A framework for modelling the regional variation of white matter microstructure

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Introduction We present a natural framework for group-wise comparison of the regional variation of tissue parameters estimated from diffusion-weighted MRI (DW-MRI) over an anatomical region of interest (ROI). The regional variation model (RVM) fits curves of parameter variation directly to the DW-MRI signals which captures the spatial changes in a natural way as well as reducing the effects of noise. Using statistical tests, we are able to localise regions of significant difference along the curves. Unlike traditional ROI analysis, we obtain a continuous representation of the parameter variation. Unlike VBM or TBSS [9], we detect differences in global trends of parameters and exploit the local coherence of parameter values in a natural way. We demonstrate the technique on the mid-sagittal corpus callosum (MSCC) in two distinct age groups and localise significant differences in the genu of the MSCC.

Methods The RVM comprises a spatial model and a diffusion model. The spatial model describes the underlying variation of the diffusion model parameters along the principal axis of the ROI or tract. These curves are mapped onto the ROI to provide a set of diffusion model parameters for each voxel. The diffusion model is used to predict the DW-MRI signals A which are then compared to the true measurements $\tilde{A}$. The spatial model is then iteratively updated until the optimal solution is found. This framework can encompass a wide range of spatial and diffusion models of varying complexity; in this study we opt for a simple ball and stick [2] diffusion model and a penalised B-spline (P-spline) spatial model [4]. P-splines use a large number of basis functions defined over equally-spaced knots. The spline is fit using penalised least squares, which adds a penalty term to the objective function based on the difference between coefficients of adjacent basis functions. The size of the penalty is controlled by a smoothing parameter λ, which is determined using generalised cross validation (GCV) [4], a technique that weighs goodness of fit against the effective dimensionality of the model. The ball and stick diffusion model is parameterised by volume fraction f, diffusivity d and fibre orientations θ and φ, each of which is described by a P-spline whose value at x is defined by $P_m(x) = \sum_{n=1}^{N_B} \alpha_{m,n} B_n(x)$, where m=f, d, θ or φ, and there are N_B basis function B_n each with coefficient $\alpha_{m,n}$. The overall objective function, which is minimised using a Levenburg-Marquardt algorithm, is given by

$$\underset{\alpha_f,\alpha_d,\alpha_\theta,\alpha_\phi}{\arg\min}\left(\sum_{i=1}^{N_G}\sum_{j=1}^{N_V}\left(\tilde{A}_{ij} - A_{ij}\left(P_f(\alpha_f,x_j), P_d(\alpha_d,x_j), P_\theta(\alpha_\theta,x_j), P_\phi(\alpha_\phi,x_j); b, \vec{G}\right)\right)^2 + \sum_{k=f,d}\lambda_k\sum_{n=1}^{N_B}\left(\Delta^2\alpha_{k,n}\right)^2\right),$$

where N_G is the number of gradient directions, N_V is the number of voxels, x_j is the position of the j^{th} voxel along the ROI axis, b is the diffusion weighting factor, G is the gradient direction and Δ^2 is a second order difference penalty on adjacent spline weights.

Experiments We demonstrate the method by tracking the white matter changes due to healthy aging in the MSCC using data sets collected by the Information eXtraction from Images (IXI) project. All data were acquired on a 3T Phillips scanner using 15 non-collinear directions with b=1000 smm^{-2} and 1 b=0 smm^{-2} T2-weighted image. We randomly select 30 subjects; 15 aged 20-29 (9F 6M) and 15 aged 60-69 (9F 6M). The MSCC is segmented semi-automatically from the FA maps of each subject using a threshold of 0.35, and the principal axis of the CC, taken to be its medial axis, is extracted using continuous medial representation [5]. Partial volume effects are estimated prior to fitting the spatial model from the b=0 image. Anatomical studies of the CC [6] have shown that fibre orientation remains constant along the mid-sagittal slice, so the spatial model used in this study can be simplified to fit θ and φ as constants. Initial values for both angles are derived from the averaged principal directions of tensor fits to the data. The remaining parameters f and d are fit using P-splines comprising 23 basis functions covering the medial axis. All α_f are initialised to 0.7 whilst all α_d are initialised to 1.5x10^{-9} m^{2}s^{-1}. We choose optimal values of λ_f and λ_d by minimising the penalised least squares objective function over all subjects.

Results Using GCV we find the optimal smoothing parameters are λ_f=λ_d=10. Figure 1 shows the average curves for f and d by group. The curves for f in Figure 1a show that the shape of variation of f is consistent among all subjects regardless of age and there is very little difference in magnitude between the groups. The curves for d in Figure 1b show variation in both shape and magnitude. The older subjects generally have higher diffusivities across the CC and the profiles of variation of d are distinct for each group. Figure 2 shows the results of the Westfall-Young permutation test [8] for group differences in f (Figure 2a) and d (Figure 2b). A significant increase in d was found in the genu in the older subjects, as well as a trend towards increased d in the anterior splenium. No significant differences were observed in f, although there was an unexpected trend towards increased f in the genu of the older subjects.

Discussion We have presented a regional variation model of white matter microstructure which estimates the variation of diffusion model parameters across an ROI directly from the DW-MRI signals. We note similarity of our method with that of Goodlett [3], who measures variation in FA and MD along streamlines; however our method is able to localise differences whereas they only test for significance across the whole tract. We also map variation along the cross-section of tracts rather than along streamlines, which provides information on many more connections. When fit to a data set with two distinct age groups, the RVM detects increases in d in the genu in older subjects, in agreement with previous studies [7]. Our method is also able to show that the regional variation of d, not just its magnitude, changes with age. Tracking these regional changes may be able to provide important information about ageing as well as disease pathologies. However, the ball and stick model is a very simple model and we still cannot determine the specific tissue changes that are occurring. In future, we plan to incorporate more complex models of diffusion into the spatial variation framework, allowing us to investigate more fundamental tissue properties such as axon radius and density. The RVM naturally pools information across the ROI, enhancing sensitivity to these hard to estimate parameters.

References [1] Basser *JMRB* 1996 [2] Behrens *MRM* 2003[3] Goodlett *NIMG* 2009 [4] Eilers *Stat Sci* 1996[5] Sun *TMI* 2007 [6] Aboitiz *Brain Research* 1992 [7] Otaa *NIMG* 2006 [8] Cox *Biometrika* 2008 [9] Smith *NIMG* 2006

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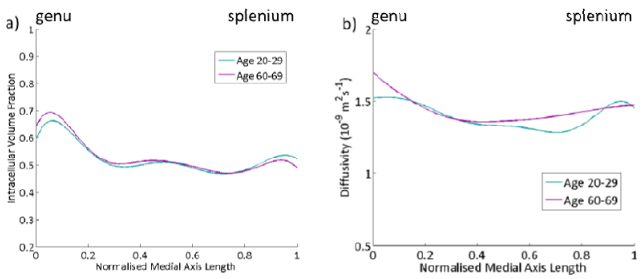

Figure 1 shows the mean spline fits for each group for a) volume fraction and b) diffusivity

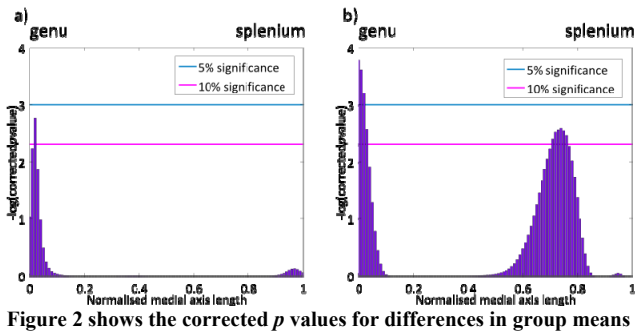

Figure 2 shows the corrected p values for differences in group means for a) volume fraction and b) diffusivity. Significant increases in diffusivity are found in the genu of the older group