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Global tractography of multi-shell diffusion-weighted imaging data using a multi-tissue model

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ABSTRACT

Diffusion-weighted imaging and tractography provide a unique, non-invasive technique to study the macroscopic structure and connectivity of brain white matter in vivo. Global tractography methods aim at reconstructing the full-brain fiber configuration that best explains the measured data, based on a generative signal model. In this work, we incorporate a multi-shell multi-tissue model based on spherical convolution, into a global tractography framework, which allows to deal with partial volume effects. The required tissue response functions can be estimated from and hence calibrated to the data. The resulting track reconstruction is quantitatively related to the apparent fiber density in the data. In addition, the fiber orientation distribution for white matter and the volume fractions of gray matter and cerebrospinal fluid are produced as ancillary results. Validation results on simulated data demonstrate that this data-driven approach improves over state-of-the-art streamline and global tracking methods, particularly in the valid connection rate. Results in human brain data correspond to known white matter anatomy and show improved modeling of partial voluming. This work is an important step toward detecting and quantifying white matter changes and connectivity in healthy subjects and patients.

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Introduction

Diffusion-weighted imaging (DWI) (Le Bihan et al., 1986) and tractography (Mori and van Zijl, 2002) provide a unique, non-invasive technique to study the macroscopic structure and connectivity of the white matter in the human brain in vivo (the human *connectome*) (Tournier et al., 2011; Dell'Acqua and Catani, 2012). Not only is mapping the connectome one of the biggest challenges in modern neuroscience, a detailed understanding of its structure and organization may also help the neuroscientific community to gain insight in a number of important disease processes (Sporns et al., 2005; Jbabdi and Johansen-Berg, 2011). Therefore, diffusion-weighted imaging and tractography are key elements in recent, large-scale efforts for mapping the human brain (Van Essen et al., 2013; Assaf et al., 2013). Yet, besides large datasets, improved analysis pipelines are needed before connectomics may reliably answer those questions, first and foremost improved microstructural modeling and tractography (Jbabdi and Johansen-Berg, 2011).

While it has been recognized early on that diffusion is sensitive to the underlying fiber geometry (Beaulieu, 2002), understanding the precise link between both is essential for accurate and robust interpretation of the measured data (Jbabdi and Johansen-Berg, 2011; Mangin et al., 2013). Hence, considerable effort has gone to modeling this so-called *local inverse problem*, beyond the (Gaussian) diffusion tensor model (Basser et al., 1994). On the one hand, a growing class of methods aims at modeling the biophysical process directly, hence deriving microstructural properties such as axon diameter, neurite density, etc. (Panagiotaki et al., 2012). On the other hand, data-driven approaches have been developed, which aim at deriving the fiber geometry with as little prior assumptions about its physical properties as possible. Arguably the most popular among these are spherical deconvolution (SD) techniques (Tournier et al., 2007; Descoteaux et al., 2009), which reconstruct the fiber orientation distribution function (fODF) based on a fiber response function that may be estimated from the data itself. However, despite the progress in this area, the local inverse problem is inherently incomplete, as the symmetric nature of the diffusion

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profile cannot discriminate crossing and fanning fiber geometries on a larger scale (Jbabdi and Johansen-Berg, 2011).

Because of the aforementioned limitations of local modeling, Mangin et al. (2013) recently advocated "a shift toward a *global inverse problem* perspective, namely the global reconstruction of the geometry of the complete white matter". Indeed, accounting for the spatial continuity of neural fibers may help in recovering locally ambiguous configurations and improve the robustness of the model fitting. Such is the motivation behind a growing class of spatially regularized fODF reconstruction methods (Goh et al., 2009; Reisert and Kiselev, 2011; Zhou et al., 2014). Global tractography (GT) methods (Poupon et al., 2000; Mangin et al., 2002; Kreher et al., 2008; Fillard et al., 2009; Reisert et al., 2011, 2014) go even further and aim at reconstructing the entire fiber configuration that best explains the measured diffusion data. Moreover, they address the ill-posed nature of diffusion tractography at the same time, i.e., they are more robust to noise and local reconstruction errors than streamline tracking (Mangin et al., 2013).

Yet, current GT methods rely on specific microstructural models with fixed parameters, which may not always be adapted to the type of data available. Kreher et al. (2008) and Fillard et al. (2009) model the fiber response as an axially symmetric diffusion tensor. Reisert et al. (2011) use the stick model for the intra-axonal compartment (Behrens et al., 2003), which they have recently extended with a separate extra-axonal compartment, modeled by a diffusion tensor (Reisert et al., 2014). Besides having to be tuned to the data at hand, these models are typically defined for white matter and therefore fail to take partial volume effects from adjacent tissues into account.

In this paper, we introduce a multi-shell spherical harmonic response function, measured from the data, into the generative model defined as part of the global tractography method of Reisert et al. (2011). In addition, we adopt the multi-tissue model of Jeurissen et al., (2014) to differentiate between white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) compartments. As such, our approach explicitly accounts for partial volume effects and does not require a white matter mask in the reconstruction.

Methods

Global tractography in the spherical harmonics basis

Particle-based global tractography methods typically model the neural fiber trajectories as chains of particles (line segments), each characterized by their position $\overrightarrow{\mathbf{x_i}}$ and orientation $\overrightarrow{\mathbf{n}}_i$ (Kreher et al., 2008; Fillard et al., 2009; Reisert et al., 2011). The fiber model $\mathcal{M}$ then consists of the set of all segments $\{X_i = (\overrightarrow{\mathbf{x}}_i, \overrightarrow{\mathbf{n}}_i)\}$ and a set of connections between their endpoints. Ultimately, we wish to maximize the posterior probability of $\mathcal{M}$ given the data D, which, according to Bayes' rule and assuming a Gibbs distribution at temperature T, can be written as

$$P(\mathcal{M}|D) \propto P(D|\mathcal{M}) \, P(\mathcal{M}) \tag{1}$$

$$= e^{-E_{\text{data}}(\mathcal{M}, D)/T} \, e^{-E_{\text{con}}(\mathcal{M})/T} . \tag{2}$$

As such, the problem becomes finding the global minimum of $E(\mathcal{M}) = E_{\text{data}}(\mathcal{M}, D) + E_{\text{con}}(\mathcal{M})$. The data energy E_{data} relates to the data likelihood and is defined as the mean squared error between the measured data D and the predicted data D', simulated from the particle configuration $\mathcal{M}$ using a generative model. The connection energy E_{con} relates to the model prior and promotes connectivity and smoothness of the reconstructed tracks.

Generative model

The central hypothesis in this work is that, for white matter, each segment has a fixed and equal contribution to the *predicted* data D'_{WM}, in the form of a fiber response kernel $K_b(\theta)$. K_b is a spherical function

depending only on the elevation angle θ and the b-value, that models the expected diffusion signal for a single fiber direction along the z-axis. As such, we can simulate the white matter signal for gradient direction $(\overrightarrow{\mathbf{g}}, b)$ by orienting the z-axis of this kernel along all segments and integrating over all segments in a voxel $\overrightarrow{\mathbf{r}}$, i.e.,

$$D'_{WM}\left(\overrightarrow{\mathbf{r}}, \overrightarrow{\mathbf{g}}, b\right) = \sum_{\substack{\left(\overrightarrow{\mathbf{x}}_i, \overrightarrow{\mathbf{n}}_i\right) \\ \overrightarrow{\mathbf{x}}_i \in \mathcal{N}\left(\overrightarrow{\mathbf{r}}\right)}} w\left(\left\|\overrightarrow{\mathbf{r}} - \overrightarrow{\mathbf{x}}_i\right\|\right) \quad K_b\left(\arccos\left(\overrightarrow{\mathbf{n}}_i \cdot \overrightarrow{\mathbf{g}}\right)\right). \tag{3}$$

In this equation, $\mathcal{N}(\overrightarrow{\mathbf{r}})$ denotes the voxel neighborhood and $w(\cdot)$ is some spatial weighting function. In the most simple case, w is a block function the size of one voxel. Cast into the basis of real, symmetric spherical harmonics (SH) (Descoteaux et al., 2009), the kernel reorientation can be described as a convolution with a SH Dirac delta function $\delta_{\overrightarrow{\mathbf{n}}_i}$ along the segment direction $\overrightarrow{\mathbf{n}}_i$. As such, the predicted white matter signal becomes

$$D'_{\text{WM}}\left(\overrightarrow{\mathbf{r}}, \overrightarrow{\mathbf{g}}, b\right) = \sum_{\substack{\left(\overrightarrow{\mathbf{x}}_i, \overrightarrow{\mathbf{n}}_i\right) \\ \overrightarrow{\mathbf{x}}_i \in \mathcal{N}\left(\overrightarrow{\mathbf{r}}\right)}} w\left(\left\|\overrightarrow{\mathbf{r}} - \overrightarrow{\mathbf{x}}_i\right\|\right) \quad (K_b * \delta_{\overrightarrow{n}_i})\left(\overrightarrow{\mathbf{g}}\right) \tag{4}$$

$$= K_b * \sum_{\substack{\left(\overrightarrow{\mathbf{x}}_i, \overrightarrow{\mathbf{n}}_i\right) \\ \overrightarrow{\mathbf{x}}_i \in \mathcal{N}\left(\overrightarrow{\mathbf{r}}\right)}} w\left(\left\|\overrightarrow{\mathbf{r}} - \overrightarrow{\mathbf{x}}_i\right\|\right) \quad \delta_{\overrightarrow{n}_i}\left(\overrightarrow{\mathbf{g}}\right) \tag{5}$$

$$= K_b * \Psi\left(\overrightarrow{\mathbf{r}}, \overrightarrow{\mathbf{g}}\right), \tag{6}$$

where $*$ is the spherical convolution operator and $\Psi(\overrightarrow{\mathbf{r}}, \overrightarrow{\mathbf{u}})$ is an SH orientation distribution function (ODF) of the segments in voxel $\overrightarrow{\mathbf{r}}$. Hence, the white matter signal is simulated by converting the segment configuration to a fiber ODF and calculating the convolution with a kernel K_b, as depicted in Fig. 1.

In addition, similar to Jeurissen et al. (2014), we introduce one or more isotropic kernels $c_j(b)$ that account for partial volume contamination of other tissue types. Typically, we will use these to model cerebrospinal fluid (CSF) and gray matter (GM), but it should be noted that these can be used to model any isotropic signal component. Hence our complete model becomes

$$D'\left(\overrightarrow{\mathbf{r}}, \overrightarrow{\mathbf{g}}, b\right) = K_b * \Psi\left(\overrightarrow{\mathbf{r}}, \overrightarrow{\mathbf{g}}\right) + \sum_j c_j(b) f_j\left(\overrightarrow{\mathbf{r}}\right), \tag{7}$$

where $f_j(\overrightarrow{\mathbf{r}})$ is the fraction of isotropic component j in voxel $\overrightarrow{\mathbf{r}}$.

Data likelihood and priors

Assuming a Gaussian data likelihood, the data energy is defined as

$$E_{\text{data}}(\mathcal{M}, D) = \kappa \left(\frac{\|D - D'\|^2}{Q \, K_0^2} + \mu \, N_p \right), \tag{8}$$

in which κ is a weighting factor. In the first term, Q is the number of acquired DWI volumes and K_0 is the amplitude of the $b = 0$ WM response function. Hence, this term expresses the mean squared error of the data relative to the kernel. Because K_0 is proportional to the intensity of the DWI data, this scaling assures that the reconstruction can handle different acquisition protocols and gradient schemes without needing to adapt the parameters. The second term imposes a L_1-prior on the total number of particles N_{p} in the model, each of which has an associated