

# EFFECTS OF TRACTOGRAPHY APPROACH ON CONSISTENCY BETWEEN ANATOMICAL AND FUNCTIONAL CONNECTIVITY ESTIMATES

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## ABSTRACT

Diffusion magnetic resonance imaging (dMRI) and resting state functional MRI (RS-fMRI) provide two complementary views of brain circuitry. dMRI facilitates the estimation of anatomical connectivity (AC) through fiber tractography, while RS-fMRI enables the estimation of functional connectivity (FC) based on temporal signal correlations between different brain areas. Recently, there is a methodological push in developing techniques to integrate dMRI and RS-fMRI for multimodal connectivity estimation, success of which highly depends on the consistency between the AC and FC estimates. Using the Human Connectome Project (HCP) data, we show increased AC-FC consistency with streamline tractography on orientation distribution functions (ODFs) compared to using conventional diffusion tensors. We also demonstrate a further, though smaller, improvement when global tractography on ODFs is deployed. Our results suggest that while accurate ODF estimation is important, more attention should be focused on improving tractography methods, which we believe could be highly beneficial.

*Index Terms*—Brain connectivity, diffusion MRI, functional MRI, resting state

## 1. INTRODUCTION

Diffusion magnetic resonance imaging (dMRI) and resting state functional MRI (RS-fMRI) have been widely used to investigate anatomical connectivity (AC) and functional connectivity (FC) of the human brain. Motivated by how anatomical wiring of the brain facilitates and shapes functional interactions between brain regions, a growing interest in integrating connectivity estimates derived from dMRI and RS-fMRI data has emerged in recent years. A number of past studies [1-4] reported a strong agreement between AC and FC, as estimated from tractography-based measures such as fiber counts and temporal correlations between RS-fMRI time courses, respectively. These findings incited new research directions, such as integrating dMRI and RS-fMRI data for multimodal connectivity estimation

[5, 6] and informing fMRI activation detection with AC priors [7].

Although earlier work comparing AC and FC suggests high consistency between their estimates, it has recently been shown that the AC-FC correlation is rather low with typical data acquisitions [8]. A fundamental factor governing the level of consistency is the way in which FC and AC are estimated. FC is traditionally defined using temporal similarities between distinct brain areas and estimated using Pearson's correlation [9]. dMRI data have overwhelmingly been modeled using tensors to date. In this approach, local diffusion process is approximated by a single Gaussian probability density function. Due to this simplistic approximation, diffusion tensors can only capture the principal diffusion direction, which makes them prone to errors induced by crossing fibers. With recent advances in dMRI acquisition, a larger number of gradient directions can now be acquired within a practical amount of time, which enables more sophisticated methods that can model multiple fiber directions, such as orientation distribution function (ODF) reconstruction [10], to be readily employed. To better exploit the high angular resolution data, ample efforts have been placed on improving ODF estimation strategies during recent years. However, much less attention has been paid to tractography methods, which are equally important for AC estimation. Streamline tractography performed on diffusion tensors or ODFs remains to be the norm. Typically, streamline tractography follows either the principal diffusion directions of diffusion tensors or largest ODF peaks in tracking fibers one at a time. Approaches that consider all fibers in aggregate have recently been explored [11]. Whether these global tractography techniques can help increase the consistency between AC and FC estimates has to date not been investigated.

In this paper, we analyze the impact of AC estimation strategies on the consistency between AC and FC estimates. Specifically, we compare conventional streamline tractography [12] against global tractography [11]. Global tractography accounts for spatial interactions among fiber orientation estimates by reconstructing all fibers simultaneously and finding the configuration that best explains the data [11]. Global tractography thus alleviates

error accumulation along reconstructed tracts, which is a major drawback of the streamline approach [11]. We hence hypothesize that fiber tracts extracted with global tractography would better resemble the macroscale neural circuitry, and thus provide higher consistency between AC and FC estimates. On the Human Connectome Project (HCP) data, we apply global tractography on constant solid angle ODF (CSA-ODF) [13], and compare it against streamline tractography on CSA-ODF as well as on diffusion tensors to examine the impact of tractography on AC-FC consistency.

## 2. METHODS

### 2.1. Functional Connectivity Estimation

Let  $\mathbf{Z}$  be a  $t \times d$  matrix containing  $d$  RS-fMRI time courses. We estimate FC using Pearson’s correlation:  $\mathbf{C} = \mathbf{Z}^T \mathbf{Z} / (t-1)$ . To control for estimation errors and indirect effects, sparse partial correlation has recently been explored [8], but to facilitate comparisons with the current literature, we chose to employ the most widely-used FC estimate in this work, and focus on studying the impact of AC estimation.

### 2.2 Anatomical Connectivity Estimation

We use the fiber counts between brain region pairs as an AC estimate. On ODFs estimated with constant solid angle constraints (Section 2.2.1), we compare fibers reconstructed using streamline tractography (Section 2.2.2) against global tractography (Section 2.2.3). Fiber tracts derived from streamline tractography applied to conventional diffusion tensors are also examined (Section 2.2.2).

#### 2.2.1. Modeling of Local Diffusion Properties

When local diffusion is modeled using diffusion tensors, only the dominant diffusion direction can be recovered at each voxel. In contrast, ODFs are more sensitive in capturing intricate intravoxel fiber geometries. ODFs are typically estimated from q-ball imaging reconstruction of high angular resolution diffusion imaging (HARDI) data acquired on one or multiple spherical shells in q-space [10]. We opt to use CSA-ODF [13] since this reconstruction method intrinsically provides sharp ODFs, which enables multiple intravoxel fiber orientations to be more easily resolved. Moreover, this method takes advantage of the additional information provided by multi-shell acquisition, which has been empirically shown to better resolve fiber crossings compared to single q-shell models [13]. Using CSA-ODF thus better exploits the multiple q-shells available in the HCP data. Further details on CSA-ODF estimation can be found in [13].

#### 2.2.2. Streamline Tractography

Conventional streamline tractography is a deterministic approach, in which a single fiber trajectory is generated for each seed point [12]. Seed points are defined on a dense grid at the voxel or subvoxel level. Fiber tracts are then reconstructed by bidirectionally traversing the direction of maximum diffusion, i.e. the largest ODF peak or the principal diffusion direction in the case of diffusion tensors. In this work, we use Euler’s method for numerically performing tractography. Starting from a seed point  $\mathbf{p}_0$ :

$$\mathbf{p}_{n+1} = \mathbf{p}_n + \mathbf{v}(\mathbf{p}_n) \Delta s \quad (1)$$

where  $\mathbf{p}_n$  is the position of the propagator at step  $n$ ,  $\mathbf{v}(\mathbf{p}_n)$  is the propagation direction at  $\mathbf{p}_n$ , and  $\Delta s$  is the fixed step size [14]. To generate smooth tracts, we compute  $\mathbf{v}(\mathbf{p}_n)$  using trilinear interpolation which combines the information of voxels within the 8-neighborhood of  $\mathbf{p}_n$  [14].

#### 2.2.3. Global Tractography

In contrast to the streamline approach, global tractography reconstructs all fiber tracts simultaneously, which enables fiber trajectories to be jointly considered in determining the most possible fiber configuration. In this approach, short fiber segments are bridged together to form the set of fiber tracts that best explains the measured dMRI data. This globally optimal tract set is found by minimizing an energy function consisting of an internal and an external energy term:  $E(\mathbf{m}) = E_{\text{int}}(\mathbf{m}) + E_{\text{ext}}(\mathbf{m}, \mathbf{D})$ . Here,  $\mathbf{m}$  is the set of all short fiber segments and  $\mathbf{D}$  is the observed dMRI signal.  $E_{\text{int}}$  encourages the short fiber segments having consistent orientations to form chains and  $E_{\text{ext}}$  forces the set of fiber tracts to be in agreement with  $\mathbf{D}$ . We note that random changes are introduced into the reconstructed fiber set to avoid getting trapped in local minima. These random changes are accepted or rejected through a Metropolis-Hastings sampler [11]. This global approach is particularly beneficial in resolving cases where local diffusion characteristics are ambiguous due to crossing fibers. Streamline tractography tends to terminate tracking at such locations, whereas global tractography exploits the geometry of surrounding fibers by considering the whole-brain fiber configuration in aggregate to compensate for the lack of reliable local information.

## 3. MATERIALS

RS-fMRI and dMRI data from 10 subjects of the HCP dataset [15] (four men, six women, aged between 22-35 years) were used in this work. The dataset comprised four RS-fMRI scans of 15 minutes per subject, with a TR of 0.72 s and a voxel size of 2 mm (isotropic). The dMRI data had a voxel size of 1.25 mm (isotropic), 3 shells ( $b=1000, 2000$  and  $3000$  s/mm<sup>2</sup>) and 288 gradient directions. Further details on acquisition can be found in [15].

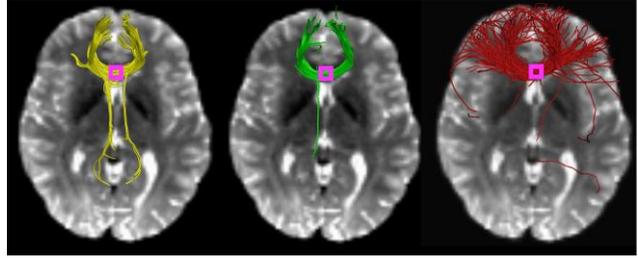
In addition to the minimal preprocessing that was already performed on the HCP RS-fMRI data [16], which included gradient distortion correction, motion correction, spatial normalization and intensity normalization, we further removed motion artifacts (estimated during motion correction) along with white matter and cerebrospinal fluid confounds, and applied a bandpass filter at 0.01 to 0.1 Hz. We divided the brain into 200 regions of interest (ROIs) by temporally concatenating preprocessed voxel time courses across scans and applying Ward clustering [17]. The number of ROIs was selected to provide a finer parcellation than standard anatomical templates (e.g. AAL), while ensuring the ROI-to-time sample ratio remains reasonable for reliable FC estimation. ROI time courses were generated by averaging voxel time courses within each ROI.

The HCP dMRI data, which have been corrected for EPI distortion, eddy current, gradient nonlinearity and motion artifacts [16], were downsampled to 2 mm isotropic resolution to reduce the computational cost. Streamline (on both diffusion tensors and ODFs) and global tractography on ODFs were carried out using Dipy [14] and MITK [18], respectively. For all methods, approximately 65,000 fibers per subject were reconstructed. The functionally derived group parcellation map was warped onto the dMRI space of each subject to facilitate the computation of fiber count.

#### 4. RESULTS AND DISCUSSION

We first present a qualitative comparison between streamline and global tractography for a representative subject. Fig. 1 shows the tracts running through an ROI within the corpus callosum as estimated using streamline tractography on diffusion tensors and ODFs, and global tractography on ODFs (in yellow, green and red, respectively). We chose this ROI since most tractography algorithms have difficulties tracking the callosal projections [11]. As apparent in Fig. 1, streamline tractography only captured the dominant U-shaped callosal radiation. This result is expected for the case of diffusion tensors since the principal diffusion directions of the tensors are ambiguous at fiber crossings. However, the same pattern was observed even with diffusion modeled using CSA-ODF, which is able to delineate multiple intravoxel diffusion directions. This shows that streamline tractography is unable to make full use of the information in the ODFs. In contrast, global tractography was able to better exploit the information in CSA-ODF and tracked the lateral transcallosal fibers.

Quantitatively, the AC-FC correlation, computed by finding the Pearson’s correlation between intra-subject AC and FC estimates and averaging these values across the group, was  $0.2289 \pm 0.016$  with streamline tractography on ODFs and  $0.1682 \pm 0.011$  with streamline tractography on diffusion tensors. The difference was found to be statistically significant at  $p=0.01$  based on the Wilcoxon signed rank test, showing that using ODFs can notably increase AC-FC



**Fig. 1.** Fiber tracts reconstructed for a representative subject using streamline tractography on diffusion tensors (left), streamline tractography on ODFs (middle), and global tractography on ODFs (right) with an ROI placed in the corpus callosum (shown with a square). While streamline tractography results were limited to the callosal radiation, global tractography also tracked bilateral projections.

consistency over diffusion tensors. With global tractography on ODFs, AC-FC consistency further increased to  $0.2568 \pm 0.017$ . The difference between global and streamline tractography on ODFs was statistically significant at  $p=0.01$ . These findings confirm our hypothesis that global tractography can better estimate the macroscale neural circuitry, leading to higher agreement between estimates of AC and FC, though the gain compared to using enhanced diffusion modeling, i.e. ODFs over tensors, was smaller. We speculate that uncertainty in fiber endpoint locations is the limiting factor. Global tractography is driven by the measurements in areas with anisotropic diffusion, whereas diffusion around white-gray matter boundaries is near-isotropic. Thus, reconstructed fibers might not terminate in the correct location. We hence argue that modeling fiber endpoint uncertainty is an under-investigated problem that has high potential in improving AC estimation. Also, Pearson’s correlation cannot distinguish direct from indirect FC. Deploying partial correlation to estimate direct FC would facilitate more appropriate comparison with AC estimates, which only reflect direct connections.

Even though we showed that the consistency between AC and FC measures can be improved by the choice of AC estimation method, higher correlation values have been previously reported in literature [1-3]. There are four possible reasons of this discrepancy. Firstly, we report our values over all brain region pairs, instead of excluding absent anatomical connections as was the case in [2] or dividing the connection structure into subsets as was done in [1]. Since anatomically unconnected brain region pairs can still show high FC [4], analyzing only anatomically connected brain regions implies discarding part of AC-FC inconsistency, which can potentially inflate the AC-FC correlation values. Secondly, we do not apply any post-processing steps on the AC estimates and directly use fiber counts to assess the consistency between AC and FC measures. Fiber counts were resampled into a Gaussian distribution in [2], which increased the average AC-FC correlation from 0.156 to 0.36. Even though this strategy increased the consistency empirically, such resampling has

no theoretical or physiological grounding. Thirdly, we do not apply distance correction to weigh down the effect of longer anatomical connections in generating AC estimates as was done in [3]. Such distance correction would lead to a positive bias in AC-FC correlation since proximal brain region pairs tend to have higher FC compared to distal region pairs on average [4]. Finally, we do not apply global RS-fMRI signal regression unlike [2, 3], since global signal regression artificially introduces negative RS correlations [19]. We observed that the AC-FC correlation increased by more than 0.05 for both streamline and global tractography when the global signal was removed. However, whether this increase has a neural basis remains to be a point of debate.

## 5. CONCLUSIONS

Streamline tractography, which remains to be the most commonly used tractography approach, is known for its inability to resolve fiber crossings and premature termination of the tracking process. On high quality multimodal data, we demonstrated that this can lead to underestimation of the correlation between estimates of AC and FC. We illustrated that this problem is more pronounced when streamline tractography is performed on conventional diffusion tensors as opposed to ODFs. We also showed that AC-FC consistency can be improved by reconstructing the fiber tracts using global tractography, which provides higher stability against noise and imaging artifacts by jointly incorporating the geometry of all fiber tracts. However, even with global tractography, AC-FC consistency is still low in absolute terms, which warrants further research in improving tractography methodologies to fully exploit the recent advances in ODF estimation.

## 6. REFERENCES

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