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DISCUSSION OF "FIBER DIRECTION ESTIMATION IN DIFFUSION MRI"

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Wong, Lee, Paul, Peng and ADNI (hereafter "Wong et al.") propose a threefold procedure—Diffusion Direction Smoothing and Tracking (DiST)—for the analysis of diffusion magnetic resonance imaging (dMRI) data. In the first step, they estimate multiple directions within a single voxel; in the second step, the estimation is sharpened by incorporating information from neighboring voxels in a smoothing operation; finally, in the third step, they reconstruct the fiber map using a fiber tracking algorithm.

A main contribution of the DiST procedure is the estimation of multiple directions within a single voxel. As Wong et al. rightly note, this poses challenges to existing methods due to problems of identifiability. Without the imposition of additional penalties or assumptions, or without the use of alternative acquisition schemes, it is generally not possible to resolve the data to the level of multiple fibers (crossing pathways) within a voxel. Wong et al. thus devise a computationally feasible and identifiable parameterization. This seems like a worthwhile addition to the literature on diffusion estimation and tracking.

I will confine the rest of my comments to the real data analysis, which raises some interesting possibilities for additional exploration and visualization. Table 1 of the paper shows the distribution of the estimated numbers of diffusion directions. Most voxels have one or two directions, and a few have as many as three. An obvious additional classification within these would show the directions themselves; especially for the voxels with multiple identified paths, it would be informative to know if there are dominant directions. But a classification of the directions for the voxels with just a single path might also prove enlightening. The results of these supplementary analyses might lead to additional insight: what would it mean (scientifically? functionally?) to have a dominant direction when there are multiple directions within voxels? What would it mean if there weren't such a direction? Do these differences correlate with subject covariates or task performance? These questions might be particularly pertinent for those voxels with two (as opposed to three, due to their relative scarcity) diffusion directions.

For the subject data that Wong et al. present, the reconstructed fiber tracts from the two methods are visually quite similar; familiarity with brain architecture and structure are no doubt helpful in interpreting the results, but a more objective or

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quantitative approach would add another dimension. A measure based on distances, or perhaps on warping functions such as are popular in functional data analysis, might provide the basis for more formal comparisons. Hypothesis tests and confidence intervals could be derived theoretically or from a bootstrap developed to build up the empirical distribution of the new measure.

Building on this idea even further, I'm curious about how to extend the proposed method to accommodate multiple subjects in a group, and to compare subjects across groups. For the first, the idea is to construct a group map that summarizes the overall behavior: aggregating (or perhaps comparing) the numbers of directions estimated at each location and what those directions are. How might this be accomplished? Presumably some locations will have dominant directions common to all (or most) subjects in a group—these would represent general structural pathways. Other regions might exhibit more individualized patterns. A simple place to start might be again with basic classification of directions within voxels, along with some rules for combining the results across subjects. Heatmaps could highlight pathways that are most common (or shared by most subjects).

The second goal is to take multiple maps of this sort, one for each study group of interest, and compare those. The distance measure that I notionally introduced before could be used here as well, this time between groups rather than individuals. An altogether different approach would be to skip the first step of creating summary maps for each group, and instead to embed the whole process in a hierarchical model, with an effect for group and subjects (with their covariates as relevant) nested within groups. Clustering of individual-level reconstructions offers yet another way of exploring differences among subjects or clinical groups.

The entire enterprise is made more challenging since age of subjects and their disease status will almost surely have effects on fiber structure, number and directions, on the distribution of directions at the voxel level, and hence of course on connectivity and brain function. Subjects at different stages or severity of disease should then presumably be separately analyzed. It would be interesting to see if these changes in terms of structure (and function?) can be detected by DiST or by one of the variations I propose in the preceding paragraphs.

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