Characterizing white matter pathology with quantitative magnetization transfer imaging: insight from a four-pool model

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Introduction: Quantitative magnetization transfer imaging (QMTI) [1] allows *in vivo* mapping of the parameters of a two-pool model of MT in tissue [2] by the analysis of off-resonance saturation data, and is useful in the study of human white matter (WM). The two-pool model parameters are the restricted-to-free proton pool size ratio (F), the forward magnetization transfer rate (k_f), and the relaxation parameters of the model compartments (R_{1f}, T_{2f}, R_{1r}, T_{2r}) [1]. However, as it has been clearly established that WM has at least two separate water compartments [3], a more comprehensive model should include four proton pools (myelin solids, myelin water, non-myelin water, and non-myelin solids) [4]. This four-pool model has been used to characterize *in vitro* samples of bovine optic nerve [5] and fresh bovine WM [6]. By simulating pulsed off-resonance saturation gradient echo (GRE) measurements, we investigated the ability of the two-pool model, more tractable for *in vivo* imaging, to reflect the more complete four-pool model, and potential changes due to pathology. Specifically, we examined the effect of increases in the inter-compartmental exchange of water, of reductions in the solid pool sizes (myelin and non-myelin), and of a simple model of pure demyelination (decreased myelin liquids and solids), on two-pool MT observations.

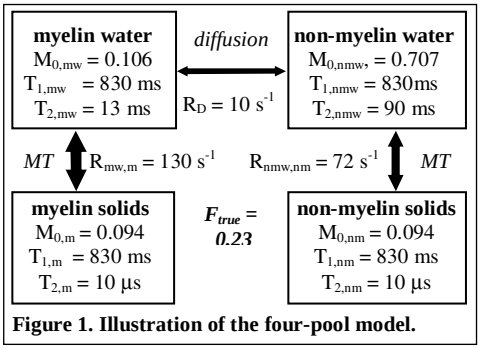

Figure 1. Illustration of the four-pool model.

Methods: A modified version of the four-pool model of bovine WM at 37°C (Figure 1) was constructed from an existing model [6], with changes to the treatment of the solid pools [7]. The coupling between compartments was modeled by first-order exchange rates R_{ij} for diffusion and MT. Simulations of MT-weighted GRE experiments [1] were conducted. Gaussian noise was added to the resulting MT data to produce an SNR of 100, and analyzed using the rectangular pulse model of [1] to yield the two-pool parameters. For each simulation, results from 500 noise iterations were averaged. First, as diffusivity changes of up to 50% have been reported in literature [8,9], the water exchange rate R_D was increased by 25 to 100% to simulate plausible pathological changes. Second, the solid pool sizes were reduced, in 25% steps (myelin and non-myelin separately). Finally, pure demyelination was simulated by 25 to 100% reductions in myelin content (solid and liquid).

Results: The two-pool MT model fits the simulated signal of the baseline four-pool model well (mean residual per point = 1%), and the parameters are reasonable (F = 0.21±0.01, k_f = 5.8±0.9 s^{-1}, R_{1f} = 1.2 s^{-1}, T_{2f} = 71±6 ms, T_{2f} = 10.1±0.3 µs). The MT signal was mildly affected by variations in the water exchange rate: the estimate of F was not affected (change < 1%), while k_f increased by up to 17% and T_{2f} decreased by a maximum of 9%, for a 100% increase in the water exchange rate. Simulated MT curves from models with reduced solid pool sizes are plotted in Figure 2, and the resulting changes in F are plotted in Figure 3. In addition, reductions in non-myelin solids resulted in a large linear decrease in k_f (as much as 80%) and a negligible change in T_{2f}, while reduced myelin solids resulted in a small, monotonic decrease of T_{2f} (< 20%) with little impact on k_f. Lastly, simulated MT curves from our model of demyelination behaved similarly to Figure 2 (right). Normalized estimates of F, k_f, and T_{2f} versus demyelination are plotted in Figure 3. In all simulations, T_{2r} and R_{1f} did not vary and were consistently recovered (10 µs & 1.2 s^{-1}, respectively).

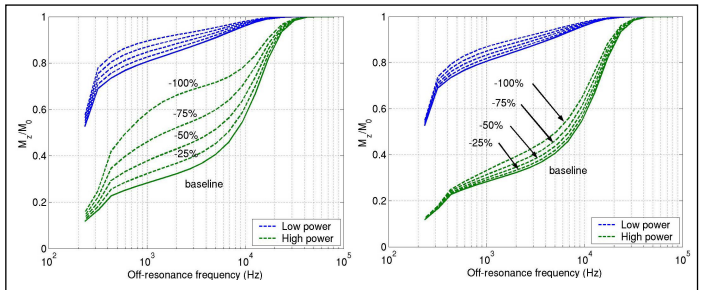

Figure 2. MT signal curves from simulated pulsed saturation, with reductions in the size of the non-myelin (left) and myelin (right) solid pool, respectively. The relative solid pool decrease is indicated on the plots.

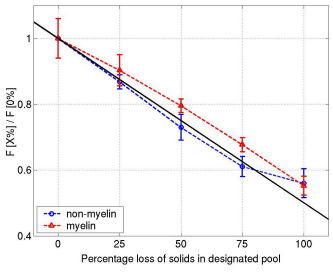

Figure 3. Estimates of F versus solid pool size decreases, for non-myelin (blue) and myelin (red) solid pools. The black line indicates the true value of F.

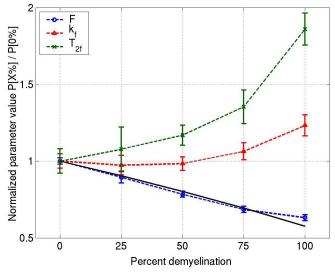

Figure 4. Two-pool parameter estimates (F, kf, T2f) , normalized to the baseline model (0%) fit value, versus demyelination. The black line indicates the true value of F.

Discussion: Based on our simulation results, a two-pool model is sufficient to describe off-resonance MT behavior in WM. Our observations relative to water exchange agree qualitatively with observations in bovine optic nerve [5]; however, water exchange has a less dramatic impact on parameters of the two-pool MT model than on the MT of the individual water components. This suggests that pathology affecting water exchange between the myelin and intra-/extra-cellular compartments, perhaps via membrane permeability variations, have very limited influence on two-pool parameter estimates from MT measurements in WM. These observations are in contrast to results from simulations of myelin water imaging [10], which showed significant sensitivity to water exchange variations. While the overall MT is more greatly affected by theoretical reductions in the non-myelin solid pool size, the estimate of F is robust and sensitive to changes in either the myelin or non-myelin solid pools. Most of the signal change is absorbed by the exchange rate k_f. Two-pool MT estimates are also sensitive to our model of pure demyelination: we observed a robust linear decrease in F which reflected the input value, accompanied by a relatively large increase in T_{2f}, and a comparatively smaller increase in k_f for large myelin decreases (loss > 50%). A more realistic model of demyelination should include a decrease of the exchange rates, to reflect common observations in lesions. In closing, two-pool QMT fits are sensitive to certain changes in the four-pool model: F is robust despite the existence of multiple solid pools, while parameters such as k_f and T_{2f} might provide insight into changes in the more complete four-pool model from limited two-pool observations.

References: [1] Sled & Pike, MRM **46**:923 (2001). [2] Morrison & Henkelman, MRM **33**:475 (1995). [3] Menon & Allen, MRM **20**:214 (1991). [4] Harrison & Henkelman MRM **33**:490 (1995). [5] Stanisz et al. MRM **42**:1128–36 (1999). [6] Bjarnason et al. MRM **54**:1070–81 (2005). [7] Portnoy & Stanisz, MRM **58**:144 (2007). [8] Bammer et al., MRM **44**:583 (2000). [9] Filippi et al., Neurology **56**:304 (2001). [10] Levesque & Pike, ISMRM 2007, p.2142.