Uncertainties of DTI parameter estimation depend on the fitting algorithm: Monte Carlo simulations and *in-vivo* data in human brain.

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INTRODUCTION: Diffusion Tensor Imaging (DTI) provides a sensitive means for the characterization of white matter fiber networks. The quality of information obtainable in DTI is dependent on many factors including equipment, acquisition parameters, and post-processing methods. Much work has been done to optimize the acquisition of diffusion weighted data (1,2). To this end, optimal b-values and gradient orientation schemes have been proposed. It is generally accepted that a b-value in the neighbourhood of 1000 s/mm^2 and gradient directions evenly distributed in 3-D space are optimal for white matter imaging (1,2), though higher b-values may be useful for elucidating more complex structures (3). However, clear consensus within the DTI community is lacking in regards to the choice of fitting algorithm. Many studies use simple and efficient linear regression techniques (2) while others have opted for more sophisticated and processor-intensive nonlinear methods (4). Nonlinear techniques have recently been shown to improve accuracy in the assessment of FA and trace for simulated data (4). For tractography applications, the principle direction of diffusion is of critical importance, yet the effect of different fitting algorithms on estimation of this parameter remains unknown. Furthermore, bias introduced by the magnitude operation as signals approach the noise floor has been shown to affect DTI acquisitions with low SNR, high diffusivity and/or high b-values (3). In this study, we have implemented a tensor fitting approach that accounts for this bias and compared it to linear, nonlinear and weighted least-squares methods using simulations and *in-vivo* data.

METHODS: DTI data was obtained from a healthy volunteer using a 3T GE system. Imaging parameters were as follows: 11 gradient orientations (based on the electrostatic-repulsion algorithm – ref.2), b-value=1000 s/mm^2, 2.6 mm isotropic voxels, and 48 slices. SNR of the b=0 image was approximately 25. The scan was repeated 14 times. Monte Carlo simulations were performed for various FA values between 0 and 0.9 using Matlab (Mathworks, Natick, MA). The SNR, b-value and gradient orientations were matched to the clinical experiment. For each FA value, 100 instances of a reference tensor $\mathbf{D_0}$ with trace 2.1 mm^2/ms were oriented uniformly in 3-D space to eliminate rotational bias. Diffusion-weighted signals were calculated and complex noise was added in quadrature. The simulation was repeated 1000 times producing 100000 data sets (100 orientations x 1000 repetitions) for each FA value. For both experimental and simulated data, tensors were fit using 4 different techniques: linear least-squares (LLS), weighted least-squares (WLS), and nonlinear least-squares (NLS) as well as a magnitude-corrected nonlinear technique (MCNLS). Jones et al. previously proposed a correction scheme that introduces an additional noise-estimation parameter to the nonlinear fitting algorithm (3). We have modified this approach by incorporating noise as a known input, thereby reducing the number of model parameters and improving computational efficiency. Noise is calculated once from the image background (5) and should be similar across all voxels. Therefore, we seek to minimize equation 1, where S_i is the measured signal and σ is the estimated noise level.

$$\sum_i \left(S_i - \sqrt{\exp(-bD)^2 + \sigma^2} \right)^2 \qquad (1)$$

RESULTS&DISCUSSION: In all simulations, fitting methods followed the theoretical chi-squared distribution with 5 degrees of freedom (11 gradient orientations minus 6 tensor parameters) with the exception of LLS, which exhibited above-normal values (Fig.1a). This is consistent with other recent findings (4). We saw similar, though slightly higher, chi-squared values in the clinical data (Fig.1d), probably due to a combination of partial-volume effects, complex fibers and/or underestimation of noise. The experimental FA distribution (Fig.1e) was calculated from voxels with a range of FAs (0.85-0.95) and therefore it is wider than the simulated distribution (Fig.1b). It should also be noted that physically impossible FA values (>1) are present due to negative eigenvalues. The standard deviation of the principle direction of diffusivity σ_{V1} is shown in Fig.1c&f. This is the mean angular deviation from the dyadic tensor average (2) and represents the degree of directional uncertainty in the principle eigenvector. These results demonstrate reduced directional reliability using LLS for voxels with high FA. This has obvious implications for tractography. Differences between fitting algorithms diminished with reduced FA, and there was no noticeable difference in chi-squared, FA or σ_{V1} below an FA of 0.6. Simulations performed with b=3000 s/mm^2 and FA=0.9 showed a tendency for LLS, WLS and NLS to underestimate FA as reported by Jones (3), while the MCNLS scheme was unbiased. At this higher b-value, uncertainty in the principle eigenvector (σ_{V1}) was indistinguishable for NLS, WLS and MCNLS (Fig.1g), though LLS performed significantly worse. Note also the large increase in σ_{V1} for b=3000 s/mm^2 relative to b=1000 s/mm^2 under otherwise identical conditions. This is due to a reduction in SNR for the diffusion-weighted images as b is increased.

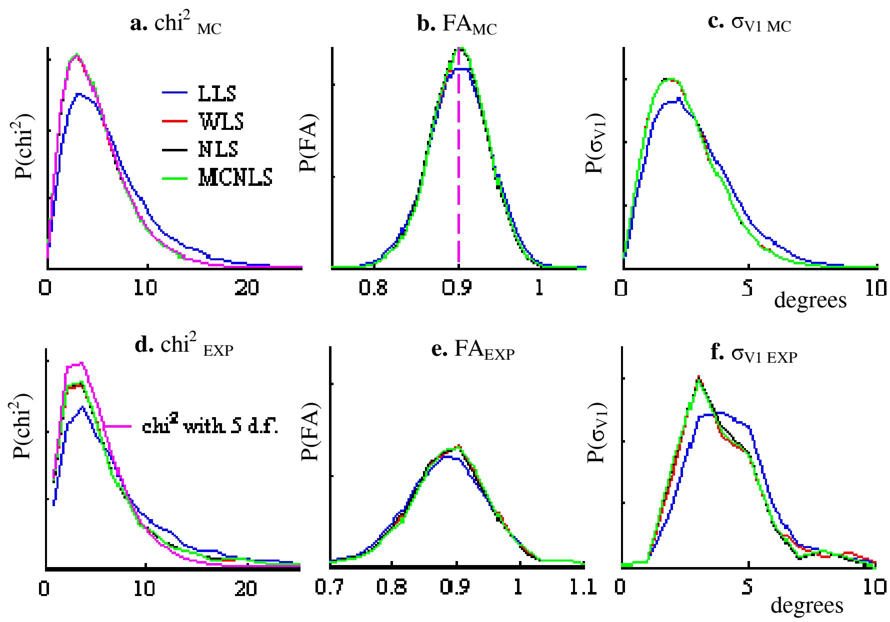
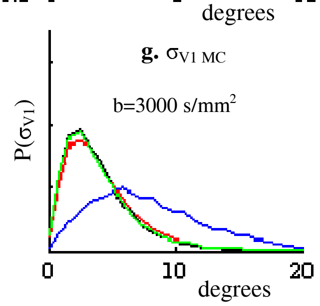


Figure 1.a-c. *Monte Carlo simulated probability distribution functions for chi^2, FA and σ_{V1} for b=1000 s/mm^2 and FA=0.9.* ***d-f.*** *Experimental results calculated from 260 voxels which had a sample mean FA between 0.85 and 0.95 to facilitate comparison.* ***g.*** *Simulated σ_{V1} for b=3000 s/mm^2.*



CONCLUSIONS: Linear least-squares fitting increases uncertainty in the direction of the principle eigenvector for voxels with high FA. Estimation of FA is less sensitive to fitting method, except at high b-value and/or low SNR, for which the magnitude-corrected fit yields the best results. For FA below 0.6, there is no significant difference between the various fitting methods.

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