The Importance of Angular Dispersion in Physiological Modeling of Transverse Diffusion Signal Decay

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Introduction: Fitting transverse diffusion signal decay to physical models can be used to estimate physiological parameters such as axonal diameters and distributions (a.d.d.)[1] and axonal packing[2], among others. These models generally assume that axons are parallel to the direction of the fiber tract. Recent optical imaging studies have indicated that axons within a single white matter (WM) tract are not perfectly aligned in the direction of the tract[3,4]; therefore, diffusion signal decay may also depend upon the angular spread, or dispersion, of axons within WM tracts. We previously reported initial results using an angular dispersion model in the long diffusion time limit to characterize transverse diffusion curves in the spinal cord[5]. Here, we report results using a more comprehensive evaluation of transverse diffusion signal decay by incorporating the angular dispersion factor into AxCaliber[1], thereby including other parameters such as Δ and a.d.d. as part of the model. Using this comprehensive model, we demonstrate the differences in derived microscopic diffusion parameters if axonal dispersion is not included in the model.

Equations:

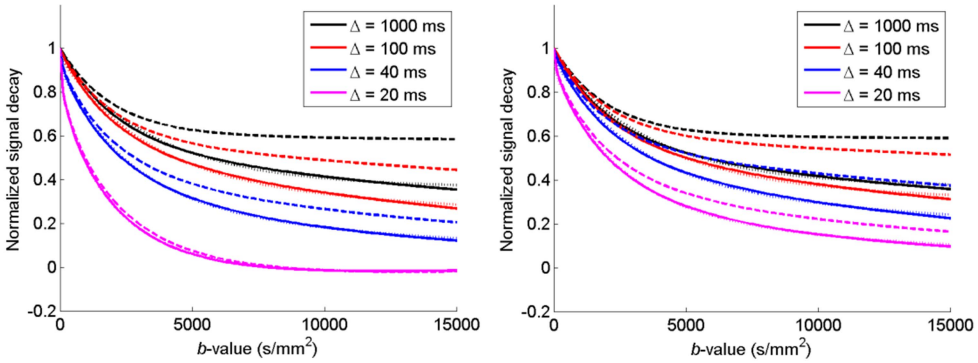
1 $$\frac{S_b}{S_0} = (1-f)e^{-bD_{ext}} + f\sum_{\theta} e^{-bD_{axon}\sin^2\theta} p(\theta)$$

2 $$S_b = S_0(1-\sum_i W_{a_i})e^{-bD_{ext}} + \sum_i W_{a_i} s(a_i, b, \Delta, D_{\text{int}})\sum_{\theta} e^{-bD_{axon}\sin^2\theta} p(\theta)$$

Methods: The previously proposed axonal dispersion model in Eq. [1] was incorporated into the expression for diffusion signal decay using AxCaliber in Eq. [2], where $s(a_i, b, \Delta, D_{int})$ is the expression for the diffusion dependent signal contribution from a single axon with radius a_i, and W_{a_i} represents the relative fraction of the axons with radius a_i. $p(\theta)$ in Eq. [1] denotes the angular probability density function (PDF) of the axons with a characteristic angle given by θ_0[5]. In the original AxCaliber model, D_{int} is the ADC along the diffusion direction that is assumed perpendicular to the fiber direction. In the combined model, the ADC along the diffusion direction is expressed as $D_{int}\cos^2\theta$, which approximates to D_{int} for well-aligned fibers.

Two theoretical analyses were performed using AxCaliber and the combined models to evaluate the signal decay (a) assuming a range of diffusion times from 20 ms to 1000 ms, and (b) with two different ranges of axonal radii. In the first analysis, Eq. [2] was used to simulate signal decay curves with Δ = 20, 40, 100, and 1000 ms, and the following parameters derived from prior fits to transverse diffusion in spinal cord: S_0 =1.0, f = 0.6, θ_0 = 6°, D_{ext} = 0.5 × 10^{-3} mm^2/s, D_{int} = 0.5 × 10^{-3} mm^2/s, and D_{axon} = 2.0 × 10^{-3} mm^2/s. The resulting curves were compared with AxCaliber curves at the same diffusion time (a) assuming no angular dispersion (θ_0 = 0°) but otherwise with the same parameters, and (b) as a fit to the original curves, therefore resulting in different values for S_0, f, and D_{ext}. All of these studies assumed a (standard) a.d.d.[6] with radii ranging from 1.03 μm to 6.56 μm derived from a histologic study of spinal cord. For the second analysis, the relative distribution of axonal radii was maintained, with the radii assumed to be three-fourths of the radii in the original distribution[6] (compressed). As a result, the axonal radii in this evaluation range from 0.78 μm to 4.92 μm. All other parameters, including the range of diffusion times, were maintained at the same values as in the previous simulation and similar curves were plotted.

Results and Discussion: Figures 1 and 2 show the results of the theoretical evaluations using the standard and the compressed a.d.d., Tables 1 and 2 show the corresponding fitted parameters when AxCaliber was used without angular dispersion. Results show that the differences between the combined model and the AxCaliber model are more apparent at longer Δ, although they are still substantial even at the Δ ~ 40 ms typical of clinical studies, especially when the a.d.d. comprises smaller axons and tighter a.d.d. Importantly, although using the AxCaliber model on its own resulted in good fitting to the original decay curve, the fitted parameters (Tables 1 and 2) were found to be very different from their corresponding true values, further highlighting the necessity to include angular dispersions as a factor in models of transverse diffusion signal decay.



Figures 1 (left) and 2 (right) *show the results of the theoretical evaluation on the standard and compressed a.d.d., respectively, Solid lines show the combined model using Δ = 20 – 1000 ms, dotted lines (where distinctly seen) show the fit using AxCaliber with θ_0 = 0°, and dashed lines show the AxCaliber curves with all parameters the same as in the corresponding combined model.*

Δ (ms)	S_0	f	D_{ext} (mm^2/s)
1000	0.9610	0.3907	0.2753 x 10^{-3}
100	0.9639	0.3913	0.2979 x 10^{-3}
40	0.9527	0.3998	0.3698 x 10^{-3}
20	0.9832	0.5457	0.5770 x 10^{-3}

Δ (ms)	S_0	f	D_{ext} (mm^2/s)
1000	0.9607	0.3907	0.2745 x 10^{-3}
100	0.9637	0.3904	0.2848 x 10^{-3}
40	0.9621	0.3932	0.3140 x 10^{-3}
20	0.9495	0.4011	0.3879 x 10^{-3}

Tables 1 (left) and 2 (right) *show the fitting parameters when AxCaliber without dispersion was used to fit the combined curves with angular dispersion using θ_0 = 6°.*

Conclusions: This study has illustrated that even for small angular dispersions of θ_0=5-10°, not incorporating the dispersion characteristic into models of diffusion signal decay can lead to inaccurate quantification of other parameters related to diffusion and axonal microstructure. We recommend that axonal dispersion be incorporated into models of diffusion signal decay.

References: (1) Assaf *et al.*, *MRM* 59: p1347, 2008 (2) Ford *et al.*, *JMRI* 8: p775, 1998 (3) Erturk *et al.*, *Nat Med* 18: p166, 2011 (4) Farrar *et al.*, *Biophys. J* 100: p1362, 2011 (5) Rangwala *et al.*, *ISMRM* 2013, p3089 (6) Makino *et al.*, *Spine* 21: p1010, 1996.