Imaging Microstructure: Magnetization Transfer Modelling

ISMRM 2015 educational program

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Highlights

- Magnetization transfer is an MRI technique that generates contrast based on the exchange of magnetization between macromolecules (proteins, lipids, cell-membranes) and water.
- Biophysical models of magnetization transfer enable intrinsic properties of tissue to be estimated and improve the specificity of imaging methods based on these models.

Target Audience

- Imaging physicists with an interest in quantitative imaging of tissue microstructure.

Purpose

The goals of this syllabus contribution are: to provide an introduction to magnetizaton transfer contrast; to present a biophysical model that describes the signal behaviour in an MRI experiment; and to compare different imaging strategies for estimating the parameters of this biophysical model.

What is magnetization transfer?

Magnetization transfer is an MRI technique that generates contrast based on the exchange of magnetization between macromolecules (proteins, lipids, cell-membranes) and water. First applied to MRI in 1989 by Wolf & Balaban [27], this technique has been widely used to in research studies to monitor changes in tissue structure that occur with development and disease. In the context of MRI, magnetization transfer is narrowly defined as exchange of magnetization between the nuclei of hydrogen atoms bound to macromolecules and those bound to water. This is distinguished from chemical exchange saturation transfer (CEST) where the exchange is with hydroden nuclei from mobile compounds [25] or the *nuclear overhauser effect* which deals more generally with exchange between dissimilar spin populations. Magnetization transfer can occur by physical (chemical) exchange of hydrogen atoms or by transfer of spin states, the latter mediated by dipolar coupling.

Biophysical models of magnetization transfer

A biophysical model that has proven widely useful for magnetization transfer experiments is to treat tissue as composed of two homogeneous compartments: hydrogen nuclei associated with water molecules and hydrogen nuclei associated with macromolecules. Each compartment is described by empirical parameters T_1 and T_2 and the exchange between the two by first order rate constants that are dependent on the compartment sizes. It follows from this model formulation that the signal observed in a standard inversion recovery experiment recovers with two exponential recovery rates, neither of which typically corresponds to the T_1 of the individual compartments. The longer of the two rates (T_1^{obs}) corresponds to the conventional notion of the tissue T_1.

The T_2 of the semisolid or restricted motion pool of spins is typically short, on the order of $10\,\mu s$ for tissue. This has the consequence that a conventional MRI experiment cannot directly observe this compartment as the signal decays away too rapidly. The presence of the restricted compartment therefore needs to be inferred from the indirect effect that these spins have through exchange of magnetization with the free pool. When modelling the behaviour of the restricted pool, a useful approximation is to ignore the transverse component of the magnetization and only

consider that component which is aligned with the applied static field. In this formulation, the T_2 is of interest as a measure of the spectral width $1/T_2$ over which the restricted spins can be saturated by off-resonance irradiation. Since T_2 of the restricted pool is short, this spectral width is much greater than that of the water. Another property of the restricted pool is that the lineshape can take a variety of forms depending on the properties of the material. In tissues, the oriented structure of membranes has been proposed to give rise to a super-Lorentzian lineshape and this function has been found to well approximate the observed lineshape.

Taken together the elements of the model described above is referred to as the binary spin bath model. Expressed as four coupled differential equations the behaviour of the magnetization in a reference frame rotating at a frequency offset Ω from resonance is given by:

$$\frac{dM_{x,f}}{dt} = -\frac{M_{x,f}}{T_{2,f}} - \Omega M_{y,f} - \mathsf{Im}(\omega_1) M_{z,f} \quad (1)$$

$$\frac{dM_{y,f}}{dt} = -\frac{M_{y,f}}{T_{2,f}} + \Omega M_{x,f} + \mathsf{Re}(\omega_1) M_{z,f} \quad (2)$$

$$\frac{dM_{z,f}}{dt} = R_{1,f}(M_{0,f} - M_{z,f}) - k_f M_{z,f} + k_r M_{z,r} + \mathsf{Im}(\omega_1) M_{x,f} - \mathsf{Re}(\omega_1) M_{y,f} \quad (3)$$

$$\frac{dM_{z,r}}{dt} = R_{1,r}(M_{0,r} - M_{z,r}) - k_r M_{z,r} + k_f M_{z,f} - W M_{z,r} \quad (4)$$

where the subscripts f and r denote the free and restricted pools and the subscripts x, y, and z denote the various components of a magnetization vector. The excitation field strength, $\omega_1 = \gamma B_1$, is complex and time varying for general pulses. By definition, $k_r = k_f/F$ where $F = M_{0,r}/M_{0,f}$ is the ratio of the pool sizes.

The transition rate W for the saturation of the restricted pool is given for continuous wave RF saturation experiments in the absence of B_0 field gradients by

$$W = \pi \omega_1^2 G(\Delta) \quad (5)$$

where G is the lineshape function for the restricted pool and Δ is the frequency offset from resonance of the continous-wave RF irradiation. When G is a Lorentzian, the behaviour of the system approximates that of the Bloch equations for small $T_{2,r}$ [15].

The notation used across studies of magnetization transfer has not been consistent and creates the potential for confusion. The table below defines the most common parameters and their correspondence.

Equations 1 through 4 are readily solved for conditions of free precession or steady irradiation [12]. An important insight from these continuous-wave irradiation experiments is that direct saturation w_1 of the free-pool by the off-resonance irradiation is an important factor in determining the steady-state and cannot be neglected. Direct saturation is even more important in modelling imaging experiments where pulsed irradiation is used to saturate the restricted pool. However, it is not obvious from equations 1 through 4 how to properly treat the effect of pulsed saturation on the restricted pool. Three approaches have been proposed to adapt these equations for pulsed experiments: (i) to model the train of pulses as an equivalent power continuous wave saturation [19]; (ii) to expand the pulse waveform as a Fourier series and sum the contributions to the saturation rate [8, 9]; and (iii) to treat the pulses as having a carrier frequency and an envelope where the saturation rate is a time varying function of the envelope [21]. Parameter estimates obtained by the different formulations are similar but not the same. Work on bounding the regimes in which the different approximations are accurate is ongoing.

Table 1: Symbols used to formulate the binary spin bath model for magnetization transfer.

Symbol	Definition	Alternate notations
$M_{0,f}$	Equilibrium magnetization of the free pool. Some formulations define this to be 1 in arbitrary units.	M_0^a
$M_{0,r}$	Equilibrium magnetization of the restricted pool.	M_0^b
F	Pool size ratio. $F = M_{0,r}/M_{0,f}$.	M_0^b (where $M_0^a = 1$) or PSR
f	Pool size fraction or bound pool fraction. $f = \frac{M_{0,r}}{M_{0,r}+M_{0,f}} = \frac{F}{1+F}$	BPF
k_f	Forward exchange rate.	RM_0^b or k
k_r	Reverse exchange rate.	RM_0^a
R	Exchange rate.	k_f/F
$T_{1,r}$	T_1 of the restricted pool. Typically taken as $1\ s$.	$1/R^b$
$T_{1,f}$	T_1 of the free pool.	$1/R^a$
Δ	Frequency of off-resonance irradiation in Hz.	
g	Gain. Ratio of maximum observed signal to $M_{0,f}$.	
W	RF saturation rate.	R_{rfb} or W^b

The idea that hydrogen nucleii bound at different sites on macromolecules can be treated as a single pool of spins is predicated on rapid exchange of magnetization between these sites and is termed homogeneous line broadening. This approximation of a single resonance frequency for the restricted pool may not hold for RF pulsation patterns with sufficiently short repetition rates and varying offset frequencies [26]. The signal behaviour under such conditions has been termed inhomogeneous magnetization transfer (ihMT) and is an area of active investigation.

Besides the treatment of pulse irradiation, a number of other variants of the binary spin model have been studied. These include three and four pool models as well models that allow for exchange of transverse magnetization.

Measurement techniques

The measurement techniques used for magnetization transfer experiments can be divided into steady state techniques and inversion recovery techniques. The former class of techniques typically employ off-resonance RF irradiation to drive the two-pool system into a steady-state from which the magnetization of the free pool is measured. A set of measurements where the off-resonance frequency is varied is called a Z-spectrum [6, 7]. Two or more spectra are typically used to constrain the parameters of the binary-spin bath model. However, an additional measurement of T_1^{obs} is needed to fully constrain the model. A variation on the steady state concept is to use on-resonance pulses such as in a steady-state-free-precession (SSFP) sequence and vary the flip angle and TR so as to achieve a variety of MT-weighted steady-states [4]. These techniques contrast with the inversion recovery approach whereby inversion of the free pool magnetization is used to estimate the restricted pool size based on the bi-exponential recovery of the inverted magnetization.

Estimating model parameters

The binary spin-bath model has six free parameters which can be chosen in a number of combinations. For instance, the parameters $T_{2,f}$, $T_{2,r}$, $T_{1,f}$, $T_{1,r}$, F, k_f are sufficient to calculate the remaining parameters. Another natural choice is $T_{2,r}$, $\frac{T_{1,f}}{T_{2,f}}$, $\frac{k_f}{T_{1,f}}$, $\frac{k_f}{F}$ since these can be estimated from the Z-spectra without specifying $T_{1,f}$ or $T_{1,r}$. Z-spectra experiments are largely insensitive to $T_{1,r}$ and this parameter is typically fixed at $1\ s$. Further simplifications can be made by constraining additional parameters. For instance the variation in $T_{2,r}$ among normal brain tissues has

been found to be relatively small such that this parameter can be fixed to allow for faster imaging experiments [28]. Similarly, on-resonance techniques are insensitive to $T_{2,r}$ and this parameter is not estimated by these techniques. In general, quantitative magnetization transfer studies require significant computation as the model parameters need to be estimated at each voxel by non-linear optimization.

Imaging of magnetization transfer

The vast majority of studies employing magnetization transfer imaging have used a metric called the magnetization transfer ratio which is the percent change in signal caused by the addition of off-resonance saturation.

$$\mathrm{MTR} = \left(\frac{M_{without} - M_{with}}{M_{without}}\right) 100\% \tag{6}$$

where M_{with} and $M_{without}$ are image intensities with and without off-resonance saturation respectively. While MTR is quantitative in the sense of providing reproducible numerical values that depend on magnetization transfer, the numerical values depend on the details of the implementation and are sensitive to multiple intrinsic tissue parameters including T_1. MTR has been used for diverse applications including mild head trauma [17], frontal lobe epilepsy [2], muscular dystrophy [16], brain tumours [18], ischemic vascular dementia [23], CNS tuberculosis [10], Alzheimer's disease [11], and dementia [13]. MTR is most commonly associated with the study of white matter in patients with multiple sclerosis (MS) where it has been used in numerous large studies.

Table 2: A selection of quantitative magnetization transfer imaging methods described for human applications

Group and selected publication(s)	Estimated parameters	Notes
Montreal Neurological Institute [22, 14]	$T_{2,f}$, $T_{2,r}$, $T_{1,f}$, F, k_f	2D spoiled gradient echo pulse sequence with off-resonance pulsed irradiation, single slice acquisition, time-varying irradiation model
University College London [19, 24]	$gM_{0,f}$, $T_{1,f}$, k_f/F, $F/T_{1,f}$, $T_{1,f}/T_{2,f}$	2D multislice spoiled gradient echo pulse sequence with off-resonance pulsed irradiation, continuous-wave irradiation model
Karl-Franzens-University of Graz [20]	f	on-resonance stimulated echo acquisition, single slice
University of Washington [28]	f, k_f, $T_{1,f}$	3D spoiled gradient echo pulse sequence with off-resonance pulsed irradiation, whole brain coverage, time-varying irradiation model
Vanderbilt University [5, 1]	F, k_f, $T_{1,f}$	fast inversion-recovery method, single slice
University Hospital Basel [4, 3]	$T_{1,f}$, F, k_f, $T_{2,f}$	On-resonance 3D balanced steady state free precession sequence, whole brain coverage

Quantitative magnetization transfer imaging is the class of imaging techniques that provide estimates of the magnetization transfer model parameters. These techniques have been developed to overcome the limitations of MTR by estimating intrinsic tissue parameters that are

independent of the implementation details and suitable for comparison across sites and studies. A growing number of such methods have proposed. These methods vary in the number of estimated parameters, the modelling of pulse saturation, as well as the scan time and coverage that can be obtained for human studies. Table 2 lists a selection of these methods along with some important characteristics.

Conclusion and Suggested Reading

The intent of these notes is to provide the reader with an introduction to the topic and some places to start with respect to further reading. The research area continues to evolve with progress being made on biophysical modelling and on faster imaging methods for clinical and pre-clinical studies. Two references that are good starting point for further reading are given below and the reader is encouraged to examine the articles listed under the references section.

- *MT: Magnetization transfer* by Tofts PS, Steens SCA , van Buchem MA *in* Quantitative MRI of the Brain: Measuring Changes Caused by Disease. P. Tofts (editor), pp. 257–299, Wiley, 2003.
- Henkelman RM, Huang X, Xiang QS, Stanisz GJ, Swanson SD, Bronskill MJ. Quantitative interpretation of magnetization transfer. Magn Reson Med 1993;29(6):759-766.

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