

REJOINDER:
**“FIBER DIRECTION ESTIMATION, SMOOTHING AND TRACKING
IN DIFFUSION MRI”**

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The discussants have raised many insightful comments, and we shall respond to them in the alphabetical order of their last names. Briefly, these comments can be grouped into three major themes: clarification of the details and limitations of our techniques (mostly from Kang and Li), discussion of possible directions for future work (mostly from Lazor) and connection to the Watson mixture distributions (mostly from Schwartzman).

JIAN KANG AND LEXIN LI: We thank Jian and Lexin for their detailed and constructive comments. Due to space constraints, we only respond to some of their comments below. Some of these responses help further clarify the details of our techniques.

Label switching: Jian and Lexin raise a good question about identifiability under label switching. In a more precise description, the proposed parametrization is only identified up to a label switching. However, we feel that it is unnecessary to further identify the labels in voxel-wise estimation. In our view, there are two types of labeling that one can assign to the directions. One is constructed to solely ensure the absolute identifiability. But such further identification of direction labels does not carry any practical meaning, and has little relevance in the estimation and subsequent steps. The second type of labels has physical meaning, here the fiber membership. But this labeling cannot be ascertained based on measurements within a single voxel. In our procedure, they are identified through the clustering procedure in the smoothing step.

Estimation of S_0 and σ : We greatly appreciate the effort spent on the discussion and numerical experiments. We agree that appropriate estimation of $S_0(\cdot)$ and σ using both b_0 and non- b_0 images will likely improve their estimation quality. This seems to be suggested by the numerical finding in Jian and Lexin’s discussion. But we do not fully understand their numerical results due to lack of details such as the exact definition of the mean square errors of the direction estimate. Therefore, we confine our discussion to why $S_0(\cdot)$ and σ are estimated separately in our paper. The major reason is computational simplicity and efficiency. As discussed in our response to Armin, the voxel-wise estimation is the most computational expensive

step in the proposed procedure. The separate estimation simplifies the voxel-wise estimation and its computation, and produces sufficiently adequate estimates based on our numerical studies.

Estimated versus observed directions: This is an important observation. In our theoretical analysis, we treat the estimated directions as if they were observed by viewing the estimation errors as the observational errors. An important question is whether the estimation errors satisfy the assumed error structure in the theoretical analysis. The independence of errors associated with different voxels is justified due to the independence assumption on the observed signal intensities across voxels. However, other properties of the sampling distribution of the estimated directions are not completely clear, due to, for example, their non-Euclidean structure. Further theoretical study could shed light on this aspect.

Fast alternatives to CV: The asymptotic result (Theorem 2) provides foundations for developing plug-in type methods for bandwidth selection. However, this approach would involve estimating several unknown quantities in the asymptotic distribution of the estimated direction, which is an intrinsically challenging problem. Moreover, apart from this difficulty, the asymptotic result also hinges on a number of assumptions. Given the complicated nature of the dMRI data, we feel that CV is to be preferred, as it depends on fewer assumptions and is nonparametric in nature.

Tuning parameters in tracking algorithm: Two key parameters of the proposed fiber tracking algorithm are the angular threshold ξ and the maximum number of projections N_{proj} . First, like most imaging techniques, the image resolution is important. The best tuning of these parameters depends on the resolution of the structures we are interested in. Typically, a certain degree of human judgment is required to obtain best tuning. From our experience, the tracking results (at least at a global level) are not very sensitive over a reasonable range of ξ and N_{proj} . Besides these pertinent issues, Jian and Lexin have proposed a few well-thought and constructive directions to extend the tracking methods, which we will not comment on due to space constraint.

NICOLE A. LAZAR: We thank Nicole for her inspiring suggestions of future directions. These directions would help to explore additional usages of diffusion MRI and answer important scientific questions.

Dominant direction in multiple directions: Nicole raises a few interesting questions about the meaning of having a dominant direction among several directions within a voxel. However, we note that the weights p_j 's in the multi-tensor model are not identifiable, and hence cannot be estimated in the voxel-wise level. Without the knowledge of p_j 's, we could not determine the dominant direction within a voxel. In order to delineate the dominant diffusion direction, additional information about the tissue microstructure is needed. The latter could be obtained through a denser sampling of the gradient directions and adopting techniques that are beyond tensor models, such as diffusion orientation models, fiber orientation models or diffusion spectral imaging.

Measures to compare fiber maps and group analysis: Nicole also suggests to construct a measure for fiber map comparison. Such a measure can then be used to compare multiple dMRIs either from the same subject or across multiple subjects. At first, a registration of dMRIs is required to align different images for comparison. Measures could then be constructed based on registered images according to different characteristics of the fiber network that are of interest. These are excellent suggestions and will make it possible to relate structural connectivity information learned from dMRI data to external variables of interests such as cognitive status or age.

Nicole suggests to compare estimated directions at a voxel-wise level and proposes a heatmap to indicate direction similarity within voxels. Although voxel-wise comparison would retain the rich local directionality information, its success hinges significantly on the registration step. Alternatively, one could formulate the comparison in terms of structural connectivity at the level of properly defined anatomical subregions. With appropriate choice of regions of interest, a weighted nondirectional graph could be constructed using the tractography results. Then comparisons could be done via such a structural connectivity graph. Due to the aggregation of directionality information across voxels within a subregion, structural connectivity is relatively more robust to the registration procedure and is less noisy compared to measures that depend directly on voxel-level data.

ARMIN SCHWARTZMAN: We thank Armin for providing further insights of the identifiability issue and connecting our work to parametric models used in directional statistics, especially to the Watson mixture distributions.

As pointed out by Armin, the multi-tensor model can be alternatively formulated as a Watson mixture on the sphere. While this connection is interesting from the modeling perspective, we contend that there is no obvious gain in terms of voxel-wise estimation under the multi-tensor model. However, this connection becomes more relevant when considering diffusion direction smoothing across voxels. Inspired by the Watson mixture, Armin proposes to adopt the distance $d^\perp(\mathbf{u}, \mathbf{v}) = [1 - (\mathbf{u}^\top \mathbf{v})]^{1/2}$, instead of $d^*(\mathbf{u}, \mathbf{v}) = \arccos(|\mathbf{u}^\top \mathbf{v}|)$ that is used in the paper, between any pair of diffusion directions \mathbf{u} and \mathbf{v} , leading to a different version of the weighted Karcher mean of the directions and, consequently, a different spatial smoothing estimator. While the d^* has an appealing interpretation of angular separation, d^\perp enjoys computational benefits as shown by Armin. However, d^\perp does not address the computational bottleneck of the proposed method. Among the three steps of the proposed procedure—voxel-wise estimation, spatial smoothing and fiber tracking—the voxel-wise estimation is the most expensive computationally, due to the difficulty in the likelihood optimization and the additional model selection procedure. Therefore, the use of d^\perp is likely to result in only moderate computational savings of the proposed procedure.

The possibility that the Watson mixture may provide theoretical developments and uncertainty quantification, owing to its direct solution of the corresponding weighted Karcher mean, is interesting and therefore warrants further investigation.

The accompanying uncertainty quantification of directions is also appealing. However, currently there is a gap between quantifying the uncertainty of the directions and the uncertainty in the tractography. Bridging this gap will require formulating a meaningful probabilistic framework that allows for propagation of uncertainty measures through a sequence of adjacent voxels.

Last, we would like to bring to one's attention that Armin's discussion on d^\perp stems from a Watson density assumption of the diffusion directions. However, the underlying objects for smoothing are the *estimated* diffusion directions from the voxel-wise estimation step. Further investigation of the sampling distribution of the *estimated* diffusion direction may shed light on the choice of metric for smoothing.

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