A Theoretical Model of Water Diffusion in Brain Tissue

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Introduction: Despite widespread clinical and research use of diffusion weighted MRI, a satisfactory biophysical explanation of the signal behavior as a function of diffusion weighting is still lacking. We present a new theoretical model for water diffusion in brain tissue that reflects the basic structure of the brain at the cellular level. The model is in considerable agreement with experiment, and the model parameters are physically reasonable.

Theory: From the point of view of diffusion, it is assumed that the neurons can be described as a collection of long cylinders, each of which contributes $C(\mathbf{q},\Delta)=\exp(-b(D_T\sin^2\theta_{gc}+D_L\cos^2\theta_{gc}))$ to the signal. Here, $\mathbf{q}=\gamma\delta\mathbf{g}$, γ is the magnetogyric ratio, $\mathbf{g}$ is the diffusion gradient, δ is the duration of the diffusion gradients, Δ is the time between the leading edges of the two diffusion gradients, $b=\mathbf{q}^2(\Delta-\delta/3)$, D_L is the diffusion coefficient along the cylinder, D_T is the diffusion coefficient in the perpendicular plane, and θ_{gc} is the angle between $\mathbf{g}$ and the cylinder axis. We assume that on the scale of the diffusion time the cylinders are impermeable to water, and that their diameter is negligible compared to the diffusion distance. Therefore, a finite D_T describes bending of the cylinders (i.e. nonzero curvature) over the length scale set by the diffusion distance. The collection of cylinders in a given voxel is described by $f(\theta,\varphi)d\Omega$, the fraction of cylinders in the solid angle $d\Omega$. In the white matter fiber tracts, the distribution of cylinders tends to peak along the direction of the fiber tract [1], where as in gray matter $f(\theta,\varphi)$ tends to be closer in appearance to a sphere. In general, $f(\theta,\varphi)$ can be expanded in spherical harmonics $Y_{lm}(\theta,\varphi)$ (Laplace series), and it is shown that a few terms ($l=2$) are sufficient to properly account for the data over most regions of the brain. In addition, water outside of the cylinders is modelled as isotropic free diffusion with an effective diffusion constant D_{eff}. This amounts to assuming that during the course of the diffusion experiment, water molecules in this compartment can freely sample extracellular space as well as nonneuronal intracellular space, such as glial cells. This is consistent with experimental observations of very weak to no time dependence of the ADC [2]. Implementing all of this leads to the following expression for the signal decay, $S(\mathbf{q})$, from a narrow pulse Stejskal-Tanner spin echo experiment

$$S(\mathbf{q})/S_0=(1-f_c)e^{-bD_{\text{eff}}}+f_cC_0(b)+2\pi f_cC_2(b)\left(a_{20}Y_{20}(\Omega)+2\sum_{m=1}^{2}\text{Re}\left(a_{2m}Y_{2m}(\Omega)\right)+2\sum_{m=1}^{2}\text{Im}\left(b_{2m}Y_{2m}(\Omega)\right)\right)+\ldots \quad (1)$$

Here, f_c is the volume fraction of cylinders, S_0 is the signal amplitude at $b=0$, $\Omega=(\theta,\varphi)$ denotes the angles of $\mathbf{q}$, and the a_{2m} and b_{2m} are expansion parameters in the Laplace series of $f(\theta,\varphi)$. The functions C_l are spherical harmonic transforms of $C(\mathbf{q},\Delta)$, and can be calculated exactly for all l. Specifically,

$$C_0(b)=\sqrt{\frac{\pi}{4b(D_L-D_T)}}\,e^{-bD_T}\,\text{erf}\left(\sqrt{b(D_L-D_T)}\right),\quad C_2(b)=\left(\sqrt{\frac{\pi}{4b(D_L-D_T)}}\,\text{erf}\left(\sqrt{b(D_L-D_T)}\right)\left(\frac{3}{2b(D_L-D_T)}-1\right)-\frac{3e^{-b(D_L-D_T)}}{2b(D_L-D_T)}\right)e^{-bD_T}. \quad (2)$$

The isotropic part of the signal C_0 is identical to a previously proposed expression for diffusion of gas in the lungs [3] and NAA in neuronal tissue [4].

Materials and methods: 153 diffusion images were acquired on a coronal slice of formalin-fixed brain from a 2-day-old baboon (courtesy of Jeffrey Neil and Terrie Inder) using a standard spin echo diffusion weighted pulse sequence with a nonselective 180° pulse implemented on a 4.7 Tesla Varian system. The imaging parameters were: 64 x 64 data matrix, field of view 6.4 cm x 6.4 cm, slice thickness 1.0 mm, TR/TE = 1.3s/67ms, and the number of averages was 2. The diffusion parameters were δ/Δ = 5 ms/50ms, and 17 b-factors ranging linearly from 0.88 to 15 ms/μm^2. For each b-factor, 9 different orientations were used according to a spherical 5-design [5], and this scheme was randomly rotated for each b-factor. The acquired images were subsequently phased using a nonlinear Bayesian phasing algorithm. The real images were then fit to the model using a nonlinear least squares algorithm.

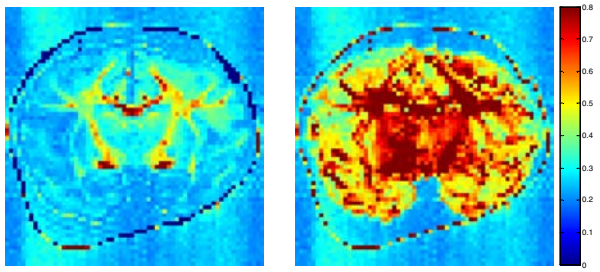

Figure 1

Results: Fig. 1 shows a coronal image of the mean square residuals of the present model (left) and the diffusion tensor model (right). It is evident that the present model does a very good job in describing the data, significantly better than the tensor model. There is some structure remaining in Fig. 1a, notably the white matter fiber bundles, such as the internal capsule. Fig. 2 displays the values of some of the fit parameters: f_c (a), D_{eff} (b), D_L (c), and D_T (d).

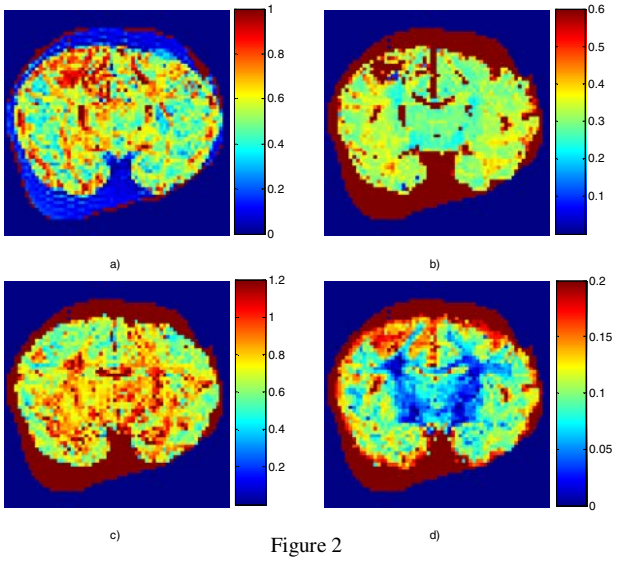

Figure 2

Discussion: The model performs very well, particularly in the gray matter. In the white matter, the residuals are larger, due to the termination of the Laplace series for $f(\theta,\varphi)$ at l = 2: Highly oriented distributions require a large number of spherical harmonics and inclusion of higher order terms into the series will decrease the residuals in the white matter fiber bundles. Likewise, the parameter maps in Fig. 2 appear reasonable and consistent with known measurements. f_c in Fig. 2a is approximately 0.47 in the gray matter, and increases to 0.82 in the white matter. D_{eff} is approximately 1.8 μm^2/ms in the formalin, and inside the brain it generally drops to around 0.35 μm^2/ms, except for the major white matter fiber bundles where it is 0.25 μm^2/ms. D_L averages to about 0.8 μm^2/ms inside the brain, which is slightly less than half the value of D_{eff} in the formalin, and with relatively low contrast across the brain. Finally, D_T is about 0.1 μm^2/ms in the predominantly gray matter regions of the brain, whereas it decreases to 0.03 μm^2/ms in the major white matter fiber tracts. This is consistent with D_T reflecting the curvature of the cylinders. Additionally, the cylindrical distribution function $f(\theta,\varphi)$ shows an expected orientational dependence on position (data not shown).

In conclusion, we have presented components of a promising biophysical model for diffusion in neural tissue, a model which reflects basic structure of the brain at the cellular level and produces reasonable estimates of the biophysical parameters.

References:

[1] J. D. Tournier et al., *Neuroimage* **23**: 1176-1185 (2004). [2] C. A. Clark et al., *MRM* **45**(6):1126-9 (2001). [3] D.A. Yablonskiy et al., *PNAS USA*. **99**(5):3111-6 (2002). [4] C. D. Kroenke et al., *MRM* **52**(5):1052-9 (2004). [5] R. H. Hardin and N. J. A. Sloane, *Discrete Comput Geom* **15**: 429-441 (1996).