8 Relaxation†

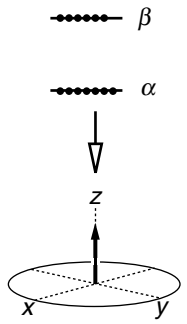
Relaxation is the process by which the spins in the sample come to equilibrium with the surroundings. At a practical level, the rate of relaxation determines how fast an experiment can be repeated, so it is important to understand how relaxation rates can be measured and the factors that influence their values. The rate of relaxation is influenced by the physical properties of the molecule and the sample, so a study of relaxation phenomena can lead to information on these properties. Perhaps the most often used and important of these phenomena in the nuclear Overhauser effect (NOE) which can be used to probe internuclear distances in a molecule. Another example is the use of data on relaxation rates to probe the internal motions of macromolecules.

In this chapter the language and concepts used to describe relaxation will be introduced and illustrated. To begin with it will simply be taken for granted that there are processes which give rise to relaxation and we will not concern ourselves with the source of relaxation. Having described the experiments which can be used to probe relaxation we will then go on to see what the source of relaxation is and how it depends on molecular parameters and molecular motion.

8.1 What is relaxation?

Relaxation is the process by which the spins return to *equilibrium.* Equilibrium is the state in which (a) the populations of the energy levels are those predicted by the Boltzmann distribution and (b) there is no transverse magnetization and, more generally, no coherences present in the system.

In Chapter 3 we saw that when an NMR sample is placed in a static magnetic field and allowed to come to equilibrium it is found that a net magnetization of the sample along the direction of the applied field (traditionally the z-axis) is developed. Magnetization parallel to the applied field is termed longitudinal.



A population difference gives rise to net magnetization along the z-axis.

This equilibrium magnetization arises from the unequal population of the two energy levels that correspond to the α and β spin states. In fact, the z-magnetization, M_z, is proportional to the population difference

$$M_z \propto \left(n_\alpha - n_\beta\right)$$

where n_α and n_β are the populations of the two corresponding energy levels. Ultimately, the constant of proportion just determines the absolute size of the signal we will observe. As we are generally interested in the *relative* size of magnetizations and signals we may just as well write

$$M_z = \left(n_\alpha - n_\beta\right) \qquad [2]$$

8.2 Rate equations and rate constants

The populations of energy levels are in many ways analogous to

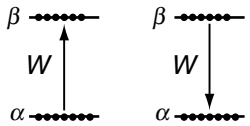
---

† Chapter 8 "Relaxation" © James Keeler 1999, 2002 and 2004

concentrations in chemical kinetics, and many of the same techniques that are used to describe the rates of chemical reactions can also be used to describe the dynamics of populations. This will lead to a description of the dynamics of the z-magnetization.

Suppose that the populations of the α and β states at time t are n_α and n_β, respectively. If these are not the equilibrium values, then for the system to reach equilibrium the population of one level must increase and that of the other must decrease. This implies that there must be *transitions* between the two levels *i.e.* something must happen which causes a spin to move from the α state to the β state or *vice versa.* It is this process which results in relaxation.

The simplest assumption that we can make about the rate of transitions from α to β is that it is proportional to the population of state α, n_α, and is a first order process with rate constant W. With these assumptions the rate of loss of population from state α is Wn_α. In the same way, the rate of loss of population of state β is Wn_β.



A transition from state α to state β decreases the population of state α, but a transition from state β to state α increases the population of state α.

However, the key thing to realize is that whereas a transition from α to β causes a *loss* of population of level α, a transition from β to α causes the population of state α to *increase*. So we can write

$$\text{rate of change of population of state } \alpha = -Wn_\alpha + Wn_\beta$$

The first term is negative as it represents a loss of population of state α and in contrast the second term is positive as it represents a gain in the population of state α. The rate of change of the population can be written using the language of calculus as $\mathrm{d}n_\alpha/\mathrm{d}t$ so we have

$$\frac{\mathrm{d}n_\alpha}{\mathrm{d}t} = -Wn_\alpha + Wn_\beta \quad .$$

Similarly we can write for the population of state β:

$$\frac{\mathrm{d}n_\beta}{\mathrm{d}t} = -Wn_\beta + Wn_\alpha \quad .$$

These equations are almost correct, but we need to make one modification. At equilibrium the populations are not changing so $\mathrm{d}n_\alpha/\mathrm{d}t = 0$; this immediately implies that at equilibrium $n_\alpha = n_\beta$, which simply is not correct. We know that at equilibrium the population of state α exceeds that of state β. This defect is easily remedied by replacing the population n_α with the *deviation* of the population from its equilibrium value $\left(n_\alpha - n_\alpha^0\right)$, where n_α^0 is the population of state α at equilibrium. Doing the same with state β gives us the final, correct, equations:

$$\frac{\mathrm{d}n_\alpha}{\mathrm{d}t} = W\left(n_\beta - n_\beta^0\right) - W\left(n_\alpha - n_\alpha^0\right) \qquad \frac{\mathrm{d}n_\beta}{\mathrm{d}t} = W\left(n_\alpha - n_\alpha^0\right) - W\left(n_\beta - n_\beta^0\right) .$$

You will recognise here that this kind of approach is exactly the same as that used to analyse the kinetics of a reversible chemical reaction.

Using Eqn. [2], we can use these two equations to work out how the z-magnetization varies with time:

$$\begin{aligned}\frac{dM_z}{dt} &= \frac{d\left(n_\alpha - n_\beta\right)}{dt} \\ &= \frac{dn_\alpha}{dt} - \frac{dn_\beta}{dt} \\ &= W\left(n_\beta - n_\beta^0\right) - W\left(n_\alpha - n_\alpha^0\right) - W\left(n_\alpha - n_\alpha^0\right) + W\left(n_\beta - n_\beta^0\right) \\ &= -2W\left(n_\alpha - n_\beta\right) + 2W\left(n_\alpha^0 - n_\beta^0\right) \\ &= -2W\left(M_z - M_z^0\right)\end{aligned}$$

where $M_z^0 = \left(n_\alpha^0 - n_\beta^0\right)$, the equilibrium z-magnetization.

8.2.1 Consequences of the rate equation

The discussion in the previous section led to a (differential) equation describing the motion of the z-magnetization

$$\frac{dM_z(t)}{dt} = -R_z\left(M_z(t) - M_z^0\right) \qquad [7]$$

where the rate constant, $R_z = 2W$ and M_z has been written as a function of time, $M_z(t)$, to remind us that it may change.

What this equations says is that the rate of change of M_z is proportional to the deviation of M_z from its equilibrium value, M_z^0. If $M_z = M_z^0$, that is the system is at equilibrium, the right-hand side of Eqn. [7] is zero and hence so is the rate of change of M_z: nothing happens. On the other hand, if M_z deviates from M_z^0 there will be a rate of change of M_z, and this rate will be proportional to the deviation of M_z from M_z^0. The change will also be such as to return M_z to its equilibrium value, M_z^0. In summary, Eqn. [7] predicts that over time M_z will return to M_z^0; this is exactly what we expect. The rate at which this happens will depend on R_z.

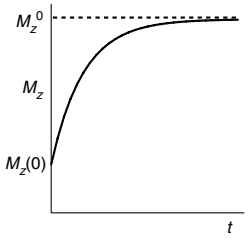
This equation can easily be integrated:

$$\int \frac{dM_z(t)}{\left(M_z(t) - M_z^0\right)} = \int -R_z dt$$

$$\ln\left(M_z(t) - M_z^0\right) = -R_z t + \text{const.}$$

If, at time zero, the magnetization is $M_z(0)$, the constant of integration can be determined as $\ln\left(M_z(0) - M_z^0\right)$. Hence, with some rearrangement:

$$\ln\left[\frac{M_z(t) - M_z^0}{M_z(0) - M_z^0}\right] = -R_z t \qquad [7A]$$



or

$$M_z(t) = \left[M_z(0) - M_z^0\right]\exp\left(-R_z t\right) + M_z^0 \qquad [7B]$$

In words, this says that the z-magnetization returns from $M_z(0)$ to M_z^0 following an exponential law. The time constant of the exponential is $1/R_z$, and this is often called T_1, the *longitudinal* or *spin-lattice relaxation time*.

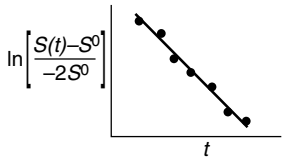
8.2.2 The inversion recovery experiment

We described this experiment in section 3.10. First, a 180° pulse is applied,

thereby inverting the magnetization. Then a delay t is left for the magnetization to relax. Finally, a 90° pulse is applied so that the size of the z-magnetization can be measured.

We can now analyse this experiment fully. The starting condition for M_z is $M_z(0) = -M_z^0$, i.e. inversion. With this condition the predicted time evolution can be found from Eqn. [7A] to be:

$$\ln\left[\frac{M_z(t) - M_z^0}{-2M_z^0}\right] = -R_z t$$



Plot used to extract a value of R_z from the data from an inversion recovery experiment.

Recall that the amplitude of the signal we record in this experiment is proportional to the z-magnetization. So, if this signal is $S(t)$ it follows that

$$\ln\left[\frac{S(t) - S^0}{-2S^0}\right] = -R_z t \qquad [7C]$$

where S^0 is the signal intensity from equilibrium magnetization; we would find this from a simple 90° – acquire experiment.

Equation [7C] implies that a plot of $\ln\left[\left(S(t) - S^0\right)/-2S^0\right]$ against t should be a straight line of slope $-R_z$. This, then, is the basis of a method of determining the relaxation rate constant.

8.2.3 A quick estimate for R_z (or T_1)

Often we want to obtain a quick estimate for the relaxation rate constant (or, equivalently, the relaxation time). One way to do this is to do an inversion recovery experiment but rather than varying t systematically we look for the value of t which results in no signal *i.e.* a null. If the time when $S(t)$ is zero is t_{null} it follows immediately from Eqn. [7C] that:

$$\ln\left[\frac{1}{2}\right] = -R_z t_{\text{null}} \quad \text{or} \quad R_z = \frac{\ln 2}{t_{\text{null}}} \quad \text{or} \quad T_1 = \frac{t_{\text{null}}}{\ln 2}$$

Probably the most useful relationship is the last, which is $T_1 \approx 1.4\ t_{\text{null}}$.

This method is rather crude, but it good enough for estimating T_1. Armed with this estimate we can then, for example, decide on the time to leave between transients (typically three to five times T_1).

8.2.4 Writing relaxation in terms of operators

As we saw in Chapter 6, in quantum mechanics z-magnetization is represented by the operator I_z. It is therefore common to write Eqn. [7] in terms of operators rather then magnetizations, to give:

$$\frac{\mathrm{d}I_z(t)}{\mathrm{d}t} = -R_z\left(I_z(t) - I_z^0\right) \qquad [8]$$

where $I_z(t)$ represents the z-magnetization at time t and I_z^0 represents the equilibrium z-magnetization. As it stands this last equation seems to imply that the operators change with time, which is not what is meant. What are changing are the populations of the energy levels and these in turn lead to changes in the z-magnetization represented by the operator. We will use this notation from now on.

8.3 Solomon equations

The idea of writing differential equations for the populations, and then transcribing these into magnetizations, is a particularly convenient way of describing relaxation, especially in more complex system. This will be illustrated in this section.

Consider a sample consisting of molecules which contain two spins, I and S; the spins are not coupled. As was seen in section 2.4, the two spins have between them four energy levels, which can be labelled according to the spin states of the two spins.

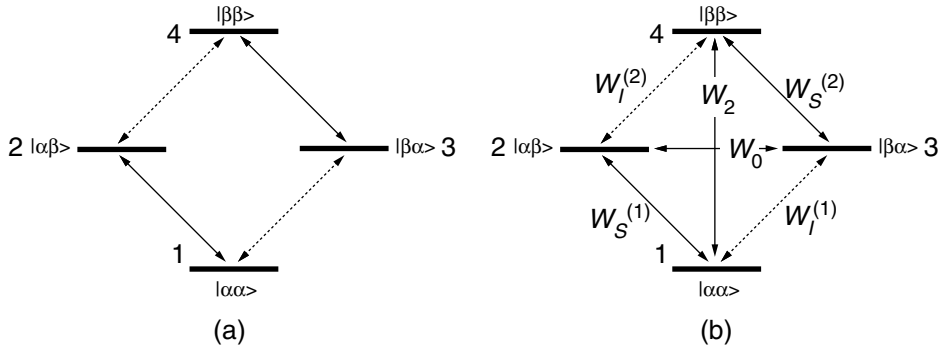


Diagram (a) shows the energy levels of a two spin system; the levels are labelled with the spin of I first and the spin of S second. The dashed arrows indicate allowed transitions of the I spin, and the solid arrows indicate allowed transitions of the S spin. Diagram (b) shows the relaxation induced transitions which are possible amongst the same set of levels.

It turns out that in such a system it is possible to have relaxation induced transitions between *all* possible pairs of energy levels, even those transitions which are forbidden in normal spectroscopy; why this is so will be seen in detail below. The rate constants for the two allowed I spin transitions will be denoted $W_I^{(1)}$ and $W_I^{(2)}$, and likewise for the spin S transitions. The rate constant for the transition between the $\alpha\alpha$ and $\beta\beta$ states is denoted W_2, the "2" indicating that it is a double quantum transition. Finally, the rate constant for the transition between the $\alpha\beta$ and $\beta\alpha$ states is denoted W_0, the "0" indicating that it is a zero quantum transition.

Just in the same was as was done in Section 8.2, rate equations can be written for the flow of population from any of the levels. For example, for level 1

$$\frac{\mathrm{d}n_1}{\mathrm{d}t} = -W_S^{(1)}n_1 - W_I^{(1)}n_1 - W_2 n_1 + W_S^{(1)}n_2 + W_I^{(1)}n_3 + W_2 n_4$$

The negative terms are rates which lead to a loss of population of level 1 and the positive terms are ones that lead to a gain in its population. As was discussed in section 8.2 the populations ought to be written as deviations from their equilibrium values, $\left(n_i - n_i^0\right)$. However, to do this results in unnecessary complexity; rather, the calculation will be carried forward as written and then at the last stage the populations will be replaced by their deviations from equilibrium.

The corresponding equations for the other populations are

$$\frac{dn_2}{dt} = -W_S^{(1)}n_2 - W_I^{(2)}n_2 - W_0n_2 + W_S^{(1)}n_1 + W_I^{(2)}n_4 + W_0n_3$$

$$\frac{dn_3}{dt} = -W_I^{(1)}n_3 - W_S^{(2)}n_3 - W_0n_3 + W_I^{(1)}n_1 + W_S^{(2)}n_4 + W_0n_2$$

$$\frac{dn_4}{dt} = -W_S^{(2)}n_4 - W_I^{(2)}n_4 - W_2n_4 + W_S^{(2)}n_3 + W_I^{(2)}n_2 + W_2n_1$$

All of this can be expressed in a more compact way if we introduce the I and S spin z-magnetizations. The I spin magnetization is equal to the population difference across the two I spin transitions, 1–3 and 2–4

$$I_z = n_1 - n_3 + n_2 - n_4 \qquad [9]$$

As discussed above, the magnetization has been represented as the corresponding operator, I_z. Likewise for the S-spin magnetization

$$S_z = n_1 - n_2 + n_3 - n_4 \qquad [10]$$

A third combination of populations will be needed, which is represented by the operator $2I_zS_z$

$$2I_zS_z = n_1 - n_3 - n_2 + n_4 \qquad [11]$$

Comparing this with Eq. [9] reveals that $2I_zS_z$ represents the *difference* in population differences across the two I-spin transitions; likewise, comparison with Eq. [10] shows that the same operator also represents the difference in population differences across the two S-spin transitions.

Taking the derivative of Eq. [9] and then substituting for the derivatives of the populations gives

$$\begin{aligned}
\frac{dI_z}{dt} &= \frac{dn_1}{dt} - \frac{dn_3}{dt} + \frac{dn_2}{dt} - \frac{dn_4}{dt} \\
&= -W_S^{(1)}n_1 - W_I^{(1)}n_1 - W_2n_1 + W_S^{(1)}n_2 + W_I^{(1)}n_3 + W_2n_4 \\
&+W_I^{(1)}n_3 + W_S^{(2)}n_3 + W_0n_3 - W_I^{(1)}n_1 - W_S^{(2)}n_4 - W_0n_2 \\
&-W_S^{(1)}n_2 - W_I^{(2)}n_2 - W_0n_2 + W_S^{(1)}n_1 + W_I^{(2)}n_4 + W_0n_3 \\
&+W_S^{(2)}n_4 + W_I^{(2)}n_4 + W_2n_4 - W_S^{(2)}n_3 - W_I^{(2)}n_2 - W_2n_1
\end{aligned} \qquad [12]$$

This unpromising looking equation can be expressed in terms of I_z, S_z *etc.* by first introducing one more operator E, which is essentially the identity or unit operator

$$E = n_1 + n_2 + n_3 + n_4 \qquad [13]$$

and then realizing that the populations, n_i, can be written in terms of E, I_z, S_z, and $2I_z\,S_z$:

$$n_1 = \tfrac{1}{4}\left(E + I_z + S_z + 2I_zS_z\right)$$

$$n_2 = \tfrac{1}{4}\left(E + I_z - S_z - 2I_zS_z\right)$$

$$n_3 = \tfrac{1}{4}\left(E - I_z + S_z - 2I_zS_z\right)$$

$$n_4 = \tfrac{1}{4}\left(E - I_z - S_z + 2I_zS_z\right)$$

where these relationships can easily be verified by substituting back in the definitions of the operators in terms of populations, Eqs. [9] – [13].

After some tedious algebra, the following differential equation is found

for I_z

$$\frac{dI_z}{dt} = -\left(W_I^{(1)} + W_I^{(2)} + W_2 + W_0\right)I_z - \left(W_2 - W_0\right)S_z - \left(W_I^{(1)} - W_I^{(2)}\right)2I_zS_z \quad [14]$$

Similar algebra gives the following differential equations for the other operators

$$\frac{dS_z}{dt} = -\left(W_2 - W_0\right)I_z - \left(W_S^{(1)} + W_S^{(2)} + W_2 + W_0\right)S_z - \left(W_S^{(1)} - W_S^{(2)}\right)2I_zS_z$$

$$\frac{d2I_zS_z}{dt} = -\left(W_I^{(1)} - W_I^{(2)}\right)I_z - \left(W_S^{(1)} - W_S^{(2)}\right)S_z - \left(W_I^{(1)} + W_I^{(2)} + W_S^{(1)} + W_S^{(2)}\right)2I_zS_z$$

As expected, the total population, represented by E, does not change with time. These three differential equations are known as the *Solomon equations*.

It must be remembered that the populations used to derive these equations are really the deviation of the populations from their equilibrium values. As a result, the I and S spin magnetizations should properly be their deviations from their equilibrium values, I_z^0 and S_z^0; the equilibrium value of $2I_zS_z$ is easily shown, from its definition, to be zero. For example, Eq. [14] becomes

$$\frac{d\left(I_z - I_z^0\right)}{dt} = -\left(W_I^{(1)} + W_I^{(2)} + W_2 + W_0\right)\left(I_z - I_z^0\right) - \left(W_2 - W_0\right)\left(S_z - S_z^0\right) - \left(W_I^{(1)} - W_I^{(2)}\right)2I_zS_z$$

8.3.1 Interpreting the Solomon equations

What the Solomon equations predict is, for example, that the rate of change of I_z depends not only on $I_z - I_z^0$, but also on $S_z - S_z^0$ and $2I_zS_z$. In other words the way in which the magnetization on the I spin varies with time depends on what is happening to the S spin – the two magnetizations are connected. This phenomena, by which the magnetizations of the two different spins are connected, is called *cross relaxation*.

The rate at which S magnetization is transferred to I magnetization is given by the term

$$\left(W_2 - W_0\right)\left(S_z - S_z^0\right)$$

in Eq. [14]; $(W_2–W_0)$ is called the cross-relaxation rate constant, and is sometimes given the symbol σ_{IS}. It is clear that in the absence of the relaxation pathways between the $\alpha\alpha$ and $\beta\beta$ states (W_2), or between the $\alpha\beta$ and $\beta\alpha$ states (W_0), there will be no cross relaxation. This term is described as giving rise to transfer from S to I as it says that the rate of change of the I spin magnetization is proportional to the deviation of the S spin magnetization from its equilibrium value. Thus, if the S spin is not at equilibrium the I spin magnetization is perturbed.

In Eq. [14] the term

$$\left(W_I^{(1)} + W_I^{(2)} + W_2 + W_0\right)\left(I_z - I_z^0\right)$$

describes the relaxation of I spin magnetization on its own; this is sometimes called the self relaxation. Even if W_2 and W_0 are absent, self relaxation still occurs. The self relaxation rate constant, given in the previous equation as a sum of W values, is sometimes given the symbol R_I or ρ_I.

Finally, the term

$$\left(W_I^{(1)} - W_I^{(2)}\right)2I_zS_z$$

in Eq. [14] describes the transfer of I_zS_z into I spin magnetization. Recall that $W_I^{(1)}$ and $W_I^{(2)}$ are the relaxation induced rate constants for the two allowed transitions of the I spin (1–3 and 2–4). Only if these two rate constants are different will there be transfer from $2I_zS_z$ into I spin magnetization. This situation arises when there is *cross-correlation* between different relaxation mechanisms; a further discussion of this is beyond the scope of these lectures. The rate constants for this transfer will be written

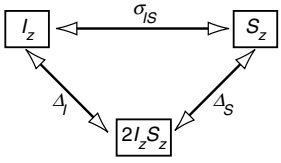
$$\Delta_I = \left(W_I^{(1)} - W_I^{(2)}\right) \qquad \Delta_S = \left(W_S^{(1)} - W_S^{(2)}\right)$$

According to the final Solomon equation, the operator $2I_zS_z$ shows self relaxation with a rate constant

$$R_{IS} = \left(W_I^{(1)} + W_I^{(2)} + W_S^{(1)} + W_S^{(2)}\right)$$

Note that the W_2 and W_0 pathways do not contribute to this. This rate combined constant will be denoted R_{IS}.

Using these combined rate constants, the Solomon equations can be written



$$\begin{aligned}
\frac{\mathrm{d}\left(I_z - I_z^0\right)}{\mathrm{d}t} &= -R_I\left(I_z - I_z^0\right) - \sigma_{IS}\left(S_z - S_z^0\right) - \Delta_I 2I_zS_z \\
\frac{\mathrm{d}\left(S_z - S_z^0\right)}{\mathrm{d}t} &= -\sigma_{IS}\left(I_z - I_z^0\right) - R_S\left(S_z - S_z^0\right) - \Delta_S 2I_zS_z \qquad [15] \\
\frac{\mathrm{d}2I_zS_z}{\mathrm{d}t} &= -\Delta_I\left(I_z - I_z^0\right) - \Delta_S\left(S_z - S_z^0\right) - R_{IS}2I_zS_z
\end{aligned}$$

The pathways between the different magnetization are visualized in the diagram opposite. Note that as $\mathrm{d}I_z^0/\mathrm{d}t = 0$ (the equilibrium magnetization is a constant), the derivatives on the left-hand side of these equations can equally well be written $\mathrm{d}I_z/\mathrm{d}t$ and $\mathrm{d}S_z/\mathrm{d}t$.

It is important to realize that in such a system I_z and S_z do not relax with a simple exponentials. They only do this if the differential equation is of the form

$$\frac{\mathrm{d}I_z}{\mathrm{d}t} = -R_I\left(I_z - I_z^0\right)$$

which is plainly not the case here. For such a two-spin system, therefore, it is not proper to talk of a "T_1" relaxation time constant.

8.4 Nuclear Overhauser effect

The Solomon equations are an excellent way of understanding and analysing experiments used to measure the nuclear Overhauser effect. Before embarking on this discussion it is important to realize that although the states represented by operators such as I_z and S_z cannot be observed directly, they can be made observable by the application of a radiofrequency pulse, ideally a 90° pulse

$$aI_z \xrightarrow{(\pi/2)I_x} -aI_y$$

The subsequent recording of the free induction signal due to the evolution of the operator I_y will give, after Fourier transformation, a spectrum with a peak of size $-a$ at frequency Ω_I. In effect, by computing the value of the coefficient a, the appearance of the subsequently observed spectrum is predicted.

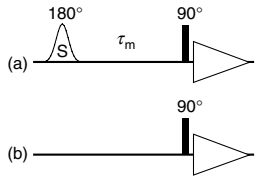
The basis of the nuclear Overhauser effect can readily be seen from the Solomon equation (for simplicity, it is assumed in this section that $\Delta_I = \Delta_S = 0$)

$$\frac{\mathrm{d}\left(I_z - I_z^0\right)}{\mathrm{d}t} = -R_I\left(I_z - I_z^0\right) - \sigma_{IS}\left(S_z - S_z^0\right)$$

What this says is that if the S spin magnetization deviates from equilibrium there will be a change in the I spin magnetization at a rate proportional to (a) the cross-relaxation rate, σ_{IS} and (b) the extent of the deviation of the S spin from equilibrium. This change in the I spin magnetization will manifest itself as a change in the intensity in the corresponding spectrum, and it is this change in intensity of the I spin when the S spin is perturbed which is termed the nuclear Overhauser effect.

Plainly, there will be no such effect unless σ_{IS} is non-zero, which requires the presence of the W_2 and W_0 relaxation pathways. It will be seen later on that such pathways are only present when there is dipolar relaxation between the two spins and that the resulting cross-relaxation rate constants have a strong dependence on the distance between the two spins. The observation of a nuclear Overhauser effect is therefore diagnostic of dipolar relaxation and hence the proximity of pairs of spins. The effect is of enormous value, therefore, in structure determination by NMR.

8.4.1 Transient experiments



Pulse sequence for recording transient NOE enhancements. Sequence (a) involves selective inversion of the S spin – shown here using a shaped pulse. Sequence (b) is used to record the reference spectrum in which the intensities are unperturbed.

A simple experiment which reveals the NOE is to invert just the S spin by applying a selective 180° pulse to its resonance. The S spin is then not at equilibrium so magnetization is transferred to the I spin by cross-relaxation. After a suitable period, called the mixing time, τ_m, a non-selective 90° pulse is applied and the spectrum recorded.

After the selective pulse the situation is

$$I_z(0) = I_z^0 \qquad S_z(0) = -S_z^0 \qquad [16]$$

where I_z has been written as $I_z(t)$ to emphasize that it depends on time and likewise for S. To work out what will happen during the mixing time the differential equations

$$\frac{\mathrm{d}I_z(t)}{\mathrm{d}t} = -R_I\left(I_z(t) - I_z^0\right) - \sigma_{IS}\left(S_z(t) - S_z^0\right)$$

$$\frac{\mathrm{d}S_z(t)}{\mathrm{d}t} = -\sigma_{IS}\left(I_z(t) - I_z^0\right) - R_S\left(S_z(t) - S_z^0\right)$$

need to be solved (integrated) with this initial condition. One simple way to do this is to use the *initial rate approximation*. This involves assuming that the mixing time is sufficiently short that, on the *right-hand side* of the equations, it can be assumed that the initial conditions set out in Eq. [16] apply, so, for the first equation

$$\left.\frac{\mathrm{d}I_z(t)}{\mathrm{d}t}\right|_{\text{init}} = -R_I\left(I_z^0 - I_z^0\right) - \sigma_{IS}\left(-S_z^0 - S_z^0\right)$$

$$= 2\sigma_{IS}S_z^0$$

This is now easy to integrate as the right-hand side has no dependence on $I_z(t)$

$$\int_0^{\tau_m} \mathrm{d}I_z(t) = \int_0^{\tau_m} 2\sigma_{IS}S_z^0\,\mathrm{d}t$$

$$I_z(\tau_m) - I_z(0) = 2\sigma_{IS}\tau_m S_z^0$$

$$I_z(\tau_m) = 2\sigma_{IS}\tau_m S_z^0 + I_z^0$$

This says that for zero mixing time the I magnetization is equal to its equilibrium value, but that as the mixing time increases the I magnetization has an additional contribution which is proportional to the mixing time and the cross-relaxation rate, σ_{IS}. This latter term results in a change in the intensity of the I spin signal, and this change is called an *NOE enhancement*.

The normal procedure for visualizing these enhancements is to record a reference spectrum in which the intensities are unperturbed. In terms of z-magnetizations this means that $I_{z,\mathrm{ref}} = I_z^0$. The difference spectrum, defined as (perturbed spectrum – unperturbed spectrum) corresponds to the difference

$$\begin{aligned} I_z(\tau_m) - I_{z,\mathrm{ref}} &= 2\sigma_{IS}\tau_m S_z^0 + I_z^0 - I_z^0 \\ &= 2\sigma_{IS}\tau_m S_z^0 \end{aligned}$$

The NOE enhancement factor, η, is defined as

$$\eta = \frac{\text{intensity in enhanced spectrum - intensity in reference spectrum}}{\text{intensity in reference spectrum}}$$

so in this case η is

$$\eta(\tau_m) = \frac{I_z(\tau_m) - I_{z,\mathrm{ref}}}{I_{z,\mathrm{ref}}} = \frac{2\sigma_{IS}\tau_m S_z^0}{I_z^0}$$

and if I and S are of the same nuclear species (*e.g.* both proton), their equilibrium magnetizations are equal so that

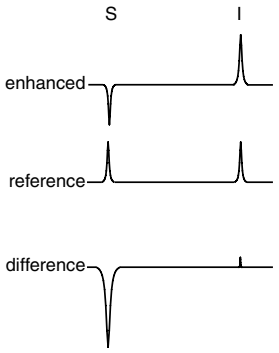
$$\eta(\tau_m) = 2\sigma_{IS}\tau_m$$

Hence a plot of η against mixing time will give a straight line of slope σ_{IS}; this is a method used for measuring the cross-relaxation rate constant. A single experiment for one value of the mixing time will reveal the presence of NOE enhancements.

This initial rate approximation is valid provided that

$$\sigma_{IS}\tau_m << 1 \text{ and } R_S\tau_m << 1$$

the first condition means that there is little transfer of magnetization from S to I, and the second means that the S spin remains very close to complete inversion.



Visualization of how an NOE difference spectrum is recorded. The enhancement is assumed to be positive.

8.4.1.1 Advanced topic: longer mixing times

At longer mixing times the differential equations are a little more difficult to solve, but they can be integrated using standard methods (symbolic mathematical programmes such as *Mathematica* are particularly useful for this). Using the initial conditions given in Eq. [16] and, assuming for simplicity that $I_z^0 = S_z^0$ the following solutions are found

$$\frac{I_z(\tau_m)}{I_z^0} = \frac{2\sigma_{IS}}{R}\left[\exp(-\lambda_2\tau_m) - \exp(-\lambda_1\tau_m)\right] + 1$$

$$\begin{aligned} \frac{S_z(\tau_m)}{I_z^0} = &\left[\frac{R_I - R_S}{R}\right]\left[\exp(-\lambda_1\tau_m) - \exp(-\lambda_2\tau_m)\right] \\ &+ 1 - \exp(-\lambda_1\tau_m) + \exp(-\lambda_2\tau_m) \end{aligned}$$

where

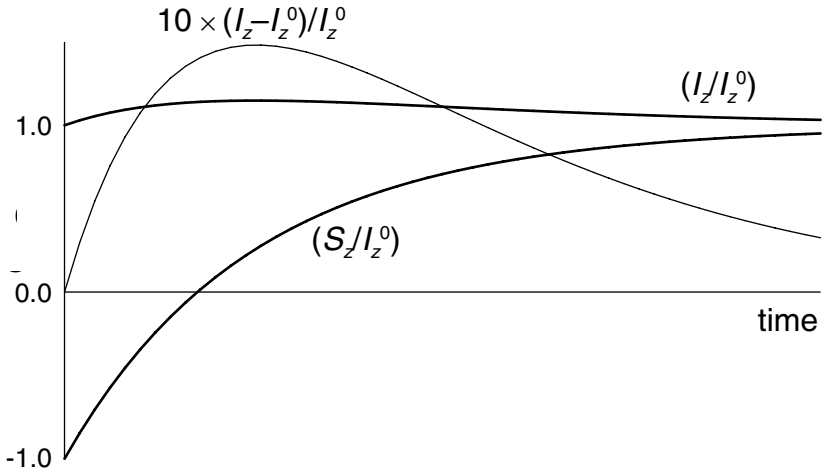
$$R = \sqrt{R_I^2 - 2R_IR_S + R_S^2 + 4\sigma_{IS}^2}$$

$$\lambda_1 = \tfrac{1}{2}\left[R_I + R_S + R\right] \qquad \lambda_2 = \tfrac{1}{2}\left[R_I + R_S - R\right]$$

These definitions ensure that $\lambda_1 > \lambda_2$. If R_I and R_S are not too dissimilar, R is of the order of σ_{IS}, and so the two rate constants λ_1 and λ_2 differ by a quantity of the order of σ_{IS}.

As expected for these two coupled differential equations, integration gives a time dependence which is the sum of two exponentials with different time constants.

The figure below shows the typical behaviour predicted by these equations (the parameters are $R_I = R_S = 5\sigma_{IS}$)



The S spin magnetization returns to its equilibrium value with what appears to be an exponential curve; in fact it is the sum of two exponentials but their time constants are not sufficiently different for this to be discerned. The I spin magnetization grows towards a maximum and then drops off back towards the equilibrium value. The NOE enhancement is more easily visualized by plotting the difference magnetization, $(I_z - I_z^0)/I_z^0$, on an expanded scale; the plot now shows the positive NOE enhancement reaching a maximum of about 15%.

Differentiation of the expression for I_z as a function of τ_m shows that the maximum enhancement is reached at time

$$\tau_{m,max} = \frac{1}{\lambda_1 - \lambda_2} \ln \frac{\lambda_1}{\lambda_2}$$

and that the maximum enhancement is

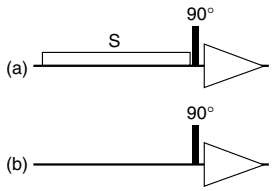
$$\frac{I_z(\tau_{m,max}) - I_z^0}{I_z^0} = \frac{2\sigma_{IS}}{R}\left[\left(\frac{\lambda_1}{\lambda_2}\right)^{\frac{-\lambda_1}{R}} - \left(\frac{\lambda_1}{\lambda_2}\right)^{\frac{-\lambda_2}{R}}\right]$$

8.4.2 The DPFGSE NOE experiment

From the point of view of the relaxation behaviour the DPFGSE experiment is essentially identical to the transient NOE experiment. The only difference is that the I spin starts out *saturated* rather than at equilibrium. This does not influence the build up of the NOE enhancement on I. It does, however, have the advantage of reducing the size of the I spin signal which has to be removed in the difference experiment. Further discussion of this experiment is deferred to Chapter 9.

8.4.3 Steady state experiments

The steady-state NOE experiment involves irradiating the S spin with a radiofrequency field which is sufficiently weak that the I spin is not affected. The irradiation is applied for long enough that the S spin is saturated, meaning $S_z = 0$, and that the steady state has been reached, which means that none of the magnetizations are changing, *i.e.* $\left(\mathrm{d}I_z/\mathrm{d}t\right) = 0$.



Pulse sequence for recording steady state NOE enhancements. Sequence (a) involves selective irradiation of the S spin leading to saturation. Sequence (b) is used to record the reference spectrum in which the intensities are unperturbed.

Under these conditions the first of Eqs. [15] can be written

$$\left.\frac{\mathrm{d}\left(I_z - I_z^0\right)}{\mathrm{d}t}\right|_{\mathrm{SS}} = -R_I\left(I_{z,\mathrm{SS}} - I_z^0\right) - \sigma_{IS}\left(0 - S_z^0\right) = 0$$

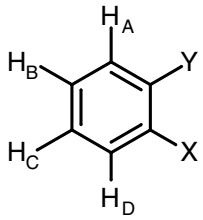
therefore

$$I_{z,\mathrm{SS}} = \frac{\sigma_{IS}}{R_I} S_z^0 + I_z^0$$

As in the transient experiment, the NOE enhancement is revealed by subtracting a reference spectrum which has equilibrium intensities. The NOE enhancement, as defined above, will be

$$\eta_{\mathrm{SS}} = \frac{I_{z,\mathrm{SS}} - I_{z,\mathrm{ref}}}{I_{z,\mathrm{ref}}} = \frac{\sigma_{IS}}{R_I}\frac{S_z^0}{I_z^0}$$

In contrast to the transient experiment, the steady state enhancement only depends on the relaxation of the receiving spin (here I); the relaxation rate of the S spin does not enter into the relationship simply because this spin is held saturated during the experiment.



Irradiation of proton B gives a much larger enhancement on proton A than on C despite the fact that the distances to the two spins are equal. The smaller enhancement on C is due to the fact that it is relaxing more quickly than A, due to the interaction with proton D.

It is important to realise that the value of the steady-state NOE enhancement depends on the ratio of cross-relaxation rate constant to the self relaxation rate constant for the spin which is receiving the enhancement. If this spin is relaxing quickly, for example as a result of interaction with many other spins, the size of the NOE enhancement will be reduced. So, although the size of the enhancement does depend on the cross-relaxation rate constant the size of the enhancement cannot be interpreted in terms of this rate constant alone. This point is illustrated by the example in the margin.

8.4.4 Advanced topic: NOESY

Pulse sequence for NOESY.

The dynamics of the NOE in NOESY are very similar to those for the transient NOE experiment. The key difference is that instead of the magnetization of the S spin being inverted at the start of the mixing time, the magnetization has an amplitude label which depends on the evolution during t_1.

Starting with equilibrium magnetization on the I and S spins, the z-magnetizations present at the start of the mixing time are (other magnetization will be rejected by appropriate phase cycling)

$$S_z(0) = -\cos\Omega_S t_1 S_z^0 \qquad I_z(0) = -\cos\Omega_I t_1 I_z^0$$

The equation of motion for S_z is

$$\frac{\mathrm{d}S_z(t)}{\mathrm{d}t} = -\sigma_{IS}\left(I_z(t) - I_z^0\right) - R_S\left(S_z(t) - S_z^0\right)$$

As before, the initial rate approximation will be used:

$$\left.\frac{\mathrm{d}S_z(\tau_\mathrm{m})}{\mathrm{d}t}\right|_{\mathrm{init}} = -\sigma_{IS}\left(-\cos\Omega_I t_1 I_z^0 - I_z^0\right) - R_S\left(-\cos\Omega_S t_1 S_z^0 - S_z^0\right)$$

$$= \sigma_{IS}\left(\cos\Omega_I t_1 + 1\right)I_z^0 + R_S\left(\cos\Omega_S t_1 + 1\right)S_z^0$$

Integrating gives

$$\int_0^{\tau_\mathrm{m}} \mathrm{d}S_z(t) = \int_0^{\tau_\mathrm{m}} \left[\sigma_{IS}\left(\cos\Omega_I t_1 + 1\right)I_z^0 + R_S\left(\cos\Omega_S t_1 + 1\right)S_z^0\right]\mathrm{d}t$$

$$S_z(\tau_\mathrm{m}) - S_z(0) = \sigma_{IS}\tau_\mathrm{m}\left(\cos\Omega_I t_1 + 1\right)I_z^0 + R_S\tau_\mathrm{m}\left(\cos\Omega_S t_1 + 1\right)S_z^0$$

$$S_z(\tau_\mathrm{m}) = \sigma_{IS}\tau_\mathrm{m}\left(\cos\Omega_I t_1 + 1\right)I_z^0 + R_S\tau_\mathrm{m}\left(\cos\Omega_S t_1 + 1\right)S_z^0 - \cos\Omega_S t_1 S_z^0$$

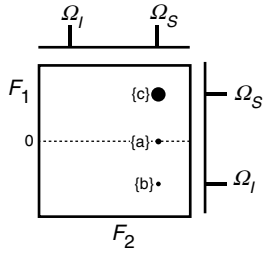
$$= \sigma_{IS}\tau_\mathrm{m} I_z^0 + R_S\tau_\mathrm{m} S_z^0 \qquad \{\mathrm{a}\}$$

$$+\cos\Omega_I t_1\left[\sigma_{IS}\tau_\mathrm{m}\right]I_z^0 \qquad \{\mathrm{b}\}$$

$$+\cos\Omega_S t_1\left[R_S\tau_\mathrm{m} - 1\right]S_z^0 \qquad \{\mathrm{c}\}$$

After the end of the mixing time, this z-magnetization on spin S is rendered observable by the final 90° pulse; the magnetization is on spin S, and so will precess at Ω_S during t_2.

The three terms {a}, {b} and {c} all represent different peaks in the NOESY spectrum.



Term {a} has no evolution as a function of t_1 and so will appear at $F_1 = 0$; in t_2 it evolves at Ω_S. This is therefore an *axial peak* at $\{F_1,F_2\} = \{0, \Omega_S\}$. This peak arises from z-magnetization which has recovered during the mixing time. In this initial rate limit, it is seen that the axial peak is zero for zero mixing time and then grows linearly depending on R_S and σ_{IS}.

Term {b} evolves at Ω_I during t_1 and Ω_S during t_2; it is therefore a cross peak at $\{\Omega_I, \Omega_S\}$. The intensity of the cross peak grows linearly with the mixing time and also depends on σ_{IS}; this is analogous to the transient NOE experiment.

Term {c} evolves at Ω_S during t_1 and Ω_S during t_2; it is therefore a diagonal peak at $\{\Omega_S, \Omega_S\}$ and as $R_s\tau_\mathrm{m} << 1$ in the initial rate, this peak is negative. The intensity of the peak grows back towards zero linearly with the mixing time and at a rate depending on R_S. This peak arises from S spin magnetization which remains on S during the mixing time, decaying during that time at a rate determined by R_S.

If the calculation is repeated using the differential equation for I_z a complimentary set of peaks at $\{0, \Omega_I\}$, $\{\Omega_S, \Omega_I\}$ and $\{\Omega_I, \Omega_I\}$ are found.

It will be seen later that whereas R_I and R_S are positive, σ_{IS} can be either positive or negative. If σ_{IS} is positive, the diagonal and cross peaks will be of opposite sign, whereas if σ_{IS} is negative all the peaks will have the same sign.

8.4.5 Sign of the NOE enhancement

We see that the time dependence and size of the NOE enhancement depends on the relative sizes of the cross-relaxation rate constant σ_{IS} and the self relaxation rate constants R_I and R_S. It turns out that these self-rates are always positive, but the cross-relaxation rate constant can be positive or negative. The reason for this is that $\sigma_{IS} = (W_2 - W_0)$ and it is quite possible for W_0 to be greater or less than W_2.

A positive cross-relaxation rate constant means that if spin S deviates from equilibrium cross-relaxation will *increase* the magnetization on spin I. This leads to an *increase* in the signal from I, and hence a *positive* NOE enhancement. This situation is typical for small molecules is non-viscous solvents.

A negative cross-relaxation rate constant means that if spin S deviates from equilibrium cross-relaxation will *decrease* the magnetization on spin I. This leads to a *negative* NOE enhancement, a situation typical for large molecules in viscous solvents. Under some conditions W_0 and W_2 can become equal and then the NOE enhancement goes to zero.

8.5 Origins of relaxation

We now turn to the question as to what causes relaxation. Recall from section 8.1 that relaxation involves transitions between energy levels, so what we seek is the origin of these transitions. We already know from Chapter 3 that transitions are caused by transverse magnetic fields (*i.e.* in the *xy*-plane) which are oscillating close to the Larmor frequency. An RF pulse gives rise to just such a field.

However, there is an important distinction between the kind of transitions caused by RF pulses and those which lead to relaxation. When an RF pulse is applied all of the spins experience the same oscillating field. The kind of transitions which lead to relaxation are different in that the transverse fields are *local*, meaning that they only affect a few spins and not the whole sample. In addition, these fields vary randomly in direction and amplitude. In fact, it is precisely their random nature which drives the sample to equilibrium.

The fields which are responsible for relaxation are generated within the sample, often due to interactions of spins with one another or with their environment in some way. They are made time varying by the random motions (rotations, in particular) which result from the thermal agitation of the molecules and the collisions between them. Thus we will see that NMR relaxation rate constants are particularly sensitive to molecular motion.

If the spins need to lose energy to return to equilibrium they give this up to the motion of the molecules. Of course, the amounts of energy given up by the spins are tiny compared to the kinetic energies that molecules have, so they are hardly affected. Likewise, if the spins need to increase their energy to go to equilibrium, for example if the population of the β state has to be increased, this energy comes from the motion of the molecules.

Relaxation is essentially the process by which energy is allowed to flow

between the spins and molecular motion. This is the origin of the original name for longitudinal relaxation: *spin-lattice relaxation*. The lattice does not refer to a solid, but to the motion of the molecules with which energy can be exchanged.

8.5.1 Factors influencing the relaxation rate constant

The detailed theory of the calculation of relaxation rate constants is beyond the scope of this course. However, we are in a position to discuss the kinds of factors which influence these rate constants.

Let us consider the rate constant W_{ij} for transitions between levels i and j; this turns out to depend on three factors:

$$W_{ij} = A_{ij} \times Y \times J\left(\omega_{ij}\right)$$

We will consider each in turn.

The spin factor, A_{ij}

This factor depends on the quantum mechanical details of the interaction. For example, not all oscillating fields can cause transitions between all levels. In a two spin system the transition between the $\alpha\alpha$ and $\beta\beta$ cannot be brought about by a simple oscillating field in the transverse plane; in fact it needs a more complex interaction that is only present in the dipolar mechanism (section 8.6.2). We can think of A_{ij} as representing a kind of selection rule for the process – like a selection rule it may be zero for some transitions.

The size factor, Y

This is just a measure of how large the interaction causing the relaxation is. Its size depends on the detailed origin of the random fields and often it is related to molecular geometry.

The spectral density, $J(\omega_{ij})$

This is a measure of the amount of molecular motion which is at the correct frequency, ω_{ij}, to cause the transitions. Recall that molecular motion is the effect which makes the random fields vary with time. However, as we saw with RF pulses, the field will only have an effect on the spins if it is oscillating at the correct frequency. The spectral density is a measure of how much of the motion is present at the correct frequency.

8.5.2 Spectral densities and correlation functions

The value of the spectral density, $J(\omega)$, has a large effect on relaxation rate constants, so it is well worthwhile spending some time in understanding the form that this function takes.

Correlation functions

To make the discussion concrete, suppose that a spin in a sample experiences a magnetic field due to a dissolved paramagnetic species. The size of the magnetic field will depend on the relative orientation of the spin and the paramagnetic species, and as both are subject to random thermal motion, this orientation will vary randomly with time (it is said to be a random function of time), and so the magnetic field will be a random function of time. Let the field experienced by this first spin be $F_1(t)$.

Paramagnetic species have unpaired electrons. These generate magnetic fields which can interact with nearby nuclei. On account of the large gyromagnetic ratio of the electron (when compared to the nucleus) such paramagnetic species are often a significant source of relaxation.

Now consider a second spin in the sample. This also experiences a random magnetic field, $F_2(t)$, due to the interaction with the paramagnetic species. At any instant, this random field will not be the same as that experienced by the first spin.

For a macroscopic sample, each spin experiences a different random field, $F_i(t)$. There is no way that a detailed knowledge of each of these random fields can be obtained, but in some cases it is possible to characterise the *overall* behaviour of the system quite simply.

The average field experienced by the spins is found by taking the ensemble average – that is adding up the fields for all members of the ensemble (*i.e.* all spins in the system)

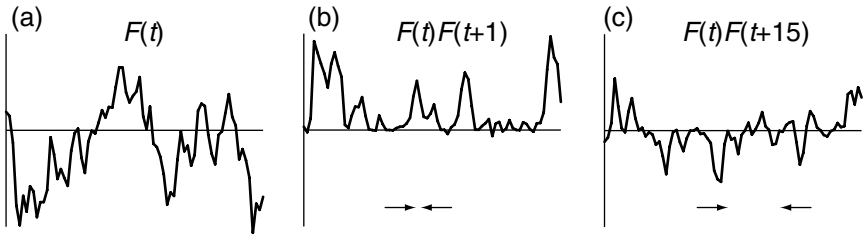
$$\overline{F(t)} = F_1(t) + F_2(t) + F_3(t) + \ldots$$

For random thermal motion, this ensemble average turns out to be independent of the time; this is a property of *stationary* random functions. Typically, the $F_i(t)$ are signed quantities, randomly distributed about zero, so this ensemble average will be zero.

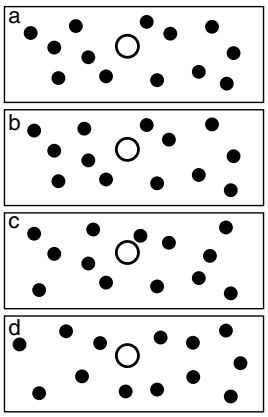
An important property of random functions is the *correlation function*, $G(t,\tau)$, defined as

$$\begin{aligned} G(t,\tau) &= F_1(t)F_1^*(t+\tau) + F_2(t)F_2^*(t+\tau) + F_3(t)F_3^*(t+\tau) + \ldots \\ &= \overline{F(t)F^*(t+\tau)} \end{aligned}$$

$F_1(t)$ is the field experienced by spin 1 at time t, and $F_1(t+\tau)$ is the field experienced at a time τ later; the star indicates the complex conjugate, which allows for the possibility that $F(t)$ may be complex. If the time τ is short the spins will not have moved very much and so $F_1(t+\tau)$ will be very little different from $F_1(t)$. As a result, the product $F_1(t)F_1^*(t+\tau)$ will be positive. This is illustrated in the figure below, plot (b).



(a) is a plot of the random function $F(t)$ against time; there are about 100 separate time points. (b) is a plot of the value of F multiplied by its value one data point later – *i.e.* one data point to the right; all possible pairs are plotted. (c) is the same as (b) but for a time interval of 15 data points. The two arrows indicate the spacing over which the correlation is calculated.



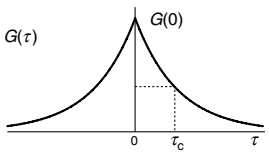
Visualization of the different timescales for random motion. (a) is the starting position: the black dots are spins and the open circle represents a paramagnetic species. (b) is a snap shot a very short time after (a); hardly any of the spins have moved. (c) is a snapshot at a longer time; more spins have moved, but part of the original pattern is still discernible. (d) is after a long time, all the spins have moved and the original pattern is lost.

The same is true for all of the other members of then ensemble, so when the $F_i(t)F_i^*(t+\tau)$ are added together for a particular time, t, – that is, the

ensemble average is taken – the result will be for them to reinforce one another and hence give a finite value for $G(t,\tau)$.

As τ gets longer, the spin will have had more chance of moving and so $F_1(t+\tau)$ will differ more and more from $F_1(t)$; the product $F_1(t)F_1^*(t+\tau)$ need not necessarily be positive. This is illustrated in plot (c) above. The ensemble average of all these $F_i(t)F_i^*(t+\tau)$ is thus less than it was when τ was shorter. In the limit, once τ becomes sufficiently long, the $F_i(t)F_i^*(t+\tau)$ are randomly distributed and their ensemble average, $G(t,\tau)$, goes to zero. $G(t,\tau)$ thus has its maximum value at $\tau = 0$ and then decays to zero at long times. For stationary random functions, the correlation function is independent of the time t; it will therefore be written $G(\tau)$.

The correlation function, $G(\tau)$, is thus a function which characterises the memory that the system has of a particular arrangement of spins in the sample. For times τ which are much less than the time it takes for the system to rearrange itself $G(\tau)$ will be close to its maximum value. As time proceeds, the initial arrangement becomes more and more disturbed, and $G(\tau)$ falls. For sufficiently long times, $G(\tau)$ tends to zero.



The simplest form for $G(\tau)$ is

$$G(\tau) = G(0)\exp\left(-|\tau|/\tau_c\right) \qquad [18]$$

the variable τ appears as the modulus, resulting in the same value of $G(\tau)$ for positive and negative values of τ. This means that the correlation is the same with time τ before and time τ after the present time.

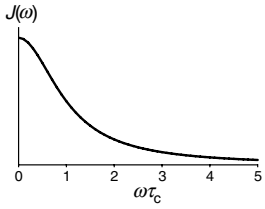
τ_c is called the *correlation time*. For times much less than the correlation time the spins have not moved much and the correlation function is close to its original value; when the time is of the order of τ_c significant rearrangements have taken place and the correlation function has fallen to about half its initial value. For times much longer than τ_c the spins have moved to completely new positions and the correlation function has fallen close to zero.

Spectral densities

The correlation function is a function of time, just like a free induction decay. So, it can be Fourier transformed to give a function of frequency. The resulting frequency domain function is called the *spectral density*; as the name implies, the spectral density gives a measure of the amount of motion present at different frequencies. The spectral density is usually denoted $J(\omega)$

$$G(\tau) \xrightarrow{\text{Fourier Transform}} J(\omega)$$

If the spins were executing a well ordered motion, such as oscillating back and forth about a mean position, the spectral density would show a peak at that frequency. However, the spins are subject to random motions with a range of different periods, so the spectral density shows a range of frequencies rather than having peaks at discreet frequencies.



Plot of the spectral density as a function of the dimensionless variable $\omega\tau_c$. The curve is a lorentzian

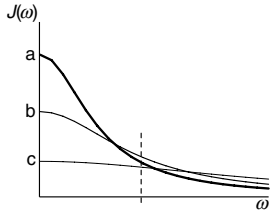
Generally, for random motion characterised by a correlation time τ_c, frequencies from zero up to about $1/\tau_c$ are present. The amount at frequencies higher that $1/\tau_c$ tails off quite rapidly as the frequency increases.

For a simple exponential correlation function, given in Eq. [18], the corresponding spectral density is a Lorentzian

$$\exp\left(-|\tau|/\tau_c\right) \xrightarrow{\text{Fourier Transform}} \frac{2\tau_c}{1+\omega^2\tau_c^2}$$

This function is plotted in the margin; note how it drops off significantly once the product $\omega\tau_c$ begins to exceed ~1.

The plot opposite compares the spectral densities for three different correlation times; curve *a* is the longest, *b* an intermediate value and *c* the shortest. Note that as the correlation time decreases the spectral density moves out to higher frequencies. However, the area under the plot remains the same, so the contribution at lower frequencies is decreased. In particular, at the frequency indicated by the dashed line the contribution at correlation time *b* is greater than that for either correlation times *a* or *c*.

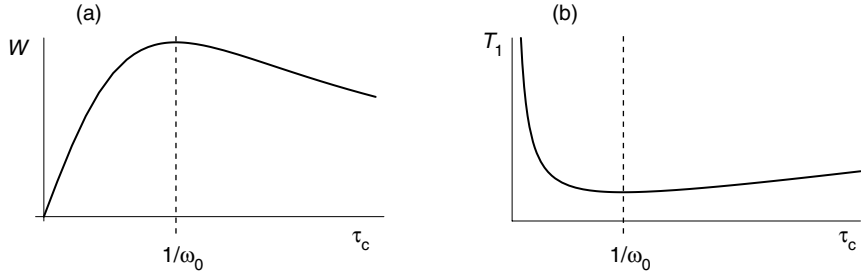


For this spectral density function, the maximum contribution at frequency ω is found when τ_c is $1/\omega$; this has important consequences which are described in the next section.

8.5.3 The "T_1 minimum"

In the case of relaxation of a single spin by a random field (such as that generated by a paramagnetic species), the only relevant spectral density is that at the Larmor frequency, ω_0. This is hardly surprising as to cause relaxation – that is to cause transitions – the field needs to have components oscillating at the Larmor frequency.

We have just seen that for a given frequency, ω_0, the spectral density is a maximum when τ_c is $1/\omega_0$, so to have the most rapid relaxation the correlation time should be $1/\omega_0$. This is illustrated in the plots below which show the relaxation rate constant, *W*, and the corresponding relaxation time ($T_1 = 1/W$) plotted as a function of the correlation time.



Plot (a) shows how the relaxation rate constant, *W*, varies with the correlation time, τ_c, for a given Larmor frequency; there is a maximum in the rate constant when $\tau_c = 1/\omega_0$. Plot (b) shows the same effect, but here we have plotted the relaxation time constant, T_1; this shows a minimum.

At very short correlation times ($\tau_c << 1/\omega_0$) there is some spectral density at the Larmor frequency, but not that much as the energy of the motion is spread over a very wide frequency range. As the correlation time increases the amount of spectral density at the Larmor frequency increases and so the relaxation rate constant increases, reaching a maximum when $\tau_c = 1/\omega_0$. After this point, the spectra density at the Larmor frequency, and hence the rate constant, falls.

In terms of the relaxation time, T_1, there is a minimum in T_1 which corresponds to the maximum in W. We see that, like Goldilocks and the Three Bears, efficient relaxation requires a correlation time which is neither too fast nor too slow.

Motion which gives rise to correlation times which are much shorter than $1/\omega_0$ is described as being in the *fast motion* (or *extreme narrowing*) limit. Put mathematically, fast motion means $\omega_0\tau_c << 1$. Motion which gives rise to correlation times which are much slower than $1/\omega_0$ is described as being in the *slow motion* (or *spin diffusion*) limit; mathematically this limit is $\omega_0\tau_c >> 1$. Clearly, which limit we are in depends on the Larmor frequency, which in turn depends on the nucleus and the magnetic field.

For a Larmor frequency of 400 MHz we would expect the fastest relaxation when the correlation time is 0.4 ns. Small molecules have correlation times significantly shorter than this (say tens of ps), so such molecules are clearly in the fast motion limit. Large molecules, such as proteins, can easily have correlation times of the order of a few ns, and these clearly fall in the slow motion limit.

Somewhat strangely, therefore, both very small and very large molecules tend to relax more slowly than medium-sized molecules.

8.6 Relaxation mechanisms

So far, the source of the magnetic fields which give rise to relaxation and the origin of their time dependence have not been considered. Each such source is referred to as a *relaxation mechanism*. There are quite a range of different mechanisms that can act, but of these only a few are really important for spin half nuclei.

8.6.1 Paramagnetic species

We have already mentioned this source of varying fields several times. The large magnetic moment of the electron means that paramagnetic species in solution are particularly effective at promoting relaxation. Such species include dissolved oxygen and certain transition metal compounds.

8.6.2 The dipolar mechanism

Each spin has associated with it a magnetic moment, and this is turn gives rise to a magnetic field which can interact with other spins. Two spins are thus required for this interaction, one to "create" the field and one to "experience" it. However, their roles are reversible, in the sense that the second spin creates a field which is experienced by the first. So, the overall interaction is a property of the pair of nuclei.

The size of the interaction depends on the inverse cube of the distance between the two nuclei and the direction of the vector joining the two nuclei, measured relative to that of the applied magnetic field. As a molecule tumbles in solution the direction of this vector changes and so the magnetic field changes. Changes in the distance between the nuclei also result in a change in the magnetic field. However, molecular vibrations, which do give such changes, are generally at far too high frequencies to give significant spectral density at the Larmor frequency. As a result, it is generally changes in orientation which are responsible for relaxation.

The pair of interacting nuclei can be in the same or different molecules, leading to intra- and inter-molecular relaxation. Generally, however, nuclei in the same molecule can approach much more closely than those in different molecules so that intra-molecular relaxation is dominant.

The relaxation induced by the dipolar coupling is proportional to the *square* of the coupling. Thus it goes as

$$\gamma_1^2\gamma_2^2\frac{1}{r_{12}^6}$$

where γ_1 and γ_2 are the gyromagnetic ratios of the two nuclei involved and r_{12} is the distance between them.

As the size of the dipolar interaction depends on the product of the gyromagnetic ratios of the two nuclei involved, and the resulting relaxation rate constants depends on the square of this. Thus, pairs of nuclei with high gyromagnetic ratios are most efficient at promoting relaxation. For example, every thing else being equal, a proton-proton pair will relax 16 times faster than a carbon-13 proton pair.

It is important to realize that in dipolar relaxation the effect is not primarily to distribute the energy from one of the spins to the other. This would not, on its own, bring the spins to equilibrium. Rather, the dipolar interaction provides a path by which energy can be transferred between the lattice and the spins. In this case, the lattice is the molecular motion. Essentially, the dipole-dipole interaction turns molecular motion into an oscillating magnetic field which can cause transitions of the spins.

Relation to the NOE

The dipolar mechanism is the only common relaxation mechanism which can cause transitions in which more than one spin flips. Specifically, with reference to section 8.3, the dipolar mechanism gives rise to transitions between the $\alpha\alpha$ and $\beta\beta$ states (W_2) and between the $\alpha\beta$ and $\beta\alpha$ states (W_0).

The rate constant W_2 corresponds to transitions which are at the sum of the Larmor frequencies of the two spins, ($\omega_{0,I} + \omega_{0,S}$) and so it is the spectral density at this sum frequency which is relevant. In contrast, W_0 corresponds to transitions at ($\omega_{0,I} - \omega_{0,S}$) and so for these it is the spectral density at this difference frequency which is relevant.

In the case where the two spins are the same (e.g. two protons) the two relevant spectral densities are $J(2\omega_0)$ and $J(0)$. In the fast motion limit ($\omega_0\tau_c << 1$) $J(2\omega_0)$ is somewhat less than $J(0)$, but not by very much. A detailed

calculation shows that $W_2 > W_0$ and so we expect to see positive NOE enhancements (section 8.4.5). In contrast, in the slow motion limit ($\omega_0\tau_c >> 1$) $J(2\omega_0)$ is all but zero and so $J(0) >> J(2\omega_0)$; not surprisingly it follows that $W_0 > W_2$ and a negative NOE enhancement is seen.

8.6.3 The chemical shift anisotropy mechanism

The chemical shift arises because, due to the effect of the electrons in a molecule, the magnetic field experienced by a nucleus is different to that applied to the sample. In liquids, all that is observable is the average chemical shift, which results from the molecule rapidly experiencing all possible orientations by rapid molecular tumbling.

At a more detailed level, the magnetic field experienced by the nucleus depends on the orientation of the molecule relative to the applied magnetic field. This is called chemical shift anisotropy (CSA). In addition, it is not only the magnitude of the field which is altered but also its *direction*. The changes are very small, but sufficient to be detectable in the spectrum and to give rise to relaxation.

One convenient way of imagining the effect of CSA is to say that due to it there are small additional fields created at the nucleus – in general in all three directions. These fields vary in size as the molecule reorients, and so they have the necessary time variation to cause relaxation. As has already been discussed, it is the transverse fields which will give rise to changes in population.

The size of the CSA is specified by a tensor, which is a mathematical object represented by a three by three matrix.

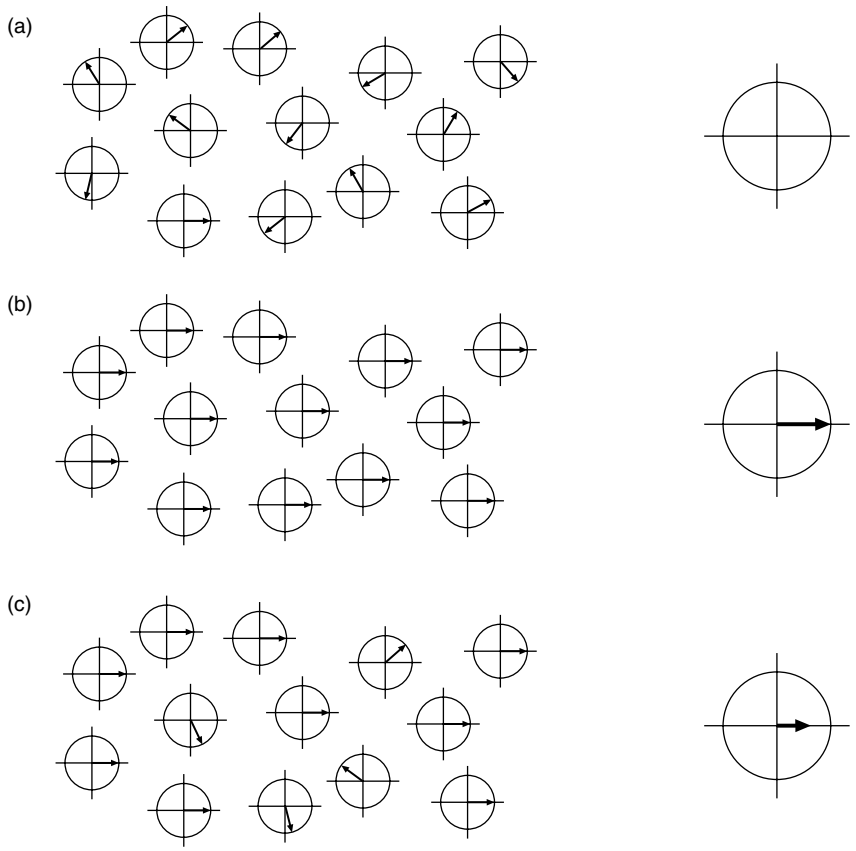
$$\sigma = \begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix}$$

The element σ_{xz} gives the size of the extra field in the x-direction which results from a field being applied in the z-direction; likewise, σ_{yz} gives the extra field in the y-direction and σ_{zz} that in the z-direction. These elements depend on the electronic properties of the molecule and the orientation of the molecule with respect to the magnetic field.

Detailed calculations show that the relaxation induced by CSA goes as the square of the field strength and is also proportional to the shift anisotropy. A rough estimate of the size of this anisotropy is that it is equal to the typical shift range. So, CSA relaxation is expected to be significant for nuclei with large shift ranges observed at high fields. It is usually insignificant for protons.

8.7 Transverse relaxation

Right at the start of this section we mentioned that relaxation involved two processes: the populations returning to equilibrium and the transverse magnetization decaying to zero. So far, we have only discussed the fist of these two. The second, in which the transverse magnetization decays, is called *transverse* (or *spin-spin*) relaxation.



Depiction of how the individual contributions from different spins (shown on the left) add up to give the net transverse magnetization (on the right). See text for details.

Each spin in the sample can be thought of as giving rise to a small contribution to the magnetization; these contributions can be in any direction, and in general have a component along x, y and z. The individual contributions along z add up to give the net z-magnetization of the sample.

The transverse contributions behave in a more complex way as, just like the net transverse magnetization, these contributions are precessing at the Larmor frequency in the transverse plane. We can represent each of these contributions by a vector precessing in the transverse plane.

The direction in which these vectors point can be specified by giving each a phase – arbitrarily the angle measured around from the x-axis. It is immediately clear that if these phases are random the net transverse magnetization of the sample will be zero as all the individual contributions will cancel. This is the situation that pertains at equilibrium and is shown in (a) in the figure above.

For there to be net magnetization, the phases must not be random, rather there has to be a preference for one direction; this is shown in (b) in the figure above. In quantum mechanics this is described as a *coherence*. An RF pulse applied to equilibrium magnetization generates transverse magnetization, or in other words the pulse generates a coherence. Transverse relaxation *destroys* this coherence by destroying the alignment of the individual contributions, as shown in (c) above.

Our picture indicates that there are two ways in which the coherence could be destroyed. The first is to make the vectors jump to new positions,

at random. Drawing on our analogy between these vectors and the behaviour of the bulk magnetization, we can see that these jumps could be brought about by local oscillating fields which have the same effect as pulses.

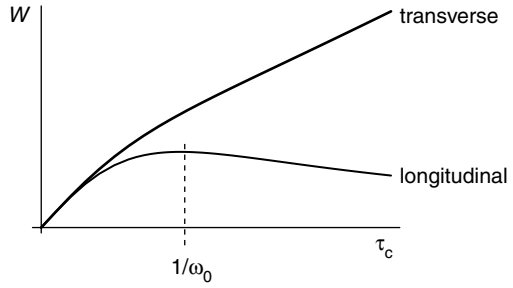
This is exactly what causes longitudinal relaxation, in which we imagine the local fields causing the spins to flip. So, *anything* that causes longitudinal relaxation will *also cause* transverse relaxation.

The second way of destroying the coherence is to make the vectors get out of step with one another as a result of them precessing at *different* Larmor frequencies. Again, a local field plays the part we need but this time we do not need it to oscillate; rather, all we need for it to do is to be different at different locations in the sample.

This latter contribution is called the *secular* part of transverse relaxation; the part which has the same origin as longitudinal relaxation is called the *non-secular* part.

It turns out that the secular part depends on the spectral density at zero frequency, $J(0)$. We can see that this makes sense as this part of transverse relaxation requires no transitions, just a field to cause a local variation in the magnetic field. Looking at the result from section 8.5.2 we see that $J(0) = 2\tau_c$, and so as the correlation time gets longer and longer, so too does the relaxation rate constant. Thus large molecules in the slow motion limit are characterised by very rapid transverse relaxation; this is in contrast to longitudinal relaxation is most rapid for a particular value of the correlation time.

The plot below compares the behaviour of the longitudinal and transverse relaxation rate constants. As the correlation time increases the longitudinal rate constant goes through a maximum. However, the transverse rate constant carries on increasing and shows no such maximum. We can attribute this to the secular part of transverse relaxation which depends on $J(0)$ and which simply goes on increasing as the correlation time increases. Detailed calculations show that in the fast motion limit the two relaxation rate constants are equal.



Comparison of the longitudinal and transverse relaxation rate constants as a function of the correlation time for the fixed Larmor frequency. The longitudinal rate constant shows a maximum, but the transverse rate constant simply goes on increasing.