Dependence of Temporal Diffusion Spectroscopy on Axon Size in White Matter Tracts of Rat Spinal Cord

Junzhong Xu[1], Kevin D Harkins[1], R Adam Horch[1], Mark D Does[1], and John C Gore[1]
[1]*Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States*

Introduction: Diffusion-weighted MRI provides a non-invasive means to characterize the microstructure of biological tissues. In white matter (WM), the transverse diffusivity has been shown to be sensitive to axon size and hence allows the possibility of measuring axon size distributions quantitatively (1). However, conventional diffusion measurements use pulsed gradient spin echo methods with relatively long diffusion times, and require high b values to increase sensitivity to smaller axons, which in turn significantly decreases SNR and increases total scanning time. In the current work, an oscillating gradient spin echo (OGSE) method was used to acquire temporal diffusion spectra with relatively short diffusion times and low b values. The results show that the temporal diffusion spectrum is sensitive to the mean axon size of WM tracts of fixed rat spinal cord, ranging from very small (~1.43μm) to large (~5.26μm) axons. A new parameter R, i.e. dispersion rate of ADC vs gradient frequency, is suggested as a sensitive indicator of mean axon size.

Methods: *Theory*: The ADC of water obtained by the cosine-modulated OGSE method can be expressed analytically inside various geometries (2), namely

$$\mathrm{ADC}(f) = 8\pi^2 \sum_k \frac{B_k a_k^2 D^2 f^2}{\delta (a_k^2 D^2 + 4\pi^2 f^2)^2} \left\{ \frac{(a_k^2 D^2 + 4\pi^2 f^2)\sigma}{2 a_k D} - 1 + \exp(-a_k D\delta) + \exp(-\frac{1}{2} a_k D \cdot TE)(1 - \cosh(a_k D\delta)) \right\} \quad [1]$$

where D is the intrinsic diffusion coefficient, σ is the gradient duration, TE is the echo time and a_k, B_k are structure and size dependent parameters (2). Note that ADC disperses with both microstructure size and gradient frequency, and in the relatively low frequency range (<200Hz), the dispersion is approximately linear (3) which simplifies the data analysis.

Tissue Preparation: Spinal cord samples were obtained (one each) from two male Sprague Dawley rats (300-420 g). Cervical sections ≈1 cm in length were cut and immediately placed in 0.5% paraformaldehyde/4% glutaraldehyde in phosphate buffer for 48 h. The samples were then washed in phosphate-buffered saline solution for at least 3 days prior to diffusion measurements (4).

Diffusion Experiments: Diffusion measurements were performed on a Varian 4.7T MRI system. An apodised cosine-modulated gradient waveform (5) was used. Each gradient waveform has a duration of 25ms, b=400s/mm^2, TE=66.5ms, TR=2s, slice thickness 2mm, FOV=5×5mm, matrix size 64×64 and NEX=8. Diffusion gradients were applied perpendicular to the WM tracts and four gradient frequencies were used, evenly ranging from 40Hz to 160Hz, corresponding to effective diffusion times approximately from 6.25ms to 1.56ms.

Computer Simulation: A computer simulation using the finite difference method (6) was performed to investigate the theoretical dependence of temporal diffusion spectra on different mean axon diameters. White matter was modeled as parallel cylinders on a hexagonal grid. The intrinsic diffusion coefficients were assumed to be 2.0μm^2/ms. The cylinders have different axon diameters corresponding to different WM tracts (see Fig.3) (7). The cylinder volume fraction is 80.57%. Δx=0.1μm, Δt=1μs. All other parameters were the same as used in the diffusion experiments.

Results and Discussion: Fig.1 shows how simulated ADC's of hexagonal cylinder arrays disperse linearly with gradient frequencies (<160Hz), and that different axon diameters yield different dispersion rates. Hence, a new parameter R, i.e. the dispersion rate of ADC vs. frequency, was defined to capture this behavior. Fig.2 shows ROI's of WM tracts, and Fig.3 shows the ADC dispersion rate R as a function of mean axon size, which is qualitatively consistent with the numerical prediction. An interesting result is that the ADC dispersion rate has an approximately linear dependence on mean axon size in different WM tracts, which implies that ADC dispersion rate may be a sensitive indicator to measure mean axon diameter, and hence is capable of differentiating different WM tracts. It should be emphasized that the method used in the current work used low b values and hence the Gaussian diffusion approximation is still valid. Therefore, measurement of an ADC dispersion rate requires only two points, and this can potentially provide a fast technique to measure mean axon size in white matter.

References: (1) Assaf MRM 2008. (2) Xu JMR 2009. (3) Xu MRI 2011. (4) Dula MRM 2010. (5) Does MRM 2003. (6) Xu PMB 2007. (7) Harkins MRM (in press). **Acknowledgement**: NIH CA128323, NS074469 and EB001744.

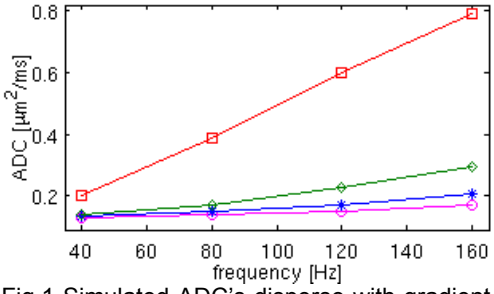

Fig.1 Simulated ADC's disperse with gradient frequencies. Note that a larger axon diameter yields a larger dispersion rate.

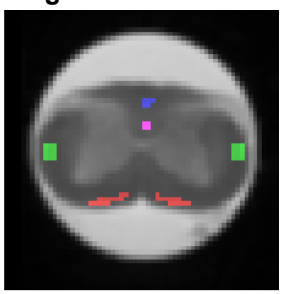

Fig.2 ROI's of WM tracts overlaid on a T2-weighted image: VST(red), RST(green),FG(blue),dCST(purple).

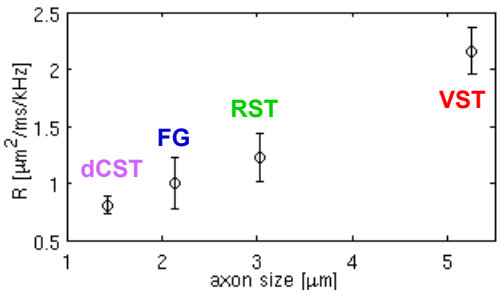

Fig.3 A typical ADC dispersion rate as a function of mean axon size (sample#1). Errorbars are standard deviations in each WM tracts.