Inconsistency in Interpretation of $T_2$ and Diffusion in White Matter

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$T_2$ and compartmentation in white matter

A multieponential $T_2$ decay curve is routinely measured in human white matter (WM), with approximately 10-15% of the signal exhibiting a $T_2$ under 50 ms and the remainder characterized by a $T_2$ of approximately 80 ms at 1.5T [MacKay1994, Whittall1997, Kolind2008]. The assignment of the short $T_2$ to myelin-associated water has been widely accepted. Undoubtedly a short $T_2$ is correlated with the existence of myelin, but perhaps the assignment to a specific water pool has yet to be proven. This abstract discusses why.

If indeed the myelin water can be identified as a separate component in the relaxation curve, its exchange with other tissue compartment water must be slow on the timescale of the myelin $T_2$. Since the myelin sheath is the barrier between the intra-axonal water in myelinated axons, and the continuous extracellular space, its slow exchange determines that the intra-axonal water is quite restricted.

The effect of long gradient pulses on restricted diffusion

When diffusion of magnitude $D$ is restricted in spaces of characteristic size $a$, when measured using NMR diffusion with pulses of length $\delta$ and separation $\Delta$, it can be classified into three regimes:

1. $\Delta D<<a^2$ free diffusion: barriers are effectively nonexistent.
2. $\Delta D>>a^2$ & $\delta D<<a^2$ restricted diffusion: the spins encounter the barriers many times during $\Delta$, but not during $\delta$.
3. $\delta D>>a^2$ rapid diffusion: in which the phase paths become similar and there is no attenuation. The formalism developed by Mitra and Halperin explains the situation intuitively in terms of a center-of-mass propagator [Mitra1995].

The diffusion along WM tracts is free and is measured to be approximately $2 \mu^2$/ms. Using this value for the intrinsic intracellular diffusion constant, given a typical in-vivo WM DTI gradient pulse length of $6-30$ms, the 3rd condition holds. This means that each intra-axonal particle samples much of the axonal cross-sectional area during each gradient pulse, for all physiologically relevant WM axon sizes. As a result, the ensemble average of the displacement of particles between the two gradient pulses is much reduced; this fact is often ignored in the analysis of DWI data.

Water in the myelin sheath is about 13% of the total water in WM, with intra-axonal water being 60% and EC water 27%. All the water is MR visible. A quick calculation of the signal remaining in WM after a typical DWI echo time of 80ms based on non-exchanging water populations with $T_2$ ~30ms in the myelin-associated water and 80ms in the IC and EC space, shows that ~67% of the remaining signal comes from intracellular spins.

The implication of this is that if the intracellular water is restricted and effectively not exchanging with the extracellular space (through the myelin), 67% of the signal does not undergo significant attenuation during a clinical DWI/DTI experiment. This would result in a 67% constant baseline in the diffusion attenuation curve as a function of $b$. From inspection of perpendicular diffusion curve in WM, particularly at high $b$-values, although a baseline may exist, it is obviously quite a bit smaller than 67%.

This apparent discrepancy could be explained in two ways:

1. If the exchange is indeed very slow and the intra-axonal water is restricted, it must have a very short $T_2$, that reduces its contribution to the signal at the echo times of clinical DWI.
2. If significant exchange occurs between the compartments, the $T_2$ times that are measured are merely apparent $T_2$ times, and the real $T_2$'s are different.

Had the former solution been true, it would probably have been discovered by now - the latter solution makes more sense. But in either case, the $T_2$ times are really not known, and exchange, $T_2$, and the diffusion signal are intimately linked. Ways of reconciling the $T_2$ and diffusion measurements will be presented.