Proton Signal Characterisation in White Matter: A Four Pool Model

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Background and Theory: NMR signals from myelin water, intra/extracellular (IE) water and also non-aqueous tissue were measured using a spectrometer capable of differentiating between these different groups of protons in bovine brain. A four pool model[1,2], like that shown in Figure 1, is required in order to model the relationships between these three signal components with the four proton pools being: non-aqueous myelin tissue (*m*), myelin water (*mw*), IE water (*i*) and non-myelin, non-aqueous tissue (*nm*). The NMR signal from the two non-aqueous tissue components decay to zero in less than 100μs and are indistinguishable from each other. The motivation for modelling the NMR behaviour of white matter was to better assess the feasibility of using the fraction of myelin water as a measure of myelination *in vivo*. In particular, we wished to establish the effect of magnetization exchange on the proportion of the myelin water component.

In Figure 1 T_1^m, T_1^{mw}, T_1^i, and T_1^{nm} represent the spin-lattice relaxation times (T_1's) for the respective proton pools and the various *k*'s represent the exchange rates between the different proton pools with directionality as shown in Figure 1. This model provides us with a set of four differential Bloch equations where $M_m(\infty)$, $M_{mw}(\infty)$, $M_i(\infty)$, and $M_{nm}(\infty)$ represent the steady state signal for each respective pool:

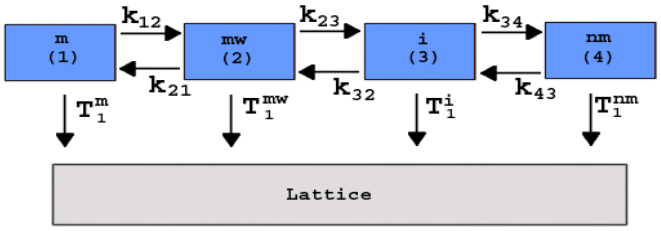

Figure 1: Schematic representation of the four proton pool model of brain white matter with labelled parameters.

$$
\begin{aligned}
M_m' &= -k_{12}M_m - \frac{M_m - M_m(\infty)}{T_1^m} + k_{21}M_{mw} \\
M_{mw}' &= -k_{21}M_{mw} - \frac{M_{mw} - M_{mw}(\infty)}{T_1^{mw}} - k_{23}M_{mw} + k_{12}M_m + k_{32}M_i \\
M_i' &= -k_{32}M_i - \frac{M_i - M_i(\infty)}{T_1^i} - k_{34}M_i + k_{23}M_{mw} + k_{43}M_{nm} \\
M_{nm}' &= -k_{43}M_{nm} - \frac{M_{nm} - M_{nm}(\infty)}{T_1^{nm}} + k_{34}M_i
\end{aligned}
\qquad [1]
$$

The cross relaxation rates between coupled pools are related as shown in equations 2. T_{cr}^{mw}, T_{cr}^D, T_{cr}^i are the cross relaxation times between: myelin tissue and myelin water, the two aqueous pools due to diffusion, and IE water and the remaining tissue pool respectively. P^m, P^{mw}, P^i, P^{nm} represent the probability of a proton being found in the myelin tissue, myelin water, IE water or non-myelin tissue pools respectively.

$$
k_{12} = \frac{1}{P^{mw}T_{cr}^{mw}}; \quad k_{21} = \frac{1}{P^mT_{cr}^{mw}}; \quad k_{23} = \frac{P^m + P^i}{P^m}\frac{1}{T_{cr}^D}; \quad k_{32} = \frac{P^m + P^i}{P^i}\frac{1}{T_{cr}^D}; \quad k_{34} = \frac{1}{P^iT_{cr}^i}; \quad k_{43} = \frac{1}{P^{nm}T_{cr}^i} \qquad [2]
$$

Methods: *In vitro* experiments were performed at 24 and 37°*C* on fresh, unfixed bovine brain placed in a 10*mm* outer diameter NMR tube. Proton signal intensities from non-aqueous tissue and mobile water were determined using an NMR spectrometer operating at 90*MHz*. All experiments had the same repetition time (*TR*) of 7*s*. The T_1's were determined using a modified inversion recovery sequence involving alternating: (90_x-*TR*) and (180_x-τ-90_x-*TR*), where the second signal was subtracted from the first in order to obtain a positive signal that decayed to zero for long *TR*. T_1 decay curves were fit using a regularized non-negative least squares algorithm[3] to obtain T_1 values. A modified free induction decay experiment (90_x-τ/2-$(180_y$-*TE*$)_8$-*TR*, τ=200μs) was used to separate the tissue signal from the water signal. Cross relaxation[4] between the tissue and the water protons, as monitored by the regrowth of the tissue proton signal, was measured using alternate (90_x-δ-90_{-x}-τ-90_x-*TR*) and (90_x-δ-90_x-τ-90_x-*TR*), where the first signal was subtracted from the second signal to eliminate T_1 effects from the tissue proton signal, but not from the water signal. Using δ=400μs allowed for complete dephasing of the tissue signal with minimal effect on the water data. Cross relaxation between the tissue and the water protons, as monitored by the water protons, was measured with the following pulse sequence: (90_x-δ-90_{-x}-τ-90_x-*TE*/2-$(180_y$-*TE*$)_n$-*TR*), using δ=400μs and *TE*=200μs. From this data T_2 distributions were extracted and separate IE and myelin signals were measured. In-house software was written to generate curves to fit the data using the differential equations 1, where the probabilities of protons being in each of the four pools was calculated experimentally from the water content values as determined by the free induction decay experiment, along with proton density values for each pool.

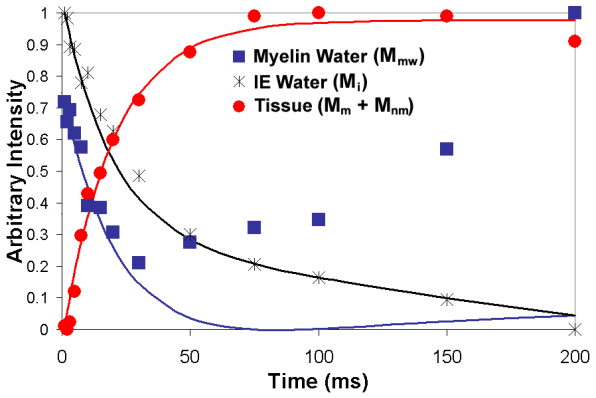

Figure 2: Arbitrary intensity raw data taken at 24°C with the fitted curves form the four proton pool model. The single tissue signal results from not being able to differentiate between the myelin and non-myelin non-aqueous signal. The discrepancy in the myelin water pool could be attributed to low signal to noise.

Results and Conclusions: Table 1 provides a summary of experimentally determined T_1's and theoretically derived T_{cr}'s calculated by the modelling software. Figure 2 shows a typical representation of the raw data along with the modelled fit for both 24 and 37°*C*. For times greater than 50*ms* the signal to noise ratio of the myelin water signal was quite low, which could account for the discrepancy between the model fit (M_{mw}) and the data. The four pool model provides an excellent fit to the data for both the IE water proton pool (M_i) and the non-aqueous proton pool (M_m + M_{nm}). Implementation of a four proton pool model to represent white matter could lead to a better understating of cross relaxation between structures in white matter and ultimately improve quantitative measures of myelin content. This study has shown that cross relaxation between myelin water and IE water (250*ms*) at 37°*C* has little effect on the amplitude of the myelin water peak using a T_2 distribution.

Temperature	$T_1^{m,mw}$	$T_1^{i,nm}$	T_{cr}^{mw}	T_{cr}^D	T_{cr}^i
24°*C*	298	878	110	1750	223
37°*C*	930	930	74	250	354

Table 1: Results from the four proton pool model. All values are in ms unless otherwise stated.

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