Available online at www.sciencedirect.com
ScienceDirect
Journal of Magnetic Resonance 191 (2008) 171–183
JMR Journal of Magnetic Resonance
www.elsevier.com/locate/jmr

A comparison between equations describing *in vivo* MT: The effects of noise and sequence parameters

Mara Cercignani [a,*], Gareth J. Barker [b]

[a] *NMR Research Unit, Department of Neuroinflammation, Institute of Neurology, London WC1N 3BG, UK*
[b] *King's College London, Institute of Psychiatry, Department of Clinical Neuroscience, Centre for Neuroimaging Sciences, London SE5 8AF, UK*

Received 14 May 2007; revised 21 December 2007
Available online 25 December 2007

Abstract

Quantitative models of magnetization transfer (MT) allow the estimation of physical properties of tissue which are thought to reflect myelination, and are therefore likely to be useful for clinical application. Although a model describing a two-pool system under continuous wave-saturation has been available for two decades, generalizing such a model to pulsed MT, and therefore to *in vivo* applications, is not straightforward, and only recently have a range of equations predicting the outcome of pulsed MT experiments been proposed. These solutions of the 2-pool model are based on differing assumptions and involve differing degrees of complexity, so their individual advantages and limitations are not always obvious. This paper is concerned with the comparison of three differing signal equations. After reviewing the theory behind each of them, their accuracy and precision is investigated using numerical simulations under variable experimental conditions such as degree of T_1-weighting of the acquisition sequence and SNR, and the consistency of numerical results is tested using *in vivo* data. We show that while in conditions of minimal T_1-weighting, high SNR, and large duty cycle the solutions of the three equations are consistent, they have a different tolerance to deviations from the basic assumptions behind their development, which should be taken into account when designing a quantitative MT protocol.

Keywords: MRI; Magnetization transfer; Two-pool model; Relaxation; Human brain

1. Introduction

The Magnetization Transfer (MT) effect is based on the exchange of magnetization occurring between groups of spins characterized by different molecular environments. In biological tissues, two or more "pools" of protons can be identified: those in free water (the free, or liquid, pool) and those bound to large molecules (referred to as restricted, semisolid, or macromolecular, pool). The latter protons are characterized by a very short transverse relaxation time (T_2) and therefore do not directly contribute to signal intensity in conventional magnetic resonance (MR) images. Nevertheless, it is possible to sensitise an MR experiment to the magnetic resonance characteristics of macromolecular protons by exposing the sample to radiofrequency (RF) energy several kilohertz away from the Larmor frequency. Protons in free water are relatively insensitive to such irradiation, but it can cause saturation of protons in the semisolid pool which, due to their short T_2 and correspondingly large line width, are responsive to irradiation at these frequencies. In these conditions, any exchange of magnetization between pools results in a decreased intensity of the observed MR signal.

From a quantitative MT model based on the exchange between two pools Henkelman et al. [1] derived a signal equation for the continuous wave (CW) case, in which RF irradiation of particular (constant) amplitude and several seconds duration is used to saturate the macromolecular pool. The parameters characterizing the two pools in the model are potentially interesting to measure, and they

* Corresponding author. Fax: +39 06 5150 1213.
E-mail address: m.cercignani@ion.ucl.ac.uk (M. Cercignani).

1090-7807/$ - see front matter
doi:10.1016/j.jmr.2007.12.012

can be estimated by fitting Henkelman's equation to a set of MR measurements obtained in the presence of MT pulses with a suitable set of amplitudes ω_1 and offset frequencies Δf.

As CW irradiation is impractical and generally not available for *in vivo* imaging experiments, *in vivo* MT-weighted MRI is generally obtained using the so-called pulsed MT acquisition, in which the long period of saturation is replaced by a much shorter irradiation pulse (typically applied just before each excitation pulse) along with intervals without irradiation (during which data is collected). For data from this type of acquisition, Henkelman's equation must be modified to allow for the short duration of the saturation pulses relative to T_1 [2]. A number of such modified signal equations for pulsed MT, all based on the same original two-pool model, have been developed [3–5]. While the numerical results published so far suggest reasonable consistency across the solutions predicted by these equations, no direct comparison is available, and the differing conventions and symbols used mean that evaluating discrepancies and similarities between them is not straightforward.

This paper is concerned with the comparison of three of these signal equations—two derived by Sled and Pike [3,6], plus that of Ramani et al. [5]. Ramani et al. used a CW power equivalent approximation (CWPE) [5] where the pulse is simply replaced by a CW irradiation with the mean square amplitude that would give the same power over the interval between MT pulses. By means of the CWPE approximation, Henkelman's steady state model can be straightforwardly applied to the *in vivo* MRI case, neglecting the imaging elements of the pulse sequence. Due its steady state nature, the implicit assumption within the equation is that the relative signal intensity in data obtained with different MT-weightings only depends on the characteristics of the MT pulse, and that T_1 and T_2 relaxations equally affect all measurements.

As Ramani's equation does not explicitly model the effects of the excitation pulses and TR, its description of the MT-weighted signal is valid only when the degree of T_1-weighting in the acquisition sequence is minimal. As it effectively assumes that the MT pulse is applied continuously, another parameter likely to affect the accuracy of Ramani's equation is the duty cycle, i.e. the duration of the MT pulse relative to the repetition period, whose effect has never formally been investigated. Sled and Pike [6] propose an alternative equation which can be fitted directly to the measured signal. Their solution is derived by approximating the pulse sequence as a series of periods of free precession, CW irradiation and instantaneous saturation of the free pool. It has the advantage of incorporating the effect of the excitation RF pulses, and also makes it possible to account for saturation effects of the excitation. Together with this solution, the authors propose also a simpler variant which neglects free precession, thus assuming a succession of instantaneous saturation of the free pool and CW irradiation of the macromolecular pool for the total duration of the interval between pulses. Both equations presented by Sled and Pike for *in vivo* applications require the numerical evaluation of ordinary differential equations (when modeling the rate of saturation of the macromolecular pool with a super-Lorentzian, see next section), at least for the estimation of the effect of the MT pulse on the free pool, and they are therefore computationally intensive. Ramani's solution has the advantage of being simpler, at the price of its inability to account for the effects of the excitation pulses. A recent paper presented an evaluation of these signal equation, validated using animal data [7]. Here we first review the theory behind them and then use numerical simulations to extend the range of experimental conditions under which each can be tested (investigating how duty cycle, saturation effects of the excitation and noise affect the MT parameters fitted by each of them). We also perform a statistical comparison between MT parameters estimated using each signal equation in healthy brain tissue from *in vivo* data.

2. Theory

2.1. Coupled Bloch equations

Assuming that the MT effect can be modeled using a liquid pool (A) and a macromolecular pool (B), the magnetization of either pool can be described by its longitudinal component (M_z^A, M_z^B) and its transverse components $(M_x^A, M_y^A, M_x^B, M_y^B)$. The exchange between pools associated with the transverse components of magnetization can be considered negligible due to the extremely short T_2 associated with the macromolecular pool [2,6]. The coupled Bloch equations for the system can thus be written as follows:

$$\frac{\mathrm{d}M_z^A}{\mathrm{d}t} = R_A\left(M_0^A - M_Z^A\right) - RM_0^B M_Z^A + RM_0^A M_Z^B + \omega_1(t)M_y^A \quad (1)$$

$$\frac{\mathrm{d}M_z^B}{\mathrm{d}t} = R_B\left(M_0^B - M_Z^B\right) - RM_0^A M_Z^B + RM_0^B M_Z^A - (R_{RFB}(\Delta f, \omega_1(t)))M_Z^B \quad (2)$$

$$\frac{\mathrm{d}M_x^A}{\mathrm{d}t} = -\frac{M_x^A}{T_2^A} - 2\pi\Delta f M_y^A \quad (3)$$

$$\frac{\mathrm{d}M_y^A}{\mathrm{d}t} = -\frac{M_y^A}{T_2^A} + 2\pi\Delta f M_x^A - \omega_1(t)M_z^A. \quad (4)$$

In Eqs. (1)–(4), T_2^A represents the transverse relaxation time of the liquid pool, M_0^A and M_0^B are the fully relaxed values of magnetization associated with the two pools (assumed dimensionless), R_A and R_B are their longitudinal relaxation rates, and R is the exchange rate constant. Δf represents the frequency offset of the pulse, while $\omega_1(t)$ is the time dependent amplitude of the pulse expressed in rad s^{-1} (i.e. the angular frequency of precession induced by the pulse). $R_{RFB}(\Delta f, \omega_1(t))$ is the rate of saturation of longitudinal magnetization in pool B due to the irradiation by the amplitude defined by Δf and $\omega_1(t)$, and depends on the transverse relaxation time of the macromolecular pool,