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Appendix E1

Signal Model

Diffusion in the corpus callosum of healthy subjects and patients with multiple sclerosis (MS) was modeled as occurring in three compartments: restricted diffusion within an intra-axonal compartment, hindered diffusion in an extra-axonal compartment, and free diffusion in cerebrospinal fluid (CSF). This three-compartment model of diffusion in white matter minimized the number of parameters for model fitting.

Intra-axonal diffusion (S_r) was modeled by restricted diffusion in impermeable parallel cylinders of diameter a (26) as follows:

$$S_r = S_0 \exp\left\{-2\gamma^2 G^2 \sum_{m=1}^{\infty} \frac{\left[2D_r\alpha_m^2\delta - 2 + 2e^{-D_r\alpha_m^2\delta} + 2e^{-D_r\alpha_m^2\Delta} - e^{-D_r\alpha_m^2(\Delta-\delta)} - e^{-D_r\alpha_m^2(\Delta+\delta)}\right]}{D_r^2\alpha_m^6[(a/2)^2\alpha_m^2 - 1]}\right\}$$

(1),

where S_0 is the signal obtained with a b value of 0 sec/mm^2 without diffusion weighting, γ is the gyromagnetic ratio, G is the gradient strength of the diffusion-encoding gradients, D_r is the diffusion coefficient of water in the restricted compartment, δ is the diffusion gradient pulse duration, Δ is the diffusion time, a is the axon diameter, and α_m are the roots of the equation $J_1'[\alpha_m(a/2)] = 0$. J_1' is the derivative of the Bessel function of the first kind, order one. The summation in Equation 1 was taken up to m = 10, with the contribution of terms m > 10 considered negligible. The signal model for intra-axonal diffusion accounts for diffusion during the gradient pulse (δ) using the Gaussian phase distribution approximation (26,27). Instead of assuming a γ distribution of axon diameters (8), we fit the data to a single axon diameter, as in the work of Alexander et al (10).

Extra-axonal hindered diffusion (S_h) was modeled by the one-dimensional Stejskal-Tanner equation parameterized by the hindered diffusion coefficient D_h (28): $S_h = S_0\exp[-(\gamma\delta G)^2(\Delta-\delta/3)D_h]$. The extra-axonal hindered diffusivity (D_h) was assumed to be related to the intra-axonal diffusivity (D_r) using the tortuosity assumption (29): $D_h = D_r(1-f_r)$. Free diffusion in CSF was modeled as isotropic Gaussian diffusion occurring with diffusion coefficient D_{csf} (9): $S_{csf} = S_0\exp[-(\gamma\delta G)^2(\Delta-\delta/3)D_{csf}]$.

The overall signal was taken to be the sum of the intra-axonal, extra-axonal, and CSF compartment signal models weighted by their respective volume fractions: f_r for the intra-axonal compartment, f_{csf} for the CSF compartment, and $f_h = 1-f_r-f_{csf}$ for the extra-axonal compartment.

Model Fitting

Model fitting was performed on a voxelwise basis in the midline sagittal section of the corpus callosum by using Markov chain Monte Carlo (MCMC) sampling, which generated posterior distributions of the model parameters given the data. A Rician noise model was adopted for

parameter estimation. The standard deviation of the noise σ was estimated by fitting the noise level in the data, and it corresponded to a signal-to-noise ratio of 20. The total number of MCMC samples calculated for each voxel was 1800. MCMC samples were saved at intervals of 100 iterations after an initial burn-in period of 20 000 iterations.

The parameters that were estimated from the model fitting were axon diameter (a), restricted fraction (f_r), and free water/CSF fraction (f_{csf}). Broad uniform priors, with ranges given in parentheses, were used for axon diameter (0.2–40.0 μm), restricted fraction (0–1), and CSF fraction (0–1). The restricted diffusion coefficient D_r was set to 1.7 μm^2/msec, which was comparable to the estimated in vivo axial diffusivity in white matter (10). The diffusion coefficient of CSF (D_{csf}) was assumed to be that of free water at 37°C (3 μm^2/msec). If we changed some of these parameters, it would have changed the absolute value of the estimated axon diameter and density; however, the relative trends would have been preserved. For example, decreasing the restricted diffusion coefficient $\underline{D_r}$ by 20% would result in a 10% decrease in the estimated axon diameter. In principle, it would be possible to fit D_r and D_{csf} with more data at the expense of a lengthier diffusion acquisition. The mean and standard deviation of the estimates for axon diameter, restricted fraction, and CSF fraction were then calculated for each voxel by taking the mean and standard deviation over the MCMC samples.

References

26. van Gelderen P, DesPres D, van Zijl PC, Moonen CT. Evaluation of restricted diffusion in cylinders. phosphocreatine in rabbit leg muscle. J Magn Reson B 1994;103(3):255–260.

27. Neuman CH. Spin echo of spins diffusing in a bounded medium. J Chem Phys 1974;60(11):4508–4511.

28. Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. J Chem Phys 1965;42(1):288–292.

29. Szafer A, Zhong J, Gore JC. Theoretical model for water diffusion in tissues. Magn Reson Med 1995;33(5):697–712.