On evaluating the accuracy and biological plausibility of diffusion MRI tractograms

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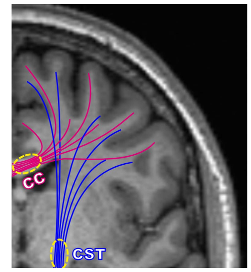
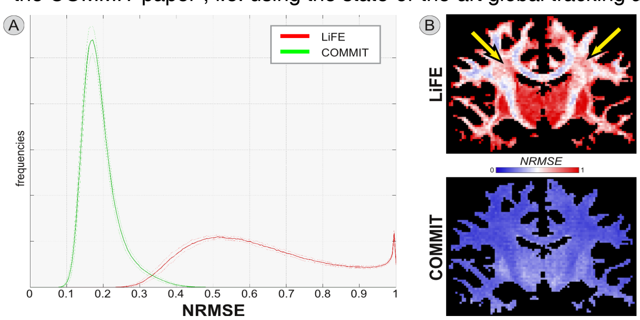
INTRODUCTION. One of the major limitations of diffusion MRI tractography is that the tractograms, i.e. set of fiber tracts, recovered by existing algorithms are not truly quantitative. Several orders of magnitude separate in fact the resolution achievable with MRI from the actual size of the axons and, consequently, each reconstructed trajectory has to be considered as representative of a coherent set of real anatomical fibers, the amount of which is not easy to assess. Hence, the structural connectivity between different brain regions, a.k.a. connectomics, is nowadays quantified by counting the number of recovered pathways or averaging some scalar maps along them; in both cases, these estimates provide only indirect measures of the true underlying neuronal connectivity[1]. A number of methods have recently started to appear to address this limitation[2-6]; in particular, COMMIT[2] and LiFE[3] have been developed upon the recently proposed framework that showed how to formulate tractography as an efficient system of linear equations[4], opening de facto the door for the practical possibility to evaluate and compare the accuracy of the tractograms.



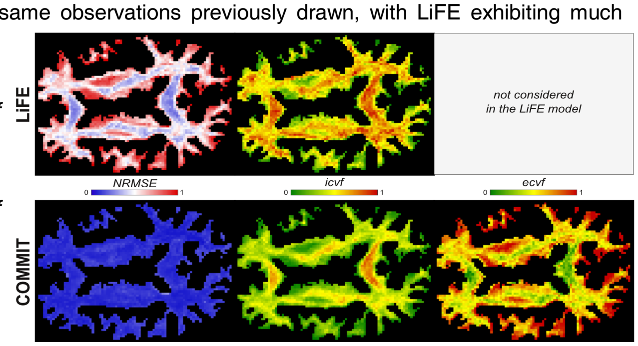
PURPOSE. These two models follow different strategies to describe the signal in each voxel. On one hand, COMMIT[2] uses a forward-model that takes into account that the diffusion MR signal can originate from distinct water pools[7], e.g. intra- and extra-cellular. On the other hand, LiFE[3] models the signal as consisting only of contributions arising from the tracts passing through each voxel (i.e. restricted diffusion). The extra-cellular space around the axons (i.e. hindered diffusion) and any partial volume that can occur with non white-matter (WM) tissue (i.e. isotropic diffusion) are not directly considered, but are “removed” with a de-meaning procedure. However, as shown by several independent studies[8-11], the relative contribution of these compartments is not homogeneous in the WM and can change considerably. The schematic representation in the top-right figure depicts such a situation: the callosal fibers projecting from the corpus callosum (CC) and the corticospinal tract (CST) consist both of tightly-packed axons (yellow circles) that progressively fan-out and eventually cross. Differences in the axonal packing density are compensated by variations in the spacing surrounding the axons themselves, i.e. extra-cellular space. This consideration is implicitly or explicitly assumed in most state-of-the-art techniques for voxelwise microstructure imaging[7-10] and independent histological studies also corroborate this hypothesis[11]. Furthermore, to be sensitive with diffusion MRI to the tissue microstructure, multiple b-values have been proven necessary[7-9]. In this abstract *we investigated the importance of* using (i) proper multi-compartment models and (ii) adequate multiple b-value acquisitions in order to be able to *evaluate the accuracy and the biological plausibility of the tractograms* using these global approaches.

METHODS. COMMIT[2] implements a very general and flexible framework, and LiFE[3] can be considered as a special case of it where only the contributions of the tracts are considered in the signal forward-model. Thus, we evaluated both models using the code available at *https://github.com/daducci/COMMIT*. For a first *assessment of the goodness of the fit* of each model, we downloaded 10 subjects from the Human Connectome Project[12] (90 images with spatial resolution 1.25 mm^3 at b=2000 s/mm^2) and used the same experimental settings as in the LiFE manuscript[3], i.e. CSD-based probabilistic tractography with 500K tracts and *NRMSE* (reported as percentages) between the measured and modeled signal as quality metric. In addition, to be able to extract the relative fractions of the intra- (*icvf*) and extra-cellular (*ecvf*) compartments in each voxel, and thus *evaluate the biological plausibility of the tractograms*, we used a 2-shell acquisition (81 images with spatial resolution 1.8×1.8×2.5 mm^3 at b=700 s/mm^2 and b=2000 s/mm^2) and the same experimental setup as in the COMMIT paper[2], i.e. using the state-of-the-art global tracking algorithm[13] with 100K candidate tracts.



RESULTS AND DISCUSSION. The *left figure* compares the ability of the two models to adequately describe the signal in each voxel. Panel (A) shows the histograms of the fitting errors (*NRMSE*, mean±std) across the 10 datasets. The plot clearly highlights significantly higher fitting errors with LiFE (68.7%±17.9%) as compared to COMMIT (19.5%±4.6%). Visual inspection in panel (B) shows that LiFE presents the highest errors in areas with crossing fibers (yellow arrows) and with partial volume with gray-matter, where the lack of the extra-cellular compartment in the model prevents an accurate fit; conversely, the smallest errors are observed in regions with densely packed axons, where indeed the extra-cellular space is greatly reduced. On the other hand, COMMIT exhibits an homogeneously low spatial distribution of the errors and definitely appears to fit the data more accurately.

In the *bottom-right figure* we tested the two models with multi-shell data. The *NRMSE* map confirms the same observations previously drawn, with LiFE exhibiting much higher fitting errors (64.8%±18.1%) than COMMIT (10.1%±2.9%) also in this case. The *icvf* map estimated with LiFE shows a spatial distribution that does not follow the expected pattern of neuronal density as found in previous studies[8-11]; this is a clear sign of an incorrect assessment of the tract contributions. On the contrary, the *icvf* and *ecvf* maps estimated with COMMIT show a spatial distribution which is in agreement with the known brain anatomy and previous independent studies[8-11]. The highest *icvf* values are in fact found in the major WM bundles, e.g. CC and CST, an homogeneous distribution is observed in crossing regions and a decreased fraction close to gray-matter. The *ecvf* map shows the opposite behavior, as expected. It is worth noting that this map (not considered in the LiFE model) follows the same spatial pattern as observed in the map of the fitting errors with LiFE. We speculate that this observation reflects the need to consider in the model the non-homogeneous extra-cellular contributions in order to adequately describe the signal in each voxel and, consequently, to be able to estimate the actual contributions of the tracts.



CONCLUSION. Our results indicate that, to be able to evaluate the accuracy and biological plausibility of tractograms with these novel global approaches[2-6], both (i) proper models which account for all possible water pools that can contribute to the diffusion MR signal and (ii) adequate multi-shell acquisitions appear to be mandatory. The lack of either of these two conditions leads to very inaccurate signal fitting and the estimated quantities do not resemble the know brain anatomy. Future work will still be required to investigate the benefits of these global approaches for brain connectivity analyses.

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