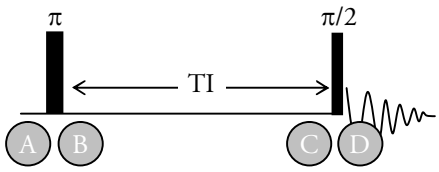
5
Relaxation

Lecture notes by Assaf Tal

Measuring T_1, T_2

Measuring T_1: Inversion Recovery (IR)

To measure T_1 of water, consider the following experiment:



Let's go through what happens to the magnetization at each of the points outlined above using the Bloch model:

A. The magnetization is at thermal equilibrium, and its magnetization vector is:

$$\mathbf{M}_A = \begin{pmatrix} 0 \\ 0 \\ M_0 \end{pmatrix}.$$

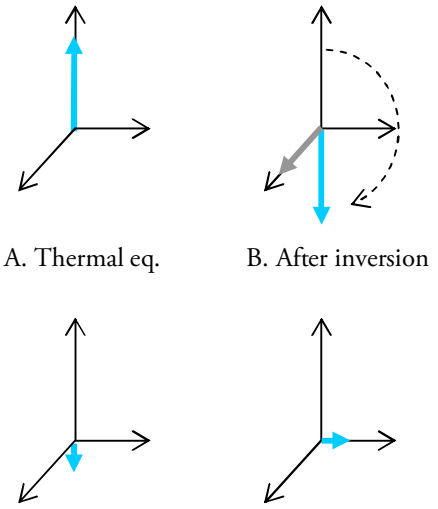
B. A hard π-pulse is used to flip the magnetization onto the –z axis:

$$\mathbf{M}_B = \begin{pmatrix} 0 \\ 0 \\ -M_0 \end{pmatrix}.$$

C. We wait a time TI. Longitudinal (T_1) relaxation kicks into effect:

$$\mathbf{M}_C = \begin{pmatrix} 0 \\ 0 \\ -M_0 e^{-TI/T_1} + \left(1 - e^{-TI/T_1}\right) M_0 \end{pmatrix}.$$

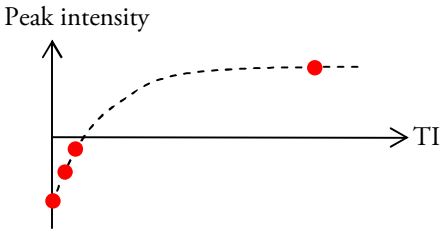
D. We excite the spin onto the xy-plane and measure.



A. Thermal eq. B. After inversion

C. After time TI D. After excitation

The magnitude of the signal will be proportional to the amount of longitudinal magnetization we have at point C just before excitation. One can perform multiple experiments and plot the magnitude of the resulting NMR peak as a function of TI, obtaining a graph like this:



One can then proceed to fit this to the theoretical decay curve and extract T_1:

$$s(TI) = -M_0 e^{-TI/T_1} + \left(1 - e^{-TI/T_1}\right) M_0 .$$

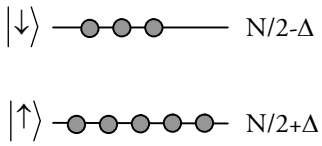
This is called an **inversion recovery** (IR) experiment. Note that for small values of TI the peaks' absorptive peak will appear inverted (pointing upside down)! It's thus important not to

phase each IR experiment independently, or you'd end up "flipping up" peaks which should actually be inverted and appear with a minus sign; rather, phase the last one having a long TI, which you know has to have an up-pointing peak, and apply the same phase to all over scans.

If our sample has multiple chemical shifts, a Fourier transform will yield a set of peaks, each recovering with its own unique T1 rate constant.

An Energy Level Look At T_1 Relaxation

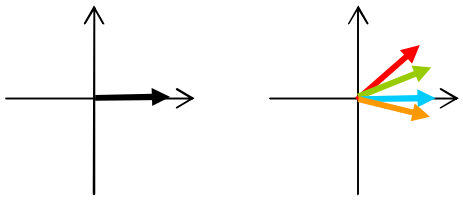
The Bloch sphere picture can be eschewed in favor of a more energy-level-diagram look at relaxation. The spin-1/2 system we'll be looking at has two possible states, "up" and "down", reflecting its alignment or anti-alignment with respect to the main B_0 field. Each level has a different energy which leads to a different Boltzmann distribution of spins. For example, if we had N spins, the "up" state would have slightly more than the "down" state:



These diagrams represent the populations, or diagonal terms of the density matrix which we've seen. Upon any disturbance of the system out of equilibrium – say, by excitation – the system will re-align itself within a time ~ T_1.

Measuring T_2: The Spin Echo

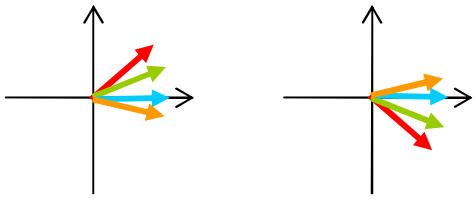
Imagine having a sample with spins having different offsets due to a combination of chemical shifts and inhomogeneity of B_0. Once you excite the spins from thermal equilibrium, they begin precessing at different rates, and eventually "spread out" in the xy-plane, due to **both B_0 inhomogeneity and a spread in chemical shifts**. This means that, if you were to acquire their signal, it would slowly die out because the spins would end up pointing in all sorts of directions and add up destructively (remember, the signal is a vector sum of the spins in the xy-plane):



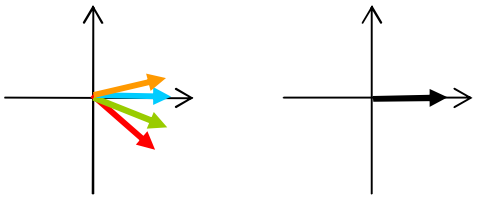
Following excitation, all spins point in the same direction

However, since each spin precesses at a different rate (= different colors), they end up dephasing

What would happen if we were to apply a 180 pulse along, say, the x-axis, after a time T? The pulse would invert our spins:



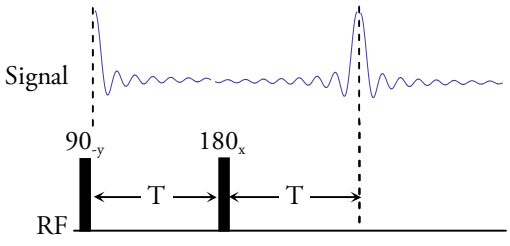
However, note the interesting part: if we were to wait an additional time T, the spins would end up re-aligning along the x-axis:



After 180_x pulse

After additional time T

The reason for this can be understood by thinking of a particular spin: suppose a particular spin acquired some phase ϕ just prior to the 180 pulse. After the pulse, its phase would be $-\phi$. After a time T its phase would increase by ϕ once again, so its phase at the end would be $(-\phi)+\phi = 0$, i.e., it's back at the x-axis. If we'd continue acquiring throughout this experiment, we'd end up seeing the signal revive back again. This is called a **spin echo**. In terms of pulse sequences:



Now, the above drawing is a bit of a lie: in reality, the echo would be somewhat smaller than the original signal intensity. To see why, we need to divide the decay mechanisms into two:

1. Decay due to microscopic T_2 effects, which cannot be reversed with a spin echo.
2. Decay due to a spatial spread of precession frequencies in the sample, as described above. This might come about because, for example, your main field is not perfectly homogeneous, $B_0 = B_0(\mathbf{r})$, leading to a precession frequency $\omega(\mathbf{r}) = \gamma B_0(\mathbf{r})$ (per chemical shift). This is sometimes called **inhomogeneous broadening**.

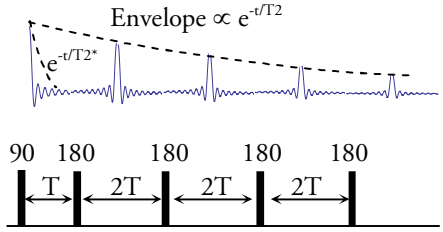
Each of these processes is characterized by its own decay constant. The microscopic decay is described by T_2 which we've already met. Inhomogeneous broadening leads to exponential-like decay in many cases and is denoted by T_2'. The combined rate, denoted $1/T_2$*, is under most circumstances given by the sum of rates:

$$\overbrace{\frac{1}{T_2^*}}^{\text{overall decay rate}} = \overbrace{\frac{1}{T_2}}^{\text{microscopic fluctuations}} + \overbrace{\frac{1}{T_2'}}^{\text{macroscopic inhomogeneous broadening}}$$

Only the inhomogeneous broadening is refocused by the 180° pulse. The microscopic fluctuations are unaffected, meaning T_2' decay will be refocused but T_2 will not, leading to:

The Carr Purcell Meiboom Gill (CPMG) Experiment

What would happen if we were to give successive 180_x pulses, spaced 2T apart? One might initially think this pattern would repeat itself indefinitely, since the spins would dephase, get flipped (by the 180), rephase, dephase again, get flipped (by the 180), rephase, dephase, ... ad infinitum; in effect, there is relaxation that needs to be taken into account. But what relaxation? Because the 180 pulse refocuses spins with different precession frequencies, there are no B_0-inhomogeneity effects in the overall decay. Only the "true microscopic decay", T_2, plays a role here:



The decay after the excitation is determined by T_2* (by both microscopic field fluctuations and field non-homogeneities), but the overall decay of the echoes is determined by T_2 alone. This furnishes us with a method of measuring the "true" T_2 microscopic decay of a sample.

Homonuclear Spin Echoes and J-Coupling

It is very important to realize that J-coupling evolution continues to evolve during a train of π pulses given on a homonuclear system, and is **not refocused** by them. This makes quantifying the T_2 decay of J-coupled species tricky. We will not spend any time on this topic, but you should keep in mind it's a non-trivial topic.

Modeling T_1, T_2

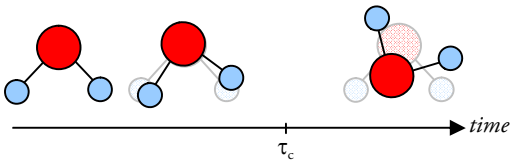
Spins Are Subjected To Microscopic Fluctuating Magnetic Fields Due To Their Thermal Motion

We've already remarked that spins are subjected to fluctuating fields due to their rotational thermal motion (see "Spin Dynamics" lecture). It is these fluctuating fields that lead to relaxation. The

fluctuating fields $\mathbf{B}_D$ felt by a spin can be composed into components transverse & longitudinal to the main B_0 field:

$$\mathbf{B}_D(t) = \mathbf{B}_{D,\perp}(t) + \mathbf{B}_{D,\parallel}(t) .$$

It is instructive to assign some orders of magnitude to these fluctuations. We define the **rotational correlation time**, τ_c, in an informal manner as follows: imagine opening your eyes at t=0, then shutting your eyes and re-opening them at some time t>0. If we open the eyes "fast enough", you can predict that the orientation of the molecule will remain close to its orientation at t=0. However, after a certain amount of time, you will not be able to predict the orientation of the molecule at all. The time-scale at which this happens is the rotational correlation time.

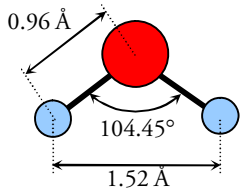


The correlation time of a molecule will depend on the temperature, its environment and its size. For a spherical molecule of hydrodynamic radius r in a liquid with viscosity η, Stoke derived an expression for the rotational correlation time:

$$\tau_c = \frac{4\pi\eta r^3}{3kT} .$$

Some numbers. For water (≈18 Da) at room temperature it is about one picosecond = 10^{-12} seconds. For ubiquitin (≈9 kDa) in water, τ_c is a few nanoseconds.

How about the size of the fluctuations? In a water molecule the sources of fluctuations are dipolar and can be divided into intra- and inter-molecular. Because the dipolar field goes as r^{-3}, the intermolecular contributions are only a second order effect, and we are left with the intramolecular ones, exerted by one hydrogen in H_2O on the other. First, we must examine the geometry of the water molecule:



The dipolar field created by one spin at the position of the other is:

$$\mathbf{B} = \frac{\mu_0}{4\pi}\frac{3\hat{\mathbf{r}}\left(\mathbf{m}\cdot\hat{\mathbf{r}}\right)-\mathbf{m}}{r^3}$$

where **r** is the vector connecting both hydrogen atoms. We see that the maximal and minimal values of **B** occur when **m** and **r** are either parallel or antiparallel, leading to the values:

$$\left|\mathbf{B}_{\max}\right| = \frac{\mu_0 m}{2\pi r^3}$$

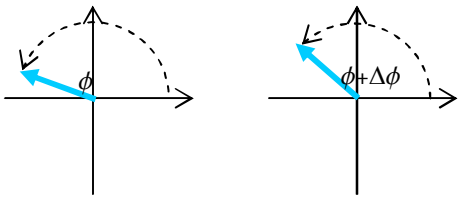
Hence the magnitude of the fluctuations vary between $\pm\left|\mathbf{B}_{\max}\right|$. Fixing $|\mathbf{r}|$=1.52Å and $|\mathbf{m}| = 1.4\times10^{-26}\frac{J}{T}$ (^{1}H magnetic moment), this amounts to

$$\left|\mathbf{B}_{\max}\right| \approx 8\times10^{-4}\ T = 8\ \text{Gauss} .$$

To a first approximation, as we will argue next, the longitudinal fluctuating field causes transverse relaxation and the transverse fluctuating field causes the longitudinal relaxation.

The Longitudinal Fluctuating Field Leads to T_2 Relaxation

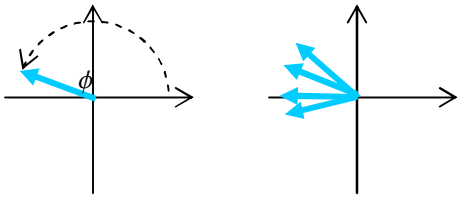
We start by showing how a fluctuating longitudinal field leads to transverse T_2 decay. Imagine exciting a spin onto the xy plane. Without the fluctuating field, it would just execute precession and make a phase $\phi=\gamma B_0 t$ after precessing for a time t. With the fluctuating field along z the precessing frequency fluctuates as well, with the end result being a slightly different precessing frequency at the end, $\phi+\Delta\phi$, where $\Delta\phi$ depends on the exact nature of the fluctuations (imagine turning a wheel with a shaking hand):



No fluctuations
("Firm hand")

With fluctuations
("Shaky hand")
Note here $\Delta\phi<0$

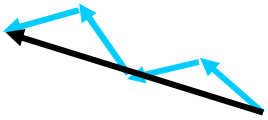
Now imagine a number of spins. In the absence of fluctuations they would all make the same angle. In the presence of fluctuations, they would fan out (remember, each spin feels a different fluctuation):



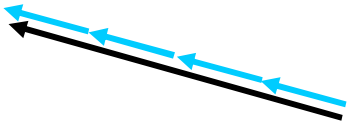
Many spins,
no fluctuations.
(microscopic view)

Many spins,
fluctuations.
(microscopic view)

This is what happens microscopically. Now, the **macroscopic** magnetization is the (vector) sum of the microscopic magnetization. What happens when you sum vectors that don't point in the same direction? They (partially) cancel out. Example:



Adding up slightly "out-of-phase" magnetization vectors leads to signal loss (smaller vector sum).



When all vectors are in-phase there is no signal loss.

You can now see why the magnetization in the plane decays:

The fluctuating z-field causes the spins to spread out (**dephase**), and hence add up destructively, leading to a decay of the macroscopic magnetization vector, **M**.

How fast does **M** decay – what determines T_2? Quite simply: the rate of fluctuations. Fast fluctuations will result in lesser dephasing and hence slower decay.

An analogy from physics might help you see this: think of diffusion. An ink is injected into two cups containing two fluids, one denser than the other. In which cup will the ink spread further? In the *less dense* fluid. The idea is that the additional collisions it undergoes per unit time in the dense fluid slow the ink down and minimize the distance it can diffuse to at a given amount of time. A similar process occurs when discussing T_2: you can think of the spin's phase as "diffusing" under the action of the fluctuating field – slower fluctuations mean "fewer collisions" and hence a "less dense" environment, leading to greater "diffusion" (dephasing, in our case).

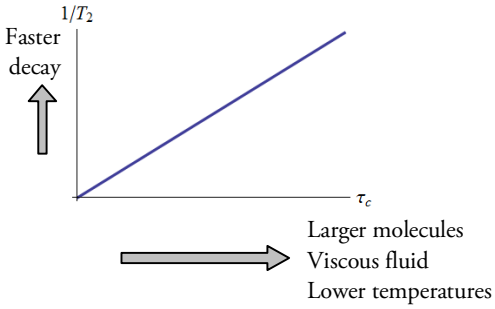
This directly relates to molecule sizes, because:

Large molecules
→ Tumble slowly
→ Slow fluctuations
→ Short T_2 (fast decay)

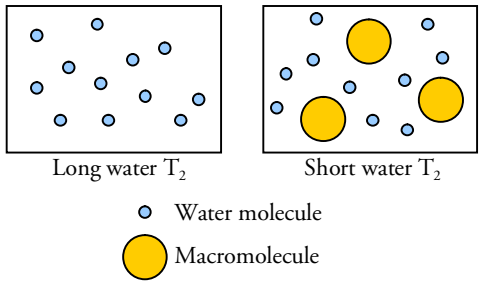
Small molecules
→ Tumble fast
→ Fast fluctuations
→ Long T_2 (slow decay)

Hence, large molecules such as proteins have short T_2s, and as a result suffer from both broad linewidths (leading to a lack of spectral resolution) and smaller signal intensities (leading to lesser SNR). This is one of the reasons why the study of large proteins can be very challenging.

We can draw this graph:



In tissue, water can be free (A) or in the vicinity of large macromolecules (B), which slow it down and lengthens its T_2:



In solids, where motion is greatly reduced, T_2 can be extremely short.

Microscopic Model for T_2

Let's assume we have a spin in the xy plane subjected to a random fluctuating field in the z-direction. We'll take a simple model for the field:

- Imagine the time axis divided into discrete steps of duration τ_c. Each τ_c, because of the particle's rotational motion, the field will assume one of two possible values $\pm B$ with equal probability. Denote by B_j the field's value at the j^{th} time step between $[j\cdot\tau_c, (j+1)\cdot\tau_c]$. We can write B_j as $B_j=B\cdot\eta_j$, where B is the field's magnitude and η_j is a random variable which assumes the values ± 1 with equal probability.
- As a result, the spin's precession frequency will be a random function equal to $\pm\gamma B$ with equal probability. Denote by $\omega_j=\gamma B_j$ the spin's angular frequency at the j^{th} time step.
- The spin will accumulate a phase $\Delta\phi_j=\omega_j\tau_c$ during the j^{th} time step.
- The total phase accumulated by the spin after N steps (and a time $N\cdot\tau_c$) will be

$$\phi=\sum_{j=1}^{N}\phi_j=\gamma B\tau_c\sum_{j=1}^{N}\eta_j\ .$$

The average phase of the spin will be zero, of course, because on average it has equal probability at each step to precess in a right-hand or left-hand sense. This is also confirmed mathematically since the expectation value of each of the η's is 0:

$$\langle\phi\rangle=\gamma B\tau_c\sum_{j=1}^{N}\langle\eta_j\rangle=0\ .$$

The standard deviation on the other hand is not zero. The standard deviation of each η_j is

$$\begin{aligned}SD(\eta_j)&=\sqrt{\mathrm{Var}(\eta_j)}\\&=\sqrt{\langle\eta_j^2\rangle-\langle\eta_j\rangle^2}\\&=\sqrt{\langle\eta_j^2\rangle}\\&=\sqrt{\tfrac{1}{2}(+1)^2+\tfrac{1}{2}(-1)^2}=1\end{aligned}$$

The standard deviation of N of these variables added together adds up a $\sqrt{N}$, which can be seen by noting that, for any two random variables X and Y:

$$\begin{aligned}&SD(X+Y)\\&=\sqrt{\mathrm{var}(X+Y)}\\&=\sqrt{\langle(X+Y)^2\rangle-(\langle X+Y\rangle)^2}\\&=\sqrt{\langle X^2\rangle+2\langle XY\rangle+\langle Y^2\rangle-\langle X\rangle^2-\langle Y\rangle^2-2\langle X\rangle\langle Y\rangle}\end{aligned}$$

In our case the variables are uncorrelated (the value of η_j and η_k have no relation if $j\neq k$), so $\langle XY\rangle=0$. So:

$$\begin{aligned}SD(X+Y)&=\sqrt{\langle X^2\rangle-\langle X\rangle^2+\langle Y^2\rangle-\langle Y\rangle^2}\\&=\sqrt{\mathrm{var}(X)+\mathrm{var}(Y)}\end{aligned}$$

which means that

$$SD(\eta_1+\eta_2+\ldots+\eta_N)=\sqrt{N}$$

and

$$SD(\phi) = \gamma B \tau_c SD\left(\sum_{j=1}^{N} \eta_j\right) = \gamma B \tau_c \sqrt{N} \ .$$

We can slightly rewrite this by using $t = N \cdot \tau_c$, where t is the total time the spin spends in the xy plane:

$$SD(\phi)_t = \gamma B \sqrt{\tau_c} \sqrt{t} \ .$$

Now, this standard deviation tells you how far the spin has come away (on average) from the x-axis. Do not confuse this with the average value of ϕ! The average phase $\langle \phi \rangle$ is zero, which tells you that, if you were to repeat this experiment many times and measure ϕ, you'd get an equal spread of positive and negative phases; but these phases you measure in each experiment will **not** be zero in general. They will have a typical magnitude given by SD(ϕ).

If you have an ensemble of spins subjected to this random field, SD(ϕ) tells you by how much the spins are spread out in the xy plane. When $SD(\phi)_{t=T2} \sim 2\pi$,

$$SD(\phi)_{t=T_2} = \gamma B \sqrt{\tau_c} \sqrt{T_2} \sim 2\pi \ ,$$

the spins will have spread out completely in the xy-plane and their vector sum should be about 0. This is exactly the mechanism of T_2 decay. We can solve for T_2 and obtain:

$$T_2 \sim \frac{1}{(\gamma B)^2 \tau_c} \ .$$

This result gives us some basic insight into T_2:

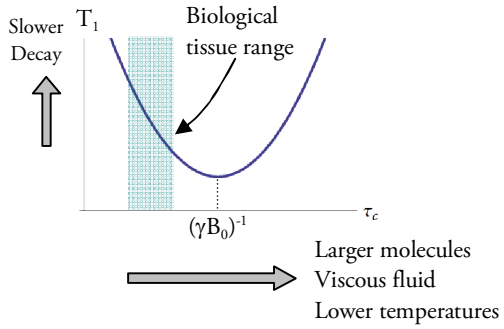
- Slower molecules with longer τ_cs will have shorter T_2s. Physically, think of the spins executing a diffusion-like process in the transverse plane under the effect of the fluctuating external field: the less "collisions" they experience the farther out they diffuse. The "collisions" experienced every τ_c serve to impede their decoherence.
- Obviously, the stronger the fluctuating field B is, the faster the signal decay (the shorter T_2 becomes).
- Interestingly, the result does not depend on B_0, which is in agreement with experimental observations that show very weak B_0 dependence on T_2. In practice there is **some** dependence due to terms our model didn't take into account.

The Transverse Fluctuating Field Leads to T_1 Relaxation

Remember one of our earliest questions when discussing relaxation: how can it be that a tiny RF component compared to B_0 can excite the spins? The answer we found is that the RF field can excite the spins if it is on resonance. We can reverse the reasoning and state the a transverse fluctuation will appreciately affect to z-component of the spins if it is resonant.

If we think of the transverse fluctuating field in terms of its frequency components, we might imagine that when $\tau_c \sim 1/(\gamma B_0)$ – that is, when the fluctuations are on resonance – the longitudinal relaxation will be most effective, leading to the shortest possible T_1. Conversely, as τ_c becomes slower or faster than $1/(\gamma B_0)$, we can predict that it will be less effective at inducing longitudinal relaxation, leading to longer T_1s.

This general analysis turns out to be quite true, and we can draw a general curve relating the correlation time and T_1 that ends up looking a bit like this:

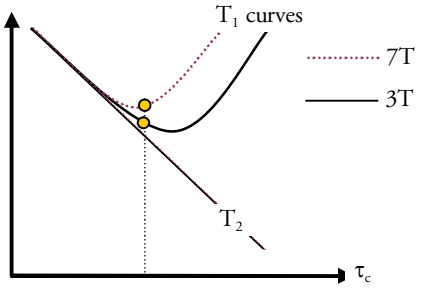


An important question now arises: on which "side" of this curve are we in biological tissue? A typical MRI magnet is ~ 3T and has a frequency of ~127 MHz for protons, so $(\gamma B_0)^{-1} \sim 10^{-8}$ sec. The correlation time for free water is $\tau_c \sim 1$

picosecond=10^{-12} sec, so we are well to the left of the "dip". This means that larger molecules or molecules in more "crowded" environments have shorter T_1s.

T_1 Increases With Increasing B_0; T_2 Is Largely Unaffected by B_0

Our T_1 curve also shows us that T_1 is expected to increase with B_0. Increasing B_0 will "push" the curve to the right and increase T_1 for a fixed τ_c (I will not derive this here, though). This is indeed consistent with what we see in actual experiments. This is illustrated in the following schematic graph:

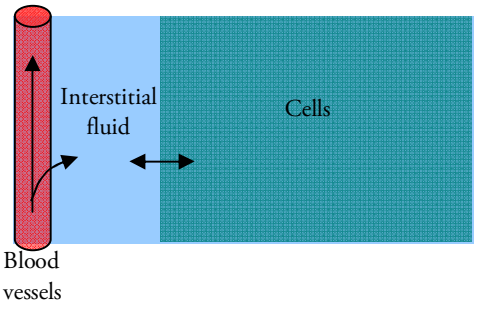


T_2 tends to slightly decrease with increasing field strength. This seems not to be indicated by our diagram, which does not depend on B_0. However, our theory was incomplete and omits more complicated effects (e.g. the transverse field can also contribute to T_2 relaxation by transferring magnetization from longitudinal to transverse states). These corrections tend to be small to negligible in fluid tissue. In semi-fluid/solid tissue such as bone and cartilage this approximation is somewhat less valid. We will not treat these more complicated cases here.

Note. T_1 does not always become longer with increasing B_0. One notable exception is phosphorous (^{31}P) imaging, in which T_1 actually becomes shorter. This comes about because of additional, more complicated effects we have not discussed here, such as *chemical shift anisotropy*, which creates field fluctuations originating from the way electrons are distributed around the nucleus. For protons (^{1}H), however, the above discussion is fairly accurate.

T_1 and T_2 Both Increase in Edema

As an example of the usage of our theory so far, let's take the relatively simple case of edema[1]. In edema, water accumulates in the interstitium, which constitutes about 25% of the body's total fluids (cells contain another two thirds, and the remainder is allocated to blood vessels and cerebrospinal fluid).



When you think of edema, the additional water tends to reduce the viscosity in the interstitial space, leading to a shorter correlation time, which – looking at the graphs of T_1 and T_2 (and on our expression for T_2) – leads to an increase in both.

[1] In Hebrew: בצקת.