Modeling Pulsed Magnetization Transfer

S. Portnoy[1], and G. J. Stanisz[2]

[1]Mice Imaging Centre, Hospital for Sick Children, Toronto, ON, Canada, [2]Imaging Research, Sunnybrook HSC, Toronto, ON, Canada

INTRODUCTION: One of the primary challenges in performing quantitative magnetization transfer (qMT) experiments *in-vivo* lies in the modeling the effects of the short, shaped radiofrequency (RF) pulses, which are used due to scan time limitations and RF heating concerns. Characterizing the behaviour of magnetization throughout these pulsed MT scans is both complex and time consuming. To minimize the complexity, several studies propose approximate methods for a simplified analysis of the experimental data. However, potential differences in the MT parameters estimated by each method may complicate the comparison of reported results. In this study, we compared three approximate methods, which are currently used in quantitative MT studies. These methods include:

1. The signal equation developed by Sled & Pike, which approximates the effect of an MT pulse on the liquid pool by an instantaneous saturation of the longitudinal magnetization, and on the semisolid pool by a rectangular pulse of equal average power (1).
2. Ramani's technique (CPWE), which approximates pulsed MT by using continuous wave (cw) MT formalism with cw power equivalent of the MT scheme (2).
3. The method proposed by Yarnykh, which neglects direct saturation of the liquid pool and approximates shaped RF pulses by equal power rectangular pulses (3).

To our knowledge, this work constitutes the first systematic comparison of the pulsed MT models that are currently applied in qMT investigations.

METHODS: The techniques described above were used to fit experimental pulsed MT data obtained from samples of wild type and *shiverer* mouse spinal cord. Data fitting was also performed using a qMT fitting algorithm we developed, which modeled shaped MT pulses by a series of short rectangular segments (50 μs in duration) whose envelope was described by the desired pulse shape. The 50 μs duration was chosen since further decreases in the length of rectangular segments induced changes in the final solution of less than 1.5%. Aside from the assumption that tissues are accurately described by a MT two pool model (4), this representation of shaped MT pulses uses no approximations. As such, this technique represents a useful standard for the evaluation of the other, more approximate models. We refer to this method as the *Minimal Approximation Magnetization Transfer* (MAMT) technique.

MR Experiments: NMR measurements were performed at 20°C on a 1.5 Tesla magnet controlled by a spectroscopy console (SMIS, Surrey, England). The pulsed MT saturation scheme consisted of a 7 second pulse train composed of 150, 15 ms Gaussian pulses with a 50 ms pulse repetition period. A series of pulsed MT measurements with varying saturation pulse flip angles, θ, and off-resonance frequencies, Δ, was obtained. Specifically, 15 off resonance irradiation frequencies were logarithmically distributed from 1-213 kHz. Data were collected at each of these offset frequencies for 2 RF pulse flip angles (θ=359°, 718°). Independent measurements of R_A^{OBS}, the apparent longitudinal relaxation rate of the liquid pool, were performed using an inversion recovery (IR) sequence with 15 inversion times logarithmically spaced from 1 to 32,000 milliseconds, 10 seconds between each acquisition and the next inversion pulse, and 4 averages. The *shiverer* and wild type spinal cord MT data were collected to probe the dependence of MT parameters on myelin content. The average SNR for all measured samples was approximately 200.

Fitting Procedures: Estimates of the MT exchange rate, R, the liquid and semisolid pool transverse relaxation times, T_2^A and T_2^B, and the semisolid pool fraction M_0^B, were obtained by least squares fitting of each model to the experimental data. To help constrain these parameters, fitting procedures were provided with the measured values of R_A^{OBS}. In data fits performed using Yarnykh's approach, all data points at offset frequencies below 2.5 kHz were excluded from the fit. This agrees with this investigator's recommendation that data not be collected at offset frequencies less than 2 kHz (3) and is consistent with his model's assumption that the direct effect is negligible. An additional result of this model's omission of the direct effect is the lack of a T_2^A estimate. Additionally, MAMT model has been validated by comparing MAMT parameters for series of agar gel phantoms and neural tissue to those obtained using cw experiments and cw MT model (4).

RESULTS: MT parameters for the *shiverer* and wild type spinal cord samples are summarized in Tables 1 and 2. For completeness, parameters obtained by Yarnykh's model when all data points were included in the fit are also shown. Values of σ, the average residual deviation from each model per point, are tabulated in the final column. Uncertainties in the MT parameters resulting from the fitting procedure are expressed in terms of the 95% confidence interval. Since the confidence intervals were not symmetric, the upper and lower bounds are indicated in parentheses below the parameter values. Provided Yarnykh's approach is used with the appropriate 2.5 kHz cutoff, all three approximate techniques, as well as the MAMT model obtain very similar estimates of the semisolid pool fraction, M_0^B and transverse relaxation time, T_2^B. In general, parameters estimated by Sled & Pike's model were closest to those obtained using the MAMT technique. Ramani et al.'s CWPE approximation resulted in lower estimates of the MT exchange constant, R and longer values of the liquid pool transverse relaxation time, T_2^A. With all data points included, the performance of Yarnykh's model worsened. The quality of the fit was reduced (higher residuals) and the MT exchange rate, R, was significantly overestimated (with substantial uncertainty), particularly in the *shiverer* spinal cord. The transverse relaxation time of the semisolid pool, T_2^B, was also overestimated.

Table 1: Fitted MT parameters for wild type spinal cord

	R [s^{-1}]	M_0^B [%]	T_2^A [ms]	T_2^B [μs]	σ [%]
Sled & Pike	25 (19-60)	4.3 (4.0-4.5)	36 (29-47)	9.3 (7.9-10.9)	0.23
Ramani et al. (CWPE)	20 (17-25)	4.3 (4.1-4.6)	40 (31-54)	9.4 (8.0-11.1)	0.25
Yarnykh (2.5 kHz cutoff)	54 (28-184)	4.0 (3.7-4.4)	n/a	9.3 (7.5-11.5)	0.30
Yarnykh (all data points)	84 (30-554)	4.0 (3.4-4.7)	n/a	10.9 (7.6-16.1)	0.67
MAMT	24 (19-32)	4.3 (4.0-4.6)	35 (29-46)	9.3 (8.3-10.1)	0.23

Table 2: Fitted MT parameters for *shiverer* spinal cord

	R [s^{-1}]	M_0^B [%]	T_2^A [ms]	T_2^B [μs]	σ [%]
Sled & Pike	34 (24-60)	2.6 (2.4-2.8)	52 (42-67)	8.4 (7.2-9.9)	0.21
Ramani et al. (CWPE)	26 (20-34)	2.6 (2.5-2.8)	57 (46-75)	8.5 (7.2-10.1)	0.22
Yarnykh (2.5 kHz cutoff)	176 (45-500)	2.4 (2.2-2.6)	n/a	8.4 (7.0-10.5)	0.27
Yarnykh (all data points)	1070 (71-5000)	2.3 (1.9-2.7)	n/a	9.8 (7.0-13.9)	0.73
MAMT	32 (24-52)	2.6 (2.5-2.8)	50 (41-64)	8.4 (7.2-9.9)	0.21

DISCUSSION & CONCLUSION: A comparison of the techniques used by Sled & Pike, Ramani et al. and Yarnykh reveals that the approximations used in Pulsed MT modeling are generally quite robust. Results suggest that the semisolid pool fraction, M_0^B, and transverse relaxation time, T_2^B, can be evaluated with reasonable accuracy, regardless of the model used. Reported values of these parameters can now be compared directly. The reliability of M_0^B estimates is encouraging, since it is an MT parameter that has a true biological meaning (i.e. the relative number of hydrogen protons that are bound to macromolecules) and which may directly reflect tissue composition. Furthermore, M_0^B has been observed to change dramatically in white matter pathologies, particularly demyelination (5). Some more caution may be required for the interpretation of the MT exchange rate, R, and the liquid pool transverse relaxation time, T_2^A, since these parameters do vary between models. The exchange rate, R, however, has demonstrated limited sensitivity to white matter pathology (5,6). Although the transverse relaxation time, T_2^A, does change with disease, its poor estimate is of less importance, since transverse relaxation of liquid pool magnetization can always be investigated with conventional MRI experiments.

REFERENCES: 1) Sled, JG, Pike, GB. *JM R*, 2000. **145**: p.24. 2) Ramani, A *et al*, *MRI*, 2002. **20**: p.721. 3) Yarnykh, VL, *MRM*, 2002. 47: p.923. 4) Henkelman RM *et al. MRM* 1993.**29**:p759 5) Odrobina, EE *et al*. *NMR Biomed*, 2005. **18**: p.277. 6) Sled, JG, Pike, GB. *MRM*, 2001. **46**(5): p.923