

## SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography

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**Target audience:** Researchers interested in the quantitative assessment of brain white matter connectivity using diffusion MRI streamlines tractography.

**Purpose:** Quantitative evaluation of brain white matter connectivity using diffusion MRI is difficult due to the non-quantitative nature of the streamlines reconstruction process<sup>[1]</sup>. Proposed solutions to this problem include heuristic correction of known reconstruction biases<sup>[2,3]</sup> (which may not compensate for all reconstruction errors) or evaluation of some diffusion model parameter along connecting pathways<sup>[4,5,6]</sup> (which relies on the quantification and interpretability of that parameter). More recently, the Spherical-deconvolution Informed Filtering of Tractograms (SIFT) method<sup>[7]</sup> was proposed for matching reconstructed streamline densities to the individual fibre population volumes estimated through spherical deconvolution of the diffusion signal<sup>[8]</sup>, through the selective removal of streamlines; by completing this process, the streamline count connecting two regions becomes an estimate of the cross-sectional area of the white matter pathway connecting those regions (up to a global scaling factor). It has been shown previously that quantitative measures of brain connectivity correlate more closely with properties estimated from human brain dissection if the SIFT method is first applied<sup>[9]</sup>. A disadvantage of this method is that even with the generation of many streamlines (which is computationally expensive), after completion of filtering the streamline density may be very low (which is not desirable for quantitative analyses<sup>[10,11]</sup>). Here we propose an alternative solution, entitled SIFT2: instead of removing streamlines, this method derives an appropriate weighting factor for each streamline, in a manner that matches the total streamlines reconstruction to the measured diffusion signal.

**Method:** As in the original SIFT method, we perform Fibre Orientation Distribution (FOD) segmentation, assign streamlines to the FOD lobes they traverse, and derive a processing mask that reduces the contribution of non-white matter voxels to the model. We denote the integral of discrete FOD lobe  $L$  as  $FOD_L$ , the streamline density attributed to that lobe as  $TD_L$ , and the value of the processing mask<sup>[7]</sup> in the voxel occupied by that lobe as  $PM_L$ ; from these we derive the proportionality coefficient  $\mu$ <sup>[7]</sup> (Eq. 1). Each streamline  $S$  has an associated weighting coefficient  $F_S$ . The streamline density in FOD lobe  $L$  is then defined as in (Eq. 2), where  $|S_L|$  is the length of streamline  $S$  through the voxel where it is attributed to FOD lobe  $L$ . The goal is to find a set of weighting coefficients  $F_S$  that minimises the cost function  $f$  (Eq. 3), where  $\lambda$  is a user-selectable regularisation multiplier that constrains the streamline weighting coefficients to be similar to other streamlines that traverse the same FOD lobes (Eq. 4). A solution is found using an iterative line search algorithm: each weighting coefficient is optimised independently, taking into account a set of correlation terms that express the estimated changes to  $TD_L$  for all  $L$  given independent Newton updates to each coefficient (Eq. 5).

$$\begin{aligned}
 (1) \quad \mu &= \frac{\sum_L PM_L \cdot FOD_L}{\sum_L PM_L \cdot TD_L} & (2) \quad TD_L &= \sum_S |S_L| e^{F_S} \\
 (3) \quad f &= \sum_L PM_L \left[ (\mu \cdot TD_L - FOD_L)^2 + \lambda \sum_S \left( \frac{|S_L|}{\sum_L |S_L|} (F_S - F_L^{\text{mean}})^2 \right) \right] \\
 (4) \quad F_L^{\text{mean}} &= \frac{1}{TD_L} \sum_S |S_L| F_S \\
 (5) \quad \frac{dTD_L}{dF_S}_{\text{corr}} &= \sum_S \left| \frac{\delta TD_L}{\delta F_S} \cdot \frac{\Delta F_S \text{ Newton}}{\Delta F_S \text{ Newton}} \right|
 \end{aligned}$$

**Data acquisition & pre-processing:** Image data were acquired from a healthy male volunteer on a 3T Siemens Tim Trio system (Erlangen, Germany). The DWI protocol was as follows: 60 diffusion-sensitisation directions at  $b=3,000\text{s.mm}^{-2}$ , 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). Diffusion images were corrected for subject motion<sup>[12]</sup>, susceptibility-induced distortions<sup>[13]</sup> and  $B_1$  bias field<sup>[14]</sup>. Fibre Orientation Distributions were estimated using Constrained Spherical Deconvolution (CSD)<sup>[15]</sup>. A tractogram of 10 million streamlines was generated using the iFOD2 probabilistic streamlines algorithm<sup>[16]</sup>, incorporating the Anatomically-Constrained Tractography framework<sup>[17]</sup>, seeding randomly throughout the white matter.

**Results:** SIFT2 was compared to performing SIFT ‘to convergence’ (removing as many streamlines as possible to achieve the best fit to the data<sup>[7]</sup>). For SIFT2 we used  $\lambda = 0.001$ , chosen based on an approximate L-curve analysis. Both the SIFT and SIFT2 methods manipulate the reconstruction in such a way that the streamline densities are in good agreement with the volume estimates derived through CSD (Figure 1). However, SIFT2 achieved a superior model fit to SIFT, whilst retaining all of the streamlines in the initial reconstruction (whereas SIFT had to remove approximately 96% of all streamlines).

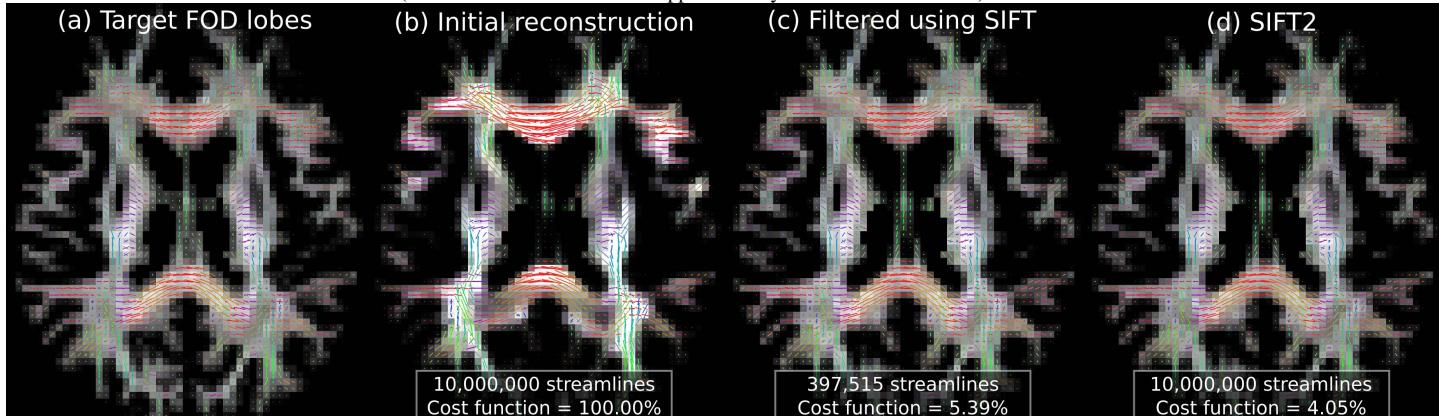


Figure 1: (a) Target FOD lobe amplitudes from FOD segmentation provided for reference; background image is total estimated WM fibre density in each voxel. (b) Streamline densities attributed to individual FOD lobes in original streamlines reconstruction (direction and color determined by segmented FOD lobe, displayed length determined by attributed streamlines density); (c) reconstruction filtered using SIFT; (d) reconstruction with appropriate streamline weights determined using SIFT2; (b-d) background images are voxel-wise streamlines densities.

**Discussion:** The SIFT and SIFT2 algorithms are designed to allow for the quantitative evaluation of white matter connectivity using streamlines tractography. Although both algorithms achieve good correspondence between the density of reconstructed connections and the underlying fibre density as estimated by spherical deconvolution, and both can be run on a desktop computer in a feasible time frame, SIFT2 does so whilst retaining a more dense reconstruction, which is preferable for quantitative analyses (for instance, structural connectome construction) to reduce unwanted variance introduced by the quantised nature of streamlines reconstructions.

**References:** [1] Jones *et al.*, NeuroImage 2013;73:239-254 [2] Hagmann *et al.*, PLoS ONE 2007;2:9 [3] Colon-Perez *et al.*, ISMRM 2012:0686 [4] Hagmann *et al.*, PNAS 2010;107:19067-19072 [5] Lo *et al.*, Jour. Neurosci. 2010;30:16876-16885 [6] Rose *et al.*, ISMRM 2010:579 [7] Smith *et al.*, NeuroImage 2013;67:298-312 [8] Tournier *et al.*, NeuroImage 2004;23:1176-1185 [9] Smith *et al.*, ISMRM 2013:2135 [10] Pannek *et al.*, ISMRM 2010:1663 [11] Cheng *et al.*, Jour. Neurosci. Meth. 2012;203:264-272 [12] Raffelt *et al.*, NeuroImage 2012;59:3976-3994 [13] Andersson *et al.*, NeuroImage 2003;20:870-888 [14] Tustison *et al.*, IEEE TMI 2010;29:1310-1320 [15] Tournier *et al.*, NeuroImage 2007;35:1459-1472 [16] Tournier *et al.*, ISMRM 2010:1670 [17] Smith *et al.*, NeuroImage 2012;62:1924-1938