussion of these restrictions.

2.5 Average Liouvillian Theory

The behavior of a spin system under the combined effect of *rf* pulses, free-precession
intervals and relaxation can be described, with good accuracy, in the framework of
the Average Liouvillian Theory (ALT). We shall present here its basic concepts
following the account of [11].

It is possible to write a general solution to Eq. 2.25 in the form

$$\sigma\,(t) = e^{-\hat{L}t_n} \prod_{j=1}^{n-1} \left[\hat{R}_j e^{-\hat{L}t_j}\right] \sigma\,(0)\,, \tag{2.75}$$

in which $t = \sum_j t_j$, and $\hat{R}_j$ is a superoperator that corresponds to the transformation
induced by a pulse, or a group of pulses, which may or may not include free precession
delays. In Eq. 2.75, we implicitly assumed that all the transformations induced by
pulses are instantaneous. If this assumption is not valid, the effect of the *rf* pulses
may be included in $\hat{L}$. Also, in the symbol $\prod_j$ it is implied that the indices j are sorted
by time from right to left in ascending order.

For the jth time step a transformed Liouvillian $\hat{L}_j^T$ can be defined as

$$\hat{L}_j^T = \hat{R}_{n-1}\hat{R}_{n-2}\cdots\hat{R}_j\hat{L}\hat{R}_j^{-1}\cdots\hat{R}_{n-2}^{-1}\hat{R}_{n-1}^{-1}. \tag{2.76}$$

Similarly, a transformed initial density matrix is defined as

$$\sigma^T\,(0) = \prod_{j=1}^{n-1} \hat{R}_j \sigma\,(0)\,. \tag{2.77}$$

Equations 2.76 and 2.77 allow to rewrite Eq. 2.75 as

$$\sigma\,(t) = \prod_{j=1}^{n} e^{-\hat{L}_j^T t_j} \sigma^T\,(0)\,. \tag{2.78}$$

Imperfections of the transformations $\hat{R}_j$ lead to losses that may be treated including
in Eq. 2.78 a scalar factor A_j, which correspond to the attenuation due to the jth step:

$$\sigma\,(t) = \prod_{j=1}^{n} A_j e^{-\hat{L}_j^T t_j} \sigma^T\,(0)$$

$$= A \prod_{j=1}^{n} e^{-\hat{L}_j^T t_j} \sigma^T\,(0)\,, \tag{2.79}$$

in which $A = \prod_{j=1}^{n} A_j$ is a measure of the total attenuation due to the entire pulse sequence, with $0 < A < 1$.

In analogy with the average Hamiltonian of Eq. 2.69, the average Liovillian is defined as

$$\hat{L}_{av} = \hat{L}^{(0)} + \hat{L}^{(1)} + \hat{L}^{(2)} \ldots, \tag{2.80}$$

where

$$\hat{L}^{(0)} = \frac{1}{t} \sum_j \hat{L}_j^T t_j,$$

$$\hat{L}^{(1)} = -\frac{1}{2t} \sum_{j>k} \left[\hat{L}_j^T t_j, \hat{L}_k^T t_k \right],$$

$$\hat{L}^{(2)} = -\frac{1}{6t} \sum_{j>k>l} \left[\hat{L}_j^T t_j, \left[\hat{L}_k^T t_k, \hat{L}_l^T t_l \right] \right] + \left[\left[\hat{L}_j^T t_j, \hat{L}_k^T t_k \right], \hat{L}_l^T t_l \right]$$

$$+ \frac{1}{2} \left\{ \left[\hat{L}_k^T t_k, \left[\hat{L}_k^T t_k, \hat{L}_l^T t_l \right] \right] + \left[\left[\hat{L}_k^T t_k, \hat{L}_l^T t_l \right], \hat{L}_l^T t_l \right] \right\} \cdots \tag{2.81}$$

Using the definition of average Liouvillian in Eq. 2.79, we obtain

$$\sigma(t) = A e^{-\hat{L}_{av} t} \sigma^T(0) = A \hat{U}_{av} \sigma^T(0). \tag{2.82}$$

The terms in $\hat{L}_{av}$ have symmetry properties that reflect those of the pulse sequence. Indeed, a handful of theorems can be used to simplify the calculation of the average Liouvillian:

1. In the case of a symmetric Liouvillian, i.e.,
   $\hat{L}_j^T = \hat{L}_{n-j+1}^T$, and all the even-order corrections vanish, i.e., $\hat{L}^{(k)} = 0$ for even k;
2. If the transformations $\hat{R}_j$ are distributed in an antisymmetric way, i.e., $\hat{R}_j = \hat{R}_{n-j}^{-1}$, the Liouvillian is symmetric, i.e., $\hat{L}_j^T = \hat{L}_{n-j+1}^T$;
3. On the contrary, if the distribution of the transformations is symmetric, i.e., $\hat{R}_j = \hat{R}_{n-j}$, the Liouvillian is symmetric only if the matrix associated to each transformation is diagonal.

Similarly to the average Hamiltonian, the existence of the average Liouvillian is guaranteed only if some requirements are met. Formally, a given Liouvillian can be written as the sum of a time-dependent and a time-independent part:

$$\hat{L}(t) = \hat{L}_0 + \lambda \hat{L}_1(t). \tag{2.83}$$

Here, $\hat{L}_1(t)$ includes all the time-dependent components that are induced by the transformations applied to the system,[2] whereas $\hat{L}_0$ includes phenomena that are constant during the experiment, such as relaxation, chemical shifts and scalar couplings.

The most important parameter in the above equation is λ, that is a measure of the strength of the influence of the applied *rf* fields on the natural spin dynamics. Indeed, the basis of ALT is the assumption that the propagator can be written at any time in an exponential form, i.e.,

$$\hat{U}(t) = e^{-\Omega(\lambda, t)}. \tag{2.84}$$

In other words, in analogy with the average Hamiltonian theory, the existence of a valid solution to the master equation that can be expressed in an exponential form is assumed. As shown by Maricq [12], the condition of validity is that $\Omega(\lambda, t)$ can be expanded in a power series in λ, although for some singularities it may not be possible to write an exponential solution to the master equation. The reader is referred to [12] for further details.

Lastly, a criterion to estimate the weight of the contribution of higher-order terms to the average Liouvillian is provided. We shall start by defining the norm $\|A\|$ of a matrix A as the square root of the largest eigenvalue λ_{max} of $(A^\mathsf{T} A)$.[3]

The following general expression can be deduced from Eq. 2.81:

$$\hat{L}^{(k)} = -\frac{1}{k} \sum_{j>} \left[\hat{L}_j^T t_j, \hat{L}^{(k-1)} \right], \tag{2.85}$$

in which the subscript $j >$ was used to indicate that the time sorting of j must be conserved. If one assumes that the eigenvalues of $\hat{L}$ are good approximations of the eigenvalues of $\hat{L}_j^T$, then

$$\frac{\|\hat{L}^{(k)}\|}{\|\hat{L}^{(k-1)}\|} \approx \frac{\sqrt{\lambda_{max}\left(\hat{L}^\mathsf{T}\hat{L}\right)} \left(\sum_j t_j\right)}{k} = \frac{t\sqrt{\lambda_{max}\left(\hat{L}^\mathsf{T}\hat{L}\right)}}{k}. \tag{2.86}$$

Higher-order terms can therefore be ignored when the above ratio is much smaller than one, i.e., if $t\sqrt{\lambda_{max}\left(\hat{L}^\mathsf{T}\hat{L}\right)} \ll k$, or simply $t\lambda_{max}\left(\hat{L}\right) \ll k$ in the case of a symmetric Liouvillian. Usually, the terms with $k > 2$ can be safely neglected.

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[2] The time dependence is not the one due to the modulation of the *rf* fields that can be removed by transforming to a rotating frame, but the one due to the fact that different transformations $\hat{R}_j$ are applied at different t_j. Therefore, $\hat{L}_1(t)$ is, strictly speaking, a *discrete* function of time.

[3] If A is symmetric, $\|A\|$ is simply equal to its largest eigenvalue.

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