Tractographic Threshold-Free Cluster Enhancement: Whole-Brain Statistical Analysis of Diffusion MRI Measures in the Presence of Crossing Fibres

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Introduction: In brain regions containing crossing fibre bundles, voxel-average diffusion MRI measures such as Fractional Anisotropy (FA) are difficult to interpret, and lack within-voxel single fibre population specificity. Recent work has focused on the development of more interpretable quantitative measures that can be associated with a specific direction within a voxel containing crossing fibres[1-5] (herein we use *dixel* to refer to a specific direction within a single voxel, corresponding to a single fibre population). Unfortunately, traditional methods for voxel-based analysis of 3D images (e.g. cluster-based methods available in SPM or FSL) cannot be applied to analyse dixel-specific measures, since the definition of the local neighbourhood for smoothing and cluster construction is ambiguous when adjacent voxels may have different fibre populations. In this work, we propose a novel statistical framework for whole-brain voxel-based analysis of dixel-specific measures, which uses fibre tractography to define each dixel's neighbourhood. We demonstrate the proposed method by investigating Apparent Fibre Density[1] (AFD) in a cohort of Alzheimer's disease (AD) patients and healthy controls.

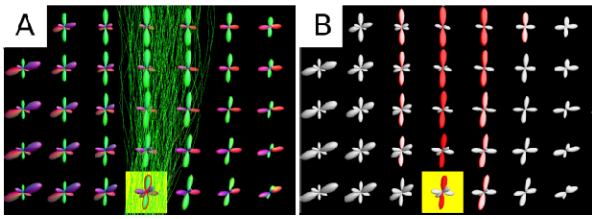

Figure 1. A) *A region of crossing fibres as resolved by fibre orientation distributions (FOD).The streamlines shown are associated with a single dixel, p, within the yellow voxel.* ***B)*** *The neighbourhood of the selected dixel. Each dixel neighbour, i, is colour-coded red, weighted in intensity by its connectivity c.*

Methods: Cluster-based statistical methods exploit correlations in voxel intensities due to shared underlying anatomy and blurring introduced by smoothing, and are hence more sensitive than voxel-based methods when the observed effect is more spatially extended than the spatial scale of the noise. In the analysis of white matter, correlations in measurements would be expected to occur along the affected white matter tract rather than isotropically. In this work, we used whole-brain probabilistic tractography to define the connectivity between each dixel and all other dixels in the brain, and used this dixel-dixel connectivity information both for smoothing (i.e. dixel-specific measures are smoothed only with other dixels that share streamlines), and to boost the belief in (enhance) the test-statistic of each dixel based on information from structurally connected dixels using a Threshold-Free Cluster Enhancement (TFCE)-like approach[6].

TFCE is a cluster-based statistical method that combines both the spatial extent and magnitude of the test-statistic, while removing the need to specify an arbitrary cluster-forming threshold[6]. In the original 3D implementation, the TFCE value at voxel p is a function of the cluster-forming threshold h, and the corresponding cluster extent, $e(h)$, as shown in Eq. 1: where $h_0 = 0.1$, $E = 0.5$, $H = 2$ and $dh = 0.1$.

$$\mathrm{TFCE}(p) = \int_{h=h_0}^{h_p} e(h)^E h^H dh \qquad (1)$$

$$e(h) = \sum_{i=1}^{n} c_i^C \qquad (2)$$

In the original work[6], the cluster extent e is defined as the number of supra-threshold voxels *spatially connected* to voxel p. In this work, we redefine e as the weighted sum of dixels *structurally connected* to dixel p, as inferred by tractography. Precisely, we define the cluster extent in Eq. 2: where n is the total number of supra-threshold dixels connected to p by tractography, C is a constant (we used 0.5), and c_i is the connectivity defined as the proportion of streamlines traversing dixel p that also traverse dixel i. By weighting each dixel by c_i, nearby dixels (i.e. those which we are certain share many axons) contribute more to the enhancement than distant dixels. Furthermore, c_i is raised to the power C, which enables the user to increase the influence of long range (probabilistically less likely) connections if the spatial extent of the effect is expected to be large. This is illustrated in Fig. 1: the streamlines shown are associated with a single dixel, p, within the yellow voxel. In Fig 1b, structurally connected dixels have been colour-coded by their connectivity to p. As in the original TFCE[6], family-wise error corrected p-values are assigned to each dixel by comparing the TFCE test-statistic with the null-distribution of maximal TFCE test-statistics generated via permutation testing.

We investigated the proposed method by performing a dixel-based analysis of AFD[1]. The AFD measure is derived from the amplitude of the Fibre Orientation Distribution[7] (FOD), and can be interpreted as being proportional to the intra-axonal volume of axons aligned with the respective orientation[1]. In this work the dixel-specific measure investigated was the integral of the AFD for each discrete FOD lobe, which is proportional to the total intra-axonal volume for a given fibre population. Data were acquired from 46 AD patients and 88 matched controls (Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing) on a 3T Siemens Trio, 60 directions, b=3000 s/mm^2, 2.3mm. DWIs were motion and bias field corrected, intensity normalised, and up-sampled by a factor of two[1]. FODs were computed by constrained spherical deconvolution[7] using MRtrix[8] and all FOD images were registered to a population-specific FOD template[9]. Final transforms were applied with FOD modulation[1]. The population FOD template was used to generate 10 million streamlines with the iFOD2[8] probabilistic tractography algorithm. SIFT[10] was applied to reduce the influences of streamline reconstruction biases on dixel-dixel connectivity estimates, reducing the total number of streamlines to 1 million. An angular threshold of 25 degrees was used to assign streamlines to dixels when computing dixel-dixel connectivity. Each dixel-specific measure was smoothed with an 8mm FWHM Gaussian kernel weighted by the neighbourhood dixel-dixel connectivity. Statistical analysis was performed with the proposed method using 5000 permutations. To visualise results, streamlines from whole-brain fibre-tracking were mapped to dixels in each voxel. Every point along each streamline was colour-coded according to the associated dixel TFCE t-value, and non-significant streamline points were excluded from the visualisation (p>0.05).

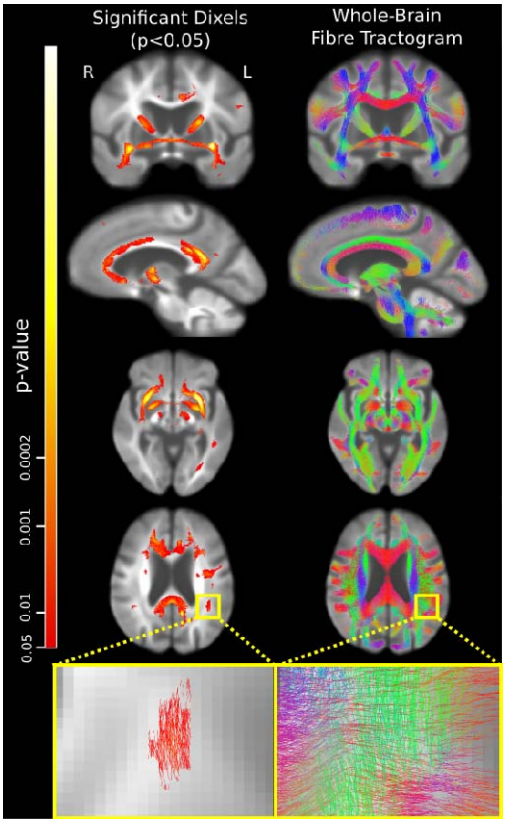

Figure 2. *Significant AFD decreases in AD compared to healthy controls. Left: statistically-significant dixels, visualised by colouring the corresponding streamlines (locally) according to the TFCE t-value (corresponding corrected p-values shown on colour bar). Right: the corresponding slice of the whole-brain tractogram (coloured by orientation, red:L-R, blue:I-S, green:A-P). Bottom: a slice of arcuate fasciculus, demonstrating the fibre population specificity of AFD in regions with crossing fibres.*

Results: Fig. 2 illustrates dixels with statistically significant AFD decreases in AD compared to healthy controls. Affected fibre tracts include the left/right uncinate fasciculus, anterior commissure, left/right cingulum (including the para-hippocampal white matter; not shown), left arcuate fasciculus, corpus callosum (genu and splenium), and anterior thalamic projections.

Discussion and Conclusion: In this work we propose a tractography-based TFCE-like method to analyse dixel-specific diffusion MRI measures[1-5] over the whole-brain, and demonstrate it using AFD[1] in a cohort of Alzheimer's disease patients. Given the increasing interest in higher-order quantitative measures, we anticipate that the proposed method (which we will make available as free and open source software) will be enthusiastically received by the diffusion MRI community.

References: [1] Raffelt D et al (2012) Neuroimage. 15;59(4):3976-94. **[2]** Dell'Acqua F et al. (2012) Hum Brain Mapp. doi:10.1002/hbm.22080. **[3]** Jbabdi S et al (2010) Neuroimage.1;49(1):249-56. **[4]** Assaf Y et al. (2005) Neuroimage.1;27(1):48-58 **[5]** Zhang H (2011) MICCAI 2011;14:82-9. **[6]** Smith S et al. (2009) Neuroimage. 1;44(1):83-98. **[7]** Tournier JD et al, (2012) Neuroimage. 35(4):1459-72. **[8]** Tournier JD et al. (2012) Int. J. of Imag. Sys. and Tech. 22(1):53-66 **[9]** Raffelt D et al. (2011) NeuroImage 56(3):1171-80. **[10]** Smith RE et al. (2012) ISMRM 0689.