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Improved tractography using asymmetric fibre orientation distributions

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ABSTRACT

Diffusion MRI allows us to make inferences on the structural organisation of the brain by mapping water diffusion to white matter microstructure. However, such a mapping is generally ill-defined; for instance, diffusion measurements are antipodally symmetric (diffusion along **x** and –**x** are equal), whereas the distribution of fibre orientations within a voxel is generally not symmetric. Therefore, different sub-voxel patterns such as crossing, fanning, or sharp bending, cannot be distinguished by fitting a voxel-wise model to the signal. However, asymmetric fibre patterns can potentially be distinguished once spatial information from neighbouring voxels is taken into account. We propose a neighbourhood-constrained spherical deconvolution approach that is capable of inferring *asymmetric* fibre orientation distributions (A-fods). Importantly, we further design and implement a tractography algorithm that utilises the estimated A-fods, since the commonly used streamline tractography paradigm cannot directly take advantage of the new information. We assess performance using ultra-high resolution histology data where we can compare true orientation distributions against sub-voxel fibre patterns estimated from down-sampled data. Finally, we explore the benefits of A-fods-based tractography using in vivo data by evaluating agreement of tractography predictions with connectivity estimates made using different in-vivo modalities. The proposed approach can reliably estimate complex fibre patterns such as sharp bending and fanning, which voxel-wise approaches cannot estimate. Moreover, histology-based and in-vivo results show that the new framework allows more accurate tractography and reconstruction of maps quantifying (symmetric and asymmetric) fibre complexity.

1. Introduction

Over the last decades, several developments in the field of magnetic resonance imaging (MRI) have allowed researchers to investigate the anatomical organisation of the brain in vivo and non-invasively at the macroscopic level. Amongst several MRI data acquisition techniques, diffusion MRI (dMRI) has shown great potential to probe the organisation of white matter and structural connection patterns of the brain at different scales (Bastiani and Roebroeck, 2015; Jbabdi et al., 2015; Mori and van Zijl, 2002; Tournier et al., 2011). The pattern of diffusion displacements of water within tissue can be used to probe the main axonal orientations, as water molecules tend to diffuse preferentially along axons. Measurements are, therefore, made sensitive to water diffusion along different orientations. One can then estimate, in each voxel, a fibre orientation distribution (fod) that encodes the fraction of fibre bundles oriented along different directions. Once all the voxel-wise fods have been successfully obtained, a tractography algorithm can be used to reconstruct structural connections between different (sub-)cortical areas.

Despite the evident success of this technology in localising major fibre bundles (e.g., Catani et al., 2012; Catani and Thiebaut de Schotten, 2008; Johansen-Berg and Behrens, 2006), limitations arise from the indirect mapping of diffusion measurements to fods. Tens of thousands of white matter axons may be contained within a single dMRI voxel, where fibres can bend very sharply (e.g., when entering the wall of a cortical gyrus), fan out (e.g., when entering the crown of a cortical gyrus) or converge (e.g. when projections from different cortical regions converge to the main body of the internal capsule). Given the limited resolution of typical dMRI acquisitions and the inherent antipodal symmetry of the sampled signal (measurements along directions **x** and –**x** are equal), all these different sub-voxel patterns cannot be distinguished when considering

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only voxel-wise measurements (Jbabdi and Johansen-Berg, 2011; Seunarine and Alexander, 2009; Tournier et al., 2011). For instance, fibres fanning out and fanning in will give rise to the same voxel-wise fod. However, spatial information can be helpful in these cases (Savadjiev et al., 2006). A sharp bend would comprise of a different spatial arrangement of fods than a fan or a crossing.

This idea of incorporating information from neighbouring voxels in the estimation of fibre patterns has been proposed before. The motivation comes from the principle of fibre continuity (Reisert et al., 2012; Reisert and Kiselev, 2011) or co-helicity (Campbell et al., 2014; Savadjiev et al., 2006, 2008); fibres should be continuous in space, therefore whatever leaves a voxel should enter one of its neighbours. Thus, a set of fods can be estimated using neighbourhoods of voxels. Using this principle, asymmetric functions have been estimated before, by spatially post-processing and regularising symmetric fods (Barmpoutis et al., 2008; Cetin et al., 2015; Ehricke et al., 2011) or by using specific geometric priors (Reisert et al., 2012; Savadjiev et al., 2006). However, there have been very few attempts to take advantage of the extra information provided by asymmetric fods in a tractography algorithm. Expanding the currently available tracking methods is not trivial (Campbell et al., 2014; Rowe et al., 2013) and simply plugging asymmetric fods into a typical tractography paradigm will not work (Ehricke et al., 2011), as current tractography methods expect within-voxel symmetric orientation information.

In this work, we propose a direct estimation of asymmetric fods (A-fods) from dMRI data based on a spherical deconvolution approach that can infer sub-voxel patterns. Key to the estimation of A-fods is the addition of neighbourhood continuity components in the fitting. The model uses a set of symmetric and asymmetric basis functions to represent A-fods and naturally extends the non-parametric constrained spherical deconvolution framework for both single (Tournier et al., 2004, 2007) and multi-shell data (Jeurissen et al., 2014). Spherical deconvolution has been very successful in estimating fibre crossings, but our proposed approach allows to further assess sharp bends and fibre dispersion, including fanning polarity. Importantly, we also propose a tractography algorithm that extends previous frameworks to make use of the estimated A-fods. We assess the increased accuracy obtained from the A-fod model and tractography algorithm using anatomically-realistic fibre patterns and tracking extracted from high resolution histology. Finally, we show examples using in vivo data, investigating the effect of fanning polarity on tractography and showing benefits in resolving connection patterns when asymmetry is considered. In the absence of ground truth in-vivo, we compare connectivity mapping estimates from our approach with measures of connectivity obtained using resting state functional MRI (rs-fMRI).

2. Theory

2.1. Asymmetric fibre orientation density functions

The main motivation for our method is shown in the toy examples of Fig. 1. Even if the voxel-wise signal cannot always be uniquely predictive of the sub-voxel fibre orientations, the local spatial arrangement of orientations can be different depending on the nature of the voxel-wise pattern. Therefore, by considering information from the neighbourhood, we aim to resolve asymmetric fibre patterns.

Voxel-wise spherical deconvolution (SD) techniques for inferring fibre orientations assume that the dMRI signal S at every voxel is the convolution of a fibre orientation distribution F and a fibre response function R:

$$S(\theta,\phi) = F(\theta,\phi) \otimes R(\theta), \tag{1}$$

where θ and ϕ are the elevation and azimuthal angles in spherical coordinates. The problem of determining F for a given response function R can be solved parametrically (Anderson, 2005; Behrens et al., 2007; Dell'acqua et al., 2010; Sotiropoulos et al., 2012) or non-parametrically (Descoteaux et al., 2007, 2009; Jeurissen et al., 2014; Tournier et al., 2004, 2007). An efficient and commonly-used non-parametric formalism for SD uses spherical harmonics (SH) (Descoteaux et al., 2007; Tournier et al., 2007), which form a linear orthonormal basis set over the unit sphere (see Supplementary material). Importantly, in the specific case of dMRI, the measurements are antipodally symmetric, and therefore only symmetric fods can be fitted to such measurements. This means that only even-order functions of the spherical harmonics basis can be considered. Asymmetric (i.e., odd-order) components can only capture noise and are therefore typically excluded from the estimation (Descoteaux et al., 2007; Tournier et al., 2007). This leads to the general formulation of SD as a constrained linear least squares problem:

$$\widehat{\boldsymbol{f}} = arg\min_{\boldsymbol{f}} \|\boldsymbol{Cf} - \boldsymbol{Y}\|^2, \ with\ \boldsymbol{Bf} \geq 0, \tag{2}$$

where $\boldsymbol{f}$ is a vector of unknown even-order coefficients, $\boldsymbol{C}$ is a matrix that encodes even-order basis functions convolved with the fibre response function, $\boldsymbol{B}$ is a matrix that maps the coefficients to the fod amplitudes on the sphere, and $\boldsymbol{Y}$ is the acquired dMRI signal in a voxel (see Supplementary material). The positivity constraint ensures that the fod amplitudes are always positive.

We extend the above framework by including the full spherical harmonics basis set in order to model asymmetric fods (A-fods). The conventional symmetric voxel-wise representation is augmented by incorporating information from neighbouring voxels. The proposed A-fod in a voxel is represented by both even and odd order SH functions. The even components are used to model the within-voxel signal, while the odd components allow for asymmetries informed by the spatial arrangement of the signal in neighbouring voxels. We devised the following cost function, minimised for the optimal set of SH coefficients to represent an A-fod:

$$\widehat{\boldsymbol{f_{all}}} = arg\min_{\boldsymbol{f_{all}}} \left\{ \|\boldsymbol{Cf_{even}} - \boldsymbol{Y_v}\|^2 + \lambda^2 \|\boldsymbol{Bf_{all}} - \boldsymbol{z}\|^2 \right\}, \ with\ \boldsymbol{Bf_{all}} \geq 0 \tag{3}$$

where $\boldsymbol{f_{all}}$ contains both odd and even-order SH coefficients and $\boldsymbol{f_{even}}$ contains only even order coefficients. As in Eq. (2), the first term minimizes the sum of squared residuals between the signal predicted by a voxel-wise symmetric fod and the acquired dMRI signal $\boldsymbol{Y_v}$ for a given voxel $\boldsymbol{v}$. The second term (weighted by the regularization parameter λ) minimizes the difference between the fod ($\boldsymbol{Bf_{all}}$) at that voxel and the conjunction of fods' amplitudes $\boldsymbol{z}$ in a 3 × 3 × 3 neighbourhood *as seen from the centre of voxel* $\boldsymbol{v}$. By including all SH coefficients, the second spatial term affects the estimation of both even and odd components. Specifically, we create a conjunction fod, comprised of $M = 252$ points on the sphere (obtained by a sphere geodesic tessellation). For each point i ($1 \leq i \leq M$) and respective orientation $\boldsymbol{u_i}$, we define a value $\boldsymbol{z}_i$ using the fods of neighbouring voxels (Fig. 2B).

One possible option for defining $\boldsymbol{z}$ could be to set $\boldsymbol{z_i} = \boldsymbol{fod}_{\boldsymbol{x}}(-\boldsymbol{u_i})$ where the fod is taken from the voxel $\boldsymbol{x}$ in a neighbourhood of $\boldsymbol{v}$ such that the line connecting the centres of $\boldsymbol{x}$ and $\boldsymbol{v}$ is closest to $\boldsymbol{u}_i$ (Fig. 2A). However, we instead use a soft version of the above to minimize the discretising effect of a voxel grid. We define $\boldsymbol{z}$ as a weighted sum over neighbouring fods:

$$\boldsymbol{z}_i = \frac{1}{c} \sum_{j \subset N(\boldsymbol{v})} e^{\frac{-\alpha_j}{\beta}} \boldsymbol{fod}_j(-\boldsymbol{u}_i) \tag{4}$$

where α_j is the angle between vectors $\boldsymbol{u_i}$ and the line connecting the centre of the voxel $\boldsymbol{v}$ to the centre of a neighbour $\boldsymbol{j}$ belonging to a subset of a 3 × 3 × 3 neighbourhood of $\boldsymbol{N(v)}$. Specifically, a neighbour $\boldsymbol{j}$ is included in the estimation of the conjunction fod $\boldsymbol{z}$ if $\alpha_j < 90°$. The parameter β can be empirically set and controls the slope of the exponential weighting function and c is a normalizing constant. Finally, and similar to the voxel-wise estimation, we enforce the positivity of the fod by adding the linear