Optimized diffusion MRI protocols for estimating axon diameter with known fibre orientation

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Introduction

We present a method that provides a diffusion weighted MRI protocol for directly estimating microstructural properties like axon diameter and density in white matter with uni-directional distribution of fibres. Feasibility of estimating axon diameter distribution [1, 2] or mean axon diameter [3] with diffusion MRI has previously been demonstrated. A computational framework has been developed in [4] which optimizes a multi-shell HARDI acquisition for sensitivity to those parameters without knowledge of fibre orientation. We adapt this framework to provide an optimized set of diffusion weightings and gradient directions for structures like the spinal cord (SC) with known single fibre orientation (i.e. single direction approach (SD)). We show that those protocols improve efficacy of axon measurements particularly in the presence of low signal-to-noise ratio (SNR). Using computer simulations we tested the ability of our method to estimate axon information on low SNR data and compared the results with orientation independent protocols. Finally we demonstrated the feasibility of measuring axon diameter and density in a fixed monkey spinal cord on a 4.7T experimental scanner using the SD approach.

Methods

Protocol Optimization: The optimization framework provides protocols with M sets of N diffusion weighting directions and a diffusion weighting b-factor assigned to every set. By minimizing the Cramér-Rao-Lower-Bound (CRLB) of axon parameters estimation the optimal combination of b-values is found. In the original method the N diffusion gradient directions are fixed to provide orientation independent (OI) measurements. For the single direction protocol we relax this condition and allow all N*M gradient directions to be optimized individually. Using this modified method we produce a single direction protocol of 120 diffusion-weighted directions (N=30, M=4) for a maximum gradient strength of 300 mT/m achievable on an experimental 4.7T Varian scanner. The final protocol is presented in Table 1. For reference we also generate an OI protocol using the original framework and the same experimental setting. *Synthetic Data:* Computer simulations are carried out to assess the accuracy of the SD protocol under low SNR conditions. For each experiment we generate 1000 samples of noise-free data with diameters 2µm, 4µm and 10µm. We simulate a SNR of 15:1 by adding Rician noise to to each of the data points. A Markov-Chain-Monte-Carlo (MCMC) approach as in [4] then estimates the posterior distribution of the model parameters from the sampled data. *Post-mortem monkey SC:* A perfusion fixated cervical spinal cord of a green monkey [5] is scanned on a 4.7T Varian experimental scanner using the SD protocol (Table 1) together with 12 additional b=0 acquisitions interleaved with the diffusion weighted data. All procedures for handling experimental animals followed guidelines approved by relevant authorities. Imaging parameters were: TE=59ms, TR=2s, slice thickness=1.2mm, 30 slices, FOV=9x9mm^2, 64x64 matrix, 2-D interpolated to 128x128. We fit a model that assumes a single axon diameter as described in [4] based on a simplification of the AxCaliber model [1] and use the tortuosity model of [6]. The posterior distributions of the model parameters, such as the diameter D and volume fraction f of the restricted compartment are estimated by an MCMC method on a voxel-by-voxel basis. To stabilize the fitting, the diffusivity in the parallel direction is fixed to 0.45µm^2/ms and f is constrained to be in the range of [0.5, 1.0]. The mean of the posterior distribution over D is reported as the index of axon diameter and the axonal density is computed as $a=f/4\pi/D^2$.

set	b [s/mm^2]	Gradient directions $N_\parallel$	$N_\perp$
1	3082.36	0	30
2	2356.83	14	16
3	13463.65	0	30
4	2366.71	1	29

Table 1: Optimized diffusion weightings and gradient directions. $N_\parallel$ is the number of parallel gradient directions; $N_\perp$ is the number of directions perpendicular to the assumed fibre

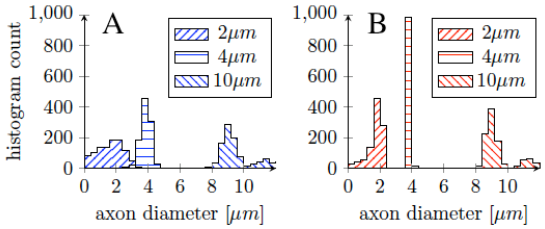

Figure 1: Histogram of MCMC samples for (A) orientation independent and (B) single direction protocol for diameters 2,4 and 10 µm

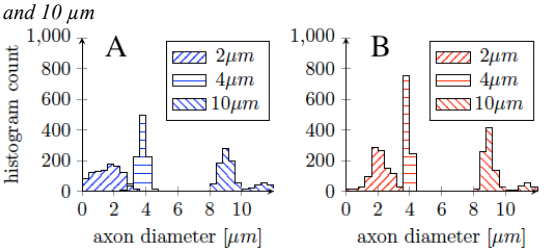

Figure 2: Histogram of estimated diameters (A) for orientation independent and (B) single direction protocol with maximal angular error of 10% in sample orientation

Results

Synthetic data: Figure 1 shows histograms of axon diameters sampled from synthetic data from of the OI protocol (A) and our modified SD approach (B). All fibre samples are oriented parallel to the direction assumed in the protocol. The SD protocol clearly lowers the sample variance compared to the reference OI protocol particularly for smaller diameters 2µm and 4µm. In Figure 2 the same experiment is repeated but we introduce some uncertainty in fibre orientation. We allow a maximal angular error of 10% between the sample and the assumed direction and distribute the sample orientations uniformly over that range. As expected, the sample variance is increased in the SD protocol is similar to the previous experiment in the OI protocol. However, the accuracy of diameter estimation remains to be higher in the SD protocol than in the OI protocol. *Post-mortem monkey SC:* Figure 3 presents maps of axon diameter (A) and axonal density (B) in the upper cervical spinal cord obtained from the post-mortem monkey SC scan. We observe left-right symmetry of axon diameter and density in all tracts, which corresponds with the known structure of the SC. Parameters are also consistent along the SC within the limits of anatomical variation. Further we can discriminate axon diameter and axonal density between anatomically different white matter tracts. Dorsal and lateral sensory tracts show small axons diameters between 1-4µm and a density of 0.03-0.08µm^{-2}. The smallest axon calibers (<1.5µm) are observed in the dorsal columns (DC) while mean axon size in the anterolateral column (ALC) is 1.5-2.5µm. The largest axons (3-4µm) are found in the corticospinal tract (CST) together with low density of 0.01-0.02µm^{-2}.

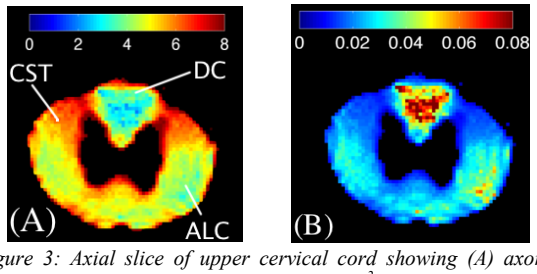

Figure 3: Axial slice of upper cervical cord showing (A) axon diameter in µm and (B) axonal density in µm^{-2} in the corticospinal tracts (CST), anterolateral column (ALC) and dorsal column (DC)

Discussion

The method provides optimal diffusion weightings and gradient directions for estimating of axonal diameter by exploiting the single fibre orientation of structures like the spinal cord. Computer simulations clearly show improved efficacy of axonal diameter and density measures compared to an orientation independent approach in low SNR regimes. A preliminary study on post-mortem monkey SC demonstrate the feasibility of measuring of axon diameters and density in biological tissue samples under low SNR conditions and high image resolution. It should be noted that we chose the number of diffusion weighted directions and different b-factors to be significantly smaller in contrast to other approaches like [1]. The moderate number of acquisition makes it possible to apply a similar protocol in-vivo and will be addressed in future studies. This limits us to estimate a single index of axon diameter rather than being able to characterize the axon diameter distribution. However, in this study we show the ability of our axonal statistics to discriminate different white matter tracts in the post-mortem monkey spinal cord based, although further work needs to validate those findings with histology.

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[1] Assaf et al., *Magn Reson Med* **59** (2008) [2] Barazany et al., *Brain* **132** (2009) [3] Alexander et al., *Proc ISMRM* (2009) [4] Alexander et al., *Magn Reson Med* **60** (2008) [5] Lundell et al., *Proc ISMRM* (2009) [6] Stanisz et al, *Magn Reson Med* **37** (1997)