Methods for quantitative relaxation parameter mapping: measuring T_1 and T_2

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1. Introduction.

The principles of measuring the two relaxation times of most interest, T_1 and T_2, are given, followed by practical approaches. Quality assurance using phantoms and normal brain white matter is described. Approaches to implementing techniques on commercial clinical scanners are given. An up-to-date version of this document and the accompanying PowerPoint slide show are available at http://www.paul-tofts-phd.org.uk/talks, in addition to other material on quantification.

The reader is assumed to understand the basic concepts of spin and gradient echoes, inversion recovery, relaxation, Bloch equations and slice selection. Although T_2* measurement has not been discussed, the methods are similar to T_2; however it has to be recognised that the measured value is dependent on how well the magnet is shimmed.

2. Principles of T_1 measurement

The longitudinal relaxation time T_1 is defined by the Bloch equation for longitudinal relaxation (in the absence of an applied RF field):

$$\frac{dM_z(t)}{dt} = \frac{M_o - M_z(t)}{T_1} \qquad [1]$$

This is an exponential approach of the longitudinal magnetisation M_z from some starting value to the equilibrium value M_0. After a pulse of flip angle (FA) θ, the solution is:

$$M_z(t) = M_0 + (M_z(0^+) - M_0)e^{-t/T_1}; \quad M_z(0^+) = M_z(0^-)\cos\theta \qquad [2]$$

$M_z(0^-)$ and $M_z(0^+)$ are the values of M_z just before and after application of the pulse. For repeated application of the pulse at intervals TR, we have:

$$M_z(TR) = M_z(0^-) \qquad [3]$$

and the steady state solution to this for $M_z(0^-)$ is:

$$M_z(0^-) = M_0 \frac{1 - e^{-TR/T_1}}{1 - \cos\theta\, e^{-TR/T_1}} \qquad [4]$$

The signal is proportional to the transverse magnetisation M_{xy} :

$$M_{xy}(t) = M_z(0^-)\sin\theta = M_0 \frac{1 - e^{-TR/T_1}}{1 - \cos\theta\, e^{-TR/T_1}} \sin\theta \qquad [5]$$

There are 4 main approaches to measuring T_1:

a) **Partial Saturation recovery.**

Repeated 90° pulses are applied, usually with a spin echo. Eqn 5 then becomes the familiar form:

$$M_{xy}(t) = M_0(1 - e^{-TR/T_1}) \quad [6]$$

By using 2 values of TR, the ratio of signals gives T_1. Optimum values of TR are chosen to give one sequence T_1w (T_1-weighted) and one PDw (PD- weighted), i.e. approximately $TR_1=T_1$ and $TR_2=3T_1$. Using a range of at least 3 TR values gives good performance over a wide range of T_1 values; eqn 6 is least squares fitted to the resulting measured signals.

For this approach to give an accurate result, the 90° pulse must efficiently destroy the longitudinal magnetisation; this is particularly critical if a short TR is used, since the regrowth of M_z is small and any residual magnetisation left after the pulse is then significant compared to this. B_1 errors will result in a flip angle other than 90° being applied, at least in some parts of the sample. This approach is relatively slow and inefficient (compared to the spoilt gradient echo method, where a more optimal FA can be used –see below).

b) **Spoilt gradient echo**

By moving from a spin echo to a spoilt gradient echo, TR can be reduced whilst still giving a reasonable SNR, resulting in a much faster imaging sequences. The signal is given by eqn 5. For a narrow range of T_1 values a pair of measurements at 2 values of FA suffice; these would optimally be T_1w (high FA) and PDw (low FA, often with some signal averaging). For a large range of T_1 values a set of at least 3 FA values should be used, and eqn 5 fitted to the measured image intensities. Inaccuracies arise, particularly at short TR's, from three factors: i) incomplete spoiling of the pulse (so that steady state transverse magnetisation builds up), ii) longitudinal relaxation during the pulse (the pulse duration is not negligible compared to TR) and iii) FA errors, particularly at 3T. The method can achieve good coverage very quickly, using a 3D acquisition, with typical TR values down to 5ms.

c) **Inversion recovery**.

Both the spin echo and the gradient echo methods above are vulnerable to B_1 (i.e. FA) errors. The IR method, although slower, is intrinsically more accurate because it does not rely on the application of a pulse with an accurately known FA.

The generalisation of the IR sequence is one with 2 repeated pulses of FA=θ_1 and θ_2 , separated by an inversion time TI (where θ_1 and θ_2 are nominally 90° and 180°):

$$[\theta_1 - TI - \theta_2 - (TR-TI)]_n$$

$M_z(2^-)$, the value of M_z just before the 2nd pulse, determines the signal:

$$M_z(2^-) = M_0 \frac{1-(1-\cos\theta_1)e^{-TI/T_1} - \cos\theta_1 e^{-TR/T_1}}{1-\cos\theta_1\cos\theta_2 e^{-TR/T_1}} \quad [7]$$

Setting θ_1 and θ_2 to their nominal values of 90° and 180° gives the familiar eqn:

$$M_z(2^-) = M_0(1-2e^{-TI/T_1} - e^{-TR/T_1}) \quad [8]$$

However the more interesting outcome is that for *arbitrary flip angles* (i.e. eqn 7), by adjusting the inversion time TI, whilst keeping θ_1, θ_2 and TR fixed, the signal takes the form:

$$M_z(2^- : TI) = A + Be^{-TI/T_1} \qquad [9]$$

where A and B are constants (which depend on θ_1, θ_2 and TR – see eqn 8) .
Thus a set of signals at a range of TI's can give an accurate T_1 value, regardless of B_1 errors, and without the need for full relaxation (i.e. no need for TR»T1). The downside to this IR approach is that sequences are relatively slow (since the inversion time must be included).

d) **Specialist methods**

There are a number of specialist methods[1], which differ quite substantially from the conventional methods described above. These include Look-Locker, DESPOT, DESPOT2, and TAPIR. They are often very fast, and sometimes can function in the presence of B_1 errors (although at the expense of worse SNR). They may be vulnerable to off-resonance effects, and usually require intimate access to the MR imager to implement the sequences.

3. Principles of T_2 measurement

The definition of T_2 comes from the Bloch equation for the decay of transverse magnetisation (again in the absence of an applied RF field):

$$\frac{dM_{xy}(t)}{dt} = \frac{-M_{xy}(t)}{T_2} \qquad [10]$$

A FID includes decay from both reversible and irreversible effects. By forming a spin echo, some sources of decay are reversed (refocused); these come from time-invariant sources, principally local static field inhomogeneities caused by sample susceptibility or magnet B_0 inhomogeneity. Any observed decay in the echo comes from irreversible (i.e. time-dependent) effects, largely arising from motion of the magnetic dipoles.

The amplitude of the spin echo, after application of 90° and 180° pulses, is:

$$M_{xy}(TR,TE) = M_0(1-e^{-TR/T_1})e^{-TE/T_2} \qquad [11]$$

Of course this is reduced if the pulses with nominal value 90° or 180° are incorrectly set (provided $TR>T_1$). Provided that the pulses are left unchanged, and that only TE is altered, then we can still obtain the correct value for T_2 from images collected at several values of TE.

$$M_{xy}(TE) = Ae^{-TE/T_2} \qquad [12]$$

The recovery time for M_z after the 180° pulse is variable (T_{rec} = TR – TE/2), and for good accuracy TR should be kept long enough that $TR\text{-}TE^{max} > 5T_1$ (otherwise the longer TE acquisitions have reduced signal, giving an artificially low value of T_2).

Practical sequences are often designed to produce two echoes (a 'dual echo' sequence) by using two selective refocusing 180° pulses; the amplitude of the 2nd echo may be reduced not only by T_2 losses but also by incomplete refocusing by the 2nd 180 pulse. Thus to obtain an accurate T_2 value multiple echoes should in principle be avoided. Slice selective 180° pulses are particularly badly behaved, and in multiple echo sequences can give the phenomenon of 'slice thinning', where subsequent refocusing operations lose transverse magnetisation. Thus progressive echo

decay may be seen in a multi-echo sequence, even if T_2 is very long, as for example in water or CSF. A hard (nonselective) pulse will refocus better, but usually cannot be used in a multislice acquisition sequence.

Thus the gold standard for T_2 acquisition is likely to be a single slice single echo sequence, repeated at several echo times, with long TR. Extra slices (well separated) can be added to improve coverage and speed. The accuracy should be monitored; this will degrade as slice cross-talk increases with slice number and closeness.

'There is no such parameter as T_2' [2] T_2 derives from Bloch's theoretical model of nuclear magnetisation (eqn 10), and in real biological tissue the transverse magnetisation almost always decays with several T_2 values[3,4]. Water compartments in different biological environments are sufficiently isolated from each other (i.e. there is slow enough exchange, at least in brain), that each one decays almost independently. In brain white matter, the signal from four compartments can be observed independently, using a single slice multi-echo sequence, typically with 16 echoes, timed from 20-1000ms. Clearly refocusing is crucial, and hard 180° pulses are used. With this insight, it is evident that estimating T_2 from a dual-echo multi-slice sequence is quite feasible; however the estimated (mono-exponential) T_2 value will depend crucially on the TE values chosen, as well as the quality of the refocusing pulse.

4. B_1 effects

Most of the method described for T_1 and T_2 are vulnerable to B_1 (i.e.. FA) errors, particularly when run in the faster modes. The four principles mechanisms are: i) inaccurate and variable setting of FA in the scanner prescan procedure ii) slice selection effects in 2D sequences produce a distribution of FA values across the slice profile; modern 3D sequences largely overcome this effect (although the pulses are still slightly selective) iii) dielectric resonance, particularly at 3T and higher, causes the RF field to be higher near the centre of the object than near its periphery iv) the RF transmission coil generally produces a nonuniform field, although body coil excitation (using the body coil not the head coil) largely alleviates this problem. To obtain acceptable accuracy, good modern methods all take account of B_1 errors in some way, either by setting out to determine the local FA in the object, or by designing a method that is not sensitive to the particular value of FA at each location in the object. There is now a range of methods for mapping local flip angle; some are acceptably fast, accurate and easy to implement[5].

5. Quality Assurance using phantoms (test objects) and normal controls

Quality Assurance is an essential part of developing and validating methods for mapping relation times[6]. Measurements in phantoms enable the accuracy (i.e. closeness to the truth) of measurements to be assessed, provided the true values are known. True values can be measured using a 'gold standard' sequence (i.e. IR or single spin echo), which is expected to behave well, or by using published values for the phantom, based on the concentration of compounds in the solutions (although this approach will have accuracy limited to maybe 5%). Phantom relaxation times usually increase by 2-3% per °C, and therefore temperature control and monitoring are essential. Phantoms can be made in-house quite simply, or bought commercially.

Measurements in normal tissue, usually brain white matter, are more realistic than in phantoms and enable in-vivo reliability and repeatability (test-retest, or random error) to be assessed. The range of normal values is relatively narrow (CV about 5%[7]). Reproducibility determines how sensitive a measurement is to changes caused by disease, ultimately determining the power of a clinical study (whether cross-sectional or serial) , and should always be in our awareness as we work to produce good measurement techniques. A quick estimate of the accuracy of T_1 and T_2 measurements can often be obtained by looking at the CSF values; T_1 should be about least 4.5s, and T_2 2.5s. Poor refocusing in a T_2 sequence will reduce estimates in CSF, often quite dramatically. If white and grey matter are the principle tissues of interest, with much shorter relaxation times that CSF, then estimates in these tissues might still be acceptable. Sources of variation

include image noise (which usually is probably NOT the limiting factor in determining reproducibility, particularly in large ROI's), scanner instability, subject movement and observer-dependent analysis procedures[8].

Multi-centre measurements present challenges which naturally force us to consider the measurement methodology in detail[7]. More information on QA philosophy, phantom design and normal values of relaxation times are given elsewhere[1,9].

6. Measurement using a clinical MR imager

Implementing techniques for relaxation time measurement on commercial MR imagers is still not straightforward. Relaxation times are not recognised by manufacturers (vendors) as having useful applications (as distinct from diffusion tensor imaging or spectroscopy, where there is now much turnkey software supplied). Some basic sequences are available, along with analysis software. However the methods are not particularly fast or accurate, compared to what is possible with in-house sequences and analysis. To write and run in-house sequences will require a research agreement with the manufacturer, and some local MR physics expertise.

T_1: The methods of choice are the spoilt gradient echo (SPGR) and fast inversion recovery (FIR). SPGR is readily available, and 3D sequences give good coverage in a reasonable time with little slice selection effects (typical whole brain coverage at 1.5x1.5x1.5 mm resolution is achieved in 10 minutes). They are however vulnerable to B_1 errors, unless a B_1 measurement can be built into the acquisition, and this limits their usefulness in quantification. At 1.5T, using body-coil excitation will control the B_1 effects, and the resulting B_1 nonuniformity will at least be fixed for each subject, provided the positioning is controlled.

FIR is slower, yet because of its invulnerability to B_1 errors (eqn 9) it is the gold standard. IR-prepared fast gradient echo or IR-prepared EPI is usually available. Provided the readout component is kept constant, its imperfections can usually be ignored (the MP-RAGE concept). By using a small number of phase encodes per shot, or a short echo train length, good accuracy can be obtained, at the expense of long acquisition time. As more phase encodes or echoes are taken per shot, accuracy decreases slightly, which is offset by acquisition times becoming practical. Typically an accuracy of about 3% can be obtained in 10 minutes.

T_2: Most scanners will have a dual-echo multi-slice 2D sequence, which uses for readout either conventional spin echo or RARE (fast spin echo or turbo spin echo, where several echoes and phase encodes are collected for each shot). These provide good coverage in a reasonable time, and are probably acceptable for most tissues (although the CSF values will most likely be too low).

7. Image analysis

Simple analysis can usually be carried out on the imager or an independent workstation. More flexible analysis usually requires setting up of an in-house system, typically based on freely available software for display and simple manipulation, often supplemented by a commercial high level programming environment such as MATLAB or IDL. Test-retest effects in the analysis can be studied, to find the contribution to the total measurement variance. ROI analysis is a straightforward way to measure a specified location in tissue; histogram analysis enables subtle effects in large volumes such as the brain or a tumour to be quantified[10]; Voxel-based morphometry (VBM) enables many locations to be tested without bias[8].

8. References

The books by Haacke et al[11] and Tofts[12] contains much relevant source material, as does an early paper[13] . The qMRI.org site (http://www.qmri.org) has material on quantification in MR. A recent paper[7] on multicentre measurements is available on line at http://www.paul-tofts-phd.org.uk/CV/reprints/multicentre-2009.pdf

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