The Asymptotic Distribution of Diffusion Tensor and Fractional Anisotropy Estimates

J. D. Carew1, C. G. Koay2, G. Wahba1, A. L. Alexander3, P. J. Basser2, M. E. Meyerand3

1Statistics, University of Wisconsin, Madison, WI, United States, 2National Institutes of Health, Bethesda, Maryland, United States, 3Medical Physics, University of Wisconsin, Madison, WI, United States

INTRODUCTION
Error propagation in diffusion tensor imaging (DTI) has general interest since it tells us how noise in diffusion-weighted images propagates to estimates of the tensor and functions of the tensor estimate (e.g., fractional anisotropy (FA)). In this paper we derive asymptotic properties of the nonlinear least squares estimator (NLSE) of the diffusion tensor. Asymptotic properties of the log-likelihood and functions of the NLSE and functions of the NLSE are derived under the assumption that the number of diffusion directions goes large, holding all else constant. We show that the NLSE of the diffusion tensor is a maximum likelihood estimator under normal noise assumptions. This connection allows us to apply the theory of maximum likelihood estimation to obtain asymptotic properties. In particular, we show that the NLSE is consistent and asymptotically normal. Furthermore, any continuously differentiable function of the tensor estimate is also consistent and asymptotically normal. To illustrate and validate the theory we derive the asymptotic distribution of FA and show, with simulations, that for as few as 6 directions, the asymptotic distribution of FA is very close to the empirical distribution.

METHODOLOGY
The diffusion tensor model for measurements \( S = (S_1,\ldots,S_n)^T \) from a single voxel with \( n \) diffusion directions is \( S = S_0 \exp(-X\beta) + \epsilon \). The diffusion encoding matrix is
\[
X = \begin{bmatrix}
    x_{11} & \cdots & x_{1n} \\
    \vdots & \ddots & \vdots \\
    x_{n1} & \cdots & x_{nn}
\end{bmatrix},
\]
where \( b_i \) is the diffusion weighting and \( g_i \) are the components of the encoding vectors. The 6 unique elements of the diffusion tensor \( D \) are in \( \beta := (D_{xx},D_{xy},D_{xz},D_{yx},D_{yy},D_{zx},D_{zy},D_{zz})^T \). We assume that the errors are independent, normal with constant variance, i.e., \( \epsilon \sim N_n(0,\sigma^2 I_n) \). This is a good assumption when the SNR is greater than 3 [1]. Under the noise assumptions, the measurements have distribution
\[
S \sim N_n(S_0 \exp(-X\beta),\sigma^2 I_n).
\]
Define the model parameter \( \theta := (\beta^T,\sigma^2)^T \). The log-likelihood of \( \theta \) given the data is
\[
\ell(\theta;S) = -\frac{1}{2} \log(2\pi\sigma^2) - \frac{1}{2\sigma^2} (S - S_0 \exp(-X\beta))^T (S - S_0 \exp(-X\beta)).
\]
The quantity in (*) is the NLS objective function. Therefore, minimizing (*) over \( \beta \) is the same as maximizing the log-likelihood. This means that the NLSE of the tensor is the maximum likelihood estimator \( \hat{\beta} \) under our noise model. This connection allows us to apply the asymptotic theory of maximum likelihood estimation.

The NLSE of the tensor is consistent and asymptotically normal. This follows from a standard result in [2]. In particular, \( \forall \alpha > 0, \lim_{n \to \infty} \text{Pr}(\|\hat{\beta} - \beta\| > \alpha) = 0 \) and \( \hat{\beta} \rightarrow_d \beta \) with rate \( n^{-1/2} \), where covariance matrix \( \text{var}(\hat{\beta}) \) is the inverse of the Fisher information (FI). The 7th diagonal of the FI is
\[
\frac{1}{2} \text{var}(\hat{\beta}_7) = \frac{1}{2\sigma^2} \sum_{i=1}^6 (S_i - S_0 \exp(-X_i\hat{\beta}))^2.
\]
The other entries in the 7th row and column of the FI are zero. The asymptotic variance of the tensor estimator is the upper left 6x6 part of the FI, which is extracted by applying a contrast matrix \( C \) to give
\[
\hat{\beta} \sim \text{N}_6(\beta,\text{var}(\hat{\beta})^{-1}).
\]

An application of the multivariate delta method [2] shows that a continuously differentiable function of the tensor estimator is consistent and asymptotically normal. This method applies to vector-valued functions of the tensor as well as scalar functions. We apply the delta method to show that the FA estimator is consistent and asymptotically normal. Express the FA estimator as \( \hat{\theta} \), where \( \theta \) is a vector-valued function of the tensor elements. The partial derivatives are
\[
\frac{\partial \hat{\theta}}{\partial \beta} = \left[ \begin{array}{c}
    \frac{\partial \hat{\theta}_1}{\partial \beta_1} \\
    \vdots \\
    \frac{\partial \hat{\theta}_n}{\partial \beta_n}
\end{array} \right], \quad \frac{\partial \hat{\theta}}{\partial \sigma^2} = \left[ \begin{array}{c}
    \frac{\partial \hat{\theta}_1}{\partial \sigma^2} \\
    \vdots \\
    \frac{\partial \hat{\theta}_n}{\partial \sigma^2}
\end{array} \right].
\]

To apply this result, evaluate the FI at the value of \( \hat{\beta} \) to give an estimator for the variance of FA, i.e.,
\[
\text{var}(\hat{\theta}) = \text{var}(\hat{\beta})^{-1} \left( \frac{\partial \hat{\theta}}{\partial \beta} \right)^T \left( \frac{\partial \hat{\theta}}{\partial \beta} \right) + \text{var}(\hat{\theta})^{-1} \left( \frac{\partial \hat{\theta}}{\partial \sigma^2} \right)^T \left( \frac{\partial \hat{\theta}}{\partial \sigma^2} \right).
\]

RESULTS
The three plots above show that the empirical distributions of the 50000 FA estimates is very close to normal for as little as 5 directions and FA values that are typical for white matter. The table summarizes the results from the nine simulations. The sample mean of the FA estimates is very close to the true value of 0.25 in all nine situations. As the number of directions increases, the sample mean gets closer to the true value of 0.25. This is expected from the consistency of the NLSE. The sample variances of the FA estimates show that the asymptotic variance is an excellent approximation with discrepancies only in the third significant digit. The simulation results also show that the variance of FA depends on the value of FA.

DISCUSSION AND CONCLUSION
The main result of this study is that the NLSE of the diffusion tensor and a function of the tensor are consistent and asymptotically normal. The simulation results show that for as few as six diffusion encoding directions the asymptotic approximations for FA are very accurate. This suggests the utility of the asymptotic approximations as the measure of variability in tensor estimates. The results of this study depend on the differentiability of the function of the tensor elements. For example the derivative of FA is not bounded at 0, so the delta method cannot be applied for completely isotropic diffusion. Some authors linearize the diffusion model and use ordinary least squares to estimate the tensor. This approach is suboptimal and more investigation is necessary to determine how it compares asymptotically to the NLSE. Finally, more research is required to extend this result for very low SNR data where the noise distribution is Rician [1].

REFERENCES