Axon diameter mapping in the presence of orientation dispersion using diffusion MRI

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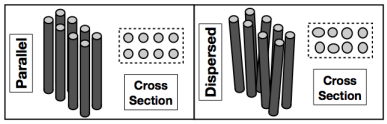

Fig 1: Schematic illustration of the overestimation of axon diameters due to orientation dispersion.

INTRODUCTION Using diffusion MRI, direct measurement of tissue microstructure features, such as axon diameter (ADI) and density, provides more specific biomarkers than DTI indices, such as diffusivities and anisotropy. A particularly successful approach, exemplified by [1,2], is the model-based strategy in which a geometric model of the microstructure of interest predicts the MR signal from water diffusing within. In estimating ADIs, the earlier attempts, e.g. [3,4], assume a model of single and known axon orientation. Recently, estimating ADIs of unknown orientation on clinical scanners has been shown to be feasible, first in simulation [5], later in fixed monkey brains and live human brains [6]. This approach assumes a simplified white matter (WM) model with a single ADI rather than a distribution to estimate a summary ADI statistic, the ADI index [6]. However, like earlier works, it still assumes a model of strictly parallel axons, a reasonable approximation only for the most coherently oriented structures, such as the corpus callosum. Most other WM areas contain fanning or bending axons, resulting in significant orientation dispersion (OD). Such dispersion, if unaccounted for, leads to overestimation of ADIs (Fig 1). In this work, we ameliorate this problem by proposing a model that captures OD explicitly and devising an efficient numerical scheme that enables ADI estimation with the model. Using both synthetic and human data experiments, we demonstrate that recovery of the ADI index is possible even in the presence of OD, which enables accurate mapping of ADIs to extend to a much wider set of WM than previously possible.

MODEL We adopt the simplified composite hindered and restricted model of diffusion (CHARMED) for WM [2,5] and generalize it to accommodate arbitrary axonal orientation distribution. Specifically, WM is modeled as a population of impermeable cylindrical axons with a single ADI, a, and orientation distribution ρ: $S^2 \rightarrow R^+$, embedded in a homogeneous medium. The intra-cellular compartment (IC) has volume fraction v_{ic}. Signal from IC is restricted and computed as $\int \rho(\mathbf{n}) A_{cyl}(\mathbf{n},a) d\mathbf{n}$, where $A_{cyl}(\mathbf{n},a)$ is the signal within a cylinder of diameter a and orientation $\mathbf{n}$, computed with the Gaussian phase distribution approximation [7]. Signal from the extra-cellular compartment (EC) is hindered and computed as $\int \rho(\mathbf{n}) D_h(\mathbf{n}) d\mathbf{n}$, where $D_h(\mathbf{n})$ is the diffusion tensor for EC embedding axons with a single orientation $\mathbf{n}$ as in [2,5]. Existing works [3-6] model $\rho(\mathbf{n})$ with a δ-function about some single orientation $\boldsymbol{\mu}$. Here we capture the essence of dispersion about a mean orientation $\boldsymbol{\mu}$ by modeling $\rho(\mathbf{n})$ with the Watson distribution, $M(1/2,3/2,\kappa)^{-1}\exp(\kappa(\boldsymbol{\mu}\bullet\mathbf{n})^2)$, where M is a confluent hypergeometric function and κ, the concentration parameter, controls the extent of OD. κ ranges from 0 for isotropically distributed orientations to $+\infty$ for a single parallel orientation. Henceforth, we refer to the two models as the Delta and Watson models. The Watson model is prohibitively expensive to compute with brute-force integration; we calculate the integral efficiently by converting it to a summation with a truncated spherical harmonic series of the Watson distribution, providing adequate approximation for κ up to 128.

EXPERIMENT We fit the Watson and Delta models to both synthetic data with prescribed OD and in vivo human data. The synthetic data experiment assesses the effect of dispersion on microstructure parameter estimation. The human data experiment evaluates each model's suitability to represent real WM tissue. In vivo imaging on a clinical 3T Philips scanner acquired 360 diffusion-weighted images of a healthy volunteer in about an hour with an optimized multi-shell HARDI protocol [6] (b = 530,700,2720,2780 s mm^{-2}): 10 sagittal slices about the midsagittal plane with in-plane resolution 128x128, 1.8x1.8x3.9mm^3 voxels, SNR at b=0 about 20. Synthetic MR signal is produced from the Watson model and in vivo imaging protocol with matching SNR (Rician noise) to simulate WM with OD. The true model parameters are v_{ic} = 0.7, a = {2,4,10,20}μm, κ = {4,8,16,32,64,128}. We fit the models to the data with the procedure given in [6], involving an initial grid search, followed by gradient descent fitting, and finally MCMC estimation. Final parameter estimates are the means of MCMC posterior distributions of parameters. We include voxels without CSF contamination (b=0 signal < 1/3 that of CSF) and crossing fibers (linearity > 0.4 & planarity < 0.2 [8]). The output from the MCMC fitting is additionally used to apply model selection via Bayes factor [9]. The MCMC provides 1000 samples at intervals of 200 iterations after a burn-in of 2000 iterations.

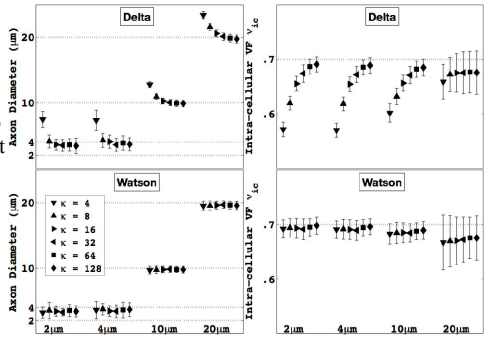

Fig 2: Estimates of a and v_{ic} from the synthetic experiment using both models. The dotted lines indicate the true parameter values.

RESULTS The synthetic experiment confirms that in the presence of OD, Delta overestimates a and underestimates v_{ic} (Fig 2); the biases increase as OD increases (i.e., κ decreases). In contrast, Watson estimates these parameters accurately (Fig 2) and quantifies the extent of OD (not shown). The human data experiment shows that, fitting to the same voxel data, when Watson gives a sufficiently high estimate of κ (> 32), both models fit to the data similarly well and give similar estimates of a and v_{ic}. In contrast, when Watson gives a low estimate of κ (< 32), Watson fits to the data better than Delta and gives different estimates of a and v_{ic}. The improved fitting is quantitatively confirmed with model selection using Bayes factor, which consistently chooses Watson over Delta. The departure in the estimates between the models reflects the trend in the synthetic data, i.e., compared to Watson, Delta gives higher a and lower v_{ic} estimates, with increasing differences for decreasing κ. Fig 4 shows the quality of fit for two representative voxels (one with low κ and the other high κ) and the parameter estimates from each model. Fig 5 shows two representative slices of the estimated parameter maps from both models, one at the midsagittal plane and the other more lateral. In the midsagittal plane, κ estimates are high; the estimates of a and v_{ic} show few differences between the models. In the more lateral slice, κ has much lower values, varies considerably in space; for the voxels with low κ, the Watson estimates of a are lower than those of Delta. Comparing across brain regions, the Watson estimates of a have similar values for both central and peripheral WM, as expected. In contrast, the Delta estimates are substantially higher in the peripheral, where OD is high, than in the midsagittal, where axons are coherently aligned.

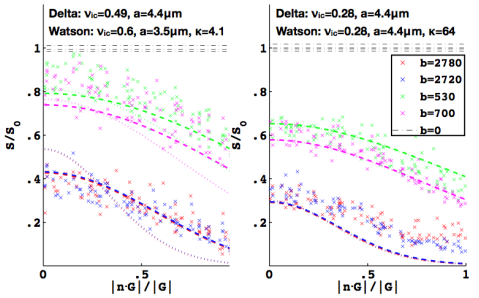

Fig 3: Quality of fit for two voxels: one with low κ, the other high κ. Results from Delta in dotted lines; Watson in dashed lines. Data in scattered points. G denotes the gradient direction and n the mean fiber orientation.

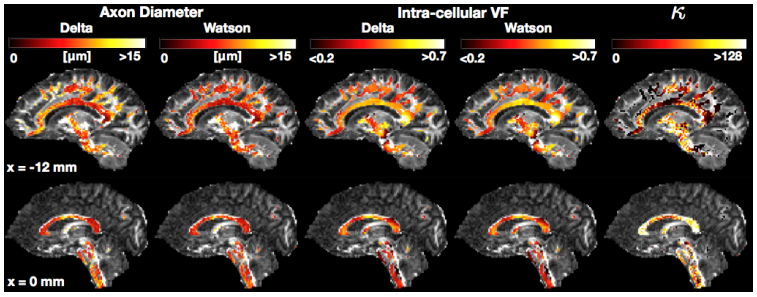

Fig 4: Maps of a and v_{ic} from both models, κ from Watson, for two representative slices.

DISCUSSION The synthetic experiment verifies that the presence of significant OD leads to biased estimates of microstructural features with the Delta model. The human data experiment demonstrates that the Watson model is more suitable than the Delta model for peripheral WM in which OD is substantial. The Watson model not only provides more accurate estimates of ADI but also quantifies the extent of OD. Future work will explore more complex models of orientation distribution to capture the effect of fanning and crossing.

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