

Mathematical modeling of the magnetization transfer effect in tissues

V Yarnykh^{1,2}

¹ Vascular Imaging Lab, Department of Radiology, University of Washington, Seattle, WA, USA

² Neurobiology Lab, Research Institute of Biology and Biophysics, Tomsk State University, Tomsk, Russian Federation

E-mail: yarnykh@uw.edu

1. Biophysical mechanisms of proton magnetization exchange in biological objects

The term magnetization transfer (MT) is commonly used to define a group of phenomena caused by incoherent exchange of magnetic energy between water and macromolecules in biological objects. Historically, the first experimental evidence of MT was the observation of bi-exponential longitudinal relaxation in muscle and water-collagen mixtures [1]. Later, saturation transfer from macromolecules to water in tissues was discovered in experiments with off-resonance radiofrequency (RF) saturation [2], which gave rise to a narrower interpretation of MT as the effect specifically related to saturation transfer. In this lecture, the common nature of these observations is highlighted in view of a general mathematical model.

Understanding of magnetization transfer in tissues is closely related to an underlying physicochemical model of proton exchange and molecular motion. Considering a tissue as a mixture of water and biological macromolecules (for example, protein globules), four distinct compartments need to be taken into account: bulk water, hydration water at the water-polymer interface (possibly can be divided into subpopulations with different residence times), hydrophilic surface groups of a polymer molecule, and bulk polymer protons not directly interacting with water. The entire picture of possible pathways of magnetization exchange is rather complex including chemical exchange between water and various functional groups of a biopolymer (e.g. amide or hydroxyl), dipolar interactions, diffusion of water molecules, and spin diffusion within the macromolecule. More details about the compartmental structure of water-macromolecular systems of various degree of complexity can be found in Refs. [1, 3-13].

For practical purposes, the model can be simplified assuming that proton exchange involving bulk water, immobilized water on the water-polymer interface, and exchangeable groups of the polymer is fast in the NMR timescale. Also, it is usually assumed that spin diffusion within the protein molecule (similar to solids) results in fast equilibration of magnetic energy between surface and bulk protons of the polymer. Correspondingly, the model can be reduced to two proton fractions with distinct spectral properties: macromolecular protons with restricted motion characterized by a very wide line of ~20-30 kHz (typically invisible in the absorption spectrum but can be observed in saturation transfer spectra) and mobile water



protons responsible for a directly observable signal with a narrow line of several Hz. Magnetic interaction between these two compartments is mostly enabled due to a relatively slow cross-relaxation process involving dipolar coupling (also termed as Nuclear Overhauser Effect, NOE) between hydration water or exchangeable protons (e.g. O-H, N-H, S-H) and adjacent non-exchangeable protons (e.g. C-H) of a biopolymer. If note, slow chemical exchange of mobile protons can contribute in a similar way and mathematically undistinguishable from cross-relaxation. This model is termed as the two-pool or binary spin-bath model, and the compartments have several synonymic definitions (free, mobile, or liquid pool for bulk water and bound, restricted, or semi-solid pool for macromolecular protons). Formally, magnetization exchange in the two-pool model is described by the effective first-order rate constant regardless of actually involved molecular mechanisms. The two-pool model provides a theoretical background for the majority of current studies of the MT effect in MRI, and it typically allows an adequate description of the observed MT phenomena within the accuracy of experimental data.

2. Two-pool model: mathematical description

Magnetization dynamics in the two-pool model is described by modified Bloch equations including cross-relaxation terms [14]:

$$dM_x^F / dt = -M_x^F / T_2^F - 2\pi\Delta M_y^F \quad (1a)$$

$$dM_y^F / dt = 2\pi\Delta M_x^F - M_y^F / T_2^F - \omega_1(t) M_z^F \quad (1b)$$

$$dM_z^F / dt = \omega_1(t) M_y^F - (R_1^F + k) M_z^F + k(1-f)/f M_z^B + R_1^F (1-f) M_0 \quad (1c)$$

$$dM_z^B / dt = -(R_1^B + k(1-f)/f + \pi\omega_1^2(t) g^B(\Delta, T_2^B)) M_z^B + k M_z^F + R_1^B f M_0, \quad (1d)$$

where $M_{x,y,z}^{F,B}$ are the x, y, and z-components of magnetization of the free (F) and bound (B) spins; Δ and $\omega_1(t)$ are the frequency offset and amplitude of an RF pulse; $g^B(\Delta, T_2^B)$ is the absorption line shape of bound spins; $R_1^{F,B} = 1/T_1^{F,B}$; k is the effective cross-relaxation rate constant for F→B transfer; f is the molar fraction of bound spins; and M_0 is the equilibrium magnetization. The lineshape function g^B was first introduced in the stationary solution of equations (1a-1d) [4] as outlined in Section 4. It was found that the standard Bloch approach resulting in the Lorentzian function g^B demonstrated a disagreement with quantitative saturation transfer experiments, and alternative line shapes (Gaussian, Superlorentzian, Kubo-Tomita) were introduced in a semi-empirical way to achieve adequate description of experimental data [4, 6, 15]. This approach was then extended to the time-dependent formalism [14]. Several studies [6, 16, 17] have demonstrated that the most adequate model for tissues is achieved with the Superlorentzian function g^B :

$$g^B(\Delta, T_2^F) = \sqrt{\frac{2}{\pi}} \int_0^{\pi/2} \frac{T_2^B}{|3\cos^2\theta - 1|} \exp\left(-2\left(\frac{2\pi\Delta T_2^B}{3\cos^2\theta - 1}\right)^2\right) \sin\theta d\theta \quad (2)$$

It is important to consider several practically useful solutions of modified Bloch equations for the two-pool model. The presence of two coupled magnetization populations in equations (1a-1d) causes two key effects observed in experiments: bi-exponential longitudinal relaxation and saturation transfer. A combined action of these effects takes place in pulsed MT imaging experiments. A more detailed

mathematical consideration and experimental applications of the two-pool model are given in next sections.

3. Relaxation in the absence of RF field

The free relaxation solution applies in the absence of the radiofrequency (RF) field. In this case, evolution of longitudinal components is independent of transverse components and has a bi-exponential form [1]:

$$M_z^F = (1 - f)M_0 + C_- \exp(-R_- t) + C_+ \exp(-R_+ t), \quad (3)$$

where

$$R_{\pm} = 1/2[R_1^F + R_1^B + k/f \pm \sqrt{(R_1^B - R_1^F + k/f - 2k)^2 + 4k^2(1 - f)/f}] \quad (4)$$

and

$$C_{\pm} = \pm \frac{(R_1^F - R_{\mp})[M_{zi}^F - M_0(1 - f)] + k[M_{zi}^F - M_{zi}^B(1 - f)/f]}{R_+ - R_-}, \quad (5)$$

where M_{zi}^F, B are the initial values of longitudinal magnetizations, which are determined by an applied RF excitation technique. There are two decay modes described by “slow” (R_-) and “fast” (R_+) eigenvalues of the relaxation matrix R defined in Section 5. The “slow” eigenvalue defines the observed $R_1 = 1/T_1$ in the two-pool model: if $R_1^F = R_1^B = R_1$, $R_- = R_1$ (exactly). The “fast” eigenvalue is on the order of the cross-relaxation rate constant defined for the bound-to-free pool transfer: assuming the same approximation (i.e. $R_1^F = R_1^B = R_1$), $R_+ = R_1 + k/f$. Relative weights of decay modes depend on initial conditions (i.e. an RF excitation scheme) and the bound pool fraction. It should be understood that standard T_1 measurement techniques applied to the two-pool system typically result in the bi-exponential dependence of the observed signal on a variable timing parameter (e.g. TR or TI), though the fast decay component can be observed only at short time intervals after excitation (<50-100 ms).

The bi-exponential relaxation equation (equation (3)) can be used for estimation of cross-relaxation parameters k and f after some approximations, which take into account the effect of a particular pulse sequence on the initial values M_{zi}^F, B . Several methods were suggested for this purpose based on different excitation schemes, such as semi-selective inversion [1,18,19], binomial excitation [18], double inversion [20], multiple inversions [21], stimulated echo preparation [22], and progressive off-resonance saturation [23].

4. Stationary RF saturation

Another important solution is for the stationary (continuous wave, CW) saturation regime, which presumes infinitely long RF irradiation (in practice during the time $> 5T_1$). This solution provides an analytical equation for data analysis in Z-spectroscopy, where the parameters of the two-pool model can be extracted from dependences of the longitudinal magnetization on the offset frequency and power of RF field. The simplest form of CW solution can be obtained for high offset frequencies assuming negligible direct saturation of the free pool [24]. Currently, the commonly accepted approach for data analysis in Z-spectroscopy (4.6) is based on the full stationary solution of equations (1a-1d) with an arbitrary lineshape describing saturation of the bound pool (typically Superlorenzian for tissues [6]):

$$M_{ss}^F / M_0^F = \frac{R_1^F R_1^B + R_1^F k(1 - f)/f + R_1^B k + R_1^F W^B}{R_1^F R_1^B + R_1^F k(1 - f)/f + R_1^B k + (R_1^F + k)W^B + (R_1^B + k(1 - f)/f)W^F + W^B W^F}, \quad (6)$$

where $M_0^F = (1-f)M_0$, and

$$W^{F,B} = \pi \omega_1^2 g^{F,B}(\Delta, T_2^{F,B}) \quad (7)$$

are the saturation rates for the free and bound pools with gB given by equation (2) and Lorentzian function gF ,

$$g^F(\Delta, T_2^F) = \frac{1}{\pi} \frac{T_2^F}{1 + (2\pi\Delta T_2^F)^2}. \quad (8)$$

A modified version of equation (6) was introduced to accommodate pulsed saturation in MT imaging by using a CW-equivalent power [25, 26] delivered during the sequence repetition time (TR).

5. Periodic off-resonance saturation in a gradient-echo sequence: MT imaging

The above solutions are relatively simple, though they are generally not applicable to MT imaging experiments in MRI. In MT imaging, off-resonance saturation is delivered by relatively short RF pulses, and these pulses are incorporated in a pulse sequence with a relatively short TR. Correspondingly, the model should take into account both pulsed MT saturation and the effects of periodic excitation and relaxation produced by a sequence. A relatively simple approximated model was developed for a spoiled gradient-echo sequence with pulsed off-resonance MT saturation [17,27]. In this model, evolution of magnetization is analyzed separately during four time intervals comprising the sequence cycle: off-resonance saturation pulse (t_m), delay for spoiling gradient (t_s), readout pulse (t_p), and delay for signal readout and relaxation (t_r). Assuming that the pulsed steady state is established, the resulting equation can be written in matrix form as

$$\mathbf{M}_z = (\mathbf{I} - \mathbf{E}_s \mathbf{E}_m \mathbf{E}_r \mathbf{C})^{-1} \{ [\mathbf{E}_s \mathbf{E}_m (\mathbf{I} - \mathbf{E}_r) + (\mathbf{I} - \mathbf{E}_s)] \mathbf{M}_{eq} + \mathbf{E}_s (\mathbf{I} - \mathbf{E}_m) \mathbf{M}_{ss} \}, \quad (9)$$

where \mathbf{M}_z is the vector with components M_z^F and M_z^B corresponding to the longitudinal magnetization immediately before the excitation pulse; \mathbf{M}_{eq} is the vector of equilibrium magnetization with elements $M_0(1-f)$ and M_0f ; \mathbf{M}_{ss} is the vector of steady-state longitudinal magnetization for which the free pool component is given by equation (6); \mathbf{I} is the unit matrix; the matrix term $\mathbf{E}_m = \exp((\mathbf{R} + \mathbf{W})t_m)$ describes off-resonance saturation by an RF pulse with duration t_m ; the terms $\mathbf{E}_s = \exp(\mathbf{R}t_s)$ and $\mathbf{E}_r = \exp(\mathbf{R}t_r)$ describe relaxation during delays before (t_s) and after (t_r) an excitation RF pulse; and the diagonal matrix $\mathbf{C} = \text{diag}(\cos\alpha, 1)$ corresponds to instant rotation of the magnetization M_z^F by an excitation pulse with the flip angle α . The matrices \mathbf{R} and \mathbf{W} are defined as follows:

$$\mathbf{R} = \begin{bmatrix} -R_1^F - k & k(1-f)/f \\ k & -R_1^B - k(1-f)/f \end{bmatrix}, \quad \mathbf{W} = -\text{diag}(\langle W^F \rangle, \langle W^B \rangle),$$

where $\langle W^{F,B} \rangle$ are the time-averaged saturation rates for the pools during the saturation pulse. Approximating RF power by its time-averaged value, $\langle \omega_1^2 \rangle$,

$$\langle \omega_1^2 \rangle = 1/t_m \int_0^{t_m} \omega_1^2(t) dt \quad (10)$$

the saturation rates can be expressed as

$$\langle W^{F,B} \rangle = \pi \langle \omega_1^2 \rangle g^{F,B}(\Delta, T_2^{F,B}), \quad (11)$$

where $gF, B(\Delta, T2F, B)$ are given by equations (2) and (8). Note that the stationary approximation for the transverse magnetization of the free pool presuming the Lorentzian function gF is limited to high offset frequencies where evolution of transverse components is sufficiently fast in the timescale of the applied RF irradiation ($t_m \gg 1/\Delta$).

Equation (9) provides a convenient model for data analysis in pulsed Z-spectroscopic experiments. This model with some variations related to the consideration of the transverse magnetization of the free pool was used in several studies [17, 27, 28] to determine cross-relaxation parameters from imaging data obtained at variable offset frequency and power of pulsed RF saturation.

6. MT imaging: simple algebraic description

Magnetization transfer ratio (MTR) is a widely used simple empiric quantitative measure of the MT effect in tissues. MTR is calculated as the percentage of a signal decrease due to off-resonance saturation: $MTR = 100(S_{ref} - S_{mt})/S_{ref}$, where S_{mt} and S_{ref} are the signal intensities with and without saturation, respectively. Whole-brain MTR mapping and histogram analysis have gained significant popularity in clinical neuroimaging studies of diseases causing diffuse brain damage, such as multiple sclerosis. Based on the theory presented in the previous section, a simple yet accurate model describing the relationship between MTR and key parameters characterizing the two-pool model as well as basic parameters of a pulse sequence can be obtained. Equation (9) can be further simplified assuming that TR is short, and the first-order approximation can be applied to exponential terms [17]. The resulting equation for MTR can be expressed as

$$MTR \approx \frac{kf(t_m/TR)\langle W^B \rangle}{k(R_1 - (1-f)\ln \cos(\alpha)/TR) + f(t_m/TR)\langle W^B \rangle(R_1 + k - \ln \cos(\alpha)/TR)}. \quad (12)$$

Additionally, we assume in equation (12) that direct saturation of the free pool is negligible ($W^B \gg W^F$), which requires frequency offsets $\Delta > 1-2$ kHz, and that $R_1^F = R_1^B = R_1$. Despite these approximations, equation (12) provides a close agreement with the full Bloch model given by equations (1a-1d) [17]. To understand basic trends affecting experimental results in MT imaging, let us consider several algebraic consequences of varying pulse sequence parameters in equation (12).

5.1. Effect of the saturation rate $\langle WB \rangle$.

Through equation (11), $\langle W^B \rangle$ is increased with an increase of the saturation power and a decrease of the offset frequency. For simplicity, we assume that the excitation flip angle α in equation (12) is low. In the weak saturation regime, $MTR \sim fT_1 \langle W^B \rangle$, thus being sensitive to macromolecular fraction and independent of k . In the strong saturation regime, MTR approaches the limit where MTR is independent of f : $MTR \sim kT_1/(1+kT_1)$. In practice, this limit is unachievable due to the presence of direct saturation of the free pool and SAR limitations (for in vivo studies). At typical conditions of clinical MT imaging, both cross-relaxation parameters (k and f) provide comparable contributions into MTR.

5.2. Effect of the excitation flip angle α .

This effect is typically overlooked in literature, since the common practice of low-angle MTR measurements is driven by the goal of the maximization of the observed MTR. In fact, as seen from the above limiting conditions, at low flip angles MTR is weighted by both cross-relaxation parameters (f and k) and T_1 . Most pathological changes in tissues result in an increase of T_1 and a decrease of f and k . Correspondingly, opposite trends in these parameters reduce pathological sensitivity of MTR. As seen from equation (12), the contribution of R_1 in the denominator terms is reduced with an increase of α

through its function $-\ln(\cos(\alpha))$. Thus, MT imaging with high excitation flip angles can provide more sensitivity to cross-relaxation parameters themselves, though the range of MTR values is reduced.

5.3. Effect of TR.

As seen from equation (12), the duty cycle of the saturation pulse, t_m/TR plays a role of the scaling factor for the saturation rate WB. Consequently, a decrease of TR results in an increased MT effect and vice versa. Additionally, a shorter TR is helpful for increasing the term $-\ln(\cos(\alpha))/TR$ to reduce the effect of T1 weighting on MTR as described above.

7. Conclusions

The MT effect plays an important role in various areas of MRI as a tool for modifying image contrast, a source of quantitative parameters for tissue characterization, and a cause of systematic errors in quantitative imaging. This lecture provides an overview of biophysical mechanisms of MT in tissues, in-depth mathematical consideration of the widely used two-pool model of MT, and a summary of experimental methods used to study MT phenomena.

Acknowledgments

The study was supported by Russian Science Foundation (project № 14-45-00040). The author acknowledges Tomsk State University Competitiveness Improvement Program for the preparation of the manuscript.

References

- [1] Edzes H T, Samulski E T 1978 The measurement of cross-relaxation effects in the proton NMR spin-lattice relaxation of water in biological systems: hydrated collagen and muscle. *J Magn Reson* **31** 207-229
- [2] Wolf S D, Balaban R S 1989 Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. *Magn Reson Med* **10** 135-144
- [3] Koenig S H, Brown R D 3rd, Ugolini R 1993 A unified view of relaxation in protein solutions and tissue, including hydration and magnetization transfer. *Magn Reson Med* **29** 77-83
- [4] Henkelman R M, Huang X, Xiang Q S, Stanisz G J, Swanson S D, Bronskill M J 1993 Quantitative interpretation of magnetization transfer. *Magn Reson Med* **29** 759-766
- [5] Kuwata K, Brooks D, Yang H, Schleich T 1994 Relaxation-matrix formalism for rotating-frame spin-lattice proton NMR relaxation and magnetization transfer in the presence of an off-resonance irradiation field. *J Magn Reson B* **104** 11-25
- [6] Morrison C, Henkelman R M 1995 A model for magnetization transfer in tissues. *Magn Reson Med* **33** 475-482
- [7] Adler R S, Swanson S D, Yeung H N 1996 A three-component model for magnetization transfer. Solution by projection-operator technique, and application to cartilage. *J Magn Reson B* **110** 1-8
- [8] Li J G, Graham S J, Henkelman R M 1997 A flexible magnetization transfer line shape derived from tissue experimental data. *Magn Reson Med* **37** 866-871
- [9] McLaughlin A C, Ye F Q, Pekar J J, Santha A K, Frank J A 1997 Effect of magnetization transfer on the measurement of cerebral blood flow using steady-state arterial spin tagging approaches: a theoretical investigation. *Magn Reson Med* **37** 501-510
- [10] Gochberg D F, Kennan R P, Maryanski M J, Gore J C 1998 The role of specific side groups and pH in magnetization transfer in polymers. *J Magn Reson* **131** 191-198
- [11] Stanisz G J, Kecojevic A, Bronskill M J, Henkelman R M 1999 Characterizing white matter with magnetization transfer and T2. *Magn Reson Med* **42** 1128-1136

- [12] Ceckler T, Maneval J, Melkowitz B 2001 Modeling magnetization transfer using a three-pool model and physically meaningful constraints on the fitting parameters. *J Magn Reson* **151** 9-27
- [13] van Zijl P C, Zhou J, Mori N, Payen J F, Wilson D, Mori S 2003 Mechanism of magnetization transfer during on-resonance water saturation. A new approach to detect mobile proteins, peptides, and lipids. *Magn Reson Med* **49** 440-449
- [14] Graham S J, Henkelman R M 1997 Understanding pulsed magnetization transfer. *J Magn Reson Imaging* **7** 903-912
- [15] Iino M 1994 Transition from Lorentzian to Gaussian line shape of magnetization transfer spectrum in bovine serum albumin solutions. *Magn Reson Med* **32** 459-463
- [16] Quesson B, Thiaudiere E, Delalande C, Dousset V, Chateil J F, Canioni P 1997 Magnetization transfer imaging in vivo of the rat brain at 4.7 T: interpretation using a binary spin-bath model with a superLorentzian lineshape. *Magn Reson Med* **38** 974-980
- [17] Yarnykh V L 2002 Pulsed Z-spectroscopic imaging of cross-relaxation parameters in tissues for human MRI: theory and clinical applications. *Magn Reson Med* **47** 929-939
- [18] Gochberg D F, Kennan R P, Gore J C 1997 Quantitative studies of magnetization transfer by selective excitation and T1 recovery. *Magn Reson Med* **38** 224-231
- [19] Gochberg D F, Gore J C 2007 Quantitative magnetization transfer imaging via selective inversion recovery with short repetition times. *Magn Reson Med* **57** 437-441
- [20] Morris G A, Freemont A J 1992 Direct observation of the magnetization exchange dynamics responsible for magnetization transfer contrast in human cartilage in vitro. *Magn Reson Med* **28** 97-104.
- [21] Gochberg D F, Kennan R P, Robson M D, Gore J C 1999 Quantitative imaging of magnetization transfer using multiple selective pulses. *Magn Reson Med* **41** 1065-1072
- [22] Ropele S, Seifert T, Enzinger C, Fazekas F 2003 Method for quantitative imaging of the macromolecular 1H fraction in tissues. *Magn Reson Med* **49** 864-871
- [23] Helms G, Piringer A 2005 Simultaneous measurement of saturation and relaxation in human brain by repetitive magnetization transfer pulses. *NMR Biomed* **18** 44-50
- [24] Grad J, Bryant R J 1990 Nuclear magnetic cross-relaxation spectroscopy. *J Magn Reson* **90** 1-8
- [25] Ramani A, Dalton C, Miller D H, Tofts P S, Barker G J 2002 Precise estimate of fundamental in-vivo MT parameters in human brain in clinically feasible times. *Magn Reson Imaging* **20** 721-731
- [26] Tozer D, Ramani A, Barker G J, Davies G R, Miller D H, Tofts P S 2003 Quantitative magnetization transfer mapping of bound protons in multiple sclerosis. *Magn Reson Med* **50** 83-91
- [27] Sled J G, Pike G B 2001 Quantitative imaging of magnetization transfer exchange and relaxation properties in vivo using MRI. *Magn Reson Med* **46** 923-931
- [28] Yarnykh V L, Yuan C 2004 Cross-relaxation imaging reveals detailed anatomy of white matter fiber tracts in the human brain. *NeuroImage* **23** 409-424