Quantification of voxel-wise total tract density: addressing the problems associated with track-count mapping

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Introduction: A biological parameter of interest that would be valuable to draw from a diffusion-weighted imaging (DWI) experiment is the local white matter axonal density. Although track-density imaging (TDI) was introduced as a qualitative tractography mapping method due to its high anatomical contrast,[1-3] the fact that this contrast is based on variations in the number of streamlines traversing different voxels makes it appealing as a potential surrogate measure of 'fibre density'. Indeed, TDI and other related methods have been applied quantitatively in a number of brain disorders.[4-7] However, several recent studies have highlighted the limitations of TDI as a quantitative tool.[8-10] The main problem relates to the fact that track-count is highly sensitive to fibre-tracking biases and errors, such that the streamline density is not necessarily reflective of the underlying biological fibre density.

To minimise these tractography biases, the post-processing method of SIFT was recently introduced,[11] which removes specific streamlines from the tractogram such that the remaining streamlines provide a solution more consistent with the underlying DWI data – as given by the Fibre Orientation Distributions (FODs) estimated using CSD.[12] The SIFT method therefore provides a more biologically meaningful measure of structural connectivity.[11,13] Importantly, since SIFT matches the angular distribution of streamline density to the FODs,[11] the TDI intensity following SIFT should ideally correspond (up to a global scaling factor) to the sum of discrete FOD lobe integrals within each voxel; this then corresponds to the DC or l=0 term of the FOD spherical harmonic expansion. The FOD DC term thus provides a direct measure of local fibre density (at native resolution and for data acquired at a high b-value)[14] that does not rely on fibre-tracking.

In this study, we characterise the reproducibility of TDI maps calculated *with* and *without* SIFT pre-processing, as well as the reproducibility of FOD DC maps, to determine which of these methods is most appropriate for quantifying fibre densities at the voxel level.

Methods: *Data acquisition:* MRI data were acquired on a Siemens 3T Tim Trio. Eight DWI datasets were acquired in a healthy subject (over 2 sessions on consecutive days, with subject repositioning following each dataset) using a twice-refocused SE-EPI (TE/TR=110/8400ms, 2.5 mm isotropic voxels, 60 DW directions, b=3000s/mm^2). To correct for susceptibility-induced geometric distortions, a pair of b=0 images with opposing phase-encode polarity was acquired. Each DWI dataset was accompanied by an anatomical T_1-weighted image (0.9 mm isotropic voxels).

Fibre-tracking: Data pre-processing: correction for motion, geometric distortions, and B_1 bias field. FODs estimated using CSD (l_{max}=8). T_1 data used for tissue segmentation (using FSL), and co-registered to DWI data. Whole-brain fibre-tracking was done using probabilistic streamlines and the Anatomically-Constrained Tractography (ACT) framework.[15] Two tractograms were generated per scan: one seeding 10 million streamlines (used for evaluating TDI without SIFT), the other seeding 100 million streamlines with subsequent filtering to 10 million using SIFT. All tractograms (8 without and 8 with SIFT) were realigned, to generate 16 TDI maps (at native 2.5 mm resolution). To assess reproducibility, coefficient of variation (CoV=stdev/mean) maps were calculated based on the TDI results without SIFT, TDI with SIFT, as well as directly from the FOD DC term.

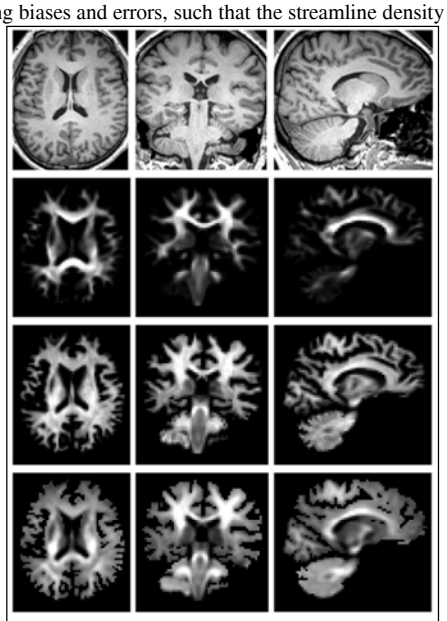

Fig.1. Top: Anatomical T_1-weighted image showing axial, coronal and sagittal locations. 2nd row: mean TDI maps. 3rd row: mean maps of TDI following SIFT. Bottom: mean FOD DC maps. Each row was windowed independently.

Results: Fig. 1 shows examples of TDI and FOD DC maps: as expected, the SIFT method converges the TDIs toward the DC term of the FODs. Fig. 2 shows example CoV maps: SIFT reduces the CoV of the generated TDIs, but the values are still substantially larger than the CoV calculated from the FOD DC maps.

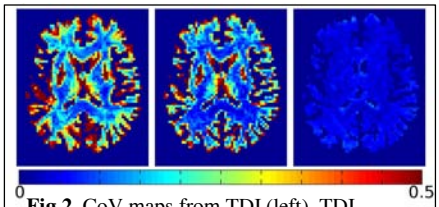

Fig.2. CoV maps from TDI (left), TDI following SIFT (middle), and FOD DC (right) maps, respectively.

Discussion: The data presented indicate that SIFT improves the quantitative characteristics of TDI; this is due to SIFT removing biases and errors in the individual tractography reconstructions, leading to a more biologically meaningful contrast and increased reproducibility. However, given that at native resolution the DC term of the FOD contains precisely the quantitative information that SIFT converges the streamline densities toward, and this parameter demonstrates substantially reduced scan-rescan variability, the application of SIFT to turn TDI (at native resolution) into a quantitative analysis tool cannot be advocated.

In fact, the DC term of the FODs could itself potentially be used as an estimate of local fibre density (akin to other methods aiming to characterise the same property)[15-17] for quantitative analysis. Such an approach would however discard the fibre orientation information present in the FODs, which could otherwise be exploited to improve image normalization, modulation, statistical inference and specificity of results, as is done in the Apparent Fibre Density method[14,18] (note that for any voxel-based analysis of tract density data, modulation will still be required to account for differences in inter-subject tract volumes; furthermore, intensity normalisation, bias field correction and a population average response function are also required for robust comparison)[14].

Conclusion: While standard TDI might be preferable in applications when high anatomical contrast is required, particularly when combined with super-resolution,[2-3] for voxel-wise quantitation of total tract density (i.e. without tract orientation information) at native resolution, FOD DC maps are preferable to TDI or other related track-count maps.

References: [1] Calamante et al, *NeuroImage* 2010;53:1233-43. [2] Calamante et al, *NeuroImage* 2012;59:286-96. [3] Calamante et al, *HBM* 2013;34:2538-48 [4] Barajas Jr et al, *AJNR* 2013,34:1319-25. [5] Stadlbauer et al, *Radiology* 2010;257:846-53. [6] Bozzali et al, *HBM* 2013;34:3158-67. [7] Bozzali et al, *Mult Scler* 2013;19:1161-8. [8] Pannek et al, *NeuroImage* 2011;55:133-41. [9] Bloy et al, *Brain Connect* 2012;2:69-79. [10] Willats et al, *NeuroImage* 2013 (in press, 10.1016/j.neuroimage.2013.11.016). [11] Smith et al, *NeuroImage* 2013;67:298-312. [12] Tournier et al, *NeuroImage* 2007;35:1459-72. [13] Smith et al, *ISMRM* 2013,p.2135. [14] Raffelt et al, *NeuroImage* 2012;59:3976-94. [15] Smith et al, *NeuroImage* 2012;62:1924-38. [16] Zhang et al, *NeuroImage* 2012;61:1000-16. [17] Reisert et al, *NeuroImage* 2013;77:166-76. [18] Raffelt et al, *ISMRM* 2013,p.0841.