A comparative study of axon diameter imaging techniques using diffusion MRI

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INTRODUCTION Axon diameter and density provide information about the function and performance of white matter pathways. Direct measurement of such microstructure features offers more specific biomarkers than DTI indices, such as diffusivities and anisotropy. A number of techniques to measure axon diameter statistics using diffusion MRI have been proposed in the literature, ranging from model-based approaches [1-4] to Q-space imaging [5], but little is known of their relative performance and consistency. In particular, within the family of model-based techniques, each may assume a different underlying tissue model or apply a different imaging protocol. It is unclear how such variations impact the estimates of microstructure features of interest. In this work, we aim to gain some insight into this issue by applying several representative model-based approaches to image the same tissue sample and quantitatively compare their microstructure estimates.

METHOD We consider a set of three techniques that enable us to examine both the effect of assuming different underlying tissue model and that of imaging with different acquisition protocol. Each technique assumes either the composite hindered and restricted model of diffusion (CHARMED) [6-7] or the minimal model of white matter diffusion (MMWMD) [2,4], and images data with either the AxCaliber protocol [1,3] or the Active Imaging-optimized AxCaliber protocol (ActiveAx) [2,4]. The three model-protocol combinations that we evaluate are CHARMED + AxCaliber (CAC), MMWMD + AxCaliber (MAC), and MMWMD + ActiveAx (MAA). The CHARMED model assumes that white matter can be modeled as a population of impermeable cylindrical axons embedded in a homogeneous medium. The axon diameters follow a two-parameter Gamma distribution and the intra-cellular compartment as a whole has some volume fraction v. The MMWMD model reduces the axon diameter distribution into a single axon diameter, which provides a summary statistic that relates to the mean axon diameter weighted by the cross-sectional area of axons, and adds a compartment of isotropic restricted diffusion to capture observed restrictions parallel to axons potentially from water trapped in glial cells. The AxCaliber protocol consists of a series of pulsed gradient spin echo measurements with varying diffusion times and gradient magnitudes and diffusion gradients are always applied perpendicular to the axons in the imaged sample. The ActiveAx protocol differs from the AxCaliber protocol in two ways: 1) it applies diffusion gradients along a dense set of directions sampled uniformly on the sphere, i.e., the gradient sampling scheme of high angular resolution diffusion imaging (HARDI); 2) it selects a much smaller set of diffusion times and gradient magnitudes that are most sensitive to the microstructure features of interest via Active Imaging optimization [2]. In summary, AxCaliber supports the estimation of a model of full axon diameter distribution but only for a priori known orientation of axons, while ActiveAx enables the estimation of axon diameter statistic for unknown orientation but at the cost of providing only a single "typical" diameter estimate.

IMAGING Ex-vivo diffusion weighted imaging (DWI) of a 32-month perfusion-fixed Vervet monkey was acquired on a 4.7-T Varian experimental system with maximum gradient strength $|\mathbf{G}|$ = 400 mT/m (See [8] for details in brain preparation). Using a conventional spin-echo with single-line readout, the datasets for the AxCaliber and ActiveAx protocols were acquired in two separate sessions. Each dataset consists of 360 images. Each image has isotropic 0.5x0.5x0.5 mm^3 voxels and 10 sagittal slices centered on the midsagittal plane of the corpus callosum. For AxCaliber, the data was acquired using a stimulated echo (STEAM) DWI sequence (TE = 23 ms, TR = 2500 ms) with a single diffusion-weighting gradient perpendicular to the midsagittal plane of the corpus callosum. The diffusion gradient pulse width (δ) was 3.5 ms and the time between gradient onset (Δ) was 15, 25, 50, 75, and 100 ms. For each Δ, diffusion gradient magnitude (G) was varied from 0 to 335 mT/m in 72 equal increments. For ActiveAx, the data was acquired using a pulsed-gradient spin-echo (PGSE) DWI sequence (TE = 36 ms, TR = 2500 ms). The protocol consists of three HARDI shells with the number of diffusion gradient directions [103, 108, 78], G = [300, 210, 300] mT/m, δ = [5.6, 7.0, 10.5] ms, and Δ = [12, 20, 17] ms, corresponding to b-values = [2084, 3084, 9550] s/mm^2. Ethical rules concerning the handling and care of live animals were followed.

ANALYSIS To quantitatively assess the techniques, we use each method to generate axon diameter estimates in 3 manually delineated regions-of-interest (ROI): the genu, midbody, and splenium of the midsagittal slice of the corpus callosum (Fig. 1). The ROIs are 8 voxels in size, placed at the identical locations in both the AxCaliber and ActiveAx datasets, carefully chosen to avoid partial-volumed voxels near the boundary of the corpus callosum. For the AxCaliber dataset, we fit the data at each voxel to both the CHARMED and the MMWMD models; for the ActiveAx dataset, we fit to the MMWMD model. The fitted parameters in the CHARMED model are the Gamma distribution parameters, α and β, the intra-cellular volume fraction, v_{ic}, and the diffusivity of the extra-cellular compartment, d_{ec}; the fixed parameter is the intra-cellular diffusivity, d_{ic}, set to $1.5\text{x}10^{-9}$ m^2/s. The fitted parameters in the MMWMD model are the single axon diameter and v_{ic}; the fixed parameters are d_{ic}, set to $0.6\text{x}10^{-9}$ m^2/s, the volume fraction of the isotropically restricted compartment, set to 0.1. In this model, d_{ec} is set to $(1\text{-}v_{ic})d_{ic}$ via a simple tortuosity model [9]. To account for the T1 effect in the STEAM-based AxCaliber protocol, the CHARMED model also fits for T1 while the MMWMD model fixes T1 to the independently measured value of 600 ms which shows little variation across the corpus callosum.

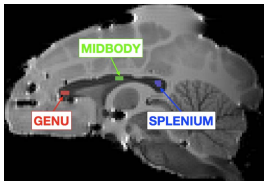

Fig. 1 An illustration of the manually placed ROIs in the midsagittal plane of the corpus callosum

	GENU	MIDBODY	SPLENIUM
CAC	1.39 ± 1.25	4.60 ± 3.13	2.12 ± 1.58
MAC	2.88 ± 1.86	10.17 ± 4.63	1.95 ± 1.48
MAA	2.07 ± 1.37	4.02 ± 2.58	1.08 ± 0.32

Table 1. Axon diameter index estimates (μm)

	GENU	MIDBODY	SPLENIUM
CAC	0.61 ± 0.07	0.54 ± 0.12	0.87 ± 0.02
MAC	0.59 ± 0.04	0.71 ± 0.08	0.72 ± 0.11
MAA	0.55 ± 0.12	0.63 ± 0.20	0.66 ± 0.12

Table 2. Intra-cellular volume fraction estimates

RESULT For the MMWMD model, we report the mean and standard deviation of the single axon diameter index estimates. For the CHARMED model, we use the estimated axon diameter distribution to generate a measure comparable to the axon diameter index, which is the mean axon diameter weighted by cross sectional area of axons as defined in [4]. The mean and standard deviation of this derived measure is reported. Tables 1 and 2 show the ROI-averaged estimates of axon diameter index and intra-cellular volume fraction for all three techniques. For all three techniques, the estimated axon diameter indices are consistent with the known trend of axon diameter variation across the corpus callosum, i.e., low in the genu and the splenium, and high in the midbody [10]. Comparing across the techniques, the estimates are overall similar. The two notable differences are that the MAC estimates of axon diameter and intra-cellular volume fraction are higher than the other two techniques.

DISCUSSION Despite considerable differences in model and acquisition, we observe similar trends between regions from all three methods that are consistent with known anatomical trends in axon diameter. This suggests that trend is robustly observable. In particular, simple models of diffusion in tissue combined with optimized economical acquisitions can provide genuine sensitivity to microstructure parameters.

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