DoubleAx: In-vivo Axon Measurement in the Human Corpus Callosum Using Angular Double-PFG MRI

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Authors:

Wenjin Zhou[1], Edward Walsh[2], David Laidlaw[3]

Institutions:

[1]Department of Computer Science and Engineering, Oakland University, Rochester Hills, MI, [2]Department of Neuroscience, Brown University, Providence, RI, [3]Department of Computer Science, Brown University, Providence, RI

Introduction:

We present a computational technique (DoubleAx) for estimating axon properties using clinically feasible angular double-pulsed field gradient (double-PFG) MRI. Our results demonstrate sensitivity to human axon properties and verify axon variations along the corpus callosum (CC) known from histology.

Methods:

The double-PFG sequence proposed by Cory [6] is the simplest form of multi-PFG, where two pairs of diffusion gradients are applied at any angle. The double-PFG sequence was implemented here on a Siemens 3T clinical scanner. One healthy female subject (age 29) with no major disease history participated in this study. The subject was scanned with informed consent and approval. Two scan sessions were acquired on two separate days. For each scan session, we acquired 11 sagittal slices covering the entire CC, centered at the midsagittal slice. By varying in-plane gradient direction, we obtained 27 MR images per slice (1.8 mm with no gap). The in-plane resolution was 128×128.

DoubleAx adopts our previous analytical water-diffusion model [10] aimed at estimating axonal properties without prior knowledge of axon orientation using angular double-PFG with clinically restricted gradient. The analytical model analyzes the MR signal obtained in double-PFG experiments given a two-compartment geometric axon model. We account for the variation in axon radii within a voxel with a gamma distribution.

The manually segmented CC spans approximately 250 to 300 voxels in each dataset, depending on the subject. For each voxel, we perform our computational fitting analysis to estimate the microstructural properties, including: mean axon radius a, volume fraction f, axon orientation u = (1, θ, φ), and intra-axonal diffusivity Di. Throughout, extra-axonal diffusivity De was held constant at 1.7×10-9 m^2/s, its expected value for in-vivo human data [9].

Results:

Fig.1 shows the estimation results in the CC over the midsagittal slice of subject scan 1. The axon radius estimation plot (Fig.1a) shows the larger axons recovered in the middle (body) and the smaller axons at the two ends (genu and splenium) of the CC. This matches the expected "low-high-low" anterior-posterior trend in axon radius observed in histology [1]. Also note that the extracted axon radius (1-5 μm), volume fraction, axon orientation, and intra-axonal diffusivity are all within the recorded human range [4, 8]. Higher volume fractions are mostly found at the two ends of the CC where axon radius is small and axons are densely packed, again matching histological observations [1].

We plot the average axon radius per CC segment for the midsagittal slice in Fig.2 to illustrate axon radius variation along the CC. The CC was divided into six segments based on anatomical geometry: (1) genu, (2-4) body, (5) isthmus, and (6) splenium. We multiply the axon radius from histology by 1.5 to account for tissue shrinkage during the histology process, as suggested in [1]. The estimates

show great consistency across two separate scans and demonstrate the robustness and sensitivity of our method in recovering the axon radius. Our estimates recovered small axons (≈1 μm) mostly in the genu and splenium, and large axons (≈ 3-5 μm) in the body of the corpus callosum, matching histological measures [2] from 10 female subjects.

We visualize the difference in computed axon-radius distribution for each segment in Fig.3. Our axon-radius distribution demonstrates good agreement with histological measures [1, 5]: a narrow distribution in the genu, isthmus, and splenium and a broader distribution in the body.

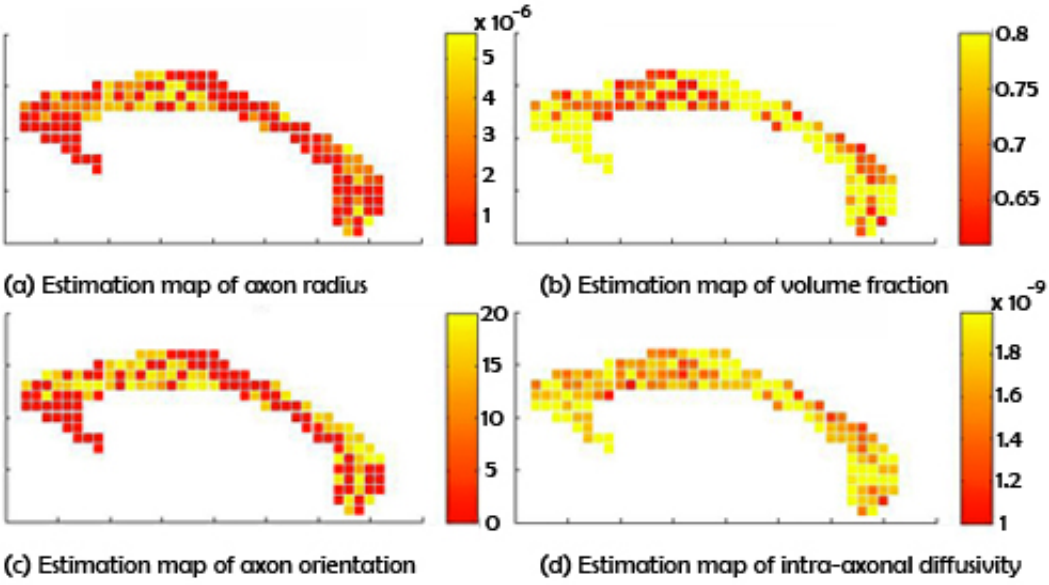


Figure 1: Estimation results in the CC from midsagittal slice of scan 1 from human subject.

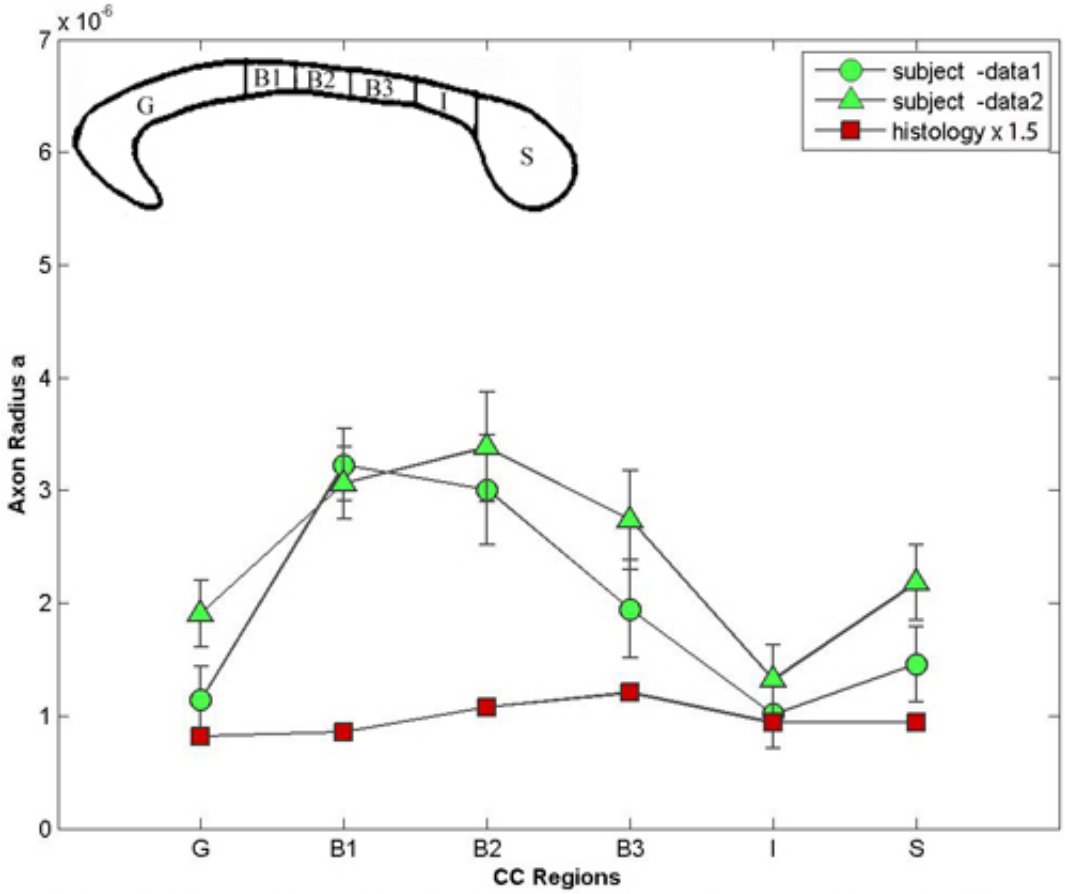
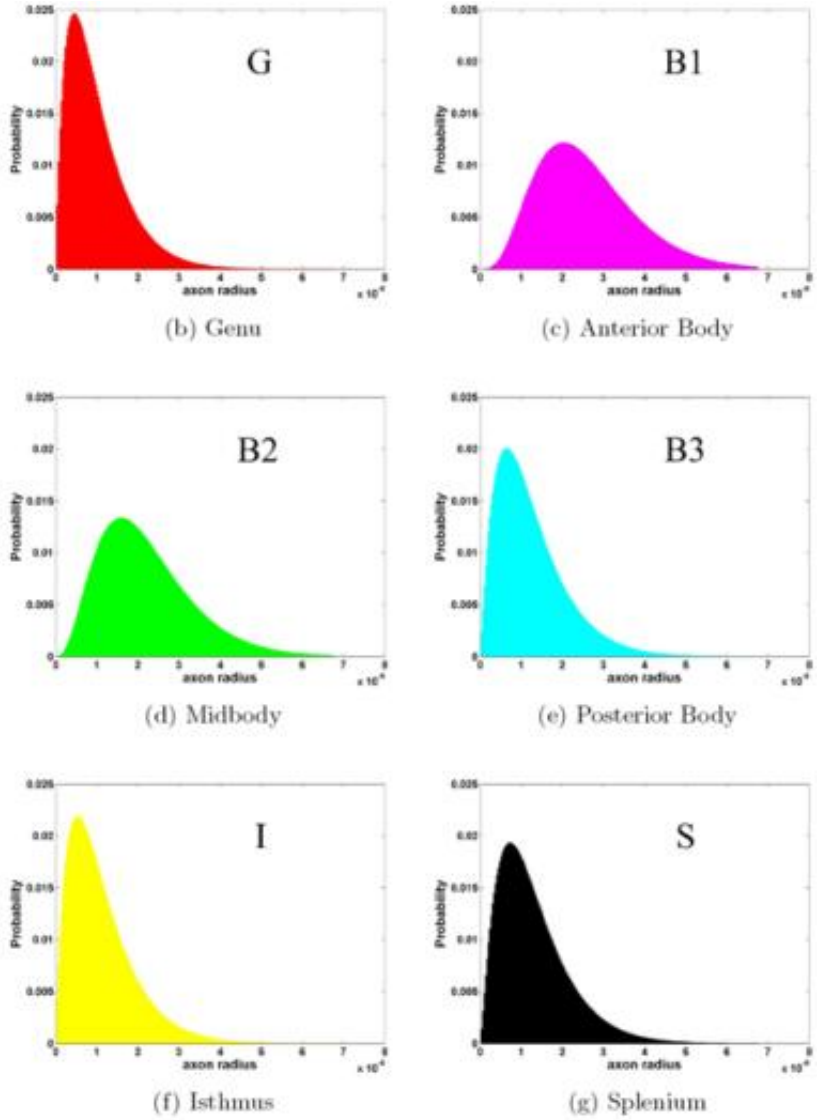


Figure 2: Comparison of trends in mean axon radius along six anatomical segments of the midsagittal slice of CC with histological measures from [1]. There are two separate datasets for the subject. We multiply the axon radius from histology by 1.5 to take into account tissue shrinkage during histology.



(b) Genu (c) Anterior Body

(d) Midbody (e) Posterior Body

(f) Isthmus (g) Splenium

Figure 3: Comparison of trends in axon-radius distribution along six anatomical segments of the midsagittal slice of CC from the subject scan 1. Our axon-radius distributions show good agreement with histological measures [1, 5]: a narrow distribution in the genu, isthmus, and splenium; and a broader distribution in the body.

Conclusions:

We have demonstrated for the first time that clinically feasible angular double-PFG experiments are sufficient for accurate reconstruction of quantitative measurements of microstructural properties in brain tissue of unknown orientation using DoubleAx. Our results show improved accuracy for small axons (radius < 3 μm), which tend to be more vulnerable to diseases [7] and typically more challenging to recover [3].

Modeling and Analysis Methods:

Diffusion MRI Modeling and Analysis

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