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Modeling Topographic Regularity in Structural Brain Connectivity with Application to Tractogram Filtering

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Abstract

Topographic regularity is an important biological principle in brain connections that has been observed in various anatomical studies. However, there has been limited research on mathematically characterizing this property and applying it in the analysis of *in vivo* connectome imaging data. In this work, we propose a general mathematical model of topographic regularity for white matter fiber bundles based on previous neuroanatomical understanding. Our model is based on a novel group spectral graph analysis (GSGA) framework motivated by spectral graph theory and tensor decomposition. The GSGA provides a common set of eigenvectors for the graphs formed by topographic proximity of nearby tracts, which gives rise to the *group graph spectral distance*, or G^2SD , for measuring the topographic regularity of each fiber tract in a tractogram. Based on this novel model of topographic regularity in fiber tracts, we then develop a tract filtering algorithm that can generally be applied to remove outliers in tractograms generated by any tractography algorithm. In the experimental results, we show that our novel algorithm outperforms existing methods in both simulation data from ISMRM 2015 Tractography Challenge and real data from the Human Connectome Project (HCP). On a large-scale dataset from 215 HCP subjects, we quantitatively show our method can significantly improve the retinotopy in the reconstruction of the optic radiation bundle. The software for the tract filtering algorithm developed in this work has also been publicly released on NITRC (<https://www.nitrc.org/projects/connectopytool>).

Keywords

Topographic regularity; Tractography; Diffusion MRI; Spectral graph theory

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1 Introduction

The brain connectivity that follows topographic regularity can be defined as *the point-to-point or region-to-region axonal connections that preserve spatial relationship between neurons* (Patel et al., 2014; Thivierge and Marcus, 2007). This property in brain connectivity implies that the neighboring relationships among the nearby neuronal projections are invariant along the projection trajectories. Topographic regularity is a ubiquitous property in vertebrate brain networks (Jbabdi et al., 2013; Patel et al., 2014) and it is believed that topographic organization of the brain connectivity is highly related to brain function segregation and integration (Jbabdi et al., 2013). For the *in vivo* study of brain connectivity, diffusion MRI (dMRI) is an important technique that has experienced tremendous progresses in the last two decades (Basser and Pierpaoli, 1996; Johansen-Berg and Behrens, 2014). In particular, the high-resolution, multi-shell dMRI data from the Human Connectome Project (HCP) (Van Essen et al., 2012) provides an unprecedented opportunity for characterizing brain connections at great detail (Shi and Toga, 2017; Tang et al., 2018). Yet, to the best of our knowledge, there has been limited research in mathematically modeling the fundamental principle of topographic regularity in connectivity research based on diffusion MRI.

Among the earliest records of topographic regularity, its presence was found in post-mortem studies of human primary visual cortex (V1) based on correlations between visual field deficits and focal lesions in V1 (Lister and Holmes, 1916). Topographic regularity of human visual cortex was also found through macroscopic identification and measurement of the line of Gennari on coronal sections from hemispheres collected at autopsy (Stensaas et al., 1974). Using Klingler's fiber dissection technique in formalin-fixed human hemispheres, topographic organization of axons in the human visual system was characterized in great detail (Ebeling and Reulen, 1988).

The *in vivo* characterization of topographic organization in visual cortex was achieved with the popularization of electrophysiological studies in the latter half of the last century. It has been clearly and repeatedly observed in animal brains that there is a preservation of spatial relationships between the visual field of the eyes and the visual cortex of the brain using multiple electrophysiological recordings, and it has been concluded that this is a clear functional consequence of anatomical topography in the early visual system (Tootell et al., 1988). This particular type of topography is known as the retinotopic organization, or retinotopy. Due to the rapid development of non-invasive *in vivo* neuroimaging techniques and the emergence of large high quality imaging data, such as the Human Connectome Project (HCP) dataset, study of topographic regularity in human brains has drawn renewed interests recently (Jbabdi et al., 2013). Retinotopic mapping techniques based on task fMRI provide a non-invasive measure of the retinotopic organization of human visual cortex (Engel et al., 1994). The topographically ordered mappings in other information transmission systems in the brain have also been revealed through task fMRI studies (Bilecen et al., 1998; Grodd et al., 2001; Weisz et al., 2004; Yousry et al., 1995). For example, somatotopic organization in the sensorimotor cortices has been identified and characterized in (Grodd et al., 2001; Yousry et al., 1995). A tonotopic map in the cochlea that projects to the auditory cortex has been found to be ordered by frequency (Bilecen et al.,

1998; Weisz et al., 2004). Using data from tracer injection studies on macaque brains, the topographic organization of cortical connections to the striatum has also been shown recently (Lehman et al., 2011). More recently, resting-state fMRI data has been used to extract the topography in functional connectivity (Haak et al., 2017).

Fiber tracking, or tractography, based on diffusion MRI (dMRI) is an important technique for *in vivo* study of white matter connectivity, and tremendous progresses have been made in this field in the last two decades (Basser and Pierpaoli, 1996; Johansen-Berg and Behrens, 2014). A few observational characterizations on the topographic organization of white matter were made in previous tractography studies. In a recent tractography-based reconstruction of human retinofugal visual pathway using HCP data (Kammen et al., 2016), topographic organization of the retinofugal visual pathways similar to post-mortem studies (Ebeling and Reulen, 1988) were observed. Somatotopy in sensorimotor pathways (Meyer et al., 1998; Ruben et al., 2001; Wahl et al., 2007) and tonotopy in auditory pathways (Morosan et al., 2001) have also been observed using tractography. These findings are in line with the recent proposition about the grid structure of fiber pathways (Wedeen et al., 2012).

Although topographic organization of white matter connectivity has been studied in the literature, we believe that a mathematical formulation of this property is essential to its understanding and valuable in neuroscientific research. Another motivation of our work is that tractography based on diffusion MRI is known to be error-prone, and false-positive dominant (Maier-Hein et al., 2017; Owen et al., 2013; Thomas et al., 2014). Consequently, removing invalid fiber tracts is a critical problem in structural connectivity analysis. Methods based on geometric models and distances have been proposed for removing outlier tracts from a fiber bundle (Aydogan and Shi, 2015; Garyfallidis et al., 2012; Kammen et al., 2016). Data-driven approaches such as the SIFT (Smith et al., 2013), LiFE (Pestilli et al., 2014) and COMMIT (Daducci et al., 2015) models have been proposed for improving the agreement between tractograms and the original diffusion data to reduce the computational artifacts from tractography algorithms. However, invalid fibers are not necessarily limited to outliers based on distance measures or computational artifacts. For bundles known to follow topographic regularity, the invalid tracts can also be those deviating from the topographic organization, which can be quantified using the methods developed here.

In this work, we first mathematically define the neuroanatomical notion of topographic regularity of fiber tracts as the preservation of the spatial relationship of nearby fiber tracts. Inspired by the mathematical formulation of tensor decomposition, we obtain a robust model of topographic regularity in fiber bundles. To the best of our knowledge, this is the first mathematical model of the neuroanatomic notion of topographic regularity in white matter fiber tracts. In addition, we apply this mathematical model to tract filtering for the removal of tracts with low topographic regularity. In our experiments, we compare our method with distance-based outlier removal and SIFT tract filtering (Smith et al., 2013) and demonstrate that our method can more effectively remove false positive tracts for the data from ISMRM 2015 Tractography Challenge (Maier-Hein et al., 2015). We also demonstrate that our method applies to different individual bundles including corticospinal tracts, callosal motor tracts and visual pathways reconstructed from the HCP data. In addition, we *quantitatively* show that, in terms of retinotopic organization, our tract filtering method produces higher

quality visual pathway fiber bundles for the HCP data as compared to distance-based filtering methods (Garyfallidis et al., 2012; Kammen et al., 2016).

A preliminary version of this work appeared in a conference paper (Wang et al., 2017). In this work, we generalize our method to group graph spectral model allowing all common eigenvalues to be used, which greatly improves the interpretability and usability of our method, and we present completely new experimental results for a systematic evaluation of the tract filtering algorithm including simulation data from 2015 ISMRM Tractography Challenge and large-scale data from HCP. We also publicly release the software for the tract filtering algorithm on the NITRC website (<https://www.nitrc.org/projects/connectopytool>).

2. Methods

2.1 Mathematical definition of topographic regularity

The topographic mapping of fiber tracts implies the neighboring relationships of nearby neurons are preserved when they connect to other nearby neurons. In this section, we first mathematically model this neuroanatomical property as illustrated in Figure 1. Below we describe our framework and definitions needed to mathematically study topographic regularity within this context.

Definition 1 (Fiber tract).—A fiber tract, or streamline, denoted as $C = \{\mathbf{x}_i \in \mathbb{R}^3 | 0 \leq i \leq L\}$ is a finite set of evenly spaced points along a curve.

Definition 2 (Tractogram).—A tractogram, or fiber bundle, Γ , is a set of fiber tracts.

Definition 3 (n -nearest-tract neighborhood).—Given a fiber tract in a tractogram, $C^0 \in \Gamma$, the n -nearest-tract neighborhood of C^0 , is the set of n spatially closest fiber tracts to C^0 , including itself, and denoted by $N_{C^0} = \{C^0, C^1, C^2, \dots, C^{n-1}\}$.

In this work, we define the distance from a tract C^k to another tract C^l as the 1-sided Hausdorff distance:

$$d_H(C^k, C^l) = \max_{\mathbf{x}_i^k \in C^k} \inf_{\mathbf{x}_j^l \in C^l} \|\mathbf{x}_i^k - \mathbf{x}_j^l\| \quad (1)$$

where $\|\mathbf{x}_i^k - \mathbf{x}_j^l\|$ is the Euclidean distance between two points $\mathbf{x}_i^k$ and $\mathbf{x}_j^l$, which are the i^{th} point on the k^{th} fiber tract C^k and the j^{th} point on the l^{th} fiber tract C^l , respectively.

Definition 4 (n -nearest-point neighborhood).—Given a fiber tract C^0 , its n -nearest-tract neighborhood $N_{C^0} = \{C^0, C^1, C^2, \dots, C^{n-1}\}$, and a point $\mathbf{x}_i^0 \in C^0$, the n -nearest-point neighborhood of $\mathbf{x}_i^0$ is defined as the set $N_{\mathbf{x}_i^0} = \{\mathbf{x}_i^0, \mathbf{x}_i^1, \mathbf{x}_i^2, \dots, \mathbf{x}_i^{n-1}\}$ such that

$\mathbf{x}_i^k, k \in [1, 2, \dots, n-1]$ is the spatially closest points to $\mathbf{x}_i^0$ on tract C^k .

Note that we have used $\mathbf{x}_i^k \in C^k$ with fixed i to denote the closest point to $\mathbf{x}_i^0$ on a neighboring tract C^k of tract C^0 . However, this does not mean that we assume the same number of points on all first tracts. Based on the n -nearest-point neighborhood, we can define the proximity measure between every pair of points within an n -nearest-point neighborhood as follows.

Definition 5 (Topographic proximity measure).—Given an n -nearest-point neighborhood of C^0 around a point $\mathbf{x}_i^0 \in C^0$, we propose a measure of proximity between any pair of points: $\{\mathbf{x}_i^k, \mathbf{x}_i^l\} \in N_{\mathbf{x}_i^0}$ as follows:

$$\rho(\mathbf{x}_i^k, \mathbf{x}_i^l) = e^{-\frac{d(\mathbf{x}_i^k, \mathbf{x}_i^l)}{\sigma^2}} \quad (2)$$

where σ is a model parameter and $d()$ is the normalized Euclidean distance computed as:

$$d(\mathbf{x}_i^k, \mathbf{x}_i^l) = \frac{\|\mathbf{x}_i^k - \mathbf{x}_i^l\|}{\max_{\{\mathbf{x}_i^k, \mathbf{x}_i^l\} \in N_{\mathbf{x}_i^0}} \|\mathbf{x}_i^k - \mathbf{x}_i^l\|}. \quad (3)$$

We call ρ the topographic proximity measure. In addition, we can define an $n \times n$ matrix $E_{\mathbf{x}_i^0}$ with elements $E_{\mathbf{x}_i^0}(k, l) = \rho(\mathbf{x}_i^k, \mathbf{x}_i^l)$, and $E_{\mathbf{x}_i^0}$ is called the topographic proximity matrix for the n -nearest-point neighborhood of $\mathbf{x}_i^0$.

The idea of topographic proximity graph construction is illustrated in Figure 2. Note that the distance measure in Eq. (3) and the topographic proximity measure in Eq. (2) are twisting and bending-invariant. Besides, because of the normalization, they are scale-invariant as well. For example, for the fibers in Figure 3(a)-(c) their topographic proximity matrices along the bundle are all identical despite the linear and nonlinear fanning or twisting. The twisting fiber bundle shown in Figure 3(c) will also yield identical topographic proximity measures along the bundle due to the rotational invariance of the distance in Eq. (3). These properties agree with the topographic regularity concept in neuroanatomy. Finally, we can define topographic regularity as follows:

Definition 6 (Topographic regularity).—A fiber tract C is topographically regular if $(E_x) = 0 \forall \mathbf{x} \in C$, where $(\cdot)$ is a measure of the variation of the topographic proximity matrices.

Our definition above interprets the neuroanatomical understanding to topographic regularity by quantifying the “spatial relationship between neuronal fibers” and the “preservation” of

such relationship. Note that the topographic variation (E_x) would not reach zero in practice and we would try to identify the fibers with minimal topographic variations. We clarify the detailed mathematic definition of topographic variation and topographic regularity in the following section.

2.2 Measuring topographic variation using group spectral graph analysis

For the numerical calculation of the topographic variation along fiber tracts, we next propose a novel graph distance inspired by the spectral graph theory (Brouwer and Haemers, 2012). We propose to first extract the common structure of the topographic proximity graphs along the neighborhood of a fiber tract and then measure the variation of the graphs with respect to the common structure. To extract the common structure of the graphs, we propose to compute their *common eigenvectors*. The notion of common eigenvectors is related to a technique called simultaneous diagonalization (Bunse-Gerstner et al., 1993) which is a special case of Tucker tensor decomposition (Tucker, 1966). In order to measure the variations with respect to the common eigenvectors, we propose to back project each individual graph onto the common eigenvectors and use the variation of the projection coefficients, which we refer to as *back-projected eigenvalues*, to represent the topographic variation. The mathematical framework of our idea is detailed in the following.

Given a tract $C = \{\mathbf{x}_1, \dots, \mathbf{x}_L\}$, we can collect the topographic proximity matrices for all $\mathbf{x}_i \in C$ as a 3rd-order tensor $\mathbf{E} = \{E_i^{K \times K} \mid 1 \leq i \leq L\}$, where K is the neighborhood size for each tract. To extract the common eigenvector(s) for the tensor $\mathbf{E}$, we adopt the following model:

$$U^* = \underset{U}{\operatorname{argmax}} K \times K \sum_{i=1}^L \|E_i U\|_F^2, s.t. U^T U = I \quad (4)$$

Note that we used E_i to denote E_{x_i} when there is no risk of confusion. In the above model, we try to find a common set of orthonormal vectors which are the most similar to all column vectors of all topographic proximity matrices. The orthonormality ensures statistical and geometrical independence of the vectors, and we denote Eq.(4). as the *group spectral graph model* (GSGM).

By differentiating the model and applying the method of Lagrange multipliers, the optimal solution U^* is defined by:

$$\Sigma U^* = \Lambda U^*, U^{*T} U^* = I, \Sigma = \sum_{i=1}^L E_i^T E_i \quad (5)$$

where I is the identity matrix, Λ^* is the diagonal matrix from Lagrange multipliers and it becomes the eigenvalue matrix when the equality holds. We shall call the optimal solution U^* the common eigenvectors of the tensor $\mathbf{E}$, and denote the Eq. (5) as *group spectral graph analysis* (GSGA).

With the common eigenvectors, we can solve the back-projected eigenvalues:

$$S_i^* = \underset{S_i}{\operatorname{argmin}} \| E_i - U^* S_i U^{*T} \|_F^2, \text{ s.t. } \operatorname{off}(S_i) = 0 \quad (6)$$

where $\operatorname{off}(S_i)$ is the off diagonal part of S_i . Note that

$$\begin{aligned} \| E_i - U^* S_i U^{*T} \|_F^2 &= \| U^{*T} E_i U^* - S_i \|_F^2 = \| \operatorname{diag}(U^{*T} E_i U^* - S_i) + \operatorname{off}(U^{*T} E_i U^* - S_i) \|_F^2, \\ &= \| \operatorname{diag}(U^{*T} E_i U^* - S_i) \|_F^2 + \| \operatorname{off}(U^{*T} E_i U^* - S_i) \|_F^2 \end{aligned}$$

where $\operatorname{diag}(\cdot)$ extracts the diagonal elements from the matrix that it operates on. The last equality is a basic property of the Frobenius norm, i.e.

$$\| A \|_F^2 = \sum_{ij} |a_{ij}|^2 = \sum_{ii} |a_{ii}|^2 + \sum_{i \neq j} |a_{ij}|^2. \text{ Resultantly, we obtain}$$

$$S_i^* = \operatorname{diag}(U^{*T} E_i U^*) \quad (7)$$

Based on the above derivations, we define the topographic variation using the back-projected spectral distance/variance:

$$\Delta_{U^*}(\{E_i \mid i = 1, 2, \dots, L\}) = \frac{1}{L} \sum_{i=1}^L \| S_i^* - \bar{S}^* \|_F^2 \quad (8)$$

where $\bar{S}^*$ is the average back-projected graph spectra. Note that

$$\| S_i^* - \bar{S}^* \|_F^2 = \| U^* S_i^* U^{*T} - U^* \bar{S}^* U^{*T} \|_F^2. \text{ Our measure is actually the variance of the topographic proximity matrices reconstructed using the common eigenvectors. We call it the group graph spectral distance, or } G^2SD.$$

Using the G^2SD measure, we can develop a tract filtering algorithm that removes irregular fiber tracts from the whole fiber bundles. Given a set of input fiber tracts, we first compute the G^2SD to measure the topographic regularity of each tract. After that, a ranking of the tracts is achieved by computing the cumulative distribution of the G^2SD values calculated from Eq. (8), i.e. the step denoted as **cumulativeDistributionEstimation**. Based on the cumulative distribution $P(\Delta_{U^*}^m)$, we then assign a binary label to each fiber according to

the threshold value μ , where $\mu \times 100\%$ is a user-specified probability. For all fibers with the false label, we can remove them from the final reconstruction. The pseudocode of our algorithm is presented in Algorithm 1. This algorithm is applicable for both whole brain tractography or the reconstruction of individual bundles.

In terms of computational complexity, our algorithm relies on pairwise tract distance computation, n-nearest-point graph construction for every point on every tract, GSGA by SVD and thresholding based on the cumulative distribution of our topographic variation. The pairwise tract distance computation requires basically two nested loops for every tract. For every point on a tract, the n-nearest-point graph construction requires the calculation of the pairwise topographic proximity for the $n \times n$ points. The GSGA requires the computation

of the SVD for the topographic proximity matrix Σ of size $n \times n$ for every tract, which has a time complexity of $O(n^3)$ (Golub and Van Loan, 2012). The thresholding requires binning the topographic variation values for all tracts. In summary, the overall complexity of our algorithm w.r.t. the number of tracts N can be written as:

$$\begin{aligned} T(N) &= T_{\text{pairwise-tract-distance}} + T_{\text{n-nearest-point}} + T_{\text{GSGA}} + T_{\text{threshold}} \\ &= O(N^2) + O(N \times n) + O(N \times n^3) + O(N \times n_{\text{bins}}) \end{aligned}$$

where n is the number of neighboring points used in the construction of the n -nearest-point graph, and n_{bins} is the number of bins used in the calculation of the cumulative distribution of topographic variation values. In our experiments, the computational time for the filtering of a fiber bundle with 10,000 tracts on a 12-core CPU is about 210 seconds.

Algorithm 1.

Tract filtering algorithm based on topographic regularity.

Input:	Fiber bundle: $\Gamma = \{C^1, C^2, \dots, C^M\}$ Neighborhood size: K Topographic proximity parameter: σ Threshold: μ
Output:	Fiber selection labels: $\Phi = \{\phi_1, \phi_2, \dots, \phi_M\}$
foreach	C^m in Γ
	$E^m \leftarrow \text{NeighborhoodGraphConstruction}(C^m, \Gamma, K, \sigma)$ //Based on Definitions 1-5
	$\Sigma^m \leftarrow [E_1^T E_1, E_2^T E_2, \dots, E_L^T E_L], E^m = \{E_1, E_2, \dots, E_L\}$
	$U^* \leftarrow \text{SVD}(\Sigma^m)$ //Based on Eq. (7)
	$S_i^* \leftarrow \text{diag}(U^*{}^T E_i^m U^*)$ //Based on Eq. (9)
	$\Delta_{U^*}^m \leftarrow \frac{1}{L} \sum_{i=1}^L \ S_i^* - \bar{S}^*\ _F^2$ //Based on Eq. (10)
end	
	$P(\Delta_{U^*}^m) \leftarrow \text{CumulativeDistributionEstimation}(\{\Delta_{U^*}^1, \Delta_{U^*}^2, \dots, \Delta_{U^*}^M\})$
foreach	C^m in Γ
	$\phi_m \leftarrow \text{bool}(\Delta_{U^*}^m \leq \eta \mid P(\Delta_{U^*}^m \leq \eta) > \mu)$
end	

3. Materials

In our experiments, we demonstrate the application of our model for topographic regularity on the filtering of fiber tracts on two datasets and different fiber bundles. Here we describe in detail the datasets and the preprocessing steps for these datasets.

ISMRM phantom data.

In our first experiment, we used the data from the ISMRM 2015 Tractography Challenge (Maier-Hein et al., 2015), where the *ground truth data* were generated using the Fiberfox software (Neher et al., 2014) using bundles segmented from an HCP subject. After that, the

challenge dataset was generated from the ground truth data to include all types of possible artifacts in diffusion imaging. The challenge dataset was generated with the aim at creating a clinical-style dataset that provides realistic bundle configurations. The challenge dataset consists of a 2mm isotropic diffusion acquisition, with 32 gradient directions at the b -value=1000 s/mm². It also contains one $b=0$ image and an optional $b=0$ volume with a reversed phase-encoding direction. For evaluation, we compare the fiber tracts generated by different algorithms with the ground truth fiber tracts.

HCP data.

For the rest of the experiments, we used the diffusion MRI (dMRI) data from the HCP Lifespan dataset and the regular cohort of young adults from the Q1 to Q3 release. The Lifespan dMRI data has an isotropic spatial resolution of 1.5mm, and each dMRI run includes 75 gradient directions distributed over 2 shells with the b -values: 1500 and 3000 s/mm². The dMRI data of the young adult cohort of HCP has an isotropic spatial resolution of 1.25 mm. The dMRI protocol was designed to acquire data with three b -values (1000, 2000, 3000 s/mm²) from 270 gradient directions. Among the 225 subjects included in the Q1–Q3 release of HCP, 215 of them completed both T1 and dMRI scans, which we use in our experiments.

Data preprocessing.

For all experiments, we computed the fiber orientation distributions (FODs) using the method developed recently for multi-shell dMRI data (Tran and Shi, 2015). This algorithm solves an adaptive energy minimization problem to jointly estimate FODs and compartment parameters from diffusion imaging data. The FODs are represented with spherical harmonics (SPHARM) and fully compatible with popular tractography tools such as the MRtrix3 (Tournier et al., 2012). The maximum SPHARM order used in each dataset was determined in proportion to the number of available gradient directions. For the ISMRM 2015 phantom data, we computed the FODs with SPHARMs up to the 8th order. For the HCP Lifespan and young adult data, we computed FODs with SPHARM order up to the 12th order and 16th order, respectively. Once the FODs were computed, we ran the iFOD1 tractography algorithm of MRtrix3 to generate the tractograms for our tract filtering experiments.

4. Experimental results

4.1 Results from the ISMRM 2015 tractography challenge data

We present the experimental results for the data from ISMRM 2015 Tractography Challenge (Maier-Hein et al., 2015). The ground truth tractogram in ISMRM 2015 challenge contains a total of 200433 tracts (Figure 4(a)). To reduce computation time, we resampled it by 10% to obtain a total of 20044 tracts. Two instances of the randomly resampled tracts are shown in Figure 4(b) and (c). We also generated a total of 20044 tracts using the FODs computed from the challenge data. We used the tractography tool from MRtrix3 with the following parameters: $\text{step_size}=0.1\text{mm}$, $\text{angle}=6^\circ$, $\text{cutoff}=0.025$ for generating the fiber tracts from the FODs. We compared results from different tract filtering algorithms with the ground truth tracts to evaluate their performance. For quantitative comparisons between a filtered

tractogram and the ground truth tractogram, we computed the mean and standard deviation of the *total tract distance* between two whole-brain tractograms X and Y, i.e.

$$\text{mean}[D(X, Y)] = \text{mean}(\min_{y \in Y} \min_{x \in X} d(y, x)) + \text{mean}(\min_{x \in X} \min_{y \in Y} d(x, y)) \text{ and}$$

$$\text{std}[D(X, Y)] = \text{std}(\min_{y \in Y} \min_{x \in X} d(y, x)) + \text{std}(\min_{x \in X} \min_{y \in Y} d(x, y)), \text{ where } d(\cdot, \cdot) \text{ is the Hausdorff distance for two fiber tracts.}$$

To examine the robustness of our method to different parameters, we applied various combinations of parameter choices to filter the tractogram in Figure 4(d) and compared the results against the ground truth in Figure 4(b). For the three parameters σ , K , and μ , we tested the following values for each parameter: $\sigma=0.001, 0.002, \dots, 0.01, 0.011, 0.012, 0.013, \dots, 0.02$; $K=20, 40, \dots, 200$; and $\mu=0.1, 0.2, \dots, 0.9$. We plotted both the mean and standard deviation of the total tract distance under different combination of the three parameters in Figure 5. For various choices of the threshold values of the parameter μ , we can observe that the proposed filtering algorithm typically produces the satisfactory results when the K and σ combinations fall into the diagonal “*grand canyon*” region in the middle of each subfigure. This means that our method is quite robust to K and σ .

For comparisons, we applied the *SIFT method* (Smith et al., 2013) combined with *fiber length filtering* to the tractogram shown in Figure 4(b). The SIFT method tries to improve the agreement between the whole volume tractogram and the diffusion data, and the fiber length filtering removes fibers that are too long and too short. In this experiment, we set the length thresholds to be $\text{mean}(\text{fiber length}) \pm k \cdot \text{std}(\text{fiber length})$, where $k=0.5, 1, 1.5, 2$, and 3 . The filtering results from $k=0.5, 1, 2$ and 3 were plotted in Figure 4(e)-(h). In addition, we presented the results of distance-based outlier removal (Garyfallidis et al., 2012). Given a tract, its Hausdorff distance to each of the other tracts in a tractogram was computed. The minimal value of these distances was then computed and used as the measure for outlier removal. We set the outlier ratio to be 30%, which matches the threshold value used in our method for results shown in Figure 4 (j). The filtered tractogram after removing 30% outlier tracts with distance-based filtering was plotted in Figure 4 (i).

The distance measures of filtered tractograms from all methods against the ground truth data in Figure 4(a) were plotted in Figure 6. For the G^2SD method, we fixed the parameters $K=120$ and $\sigma=0.01$ and only vary the threshold μ . As illustrated in Figure 5, our method is very robust with respect to parameter choices. Using these same set of parameter choices, we also compared the filtered tractograms from G^2SD against the second set of randomly generated ground truth data shown in Figure 4(b). We can see clearly from Figure 6 that the curves from the two different runs almost overlap. This further demonstrates the robustness of the G^2SD method with respect to the choices of the parameters K and σ . From the plots shown in Figure 6, we can observe that the proposed G^2SD method outperforms other methods with much smaller mean and comparable or better standard deviations for a wide range of choices in the parameter μ . Overall, this experiment shows that the performance of our method is robust to parameter selections, which makes the parameter choice relatively straightforward in its application to real data experiments.

4.2 Results for filtering individual bundles for the HCP data

In this experiment, we apply our tract filtering method to different bundles known to be topographically regular, including the callosal motor fibers, corticospinal tracts, and the optic radiation fibers in the visual pathway.

Callosal motor fibers.—Somatotopic organization of callosal motor fibers (CMF) has been studied and established previously (Wahl et al., 2007). Here we reconstructed the CMF from the HCP Lifespan data using FOD-based tractography of the MRtrix tool based on the precomputed *FreeSurfer Aseg* labels (Fischl et al., 2002). Specifically, we used the precentral gyrus masks as the seeds in tractography and kept tracts connecting precentral gyrus masks on both hemispheres. We generated a total of 50K tracts for each subject with the following tractography parameters: `step_size=0.1mm`, `angle=10°`, `cutoff=0.01`. Representative tractography results for filtering CMF tracts are shown in Figure 7. We can see that our method effectively removed irregular fibers and produced topographically more regular fiber bundles. As a comparison, we also applied the same distance-based outlier removal described in the previous experiment and the results were plotted in Figure 7. We can see that our method and distance-based filtering both successfully removed outlier tracts and achieved comparable performance in this experiment.

Corticospinal tract.—Somatotopic organization in corticospinal tract (CST) is also well-known and has been studied extensively (Lee et al., 2016; Rizzolatti and Luppino, 2001). We reconstruct the CST from the HCP data of young adults using FOD-based tractography. The precentral gyrus and brainstem regions from the *FreeSurfer Aseg* labels were used as inclusion ROIs for CST bundle generation. Note that these ROIs are not always precise for CST reconstruction thus tract filtering is necessary to obtain satisfactory results. We first compute a whole-brain tractogram containing 500K tracts with the following parameters: `step_size=0.1mm`, `angle=3.5°`, `cutoff=0.01`. The CST bundle is then extracted as those tracts passing through both the precentral and brainstem ROIs. The resulting CST bundles contain around 5K tracts. Due to the inaccuracy in ROIs, the fiber bundles might contain a significant number of invalid tracts. As a comparison, the distance-based outlier removal was also applied with the same outlier ratio = 50%. The results from both methods are shown in Figure 8. We can see that our method outperformed distance-based outlier removal and generated more organized and anatomically correct CST bundles. We also presented more detailed visualization of the topographic organization of the tracts for the CST of subject 101107 in Figure 9. For this subject, we can observe that both distance-based outlier removal and our method removed outlier tracts that deviated from the majority of the tracts in the bundle. In addition, our method more successfully removed topographically disorganized internal tracts (highlighted in the red box) according their cortical projection to the precentral gyrus.

Optic radiation.—The retinotopic organization of visual pathway is one of the most representative examples with topographic organization. Using FODs computed from the young adult cohort of HCP data, we first reconstructed retinofugal visual pathway fiber bundles based on the method proposed in (Kammen et al., 2016). Following the method in (Kammen et al., 2016), we reconstructed the optic radiation bundle using the lateral

geniculate nucleus (LGN) as the *seed* and the primary visual cortex (V1) as an inclusion region. For each bundle, around 10K tracts were generated before the application of tract filtering methods, which we denoted as the original tracts in each bundle. We compared our method with the spectral clustering based tract filtering adopted in (Kammen et al., 2016) and the distance-based outlier removal. More detail of the spectral clustering based filtering can be found in (Kammen et al., 2016). For the distance-based outlier removal, the outlier ratio was chosen as 30% that matches the parameter value of μ used in our method.

Three representative results from all methods are shown in Figure 10. We can observe that both our method and the outlier removal method removed the spurious tracts effectively. For a close examination of the topographic organization of the filtered tracts from each method, we colored the tracts with the eccentricity and plotted the results in Figure 11. Following the approach in (Kammen et al., 2016), the eccentricity of each tract was derived from their projection to the primary visual cortex, where the eccentricity was assigned with the template-based approach from (Benson et al., 2012). We can clearly see that the results from our method exhibit the highest coherence in terms of preserving the retinotopy, especially in the region highlighted by the dashed ellipse. In addition, we plotted a closed-up medial view of the optic radiation bundle of subject 10037 in Figure 12. From the results shown in both Figure 11 and Figure 12, we can see that our method achieved a better balance in removing disorganized tracts and preserving the Meyer's loop that bends anteriorly before projecting toward the visual cortex, which is known to be an important anatomical feature of the optic radiation bundle.

4.3 Quantitative experiment

The retinotopic organization of the visual cortex refers to a point-to-point mapping of the retinal space onto the visual cortex (Engel et al., 1997). In (Benson et al., 2012), an automated technique was developed that assigns to each vertex in the visual cortex two coordinates: angle and eccentricity. By leveraging this anatomical information, a novel validation method was proposed to measure the retinotopic organization of visual pathway fiber bundles based on the eccentricity component (Aydogan and Shi, 2016). They observed that the eccentricity values form a "U" shape function of the cross-section of the optic radiation projecting onto V1, and proposed to quantify the topographic regularity of the tracts based on the mean-squared-error (MSE) measure from a quadratic regression analysis of fiber tracts and eccentricity. In this experiment, we adopted the same regression analysis and used the resulting MSE to quantify the performance of different methods. Specifically, we applied our tract filtering method to the optic radiation bundles from all 215 HCP subjects used in (Kammen et al., 2016) and compared the corresponding MSE measures with those from spectral clustering used in (Kammen et al., 2016) and the distance-based outlier removal used in experiments in section 4.1 and 4.2.

As an illustration, we show in Figure 13 (a)-(d) the tract filtering results for an HCP subject with varying threshold values μ from 0.1 to 0.9. For the other two parameters K and σ , we fixed their values according to results from the simulation experiment, i.e. $K=120$ and $\sigma=0.01$. From Figure 13 (a)-(d), we can observe that the filtered tracts become visually more organized with the increase of the threshold value μ . On the other hand, we can also see the

integrity of the bundle is affected when the parameter μ is too big. For the large-scale experiment, we used the same parameter values for $K=120$, $\sigma=0.01$ and vary the parameter μ from 0.1 to 0.5. The mean MSE values from regression analysis for all 215 subjects are plotted in Figure 13 (e) together with results from the original tracts, spectral clustering, and distance-based outlier removal, which clearly shows that our method achieved the best performance in preserving the topography of the fiber tracts. We also observed that our method achieved the best performance at $\mu=0.3$. To further illustrate the detail of the improved topographic regularity achieved by all filtering methods, we plotted the histogram of the difference between the MSE of the filtered tractogram and the MSE of the original bundle from all 215 HCP subjects. We denoted $\mathbf{D}$ as the paired difference of the MSE values between a filtered tractogram and the original bundle for each subject. The histograms of $\mathbf{D}$ from different methods were plotted in Figure 14. The clear asymmetry of the histograms from our results confirm the improvement in MSE due to our method. More detailed statistics of the $\mathbf{D}$ values are further summarized in Table 1.

5 Discussion

While there has been a relatively rich literature on functional topography, research on modeling and analyzing the structural topography of white matter connectivity is sparse. In this work, we proposed a mathematical model of topographical regularity for white matter fiber bundles and used it to develop a tract filtering algorithm. Given a fiber tract generated by any tractography algorithm, our main idea is to first establish a local topographic representation at each point on the tract and then quantify the topographic regularity of the entire fiber using *group spectral graph analysis*. This ultimately led to the definition of the *group graph spectral distance* (G^2SD) measure and the tract filtering algorithm in Algorithm 1. In our experiments, we compared our method with the SIFT method and distance-based outlier removal on the filtering of a synthetic whole brain tractogram from the ISMRM 2015 Tractography Challenge and showed that our method achieved better results as compared to the other alternative methods. On real data from the HCP, we showed that our method outperforms other methods for filtering three different types fiber bundles well-known for their topography, including the corticospinal tract, callosal motor fibers, and the optic radiation. In addition, we conducted quantitative comparisons on a large-scale dataset of 215 HCP subjects and showed that the proposed method outperformed the conventional outlier removal and the spectral clustering method used in previous works for the reconstruction of the optic radiation fiber bundle.

Our work is related to the recent developments of novel tractography algorithms that aimed to improve the regularity in the generated tractograms. Global tractography algorithms were developed to incorporate regularizations into tractography formulations (Christiaens et al., 2015; Jbabdi et al., 2007; Mangin et al., 2013; Reisert et al., 2011; Wu et al., 2016). For example, in (Christiaens et al., 2015), a connection energy was considered as a regularization term in the formulation and solved via a Reversible Jump Markov Chain Monte Carlo (RJMCMC) algorithm. In another related work, Aydogan and Shi proposed a novel tractography algorithm inspired by topographic regularity in brain connectomes and demonstrated improved retinotopy in the reconstructed visual pathways (Aydogan and Shi, 2016). Instead of developing new tractography algorithm that generates valid fiber tracts, in

this work, we proposed to remove invalid tracts from any given fiber bundle based on our model of topographic regularity. Integrating our model into tractography algorithm may be very interesting.

For the quantification of the topographic regularity, we adopted the group graph spectral distance to capture the variations among the topographic proximity measures along the tracts. This is motivated by the spectral graph theory and its well-established tools for the modeling of the common structures of graphs. There is definitely room for the development of novel measures to quantify the topographic regularity of the fiber tracts. For future work, we are interested in exploring novel combinations of graph construction methods and graph distance measures for studying topographic regularity. In our large-scale quantitative evaluation of retinotopy of the optic radiation, we used the regression analysis approach developed in (Aydogan and Shi, 2016), which depends on a structural template of retinotopy and a parametric representation of the retinotopy with respect to the fiber tracts. Note also that the MSE values of the results by the topographic tractography method in (Aydogan and Shi, 2016) can be even smaller than the MSE values of our filtering method. This is due to the parallel tract assumption adopted in their method. On the other hand, the method developed in this work can be generally applied to fiber tracts generated from arbitrary tractography algorithms.

For future work, we will also explore alternative approaches for the validation of topographic regularity based on the comparison and integration of the structural topography from tractography and the functional topography computed with functional MRI (fMRI). Retinotopy mapping is one of the most well-established techniques in the extraction of functional topography in the striate cortex (Wandell and Winawer, 2015). In our experiments, we showed the agreement between the retinotopy map proposed in (Benson et al., 2012) and the visual pathways reconstructed by our method. For further research, it will be interesting to investigate the filtered and topographically regular fiber tracts can help enhance the resolution in functional retinotopy mapping, which usually has limited spatial resolution (2~3mm). In a recent work, we proposed a novel independent component analysis (ICA) of fMRI data by incorporating a topographic regularization with the filtered fiber tracts (Wang and Shi, 2017). We showed that this greatly improved our ability in detecting topographically regular components across the motor cortices. In addition to sensory and motor pathways, the topography in other more complicated brain networks such as the cortico-striato pathways were reported in tracer injection studies on macaque monkeys (Haber and Knutson, 2010; Lehman et al., 2011). It will thus be valuable to explore whether tract-regularized analysis of functional connectivity will help elucidate such topography with *in vivo* data.

In summary, we have developed a novel method for modeling the topographic regularity of fiber tracts generated by tractography analysis of diffusion MRI data. Our method is general and can be applied to fiber tracts generated by any algorithm. Although we mainly demonstrated our method for individual bundle reconstruction, the application of this method to whole-brain tractograms is straightforward as we demonstrated in the experiment with ISMRM 2015 challenge data. The tract filtering tool developed in this work has been release publicly on NITRC (<https://www.nitrc.org/projects/connectopytool>).

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Figure 1.
An example of a topographically regular fiber bundle.

Figure 2.

A schematic diagram of topographic proximity graph construction for two points x_1^0 and x_L^0 on a fiber tract C^0 .

Figure 3.
Topographically regular bundles with invariant affinity graphs. (a) Linear fanning; (b) Nonlinear fanning; (c) Nonlinear fanning and twisting.

Figure 4.

Tract filtering results with ISMRM 2015 challenge data. (a) The original ground truth tractogram. (b) and (c) show two different sub-sampling of the ground truth tractograms with 10% of the original tracts. (d) The tractogram generated by FOD-based tractography from the challenge data. (e)-(h) Filtered tractogram generated by a combination of the SIFT and length-based filtering with the threshold parameter $TH=3\sigma$, $TH=2\sigma$, $TH=1\sigma$, $TH=0.5\sigma$. (i) Filtered tractogram with distance-based outlier removal by setting the outlier ratio = 30%. (j) Results from out method with $K=120$, $\sigma=0.01$ and $\mu=0.3$.

Figure 5.

Quantitative comparisons of the filtered tractograms from the proposed G^2SD and the ground truth data in Figure 4(b) from the ISMRM 2015 Challenge. Top: mean of the total tract distance; Bottom: standard deviation of the total tract distance. For each choice of the threshold parameter $\mu=0.1, 0.3, 0.5, 0.7$ and 0.9 , the mean (top) and standard deviation (bottom) of the total tract distance are plotted for different choices of (K, σ) in each sub-panel. The dashed contours are the level contours corresponding to the annotated values on the plots. Regions enclosed by the level contours have smaller values than annotated values.

Figure 6.

A comparison of tractogram generated by different filtering methods with the ground truth from the ISMRM 2015 challenge data. Left: mean of the total tract distance; Right: standard deviation of the total tract distance. For the proposed G²SD method, K and σ are fixed to be 120 and 0.01 and only the threshold μ varies from 0.1 to 0.9.

Figure 7.

Anterior view of the results of CMF filtering for subjects LS2001, LS2009 and LS2037 from the Lifespan dataset of HCP. Top row: original CMF tracts generated from FOD-based tractography connecting the motor cortices of both hemispheres; Mid row: CMF bundles filtered by distance-based outlier removal with the outlier ratio set to 30%. Bottom row: filtered tracts from our method. Parameters used in our tract filtering algorithm are: $K=120$, $\sigma=0.01$, $\mu=0.3$.

Figure 8.

Anterior view of the results of CST filtering for subjects: 101107, 102311 and 106521 from HCP. Top row: original CST bundle extracted from a whole-brain tractogram using anatomical ROIs. Mid row: CST bundle filtered by distance-based outlier removal with outlier ratio equal to 50%; Bottom row: filtered CST bundles from our method. The parameters used in our filtering algorithm are: $K=120$, $\sigma=0.01$, $\mu=0.5$.

Figure 9.

A detailed illustration of the topographic organization in the CST bundle of subject 101107. Because many tracts leave the brainstem around the midbrain, the superior half of the bundle was obtained for visualization here by cutting the tracts at the midbrain region. Respectively, (a), (b) and (c) show the tract from the original CST, the result from distance-based outlier removal with 50% outlier ratio, and the result from our topographic tract filtering with $K=120$, $\sigma=0.01$ and $\mu=0.5$. The first column shows the fiber tracts and second column visualizes the topographic arrangement of the tracts by connecting both ends of a tract with a

straight line and coloring the lines according to their laterality on the precentral gyrus. The colors vary from blue to red as the tracts move from medial to lateral along the precentral gyrus.

Figure 10.

Results of filtering reconstructed optic radiation bundles from three HCP subjects: 100307(top row), 103414 (middle row) and 106319 (Bottom row). From left to right are the results of the original bundle, spectral clustering, distance-based outlier removal (outlier ratio = 30%), and the proposed method ($K=120$, $\sigma=0.01$, $\mu=0.3$), respectively.

Figure 11. Topographic organization of the optic radiation bundles of subject 100307 filtered by different methods. The streamlines are color-coded based on the eccentricity derived from their projection to the primary visual cortex.

Figure 12.

A medial view comparison of the optic radiation bundle of subject 100307. As highlighted in the red box, our method achieved a better preservation of the Meyer's loop than the filtered tracts from distance-based outlier removal.

Figure 13.

(a)-(d) shows the filtered optic radiation of subject 100307 with the following parameter choices from our method: ($K=120$, $\sigma=0.01$, $\mu=0.1$), ($K=120$, $\sigma=0.01$, $\mu=0.2$), ($K=120$, $\sigma=0.01$, $\mu=0.7$), ($K=120$, $\sigma=0.01$, $\mu=0.9$), respectively (e) The overall MSE measures of topographic regularity of filtered tractograms from different methods: original bundle, spectral clustering, distance-based outlier removal with outlier ratio = 30%, and our method with varied threshold values from 0.1 to 0.5.

Figure 14. Histograms of the pairwise difference of MSE for the bundles from different filtering methods versus the original bundles.

Table 1.

Statistics of D that denotes the pairwise difference of the MSE measure of topography

D	Spectral clustering	Distance-based outlier removal (30%)	Our method (K=120, $\sigma=0.01$)				
			$\mu=0.1$	$\mu=0.2$	$\mu=0.3$	$\mu=0.4$	$\mu=0.5$
(mean $\pm$ std)	-1.2 $\pm$ 1.28	-1.25 $\pm$ 1.9	-1.64 $\pm$ 1.24	-1.90 $\pm$ 1.68	-1.96 $\pm$ 2.11	-1.93 $\pm$ 2.56	-1.81 $\pm$ 3.00