Common Spin Relaxation Mechanisms

This lecture gives an overview of common liquid-state spin relaxation mechanisms. We will assume rotational modulation for all interaction anisotropies and use irreducible spherical tensor notation for the Hamiltonians. Full derivations for the rotational decompositions may be found in the rotations lecture; in particular, we will be using the following expansion a lot:

$$\hat{\vec{L}}\cdot\mathbf{A}\cdot\hat{\vec{S}}=\sum_{\substack{k,n=\\ \{\mathrm{X,Y,Z}\}}}a_{kn}\hat{L}_k\hat{S}_n=a_0^{(0)}\hat{T}_0^{(0)}+\sum_{m=-1}^{1}a_m^{(1)}\hat{T}_m^{(1)}+\sum_{m=-2}^{2}a_m^{(2)}\hat{T}_m^{(2)} \tag{1}$$

where the irreducible spherical tensor operators $\hat{T}_m^{(l)}$ and the associated coefficients $a_m^{(l)}$ are tabulated in the rotations lecture handout. A spherical tensor operator is rotated in the following way:

$$\hat{\hat{R}}(\alpha,\beta,\gamma)\hat{T}_m^{(l)}=\sum_{m'=-l}^{l}\hat{T}_{m'}^{(l)}\mathfrak{D}_{m',m}^{(l)}(\alpha,\beta,\gamma) \tag{2}$$

where we will abbreviate the time dependence of Wigner functions into $\mathfrak{D}_{m',m}^{(l)}(t)$. Isotropic rotational diffusion approximation will be used throughout – anisotropic rotational diffusion cases are analytically cumbersome and are best handled numerically.

Dipole-dipole and hyperfine mechanisms

Stochastic modulation of magnetic dipole interaction is the most ubiquitous relaxation mechanism in spin-½ systems. In the diamagnetic case it stems from the inter-nuclear dipolar interaction and in paramagnetic cases from electron-nuclear and inter-electron dipolar interactions. In liquids the dipolar mechanism is always active because the interaction tensor is aligned with molecular structure and the interaction is modulated by the rotational diffusion. The latter has a timescale of nanoseconds and usually has some spectral density at NMR and EPR transition frequencies.

Both inter-nuclear dipole coupling and electron-nuclear hyperfine coupling are anisotropic bilinear interactions. In their eigenframe, they have the following general Hamiltonian:

$$\hat{H}_1=\hat{\vec{L}}\cdot\mathbf{A}\cdot\hat{\vec{S}}=a_{\mathrm{XX}}\hat{L}_{\mathrm{X}}\hat{S}_{\mathrm{X}}+a_{\mathrm{YY}}\hat{L}_{\mathrm{Y}}\hat{S}_{\mathrm{Y}}+a_{\mathrm{ZZ}}\hat{L}_{\mathrm{Z}}\hat{S}_{\mathrm{Z}}=\frac{Ax}{\sqrt{6}}\hat{T}_0^{(2)}+\frac{Rh}{2}\left[\hat{T}_{-2}^{(2)}+\hat{T}_2^{(2)}\right] \tag{3}$$

where $Ax=2a_{\mathrm{ZZ}}-(a_{\mathrm{XX}}+a_{\mathrm{YY}})$ and $Rh=a_{\mathrm{XX}}-a_{\mathrm{YY}}$. The rhombicity is zero for the point dipole interaction). Only the traceless part is included in Equation (3) because the isotropic part is not rotationally modulated and therefore belongs to $\hat{H}_0$ (see the Redfield theory lecture). We will assume that the static Hamiltonian only contains Zeeman interaction

$$\hat{H}_0=\omega_{\mathrm{L}}\hat{L}_{\mathrm{Z}}+\omega_{\mathrm{S}}\hat{S}_{\mathrm{Z}} \tag{4}$$

Rotating the Hamiltonian in Equation (3) using Equation (2) yields:

$$\begin{gathered}\hat{H}_1(t)=\frac{Ax}{\sqrt{6}}\sum_{m=-2}^{2}\mathfrak{D}_{m,0}^{(2)}(t)\hat{T}_m^{(2)}+\frac{Rh}{2}\left[\sum_{m=-2}^{2}\mathfrak{D}_{m,-2}^{(2)}(t)\hat{T}_m^{(2)}+\sum_{m=-2}^{2}\mathfrak{D}_{m,2}^{(2)}(t)\hat{T}_m^{(2)}\right]=\\ =\sum_{m=-2}^{2}\left[\frac{Ax}{\sqrt{6}}\mathfrak{D}_{m,0}^{(2)}(t)+\frac{Rh}{2}\left(\mathfrak{D}_{m,-2}^{(2)}(t)+\mathfrak{D}_{m,2}^{(2)}(t)\right)\right]\hat{T}_m^{(2)}\end{gathered} \tag{5}$$

Using the notation introduced in the Redfield theory lecture, we can write:

$$\hat{H}_1(t)=\sum_{m=-2}^{2} q_m(t)\hat{Q}_m=\sum_{m=-2}^{2} q_m^*(t)\hat{Q}_m^\dagger$$
$$q_m(t)=\left[\frac{Ax}{\sqrt{6}}\mathfrak{D}_{m,0}^{(2)}(t)+\frac{Rh}{2}\left(\mathfrak{D}_{m,-2}^{(2)}(t)+\mathfrak{D}_{m,2}^{(2)}(t)\right)\right],\qquad \hat{Q}_m=\hat{T}_m^{(2)} \tag{6}$$

The correlation functions may be obtained from the expressions derived in the previous lecture:

$$g_{km}(\tau)=\left\langle q_k(0)q_m^*(\tau)\right\rangle=\ldots=$$
$$=\frac{Ax^2}{6}\left\langle\mathfrak{D}_{k,0}^{(2)}(0)\mathfrak{D}_{m,0}^{(2)*}(\tau)\right\rangle+\frac{Rh^2}{4}\left\langle\mathfrak{D}_{k,-2}^{(2)}(0)\mathfrak{D}_{m,-2}^{(2)*}(\tau)\right\rangle+\frac{Rh^2}{4}\left\langle\mathfrak{D}_{k,2}^{(2)}(0)\mathfrak{D}_{m,2}^{(2)*}(\tau)\right\rangle= \tag{7}$$
$$=\frac{Ax^2+3Rh^2}{30}\delta_{km}e^{-\tau/\tau_C}=\frac{\Delta_A^2}{30}\delta_{km}e^{-\tau/\tau_C},\qquad \Delta_A^2=Ax^2+3Rh^2$$

For the point dipolar interaction:

$$Ax=6\frac{\gamma_L^2\gamma_S^2\hbar^2}{r^3}\frac{\mu_0}{4\pi},\qquad Rh=0 \tag{8}$$

The Redfield integral can now be written in a form that allows analytical evaluation:

$$\hat{\hat{R}}=-\sum_{km}\int_0^\infty\left\langle q_k(0)q_m^*(\tau)\right\rangle\hat{\hat{Q}}_k e^{-i\hat{\hat{H}}_0\tau}\hat{\hat{Q}}_m^\dagger e^{i\hat{\hat{H}}_0\tau}d\tau=-\frac{\Delta_A^2}{30}\sum_{m=-2}^{2}\int_0^\infty e^{-\tau/\tau_C}\hat{\hat{T}}_m^{(2)}e^{-i\hat{\hat{H}}_0\tau}\hat{\hat{T}}_m^{(2)\dagger}e^{i\hat{\hat{H}}_0\tau}d\tau \tag{9}$$

Although this integral is just a bunch of commutators, no progress can be made with it without getting bogged down in manual evaluation – a very tedious process that is best delegated to Mathematica (see the "relaxation engine" package posted to the web site).

The diagonal elements of the resulting relaxation superoperator are called the *self-relaxation rates*. In particular for $\hat{L}_Z$ and $\hat{S}_Z$ (note the normalization) we get the following *longitudinal relaxation rates*:

$$\frac{1}{T_1^L}=-\mathrm{Re}\frac{\left\langle\hat{L}_Z\middle|\hat{\hat{R}}\middle|\hat{L}_Z\right\rangle}{\left\langle\hat{L}_Z\middle|\hat{L}_Z\right\rangle}=\ldots=\frac{\Delta_A^2\tau_c}{360}\left(\frac{3}{1+\omega_L^2\tau_c^2}+\frac{6}{1+(\omega_L+\omega_S)^2\tau_c^2}+\frac{1}{1+(\omega_L-\omega_S)^2\tau_c^2}\right)$$
$$\frac{1}{T_1^S}=-\mathrm{Re}\frac{\left\langle\hat{S}_Z\middle|\hat{\hat{R}}\middle|\hat{S}_Z\right\rangle}{\left\langle\hat{S}_Z\middle|\hat{S}_Z\right\rangle}=\ldots=\frac{\Delta_A^2\tau_c}{360}\left(\frac{3}{1+\omega_S^2\tau_c^2}+\frac{6}{1+(\omega_S+\omega_L)^2\tau_c^2}+\frac{1}{1+(\omega_S-\omega_L)^2\tau_c^2}\right) \tag{10}$$

There are two important limiting cases – one is *extreme narrowing*, where $\tau_c\ll\omega_{L,S}$ and all denominators are equal to unity (this is often the case in non-viscous liquids), meaning that the expressions become particularly simple:

$$\frac{1}{T_1^L}=\frac{1}{T_1^S}=\frac{\Delta_A^2\tau_c}{36} \tag{11}$$

The other is encountered in high-field ESR spectroscopy where the frequency of the electron is much greater than the frequency of the nucleus and so $\omega_E+\omega_N\approx\omega_E-\omega_N\approx\omega_E$, meaning that:

$$\frac{1}{T_1^E}=\frac{\Delta_A^2\tau_c}{36}\frac{1}{1+\omega_E^2\tau_c^2},\qquad \frac{1}{T_1^N}=\frac{\Delta_A^2\tau_c}{360}\left(\frac{3}{1+\omega_N^2\tau_c^2}+\frac{7}{1+\omega_E^2\tau_c^2}\right) \tag{12}$$

The diagonal terms corresponding to $\hat{L}_+$ and $\hat{S}_+$ states are called *transverse relaxation rates*:

$$\frac{1}{T_2^{\mathrm{L}}}=\frac{\Delta_{\mathrm{A}}^2\tau_{\mathrm{c}}}{720}\left(4+\frac{3}{1+\omega_{\mathrm{L}}^2\tau_{\mathrm{c}}^2}+\frac{6}{1+\omega_{\mathrm{S}}^2\tau_{\mathrm{c}}^2}+\frac{6}{1+\left(\omega_{\mathrm{L}}+\omega_{\mathrm{S}}\right)^2\tau_{\mathrm{c}}^2}+\frac{1}{1+\left(\omega_{\mathrm{L}}-\omega_{\mathrm{S}}\right)^2\tau_{\mathrm{c}}^2}\right)$$
$$\frac{1}{T_2^{\mathrm{S}}}=\frac{\Delta_{\mathrm{A}}^2\tau_{\mathrm{c}}}{720}\left(4+\frac{3}{1+\omega_{\mathrm{S}}^2\tau_{\mathrm{c}}^2}+\frac{6}{1+\omega_{\mathrm{L}}^2\tau_{\mathrm{c}}^2}+\frac{6}{1+\left(\omega_{\mathrm{S}}+\omega_{\mathrm{L}}\right)^2\tau_{\mathrm{c}}^2}+\frac{1}{1+\left(\omega_{\mathrm{S}}-\omega_{\mathrm{L}}\right)^2\tau_{\mathrm{c}}^2}\right) \qquad (13)$$

In the extreme narrowing limit the rates of longitudinal and transverse relaxation are equal.

Nuclear Overhauser effect

The relaxation superoperator also has off-diagonal elements. In particular, the term corresponding to the relaxation-driven longitudinal magnetization transfer between different spins is known as the Overhauser effect. The corresponding rate is:

$$\sigma_{\mathrm{LS}}=-\mathrm{Re}\frac{\left\langle\hat{L}_{\mathrm{Z}}\middle|\hat{\hat{R}}\middle|\hat{S}_{\mathrm{Z}}\right\rangle}{\sqrt{\left\langle\hat{L}_{\mathrm{Z}}\middle|\hat{L}_{\mathrm{Z}}\right\rangle\left\langle\hat{S}_{\mathrm{Z}}\middle|\hat{S}_{\mathrm{Z}}\right\rangle}}=\ldots=\frac{\Delta_{\mathrm{A}}^2\tau_{\mathrm{c}}}{360}\left(\frac{1}{1+\left(\omega_{\mathrm{L}}-\omega_{\mathrm{S}}\right)^2\tau_{\mathrm{c}}^2}-\frac{6}{1+\left(\omega_{\mathrm{L}}+\omega_{\mathrm{S}}\right)^2\tau_{\mathrm{c}}^2}\right) \qquad (14)$$

Unlike the self-relaxation rate (which is always positive), this expression can change sign, meaning that the nuclear Overhauser effect (NOE) is negative for small molecules in non-viscous liquids, but becomes positive for large molecules in strong magnetic fields. Because of its distance dependence NOE is one of the cornerstones of NMR structure determination.

The equation describing longitudinal relaxation and magnetization transport between two spins with a rotational diffusion modulated dipolar interaction was found in the previous lecture to be

$$\frac{d}{dt}\begin{bmatrix}\left\langle\hat{I}_{\mathrm{Z}}\right\rangle-\left\langle\hat{I}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\\ \left\langle\hat{S}_{\mathrm{Z}}\right\rangle-\left\langle\hat{S}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\end{bmatrix}=-\begin{bmatrix}\rho_{II} & \sigma_{IS}\\ \sigma_{IS} & \rho_{SS}\end{bmatrix}\begin{bmatrix}\left\langle\hat{I}_{\mathrm{Z}}\right\rangle-\left\langle\hat{I}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\\ \left\langle\hat{S}_{\mathrm{Z}}\right\rangle-\left\langle\hat{S}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\end{bmatrix}$$
$$\Downarrow \qquad (15)$$
$$\begin{bmatrix}\left\langle\hat{I}_{\mathrm{Z}}\right\rangle-\left\langle\hat{I}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\\ \left\langle\hat{S}_{\mathrm{Z}}\right\rangle-\left\langle\hat{S}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\end{bmatrix}(t)=\exp\left(-\begin{bmatrix}\rho_{II} & \sigma_{IS}\\ \sigma_{IS} & \rho_{SS}\end{bmatrix}t\right)\begin{bmatrix}\left\langle\hat{I}_{\mathrm{Z}}\right\rangle-\left\langle\hat{I}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\\ \left\langle\hat{S}_{\mathrm{Z}}\right\rangle-\left\langle\hat{S}_{\mathrm{Z}}^{\mathrm{eq}}\right\rangle\end{bmatrix}(0)$$

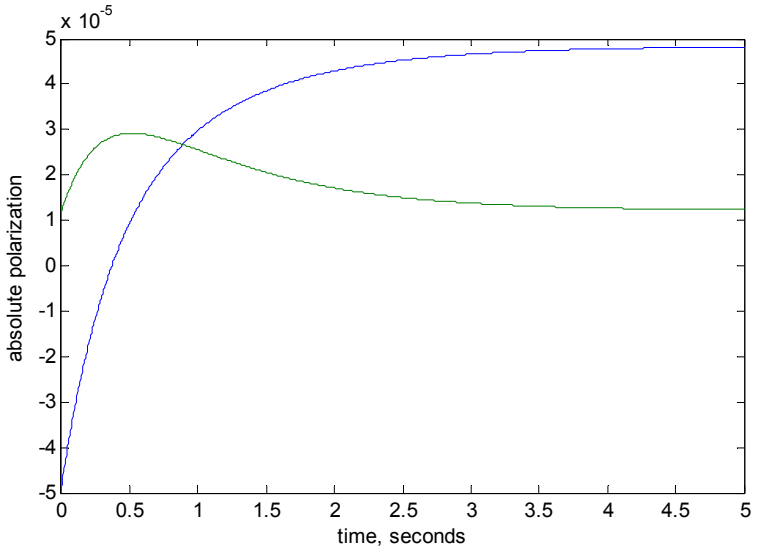
where the self-relaxation rates are:

$$\rho_{II}=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_{\mathrm{c}}}{r_{IS}^6}\left(\frac{3}{1+\omega_I^2\tau_{\mathrm{c}}^2}+\frac{6}{1+(\omega_I+\omega_S)^2\tau_{\mathrm{c}}^2}+\frac{1}{1+(\omega_I-\omega_S)^2\tau_{\mathrm{c}}^2}\right)$$
$$\rho_{SS}=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_{\mathrm{c}}}{r_{IS}^6}\left(\frac{3}{1+\omega_S^2\tau_{\mathrm{c}}^2}+\frac{6}{1+(\omega_I+\omega_S)^2\tau_{\mathrm{c}}^2}+\frac{1}{1+(\omega_I-\omega_S)^2\tau_{\mathrm{c}}^2}\right) \qquad (16)$$

and the cross-relaxation rate is:

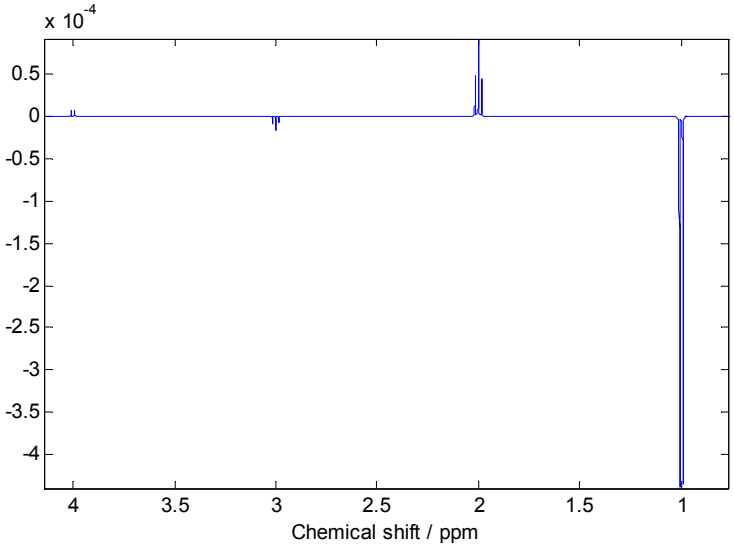
$$\sigma_{IS}=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_{\mathrm{c}}}{r_{IS}^6}\left(\frac{6}{1+(\omega_I+\omega_S)^2\tau_{\mathrm{c}}^2}-\frac{1}{1+(\omega_I-\omega_S)^2\tau_{\mathrm{c}}^2}\right) \qquad (17)$$

Assuming a room temperature ^{1}H-^{13}C spin system in a 600 MHz magnet with inter-nuclear distance of 1.03 Angstrom and a rotational correlation time of 100 ps with proton magnetization inverted at time zero, we get the following curves for the time dependence of the longitudinal magnetization:



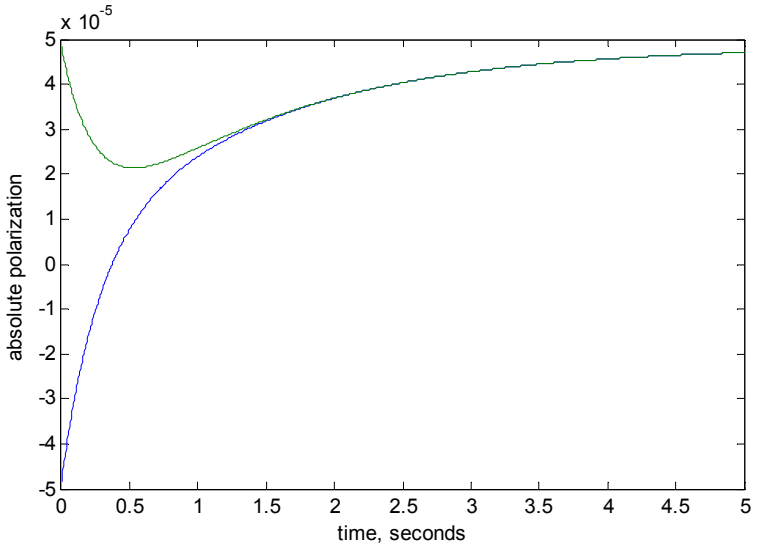
Several things in this figure are worth noting. Firstly, the room temperature equilibrium polarization of ^{13}C is approximately a factor of four smaller than that of protons, a consequence of the smaller magnetogyric ratio. Secondly, an enhancement of ^{13}C polarization, by nearly a factor of three may be obtained via the Overhauser effect if the nearby proton is inverted. Thirdly, the three relaxation parameters ρ_{II}, ρ_{SS} and σ_{IS} may be extracted by fitting. Inter-atomic distance and rotational correlation time may then be determined by solving Equations (16) and (17).

A manual NOE measurement experiment involves inverting the source spin, waiting for a variable "mixing" time and running a pulse-acquire experiment. Thermal equilibrium NMR spectrum is typically subtracted from the data to bring it into the form stipulated by Equation (15). A typical picture (a chain of four protons with 2 Angstrom spacing at 600 MHz and a correlation time of 200 ps) is given below



The peaks are integrated, the integrals plotted against time and fitted to Equation (15), in most cases directly with respect to the distance and the correlation time.

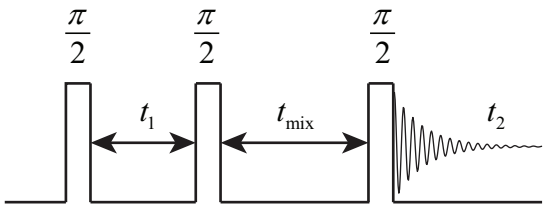
As expected from the appearance of Equation (17), homonuclear Overhauser effect becomes negative for long correlation times. Longitudinal magnetization dynamics in a room-temperature ^{1}H-^{1}H spin system in a 600 MHz magnet with the a distance of 2.00 Angstrom and a correlation time of 1 ns is shown below



In multi-nuclear systems the two-spin approximation described above is often invalid and the distances resulting from such fitting runs can only be viewed as approximate.

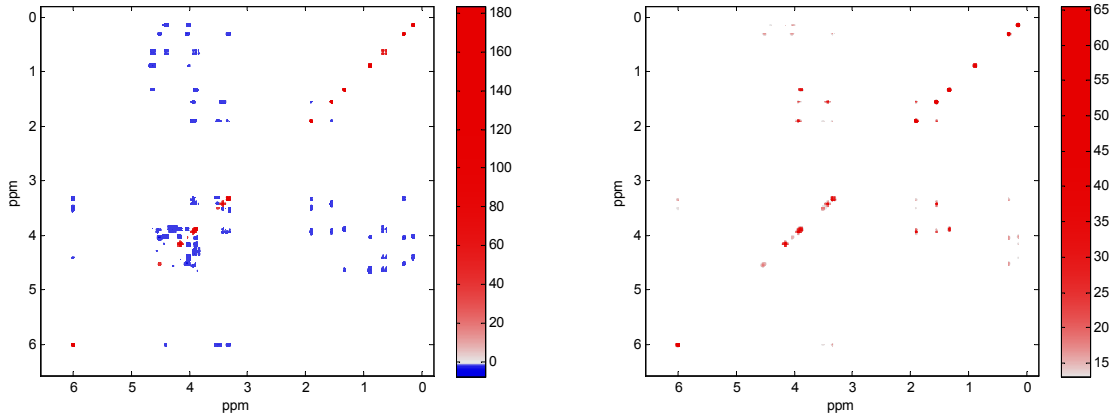
NOESY spectroscopy

NOESY is a two-dimensional NMR experiment that is sensitive to the longitudinal magnetization transfer via the Overhauser effect. The block diagram of the experiment is



A fairly complicated phase cycle and gradient selection process is used to ensure that only the desired magnetization transfer paths are manifested in the recorded signal – see the literature and Spinach source code for further information on the implementation of NOESY sequences. Typical mixing times are between 50 and 500 ms, depending on the relaxation times present in the system.

NOESY spectra of sucrose in a 400 MHz magnet with mixing time of 500ms and correlation times of 200 ps (non-viscous solvent, left) and 1 ns (viscous solvent, right) are shown below. Note the sign and the amplitude of cross-peaks in both cases.



Because the spin systems are usually complex and many magnetization transfer paths are present, NOESY peaks are not quantitatively related to distances – in protein structure determination they are binned into "strong", "medium" and "weak". They are, however, a reliable indication of spatial proximity.

Chemical shielding anisotropy and *g*-tensor anisotropy mechanisms

The nuclear and electron Zeeman interaction anisotropy, that is, the orientation dependence of the spin energy level splitting in an external magnetic field, is another common cause of spin relaxation in both radicals and neutral molecules. The electron *g*-tensor acquires its orientation dependence predominantly from the spin-orbit coupling, because the orbital contribution to the electron magnetic moment is anisotropic and the nuclear magnetic shielding essentially inherits the symmetry of the surrounding electron shell. In the majority of cases the chemical shift tensor is anisotropic, even for protons. The typical anisotropy of the proton chemical shift is a few ppm; in the case of ^{15}N or ^{19}F nuclei it can reach hundreds of ppm and play a major role in determining the relaxation behaviour.

The Hamiltonian for a single spin-½ with an anisotropic Zeeman interaction with the external magnetic field contains the constant term H_0, corresponding to either the *g*-factor or the chemical shift, and the time-dependent term $H_1(t)$ resulting from the rotational modulation of the anisotropy:

$$\hat{H}_0 = \omega_{\rm n}\hat{I}_Z, \qquad \hat{H}_1(t) = \frac{Rh}{2}\sum_{m'=-2}^{2}\hat{T}_{2,m'}\mathfrak{D}^{(2)}_{m',-2}(t) + \frac{Rh}{2}\sum_{m'=-2}^{2}\hat{T}_{2,m'}\mathfrak{D}^{(2)}_{m',2}(t) + \frac{Ax}{\sqrt{6}}\sum_{m'=-2}^{2}\hat{T}_{2,m'}\mathfrak{D}^{(2)}_{m',0}(t) \qquad (18)$$

The axiality and rhombicity parameters are defined in the same way as in Equation (3), but now refer to the Zeeman interaction tensor. Because the magnetic field is assumed to be directed along the *Z*-axis of the laboratory frame, quite a few terms in the irreducible spherical tensor definitions disappear:

$$\hat{T}_{2,\pm 2} = 0, \qquad \hat{T}_{2,\pm 1} = \mp\frac{1}{2}\hat{I}_{\pm}B_Z, \qquad \hat{T}_{2,0} = +\sqrt{\frac{2}{3}}\hat{I}_Z B_Z \qquad (19)$$

Running through the procedure given in Equations (5)-(9) results in the following relaxation rates for the longitudinal and transverse magnetization:

$$\frac{1}{T_1} = \frac{\Delta_{\rm A}^2}{30}\frac{\tau_c}{1+\tau_{\rm c}^2\omega_{\rm n}^2}, \qquad \frac{1}{T_2} = \frac{\Delta_{\rm A}^2\tau_{\rm c}}{180}\left(4+\frac{3}{1+\tau_{\rm c}^2\omega_{\rm n}^2}\right) \qquad (20)$$

where $\Delta_{\rm A}^2$ now refers to the Zeeman interaction tensor. It is worth noting that the frequency-independent term in the transverse relaxation rate is the chief cause of the sensitivity and line width problems that NMR spectroscopy encounters for large molecules. The chemical shielding anisotropy of

^{13}C and ^{15}N nuclei is of the order of 100 ppm, and for the molecules with rotational correlation times greater than about 50 ns the transverse relaxation becomes extremely fast, leading to intractably broad lines and huge magnetization losses during coherence transfer stages.

Cross-correlated relaxation

One of the less obvious features of spin relaxation theory as applied to rigid or conformationally restricted molecules is the fact that molecular rotation does not drive *all* correlation functions to zero. In fact, in a tumbling rigid molecule the interaction tensors keep constant orientation with respect to one another, meaning that the orientational functions for the corresponding interactions may not be averaged independently and stay correlated at all times.

Consider a two-spin system with a dipolar interaction and anisotropic magnetic shielding of one of the spins. The Hamiltonian can be written as follows

$$\hat{H} = \omega_1 \hat{I}_Z + \omega_2 \hat{S}_Z + \hat{\vec{I}} \cdot \mathbf{D} \cdot \hat{\vec{S}} + \hat{\vec{S}} \cdot \mathbf{C} \cdot \vec{B} \tag{21}$$

Using Equations (1) and (2) to move to the irreducible spherical tensor notation, and assuming the magnetic induction is applied along the *Z* axis of the laboratory frame of reference, we obtain the following expression for the Hamiltonian:

$$\hat{H} = \omega_1 \hat{I}_Z + \omega_2 \hat{S}_Z - \frac{\Delta D}{\sqrt{6}} \sum_{k=-2}^{2} \hat{T}_{2,k}^{DD} \mathfrak{D}_{k,0}^{(2)}(t) - \frac{\Delta C}{\sqrt{6}} \sum_{k=-2}^{2} \sum_{n=-2}^{2} \hat{T}_{2,k}^{CSA} \mathfrak{D}_{k,n}^{(2)}(t) \mathfrak{D}_{n,0}^{(2)}(\theta) \tag{22}$$

where θ is the angle between the dipolar and the shielding tensor axis, $\Delta D = \gamma_I \gamma_S \hbar \mu_0 / 4\pi r^3$ is the dipolar interaction anisotropy, $\Delta C = \gamma_S B_0 \Delta\sigma / 3$ is the Zeeman interaction anisotropy and $\Delta\sigma = \sigma_{\parallel} - \sigma_{\perp}$ is the chemical shift anisotropy. The Hamiltonian contains two sets of Wigner functions: $\mathfrak{D}_{n,k}^{(2)}(\theta)$ describe the rotation of the CSA tensor axis relative to the dipole tensor axis and $\mathfrak{D}_{n,k}^{(2)}(t)$ describe the overall molecular reorientation.

Using Equations (5)-(9) and letting *Mathematica* do the pencilwork results in the following equations for relaxation and cross-relaxation of longitudinal magnetization:

$$\frac{d}{dt}\begin{bmatrix} \langle \hat{I}_Z \rangle \\ \langle \hat{S}_Z \rangle \\ \langle 2\hat{I}_Z \hat{S}_Z \rangle \end{bmatrix} = -\begin{bmatrix} \rho_{II} & \sigma_{IS} & 0 \\ \sigma_{IS} & \rho_{SS} & \delta_{S,IS} \\ 0 & \delta_{S,IS} & \rho_{ISIS} \end{bmatrix} \begin{bmatrix} \langle \hat{I}_Z \rangle - \langle \hat{I}_Z^{(eq)} \rangle \\ \langle \hat{S}_Z \rangle - \langle \hat{S}_Z^{(eq)} \rangle \\ \langle 2\hat{I}_Z \hat{S}_Z \rangle \end{bmatrix} \tag{23}$$

with the following expressions for the coefficients (note the cubic distance dependence in the cross-correlation term $\delta_{S,IS}$):

$$\rho_{II}=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_c}{r_{IS}^6}\left(\frac{3}{1+\omega_I^2\tau_c^2}+\frac{6}{1+(\omega_I+\omega_S)^2\tau_c^2}+\frac{1}{1+(\omega_I-\omega_S)^2\tau_c^2}\right)$$

$$\rho_{SS}=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_c}{r_{IS}^6}\left(\frac{3}{1+\omega_S^2\tau_c^2}+\frac{6}{1+(\omega_I+\omega_S)^2\tau_c^2}+\frac{1}{1+(\omega_I-\omega_S)^2\tau_c^2}\right)+$$

$$+\frac{2}{15}\frac{\gamma_S^2\tau_c(\Delta\sigma)^2B_0^2}{1+\omega_S^2\tau_c^2}$$

$$\rho_{ISIS}=\frac{3}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\gamma_I^2\gamma_S^2\hbar^2\tau_c}{r_{IS}^6}\left(\frac{1}{1+\omega_I^2\tau_c^2}+\frac{1}{1+\omega_S^2\tau_c^2}\right)+\frac{2}{15}\frac{\gamma_S^2\tau_c(\Delta\sigma)^2B_0^2}{1+\omega_S^2\tau_c^2} \qquad (24)$$

$$\sigma_{IS}=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_c}{r_{IS}^6}\left(\frac{6}{1+(\omega_I+\omega_S)^2\tau_c^2}-\frac{1}{1+(\omega_I-\omega_S)^2\tau_c^2}\right)$$

$$\delta_{S,IS}=-\frac{2}{5}\left(\frac{\mu_0}{4\pi}\right)\frac{\gamma_I\gamma_S^2\hbar B_0}{r_{IS}^3}\frac{\tau_c}{1+\omega_S^2\tau_c^2}\Delta\sigma_g$$

where $\Delta\sigma_g=\Delta\sigma\left(3\cos^2\theta-1\right)/2$ is the so-called geometrically weighted shielding anisotropy parameter, which in the case of a shielding tensor with three different eigenvalues values becomes

$$\Delta\sigma_g=\frac{1}{2}\sigma_{XX}\left(3\cos^2\theta_{X,IS}-1\right)+\frac{1}{2}\sigma_{YY}\left(3\cos^2\theta_{Y,IS}-1\right)+\frac{1}{2}\sigma_{ZZ}\left(3\cos^2\theta_{Z,IS}-1\right) \qquad (25)$$

where the three angles are the angles between the inter-nuclear vector and the three eigenvectors of the CSA tensor.

Large molecules and complex motion models

The unfortunate reality of relaxation theory calculations is that only the simplest cases may be derived and analysed by a skilled human in a reasonable amount of time. For large systems with multiple cross-correlated interactions the only realistic way towards the relaxation superoperator is numerical. Ideally, a computer program should request the interaction tensors and the parameters of the diffusion model from the user and just return the relaxation superoperator. At the time of writing, the only software package that can realistically do this for complex NMR and EPR systems is *Spinach*.

Lipari-Szabo analysis of local motion

Both isotropic and anisotropic rotational diffusion are not good approximations in systems exhibiting local as well as global motion. A typical situation in a protein is global tumbling with a rotational correlation time of a few nanoseconds and more or less restricted local motion of each amino acid residue within the secondary and tertiary protein structure. Under the reasonable assumption that the two motions are uncorrelated with one another, the following expression emerges for the Fourier transform of the correlation function:

$$J(\omega)=\frac{S^2\tau_C}{1+\omega^2\tau_C^2}+\frac{\left(1-S^2\right)\tau}{1+\omega^2\tau^2},\qquad \tau=\left(\frac{1}{\tau_C}+\frac{1}{\tau_{\text{int}}}\right)^{-1} \qquad (26)$$

where τ_C is the correlation time of the global rotational diffusion, τ_{int} is the correlation time of the local motion and S^2 is called *order parameter*. It can be interpreted as a fraction of the full body angle that is spanned by the restriction cone of the internal motion. The spectral density in Equation (26) is used as a drop-in replacement for the isotropic rotational diffusion spectral density:

$$J(\omega)=\frac{\tau_{\mathrm{C}}}{1+\omega^2\tau_{\mathrm{C}}^2} \tag{27}$$

It is easy to see that Equation (26) reduces to Equation (27) in the limit of perfect internal order, *i.e.* when $S^2=1$ and in the limit of completely unrestricted internal motion when $S^2=0$.

In practical measurements the order parameters are extracted from the simultaneously measured longitudinal relaxation rates, transverse relaxation rates and NOE transfer rates at several different magnetic fields. In terms of the corresponding spectral densities, and including CSA as well as DD relaxation mechanism, those rates are:

$$\begin{aligned}
R_{1,I}&=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{1}{r_{IS}^6}\Big(3J(\omega_I)+6J(\omega_I+\omega_S)+J(\omega_I-\omega_S)\Big)+\frac{2\gamma_S^2(\Delta\sigma_I)^2B_0^2}{15}J(\omega_I)\\
R_{1,S}&=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{1}{r_{IS}^6}\Big(3J(\omega_S)+6J(\omega_I+\omega_S)+J(\omega_I-\omega_S)\Big)+\frac{2\gamma_S^2(\Delta\sigma_I)^2B_0^2}{15}J(\omega_S)\\
R_{2,I}&=\frac{\gamma_I^2\gamma_S^2\hbar^2}{20}\left(\frac{\mu_0}{4\pi}\right)^2\frac{1}{r_{IS}^6}\begin{pmatrix}4J(0)+3J(\omega_I)+6J(\omega_S)+\\+6J(\omega_I+\omega_S)+J(\omega_I-\omega_S)\end{pmatrix}+\frac{\gamma_S^2(\Delta\sigma_I)^2B_0^2}{45}\Big(4J(0)+3J(\omega_I)\Big)\\
R_{2,S}&=\frac{\gamma_I^2\gamma_S^2\hbar^2}{20}\left(\frac{\mu_0}{4\pi}\right)^2\frac{1}{r_{IS}^6}\begin{pmatrix}4J(0)+3J(\omega_S)+6J(\omega_I)+\\+6J(\omega_I+\omega_S)+J(\omega_I-\omega_S)\end{pmatrix}+\frac{\gamma_S^2(\Delta\sigma_S)^2B_0^2}{45}\Big(4J(0)+3J(\omega_S)\Big)\\
\sigma_{IS}&=\frac{\gamma_I^2\gamma_S^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{1}{r_{IS}^6}\Big(6J(\omega_I+\omega_S)-J(\omega_I-\omega_S)\Big)
\end{aligned} \tag{28}$$

The fitting proceeds using non-linear least squares method; assuming that enough field points are available, correlation times and order parameters may be extracted for a variety of global and local rotational diffusion models.