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The effects of SIFT on the reproducibility and biological accuracy of the structural connectome

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ABSTRACT

Diffusion MRI streamlines tractography is increasingly being used to characterise and assess the structural connectome of the human brain. However, issues pertaining to quantification of structural connectivity using streamlines reconstructions are well-established in the field, and therefore the validity of any conclusions that may be drawn from these analyses remains ambiguous. We recently proposed a post-processing method entitled "SIFT: Spherical-deconvolution Informed Filtering of Tractograms" as a mechanism for reducing the biases in quantitative measures of connectivity introduced by the streamlines reconstruction method. Here, we demonstrate the advantage of this approach in the context of connectomics in three steps. Firstly, we carefully consider the model imposed by the SIFT method, and the implications this has for connectivity quantification. Secondly, we investigate the effects of SIFT on the reproducibility of structural connectome construction. Thirdly, we compare quantitative measures extracted from structural connectomes derived from streamlines tractography, with and without the application of SIFT, to published estimates drawn from post-mortem brain dissection. The combination of these sources of evidence demonstrates the important role the SIFT methodology has for the robust quantification of structural connectivity of the brain using diffusion MRI.

Introduction

Diffusion MRI streamlines tractography is increasingly being used as one of many image analysis tools in the rapidly-evolving field of connectomics (Hagmann, 2005; Sporns et al., 2005). In this framework, the grey matter of the brain is parcellated in some manner, and the connections reconstructed using streamlines tractography used to infer structural connectivity between the parcellated areas (Hagmann et al., 2008). This allows for the evaluation of the resulting 'connectome' matrix using a wide range of analysis tools made possible using graph theory to make inferences about the connectional architecture of the brain (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010), or perturbations to this connectivity in pathology and disease (Bassett and Bullmore, 2009; Griffa et al., 2013).

Most studies to date have used the number of streamlines connecting each node pair as a measure of 'connection density'. This is however contrary to a fundamental limitation of streamlines tractography approaches that is well-established in the field: streamline count is not a valid marker of axonal fibre count (Jones et al., 2013). Construction of the structural connectome (or indeed any other quantitative method) using streamline count alone is therefore inadvisable. The approaches employed in the literature for addressing this issue include the following:

- Employing heuristics that make estimates regarding the nature of biases in the streamlines reconstruction process (e.g. increased streamline seeding in longer pathways) in order to explicitly correct for them (e.g. Hagmann et al., 2007; Colon-Perez et al., 2012). This assumes that the heuristics employed are a complete parameterization of the reconstruction biases present in the data, which is not guaranteed.
- Applying a threshold to generate a binary connectivity matrix in an attempt to circumvent the non-quantitative nature of streamline-based connectivity. This 'connected-or-not-connected' interpretation of structural connectivity may enable various sophisticated graph-theoretic analysis methods, but is not reflective of the actual underlying

Abbreviations: ACT, Anatomically-Constrained Tractography; $b = 0$, image with zero diffusion-weighting; CoV, coefficient of variation; DWI, diffusion-weighted imaging; FOD, Fibre Orientation Distribution; FoV, Field of View; GM-WM interface, grey matter–white matter interface; ICC, intra-class correlation coefficient; SIFT, Spherical-deconvolution Informed Filtering of Tractograms; TDI, Track Density Imaging; wmCoV, weighted mean coefficient of variation.

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structure of the brain, where a wide spectrum of connectivity strength exists between various regions (Markov et al., 2011).
- Calculation of some quantitative parameter along the pathway connecting the nodes, rather than (or in addition to) the streamline counts (e.g. Hagmann et al., 2010; Lo et al., 2010; Pannek et al., 2013). This is comparable to using the streamlines connecting each node pair to define a mask in a voxel-based analysis, so may not be an appropriate metric for use in more complex graph-theoretic analyses due to the interpretation of the relevant quantitative parameter or the confound of crossing fibres.

We recently proposed the "Spherical-deconvolution Informed Filtering of Tractograms (SIFT)" algorithm as a mechanism for addressing these quantification issues (Smith et al., 2013). By imposing a model that maps a streamlines reconstruction back to the acquired diffusion image data, and modifying a reconstruction to improve its correspondence with the image data given this model, the number of streamlines connecting two regions of the brain becomes a proportional estimate of the total cross-sectional area of the white matter fibre pathway connecting those regions; this is inherently a highly biologically relevant measure of 'structural connectivity'. We therefore advocate that such a processing step is essential to ensure that any conclusions drawn about the structural connectedness of the brain, or differences in structural connectivity between subjects, are biologically relevant and not due to systematic errors in reconstruction processes and analyses.

In this work, we interrogated the effects of the SIFT algorithm on the estimated structural connectome in three ways. Firstly, we use a simple synthetic phantom to highlight the importance of imposing such a model on a streamlines reconstruction before the connectome is generated. Secondly, we investigated the effects of SIFT on the reproducibility of the structural connectome. Thirdly, we compared the tractograms and connectomes with and without the application of SIFT to quantitative and qualitative estimates of white matter connectivity derived from published post mortem brain dissection experiments; given the lack of a true quantitative gold standard to assess whole-brain tracking results, these ex vivo results provide important (if imperfect) measures of white matter connectivity from a source other than diffusion MRI to which streamlines reconstructions may be compared.

Methods

Implications of the SIFT model

In the SIFT method, a simple model is imposed that maps a streamlines reconstruction back to the measured diffusion signal, as a means for reducing some of the major reconstruction biases of streamlines tractography. The model is described in detail in Smith et al. (2013), and is summarized briefly below:

- The density of a discrete fibre population within any voxel in the image can be estimated (up to a global scaling factor) using the integral of the relevant lobe of the Fibre Orientation Distribution (FOD) for that voxel as estimated using spherical deconvolution (Tournier et al., 2004).[3]
- Each streamline represents some cross-sectional area of white matter; the product of this area with the streamline length through a particular voxel therefore defines the volume occupied by the white matter reconstructed by that individual streamline in that voxel.

[3] Note that we use the integral of each discrete FOD lobe rather than the more commonly-adopted FOD peak amplitude; as the FOD is a distribution by design, its integral over some range (in this case, the solid angle corresponding to a discrete FOD lobe) defines the density within that range. The FOD peak amplitude is only a noisy proxy for this density. A non-parametric method for segmenting FODs that provides the integral of each discrete lobe is described in Smith et al. (2013).

The SIFT method attempts to match the white matter volumes estimated by the streamlines reconstruction to those estimated using spherical deconvolution; it does this through selective removal of streamlines from the reconstruction (thus, its acronym "SIFT").

If SIFT achieves an accurate correspondence between these data, then the streamlines reconstruction inherently provides a more meaningful and interpretable quantification of connectivity; specifically, the *number of streamlines* connecting two areas of the grey matter becomes proportional to the *total cross-sectional area* of the white matter fibres connecting those areas. For the purposes of this study, we assume that this cross-sectional area is then proportional to the *number of fibres* along the connecting pathway; this is not precisely true however, and the implications of this assumption are addressed in the Discussion section.

Synthetic example

To illustrate the importance of this model, consider the simple synthetic example shown in Fig. 1a, which extends a concept introduced in Smith et al. (2013). This phantom consists of a solitary voxel with two discrete fibre populations (coloured red and blue), surrounded by four labelled regions of interest; this example is akin to the parcellated cortex encapsulating the white matter. From the physical underlying structure, it is clear that the density of connections between regions L and R is half of that between regions I and S; this is reflected in the connection densities in the structural connectome (bottom row). Following spherical deconvolution, this difference in fibre density is evident in the relative sizes of the FOD lobes (Fig. 1b), though the precise geometry of the fibre crossing is lost. Due to the mechanisms by which tractography algorithms initiate and propagate streamlines (typically, randomly or uniformly seeding throughout the voxel, propagating with equal likelihood in either fibre direction), these algorithms would likely yield an equal number of streamlines for the connections L↔R and I↔S (Fig. 1c); the resulting connectome matrix is similar in distribution to the ground truth, but the information regarding relative connection densities is lost. By contrast, SIFT uses the relative sizes of the FOD lobes to produce a reconstruction where there are half as many streamlines connecting L↔R as there are connecting I↔S (Fig. 1d); the streamline count connecting regions is therefore reflective of the actual underlying fibre density connecting those regions, and the estimated structural connectome matches the known structural connectivity of the phantom (up to a global scaling factor). This simple example highlights the issues related to quantifying the structural connectome using diffusion MRI fibre-tracking (even when an appropriate crossing-fibre model such as spherical deconvolution is used), and the influence that the SIFT method has on this quantification.

Note that although in this simplistic example the error in reconstruction density may be corrected by scaling the seed density of each fibre population by the relevant FOD lobe size, such a modification is not appropriate for a whole-brain reconstruction, due to the interaction between seed density and reconstructed streamline density between voxels that share common streamlines. What is necessary is for the complete streamlines reconstruction to possess the appropriate density in every fibre population, in every voxel, throughout the entire brain white matter; this is precisely what SIFT is designed to provide.

In vivo data acquisition

All image data for this study were acquired using a Siemens 3 T Tim Trio system (Erlangen, Germany) and a 12-channel head coil. The diffusion-weighted imaging (DWI) acquisition was as follows: twice-refocused spin-echo sequence (Reese et al., 2003), Field of View (FoV) $240 \times 240 \times 150$ mm^3, matrix size 96×96, parallel acceleration factor 2, phase partial Fourier 6/8, 2.5 mm isotropic resolution, 60 diffusion sensitization directions with $b = 3000$ s·mm^{-2}, TE/TR = 110/8400 ms, 10 minute acquisition time. A pair of $b = 0$ images with no