THE ANALYTIC DISTRIBUTION OF FRACTIONAL ANISOTROPY IN DIFFUSION MRI

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INTRODUCTION: Fractional anisotropy (FA) is a popular scalar measure of voxelwise diffusion characteristics, computed by a nonlinear transformation of the tensor eigenvalues [1]. Despite its ubiquitous use in diffusion MRI studies, the statistical distribution of FA has remained unknown; statistical inference on FA images has either involved a Gaussianity assumption, known to be invalid given the finite support of FA, or relied on computationally expensive non-parametric resampling approaches [2,3], that can suffer from inaccurate uncertainty estimates [4,5]. In the analytic realm, perturbation analysis has been used to derive approximate uncertainties [6], while FA has been examined with respect to relative anisotropy [7], a chi-square distributed measure [2]. We present an analytic solution for the FA distribution. Under the assumption of Gaussian distributed eigenvalues, FA is shown to follow a transformed doubly non-central beta distribution. Generalisation to arbitrary eigenvalue distributions results in a mixture of transformed doubly non-central beta distributions. Inferential statistical tests, valid for arbitrary experimental conditions, can now be derived from these analytic expressions.

THEORY: The relationship between tensor eigenvalues and FA geometrically describes a cone with axis [1,1,1] and aperture set by the FA value. We derive the analytic expression for the distribution of FA, $p(f)$, under the assumption of Gaussian distributed tensor eigenvalues, $\lambda_j \sim N(\mu_j, \sigma^2)$, $j=1,2,3$, through rotation of the cone to align with the z-axis, equivalent to a change of variables, and marginalisation of the joint probability density:

$$p(f) = \sum_{n=0}^{\infty}\sum_{m=0}^{n} h\left(\frac{\mu_z^2}{2\sigma^2}, m\right) h\left(\frac{\mu_x^2+\mu_y^2}{2\sigma^2}, n-m\right)\frac{4f}{3}\frac{\left(1-\frac{2}{3}f^2\right)^m\left(\frac{2}{3}f^2\right)^{n-m}}{B(m+1, n-m+1)}, \; f \in [0,1], \quad \text{where} \quad h(s,j) = \frac{s^j e^{-s}}{j!} \quad \text{and} \quad \begin{bmatrix}\mu_x \\ \mu_y \\ \mu_z\end{bmatrix} = R_x\left(\tan^{-1}\sqrt{2}\right)R_z(\pi/4)\begin{bmatrix}\mu_1 \\ \mu_2 \\ \mu_3\end{bmatrix} \quad (1)$$

Here R_x and R_z in Eq.(1) are rotation matrices. Eq.(1) is a transformed doubly noncentral beta distribution. The infinite sum consists of a finite number of significantly non-zero terms, and therefore can be computed efficiently. Our second result generalises Eq.(1) to arbitrary eigenvalue distributions, through a semi-parametric kernel density construction of each eigenvalue distribution, with kernel width σ and kernel centre locations $\{\mu_{x,i}, i=1,...N_x\}$, $\{\mu_{y,j}, j=1,...N_y\}$, $\{\mu_{z,k}, k=1,...N_z\}$ and weights $\{w_{x,i}, i=1,...N_x\}$, $\{w_{y,j}, j=1,...N_y\}$, $\{w_{z,k}, k=1,...N_z\}$:

$$p(f) = \sum_{i=1}^{N_x}\sum_{j=1}^{N_y}\sum_{k=1}^{N_z}\sum_{n=0}^{\infty}\sum_{m=0}^{n} w_{x,i}w_{y,j}w_{z,k} h\left(\frac{\mu_{z,k}^2}{2\sigma^2}, m\right) h\left(\frac{\mu_{x,i}^2+\mu_{y,j}^2}{2\sigma^2}, n-m\right)\frac{4f}{3}\frac{\left(1-\frac{2}{3}f^2\right)^m\left(\frac{2}{3}f^2\right)^{n-m}}{B(m+1, n-m+1)}, \; f \in [0,1] \quad (2)$$

METHODS: Data were simulated by sampling from tensor eigenvalue distributions for varying tensor shapes, with constant mean diffusivity (MD) = 0.7×10^{-3} mm^2/s and varying signal-to-noise-ratio (SNR) = MD/σ. Resultant empirical FA distributions were compared with Eq.(1), parameterised by the means and variance of the eigenvalue distributions. Experimental data for three healthy subjects were acquired on a 3T Siemens TIM Trio, single-shot EPI sequence, TR/TE=7720/80ms, slice thickness=2mm, matrix size=128x128, 60 diffusion directions b=1000s/mm^2 and 5 non-diffusion-weighted volumes. FA maps were computed via multilinear regression. Grey matter, white matter (WM) and CSF were segmented using FSL FAST, and the corpus callosum was manually delineated in each subject. ROI-specific empirical FA distributions were compared with Eq.(2).

RESULTS: The transformed doubly noncentral beta distribution, Eq.(1), accurately models the distribution of FA across tensor shapes and SNR levels when eigenvalues are Gaussian distributed (Fig.1). Decreased SNR leads to more diffuse FA distributions. In higher SNR and more anisotropic tensor shapes (Fig.1B-D), the distribution is unimodal with a clear peak, while isotropic tensors (Fig.1A) give rise to maximal values at the lower extreme of the distribution, as expected. The experimental data demonstrated varying degrees of non-Gaussianity in the eigenvalue distributions (data not shown), which necessitated the mixture distribution, Eq.(2). Fig.2 displays results for representative subjects and regions. Both Eq.(2) and a Gaussian approximation well-modelled the FA distribution in WM (Fig.2A), however for CSF (Fig.2B) the kurtotic and peaked distribution was well-modelled by Eq.(2) and not a Gaussian, as was the case for the localised WM-ROI of the Corpus Callosum (Fig.2C).
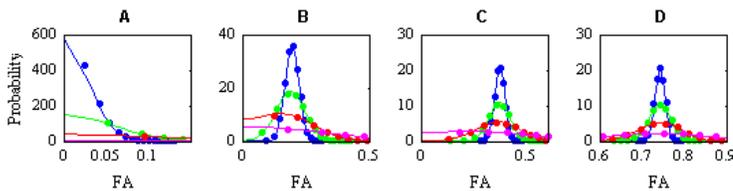
Fig.1 Empirical (dots) vs analytic Eq.(1) (lines) FA distributions, across SNR = MD/σ = 20 (blue), 10 (green), 5 (red), 2 (magenta) **A.** Isotropic tensor, μ = [0.7,0.7,0.7]. **B.** Oblate tensor, μ = [0.8,0.8,0.5]. **C.** Prolate tensor, μ = [1.1,0.5,0.5]. **D.** Highly prolate tensor. μ = [1.8,0.15,0.15]. Eigenvalue mean units: x10^{-3}mm^2/s.
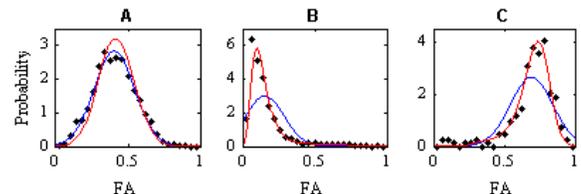
Fig.2 Experimental empirical FA distributions (dots) vs analytic Eq.(2) (red) and Gaussian (blue) distributions. **A.** Subject 1, WM. **B.** Subject 2, CSF. **C.** Subject 3, Corpus Callosum.

CONCLUSION: An analytic form for the statistical distribution of FA has been presented that is valid for both an assumption of eigenvalue normality and for arbitrary eigenvalue distributions. The resultant distribution is a transformed doubly noncentral beta distribution, generalised to a mixture of transformed doubly noncentral beta distributions. Our result eliminates the need for resampling procedures and provides an exact expression for the uncertainty in the distribution of FA.

References: [1] Basser (1995) *NMR Biomed.* 8:333-344. [2] Pajevic & Basser (2003) *JMR* 161:1-14. [3] Chung *et al* (2008) *NeuroImage* 39:1693-1705. [4] Chung, Lu, Henry (2006) *NeuroImage* 33:531-541. [5] Yuan *et al* (2008) *IEEE TMI* 27:1506-1514. [6] Chang *et al* (2007) *MRM* 57:141-149. [7] Hasan *et al* (2004) *MRM* 51:413-417.