Polynomial models of the spatial variation of axon radius in white matter

G. L. Morgan[1], R. D. Newbould[2], B. Whitcher[2], and D. C. Alexander[1]
[1]Centre for Medical Image Computing, University College London, London, United Kingdom, [2]Clinical Imaging Centre, GlaxoSmithKline, London, United Kingdom

Introduction White matter axon radius r is a potentially useful clinical biomarker that can be derived from diffusion weighted imaging (DWI) however its estimation in a clinical setting is hampered by poor signal-to-noise ratio and limited sensitivity to small axon radii at low gradient strengths. Most axon radius studies to date have been performed on *ex vivo* tissue samples [1,2] which allow long acquisition times. Moreover, these studies assume prior knowledge of tissue orientation to reduce acquisition requirements. Recently, a new directionally invariant protocol has been developed [3] which provides sensitivity to the axon radius distribution within clinically acceptable scan times and hardware limitations. This technique has been demonstrated using live human subjects in a clinical scanner [4]. However, even with unusually high clinical gradient strengths of 60mT/m, the resulting mean radius index ρ has low signal-to-noise. In this study we introduce a technique for mapping ρ that exploits the spatial coherence of axon radius distribution across the corpus callosum (CC). Specifically, we fit a polynomial model of the spatial variation of ρ. This significantly reduces the total number of parameters to estimate compared to fitting in each voxel separately and provides sensitivity to axon radius even at typical clinical gradient strengths of 40mT/m or less.

Methods *Model:* Histology studies of the human CC show that axon radius distribution varies smoothly along the anterior-posterior (A-P) axis while remaining approximately constant in the superior-inferior (S-I) direction [5]. We hypothesise that this variation can be captured by modelling the axon radius index ρ as a polynomial function of A-P position. Instead of fitting the parameter separately in each individual voxel, our technique pools all the data within a region of interest (ROI) and fits the polynomial coefficients that best describe ρ in all voxels simultaneously. *Simulation experiment:* To test our technique, we construct a synthetic ROI to represent the mid-sagittal section of the CC. At each unique A-P voxel position within the ROI we assign a gamma distribution for r based on the electron microscopy studies by Aboitiz et al [5]. We keep the intra-axonal volume fraction f approximately constant ($f \approx 0.73$) across the ROI. We use the experiment design framework in [3] to generate 14 multi-shell acquisition protocols with maximum gradient strengths varying from 20mT/m to 200mT/m. Each acquisition protocol comprises 260 measurements (240 gradient directions divided optimally into 3 HARDI shells and 20 b=0 s/mm^2 measurements). For each acquisition protocol, we use Monte Carlo simulations of diffusion [6] to generate synthetic data in the ROI with additive Rician noise at SNR=20. We then estimate ρ and f in each individual voxel and across the whole ROI using the polynomial model. We fit the simplified CHARMED model in [3,4], which assumes that the axons in each voxel are randomly packed parallel cylinders of equal radius. For each data set, we fit polynomials for ρ from order 0 to 5 and use the Bayesian Information Criterion (BIC) [7] to determine the optimal choice. We hypothesize that the single axon radius estimate should reflect the following statistic of the axon radius distribution $\eta_T = \int_T^\infty r^3 p(r)dr \Big/ \int_T^\infty r^2 p(r)dr$ where T is a threshold which defines the minimum value of r we are sensitive to for each protocol and $p(r)$ is the true axon distribution. We define T for each protocol as the minimum radius that causes a 5% signal attenuation in the highest b-value measurement. T varies from 2.3μm at $|\mathbf{G}|_{max}$=20mT/m to 1.4μm at 200mT/m. *Human experiment*: We acquire live human brain data on a 3T Siemens Tim Trio scanner using the 32-channel head coil scanner with $|\mathbf{G}|_{max}$=38mT/m. The acquisition protocol consists of 3 PGSE sequences. The sequences comprise 70, 75, 94 directions at TE=109ms with b values of 687, 645, 2783 s/mm^2 respectively and 20 b=0 s/mm^2 measurements. We manually select an ROI containing the mid-sagittal section of the CC and as per the simulation experiment, we estimate ρ and f in each voxel and across the ROI using the polynomial method.

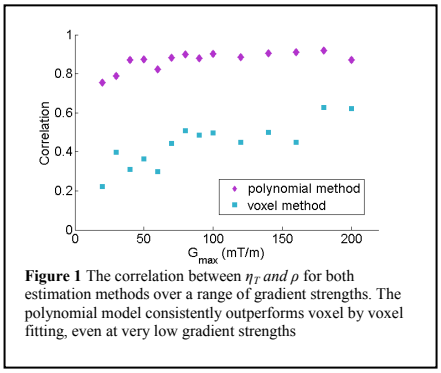

Figure 1 The correlation between η_T *and* ρ for both estimation methods over a range of gradient strengths. The polynomial model consistently outperforms voxel by voxel fitting, even at very low gradient strengths

Results *Simulation experiment*: From the BIC, we find that the fifth-order polynomial best describes the variation of ρ across the CC for all acquisition protocols. We compute the correlation of ρ and η_T for both fitting methods excluding any ρ below T. Figure 1 shows that estimates of ρ from the polynomial method correlate better with η_T than estimates using voxel-by-voxel fitting at all gradient strengths. In Figure 2 we take a closer look at the results for $|\mathbf{G}|_{max}$= 40mT/m, the maximum gradient strength achievable on a typical clinical scanner. The voxel method estimates unrealistically low values of ρ (close to zero) in a significant number of voxels in both the genu and splenium. In the remaining voxels it provides weak correlation to η_T. The polynomial method also fails to fit sensible values for ρ in the genu as the axon radius distribution in this region is below T; however in the midbody and splenium it is able to recover the underlying trend of η_T. *Human experiment:* Figure 3 shows the estimated values of ρ from the human brain data. Using the BIC, we find that the third-order polynomial provides the optimal model for radius variation. This model is able to extract the general low-high-low-high trend we expect from histology [5]. If we fit the parameters in each voxel individually we get plausible results in the midbody; however estimates in the genu and splenium estimates are not sensible and we no longer see the expected trend.

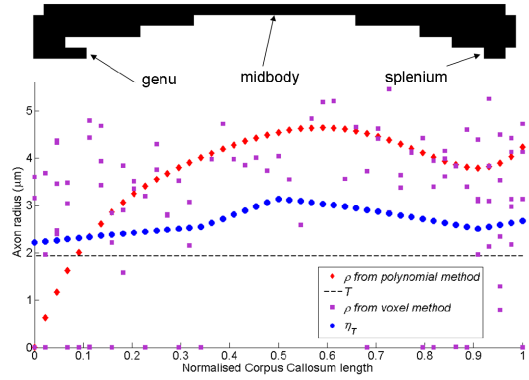

Figure 2 This shows plots of η_T and ρ (estimated using both polynomial and voxel methods) in the region of interest, from the simulation experiment with $|\mathbf{G}|_{max}$=40mT/m

Discussion We have presented a technique for estimating axon radius in the CC which uses polynomials to describe the variation of ρ across the ROI. Unlike the voxel-by-voxel fitting methods, the estimates obtained using our method are strongly correlated with η_T and they capture the general trends we expect to see in the CC, both for simulated and human brain data. While the technique does struggle in the genu we believe this is due to the lack of sensitivity to the very small radii which dominate this region. In future, we plan to improve the fitting technique to model variation in the S-I direction as well as the A-P direction and to investigate ways to improve fitting in the genu. The next step will be to investigate intersubject variation by fitting the model for multiple subjects. Our eventual aim is to use the parameters of the polynomial model of ρ as a clinical biomarker for white matter diseases such as schizophrenia and multiple sclerosis with more statistical power than voxel-by-voxel estimates.

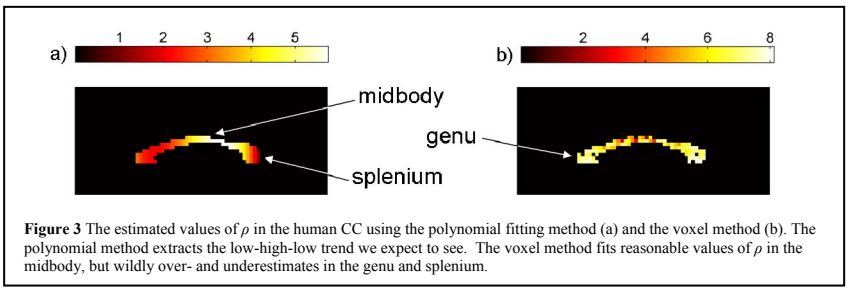

Figure 3 The estimated values of ρ in the human CC using the polynomial fitting method (a) and the voxel method (b). The polynomial method extracts the low-high-low trend we expect to see. The voxel method fits reasonable values of ρ in the midbody, but wildly over- and underestimates in the genu and splenium.

References [1] Stanisz, MRM 1997; [2] Assaf, MRM 2004; [3] Alexander, MRM 2008; [4] Alexander, ISMRM 2009; [5] Aboitiz, Brain Research 1992; [6] Hall, TMI 2009; [7] Schwarz, Ann Stat 1978

This work is supported by EPSRC and GlaxoSmithKline