Evidence for the improved biological interpretability of white matter connectivity derived following tractogram filtering using SIFT

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Introduction: Diffusion MRI streamlines tractography is increasingly being used to characterise the structural connectivity (or 'connectome'[1]) of the human brain, using grey matter parcellation methods to define network nodes, and pathways inferred from whole-brain fibre-tracking (the 'tractogram') to provide the connections between those nodes[2]. To do this, an appropriate measure of structural connectivity is required; however the streamline count between two brain regions is an unreliable quantification of white matter connectivity[3]. Alternative measures for constructing these networks have been proposed, such as: applying a threshold to the streamline counts; using *ad hoc* heuristics to compensate for known streamlines reconstruction biases e.g. streamline length[4]; and evaluating quantitative metrics along the connecting pathways[5]. However, even using these approaches, the biological interpretability of the resulting networks remains limited. It has been proposed that if the tractogram is first processed using an appropriate streamlines filtering algorithm, the streamline count in the resulting tractogram can then be used as a biologically-relevant connectivity metric for the construction of these networks[6]. Here we investigate this proposition by comparing the properties of streamlines reconstructions before and after filtering to quantitative estimates from brain dissection, and evaluate the effect of this filtering on the connectome.

Method: Due to the greedy, locally-optimal nature of streamlines tractography algorithms, particular pathways in the brain may be over- or under-emphasized in whole-brain fibre-tracking reconstructions (e.g. over-definition of longer pathways due to increased seeding volume). The SIFT algorithm[6] can alleviate such effects, by assuming that each streamline contributes some white matter volume per unit length, and selectively removing streamlines from a tractogram to make it more consistent with the voxel-wise fibre population volumes estimated using spherical deconvolution[7]. This algorithm has been shown to reduce the prevalence of known streamlines reconstruction biases[6]. An important benefit of this filtering is that the resultant number of streamlines connecting a pair of grey matter regions intrinsically provides an estimate of the cross-sectional area of the white matter pathway connecting those regions, and therefore provides a biologically meaningful measure that can be used in the construction of the connectome.

To evaluate this metric, we compared properties of whole-brain fibre-tracking reconstructions (with and without application of the SIFT algorithm) to properties of the human brain white matter reported from post-mortem dissection[8]. Quantitatively, we calculated the proportions of intra-hemispheric long-range connections (defined as the fraction of streamlines that were longer than 50mm, and connected a grey matter node in a frontal or temporal lobe to a different lobe within the same hemisphere), and callosal fibres (defined as the fraction of inter-hemispheric node connections). Qualitatively, we generated histograms of streamline lengths, and assessed them based on the fact that the number of white matter fibres of a particular length is expected to be inversely proportional to that length[8].

Data acquisition & pre-processing: Image data were acquired from 5 healthy volunteers (1 female) on a 3T Siemens Tim Trio system (Erlangen, Germany). The DWI protocol was as follows: 60 diffusion-sensitisation directions at b=3,000s.mm^{-2}, 7 b=0 volumes, 60 slices, 2.5mm isotropic voxels. An anatomical T1-weighted image was acquired using an MPRAGE sequence (TE/TI/TR = 2.6/900/1900ms, 9° flip, 0.9mm isotropic voxels), and processed using the FreeSurfer pipeline[9], with grey matter nodes of the connectome network defined using the Desikan-Killiany atlas segmentation[10]. Diffusion images were corrected for subject motion[11] and susceptibility-induced distortions[12]. Fibre Orientation Distributions were estimated using Constrained Spherical Deconvolution[7]. Tractograms were generated using the iFOD2 probabilistic streamlines algorithm[13], incorporating the Anatomically-Constrained Tractography framework[14]. Four tractograms were produced, each consisting of 10 million streamlines; two were seeded throughout the white matter (denoted 'WM'), the other two seeded from the grey matter – white matter interface (denoted 'GMWMI')[14]; for each tractogram pair, one was created by generating 10 million streamlines (denoted '10m'), the other by generating 100 million streamlines and filtering down to 10 million using SIFT (denoted '100m→10m').

Results: Both quantitative (Table 1) and qualitative (Figure 1) properties of the whole-brain fibre-tracking reconstructions correlate more closely with those estimated from dissection when the SIFT algorithm is applied; this correlation is further enhanced by seeding at the GMWMI instead of throughout the WM. Track Density Images[15] and connectome matrices for the four reconstructions from an example male volunteer are shown in Figure 2. The tractograms filtered using SIFT appear more sparse, and show clear increases in intra-node connections (matrix diagonals) and decreases in inter-hemispheric connections; this is reflected in the relative streamline density within the superficial white matter and corpus callosum in the corresponding TDIs.

	I-H L-R	Callosal fibres
Dissection	≈ 2%	≈ 2%
10m WM	15.9 ± 2.8%	19.7 ± 2.3%
100m→10m WM	4.9 ± 1.1%	5.2 ± 1.1%
10m GMWMI	7.7 ± 1.9%	11.1 ± 2.1%
100m→10m GMWMI	2.6 ± 0.9%	3.2 ± 1.0%

Table 1: Proportion of specific white matter fibre connections from dissection or whole-brain streamlines reconstruction data (mean ± standard deviation for 5 volunteers). 'I-H L-R' = intra-hemispheric, long-range connections.

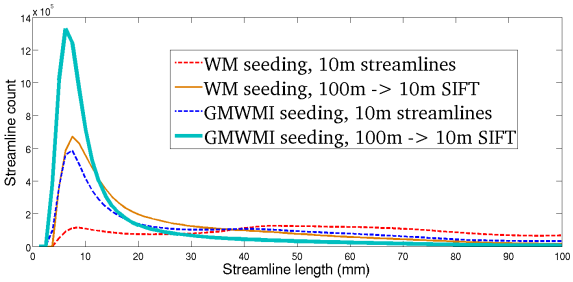

Figure 1: Streamline length histograms for an example male volunteer. Dissection experiments predict an inverse proportionality between fibre count and length.

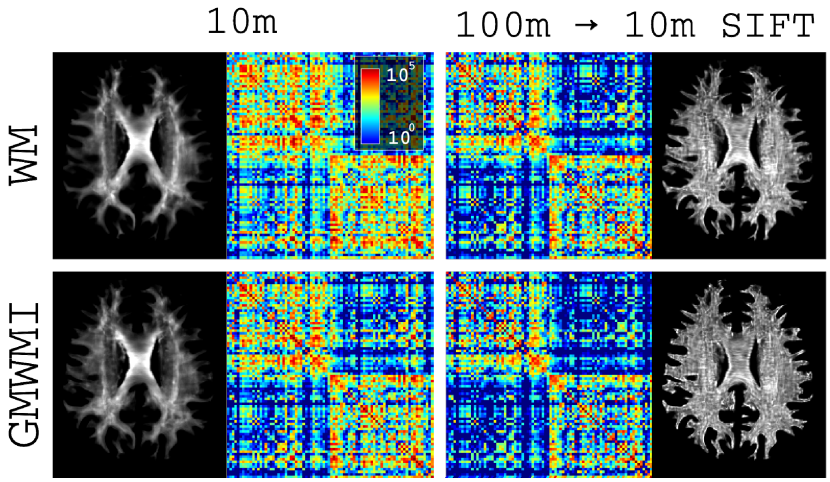

Figure 2. Track Density Images (TDI) (axial, corpus callosum mid-body) and connectome matrices for four streamlines reconstructions for an example male volunteer. Left hemisphere is on the right in TDIs, on the left in matrices. Sub-cortical structures appear in matrix centre. Matrix colour bar is logarithmic, values are streamline counts.

Discussion: We have shown that quantitative and qualitative properties of whole-brain fibre-tracking reconstructions more closely mimic those estimated from brain dissection when pre-processed using the SIFT algorithm. This result suggests that the streamline count between grey matter regions is a biologically relevant metric for quantitative tractography analyses (such as connectomics), as long as the reconstruction provides a tractogram that is an adequate match to the diffusion signal.

References: [1] Sporns et al., PLoS Comput Biol 2005:1;e42 [2] Hagmann et al., PLoS ONE 2007:2;9 [3] Jones et al., NeuroImage 10.1016/j.neuroimage.2012.06.081 [4] Colon-Perez et al., ISMRM 2012:0686 [5] Rose et al., ISMRM 2010:579 [6] Smith et al., ISMRM 2012:0689 [7] Tournier et al., NeuroImage 2007:35;1459-1472 [8] Schüz and Braitenberg, Taylor and Francis London 2002:377-386 [9] Dale et al., NeuroImage 1999:9;179-194 [10] Desikan et al., NeuroImage 2006:31;968-980 [11] Raffelt et al., NeuroImage 2012:59;3976-3994 [12] Holland et al., NeuroImage 2010:50;175-183 [13] Tournier et al., ISMRM 2010:1670 [14] Smith et al., NeuroImage 2012:62;1924-1938 [15] Calamante et al., NeuroImage 2010:53;1233-1243