Apparent Fibre Density: A New Measure for High Angular Resolution Diffusion-Weighted Image Analysis

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Introduction

Numerous clinical studies have used voxel based analysis of diffusion tensor (DT) invariants, such as fractional anisotropy (FA) [1], to investigate group differences in white matter (see [2] for a review). However, results are difficult to interpret in regions with crossing fibres due to the simple Gaussian diffusion model assumed with the DT. High Angular Resolution Diffusion-weighted Imaging (HARDI) [3] has been employed by a number of higher order models (HOM) (such as Q-ball [4] and Constrained Spherical Deconvolution (CSD) [5]) to resolve crossing fibres by estimating diffusion or Fibre Orientation Distribution (FOD) functions. Fibre tractography and connectivity studies benefit from HOM [6], however HOM for whole brain voxel based analysis has been largely unexplored. Recent work by Jbabdi et al. [7] used the crossing fibre model outlined in [6] for comparing partial volume fractions (PVF) of fibres between groups, assuming that PVF may be more interpretable than FA in regions with crossing fibres. This method permits differences to be detected in different fibre tracts within a multiple fibre voxel. However, this approach establishes correspondence using an FA-based skeletonisation procedure, and thus only takes a relatively small amount of the white matter into consideration, with no explicit attempt to match actual white matter tracts across individuals.

In this paper, we present a novel measure, called *Apparent Fibre Density* (AFD), which enables voxel wise comparisons to be made over all orientations. The AFD measure is based on information provided by FODs. Any differences in the FOD amplitude along a given orientation can be attributed to differences in the relative *amount of underlying axons* thought to be aligned with this orientation. We refer to the amount of axons for a given orientation as '*Apparent'* Fibre Density because it is not an absolute measure of density. To compare differences in AFD across patient groups, correspondence between FODs is required. This is typically obtained using non-rigid registration; however this process alters a fibre bundle's total volume and therefore its total AFD. Consequently, in order to make robust comparisons of AFD across individuals, we include information that is captured by the deformation field by modulating the FOD during the spatial normalisation process using the Jacobian matrix, **J**, at each point in the deformation field. In this study, we assume that the AFD along any given orientation within a FOD is not affected by scaling along its axis, since that would leave its cross-sectional area (and hence its axonal density) unchanged. However, scaling perpendicular to its axis will modify its AFD by an amount proportional to the corresponding change in cross-sectional area.

Method

Diffusion weighted data needs to be re-oriented during spatial normalisation [8]. A method for reorienting FODs was recently proposed [9] where FODs are approximated by the sum of a number of equally distributed, weighted, spherical harmonic (SH) delta functions (Fig 1b). The delta function orientations are then modified using the Jacobian matrix, **J** (Fig 1c). In [9], to preserve the partial volume of each fibre population, the original delta function weights were retained when summing the rotated delta functions to form the re-oriented FOD. However, in this work we *modulate the weight of each delta function* in order to account for changes in cross-sectional area that would affect AFD (Fig 1d). The modulated weight, m, for a delta function along a Cartesian vector, $\hat{\mathbf{v}}$, is computed by $m = w\|\mathbf{J}\hat{\mathbf{v}}\|/\det(\mathbf{J})$, where w is the weight computed during approximation [9]. The re-oriented and modulated FOD is then computed by summing each delta function with the modified weights.

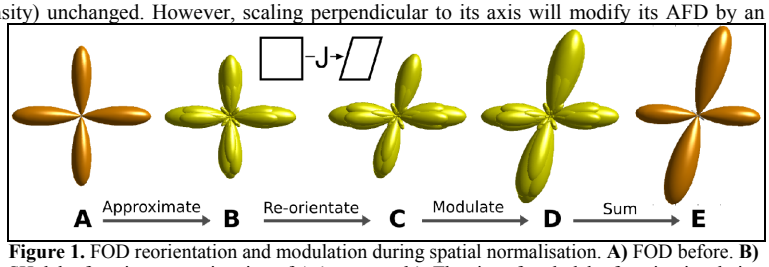

Figure 1. FOD reorientation and modulation during spatial normalisation. **A)** FOD before. **B)** SH delta function approximation of A (*not to scale*). The size of each delta function is relative to its weight required to approximate A. **C)** Reoriented delta functions using the Jacobian matrix, **J**, illustrated by the square (shear and scale applied). **D)** Modulated delta functions. **E)** Delta function SH coefficients are summed to obtain the reoriented and modulated FOD.

To compute the deformation field required to normalise FOD data, we implemented a Symmetric Diffeomorphic Image Registration [10] that exploits the information provided by FODs to better align regions with crossing fibres. Optimisation was achieved using the sum of squares difference of the FOD SH coefficients [9]. Reorientation of FODs was completed at each iteration based on the output of the previous iteration. To reduce noise, registration was performed using a SH degree (*lmax*) of 4 and the final transformations were applied to *lmax* 8.

After spatial normalisation of FODs, differences in AFD were determined by performing a t-test on the FOD amplitudes between groups along corresponding orientations and voxels. To minimise any effect of imperfect registration, data were convolved in the spatial domain with an 8mm FWHM Gaussian kernel followed by smoothing in the orientation domain by truncating the FOD SH to *lmax* 4.

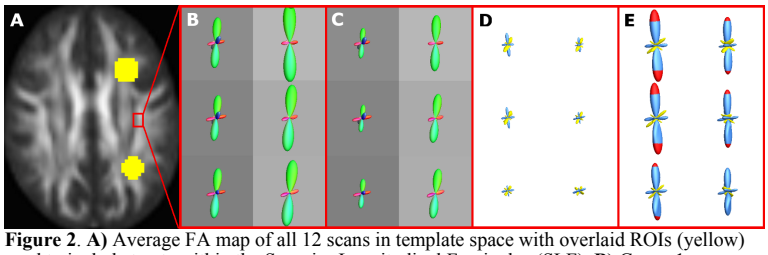

Figure 2. **A)** Average FA map of all 12 scans in template space with overlaid ROIs (yellow) used to include tracts within the Superior Longitudinal Fasciculus (SLF). **B)** Group 1 average FODs before being altered (overlaid on FA). **C)** Group 1 average FODs after SLF was altered in patient space to simulate pathological effects. **D)** No natural statistical difference in AFD is detected between groups. The t-statistic is displayed as a function of orientation using spherical harmonics. Orientations with positive t-statistics are coloured blue, negative are yellow, and those with a significant t-statistic are coloured red ($p<0.05$ corrected for multiple comparisons within a voxel). **E)** A statistical difference in AFD between groups was detected after the SLF of group 1 as modified as shown in C.

Experiments & Results

We investigated voxel based analysis of AFD using data from 12 healthy volunteers, collected on a 3T Siemens Trio with 60 directions at b=3000 s/mm^2. FODs were computed using CSD [5], and registered to an unbiased group average template. Images were split into two groups and statistical analysis of AFD was performed over 300 equally distributed orientations. P-values were corrected for multiple comparisons within each voxel using a Bonferroni correction assuming 15 independent parameters for FODs with *lmax* 4 (15 SH coefficients). Results for each voxel in template space are displayed on the surface of a sphere by remapping the t-statistic of all tested orientations to spherical harmonics (Fig. 2d). Note that no significantly differences were observed.

In a similar experiment, we induced a difference in the superior longitudinal fasciculus (SLF) between the two groups to simulate pathological effects. The SLF contains many voxels with crossing fibres and was chosen to illustrate the ability of our approach to identify differences in distinct orientations within a voxel. To induce a difference between groups, group 1 images were altered in their native space by reducing the amplitude of FODs along SLF orientations (Fig 2b&c). SLF voxels and orientations where identified using probabilistic tractography [11] performed in subject space by including tracts that connected two ROIs manually defined in template space (Fig 2a). Voxel based analysis of AFD was performed in template space as described above and results are shown in Fig 2e. Significant orientations ($p < 0.05$, corrected for multiple comparisons per voxel only) are shaded red. Note that a significant difference is only detected along the orientations corresponding to the SLF while no significant difference is observed in other fibre orientations.

Discussion and Conclusion

We have developed a novel method for investigating group differences in white matter using HARDI. The proposed technique permits the detection of AFD differences in specific orientations corresponding to different fibre bundles or tracts. Future work will focus on improving the robustness of AFD statistical analysis and applying it to investigate differences between diseased and healthy populations.

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