Definition of connection significance using probabilistic tractography

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Introduction – Probabilistic fibre tracking methods provide an estimate of the confidence of cerebral anatomical connections identified by fibre tracking processes [1-3]. Connection probability is normally presented as a map of the frequency of connection of each voxel to the start point or region, for a number of iterations of a streamline process through a field of voxel fibre orientation probability density functions (PDFs). Connection probability defined in this way has two undesirable properties. 1. There is a decrease in connection probability with distance from the start point as the number of streamlines present decreases; 2. A 'flare' of relatively high connection probability around the start point is observed, due to the finite extent of voxel PDFs perpendicular to the best estimate of fibre orientation. Thresholding of the frequency of connection probability maps generally yields a pattern of connection that is distorted due to these distance-related effects. We present an improved definition of connection probability from a seed voxel based on the statistics of a null frequency of connection map, therefore reducing these artefacts and improving the precision of fibre tract localisation.

Statistical methods - We correct the conventional frequency of connection map by comparison with a null frequency of connection map generated by applying the PICo probabilistic tracking method [1,2] with uninformative PDFs. These uninformative PDFs differ from those used in conventional probabilistic fibre tracking in that they have uniform fibre orientation probability. The resulting null frequency of connection from a single seed voxel for a target voxel at x after n iterations, $\mu_N(x,n)$, is well described by a Poisson distribution (which we define as $V_N(x,n)$), as for each random iteration each pixel will either be identified as connected or not [4]. A Kolmogorov-Smirnov test comparing the observed distribution of repeated null distributions with a theoretical Poisson distribution for each voxel demonstrates that the observed distributions are not discernable from a Poisson distribution in areas with adequate sampling. We assume that for $n' \gg n$, the expectation value of $V_N(x,n)$ may be obtained from $\bar{V}_N(x,n) = n\mu_N(x,n')/n'$ to a good approximation. This allows us to estimate the standard deviation of $V_N(x,n)$ using the standard Poisson distribution relationship $\sigma_N(x,n) = \sqrt{\bar{V}_N(x,n)}$. $V_N(x,n)$ may then be compared with the voxel values $\mu(x,n)$ from a PICo frequency of connection map generated using the standard informative PDFs. First, the Z statistic [4] for each pixel is calculated according to $Z(x,n) = \left(\mu(x,n) - \bar{V}_N(x,n)\right)/\sigma_N$. This allows us to determine those voxels where $\mu(x,n) > \bar{V}_N(x,n)$ - where the PICo frequency of connection map has values greater than those predicted by the null frequency of connection map. In these voxels we then estimate the significance of this positive Z statistic by estimating the probability of observing $\mu(x,n)$ from the null distribution $V_N(x,n)$ (i.e purely by chance), again using the standard Poisson statistical relationship [4]: $p(\mu(x,n)) = e^{-\bar{V}_N(x,n)}\bar{V}_N(x,n)^{\mu(x,n)}/\left(\mu(x,n)!\right)$. If $\bar{V}_N(x,n)$ is not available at x (due to undersampling of $\mu_N(x,n')$), we assume $\mu_N(x,n') = 1$ for the purposes of estimating $p(\mu(x,n))$. False positive connections are reduced by removing those significantly connected voxels that cannot trace a significant path to the start point.

Data acquisition - Images were acquired using a 3T Philips Achieva scanner using pulsed gradient spin echo EPI with TE = 54 ms, TR = 11884 ms, G = 62 mTm^{-1}, phase encoding left-right, 112 × 112 matrix, SENSE factor 2.5, reconstructed resolution 1.875 mm, slice thickness 2.1 mm, 60 slices, 61 diffusion sensitisation directions at b = 1200 smm^{-2} (Δ, δ = 28.5, 13.5 ms), and 1 b = 0 image. Two image sets with identical diffusion gradients but opposite direction k space traversal were acquired to allow for distortion corrections using a variation of the reversed phase encoding gradient method [5].

Results – Figures 1-5 show a standard PICo frequency of connection map, μ from an arbitrary seed voxel in the posterior left superior temporal gyrus, as indicated by the arrows (obtained with n = 1000), the corresponding null distribution, μ_N (obtained with n' = 20,000), the Z map, the p map plotted as (1-p), and the final p map threshold at p = 0.05 displaying p as before with false positive reduction.

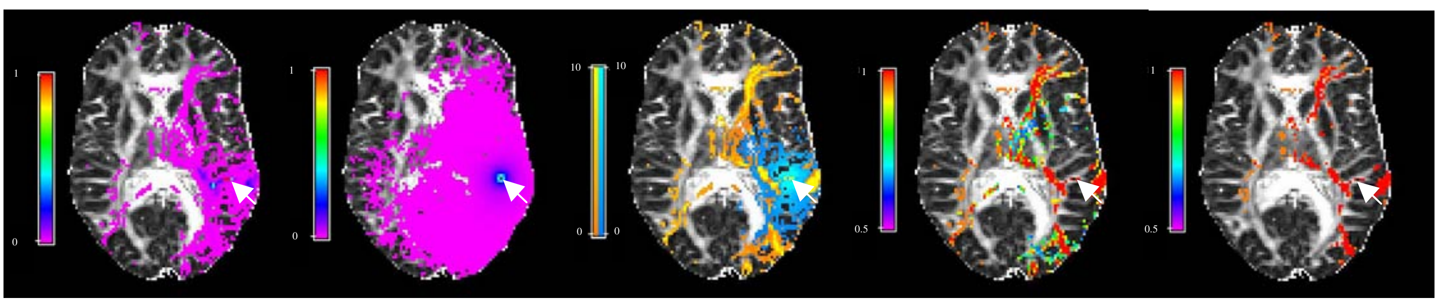

Fig. 1: μ map Fig. 2: μ_N (null distribution) map Fig. 3: Z map Fig. 4: p map Fig 5: final p map

Discussion and conclusion – The standard frequency of connection map, μ, demonstrates a spread of high connectivity near to the start point and widespread lower confidence connections at distance (Fig. 1), while the null map, μ_N, shows relatively isotropic connectivity modulated by CSF spaces (Fig 2). The Z map identifies connections in μ around the start point with negative Z scores (Fig. 3), where the frequency of connection is less than would be expected from the null distribution (i.e. by chance), even though they have relatively high frequency of connection values (Fig. 1). By definition these represent areas with non-significant connection to the start point. The p map (Fig. 4) shows more significant connections (lower p) closer to the point of origin within a well-defined fibre bundle. There is still a slight drop-off in the significance of connection with distance as the observed connection frequency becomes closer to the null distribution (as is to be expected due to the propagation of the dispersive effects on the streamline tracking of the voxel PDFs). However, some distant points that demonstrate relatively low frequency of connection in the μ map demonstrate significant connection in comparison with the null distribution (p<0.05). Whilst many of these distant points of connection appear reasonable, others are likely to represent sporadic false positive long range connections resulting from the probabilistic tracking process. These are reduced in the final map (Fig. 5.) by imposing the condition of significant path of connection on each individual voxel. Investigation is required into the application of these methods to the larger start regions commonly used in tracking experiments, which may require alternative statistical treatment and potentially the need to correct for multiple statistical comparisons.

References – 1. Parker, G.J. and D.C. Alexander. Lect. Notes Comp. Sci., 2003. 2737: p. 684-695. 2. Parker, G.J.M., H.A. Haroon and C.A.M. Wheeler-Kingshott. JMRI., 2003. 18: p. 242-254. 3. Behrens, T.E.J et al MRM 2003. 50: p. 1077-1088 4. Altman, D.G., Practical Statistics for Medical Research. 1999, London: Chapman and Hall. 5. Morgan, P.S., R.W. Bowtell, D.J.O. McIntyre and B.S. Worthington JMRI, 2004. 19: p. 499-507.

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