Signal intensity from most Magnetic Resonance (MR) pulse sequences does not relate directly to any single physical parameter (although all sequences have signal which is proportional to proton density (PD) (scaled by an arbitrary gain which is scanner, session and object dependant)). There are a number of parameters that can influence the MR signal, the most common being $T_1$, $T_2$, magnetisation transfer related parameters (ranging from the relatively simple Magnetisation Transfer Ratio (MTR) to the rate constants and volume fractions of the different tissue compartments involved (quantitative MT (qMT))), diffusion parameters (including diffusivity and anisotropy), flow and perfusion. The signal we measure is a complex function of these, plus sequence parameters such as TE and TR.

Empirically, it has been found that $T_1$-weighted images (i.e. images with a short TE and short TR) are particularly good for showing anatomic detail. They can be collected with high spatial resolution, and have excellent contrast between grey-matter and white-matter. $T_2$-weighted images (i.e. images with a long TE and long TR), on the other hand, are particularly good for detecting pathology, with fluid (e.g. CSF, oedema) appearing bright. In this lecture, we investigate the factors that influence MR relaxation times in (relatively simple, single component) systems, introducing the concepts of the dipolar field, correlation times and the spectral density function. Similarly, we introduce the concept of the diffusion and apparent diffusion coefficients, appropriate for measurements in such systems. We then describe the additional confounds that exist in more complex systems such as real tissues, and give examples of how the multiple compartments that are seen can be modelled.

$T_1$ and $T_2$ relaxation in (relatively) simple systems

The dipolar field

The observed MR signal can be considered to result from a net magnetisation which is the sum of the effects of the magnetic moments associated with the all the MR visible nuclear spins (typically protons in the case of MR imaging) in the sample. Each individual proton is a highly magnetic dipole (on the microscopic scale) which produces its own magnetic field in addition to the applied $B_0$, so any particular nucleus will experience the dipolar field arising from the other nuclei, particularly those close by. The dipoles are in constant (random, Brownian) motion, but the average over all the spins of their effects on one another can be characterised by a correlation function, which describes how likely it is that the field experienced at a particular instant $t$ is the same as at a later time $t+\tau$. Associated with this correlation function is a characteristic time, the correlation time $\tau_c$. (For times much less than $\tau_c$ the spins have not moved much and the correlation function is high, while at times much
greater than $\tau_c$ the spins have moved to completely new positions and the correlation function has fallen to near zero; at time close to $\tau_c$ the correlation function has intermediate values).

In pure water the correlation time is about $10^{12}$ s, i.e. the dipolar field contains fluctuations at frequencies up to about $10^{12}$ Hz. In tissue, water exists in several physico-chemical forms, characterised by whether it is free to move, or bound to large molecules. It is slowed down by interactions with other compounds and the correlation time increases which, as shown below, changes its relaxation times.

The dipolar field & transverse relaxation

$T_2$ is the time constant for decay of the transverse magnetisation (i.e. in a plane perpendicular to $B_0$) after an RF pulse in a *homogeneous* (i.e. uniform) static magnetic field, while $T_2^*$ is the time constant in an *inhomogeneous* static field. After a $90^\circ$ pulse, all the spins are aligned along the $y'$ direction in the rotating frame. If $B_0$ was the only field present, they would stay aligned along $y'$ (perfectly in phase with each other) indefinitely. The dipolar field, however, causes the spins to precess away from $y'$, each at a different rate, such that after a time they will be out of phase i.e. all pointing in different directions with a net vector sum of zero. The net transverse magnetisation, and hence signal, decay exponentially, with a time constant $T_2$; if the main magnetic field is inhomogeneous then additional, reversible, effects must also be taken into account:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

The dipolar field & longitudinal relaxation

$T_1$ is the time constant for recovery of longitudinal magnetisation (i.e. along $B_0$) after a perturbation; longitudinal relaxation requires that the longitudinal magnetisation $M_z$ decays from a high energy state ($M_z$ negative) towards its low energy state ($M_z = +M_0$, the equilibrium magnetisation). For this to happen, individual spins must lose energy to the surrounding tissue. Quantum mechanics tells us that the energy difference between these states is $\Delta E = hv_0$, so the spin must emit a photon of frequency $v_0$ (the Larmor frequency). Such emission can happen spontaneously, but if there is an external electromagnetic field (such as the dipole field) which is changing at the frequency associated with the transition, the likelihood of transition will be greatly increased through to an effect known as stimulated emission.

Model of relaxation using Bloch equations

To understand the effect of the local dipolar field $B_L$ on a spin with magnetic moment $\mu$, the Bloch equations in the rotating frame are helpful:

$$\frac{d\mu_y}{dt} = (\gamma\mu_y'B_{Lyz} - \mu_z'B_{Lz'})$$

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From Foster and Hutchinson, Practical Nuclear Magnetic Resonance Imaging, (Oxford University Press (1987))
These show that T₂ processes (i.e. alterations in μₓ′ and μᵧ′ can be brought about by Bₓ′Lₓ′, Bₓ′Lz′ or Bz′Lz′, i.e. local field fluctuations along x′, y′ or z′. Transferring to the laboratory frame, those along x′ and y′ (in the rotating frame) correspond to fluctuations at or near the Larmor frequency in the laboratory frame. Those along z′ (=z) correspond to fluctuations near to zero frequency in the laboratory frame. Similarly, T₁ processes (i.e. alterations in μz′) can only be brought about by Bₓ′Lₓ′ and Bz′Lz′ i.e. fluctuations at or near the Larmor frequency in the laboratory frame.

Spectral density J(ω)

These ideas about of motion can be formalised into the concept of spectral density. This is the 'amount of field fluctuation' at a particular frequency. The form of the spectral density function depends on that of the correlation function; if the former is a simple exponential (a reasonable approximation for simple types of motion) it is given by

\[ J(ω) = \frac{2τ_c}{1 + ω^2τ_c^2} \]

which is constant up to a frequency of about 1/τ_c, then tails away to zero.

The area under the J(ω) curve is constant; thus if the motion is slowed down (e.g. by partly binding the water, or by reducing the temperature) τ_c is increased and there are more field fluctuations at low frequencies, and less at high frequencies.

T₁ and T₂ are approximately related to the spectral density as follows:

\[ T_1(ω_0)^{-1} = A J(ω_0) \]
\[ T_2(ω_0)^{-1} = A (J(0) + J(ω_0)) \]

where A is a constant.

T₂ is usually dominated by slow fluctuations, arising from macro-molecules (since J(0)>J(ω₀)), whilst T₁ is dominated by more rapid motion (at the Larmor frequency ω₀) and is most efficient when there is motion with a correlation time such that ω₀τ_c ~ 1. Molecules that are moving much faster than this (ω₀τ_c << 1), are described as being in the extreme narrowing limit; those moving more slowly (such that ω₀τ_c >> 1) are said to be in the spin diffusion limit; in both cases T₁ relaxation will be slower.
**Dependence on field strength and temperature**

A plot of $T_1$ and $T_2$ vs. correlation time for this simple model shows several regions which can be understood in terms of the altering spectral density as the correlation time is changed.

Pure water has fluctuations up to well beyond the Larmor frequency, so altering the field has no effect on $J(\omega_0)$. Thus its $T_1$ and $T_2$ are independent of field. ($T_1 \sim 4s; T_2 \sim 2.5s$).

Bound water has fluctuations only up to about $10^8$ Hz, however, so the Larmor frequency is in the tail of the distribution. Increasing the field reduces $J(\omega_0)$ and hence increases $T_1$, but has little effect on $T_2$.

$T_1$ has a minimum at a correlation time of $1/\omega$.

Because molecular motion, and thus the spectral density, depends on temperature, altering the temperature usually alters the relaxation times. For tissue and agarose phantoms they increase by about 3% per °C; in vivo, of course, such temperature variations are unusual.

**Other effects** …

The dipole-dipole interaction is not the only process that can lead to randomly varying fields, and thus affect relaxation rates. Other contributions include:

- Paramagnetic effects: unpaired electrons can create a magnetic field that can affect nearby protons in a similar way to a nuclear dipole, but which is several orders of magnitude larger in size. A proton moving near a paramagnetic ion may thus undergo significant relaxation.

- Chemical shift anisotropy: in the presence of a strong applied magnetic field, electrons in a molecule can ‘shield’ the nucleus, slightly reducing the effective field. While in bulk this simply leads to a slightly different resonant frequency, at the level of an individual molecule the effect depends on the orientation with respect the main field, and can thus change with motion and affect relaxation.

**Diffusion in (relatively) simple systems**

**The Einstein equation**

Collisions between molecules lead to any particular molecule undergoing a ‘random walk’, and the Einstein equation says that the molecules root mean square displacement from its initial position increases with time according to:

$$r. m. s = \sqrt{\langle r^2 \rangle} = \sqrt{6Dt}$$
Here D is the diffusion coefficient, which in an MR experiment leads to a loss of signal in the presence of magnetic field gradients given by $S = S_0 e^{-bD}$, where b is a function of the applied gradient strength, and duration and separation.

The Einstein equation assumes that diffusion is free or unhindered, but if diffusion is restricted or hindered (as is always the case in tissue, due to cell membranes and other structures, Einstein’s equation is not valid anymore and changing the observation time (diffusion time) can change value that we measure for D. Despite this, we conventionally still estimate r.m.s displacement at a time t (from the degree of signal loss), and calculate D from slope of curve. We refer to this (inherently underestimated) value as the Apparent Diffusion Coefficient (ADC).

**Dependence on field strength and temperature**

Unlike $T_1$ and $T_2$ relaxation, diffusion values are not expected to change with field strength.

Because molecular motion depends on temperature, altering the temperature alters the diffusion rates. In phantoms, this can be modelled by fitting to an Arrhenius activation law which after rearrangement takes the form:

$$\ln D = \ln D_0 - B \left( \frac{1}{T} - \frac{1}{T_0} \right) + C \left( \frac{1}{T} - \frac{1}{T_0} \right)^2$$

with changes in the range 1.7-3.2% per °C for typical liquids and gels. As with relaxation times, temperature variations are unusual in vivo, of course.

**Other effects …**

In a test tube, diffusion is largely isotropic, and is characterised by a single diffusion constant; in the brain diffusion may be anisotropic, as barriers to diffusion (e.g. axon walls and cellular microstructures) are oriented, and the system is characterised by different ADCs in different directions. The simplest description is then given by the diffusion tensor:

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

The eigenvalues of the tensor describe the degree of diffusion along three perpendicular axes, while the eigenvectors indicate the orientation of these axes relative to the magnet coordinates. In particular, the direction of the principle eigenvector (the eigenvector associated with the largest eigenvalue) is often assumed to approximate to the local orientation of white matter fibres within a particular voxel, allowing tractography algorithms to map out complete (putative) white matter fibre bundles (“tracts”).
Relaxation and diffusion in more complex systems

In tissue, all of the above effects (and others) are happening simultaneously, and we are measuring the signal from a mixture of different microscopic compartments at a macroscopic level. Even if there are no gross partial volume effects (i.e. we are measuring a single, relatively homogeneous tissue), it is not obvious how the contributions of the various bound and more free molecules will combine, and whether or not we will see a single relaxation rate or diffusion value, or several different values.

Fast Exchange Two State model (FETS)

In the Fast Exchange Two State model, free water has relatively low relaxation rates (rate = 1/relaxation time). The two water compartments (states) are in good contact (exchange), and the bound water effectively relaxes the free water. The observed relaxation rate is then a weighted average of the individual relaxation rate of the bound and free water:

$$\frac{1}{T_{1,2 \, observed}} = \frac{b}{T_{1,2 \, bound}} + \frac{1 - b}{T_{1,2 \, free}}$$

where b is the fraction of bound water.

Similar equations hold for other measurements, including diffusion values, if the exchange between the compartments is fast enough. Fast exchange usually assumed for $T_1$ measurements, and there is little evidence of multi-exponential behaviour, but this is not true for $T_2$. For diffusion, the situation is more complex, as it has been shown that multi-exponential behaviour can occur even within a single compartment (due to differing processes near to and far away from the walls).

Multi-exponential $T_2$ measurements

If multiple echo time data are collected then several, independently decaying, components may be distinguishable. These can be assigned to intra- and extra-cellular water, and, if the inter echo spacing is short enough, the data may also include a component whose very short $T_2$ suggests it is due to myelin water (i.e. water trapped between the lipid bilayers of the myelin sheath). Collecting a large (>= 32) number of echoes and fitting the resulting data to a spectrum of $T_2$ values

[See Fornasa F. for a simple review of many of the factors influencing the rate of diffusion in tissue].

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using non-negative least squares (NNLS) allows this very short $T_2$ component ($\leq 20\,\text{ms}$) to be extracted\(^2\). Such experiments are very time consuming (and until recently could collect data from only a limited number of relatively thick slices), but have been shown to correlate well with independent measures of myelination.

Relatively recently, steady state imaging techniques have allowed 3D high resolution whole brain $T_2$ measurements to be made in acceptable imaging times\(^3\), and these have also been extended to allow multiple components to be detected, with parameters and modelling specifically tailored to the detection of myelin water\(^4\). While not directly comparable to the multi-echo technique, due to different assumptions made in the models, myelin water fraction maps derived from such $mcDESPOT$ (multi component driven equilibrium single point observation of $T_1/T_2$) compare well with previously reported values.

Higher order diffusion models

If multiple $b$-values are used, it can be seen that the resulting signal decay curves do not follow the simple single exponential decay predicted by the diffusion tensor model. In addition, it is clear that when measuring with voxel sizes of 2-3mm, there may be multiple fibres (oriented in different directions) present within each voxel.

The q-space formulation\(^5,6\) allows the shape of the displacement profile to be determined in all directions (without imposing a specific tensor model), and allows characteristic distances to be extracted which give information about tissue structure. The number of measurements and very high $b$-values required make the technique impractical in vivo, however.

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\(^5\) P.T Callaghan, PGSE-MASSEY, a sequence for overcoming phase instability in very-high-gradient spin-echo NMR. J. Magn. Reson. 1990; 88:493

Instead, a number HARDI (High Angular Resolution Diffusion Imaging) based schemes have been devised to determine fibre orientation from data collected from gradients with a single (clinically achievable) b-value but a large number of orientations. These include tensor mixture modelling\(^7\), q-ball imaging\(^8\), spherical deconvolution\(^9\), and PAS-MRI\(^10\).

More recently, interest has re-emerged into direct axonal diameter measurements\(^{11-13}\), with a combination of optimisation of diffusion gradients and carefully defined models making these feasible in vivo (at least in certain situations)\(^{14}\).

**Final thoughts:**

Relaxation time and diffusion measurements can reveal information about the molecular environment of the molecules giving rise to the MR signal. While theories exist to directly link molecular motion to MR signal values, these are unlikely to include all the relevant factors even in simple, single-component, situations such as may be experienced in phantoms; in vivo, the complexities of tissue structure lead to additional complexities so, while techniques are now available that provide valuable insights into biologically relevant tissue parameters, results should still be interpreted with caution!

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