# Characterization of diffusion signal decay in the spinal cord based on angular dispersion of axons

Novena Rangwala[1], David Hackney[1], and David Alsop[1]
[1]*Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States*

**Purpose** Quantitative models of diffusion signal decay in white matter can potentially be used to guide interpretation of pathological changes and to extract quantitative physiologic parameters from the decay curves. A number of reports have used models of restriction across axonal membranes and myelin to fit transverse diffusion signal decay curves in white matter tracts. While these have had some success at fitting data over limited ranges of diffusion time, they struggle to successfully explain the relative independence of the signal vs. *b*-value at large diffusion times[1]. A general characteristic of these models is that they assume that axons in a tract are all perfectly aligned. As highlighted by recent *ex vivo* optical studies[2], however, even axons in a single tract are not perfectly aligned with each other. Deviations of the order of 10° are typical. Here we consider the possibility that all or most of the characteristics of the transverse diffusion signal decay curves in white matter tracts at longer diffusion time can be described by impermeable axons with a distribution of directions relative to the tract axis. A quantitative model is described and applied to diffusion-weighted (DW) spinal cord images *in vivo* across a range of *b*-values and diffusion times, Δ.

$$p(\theta)=\frac{\sin\theta}{F\left(\frac{\theta_0}{\sqrt{2}}\right)\sqrt{2\theta_0^2}}e^{-\frac{\theta^2}{2\theta_0^2}}d\theta \quad \dots [1]$$

$$S(b)=(1-f)e^{-bD_{ext}}+f\int_0^{\infty}d\theta\, e^{-bD_{axon}\sin^2\theta}p(\theta) \quad \dots [2]$$

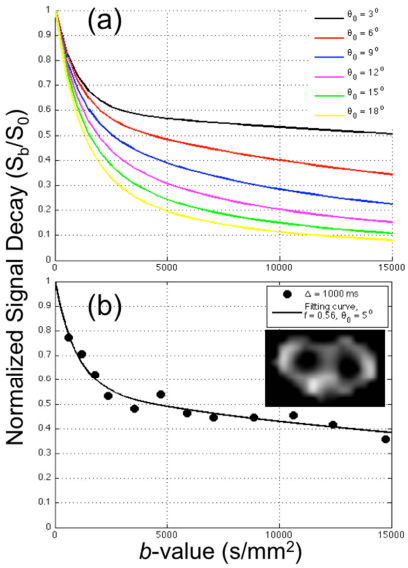


**FIGURE 1**: (a) shows theoretical signal decay curves with $\theta_0$ = 3°–18° and $f$ = 0.6, and (b) the fit to white matter from *in vivo* SC data with Δ = 1000 ms and *b*-values of up to 14750 s/mm$^2$ in one volunteer. The DW image with $b$ = 14750 s/mm$^2$ is shown as an inset.

**Methods** *Theory*: Consider a Gaussian distribution of axon angles within the spinal cord, which can be written as Eq. [1], where $F$ is the Dawson integral and $\theta_0$ is the mean dispersion angle of the axons in the region of interest (ROI). Assuming that transverse diffusion through the myelin layers surrounding an axon is zero due to the high impermeability of myelin and the axon radius is small compared to 1/q, we can express the measured transverse diffusion coefficient ($D_{trans}$) as a function of the longitudinal diffusion within the axon ($D_{axon}$) weighted by its angle ($\theta$) with the spinal cord axis, as $D_{trans} = D_{axon}\sin^2\theta$. It is then possible to model the signal decay with *b*-value ($b$) as Eq. [2], where $D_{ext}$ is the extra-axonal diffusion coefficient and $f$ is the fraction of the signal coming from axons (axonal fraction).

*In-vivo data*: The model was used to fit data acquired with a DW echo planar imaging (EPI) acquisition using stimulated echo acquisition mode (STEAM[3]) excitation in the cervical spinal cord (C4-C5) in six healthy volunteers (3 female, age = 18–32 years). Twelve DW images were acquired with progressively increasing *b*-values and repeated for Δ = 250, 500, 1000 ms. The maximum possible *b*-values corresponding to increasing Δ were 3650, 7350, and 14750 s/mm$^2$, and increased spacing was used between the higher *b*-values.

Images were reconstructed from the raw *k*-space data. After subtraction of the noise floor, an ROI was selected to include (a) the entire spinal cord (~80 pixels), and (b) white matter within the posterior funiculus (~8 pixels). For each volunteer, the signal decay curves ($S_b$) for the selected Δ were input to Eq. [2], with unknowns $S_0$, axonal signal fraction ($f$), and average dispersion angle ($\theta_0$). $D_{axon}$ and $D_{ext}$ were assumed to be 2 × 10$^{-3}$ mm$^2$/s, the average longitudinal diffusion in spinal cord, and 1.03 x 10$^{-3}$ mm$^2$/s, the trace diffusion coefficient in spinal cord, respectively[4]. These ADCs were pre-set to improve the robustness of the fitting by limiting the number of unknown values. Two-tailed *t*-tests were used to compare fitting parameters $f$ and $\theta_0$ over Δ pairs. The routine was implemented in MATLAB (The Mathworks, Natick, MA).

**Results** Simulations show the signal decay curves as a function of angular dispersion. (Fig. 1a) for $f$ = 0.6. These signal decays show the initial faster decline and then persistent high *b*-value signal typically seen *in vivo*.

Applying Eq. [2] to the ROI from the white matter region of the spinal cord shows excellent fits (Fig. 1b) out to $b$ ~ 14750 s/mm$^2$ (image shown in Fig. 1b inset). For the entire cord ROI, the required axonal dispersion is larger, representing contamination of gray matter regions of the cord. Importantly, angular dispersions of only 11° (Table 1) can produce the main features of the white matter decay curves.

**Discussion and Conclusions** The results emphasize that angular dispersion of only 10° at the microscopic level can have a major effect on diffusion models of transverse diffusion in white matter tracts. Such dispersion can potentially explain all of the signal characteristics of high *b*-value diffusion curves at intermediate to long diffusion times. Further work combining the angular dispersion model with more sophisticated models of intra-axonal diffusion[5] will extend the work to shorter diffusion times and potentially enable the separation of axon size and angular dispersion contributions to the diffusion decay curves. Recognizing the importance of angular dispersion in high *b*-value diffusion images of white matter may also alter the qualitative interpretation of contrast and pathological alterations in such diffusion weighted images and in derived anisotropy parameters. These observations may aid in the understanding of pathology resulting from spinal cord injury and can potentially be extended to apply to more complicated axonal structures in the brain.

**TABLE 1** shows the fitting results (mean ± SD) across volunteers, applied to ROIs from the whole cord and from WM. The *s indicate statistically significant differences in $\theta_0$ between Δ = 500ms and 1000ms (α = 0.047). No other pairs showed statistically significant differences.

| Δ (ms) / | Cord ROI | | WM ROI | |
|---|---|---|---|---|
| $b_{max}$ (s/mm$^2$) | $f$ | $\theta_0$ (°) | $f$ | $\theta_0$ (°) |
| 250 / 3650 | 0.65 ± 0.25 | 19.1 ± 12.9 | 0.72 ± 0.28 | 11.6 ± 7.3 |
| 500 / 7350 | 0.51 ± 0.1 | 14.2 ± 5.8 | 0.76 ± 0.16 | *11.3 ± 4.5 |
| 1000 / 14750 | 0.43 ± 0.08 | 10.9 ± 2.6 | 0.65 ± 0.2 | *6.5 ± 2.7 |

**References**: (1) Nilsson *et al.*, *Magn Reson Imag*, 27:p176, 2009 (2) Erturk *et al.*, *Nature Med*, 18:p166, 2012 (3) Frahm *et al.*, *J Magn Reson*, 64:p81, 1985 (4) Holder *et al.*, *Am J Neurorad*, 21:p1799, 2000 (5) Assaf *et al.*, *Magn Reson Med*, 59:p1347, 2008.