Published in final edited form as:

Med Image Anal. 2020 January ; 59: 101543. doi:10.1016/j.media.2019.101543.

Mitigating Gyral Bias in Cortical Tractography via Asymmetric Fiber Orientation Distributions

Ye Wu^a, Yoonmi Hong^a, Yuanjing Feng^{b,**}, Dinggang Shen^{a,c,**}, Pew-Thian Yap^{a,*}

^aDepartment of Radiology and Biomedical Research Imaging Center (BRIC) University of North Carolina at Chapel Hill, NC, U.S.A.

^bInstitute of Information Processing and Automation, Zhejiang University of Technology, Hangzhou, China

^cDepartment of Brain and Cognitive Engineering, Korea University, Seoul, Republic of Korea

Abstract

Diffusion tractography in brain connectomics often involves tracing axonal trajectories across gray-white matter boundaries in gyral blades of complex cortical convolutions. To date, gyral bias is observed in most tractography algorithms with streamlines predominantly terminating at gyral crowns instead of sulcal banks. This work demonstrates that asymmetric fiber orientation distribution functions (AFODFs), computed via a multi-tissue global estimation framework, can mitigate the effects of gyral bias, enabling fiber streamlines at gyral blades to make sharper turns into the cortical gray matter. We use ex-vivo data of an adult rhesus macaque and in-vivo data from the Human Connectome Project (HCP) to show that the fiber streamlines given by AFODFs bend more naturally into the cortex than the conventional symmetric FODFs in typical gyral blades. We demonstrate that AFODF tractography improves cortico-cortical connectivity and provides highly consistent outcomes between two different field strengths (3T and 7T).

Graphical Abstract

*Primary corresponding author: ptyap@med.unc.edu (Pew-Thian Yap). **Secondary corresponding authors: fyjing@zjut.edu.cn (Yuanjing Feng), dgshen@med.unc.edu (Dinggang Shen).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Diffusion MRI; tractography; gyral bias; asymmetric fiber orientation distribution

1. Introduction

Diffusion magnetic resonance imaging (DMRI) (Johansen-Berg and Behrens, 2013) is a powerful imaging technique for non-invasive quantification of tissue microstructure and mapping of axonal trajectories by probing the diffusion patterns of water molecules in the living human brain. DMRI-based connectomics is widely used for understanding neurological development associated with the cerebral cortex (Johansen-Berg and Behrens, 2013; Yamada et al., 2009; Mori and van Zijl, 2002).

A white matter (WM) fiber tract is a collection of axons in the central nervous system with common origin and destination sites, typically in the cortical gray matter (GM) (Makris et al., 1997; Noback et al., 2011; Robertson, 1978). These tracts have long range and involve axons traversing from cortical GM sites through the superficial WM, then the deep WM, and into a distant cortical or subcortical structure. For an accurate connectivity map of the brain, estimated fiber streamlines must be able not only to follow major fiber bundles through the deep WM, but must also correctly follow axonal trajectories as they cross the WM-GM boundary. However, it is shown that up to 70% of the streamlines produced by the state-of-the-art tractography algorithms actually do not reach the GM, even with high angular resolution diffusion imaging (HARDI) (Côté et al., 2013; Maier-Hein et al., 2017). This can be attributed to the complexity of fiber arrangement in the superficial WM, which resides beneath the cortical sheet (Reveley et al., 2015). This in turn causes gyral bias, with streamlines preferentially terminating at gyral crowns rather than sulcal banks (Van Essen et al., 2013a; Schilling et al., 2018). Gyral bias stems from the technical difficulties in tracing highly-curved axonal trajectories across WM-GM boundaries in gyral blades (Van Essen et al., 2013a). The shortcomings of existing tractography algorithms may lead to severe bias in connectivity analysis (Reveley et al., 2015).

Gyral bias can be mitigated by increasing the spatial resolution of DMRI data (Sotiropoulos et al., 2016; Heidemann et al., 2012) or imposing constraints derived from anatomical (e.g., T1-weighted) images (St-Onge et al., 2018; Teillac et al., 2017; Smith et al., 2012). In this paper, we will however introduce an approach to mitigate the gyral bias that does not rely on time-consuming and expensive high-resolution data as well as hypothetical cortical connections derived from anatomical images. Our technique utilizes subvoxel asymmetry and fiber continuity to improve cortical tractography of highly-curved axonal trajectories.

The orientation information at each voxel is typically encoded as a fiber orientation distribution function (FODF), which is typically computed by using spherical deconvolution (SD) (Tournier et al., 2004, 2007). The SD method assumes that the signal profile can be represented as the convolution of the FODF with a fiber response function (RF) estimated from voxels that contain coherent single-directional axonal bundles. FODFs are typically assumed to be antipodal symmetric, implying that an orientation in a positive hemisphere is

always identical to its counterpart in the negative hemisphere. However, this symmetry limits the FODF in representing complex WM geometries such as fanning and bending.

The basic idea of this paper is to incorporate information from neighboring voxels in estimating *asymmetric* FODFs (AFODFs). To date, the impact of AFODFs on the gyral bias has not been investigated. We extend the multi-tissue model in (Jeurissen et al., 2014) to account for the different polarity of fiber orientations separately in order to capture the asymmetry of the underlying fiber geometry in a local neighborhood. We estimate the AFODF at each voxel by enforcing orientation continuity across voxels. We assume that a fiber streamline leaves a voxel along direction $\mathbf{u}$ and enters a neighboring voxel along the reverse direction $-\mathbf{u}$ with higher fiber continuity. Our continuity constraint is constructed to minimize the difference between the two fiber orientation within the neighborhood. Existing methods for estimating AFODF (Barmpoutis et al., 2008; Cetin Karayumak et al., 2018; Ehricke et al., 2011) typically involves smoothing a field of FODFs taking into account fiber continuity across neighborhood ODFs. However, these methods, e.g., (Bastiani et al., 2017), rely on initialization based on symmetry FODFs and update the corresponding FODFs voxel-wisely according to neighborhood information.

Unlike (Cetin Karayumak et al., 2018; Bastiani et al., 2017; Reisert et al., 2012), our approach is formulated as a convex problem and does not require initialization with pre-computed symmetric FODFs. Instead, we estimate the AFODFs directly from the data by imposing the fiber continuity constraint across voxels. Moreover, our algorithm provides the global solution for multiple voxels simultaneously, taking into account the fiber continuity constraint, instead of solving for each voxel individually. The convexity of our problem formulation allows efficient optimization for large-scale global solutions, unlike the non-convex formulation in (Auría et al., 2015).

Part of this work was presented in (Wu et al., 2018). Herein, we (i) provide a more detailed description of the proposed method; (ii) devise a novel tractography algorithm; (iii) reformulate the fiber continuity term using the von Mises-Fisher distribution; (iv) optimize the algorithm for accelerated global solutions of multiple voxels; (v) provide new insights into consistency across scanners and spatial resolutions; and (vi) compare fiber densities at gyral crowns and sulcal banks determined based on histology and diffusion tractography. None of these is part of the conference publication.

We describe our method in detail in the Methods section and demonstrate its effectiveness with ex-vivo and in-vivo data in the Experimental Results section. We further provide discussion in the Discussion section before concluding in the Conclusion section.

2. Methods

2.1. Multi-Tissue Asymmetric Fiber Orientation Distribution

The FODF $F(\mathbf{u})$, $\mathbf{u} \in \mathbb{S}^2$ usually assumes antipodal symmetry in the sense that $F(\mathbf{u}) = F(-\mathbf{u})$. However, this symmetry limits the FODF in representing complex configurations such as fanning and bending, both very common in gyral blades (see Figure 1). We extend the multi-tissue constrained spherical deconvolution (MT-CSD) framework (Jeurissen et al., 2014) by

incorporating information from neighborhood voxels to allow FODF asymmetry for better representation of complex configurations (Cetin Karayumak et al., 2018; Bastiani et al., 2017; Reisert et al., 2012).

MT-CSD decomposes the diffusion signal $S_{\mathbf{p}}(\mathbf{g})$, for gradient direction $\mathbf{g} \in \mathbb{S}^2$ and voxel location $\mathbf{p} \in \mathbb{R}^3$, into $M \in \mathbb{N}^+$ tissue types, each of which is represented by the spherical convolution of an axially symmetric RF $R_i(\mathbf{g}, \cdot)$ (Tournier et al., 2007; Jeurissen et al., 2014) with an FODF $F_{\mathbf{p},i}(\cdot)$, $1 \leq i \leq M$, giving an overall signal

$$S_{\mathbf{p}}(\mathbf{g}) = \int_{\mathbf{u} \in \mathbb{S}^2} \sum_{i=1}^M R_i(\mathbf{g}, \mathbf{u}) F_{\mathbf{p},i}(\mathbf{u}) d\mathbf{u}. \quad (1)$$

A typical multi-tissue model accounts for signal contributions from white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF), with $M=3$. For convenience, the GM and CSF compartments are considered isotropic and the asymmetry will be considered only for the WM compartment.

To improve robustness to noise, FODFs are often estimated with some form of regularization (Tournier et al., 2007; Auria et al., 2015). We regularize the estimation of AFODFs via the fiber continuity constraint (see Figure 2). A fiber streamline leaving a voxel $\mathbf{p}$ along direction $\mathbf{u}$ should enter the adjacent voxel $\mathbf{q} \in \mathcal{N}_{\mathbf{p}}$ along direction $-\mathbf{u}$ with higher possibility. Here, we denote the $\mathcal{N}_{\mathbf{p}}$ as a second order neighbourhood of $\mathbf{p}$. We measure the discontinuity $\Phi(\cdot)$ of the FODFs of N voxels, denoted as $\mathbf{F}$, over direction $\mathbf{u} \in \mathbb{S}^2$ by

$$\Phi(\mathbf{F}) = \sum_{\mathbf{p} \in \{\mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_N\}} \int_{\mathbf{u} \in \mathbb{S}^2} \left| F_{\mathbf{p}}(\mathbf{u}) - \frac{1}{K_{\mathbf{p},\mathbf{u}}} \sum_{\mathbf{q} \in \mathcal{N}_{\mathbf{p}}} W(\langle \hat{\mathbf{v}}_{\mathbf{p},\mathbf{q}}, \mathbf{u} \rangle) F_{\mathbf{q}}(\mathbf{u}) \right| d\mathbf{u}, \quad (2)$$

where $W(\langle \hat{\mathbf{v}}_{\mathbf{p},\mathbf{q}}, \mathbf{u} \rangle)$ denotes a directional probability distribution function (PDF) that is decided by the angular difference between $\mathbf{u}$ and $\hat{\mathbf{v}}_{\mathbf{p},\mathbf{q}} = \frac{\mathbf{q} - \mathbf{p}}{\|\mathbf{q} - \mathbf{p}\|}$.

$K_{\mathbf{p},\mathbf{u}} = \sum_{\mathbf{q} \in \mathcal{N}_{\mathbf{p}}} W(\langle \hat{\mathbf{v}}_{\mathbf{p},\mathbf{q}}, \mathbf{u} \rangle)$ is a normalization term. We choose $W(\langle \hat{\mathbf{v}}_{\mathbf{p},\mathbf{q}}, \cdot \rangle)$ to be the von Mises-Fisher distribution with reference direction $\hat{\mathbf{v}}_{\mathbf{p},\mathbf{q}}$ (see Directional PDF).

The FODF is commonly represented as a series of real spherical harmonics (SHs) with even-order (Tournier et al., 2004; Frank, 2002). Odd-order SHs typically capture only noise (Hess et al., 2006) and are therefore not included in the representation. Unlike (Bastiani et al., 2017), which attempts to capture the asymmetry using an additional component represented by odd-order SHs, we represent the WM AFODF using two sets of spherical harmonic coefficients:

$$F_{\mathbf{p}}(\mathbf{u}) = \begin{cases} \mathbf{y}(\mathbf{u}) \cdot \mathbf{x}_{\text{WM}}^+(\mathbf{p}), & \mathbf{u} \in \mathbb{S}_+^2, \\ \mathbf{y}(\mathbf{u}) \cdot \mathbf{x}_{\text{WM}}^-(\mathbf{p}), & \mathbf{u} \in \mathbb{S}_-^2, \end{cases} \quad (3)$$

where $\mathbf{y}(\mathbf{u})$ is the real even-order SH basis sampled in direction $\mathbf{u}$, and $\mathbf{x}_{\text{WM}}^+(\mathbf{p})$ and $\mathbf{x}_{\text{WM}}^-(\mathbf{p})$ are the corresponding SH coefficients at location $\mathbf{p}$ for the positive and negative hemispheres ($\mathbb{S}_+^2$ and $\mathbb{S}_-^2$). Note that discontinuity between the hemispheres can be avoided because (i) SH representation with finite order is smooth and discourages abrupt changes, and (ii) the fiber continuity constraint, applied throughout $\mathbb{S}^2$, is directionally smooth thanks to the weighting mechanism based on the von Mises-Fisher distribution. In this paper, we set the maximum SH order as 8. Following (Jeurissen et al., 2014), we use a multi-tissue formulation and represent the GM and CSF FODFs using zeroth-order SH coefficients.

2.2. Directional PDF

The directional PDF should decrease monotonically with the decreasing angular difference between the direction $-\mathbf{u}$ and a reference direction $\hat{\mathbf{v}}_{\mathbf{p}, \mathbf{q}}$. We employ a von Mises-Fisher distribution over the sphere (Mardia and Jupp, 2000) and set

$$W(\langle \hat{\mathbf{v}}_{\mathbf{p}, \mathbf{q}}, \mathbf{u} \rangle | \kappa) = \frac{\kappa^{1/2}}{(2\pi)^{3/2} I_{1/2}(\kappa)} \exp(-\kappa \langle \hat{\mathbf{v}}_{\mathbf{p}, \mathbf{q}}, \mathbf{u} \rangle), \quad (4)$$

where $\kappa \geq 0$ and $I_{1/2}$ denotes the modified Bessel function of the first kind at order 1/2. The greater the value of κ the higher the concentration of the distribution around the reference direction $\hat{\mathbf{v}}_{\mathbf{p}, \mathbf{q}}$. In particular, when $\kappa = 0$, the distribution is uniform over the sphere, and as $\kappa \rightarrow \infty$, the distribution tends to a point density. The distribution is rotationally symmetric around $\hat{\mathbf{v}}_{\mathbf{p}, \mathbf{q}}$ and is unimodal for $\kappa > 0$. The value of κ was set to 4, giving a half width at half maximum value of 56.5° . More details about von Mises-Fisher distribution can be found in (Kumar et al., 2008; Zhang et al., 2007).

2.3. Problem Formulation

We group the signal vectors of N voxels at locations $\mathbb{P} = \{\mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_N\}$ as columns of matrix $\mathbf{S}$ and the SH coefficients of the corresponding AFODFs as columns in matrix $\mathbf{X}$. With a set of directions $\mathbb{U} = \{\mathbf{u}_1, \mathbf{u}_2, \dots, \mathbf{u}_K\}$, we aim to solve the SH coefficients of the N voxels simultaneously as follows:

$$\hat{\mathbf{X}} = \arg \min_{\mathbf{X}} \left\| \mathbf{R}\mathbf{X} - \mathbf{S} \right\|_F^2 \text{ s.t. } \mathbf{B}\mathbf{X} \geq 0 \text{ and } \Phi(\mathbf{F}) \leq \delta, \quad (5)$$

where

$$\mathbf{X} = \begin{bmatrix} \mathbf{x}_{\text{WM}}^+(\mathbf{p}_1) & \dots & \mathbf{x}_{\text{WM}}^+(\mathbf{p}_N) \\ \mathbf{x}_{\text{WM}}^-(\mathbf{p}_1) & \dots & \mathbf{x}_{\text{WM}}^-(\mathbf{p}_N) \\ x_{\text{GM}}(\mathbf{p}_1) & \dots & x_{\text{GM}}(\mathbf{p}_N) \\ x_{\text{CSF}}(\mathbf{p}_1) & \dots & x_{\text{CSF}}(\mathbf{p}_N) \end{bmatrix}$$

and $\mathbf{R} = [\mathbf{R}_{\text{WM}}, \mathbf{R}_{\text{WM}}, \mathbf{R}_{\text{GM}}, \mathbf{R}_{\text{CSF}}]$. Matrix $\mathbf{R}$ maps the SH coefficients to the diffusion signal by spherical convolution. $\mathbf{B}$ is a block diagonal matrix consisting of $\mathbf{Y}$, $\mathbf{Y}$, y_0 and y_0 , where $\mathbf{Y} = [\mathbf{y}(\mathbf{u}_1), \dots, \mathbf{y}(\mathbf{u}_K)]^\top$ and $y_0 = \sqrt{\frac{1}{4\pi}}$ is the zero-order SH basis. $\mathbf{B}$ maps the SH coefficients to the AFODF amplitudes at directions $\mathbb{U}$ to impose nonnegativity constraint by $\mathbf{B}\mathbf{X} \geq 0$ for all tissue types. In (5), δ controls the strictness of the fiber continuity constraint and $\|\cdot\|_F$ is the Frobenius norm. $\Phi(\mathbf{F})$, defined in (2), is computed only for the WM AFODF. We let

$$\widehat{\mathbf{W}}(\mathbf{u}) = \begin{bmatrix} \widehat{W}(\mathbf{p}_1, \mathbf{p}_1, \mathbf{u}) & \dots & \widehat{W}(\mathbf{p}_N, \mathbf{p}_1, \mathbf{u}) \\ \vdots & \ddots & \vdots \\ \widehat{W}(\mathbf{p}_1, \mathbf{p}_N, \mathbf{u}) & \dots & \widehat{W}(\mathbf{p}_N, \mathbf{p}_N, \mathbf{u}) \end{bmatrix}, \quad (6)$$

with

$$\widehat{W}(\mathbf{p}, \mathbf{q}, \mathbf{u}) = \begin{cases} \frac{W(\langle \widehat{\mathbf{v}}_{\mathbf{p}, \mathbf{q}}, \mathbf{u} \rangle)}{K_{\mathbf{p}, \mathbf{u}}} & \mathbf{q} \in \mathcal{N}_{\mathbf{p}}, \\ 0 & \text{otherwise,} \end{cases} \quad (7)$$

and the normalization term $K_{\mathbf{p}, \mathbf{u}}$ defined in (2). Let $\mathbf{A}$ be a block diagonal matrix consisting of $\mathbf{Y}$, $\mathbf{Y}$, 0 and 0, which removes the isotropic components from $\mathbf{B}$ and maps the SH coefficients to the AFODF amplitudes. We further define the operator $\circ$ as

$$\mathbf{A}\mathbf{X} \circ \widehat{\mathbf{W}} = \begin{bmatrix} (\mathbf{A}\mathbf{X})_1 \widehat{\mathbf{W}}(\mathbf{u}_1) \\ \vdots \\ (\mathbf{A}\mathbf{X})_K \widehat{\mathbf{W}}(\mathbf{u}_K) \end{bmatrix}, \quad (8)$$

where $(\mathbf{A}\mathbf{X})_i$ is the i -th row of $\mathbf{A}\mathbf{X}$ and corresponds to direction $\mathbf{u}_i$, $1 \leq i \leq K$. Then, the problem (5) can be rewritten as

$$\widehat{\mathbf{X}} = \arg \min_{\mathbf{X}} \left\| \mathbf{R}\mathbf{X} - \mathbf{S} \right\|_F^2 \text{ s.t. } \mathbf{B}\mathbf{X} \geq 0 \text{ and } \left\| \mathbf{A}\mathbf{X} \circ \widehat{\mathbf{W}} - \mathbf{A}\mathbf{X} \right\|_F \leq \delta, \quad (9)$$

which is a linear least-squares problem with linear inequality constraints that can be solved efficiently using convex optimization.

2.4. Optimization

We solve the high-dimensional optimization problem (9) using the alternating direction method of multipliers (ADMM) (Boyd et al., 2011). We note that (9) can be equivalently written as

$$\begin{aligned} \min_{\mathbf{X}, \mathbf{Z}} \frac{1}{2} \left\| \mathbf{R}\mathbf{X} - \mathbf{S} \right\|_F^2 + \frac{\lambda}{2} \left\| \mathbf{A}\mathbf{X} - \mathbf{A}\mathbf{Z} \circ \widehat{\mathbf{W}} \right\|_F^2 \\ \text{s.t. } \mathbf{B}\mathbf{X} \geq 0, \mathbf{B}\mathbf{Z} \geq 0, \end{aligned} \quad (10)$$

where $\mathbf{Z}$ is an auxiliary variable. Let $\mathbf{H}$ be the multiplier for $\mathbf{AX} - \mathbf{AZ} \circ \widehat{\mathbf{W}} = \mathbf{0}$. Then, each iteration of ADMM involves minimizing the augmented Lagrangian

$$L_\lambda(\mathbf{X}, \mathbf{Z}, \mathbf{H}) = \frac{1}{2} \left\| \mathbf{RX} - \mathbf{S} \right\|_F^2 + I_+(\mathbf{BX}) + \frac{\lambda}{2} \left\| \mathbf{AX} - \mathbf{AZ} \circ \widehat{\mathbf{W}} + \mathbf{H} \right\|_F^2 + I_+(\mathbf{BZ}), \quad (11)$$

alternatingly for $\mathbf{X}$, $\mathbf{Z}$ and updating $\mathbf{H}$. $I_+(\mathbf{Q})$ takes 0 if $\mathbf{Q} \geq 0$ and ∞ otherwise. More specifically, let $\mathbf{X}^j$, $\mathbf{Z}^j$ and $\mathbf{H}^j$ denote the variables at iteration j . Then, we have

$$\mathbf{X}^{j+1} = \arg \min_{\mathbf{X}} \frac{1}{2} \left\| \mathbf{RX} - \mathbf{S} \right\|_F^2 + I_+(\mathbf{BX}) + \frac{\lambda}{2} \left\| \mathbf{AX} - \mathbf{AZ}^j \circ \widehat{\mathbf{W}} + \mathbf{H}^j \right\|_F^2, \quad (12)$$

$$\mathbf{Z}^{j+1} = \arg \min_{\mathbf{Z}} \frac{\lambda}{2} \left\| \mathbf{AX}^{j+1} - \mathbf{AZ} \circ \widehat{\mathbf{W}} + \mathbf{H}^j \right\|_F^2 + I_+(\mathbf{BZ}), \quad (13)$$

and update $\mathbf{H}^{j+1}$ by

$$\mathbf{H}^{j+1} = \mathbf{H}^j + \mathbf{AX}^{j+1} - \mathbf{AZ}^{j+1} \circ \widehat{\mathbf{W}}. \quad (14)$$

A typical stopping criterion is to check whether $\mathbf{H}^j$ has stopped changing, i.e., $\|\mathbf{H}^{j+1} - \mathbf{H}^j\|_F / \|\mathbf{H}^j\|_F \leq \epsilon$ for a user-defined choice of ϵ . Problem (12) can be written as

$$\mathbf{X}^{j+1} = \arg \min_{\mathbf{X}} \frac{1}{2} \left\| \begin{bmatrix} \mathbf{R} \\ \lambda \mathbf{A} \end{bmatrix} \mathbf{X} - \begin{bmatrix} \mathbf{S} \\ \lambda (\mathbf{AZ}^j \circ \widehat{\mathbf{W}} - \mathbf{H}^j) \end{bmatrix} \right\|_F^2 \quad (15)$$

with $\mathbf{BX} \geq 0$,

and can be solved efficiently via quadratic programming (Stellato et al., 2018). Problem (13) can be solved efficiently using thresholding, i.e., $\mathbf{Z}^{j+1} = \mathbf{A}^{-1}(\mathbf{AX}^{j+1} \circ \widehat{\mathbf{W}}^{-1} + \mathbf{H}^j \circ \widehat{\mathbf{W}}^{-1})$ if $\mathbf{BZ}^{j+1} \geq 0$, and $\mathbf{Z}^{j+1} = \mathbf{0}$ otherwise. The algorithm is summarized in Algorithm 1.

2.5. AFODF Tractography

We introduce a tractography algorithm that caters to AFODFs using the direction getter mechanism described in (Garyfallidis et al., 2014; Amirbekian, 2016). The deterministic maximum direction getter returns the most probable direction from a fiber orientation distribution. When multiple plausible directions are available, the choice of best direction is dependent on the direction of the previous fiber segment.

Algorithm 1: AFODF Computation

Input: $\mathbf{S}, \mathbf{R}_{\text{WM}}, \mathbf{R}_{\text{GM}}, \mathbf{R}_{\text{CSF}}, \mathbf{U} \subset \mathbb{S}^2$;
Parameters: λ, κ ;
 Calculate $\widehat{\mathbf{W}}(\mathbf{u})$ for $\mathbf{u} \in \mathbf{U}$ via (6);
while $\|\mathbf{H}^{j+1} - \mathbf{H}^j\|_F / \|\mathbf{H}^j\|_F \geq \epsilon$ **do**
 $j \leftarrow j + 1$;
 Update $\mathbf{X}^j$ by (12);
 Update $\mathbf{Z}^j$ by (13);
 Update $\mathbf{H}^j$ by (14);
end
 Calculate AFODFs via (3)

We extend the method described in (Bastiani et al., 2017) and the direction getter mechanism to work with AFODFs (Figure 3). Similar to the deterministic fiber tracking method, we track along the most probable directions subject to the tracking constraints (e.g., maximum turning angle, anisotropy, etc.) (Amirbekian, 2016).

Unlike (Bastiani et al., 2017), in our algorithm the direction may change within a voxel by following the most probable direction without referring to the direction in the previous voxel. The details of our multi-step algorithm are provided below (see Figure 3 and summary in Algorithm 2):

- Step A-1 (or B-1): Identify a sub-volume (non-shaded in Figure 3) based on the half-space defined by position $\mathbf{r}_0$ (or $\mathbf{r}_1$) and the plane through the voxel center that is perpendicular to $\mathbf{r}_0$ (or $\mathbf{r}_1$).
- Step A-2 (or B-2): Determine the most probable direction ($\widehat{\mathbf{d}}_1$ in A-2, $\widehat{\mathbf{d}}_2$ in B-2) in the sub-volume defined in Step A-1 (or B-1) for streamline propagation. The sign of direction is flipped whenever necessary.
- Step A-3 (or B-3): The direction of propagation and position are updated ($i = 0$ for A-3, $i = 1$ for B-3) using

$$\widehat{\mathbf{d}}_{i+1} \leftarrow \frac{\widehat{\mathbf{d}}_i + \widehat{\mathbf{d}}_{i+1}}{\|\widehat{\mathbf{d}}_i + \widehat{\mathbf{d}}_{i+1}\|} \text{ and } \mathbf{r}_i = \mathbf{r}_{i-1} + s_i \widehat{\mathbf{d}}_{i+1}. \quad (16)$$

Similar to (Bastiani et al., 2017), the step size s_i is determined by the multiplication of the AFODF value associated with $\widehat{\mathbf{d}}_i$ and a scale ρ .

Algorithm 2: AFODF Tractography

Input: AFODFs, $\mathbb{U} \subset \mathbb{S}^2$;

for each seed do

while stopping condition not met do

 Search the voxel subspace defined by the position vector with the normal vector (Step A-1 or B-1);

 Search the forward direction and forward length within the subspace (Step A-2 or B-2);

 Update the forward direction (Step A-3 or B-3);

 Update the step size via (16);

end

end

2.6. Evaluation Metrics

2.6.1. Asymmetry Index (ASI)—Based on (Cetin Karayumak et al., 2018), we define an asymmetry index that measures the difference between $F(\mathbf{u})$ and $F(-\mathbf{u})$ for a set of directions $\mathbb{U} = \{\mathbf{u}_1, \mathbf{u}_2, \dots, \mathbf{u}_K\}$:

$$\text{ASI} = \sqrt{1 - \left(\frac{\sum_{\mathbf{u} \in \mathbb{U}} F(\mathbf{u})F(-\mathbf{u})}{\sum_{\mathbf{u} \in \mathbb{U}} F(\mathbf{u})^2} \right)^2}, \quad (17)$$

which has a value of 0 when $F(\mathbf{u}) = F(-\mathbf{u})$ for all $\mathbf{u} \in \mathbb{U}$.

2.6.2. Model Discrepancy Index (MDI)—A model discrepancy indices (MDI) is used to measure the distance between an AFODF and its symmetric counterpart. A Chebyshev distance is used to measure the greatest FODF difference on a unit sphere $\mathbb{S}^2$. Let $\hat{F}_1$ and $\hat{F}_2$ be the two kinds of FODFs, e.g., asymmetric and symmetric, which are normalized to range [0,1]. Then, the MDI is defined as

$$\text{MDI} = \lim_{p \rightarrow \infty} \left(\sum_{\mathbf{u} \in \mathbb{U}} |\hat{F}_1(\mathbf{u}) - \hat{F}_2(\mathbf{u})|^p \right)^{1/p}, \quad (18)$$

which ranges from 0 to 1.

2.6.3. Interscan Consistency Index (ICI)—Based on (Streiner, 2003), we introduce an interscan consistency index (ICI) to measure the similarity of the distributions of the streamline endpoints of the same subject between two different scans (e.g., 3T and 7T scans). Given two vectors, $\mathbf{c}_1 = [c_{1,1}, \dots, c_{1,n}]$ and $\mathbf{c}_2 = [c_{2,1}, \dots, c_{2,n}]$, that represent the fractions of endpoints in n regions of interest (ROIs), the index is defined as

$$\text{ICI} = \left| \frac{\sigma_{\mathbf{c}_1, \mathbf{c}_2}}{\sigma_{\mathbf{c}_1, \mathbf{c}_1} \sigma_{\mathbf{c}_2, \mathbf{c}_2}} \right|, \quad (19)$$

where

$$\sigma_{c_1, c_2} = \frac{1}{n} \sum_{i=1}^n (c_{1,i} - \bar{c}_1)(c_{2,i} - \bar{c}_2),$$

$$\bar{c}_k = \frac{1}{n} \sum_{i=1}^n c_{k,i}.$$

ICI ranges from 0 (inconsistent) to 1 (consistent). Note that ICI is quite general and can be used to measure the interscan consistency of quantities other than endpoint statistics.

2.6.4. Intra-Class Coefficient (ICC)—Reproducibility was quantified by calculating the robust intra-class coefficient (ICC) between two scans (Shevlyakov and Smirnov, 2011). ICC of two measurement vectors $\mathbf{x} = [x_1, \dots, x_n]$ and $\mathbf{y} = [y_1, \dots, y_n]$ is defined as¹

$$\text{ICC} = \left| \frac{\sum_{i=1}^n (x_i - (\bar{x} + \bar{y})/2)(y_i - (\bar{x} + \bar{y})/2)}{(n-1)(\delta_x^2 + \delta_y^2)/2} \right|, \quad (20)$$

where $\bar{x}$ and $\bar{y}$ are the mean of $\mathbf{x}$ and $\mathbf{y}$, respectively, and δ_x and δ_y are the standard deviations of $\mathbf{x}$ and $\mathbf{y}$, respectively. ICC ranges from 0 (unreproducible) to 1 (reproducible).

3. Experimental Results

3.1. Materials

To demonstrate the advantages of AFODFs, we utilized a macaque DMRI dataset with histological data² for validation. The brain was placed in liquid Fomblin (California Vacuum Technology, CA) and scanned on a Varian 9.4T, 21 cm bore magnet. The structural image was acquired using a 3D gradient echo sequence (TR=50ms; TE=3ms; flip angle=45°) at 200 μm isotropic resolution. The diffusion data were acquired with a 3D spin-echo diffusion-weighted EPI sequence at 400 μm isotropic resolution. The b-values were set to 3000, 6000, 9000, and 12000 s/mm², which due to the decreased diffusivity of ex-vivo tissue (Dyrby et al., 2011), were expected to replicate the signal attenuation profile for in vivo tissue with b-values of 1000, 2000, 3000, and 4000 s/mm² (Schilling et al., 2018). A gradient table of 404 uniformly distributed directions was used to acquire diffusion-weighted volumes with 16 additional non-diffusion-weighted volumes collected at b=0 s/mm². More acquisition details can be found in (Schilling et al., 2018).

We further utilized the 3T and 7T DMRI dataset (see Table 2) of a subject (ID: 105923) scanned in the Human Connectome Project (HCP) (Van Essen et al., 2013b). More acquisition details are given in (Sotiropoulos et al., 2016; Van Essen et al., 2013b). For reproducibility study, we randomly selected 10 subjects from the HCP test-retest dataset. To demonstrate the robustness of our method under various imaging conditions, we reduced the

¹<http://www.nisox.org/Software/Scripts/Matlab/>

²<https://www.nitrc.org/projects/e39macaque>

number of diffusion-weighted images for each shell, i.e., from 90 to 18, 30, and 45 uniformly distributed gradient directions, resulting in 54 (18×3), 90 (30×3) and 135 (45×3) images for three shells combined. We also resampled the images spatially from $(1.25\text{mm})^3$ to $(2.5\text{mm})^3$ and $(5\text{mm})^3$.

Tissue segmentation (CSF, cortical GM, deep GM, and WM) was performed using the T1-weighted image using the pipeline described in (Smith et al., 2012). The pipeline was performed using MRtrix software package (Tournier et al., 2012). A mask generated based on the cortical and deep GM volume fraction maps was warped to the space of the diffusion-weighted images for tractography seeding. The cortical regions were labeled based on the Destrieux atlas (Destrieux et al., 2010).

According to (Jeurissen et al., 2014), a fiber RF is estimated from the diffusion signal for each b -shell and each tissue type. Tissue types are determined by the tissue segmentation map warped to the diffusion-weighted images. The WM RF is estimated by averaging the reoriented diffusion signal profiles of voxels with high anisotropy in WM tissue. The isotropic RFs for GM and CSF are estimated from isotropic representative voxels of GM and CSF, respectively, where these voxels were randomly selected with the maximum harmonic order being fixed as 0 as the isotropic model.

3.2. Macaque

Figure 4 shows the intravoxel architecture as given by FODFs and AFODFs in sulcal banks and fundi. Many areas in both WM and GM show multiple fiber populations. In agreement with previous studies (Leuze et al., 2014), we see that AFODFs are largely oriented perpendicularly to the WM-GM boundary at the sulcal banks. Tractography results in Figure 5 confirm this observation, validating that AFODFs improve tractography across WM-GM boundaries. This increases cortical coverage and reduces gyral bias.

Figure 7 shows the ratios of average fiber densities of gyral crowns to sulcal banks for the gyral blades listed in Table 1 and shown in Figure 6. Fiber density is computed as the number of streamlines per voxel. The fiber density ratio are estimated in the histology following the previous study (Schilling et al., 2018). FODF tractography is biased towards gyral crowns in comparison with the axonal density ratios given by the histological data in many gyral blades, for both WM and GM seeding. AFODF tractography yields density ratios that match the histological data better.

3.3. 3T and 7T

3.3.1. Intravoxel Architecture—Figure 8 compares the symmetric and asymmetric FODFs based on the HCP data. Close-up views of gyral blades are shown in Figure 9. It can be observed that the AFODFs reflect the bending and branching characteristics of cortical WM pathways. The asymmetry of the AFODFs becomes more apparent for voxels nearer to the cortex. This is confirmed by the ASI and MDI maps shown in Figure 10, indicating higher asymmetry and greater model discrepancy in superficial WM than subcortical WM. The asymmetry stems from the curved nature of the axonal trajectories in these regions.

3.3.2. Tractography—Tractography results in Figure 11 indicate that AFODFs yield a significantly greater amount of streamlines. The same GM seeds were used for tractography and streamlines not connecting cortico-cortically/cortico-subcortically or shorter than 10mm were deemed ‘invalid’ and removed. The ‘valid’ streamlines were retained. The maximum turning angle was set to 50°, unless mentioned otherwise, for the rest of the paper. Figure 12 shows the tractography results in a gyral blade, indicating that symmetric FODFs are less likely to produce streamlines that turn into the sulcal banks. This problem is mitigated by AFODFs.

Figure 13 shows the distribution of the endpoints of fiber streamlines on the cortical surface, confirming that AFODF tractography reduces gyral bias with a more uniform coverage of the cortex across gyral crowns and sulcal banks. This observation is confirmed quantitatively in Figure 14, which shows that AFODFs yield higher fractions of valid streamlines. This indicates that there is a high probability that a streamline initiated from a GM voxel will connect with another GM voxel.

3.3.3. Consistency of Endpoint Coverage—We further investigated the distribution of the streamline endpoints at the cortex. For the same subject, the distribution should ideally not vary with changes in imaging conditions. Based on the ROIs given by the Destrieux atlas, we computed the fraction of endpoints in each ROI (i.e., number of endpoints in ROI divided by total number of endpoints over all ROIs). We then computed the ICI based on (19) of the endpoint count fractions of streamlines obtained with symmetric and asymmetric FODFs using datasets acquired with 3T and 7T scanners. Figure 15 shows the ICI values of streamline endpoints in gyri and sulci, indicating that AFODFs result in greater consistency across field strengths for both gyri and sulci.

To evaluate the uniformity of the spatial distribution of the streamline endpoints at the cortex, we also computed the standard deviations of the fiber densities (count per volume) across voxels in different cortical regions. GM and WM masks were generated for tractography seeding. The results in Figure 16 indicate that AFODF tractography yields much lower standard deviations than FODF tractography.

3.3.4. Connectivity—Based on normalized streamline counts, we constructed a connectivity matrix ($\mathbf{C}$) computed by counting streamlines connecting two regions. The connectivity matrix was normalized by $\tilde{\mathbf{C}} = \mathbf{D}^{-\frac{1}{2}} \mathbf{C} \mathbf{D}^{-\frac{1}{2}}$, where $\mathbf{D}$ is the degree matrix. AFODFs yield a higher ICI value of 0.94 of the vectorized 3T and 7T connectivity matrices, compared with the lower ICI value of 0.90 given by FODFs.

3.4. Comparison with State of the Art

In this section, we compare our method with a state-of-the-art method presented by Bastiani et al. (2017).

3.4.1. Intravoxel Architecture—Figure 17 shows the AFODFs in some regions with fiber bending, fanning, and crossing. Figure 18 shows the corresponding results for low-

resolution data. Both figures indicate that our method results in AFODFs with less spurious peaks and better reflect bending and fanning trajectories.

3.4.2. Optic Radiation—Figure 19 shows the optic radiation (OR) reconstructed using different methods. The OR connects the thalamus and regions including lingual cortex, pericalcarine cortex, cuneus cortex, and lateraloccipital cortex. The OR is key to the visual system and a key structure at risk in WM diseases such as multiple sclerosis. It is challenging to reconstruct the OR due to the sharp turning angle in Meyer's loop and the presence of kissing and crossing fibers along the pathway. Part of the optic radiation, Meyer's loop sweeps back on itself into the temporal lobe, just lateral to the temporal horn of the lateral ventricle. Here, the OR was reconstructed using the White Matter Query Language (WMQL) (Wassermann et al., 2016) with regions determined using FreeSurfer cortical parcellation (Destrieux et al., 2010). The results demonstrate the consistency of our method across spatial resolutions.

3.4.3. Fiber Density—We used the HCP test-retest dataset described in Section 3.1 for assessing reproducibility in terms of fiber density. Reliability was assessed via the mean squared difference (MSD) between the test-retest fiber density images. The fiber density image is computed via track density imaging (TDI) (Calamante et al., 2010) by counting the number of tracts passing through each imaging voxel at the WM-GM interface. TDI generates density maps with high anatomical contrast and has been used as a surrogate measure of fiber density in many studies (Jeurissen et al., 2017; Wright et al., 2017). Figure 20 shows the MSD values in logarithmic scale for different angular and spatial resolutions, indicating that our method exhibits the greatest reliability.

3.4.4. Connectivity—Figure 21 shows the ICC values of normalized streamline counts between gyri and sulci, indicating that our method is significantly more reliable between test-retest scans, irrespective of the number of gradient directions per shell. Figure 22 indicate that AFODFs generated by both Bastiani et al.'s method (Bastiani et al., 2017) and the proposed method result in greater gyri-sulci and sulci-sulci connections than symmetric FODFs. A closer look at the results also shows our method yields higher reliability with more connections to the sulcal banks compared with Bastiani et al.'s method (Bastiani et al., 2017).

4. Discussion

We have introduced a global estimation framework for asymmetric fiber orientation distribution functions (AFODFs). We have shown that AFODFs can resolve subvoxel fiber configurations and mitigate gyral bias in cortical tractography. We have demonstrated that AFODF tractography is reproducible across test-retest datasets. Our work supports the fact that spatial information across voxels is useful for inferring subvoxel asymmetric orientations, in line with previous work (Yap et al., 2014; Goh et al., 2009).

Unlike (Bastiani et al., 2017), which attempts to capture the asymmetry using an additional component represented by odd-order SHs, we represent the WM AFODF using two sets of spherical harmonic coefficients. We also note that SH representation with finite order is

smooth and discourages abrupt changes, and the fiber continuity constraint, applied throughout $\mathbb{S}^2$, is directionally smooth thanks to the von Mises-Fisher weighting.

Our method involves a global optimization problem in the sense that the solutions for all voxels are obtained simultaneously. This is an important feature of our method since the fiber continuity constraint causes the solutions of the voxels to be interdependent. Unlike existing methods of global orientation estimation (Schwab et al., 2018b,a; Pesce et al., 2018; Auría et al., 2015), our formulation is convex and does not rely on initialization based on symmetric FODFs (Bampoutis et al., 2008; Reisert et al., 2012; Cetin Karayumak et al., 2018). This allows the AFODFs to be estimated directly from the diffusion-weighted images.

We have demonstrated that AFODFs are successful in mitigating gyral bias with fuller coverage of both gyral crowns and sulcal banks (Figure 13). Unlike existing methods for mitigating gyral bias (Girard et al., 2014; Smith et al., 2012; Heidemann et al., 2012; St-Onge et al., 2018; Teillac et al., 2017), the proposed method does not rely on specialized high-resolution imaging techniques and anatomical priors that are derived, for example, from T1-weighted images.

Mitigating gyral bias is also important for reliable inference of anatomical pathways connecting cortical regions (Schilling et al., 2018; Reveley et al., 2015). With the proposed method, over 95% of streamlines initiated from cortical GM voxels connect to another cortical GM voxels (Figure 14) with high consistency across different field strengths. Mitigating gyral bias also improves tract reproducibility (Figures 19 – 22). These results provide evidence indicating that improving tractography in the superficial WM helps detection of long-range cortical connections (Reveley et al., 2015).

While effective, our method has the following limitations that can be addressed in the future:

- i. A fixed set of fiber RFs throughout the whole brain, ignoring spatial changes associated with, for example, brain development (Wu et al., 2019).
- ii. Multi-shell data are required to tease out the signal contributions from multiple compartments and single-shell data might not work well with our method.
- iii. The geometry of the cortical surface is not taken into account to improve tractography (St-Onge et al., 2018).

5. Conclusion

In this work, we have presented a method for estimation of asymmetric fiber orientation distribution functions (AFODFs) with a multi-tissue global framework to mitigate gyral bias in cortical tractography. Our method allows robust estimation of realistic subvoxel fiber configurations. We showed that fiber streamlines at gyral blades were able to make sharper turns in gyral blades into the cortical gray matter with AFODFs than conventional FODFs. We also showed that AFODF tractography results in better cortico-cortical connectivity. Experimental results also indicate that our method yields greater consistency across different

imaging conditions. Comparison with histological data also confirms the efficacy of our method.

Acknowledgment

This work was supported in part by NIH grants (NS093842, EB022880, and EB006733) and an NSFC grant (61379020). Data were provided in part by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. The macaque dataset³ was made available by Schilling et al. (2018).

References

- Amirbekian B, 2016 Modeling of white matter architecture and networks using diffusion MRI: Tools, methods and applications. Ph.D. thesis, University of California, San Francisco.
- Auría A, Daducci A, Thiran JP, Wiaux Y, 2015 Structured sparsity for spatially coherent fibre orientation estimation in diffusion MRI. *NeuroImage* 115, 245–255. [PubMed: 25944612]
- Barmpoutis A, Vemuri BC, Howland D, Forder JR, 2008 Extracting tractosemas from a displacement probability field for tractography in DW-MRI. In: *International Conference on Medical Image Computing and Computer-Assisted Intervention* Springer, pp. 9–16.
- Bastiani M, Cottaar M, Dikranian K, Ghosh A, Zhang H, Alexander DC, Behrens TE, Jbabdi S, Sotiropoulos SN, 2017 Improved tractography using asymmetric fibre orientation distributions. *NeuroImage* 158 (December 2016), 205–218. [PubMed: 28669902]
- Boyd S, Parikh N, Chu E, Peleato B, Eckstein J, et al., 2011 Distributed optimization and statistical learning via the alternating direction method of multipliers. *Foundations and Trends® in Machine learning* 3 (1), 1–122.
- Calamante F, Tourner JD, Jackson GD, Connelly A, 2010 Track-density imaging (TDI): Super-resolution white matter imaging using whole-brain trackdensity mapping. *NeuroImage* 53 (4), 1233–1243. [PubMed: 20643215]
- Cetin Karayumak S, Özarslan E, Unal G, 2018 Asymmetric orientation distribution functions (AODFs) revealing intravoxel geometry in diffusion MRI. *Magnetic Resonance Imaging* 49, 145–158. [PubMed: 29550369]
- Côté MA, Girard G, Boré A, Garyfallidis E, Houde JC, Descoteaux M, 2013 Tractometer: Towards validation of tractography pipelines. *Medical Image Analysis* 17 (7), 844–857. [PubMed: 23706753]
- Destrieux C, Fischl B, Dale A, Halgren E, 2010 Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage* 53 (1), 1–15. [PubMed: 20547229]
- Dyrby TB, Baaré WF, Alexander DC, Jelsing J, Garde E, Sogaard LV, 2011 An ex vivo imaging pipeline for producing high-quality and high-resolution diffusion-weighted imaging datasets. *Human brain mapping* 32 (4), 544–563. [PubMed: 20945352]
- Ehrcke H-H, Otto K-M, Klose U, 2011 Regularization of bending and crossing white matter fibers in MRI q-ball fields. *Magnetic resonance imaging* 29 (7), 916–926. [PubMed: 21705163]
- Frank LR, 2002 Characterization of anisotropy in high angular resolution diffusion-weighted MRI. *Magnetic Resonance in Medicine* 47 (6), 1083–1099. [PubMed: 12111955]
- Garyfallidis E, Brett M, Amirbekian B, Rokem A, van der Walt S, Descoteaux M, Nimmo-Smith I, 2014 Dipy, a library for the analysis of diffusion MRI data. *Frontiers in Neuroinformatics* 8, 8. [PubMed: 24600385]
- Girard G, Whittingstall K, Deriche R, Descoteaux M, 2014 Towards quantitative connectivity analysis: Reducing tractography biases. *NeuroImage* 98, 266–278. [PubMed: 24816531]

³<https://www.nitrc.org/projects/e39macaque>

- Goh A, Lenglet C, Thompson PM, Vidal R, 2009 Estimating orientation distribution functions with probability density constraints and spatial regularity. In: International Conference on Medical Image Computing and Computer-Assisted Intervention Springer, pp. 877–885.
- Heidemann RM, Anwander A, Feiweier T, Knösche TR, Turner R, 2012 k-space and q-space: Combining ultra-high spatial and angular resolution in diffusion imaging using ZOOPPA at 7T. *NeuroImage* 60 (2), 967–978. [PubMed: 22245337]
- Hess CP, Mukherjee P, Han ET, Xu D, Vigneron DB, 2006 Q-ball reconstruction of multimodal fiber orientations using the spherical harmonic basis. *Magnetic Resonance in Medicine* 56 (1), 104–117. [PubMed: 16755539]
- Jeurissen B, Descoteaux M, Mori S, Leemans A, 2017 Diffusion MRI fiber tractography of the brain. *NMR in Biomedicine*, e3785. [PubMed: 28945294]
- Jeurissen B, Tournier JD, Dhollander T, Connelly A, Sijbers J, 2014 Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *NeuroImage* 103, 411–426. [PubMed: 25109526]
- Johansen-Berg H, Behrens TE, 2013 Diffusion MRI: from quantitative measurement to in vivo neuroanatomy. Academic Press.
- Kumar R, Barmpoutis A, Vemuri BC, Carney PR, Mareci TH, Jun, 2008 Multi-fiber reconstruction from DW-MRI using a continuous mixture of von Mises-Fisher distributions In: Proc. IEEE Computer Society Conf. Computer Vision and Pattern Recognition Workshops. IEEE, pp. 1–8.
- Leuze CW, Anwander A, Bazin PL, Dhital B, Stüber C, Reimann K, Geyer S, Turner R, 2014 Layer-specific intracortical connectivity revealed with diffusion MRI. *Cerebral Cortex* 24 (2), 328–339. [PubMed: 23099298]
- Maier-Hein KH, Neher PF, Houde JC, Côté MA, Garyfallidis E, Zhong J, Chamberland M, Yeh FC, Lin YC, Ji Q, Reddick WE, Glass JO, Chen DQ, Feng Y, Gao C, Wu Y, Ma J, Renjie H, Li Q, Westin CF, Deslauriers-Gauthier S, González JOO, Paquette M, St-Jean S, Girard G, Rheault F, Sidhu J, Tax CM, Guo F, Mesri HY, Dávid S, Froeling M, Heemskerk AM, Leemans A, Boré A, Pinsard B, Bedetti C, Desrosiers M, Brambati S, Doyon J, Sarica A, Vasta R, Cerasa A, Quattrone A, Yeatman J, Khan AR, Hodges W, Alexander S, Romascano D, Barakovic M, Auría A, Esteban O, Lemkaddem A, Thiran JP, Cetingul HE, Odry BL, Mailhe B, Nadar MS, Pizzagalli F, Prasad G, Villalon-Reina JE, Galvis J, Thompson PM, Requejo FDS, Laguna PL, Lacerda LM, Barrett R, Dell'Acqua F, Catani M, Petit L, Caruyer E, Daducci A, Dyrby TB, Holland-Letz T, Hilgetag CC, Stieltjes B, Descoteaux M, 2017 The challenge of mapping the human connectome based on diffusion tractography. *Nature Communications* 8 (1), 1349.
- Makris N, Worth AJ, Sorensen AG, Papadimitriou GM, Wu O, Reese TG, Wedeen VJ, Davis TL, Stakes JW, Caviness VS, Kaplan E, Rosen BR, Pandya DN, Kennedy DN, 1997 Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging. *Annals of Neurology* 42 (6), 951–962. [PubMed: 9403488]
- Mardia KV, Jupp PE, 2000 Distributions on spheres. *Directional Statistics* (i), 159–192.
- Mori S, van Zijl PCM, 2002 Fiber tracking: principles and strategies - a technical review. *NMR in Biomedicine* 15 (7–8), 468–480. [PubMed: 12489096]
- Noback CR, Strominger NL, Demarest RJ, Ruggiero DA, 2011 *The Little Black Book of Neuropsychology*. No. 744. Springer US, Boston, MA.
- Pesce M, Repetti A, Auría A, Daducci A, Thiran J-P, Wiaux Y, 2018 Fast fiber orientation estimation in diffusion MRI from kq-space sampling and anatomical priors. arXiv preprint arXiv:1802.02912.
- Reisert M, Kellner E, Kiselev VG, 2012 About the geometry of asymmetric fiber orientation distributions. *IEEE Transactions on Medical Imaging* 31 (6), 1240–1249. [PubMed: 22345527]
- Reveley C, Seth AK, Pierpaoli C, Silva AC, Yu D, Saunders RC, Leopold DA, Ye FQ, 2015 Superficial white matter fiber systems impede detection of long-range cortical connections in diffusion MR tractography. *Proceedings of the National Academy of Sciences* 112 (21), E2820–E2828.
- Robertson RT, 1978 *Neuroanatomical research techniques*. Academic Press.
- Schilling K, Gao Y, Janve V, Stepniewska I, Landman BA, Anderson AW, 2018 Confirmation of a gyral bias in diffusion MRI fiber tractography. *Human Brain Mapping* 39 (3), 1449–1466. [PubMed: 29266522]

- Schwab E, Haeffele B, Charon N, Vidal R, 2018a Separable dictionary learning with global optimality and applications to diffusion MRI. arXiv preprint arXiv:1807.05595.
- Schwab E, Vidal R, Charon N, 2018b Joint spatial-angular sparse coding for dMRI with separable dictionaries. *Medical image analysis* 48, 25–42. [PubMed: 29803921]
- Shevlyakov G, Smirnov P, 2011 Robust estimation of the correlation coefficient: An attempt of survey. *Austrian Journal of Statistics* 40 (1&2), 147–156.
- Smith RE, Tournier JD, Calamante F, Connelly A, 9 2012 Anatomically constrained tractography: Improved diffusion MRI streamlines tractography through effective use of anatomical information. *NeuroImage* 62 (3), 1924–1938. [PubMed: 22705374]
- Sotiropoulos SN, Hernández-Fernández M, Vu AT, Andersson JL, Moeller S, Yacoub E, Lenglet C, Ugurbil K, Behrens TE, Jbabdi S, 7 2016 Fusion in diffusion MRI for improved fibre orientation estimation: An application to the 3T and 7T data of the human connectome project. *NeuroImage* 134, 396–409. [PubMed: 27071694]
- St-Onge E, Daducci A, Girard G, Descoteaux M, 2018 Surface-enhanced tractography (SET). *NeuroImage* 169, 524–539. [PubMed: 29258891]
- Stellato B, Banjac G, Goulart P, Bemporad A, Boyd S, 2018 Osqp: An operator splitting solver for quadratic programs. In: 2018 UKACC 12th International Conference on Control (CONTROL) IEEE, pp. 339–339.
- Streiner DL, 2003 Starting at the beginning: an introduction to coefficient alpha and internal consistency. *Journal of personality assessment* 80 (1), 99–103. [PubMed: 12584072]
- Teillac A, Beaujoin J, Poupon F, Mangin JF, Poupon C, 2017 A novel anatomically-constrained global tractography approach to monitor sharp turns in gyri In: *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*. Vol. 10433 LNCS. Springer, pp. 532–539.
- Tournier JD, Calamante F, Connelly A, 2007 Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained superresolved spherical deconvolution. *NeuroImage* 35 (4), 1459–1472. [PubMed: 17379540]
- Tournier JD, Calamante F, Connelly A, 3 2012 MRtrix: Diffusion tractography in crossing fiber regions. *International Journal of Imaging Systems and Technology* 22 (1), 53–66.
- Tournier JD, Calamante F, Gadian DG, Connelly A, 2004 Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage* 23 (3), 1176–1185. [PubMed: 15528117]
- Van Essen DC, Jbabdi S, Sotiropoulos SN, Chen C, Dikranian K, Coalson T, Harwell J, Behrens TE, Glasser MF, 2013a Mapping connections in humans and non-human primates. aspirations and challenges for diffusion imaging In: *Diffusion MRI: From Quantitative Measurement to In vivo Neuroanatomy: Second Edition* Elsevier, pp. 337–358.
- Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, 10 2013b The WU-Minn human connectome project: An overview. *NeuroImage* 80, 62–79. [PubMed: 23684880]
- Wassermann D, Makris N, Rath Y, Shenton M, Kikinis R, Kubicki M, Westin C-F, Dec. 2016 The white matter query language: a novel approach for describing human white matter anatomy. *Brain structure & function* 221, 4705–4721. [PubMed: 26754839]
- Wright DK, Johnston LA, Kershaw J, Ordidge R, O'Brien TJ, Shultz SR, 2017 Changes in apparent fiber density and track-weighted imaging metrics in white matter following experimental traumatic brain injury. *Journal of neurotrauma* 34 (13), 2109–2118. [PubMed: 28152648]
- Wu Y, Feng Y, Shen D, Yap P-T, 2018 A Multi-Tissue global estimation framework for asymmetric fiber orientation distributions In: *International Conference on Medical Image Computing and Computer-Assisted Intervention*. Springer, pp. 45–52.
- Wu Y, Lin W, Shen D, Yap P-T, Consortium., U. B. C. P., 2019 Asymmetry spectrum imaging for baby diffusion tractography. In: *International Conference on Information Processing in Medical Imaging* Springer, pp. 319–331.
- Yamada K, Sakai K, Akazawa K, Yuen S, Nishimura T, 2009 MR tractography: A review of its clinical applications. *Magnetic Resonance in Medical Sciences* 8 (4), 165–174. [PubMed: 20035125]
- Yap P-T, An H, Chen Y, Shen D, 2014 Fiber-driven resolution enhancement of diffusion-weighted images. *NeuroImage* 84, 939–950. [PubMed: 24060317]

Zhang F, Goodlett C, Hancock E, Gerig G, 2007 Probabilistic fiber tracking using particle filtering. International Conference on Medical Image Computing and Computer-Assisted Intervention 10, 144–152.

Highlights

- Gyral bias can be mitigated by asymmetric fiber orientation distribution functions (AFODFs).
- Novel estimation technique to simultaneously solve for the AFODFs of all voxels subject to the fiber continuity constraint.
- Extensive evaluations demonstrate that AFODF tractography improves cortico-cortical connectivity and is highly consistent across field strengths.
- Method effectiveness confirmed by evaluation with histological data.

Figure 1:

Existing tractography algorithms typically produce biased fiber streamlines that predominantly terminate at gyral crowns, which contradicts actual histology showing that axonal trajectories in gyral blades traverse perpendicularly into gyral crowns and sulcal banks. Gyral bias is caused by the ambiguity of the fiber orientation distribution functions (FODFs) in voxels traversed by bending and fanning trajectories. The inability to trace the fiber streamlines correctly in the superficial WM impedes the detection of long-range cortical connections (Reveley et al., 2015).

Figure 2:

To mitigate gyral bias, we allow the FODF to be asymmetric. This asymmetry is estimated with the orientation consistency constraint across voxels. This constraint links all voxels and necessitates their AFODFs to be estimated concurrently (see the box of constraints). The signal ($S_{\mathbf{p}}(\mathbf{g})$) is represented as the convolution ($\otimes$) of multi-tissue response functions ($\mathbf{R}$) with the asymmetric FODFs ($F_{\mathbf{p}}$).

Figure 3:
 AFODF tractography algorithm for sharp sub-voxel bending. Tracking order: A-1, A-2, A-3, B-1, B-2, B-3. A-Steps: Tracking across voxels. B-Steps: Tracking within a voxel.

Figure 4:
AFDOFs capture the bending and branching fiber populations at the WM-GM boundary.
Orientations are mostly perpendicular to the WM-GM surface. (Macaque data)

Figure 5:
AFDOFs estimated from low-resolution DMRI capture the bending and branching fiber populations at the WM-GM boundary. Orientations are mostly perpendicular to the WM-GM surface. (Macaque data)

Figure 6:

Gyral blades and gyri labeled based on the structural image. The brown areas and the adjacent lake blue areas merge into gyri. (Macaque data)

Figure 7:

The histological ground truth density ratios are shown as blue circles (mean $\pm$ 95% confidence interval). Results for Both WM seeding GM seeding are shown. Logarithmic scale is used for the vertical axis. (Macaque data). Ground truths for fiber density ratio are shown as blue dots and standard deviation error bar.

Figure 8:
Min-max normalized FODFs and AFODFs. The background is the T1-weighted image of the same subject.

Figure 9:

Close-up views of FODFs and AFODFs in gyral blades. AFODFs capture the bending and branching fiber trajectories. At the superficial WM, fiber orientations are mostly perpendicular to the WM-GM interface.

Figure 10: FODF asymmetry (ASI) and model discrepancy (MDI) of the 3T and 7T dataset. Axial, sagittal, and coronal views of each case are shown. FODFs near the cortex exhibit a higher values, indicating greater asymmetry.

Figure 11:

Tractography results using FODFs and AFODFs for the 3T and 7T datasets. The same GM seeds were used for tractography and streamlines not connecting cortico-cortically/ corticosubcortically or shorter than 10mm were removed. In the background is the cortical GM tissue map of the same subject.

Figure 12:

Comparison of tractography results in gyral blades. Streamlines within a 5mm slab are shown. The background image is the cortical GM from the same subject.

Figure 13:
Coverage of the cortex by streamline endpoints (red).

Figure 14:

Fractions of valid streamlines for various maximum turning angles. The same GM seeds were used for tractography and we removed streamlines not connecting cortico-cortically/cortico-subcortically or shorter than 10mm. The retained streamlines are denoted as 'valid'. A higher fraction of valid streamlines usually indicated the greater connecting cortico-cortically/cortico-subcortically.

Figure 15:

ICI values, computed between 3T and 7T data, for endpoint coverage of gyri and sulci.

Figure 16:
Standard deviations of fiber densities at gyral and sulcal WM-GM boundaries, which exhibits a lower value for the greater reliability.

Figure 17:

AFODFs capture the bending and branching fiber trajectories. At the superficial WM, fiber orientations are mostly perpendicular to the WM-GM interface (blue box). Voxel size: $(1.25\text{mm})^3$. The reference image is the T2 image from the same subject.

Figure 18:

AFODFs capture the bending and branching fiber trajectories at low-resolution data. Voxel size: $(2.5\text{mm})^3$. The reference image is the T2 image from the same subject.

Figure 19:

Comparison of the optic radiation (OR) reconstructed via data of various spatial resolutions. The OR is defined as a connection between the thalamus and regions including lingual cortex, pericalcarine cortex, cuneus cortex, and lateraloccipital cortex. The background image is the T2 image from the same subject.

Figure 20:

The MSD values of fiber density map in logarithmic scale at the WM-GM boundaries for different angular (Top) and spatial resolutions (Bottom), which exhibits a lower value for the greater reliability.

Figure 21:

ICC value of normalized streamline counts for three connection patterns (Sulci-Sulci, Gyri-Gyri, Gyri-Sulci) with respect to the number of gradient directions per shell, which exhibits a higher value for the greater reliable between test-retest scans.

Figure 22: Connectivity between the cortical regions listed in Table 3 defined by the Destrieux Atlas (Destrieux et al., 2010). Of which three connection patterns (Sulci-Sulci, Gyri-Gyri, Gyri-Sulci) with respect for different angular (Left) and spatial resolutions (Right) are shown.

Table 1:

Abbreviations of gyral blades (Schilling et al., 2018).

Abbreviation	Name
SFG	superior frontal gyrus
IFG	inferior frontal gyrus
LorG	lateral orbital gyrus
Gre	gyrus rectus
PrG	pre- central gyrus
INS	insula
ITG	inferior temporal gyrus
PCgG	posterior cingulate gyrus
FuG	fusiform gyrus
SPL	superior parietal lobule
IOG	inferior occipital gyrus
CUN	cuneus
MFG	medial frontal gyrus
FOG	frontal orbital gyrus
MorG	medial orbital gyrus
ACgG	anterior cingulate gyrus
STG	superior temporal gyrus
MTG	middle temporal gyrus
PoG	postcentral gyrus
SMG	supramarginal gyrus
AnG	angular gyrus
LiG	lingual gyrus
OG	occipital gyrus

Table 2:

Summary of HCP 3T and 7T DMRI protocols.

	3T	7T
Spatial resolution	(1.25 mm) ³ , LR/RL phase encoding	(1.05 mm) ³ , AP/PA phase encoding
Acceleration	Multiband = 3	Multiband = 2, GRAPPA = 3
Total echo train length	84.24 ms	41 ms
Gradient strength (max)	100 mT/m	70 mT/m
b-value (s/mm ²)	1000, 2000, 3000	1000, 2000
Gradient directions	270	130

Table 3:

Labels of gyri and sulci (Destrieux et al., 2010).

ID	Name
1	ctx_lh_Lat_Fis-ant-Horizont
2	ctx_lh_Lat_Fis-ant-Vertical
3	ctx_lh_Lat_Fis-post
4	ctx_lh_Pole_occipital
5	ctx_lh_Pole_temporal
6	ctx_lh_S_calcarine
7	ctx_lh_S_central
8	ctx_lh_S_cingul-Marginalis
9	ctx_lh_S_circular_insula_ant
10	ctx_lh_S_circular_insula_inf
11	ctx_lh_S_circular_insula_sup
12	ctx_lh_S_collaL_transv_ant
13	ctx_lh_S_collaL_transv_post
14	ctx_lh_S_front_inf
15	ctx_lh_S_front_middle
16	ctx_lh_S_front_sup
17	ctx_lh_S_interprim-Jensen
18	ctx_lh_S_intrapariet_and_P_trans
19	ctx_lh_S_oc_middle_and_Lunatus
20	ctx_lh_S_oc_sup_and_transversal
21	ctx_lh_S_occipital_ant
22	ctx_lh_S_oc-temp_lat
23	ctx_lh_S_oc-temp_med_and_Lingual
24	ctx_lh_S_orbital_lateral
25	ctx_lh_S_orbital_med-olfact
26	ctx_lh_S_orbital-H_Shaped
27	ctx_lh_S_parieto_occipital
28	ctx_lh_S_pericallosal
29	ctx_lh_S_postcentral
30	ctx_lh_S_precentral-inf-part
31	ctx_lh_S_precentral-sup-part
32	ctx_lh_S_suborbital
33	ctx_lh_S_subparietal
34	Ctx_lh_S_temporal_inf
35	ctx_lh_S_temporal_sup
36	ctx_rh_Lat_Fis-ant-Horizont
37	ctx_rh_Lat_Fis-ant-Vertical
38	ctx_rh_Lat_Fis-post
39	ctx_rh_Pole_occipital

ID	Name
40	ctx_rh_Pole_temporal
41	ctx_rh_S_calcarine
42	ctx_rh_S_central
43	ctx_rh_S_cingul-Marginalis
44	ctx_rh_S_circular_insula_ant
45	ctx_rh_S_circular_insula_inf
46	ctx_rh_S_circular_insula_sup
47	ctx_rh_S_collat_transv_ant
48	ctx_rh_S_collat_transv_post
49	ctx_rh_S_front_inf
50	ctx_rh_S_front_middle
51	ctx_rh_S_front_sup
52	ctx_rh_S_interm_prim-Jensen
53	ctx_rh_S_intrapariet_and_P_trans
54	ctx_rh_S_oc_middle_and_Lunatus
55	ctx_rh_S_oc_sup_and_transversal
56	ctx_rh_S_occipital_ant
57	ctx_rh_S_oc-temp_lat
58	ctx_rh_S_oc-temp_med_and_Lingual
59	ctx_rh_S_orbital_lateral
60	ctx_rh_S_orbital_med-olfact
61	ctx_rh_S_orbital-H_Shaped
62	ctx_rh_S_parieto_occipital
63	ctx_rh_S_pericallosal
64	ctx_rh_S_postcentral
65	ctx_rh_S_precentral-inf-part
6	ctx_rh_S_precentral-sup-part
67	ctx_rh_S_suborbital
68	ctx_rh_S_subparietal
69	ctx_rh_S_temporal_inf
70	ctx_rh_S_temporal_sup
71	ctx_lh_G_cingul-Post-dorsal
72	ctx_lh_G_cingul-Post-ventral
73	ctx_lh_G_cuneus
74	ctx_lh_G_front_inf-Opercular
75	ctx_lh_G_front_inf-Orbital
76	ctx_lh_G_front_inf-Triangul
77	ctx_lh_G_front_middle
78	ctx_lh_G_front_sup
79	ctx_lh_G_Ins_lg_and_S_cent_ins
80	ctx_lh_G_insular_short
81	ctx_lh_G_occipital_middle

ID	Name
82	ctx_lh_G_occipital_sup
83	ctx_lh_G_oc-temp_lat-fusifor
84	ctx_lh_G_oc-temp_med-Lingual
85	ctx_lh_G_oc-temp_med-Parahip
86	ctx_lh_G_orbital
87	ctx_lh_G_pariet_inf-Angular
88	ctx_lh_G_pariet_inf-Supramar
89	ctx_lh_G_parietal_sup
90	ctx_lh_G_postcentral
91	ctx_lh_G_precentral
92	ctx_lh_G-precuneus
93	ctx_lh_G_rectus
94	ctx_lh_G_subcallosal
95	ctx_lh_G_temp_sup-G_T_transv
96	ctx_lh_G_temp_sup-Lateral
97	ctx_lh_G_temp_sup-Plan_polar
98	ctx_lh_G_temp_sup-Plan_tempo
99	ctx_lh_G_temporal_inf
100	ctx_lh_G-temporal_middle
101	ctx_rh_G_cingul-Post-dorsal
102	ctx_rh_G_cingul-Post-ventral
103	ctx_rh_G_cuneus
104	ctx_rh_G_front_inf-Opercular
105	ctx_rh_G_front_inf-Orbital
106	ctx_rh_G_front_inf-Triangul
107	ctx_rh_G_front_middle
108	ctx_rh_G_front_sup
109	ctx_rh_G_Ins_lg_and_S_cent_ins
110	ctx_rh_G_insular_short
111	ctx_rh_G_occipital_middle
112	ctx_rh_G_occipital_sup
113	ctx_rh_G_oc-temp_lat-fusifor
114	ctx_rh_G_oc-temp_med-Lingual

ID	Name
11 5	ctx_rh_G_oc-temp_med-Parahip
11 6	ctx_rh_G_orbital
11 7	ctx_rh_G_pariet_inf-Angular
11 8	ctx_rh_G_pariet_inf-Supramar
11 9	ctx_rh_G_parietal_sup
12 0	ctx_rh_G_postcentral
12 1	ctx_rh_G_precentral
12 2	ctx_rh_G_precuneus
12 3	ctx_rh_G_rectus
12 4	ctx_rh_G_subcallosal
12 5	ctx_rh_G_temp_sup-G_T_transv
12 6	ctx_rh_G_temp_sup-Lateral
12 7	ctx_rh_G_temp_sup-Plan_polar
12 8	ctx_rh_G_temp_sup-Plan_tempo
12 9	ctx_rh_G_temporal_inf
13 0	ctx_rh_G_temporal_middle