INFERRING MICRON-SCALE TISSUE STRUCTURE USING EXTREME VALUE THEORY FOR CYLINDRICALLY-RESTRICTED DIFFUSION

L. A. Johnston[1,2], D. Wright[2], R. H. Philipsen[3], S. C. Kolbe[2], J. A. Bourne[4], I. M. Mareels[1], and G. F. Egan[2]

[1]Electrical and Electronic Engineering and NICTA VRL, University of Melbourne, Parkville, VIC, Australia, [2]Howard Florey Institute, Florey Neuroscience Institutes, Parkville, VIC, Australia, [3]Technical University of Eindhoven, Netherlands, [4]Australian Regenerative Medicine Institute, Monash University, Australia

INTRODUCTION: The ability to infer micron-scale tissue structure from voxel-scale diffusion weighted MRI data is of great potential benefit in the study of neurological disorders and diseases [1]. The AxCaliber method [2,3] was recently proposed for the inference of axon diameter distributions from q-space acquisitions. The restricted diffusion component in AxCaliber is based on the short gradient pulse approximation, while previously the CHARMED framework [4] employed a constant field gradient approximation. We take a probabilistic approach, similar in concept to [5], and derive expressions for cylindrically-restricted diffusion via the theory of extremes, without need for pulse duration or diffusion time approximations. Our second contribution is to derive a closed-form expression for non-exponential decay in q-space imaging, that is the physically meaningful result of an expectation over the relevant geometry-dependent distribution of apparent diffusion coefficients (ADCs).

THEORY: Our first conjecture is that the distribution of phase, φ, from restricted diffusion in a pulsed gradient spin echo experiment is governed by extreme value theory. Considering herein cylinders of radius R, Brownian motion trajectories with maximal radial coordinates define the diffusion weighting, as trajectories that do not interact with the boundary behave as freely diffusing particles. The relevant extreme value distribution for random variables with positive support is the Fréchet distribution [6]. The phase variance is therefore posited to be as follows:

$$\mathrm{var}(\varphi) = 2\times 4\pi^2 q^2(\Delta-\delta/3)D, \quad \text{where the ADC is } D = D_{\text{free}}e^{-\left(\frac{R}{b}\right)^{-c}}, \quad b,c>0. \tag{1}$$

The Fréchet constants b and c can be determined through simulations. Our second conjecture is that the restricted component of signal decay, E_{res}, is an expectation over the distribution of D. Under the assumption that $p(D) \sim \mathrm{Gamma}(\alpha,\beta)$, E_{res} has the following closed-form expression:

$$E_{res} = \int E_{res}(D)p(D)\,dD = \int e^{-4\pi^2q^2(\Delta-\delta/3)D}\,\frac{D^{\alpha-1}e^{-D/\beta}}{\beta^{\alpha}\Gamma(\alpha)}\,dD = \frac{1}{\left(1+4\pi^2q^2(\Delta-\delta/3)\beta\right)^{\alpha}}. \tag{2}$$

Eqs.(1)-(2) can be employed to infer the density of cylinder radii, $p(R)$, from measured diffusion decay curves, through estimation of α and β.

METHODS: Simulated PGSE data were generated by sampling 2-d Brownian motion trajectories restricted to circles of radius R via reflection at the boundaries, under the assumption of long cylinders perpendicular to the imaging plane. Sets of trajectories were generated for $R \in$ (0,150], g = [200,400,600]mT/m, δ = [2,4,6] ms, Δ = [30,60,90,120,150] ms, D_{free} = [0.5,1,2] μm^2/ms. The simulated phase distributions were tested for Gaussianity (Kolmogorov-Smirnov test), and Eq.(1) was fit using nonlinear least squares, along with a quadratic approximation for R < 10μm. **Experimental PGSE data** of an *ex vivo* marmoset brain was acquired (Brüker 4.7T MRI), TR/TE=3500/16.12ms, mid-sagittal slice, FOV = 5.12x2.56cm^2, matrix size = 128x64, NEX=4, 16 evenly spaced gradient values with $g_{\max}$=960mT/m, δ=4ms, Δ={30,60}ms. Four regions-of-interest in the corpus callosum were manually delineated (Fig.2). Eq.(2) was optimised via nonlinear least squares.

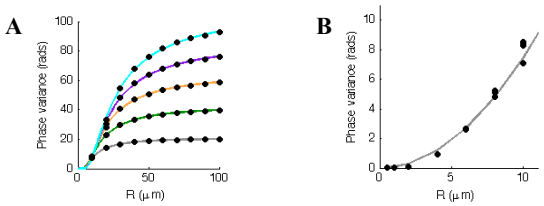

Fig.1 Example of empirical phase variance for cylinder-restricted diffusion, g=400mT/m, δ=4ms, D_{free}=2μm^2/ms. **A.** Simulated data (black dots) and Fréchet model fits, Eq.(1), for Δ=30ms (gray), 60ms (green), 90ms (orange), 120ms (purple), 150ms (cyan). **B.** Simulated data (black dots) and quadratic approx. to Eq.(1) for R<10μm (gray).

RESULTS: For each simulated dataset from each parameter combination, the assumption of Gaussian phase was shown to hold (KS-test returned Gaussian even at high significance level α=0.1). The Fréchet -weighted expression Eq.(1) accurately fit the simulated data (Fig.1A), while a quadratic approximation fit equally well for small R, in agreement with [7]. The best fits of a hindered/restricted 2-compartment model $E = fE_{\text{hind}}+(1-f)E_{\text{res}}$, $0 \lesssim f \lesssim 1$, with the hindered compartment also modelled by an expectation over ADC distribution, returned excellent agreement with the data (Fig.3). The estimated parameters describing $p(D)$ were used to infer $p(R)$ via Eq.(1), the result of which is shown in Fig.4. As expected [3], the genu and splenium of the corpus callosum display a more peaked axon distribution, while the mid-regions are more dispersed across axon widths.

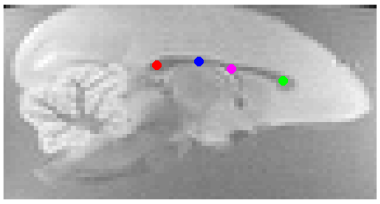

Fig.2 Ex vivo marmoset brain showing four regions of interest in corpus callosum.

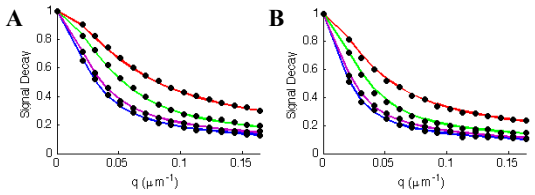

Fig.3 Experimental diffusion signal decays (black dots) and non-exponential decay model fits, Eq.(2). Colours index ROIs in Fig.2. **A.** Δ=30ms **B.** Δ=60ms.

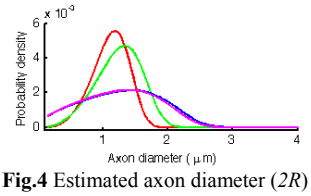

Fig.4 Estimated axon diameter (2R) densities inferred from data in Fig.3. Colours index ROIs in Fig.2.

CONCLUSION: We have demonstrated that extreme value theory accurately predicts restricted diffusion in cylinders, and furthermore that non-exponential signal decay in q-space acquisitions can be accurately described in closed-form by an expectation over the distribution of ADCs. Together, these two results have provided an alternative to the AxCaliber method for inference of axon densities, demonstrated here in marmoset corpus callosum. Future work will focus on non-cylindrical geometries and *in vivo* applications through optimisation of acquisition parameters.

References: [1] Jespersen *et al* (2007) *NeuroImage* 34:1473-1486. [2] Assaf *et al* (2008) *MRM* 59:1347-1354. [3] Barazany *et al* (2009) *Brain* 132:1210-1220. [4] Assaf *et al* (2004) *MRM* 52:965-978. [5] Yablonskiy *et al* (2003) *MRM* 50:664-669. [6] Kotz and Nadarajah (2000) *Extreme Value Distributions: theory and applications*, World Scientific. [7] van Gelderen *et al* (1994) *JMR-B* 103:255-260.