Characterization of myelin damage in multiple sclerosis using myelin water imaging: Insight from simulations on a four pool model of white matter

I. R. Levesque[1], and G. B. Pike[1]

[1]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

Introduction:

Magnetic resonance imaging is a very sensitive technique for the study of white matter (WM) damage in multiple sclerosis (MS), but suffers from a general lack of specificity to the underlying pathology. Quantitative imaging techniques that provide putative in vivo measures related to myelin, such as myelin water imaging [1], have been developed and shown to correlate strongly with demyelination [2]. To help further the understanding of WM, a four-pool model has been proposed and characterized [3], and its properties have recently been measured in bovine WM [4]. While perhaps overly complicated for routine in vivo imaging applications, this model can provide insight into the impact of changes in the four-pool complex on observations made using established methods for quantitative imaging. We have studied the effect of modeling tissue pathology on the resulting T_2 spectrum by simulating CPMG measurements using a four-pool model, analysed using a multi-component T_2 model.

Methods:

A modified four-pool model of bovine white matter, illustrated in Figure 1, was constructed from an existing model [4], with changes to the treatment of the solid pool [5]. The non-myelin pool is used here to describe the intra- and extra-cellular component observed in myelin water MRI experiments. This model was used in simulations of a 32-echo CPMG sequence with echo-spacing (τ_{180}) of 10 ms, a repetition time (TR) of 3 s, and composite refocusing pulses, identical to that which is used in our imaging experiments. The saturation effect of the refocusing pulses on the semi-solid pools was approximated using a simple model for pulsed saturation adapted for on-resonance pulses [6]. The resulting decay curves were analyzed using non-linear least-squares (NNLS) using a 120-component T_2 model with logarithmically-spaced values and no regularization [7]. To simulate pathological situations observed in MS, the model parameters were modified in three ways: *i*) "pure demyelination" (absolute decrease of myelin and myelin water), *ii*) "pure edema" (increase in non-myelin water), and *iii*) "combined demyelination and edema" (decrease of myelin and myelin water with concurrent increase in non-myelin water). Since enlargement of compartmental spaces can result in increases in the T_2 of the water in that compartment [8], the models with "edema" were also simulated with modest increases (up to 20%) of $T_{2,nmw}$ in addition to increases in the non-myelin water content. Furthermore, myelin breakdown has the potential to cause increases in the diffusion-mediated movement of water between the myelin and non-myelin compartments: the impact of a 20% change in the rate was also evaluated in the models with "demyelination". We evaluated the subsequent impact on spectral metrics such as the total observed signal (S_{total} = integral of the entire spectrum), the myelin water fraction (MWF = observed signal with T_2<50ms / total observed signal), and the average T_2 of the spectrum ($\langle T_2 \rangle$) and each peak (short: $\langle T_2 \rangle_{short}$, intermediate: $\langle T_2 \rangle_{interm}$).

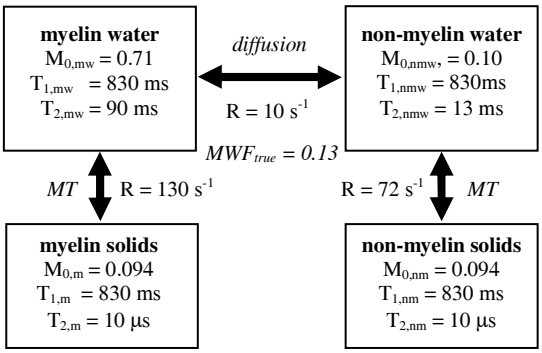

Figure 1. Illustration of the four-pool model, with pool parameters. Exchange is indicated by the normalized exchange rate between each pair of pools. (MT = magnetization transfer)

Results:

The saturation effects of the refocusing pulses in these simulations were negligible, confirming the relative insensitivity of the CPMG signal to semi-solid tissue component saturation. The observations for the models of pathology are summarized in Table 1. The total observed spectrum signal S_{total} varied directly with total input magnetization in all cases, and the average T_2 of the short peak ($\langle T_2 \rangle_{interm}$ = 12 ms) did not change in any of the cases; both are omitted from Table 1.

Discussion:

We have modeled the effect of pathology in simulations of CPMG experiments using a four-pool model of WM, providing insight on the analysis of T_2 spectra from a forward-problem perspective, assuming that bovine WM can be taken as a reasonable model for human WM. Our simulations reflect the negligible semi-solid saturation effect of composite refocusing pulses widely used in CPMG imaging sequences. All pathological models resulted in effective decreases in the observed MWF. However, changes in the log-averaged T_2 values of the spectrum ($\langle T_2 \rangle$) and of the intermediate peak ($\langle T_2 \rangle_{interm}$) differed for each of the models: the "pure demyelination" model resulted in increases in both, while the values remained stable for the "pure edema" model. The "combined" model showed a mitigated increase in the $\langle T_2 \rangle$ and $\langle T_2 \rangle_{interm}$; interestingly, the associated change in $\langle T_2 \rangle$ for this model is mostly mediated by the myelin water, such that a large change in $\langle T_2 \rangle$ still reflects true demyelination while slight changes in $\langle T_2 \rangle$ may indicate edema. Increases in the non-myelin water T_2 ($T_{2,nmw}$) acted as a confounding factor to these distinctions, making the "edema" model resemble the "demyelination" model. The slight increase in the exchange between myelin and non-myelin water compartments results in over-estimation of the MWF decrease. Our results highlight the changes observed in the multi-component T_2 spectrum under specific pathology models, and set objectives for the precision required to identify such pathological effects in MRI experiments.

Table 1. Summary of observations for the pure demyelination, pure edema, and combined models.

Model / Metric	Baseline estimate	"Pure demyelination" $\Delta M_{0,mw}$ = -20 to -100 %	"Non-myelin edema" $\Delta M_{0,cw}$ = + 10%, + 20%	"Demyelination with edema" $\Delta M_{0,mw}$ = -20 to -80 % $\Delta M_{0,cw}$ = + 5% to + 20%
$\langle T_2 \rangle$	68 ms	Increase of 5-22 ms	increase of 1-2 ms	increase up to 17 ms with MWF decrease increase of 1-2 ms with "edema"
$\langle T_2 \rangle_{interm}$	84 ms	increase of 1.5-7 ms	no effect (<0.5 ms)	no effect (<0.5 ms)
MWF	0.106	decreases of 18%, 47% and 100% correlated with input myelin water	decreases of 10% and 18% with increasing edema	decreases of 8-80 % correlated strongly with input myelin water, weakly with edema
Effect of $T_{2,nmw}$ increase with "edema"	(n/a)	(no effect)	corresponding increase in $\langle T2 \rangle$ and $\langle T2 \rangle_{interm}$	increase in $\langle T2 \rangle$ and $\langle T2 \rangle_{interm}$ now dominated by change in $T_{2,nmw}$
Effect of 20% increase in exchange with "demyelination"	(n/a)	decreases of 22%, 49% and 100% correlated with input myelin water	(no effect)	slight over-estimation of decrease in MWF

References

1. Mackay *et al*. Magn. Reson. Med. (1994) **32** :673
2. Moore *et al*. Neurology (2000) **55**:1506
3. Stanisz *et al*. (1999) Magn. Reson. Med. **42**:1128
4. Bjarnason *et al*. Magn. Reson. Med. (2005) **54**:1072
5. Morrison *et al*. J. Magn. Reson. B (1995) **108**:103
6. Sled & Pike J. Magn. Reson. (2000) **145**:24
7. Whittall & MacKay J. Magn. Reson. (1989) **84**:64
8. Stanisz *et al*. Magn. Reson. Imag. (2004) **51**:47