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A Bayesian Approach to Fiber Orientation Estimation Guided by Volumetric Tract Segmentation

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Abstract

Diffusion magnetic resonance imaging (dMRI) provides information about the microstructure of white matter in the human brain. From dMRI, streamlining tractography is often used to reconstruct computational representations of white matter tracts from which differences in structural connectivity can be explored. In the fiber tracking process, anatomical information can help reduce tracking errors caused by crossing fibers and image noise. In this paper, we propose a Bayesian method for estimating *fiber orientations* (FOs) guided by anatomical tract information using *diffusion tensor imaging* (DTI), which is a standard clinical and research dMRI protocol. The proposed method is named *Fiber Orientation Reconstruction guided by Tract Segmentation* (FORTS). A first step segments and labels the white matter tracts volumetrically, including explicit representations of crossing regions. A second step estimates the FOs using the diffusion information and the anatomical knowledge from segmented white matter tracts. A single FO is estimated in the noncrossing regions while two FOs are estimated in the crossing regions. A third step carries out streamlining tractography that uses information from both the segmented tracts and the estimated FOs. Experiments performed on a digital crossing phantom, a physical phantom, and brain DTI of 18 healthy subjects show that FORTS is able to use the anatomical information to produce FOs with better accuracy and to reduce anatomically incorrect streamlines. In particular, on the brain DTI data, we studied the connectivity of anatomically defined tracts to cortical areas, which is not straightforwardly achievable using only volumetric tract segmentation. These connectivity results demonstrate the potential application of FORTS to scientific studies.

Keywords

DTI; fiber orientation estimation; volumetric tract segmentation

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1. Introduction

Diffusion magnetic resonance imaging (dMRI) has enabled the reconstruction of white matter tracts by capturing the anisotropy of the water diffusion in tissue. In a basic dMRI strategy, *diffusion tensor imaging* (DTI) models the water diffusion as a diffusion tensor (Basser et al., 1994). More advanced diffusion imaging techniques, such as *high angular resolution diffusion imaging* (HARDI) (Tuch et al., 2002) and *diffusion spectrum imaging* (DSI) (Wedeen et al., 2005), have been used to represent crossing fibers. However, compared to DTI, HARDI and DSI usually require longer acquisition times, which currently limits their clinical use.

Using dMRI, the technique of tractography can be used to track the neural fiber bundles in the human brain (Mori et al., 1999; Basser et al., 2000). Many tractography methods use a streamlining technique based on *fiber orientations* (FOs) computed from the dMRI measurements (Behrens et al., 2007; Lazar et al., 2003; Malcolm et al., 2010; Descoteaux et al., 2009; Wedeen et al., 2008). With the large number of existing DTI data sets and ongoing DTI acquisitions, tractography based on DTI is still a widely used and important tool for scientific studies on a variety of diseases (Audoin et al., 2007; Planetta et al., 2013; Poudel et al., 2014; Zhou et al., 2008; Shenton et al., 2012; Kubicki et al., 2005). In addition, tractography on DTI is also used to investigate the human connectome, which can give a structural description of the human brain network (Horn et al., 2014; Wang et al., 2013; Zhu et al., 2013).

In the fiber tracking process, anatomical knowledge of tracts can help overcome errors caused by crossing fibers and image noise (Cheng et al., 2006). Several works have explored the use of anatomical information to aid fiber tracking. Cheng et al. (2006) obtain anatomical information from an initial fiber tracking, where the center line of a fiber bundle is calculated. Then the final fiber tracking is guided by the center line. Aranda et al. (2014) use a “flocking” model to incorporate the interactions between neighbor fiber streamlines. By examining the collective behavior of the pathways belonging to the same group, the propagation direction is modified. However, as the anatomical information also comes from tractography, no real prior anatomical knowledge is incorporated in Cheng et al. (2006) and Aranda et al. (2014). Kleinnijenhuis et al. (2012) use an additional image modality, high field gradient echo magnetic resonance imaging, to provide anatomical information and inform fiber tracking. Yet the method is limited to DTI data sets where high field (such as 7T) gradient echo images have also been acquired. Furthermore, all of these methods are based on local cues about possible FOs; they do not use knowledge of the positions of tracts and their likely regions of overlap.

Another source of anatomical information, which has not received much attention, is volumetric tract segmentation (Bazin et al., 2011; Awate et al., 2007; Yendiki et al., 2011; Nazem-Zadeh et al., 2011; Ye et al., 2015). Results from these methods contain tract information such as shape and location, and can be used to inform fiber tracking. Volumetric tract segmentation labels each voxel with a tract class and does not necessarily require the process of fiber tracking.

In this work, we explore the incorporation of anatomical knowledge into DTI-based FO estimation by using guidance from volumetric segmentation of fiber tracts. We use the DOTS algorithm described in Bazin et al. (2011) to provide the volumetric segmentation because 1) it is based on DTI data, 2) it provides anatomical tract information, and 3) it is able to identify crossing tracts. This work is an extension of a previous conference paper (Ye et al., 2012), which presents a method to track fibers through crossing regions with the aid of volumetric tract segmentation. The proposed method is named *Fiber Orientation Reconstruction guided by Tract Segmentation* (FORTS). Here, we generalize the FO estimation to complete tracts in both noncrossing and crossing regions and provide a Bayesian framework for the estimation algorithm. In particular, we use the *maximum a posteriori* (MAP) estimation criterion to estimate the FOs. The anatomical information from volumetric tract segmentation is modeled in the prior distribution together with the spatial smoothness of the FOs. The diffusion information is encoded in the likelihood term. The calculus of variations is applied to the resulting objective function to yield Euler-Lagrange equations, which are solved iteratively to estimate the FOs. Using the estimated FOs, a streamlining fiber tracking strategy is also presented. We performed FORTS on a digital crossing phantom, the Fiber Cup phantom (Fillard et al., 2011; Poupon et al., 2008), and brain DTI data for validation. In particular, on the brain DTI data, we studied the connectivity of anatomically defined tracts to cortical areas, which is not straightforwardly achievable using only volumetric tract segmentation, to demonstrate the potential application of FORTS to scientific studies.

2. Methods

In this section, we first describe the DOTS algorithm for volumetric tract segmentation. Then we describe our MAP framework and the FORTS algorithm for FO estimation using the results of tract segmentation. We also describe a streamlining fiber tracking strategy using the estimated FOs and tract segmentation. Finally, the seeding strategy and cortical label representation for the connectivity analysis are presented.

2.1. DOTS Algorithm

DOTS is an atlas-based volumetric tract segmentation algorithm using a *Markov random field* (MRF) framework (Bazin et al., 2011). It is available at <http://www.nitrc.org/projects/dots/>. The atlas of the white matter tracts is built according to Mori et al. (2005). The energy function specifying the MRF is given by

$$E(l) = \sum_x \left(V_1(x, l(x)) + \sum_{y \in N_x} V_2(x, y, l(x), l(y)) \right). \quad (1)$$

Here, V_1 is a unary energy term at x with the label of $l(x)$, and V_2 is a pairwise energy term that models the interaction between the voxel at x labeled as $l(x)$ and the voxels in its neighborhood N_x at location y with the label of $l(y)$. Note that the DOTS algorithm is able to resolve crossing tracts by explicitly treating the crossing region of each pair of crossing

tracts as a separate case. Thus $\mathcal{L}(x)$ and $\mathcal{L}(y)$ are sets of single tract labels. For example, suppose tract a and b cross. Then the crossing region of a and b would be labeled as $\{a, b\}$ and the noncrossing part of tract a and b would be $\{a\}$ and $\{b\}$, respectively. The unary term combines the diffusion information in the data with the atlas to model the likelihood of label $\mathcal{L}(x)$ at location x :

$$V_1(x, \mathcal{L}(x)) = d(x) u_{\mathcal{L}(x)}(x) c_{\mathcal{L}(x)}(x). \quad (2)$$

Here, $d(x)$ represents the shape of the tensor, which contributes to distinguishing noncrossing, crossing, and isotropic regions; $u_{\mathcal{L}(x)}(x)$ is computed from the registered statistical atlas, which indicates the likelihood of the location of x belonging to label $\mathcal{L}(x)$; and $c_{\mathcal{L}(x)}(x)$ compares the tensor with the directional information in the atlas and takes large value when the directional information agrees. The pairwise term uses the connection information from DTI to encode the interaction between neighbor voxels:

$$\sum_{y \in N_x} V_2(x, y, \mathcal{L}(x), \mathcal{L}(y)) = s(x, y^+) V_1(y^+, \mathcal{L}(y^+))_{\mathcal{L}(y^+) \cap \mathcal{L}(x) \neq \emptyset} + s(x, y^-) V_1(y^-, \mathcal{L}(y^-))_{\mathcal{L}(y^-) \cap \mathcal{L}(x) \neq \emptyset}. \quad (3)$$

Here, $\mathbb{1}$ is an indicator function, $s(x, y)$ measures the directional similarity between neighbors, and y^+ and y^- are two neighbor voxels of x . Specifically, let the PEV of the

tensor at x be $\mathbf{v}_x$ and $\mathbf{r}_{xy}$ be the vector pointing from x to y ; then $y^+ = \arg \max_{y \in N_x, \mathbf{r}_{xy} \cdot \mathbf{v}_x > 0} s(x, y)$ and $y^- = \arg \max_{y \in N_x, \mathbf{r}_{xy} \cdot \mathbf{v}_x \leq 0} s(x, y)$. Each voxel is assigned a label after the energy function is optimized. Details about the specification of V_1 and V_2 and the optimization of $E(\mathcal{L})$ are found in Bazin et al. (2011).

After the MRF assigns a label to each voxel, the noncrossing and crossing regions of a tract are combined to create a representation of the complete tract.

2.2. MAP Estimation of FOs

Consider a region in the brain that is segmented as tract $\mathcal{L} = \mathcal{L}_n \cup \mathcal{L}_c$ by DOTS, where $\mathcal{L}_n$ and $\mathcal{L}_c$ are the noncrossing and crossing regions, respectively. We seek to estimate the FOs (unit vectors) in the whole tract with guidance from both the volumetric tract segmentation and diffusion information. For this purpose, three core assumptions are made: 1) fibers propagate smoothly inside a tract; 2) fibers located at a tract surface propagate orthogonally to the surface normals except at tract ends; and 3) in noncrossing tract regions, the FOs generally agree with the PEVs of the diffusion tensors. As described next, we use an MAP estimation strategy that incorporates these three assumptions.

Given the diffusion tensors and the tract segmentation, the PEVs, represented by the symbol $\mathbf{v}$, of the tensors and the tract surface normals, represented by the symbol $\mathbf{g}$, of the whole

tract $\mathcal{L}$ can be calculated. Note that to account for possible inaccuracy and roughness of tract segmentation, we first apply a morphological restoration and then a Gaussian smoothing to the whole tract segmentation $\mathcal{L}$. Thus, the tract surface normal is calculated as

$$\mathbf{g} = \frac{\nabla G_{\sigma}(\mathcal{L} \circ B \bullet B)}{|\nabla G_{\sigma}(\mathcal{L} \circ B \bullet B)|}, \quad (4)$$

where “ $\circ$ ” and “ $\bullet$ ” represent morphological opening and closing, respectively, B is a structural element, and $G_{\sigma}(\cdot)$ is Gaussian smoothing. The morphological opening and closing form a morphological restoration process (Schonfeld and Goutsias, 1991), which improves the quality of tract segmentation and surface normal computation. In this work, the radius of the structural element is 1 mm, and the standard deviation of the Gaussian kernel is 0.35 mm. The estimate of the FO $\mathbf{f}$ can then be formulated as

$$\hat{\mathbf{f}} = \arg \max_{|\mathbf{f}|=1} P(\mathbf{f}|\mathbf{v};\mathbf{g}), \quad (5)$$

where the constraint of $|\mathbf{f}| = 1$ ensures that the FOs are estimated as unit vectors. Note that the semicolon in Eq. (5) indicates that $\mathbf{g}$ is treated as a deterministic parameter of the density rather than a random variable.

We can expand $P(\mathbf{f}|\mathbf{v};\mathbf{g})$ as follows

$$P(\mathbf{f}|\mathbf{v};\mathbf{g}) = \frac{P(\mathbf{f};\mathbf{g})P(\mathbf{v}|\mathbf{f})}{\int P(\mathbf{f};\mathbf{g})P(\mathbf{v}|\mathbf{f})d\mathbf{f}} = \frac{1}{Z} P(\mathbf{f};\mathbf{g})P(\mathbf{v}|\mathbf{f}) \propto P(\mathbf{f};\mathbf{g})P(\mathbf{v}|\mathbf{f}), \quad (6)$$

where $Z = \int P(\mathbf{f};\mathbf{g})P(\mathbf{v}|\mathbf{f})d\mathbf{f}$ is a constant. Here, $P(\mathbf{f};\mathbf{g})$ is the prior distribution of the FO, where the surface normal $\mathbf{g}$ is considered a parameter, and $P(\mathbf{v}|\mathbf{f})$ is the likelihood term. We specify each of these terms in the following sections.

2.2.1. Prior Distribution—The prior distribution contains information about smoothness and tract segmentation. It can be modeled as

$$P(\mathbf{f};\mathbf{g}) = P_1(\mathbf{f})P_2(\mathbf{f};\mathbf{g}), \quad (7)$$

where $P_1(\mathbf{f})$ ensures smoothness and $P_2(\mathbf{f};\mathbf{g})$ enforces a tract constraint. First, $P_1(\mathbf{f})$ is modeled using the gradients of $\mathbf{f}$ to preserve smoothness:

$$P_1(\mathbf{f}) \propto e^{-\alpha \sum_{x \in \mathcal{L}} |\nabla \mathbf{f}(x)|^2}, \quad (8)$$

where α is a constant to be specified by the user. Given this term, when the FOs are smoother, the sum of squared gradient magnitudes are smaller, and this corresponds to a higher value of the prior density. Second, to encourage the fibers to propagate in a direction orthogonal to the tract surface normals, $P_2(\mathbf{f}; \mathbf{g})$ is modeled using the inner product between $\mathbf{f}$ and $\mathbf{g}$:

$$P_2(\mathbf{f}; \mathbf{g}) \propto e^{-\sum_{x \in \mathcal{L}} \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2}. \quad (9)$$

Thus, higher prior probability is given when the FO is closer to being orthogonal to the tract surface normal. The function $\mu(x)$ is used to discriminate between the sides of tracts and the ends of tracts. Since tract ends are usually in noncrossing regions and the PEVs at tract ends are close to being parallel to the tract surface normals, $\mu(x)$ is specified as:

$$\mu(x) = \begin{cases} 0, & \text{if } |\mathbf{g}(x) \cdot \mathbf{v}(x)| > t \text{ and } x \in \mathcal{L}_n \\ \mu_0 & \text{otherwise} \end{cases}, \quad (10)$$

where t is a threshold ($t = 0.5$ in this work) and μ_0 controls the influence of tract segmentation when the surface normal constraint is used. Note that $\mathbf{g}(x)$ and $\mathbf{v}(x)$ are unit vectors. In practice, this criterion gives a good identification of the tract ends. Therefore, the complete joint prior density is modeled as

$$P(\mathbf{f}; \mathbf{g}) \propto e^{-\sum_{x \in \mathcal{L}} (\alpha |\nabla \mathbf{f}(x)|^2 + \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2)}, \quad (11)$$

where α and $\mu(x)$ together decide the relative weightings of the constraints of smoothness and tract segmentation.

2.2.2. Likelihood—Suppose the likelihood $P(\mathbf{v}|\mathbf{f})$ is independent between voxels. Then we have

$$P(\mathbf{v}|\mathbf{f}) = \prod_{x \in \mathcal{L}} p(\mathbf{v}(x)|\mathbf{f}(x)), \quad (12)$$

where $p(\mathbf{v}(x)|\mathbf{f}(x))$ is the local likelihood term at each voxel x . The local likelihood term is modeled differently in different regions. In crossing regions, we model the FO and the PEV as independent variables because the PEV is no longer a valid estimate of the FO. Thus, the

likelihood term is a uniform distribution in each direction. In noncrossing regions, the PEV provides an estimate of the FO, and the likelihood term is modeled as a Gaussian distribution, which is motivated by the use of sums of squared differences in energy functions to describe dissimilarities between vectors, for example, in gradient vector flow (Xu and Prince, 1997, 1998). Therefore, the local likelihood term in the complete tract is modeled as

$$p(\mathbf{v}(x)|\mathbf{f}(x)) = \begin{cases} \text{constant}, & x \in \mathcal{L}_c \\ \frac{1}{Z_l} e^{-\lambda_0 |\mathbf{v}(x) - \mathbf{f}(x)|^2}, & x \in \mathcal{L}_n \end{cases}, \quad (13)$$

where Z_l is a normalization constant and λ_0 is a constant that controls the influence of data fidelity (the agreement between the PEV and the estimated FO) in noncrossing regions. Larger λ_0 leads to more influence from the PEV on the FO estimation.

2.2.3. Objective Function and Optimization—Now that the prior density and likelihood terms have been specified, and using the assumption of voxel independence, we can write the FO estimate as

$$\begin{aligned} \hat{\mathbf{f}} &= \arg \max_{|\mathbf{f}(x)|=1} P(\mathbf{f}; \mathbf{g}) \prod_{x \in \mathcal{L}} p(\mathbf{v}(x)|\mathbf{f}(x)) \\ &= \arg \max_{|\mathbf{f}(x)|=1} \left\{ \prod_{x \in \mathcal{L}_n} e^{-(\alpha |\nabla \mathbf{f}(x)|^2 + \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2)} e^{-\lambda_0 |\mathbf{v}(x) - \mathbf{f}(x)|^2} \right\} \times \left\{ \prod_{x \in \mathcal{L}_c} e^{-(\alpha |\nabla \mathbf{f}(x)|^2 + \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2)} \right\}. \end{aligned} \quad (14)$$

By taking the logarithm and combining noncrossing and crossing regions, we have

$$\hat{\mathbf{f}} = \arg \min_{|\mathbf{f}(x)|=1} \sum_{x \in \mathcal{L}} (\alpha |\nabla \mathbf{f}(x)|^2 + \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2 + \lambda(x) |\mathbf{v}(x) - \mathbf{f}(x)|^2), \quad (15)$$

where

$$\lambda(x) = \begin{cases} \lambda_0, & x \in \mathcal{L}_n \\ 0, & x \in \mathcal{L}_c \end{cases}. \quad (16)$$

To solve the minimization problem, we write the objective function in Eq. (15) in continuous form and relax the constraint of $|\mathbf{f}(x)| = 1$:

$$E(\mathbf{f}) = \int \alpha |\nabla \mathbf{f}(x)|^2 + \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2 + \lambda(x) |\mathbf{v}(x) - \mathbf{f}(x)|^2 dx. \quad (17)$$

For convenience, hereafter we drop the location x in the equations. Suppose $\mathbf{f} = (f_x, f_y, f_z)$, $\mathbf{v} = (v_x, v_y, v_z)$, and $\mathbf{g} = (g_x, g_y, g_z)$; then the Euler-Lagrange equations for Eq. (17) can be obtained using calculus of variations (Courant and Hilbert, 1966):

$$\begin{aligned} \alpha \nabla^2 f_x &= \mu g_x (f_x g_x + f_y g_y + f_z g_z) + \lambda (f_x - v_x), \\ \alpha \nabla^2 f_y &= \mu g_y (f_x g_x + f_y g_y + f_z g_z) + \lambda (f_y - v_y), \\ \alpha \nabla^2 f_z &= \mu g_z (f_x g_x + f_y g_y + f_z g_z) + \lambda (f_z - v_z). \end{aligned} \quad (18)$$

Using the numerical strategy in Horn and Schunck (1981), the following iterations can be applied to estimate $\mathbf{f}$ (see Appendix A for a derivation). At the k -th iteration,

$$\begin{aligned} f_x^{k+1} &= \overline{f_x^k} - \frac{\mu g_x (g_x \overline{f_x^k} + g_y \overline{f_y^k} + g_z \overline{f_z^k})}{\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2)} + \frac{\lambda [(\alpha + \lambda)(v_x - \overline{f_x^k}) + \mu (g_y^2 + g_z^2)(v_x - \overline{f_x^k}) - \mu g_x g_y (v_y - \overline{f_y^k}) - \mu g_x g_z (v_z - \overline{f_z^k})]}{(\alpha + \lambda)(\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2))}, \\ f_y^{k+1} &= \overline{f_y^k} - \frac{\mu g_y (g_x \overline{f_x^k} + g_y \overline{f_y^k} + g_z \overline{f_z^k})}{\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2)} + \frac{\lambda [(\alpha + \lambda)(v_y - \overline{f_y^k}) - \mu g_x g_y (v_x - \overline{f_x^k}) + \mu (g_x^2 + g_z^2)(v_y - \overline{f_y^k}) - \mu g_x g_z (v_z - \overline{f_z^k})]}{(\alpha + \lambda)(\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2))}, \\ f_z^{k+1} &= \overline{f_z^k} - \frac{\mu g_z (g_x \overline{f_x^k} + g_y \overline{f_y^k} + g_z \overline{f_z^k})}{\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2)} + \frac{\lambda [(\alpha + \lambda)(v_z - \overline{f_z^k}) - \mu g_x g_z (v_x - \overline{f_x^k}) - \mu g_y g_z (v_y - \overline{f_y^k}) + \mu (g_x^2 + g_y^2)(v_z - \overline{f_z^k})]}{(\alpha + \lambda)(\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2))}, \end{aligned} \quad (19)$$

where $\overline{f_x^k}$, $\overline{f_y^k}$, and $\overline{f_z^k}$ are the local averages of f_x^k , f_y^k , and f_z^k , respectively.

Eq. (19) gives an iterative algorithm for the estimation of the FOs throughout a given tract $\mathcal{L}$. The initial values for $\mathbf{f}$ are provided by the PEVs in the noncrossing regions and zero vectors in the crossing regions. After each iteration k , we project nonzero $\mathbf{f}^{k+1}$ onto the unit sphere $\|\mathbf{f}\|_1 = 1$ by normalization: $\mathbf{f}^{k+1} := \frac{\mathbf{f}^{k+1}}{\|\mathbf{f}^{k+1}\|_1}$. The iterative update terminates when the average difference between normalized $\mathbf{f}^{k+1}$ and $\mathbf{f}^k$ is below a threshold or the maximal number of iterations is reached. Assuming the update terminates at the K -th iteration, we have the normalized vectors $\mathbf{f}^{K+1}$ as the final estimated FOs. Note that because in noncrossing regions the FOs are initialized by the PEVs, which are good estimates of FOs, and in crossing regions the FOs are constrained by smoothness and tract segmentation geometry, even when the maximal number is reached, the estimated FOs are in globally desired direction.

2.3. Fiber Tracking Using the Estimated FOs

Given the estimated FOs in each tract, streamlining fiber tracking can be performed. Here we use a strategy that is similar to the FACT algorithm (Mori et al., 1999). Each FO is used to propagate the fiber streamlines in the current voxel until they reach the next voxel. For a

streamline seeded in a tract, the FOs of the corresponding tract are used for propagation inside the tract, and outside the tract the PEVs are used.

A starting *fractional anisotropy* (FA) threshold is used to initialize fiber tracking: only voxels with FA larger than the starting threshold can be used as seeding voxels. A stopping FA threshold is used to terminate fiber tracking: in noncrossing regions, when a streamline reaches a voxel with FA below the stopping FA threshold, fiber tracking is terminated; in crossing regions, the stopping FA threshold is not used. A turning angle threshold is also employed for terminating the fiber tracking: when the angle between the FOs in the current step and the previous step is larger than the turning angle threshold, fiber tracking is terminated. In this work, both the starting and stopping FA thresholds are 0.2 and the angle threshold is 40°, which are typical values in deterministic streamlining fiber tracking algorithms (Thomas et al., 2011; Wu et al., 2007).

2.4. Connectivity Analysis

For the brain DTI data, we studied connectivity of anatomically defined tracts to cortical regions. The seeding voxels were decided as follows. For each tract, we first calculated the signed distance map from the corresponding binary tract segmentation mask. Then, among the voxels inside the tract, we selected the ones that are more than $d = 3$ voxels away from the tract boundary. This step is to account for possible segmentation errors near the boundaries in DOTS. Finally, among these voxels, only those in the noncrossing regions were used as seeding voxels.

The connectivity is then represented by the counts of reconstructed streamlines hitting the cortical labels. Note that we use the term “counts of streamlines” instead of fiber counts (as suggested in Jones et al. (2013)), because tractography does not produce estimates of actual nerve fibers. The cortical labels were obtained on T1-weighted images using the method in Desikan et al. (2006) as implemented in the FreeSurfer software (Fischl, 2012) (<https://surfer.nmr.mgh.harvard.edu/>). These labels were then extended inward by three voxels so that the connectivity results are robust to FA thresholds in fiber tracking.

3. Results

FORTS was first performed on a 3D digital crossing phantom, then on the Fiber Cup phantom (Fillard et al., 2011; Poupon et al., 2008), and finally on brain DTI data from 18 healthy subjects. In all three experiments, FORTS was compared with two FO estimation methods on DTI: the BEDPOSTX algorithm (Behrens et al., 2007) as implemented in the FSL software (Jenkinson et al., 2012) (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) and the CFARI algorithm (Landman et al., 2012) as implemented in the JIST software (Lucas et al., 2010) (<http://www.nitrc.org/plugins/mwiki/index.php/jist:CFARI>). BEDPOSTX uses a ball-and-stick model to resolve crossing fibers (Behrens et al., 2007) and CFARI uses a multi-tensor model with a fixed tensor basis to estimate crossing FOs (Landman et al., 2012).

3.1. Digital Crossing Phantom

A 3D digital crossing phantom simulating two tracts crossing was generated for a proof-of-concept experiment (see Figure 1). One b_0 image (the image without diffusion weighting)

and 30 diffusion gradient directions with b -values of 700 s/mm^2 were used. The b_0 image has intensity $S_0 = 1$. Rician noise ($\sigma = 0.05$, signal-to-noise ratio: $S_0/\sigma = 20$) was added to the *diffusion weighted images* (DWIs). We used the labels of the two tracts as the segmentation. An example of the FOs estimated by FORTS ($\alpha = 3$, $\lambda_0 = 1$, and $\mu_0 = 50$) is shown in Figure 1, where it can be seen that the crossing FOs are correctly estimated. Figure 1 also shows that BEDPOSTX and CFARI produced noisier results than FORTS.

To quantitatively evaluate the results, we use the following error measure at each voxel:

$$e_{\text{FO}} = \max \left(\frac{1}{N_1} \sum_{i=1}^{N_1} \min_j \arccos(\mathbf{v}_i \cdot \mathbf{u}_j), \frac{1}{N_2} \sum_{j=1}^{N_2} \min_i \arccos(\mathbf{v}_i \cdot \mathbf{u}_j) \right) \cdot \frac{180^\circ}{\pi}. \quad (20)$$

Here, N_1 is the number of estimated FOs $\mathbf{v}_i$, and N_2 is the number of ground truth FOs $\mathbf{u}_j$. N_2 can be 1 or 2, depending on whether crossing fibers exist at the location. The first term in the max function measures how far away the estimated directions are from the ground truth, and the second term in the max function measures how accurate the true directions are estimated. Both terms are expected to be small when a good estimate is achieved, therefore a max operation is used to report the worst of the two errors. Because the challenge is to estimate crossing FOs, we focus on the comparison in the crossing region. The means and standard deviations of FO estimation errors in the crossing region are shown in Figure 2(a). FORTS estimates the crossing FOs more accurately than BEDPOSTX and CFARI.

Next, we studied the effects of the parameters in FORTS. Since there are only two degrees of freedom in choosing the parameters, we fixed $\lambda_0 = 1$ and tested different combinations of α and μ_0 . The average errors in the whole phantom are shown in Figure 2(b). It can be seen that with the true tract labels the error is reduced when proper parameter settings are used. For example, $\alpha = 10$ and $\mu_0 = 50$ achieves the best results among the tested cases.

3.2. Fiber Cup Phantom

FORTS was also run on the Fiber Cup phantom (Fillard et al., 2011; Poupon et al., 2008) and compared with BEDPOSTX and CFARI. For this experiment, we selected the acquisition with 3 mm isotropic resolution and a b -value of 650 s/mm^2 , which most resembles standard DTI protocols. The acquisition has two repeated scans, and each of them has one b_0 image and 64 gradient directions.

Since DOTS cannot be run without a prior probability of the tract locations, the 3D tract segmentation required by FORTS was manually delineated on the phantom. We defined five tracts, which can be seen overlaid on a b_0 axial image in Figure 3(a). Then, the proposed FO estimation was carried out with $\alpha = 3$, $\lambda_0 = 1$, and $\mu_0 = 50$. We highlight two regions which include crossing tracts and compare the proposed FO estimation results with BEDPOSTX and CFARI in Figure 3(a). It can be seen that FORTS is able to resolve crossing FOs with the manually defined tracts, while the other two methods often fail to recover the crossing fibers.

Next, we tested different parameter settings for FORTS. We show three representative cases in Figure 3(b) for the two highlighted regions in Figure 3(a). Overall, the results are similar with different settings, while subtle differences can be observed. For example, in Figure 3(b) we highlight regions in the first column to compare different μ_0 with the same α , where increasing the constraint from tract segmentation leads to more horizontal FOs; in the second column, the highlighted voxel demonstrate the difference of using different smoothing parameter α . Note that here we are not claiming one parameter is necessarily better than another. Instead, these results all in general agree with the tract geometry, which indicates robustness of the method to parameters.

3.3. Brain DTI

The proposed method was applied to a brain DTI data set comprising 18 healthy subjects, where T1-weighted images were also acquired. The DWIs and T1-weighted images were acquired on a 3T MR scanner (Intera, Philips Medical Systems, Netherlands) using a multi-slice, single-shot EPI sequence. The DTI sequence consists of 30 diffusion gradient directions, each with $b = 700 \text{ s/mm}^2$, and one b_0 image. The native in-plane resolution is $2.2 \text{ mm} \times 2.2 \text{ mm}$ (matrix size: 96×96), and the native slice thickness is 2.2 mm . The scanner resampled the slices and generated the output resolution of $0.828 \text{ mm} \times 0.828 \text{ mm} \times 2.2 \text{ mm}$ (matrix size: 256×256). The in-plane resolution of the T1-weighted images is $0.828 \text{ mm} \times 0.828 \text{ mm}$ (matrix size: 256×256), and the slice thickness is 1.1 mm . The T1-weighted images were then isotropically resampled to the resolution of 0.828 mm and processed by the FreeSurfer software to obtain cortical labels. We transformed the DWIs to the space of the T1-weighted image by registering the b_0 image, and isotropically resampled the DWIs, yielding an isotropic voxel resolution of 0.828 mm . The diffusion tensors were calculated with CATNAP (Landman et al., 2007).

DOTS was applied to the acquired diffusion data set. In this experiment, we demonstrate the results for the tracts of the *anterior/posterior/superior thalamic radiation* (ATR/PTR/STR), the *frontal/posterior/superior CC* (CCF/CCP/CCS), the *corticopontine tract* (CPT), and the *optic radiation* (OPR). Except for the CCF, the CCP, and the CCS, which cross the midline of the brain, we selected the left side of these tracts for demonstration. Using the tract segmentation from DOTS, we estimated the FOs within each tract and then carried out tractography using these results.

This experiment on brain dMRI consists of two parts. First, we selected one representative subject from the 18 subjects for performance evaluation, where results of FORTS are compared with those of competing methods. Second, using all 18 subjects we performed a preliminary study on tract connectivity to cortical areas in order to demonstrate the potential application of FORTS to scientific studies.

3.3.1. Demonstration on a Representative Subject—We first compared FORTS fiber tracking results with four other methods on a representative subject. First, FACT (Mori et al., 1999) was used as a baseline tractography method. The method is based on the single tensor model and cannot resolve crossing fibers. Second, we used the BEDPOSTX algorithm (Behrens et al., 2007) to estimate FOs followed by the XST algorithm (Qazi et al.,

2009) to perform fiber tracking. Third, we applied the CFARI algorithm and INFAC tracking, which are both described in Landman et al. (2012). Fourth, a Gibbs global tracking method (Reisert et al., 2011) implemented in MITK (Wolf et al., 2005) was performed. This method reconstructs fiber streamlines simultaneously with small line segments by solving the best configuration according to diffusion data.

Seeds were placed for each tract as described in Section 2.4. Note that because there is no concept of seeds in global tracking, for the Gibbs tracking we selected all fiber streamlines that intersect with the corresponding seeding mask used for the other algorithms. Based on the fiber tracking results, the connectivity of fiber tracts to cortical labels was also calculated and compared. The fiber tracking results and the connectivity results are shown in Figures 4 to 9. The tracked streamlines are overlaid on the FA map and the tract segmentation is also displayed.

As can be seen in Figure 4, in contrast to the other three methods, FORTS does not create the false ATR streamlines that cross the hemisphere. FORTS also reduces the false PTR and STR streamlines that connect to the cerebellum. The reduction of false fiber streamlines can also be observed from the connectivity results in Figure 5. FORTS does not produce the connections between the hemispheres, which reflects that fewer false streamlines are tracked. It also produces a more concentrated connectivity pattern, which is consistent with the tract geometry of DOTS segmentation.

Figures 6(a) and 6(b) show that for the CCF and the CCP FORTS does not generate the false CC streamlines that enter the cingulum tract which propagate in the anterior-posterior direction. This is also demonstrated in the connectivity maps in Figure 7 (the first and second rows). For the CCS, FORTS prevents the streamlines from entering the corticopontine tract that propagates in the inferior-superior direction, as shown in Figure 6(c). Figure 7 (the third row) shows the difference in CCS connectivity between the methods.

In Figure 8(a), FORTS does not produce the false CPT streamlines that enter the cerebellum or propagate to the anterior or posterior regions of the brain as in the other methods. It should also be noted that, as shown in Figure 8(b), the CPT produced by FORTS shows a strong connection to the precentral cortical label, which is consistent with the CPT definition, while in the other methods the CPT is connected to both precentral and postcentral cortical regions.

In Figure 9(a), which shows the OPR, FORTS does not generate the false streamlines entering the CCP pathway and crossing the mid-sagittal plane. The connectivity map in Figure 9(b) also demonstrates that the false streamlines are reduced with FORTS, where a more concentrated pattern that agrees with tract segmentation geometry is observed.

3.3.2. A Study on Connectivity Patterns in 18 Normal Subjects—To show a potential application of FORTS in a scientific application, we studied the connectivity patterns of the tracts studied above. For each tract, let N_i be the number of streamlines

hitting the cortical label i . We define a normalized connectivity for i , so that connectivity can be compared across different subjects:

$$C_i = \frac{N_i}{\sum_j N_j}. \quad (21)$$

The matrices showing the normalized connectivity of each tract to the cortical areas are shown in Figure 10, where the means, the standard deviations, and the medians of the normalized connectivity are plotted. The color represents the values of the means/standard deviations/medians of the connectivity, where larger values are represented by brighter colors. The colorbar on the right side indicates the actual value to which a color corresponds. Here “lh” and “rh” represent left and right hemispheres, respectively. It can be seen that no false connection across the hemisphere is created for the ATR, the PTR, and the STR. The ATR shows consistent connection to the lateral orbitofrontal area and the rostral middle frontal area. The PTR shows consistent connection to the inferior parietal area and the superior parietal area. The STR shows consistent connection to the postcentral area and the precentral area. The CCF is consistently connected to both left and right rostral anterior cingulate areas, rostral middle frontal areas, and superior frontal areas; the CCP is consistently connected to both left and right isthmus cingulate areas, precuneus areas, and superior parietal areas; and the CCS is consistently connected to both left and right superior frontal areas. For the CPT and the OPR, no false connection across the hemisphere is created. The CPT is consistently connected to the pre-central area, and the OPR is consistently connected to the fusiform and the lateral occipital area. It can also be observed that relatively higher standard deviations are associated with higher means and medians of the normalized connectivity.

4. Discussion

FORTS estimates the FOs within named white matter tracts using guidance from volumetric tract segmentation. It provides information that is not available in voxel labeling results, such as connectivity. In this work, we have demonstrated the application of the proposed method for connectivity studies, which is not straightforward using volumetric segmentation results alone.

The choice of parameters μ_0 and α should be made with respect to the tract shape and segmentation quality. For example, FO estimation can be affected by the accuracy of the segmentation algorithm. The weighting parameter μ_0 controls the influence of the segmentation and a smaller value of μ_0 should be used with less accurate segmentation. In the Fiber Cup experiment, although results indicate that using only the smoothness constraint leads to results that are similar to those when tract geometry is also incorporated ($\mu_0 = 0$), there can be cases where smoothness alone is insufficient. For example, for a U-shaped crossing region, identical FOs that conflict with the tract shape can be generated without using tract surface normals.

The FO estimation is also affected by the tract model that is used by the segmentation algorithm. For example, in the Fiber Cup phantom, the tracts could be defined differently. If the tract with three branches (the blue one in Figure 3(a)) were defined as three separate tracts, the estimated FOs could become slightly different accordingly. Similarly, if another tract segmentation algorithm were to be used, the resulting FO estimates would follow the new tract definitions. In addition, if the method were to be applied on patients, the FO estimation results could be influenced by the presence of disease, because the segmentation performance could be affected.

In the present implementation of FORTS, streamlines that fall outside the segmented tracts are discouraged. Thus, it is likely that streamlines for tracts not modeled will not be generated. For example, the lateral CC streamlines are not tracked in FORTS because they are not included in the DOTS atlas (which is based on the Mori et al. (2005) tract atlas). While future modification to FORTS to allow for discovery of these unmodeled tracts is possible, in the present version the burden of modeling and/or discovering tracts falls on the segmentation algorithm. We note that in the Fiber Cup phantom FOs in the tract simulating the lateral CC were found (the red tract in Figure 3(a)); this result indicates that lateral CC FOs could be estimated if such a tract segmentation were available in the real brain DTI.

There are ways to extend and further improve this methodology. For example, we have applied FORTS on the DTI model and it would be interesting to combine the guidance of volumetric tract segmentation with models that allow multiple FOs in a voxel (Tournier et al., 2007; Tuch, 2004; Landman et al., 2012; Michailovich et al., 2011). In noncrossing regions, the FOs to be estimated should agree with tract segmentation and the single raw FOs calculated from these more advanced techniques. In crossing regions, it can be either using only the information from tract segmentation as proposed in this paper or also considering one of the crossing raw FOs. In the first case, FORTS can be readily applied. In the latter case, the energy function in Eq. (15) becomes

$$\hat{\mathbf{f}} = \arg \min_{|\mathbf{f}(x)|=1} \sum_{x \in \mathcal{L}} (\alpha |\nabla \mathbf{f}(x)|^2 + \mu(x) |\mathbf{g}(x) \cdot \mathbf{f}(x)|^2 + \lambda_0 |S(\mathbf{v}_1(x), \mathbf{v}_2(x), \dots, \mathbf{v}_n(x)) - \mathbf{f}(x)|^2),$$

(22)

where $S(\cdot)$ is an orientation selection function, and $\mathbf{v}_i(x)$'s are the raw FOs estimated without the guidance from tract segmentation. If the selection is determined beforehand, for example, by applying a first run of the proposed FO estimation without using crossing directions (as in the first case) and choosing the closest $\mathbf{v}_i$ to the estimated FO, then the proposed optimization can still be applied. If the selection is also iteratively updated, the extension may not be straightforward and the current optimization needs to be modified to solve the minimization problem. Another issue in the orientation selection is the possible discrepancy between the segmentation and the raw FOs $\mathbf{v}_i(x)$. For example, a region identified by the segmentation as a crossing region can contain only one raw FO or a region

labeled as noncrossing can have multiple raw FOs. In these cases, the selection of $v_A(x)$ can be nontrivial.

FORTS also potentially provides an algorithm for joint fiber tracking/labeling. As seen in the results, with a proper seeding mask inside a segmented tract, the tracked streamlines can also be viewed as the streamlines with the corresponding tract label. Currently, the seeding mask is chosen empirically and cannot guarantee to track the complete set of streamlines belonging to the tract. A further exploration into the seeding mask and false positive removal may solve the issue and provide simultaneous fiber tracking and labeling.

We have used the streamline count as a measure of connectivity to demonstrate the performance of the proposed method. It also gives a potential scientific application of studying connectivity of tracts. It should be noted that, for scientific studies, the streamline count is not necessarily an accurate quantitative measure of strength of connectivity (Jones et al., 2013), which could also be a reason for the relatively large variations in the normalized connectivity in Figure 10(b). Instead, the connectivity patterns provide a qualitative evaluation of connectivity (Jones et al., 2013).

5. Summary and Conclusion

We have proposed a Bayesian approach to FO estimation guided by volumetric tract segmentation. The prior information encodes spatial smoothness of the FOs and the constraint of volumetric tract segmentation, and the likelihood term ensures data fidelity. By maximizing the posterior probability density of FOs, an objective function is achieved. Using calculus of variations, the FO is estimated by iteratively solving the Euler-Lagrange equations. Then, a streamlining fiber tracking strategy using the estimated FOs is presented.

Experiments performed on a digital crossing phantom, the Fiber Cup phantom, and brain DTI data demonstrate that the proposed method can reduce the effect of noise, resolve crossing fibers, and reduce anatomically incorrect streamlines. The experiments on tract connectivity to cortical regions also show the potential application of the proposed method to scientific studies.

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Appendix A. Derivation for the Iterative FO Update

Using the approximation in Horn and Schunck (1981), we have

$$\begin{aligned}\nabla^2 f_x &= \overline{f_x} - f_x, \\ \nabla^2 f_y &= \overline{f_y} - f_y, \\ \nabla^2 f_z &= \overline{f_z} - f_z, \quad (\text{A.1})\end{aligned}$$

where $\overline{f_x}$, $\overline{f_y}$, and $\overline{f_z}$ are the local averages of f_x , f_y , and f_z , respectively. Using Eq. (A.1), Eq. (18) can be written as

$$\begin{aligned}\alpha(\overline{f_x} - f_x) &= \mu g_x(f_x g_x + f_y g_y + f_z g_z) + \lambda(f_x - v_x), \\ \alpha(\overline{f_y} - f_y) &= \mu g_y(f_x g_x + f_y g_y + f_z g_z) + \lambda(f_y - v_y), \\ \alpha(\overline{f_z} - f_z) &= \mu g_z(f_x g_x + f_y g_y + f_z g_z) + \lambda(f_z - v_z).\end{aligned} \quad (\text{A.2})$$

Solving Eq. (A.2), we have:

$$\begin{aligned}
f_x &= \overline{f_x} - \frac{\mu g_x (g_x \overline{f_x} + g_y \overline{f_y} + g_z \overline{f_z})}{\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2)} + \frac{\lambda [(\alpha + \lambda)(v_x - \overline{f_x}) + \mu (g_y^2 + g_z^2)(v_x - \overline{f_x}) - \mu g_x g_y (v_y - \overline{f_y}) - \mu g_x g_z (v_z - \overline{f_z})]}{(\alpha + \lambda)(\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2))}, \\
f_y &= \overline{f_y} - \frac{\mu g_y (g_x \overline{f_x} + g_y \overline{f_y} + g_z \overline{f_z})}{\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2)} + \frac{\lambda [(\alpha + \lambda)(v_y - \overline{f_y}) - \mu g_x g_y (v_x - \overline{f_x}) + \mu (g_x^2 + g_z^2)(v_y - \overline{f_y}) - \mu g_y g_z (v_z - \overline{f_z})]}{(\alpha + \lambda)(\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2))}, \\
f_z &= \overline{f_z} - \frac{\mu g_z (g_x \overline{f_x} + g_y \overline{f_y} + g_z \overline{f_z})}{\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2)} + \frac{\lambda [(\alpha + \lambda)(v_z - \overline{f_z}) - \mu g_x g_z (v_x - \overline{f_x}) - \mu g_y g_z (v_y - \overline{f_y}) + \mu (g_x^2 + g_y^2)(v_z - \overline{f_z})]}{(\alpha + \lambda)(\alpha + \lambda + \mu (g_x^2 + g_y^2 + g_z^2))}.
\end{aligned}$$

(A.3)

Then the problem is solved by iteratively updating $\mathbf{f}$, which leads to Eq. (19).

Figure 1.
An example of estimated FOs in the crossing phantom test overlaid on the FA map.

Figure 2.

(a) The means and standard deviations of FO estimation errors in the crossing region and (b) average FO errors of FORTS with different parameter settings.

Figure 3.

(a) The Fiber Cup phantom (b_0 image), manually delineated 3D tract segmentation, and estimated FOs in the two highlighted regions which include crossing fiber tracts. (b) FORTS results in the highlighted regions in (a) with different parameters.

Figure 4. Fiber tracking results overlaid on the FA map: (a) ATR, (b) PTR, and (c) STR.

Figure 5.

Connectivity to cortical labels: ATR, PTR, and STR. The orientation is identified in the first column.

Figure 6. Fiber tracking results overlaid on the FA map: (a) CCF, (b) CCP, and (c) CCS.

Figure 7. Connectivity to cortical labels: CCF, CCP, and CCS. The orientation is identified in the first column.

Figure 8.

Results for the left CPT. (a) Fiber tracking results overlaid on the FA map. (b) Connectivity to cortical labels; the orientation is identified in the first column.

Figure 9.

Results for the left OPR. (a) Fiber tracking results overlaid on the FA map. (b) Connectivity to cortical labels; the orientation is identified in the first column.

Figure 10. Normalized connectivity of each tract to the cortical areas: (a) mean, (b) standard deviation, and (c) median. “lh” and “rh” represent left and right hemispheres, respectively.