Mapping mean axon diameters using diffusion MRI with oscillating gradients

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Audience: Investigators who are interested in characterizing neural microstructure quantitatively using diffusion MRI.

Purpose: It is well known that nerve conduction velocity is directly proportional to axon diameter, and hence mapping axon diameter has significant clinical and research potential to provide information about nerve function. Previously, such histological information could be obtained only via invasive tissue biopsies. Recently, diffusion MRI based methods, such as AxCaliber[1] and ActiveAx[2], have been developed to map axon diameters non-invasively. However, because of the relatively long diffusion times used in conventional pulsed gradient spin echo (PGSE) methods, the sensitivity to small axons is significantly reduced. To compensate, PGSE-based methods usually use very large q or b values and long scanning times. The current study presents a different approach that uses the oscillating gradient spin echo (OGSE) method[3] to reduce effective diffusion times and thereby significantly enhance the detection sensitivity to small axons.

Methods: *Theory*: The diffusion signal of white matter can be expressed as the sum of signals arising from intra- and extra-axonal space, namely, $S = f_{in} \cdot S_{in}(AxD_{mean}, D_{in}) + (1-f_{in}) \cdot \exp(-b * D_{ex})$ [1]. Note that S_{ex} is assumed to be hindered diffusion with a constant diffusion coefficient[1] D_{ex}, and S_{in} is restricted diffusion inside cylindrical axons with a mean axon diameter AxD_{mean} and intrinsic diffusion coefficient D_{in}. For cosine-modulated OGSE measurements, the analytical signal attenuation has been derived, namely[3],

$$S_{in}(G) = \exp\left\{-2(\gamma g)^2 \sum_n \frac{B_n \lambda_n^2 D_{in}^2}{(\lambda_n^2 D_{in}^2 + (2\pi f)^2)^2} \left\{ \frac{(\lambda_n^2 D_{in}^2 + (2\pi f)^2)}{\lambda_n D_{in}} \left[\frac{\delta}{2} + \frac{\sin(4\pi f \delta)}{8\pi f} \right] - 1 + \exp(-\lambda_n D_{in} \delta) + \exp(-\frac{1}{2}\lambda_n D_{in} TE)(1 - \cosh(\lambda_n D_{in} \delta)) \right\} \right\} \quad [2]$$

where f is the oscillation frequency, δ the gradient duration, TE the echo time, λ_n, B_n are structure dependent parameters.

Tissue preparation: Six Sprague Dawley rats were euthanized and cervical sections ≈ 1 cm in length were cut and immediately placed in fixatives as suggested previously[4]. After imaging measurements, samples were prepared, cut and stained with Toluidine blue for histology using light microscopy (40X).

Ex vivo imaging: All images were acquired with 4-shot echo-planar acquisitions on a 7T Varian magnet with a 12mm microgradient coil. Field-of-view = 5×5 mm, matrix size = 64×64, yielding a spatial resolution of 78 μm. TR = 4 sec, TE = 58 ms, slice thickness = 2 mm, NEX = 80, and the diffusion gradient was applied perpendicular to the spinal cord tracts. The apodised cosine-modulated waveform[5] was used with five frequencies (50, 100, 150, 200, 250 Hz) and five b values (0, 500, 1000, 1500, 2000 s/mm^2).

Results and Discussion: For each rat spinal cord, ROIs corresponding to six different white matter tracts were manually drawn on the corresponding T_2-weighted images (see Fig.1). The corresponding regions on stained histological slices were segmented, and then the area-weighted mean axon diameters[2,4] were obtained. Fig.2 shows the signal attenuations (open markers) of six white matter tracts of a representative spinal cord. These data were fit to Eq.[1] providing estimates of the mean axon diameter (fitted AxD), intra-axonal proton fraction (f_{in}), intra- and extra-axonal diffusion coefficients (D_{in} and D_{ex}) for each white matter tract. Fig.3 shows correlations of parameter estimates with mean axon diameters obtained from histology. It is clear that the fitted AxDs correlate well with histological mean AxDs (correlation coeffient r = 0.83 and p < 0.001), and the identity line (perfect match) is within the 75% confident intervals (black dashed lines) of the linear fitting. The other fitted parameters showed little correlation with histological mean AxDs. The large variations of D_{in} and D_{ex} showed is presumably because, even with OGSE at f = 250 Hz, the diffusion time is not short enough to identify intrinsic diffusion coefficient.

Conclusion: Due to the relatively long diffusion times used, small axons are usually overestimated using PGSE-based models[2]. In the current study, the OGSE measurements used much shorter effective diffusion times to enhance detection sensitivity to small axons, and the fitted mean axon diameters are in good agreement with histology.

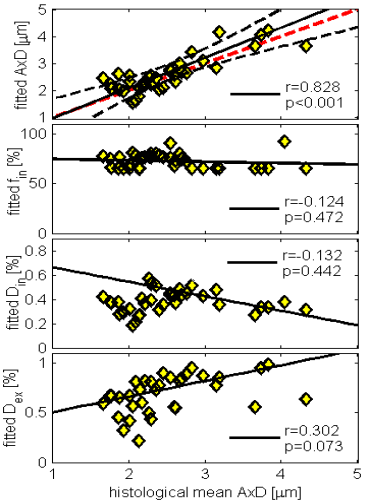

Fig.3 Summarized correlations of all fitted parameters vs mean axon diameters obtained from histology. Black lines are linear fittings, and r (correlation coefficient) and p values were given by Pearson correlations.

References:
(1) Assaf et al. MRM 2008
(2) Alexander et al. Neuroimage 2010
(3) Xu et al. JMR 2009
(4) Harkins et al. MRM 2012
(5) Does et al. MRM 2003

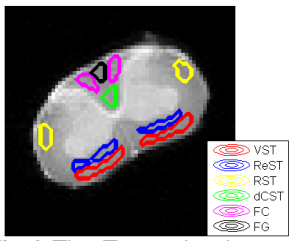

Fig.1 The T_2-weighted image of a representative spinal cord overlaid with ROIs of six different white matter tracts.

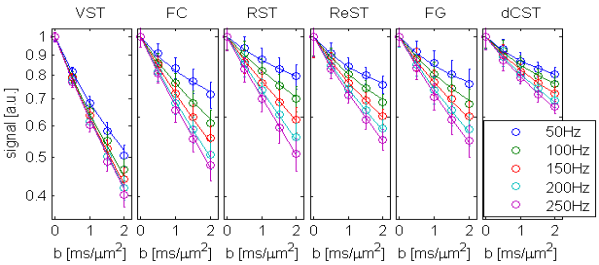

Fig.2 Signal attenuation vs b values of experimental data (markers) fitted to Eq.[1] (curves). The errorbars represent the standard deviations inside each ROI.