The Asymptotic Distribution of Diffusion Tensor and Fractional Anisotropy Estimates

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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 describe the limiting behavior of the NLSE and functions of the NLSE as the number of diffusion directions gets 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 directly 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.

METHODS

The diffusion tensor model for measurements $S = (S_1, \ldots, S_n)'$ from a single voxel with n diffusion directions is $S = S_0 \exp(-\mathbf{X}\boldsymbol{\beta}) + \boldsymbol{\epsilon}$. The diffusion encoding matrix is

$$\mathbf{X} := b \begin{bmatrix} g_{x1}^2 & g_{y1}^2 & g_{z1}^2 & 2g_{x1}g_{y1} & 2g_{y1}g_{z1} & 2g_{x1}g_{z1} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ g_{xn}^2 & g_{yn}^2 & g_{zn}^2 & 2g_{xn}g_{yn} & 2g_{yn}g_{zn} & 2g_{xn}g_{zn} \end{bmatrix}$$

, where b is the diffusion weighting and the g_{ij} are the components of the gradient encoding vectors. The 6 unique elements of the diffusion tensor $\mathbf{D}$ are in $\boldsymbol{\beta} := (D_x, D_y, D_z, D_{xy}, D_{yz}, D_{xz})'$. We assume that the errors are independent, normal with constant variance, i.e., $\boldsymbol{\epsilon} \sim \mathcal{N}_n(\mathbf{0}, \sigma^2 \mathbf{I}_n)$. This is a good assumption when the SNR is greater than 3 [1]. Under the noise assumptions, the measurements have distribution $S \sim \mathcal{N}_n(S_0 \exp(-\mathbf{X}\boldsymbol{\beta}), \sigma^2 \mathbf{I}_n)$. Define the model parameter $\boldsymbol{\theta} := (\boldsymbol{\beta}, \sigma^2)'$. The log-likelihood of $\boldsymbol{\theta}$ given the data is

$$l(\boldsymbol{\theta}|S) = -\frac{n}{2}\log(2\pi\sigma^2) - \frac{1}{2\sigma^2}\underbrace{[S - S_0\exp(-\mathbf{X}\boldsymbol{\beta})]'[S - S_0\exp(-\mathbf{X}\boldsymbol{\beta})]}_{(*)}.$$

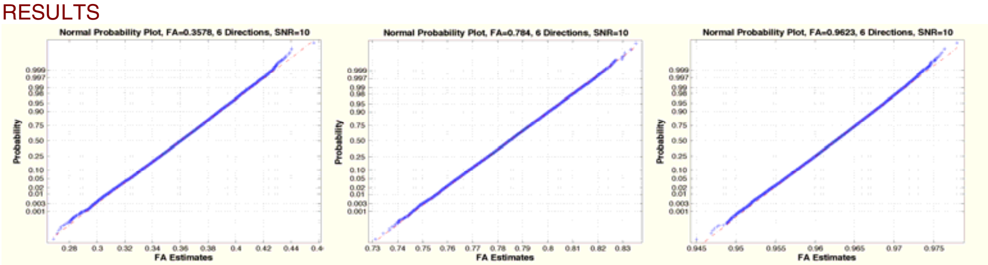
The quantity in (*) is the NLS objective function. Therefore, minimizing (*) over $\boldsymbol{\beta}$ is the same as maximizing the log-likelihood. This means that the NLSE of the tensor is the maximum likelihood estimator $\hat{\boldsymbol{\theta}}$ under our noise model. This connection allows us 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, $\forall a > 0, \lim_{n\to\infty} P(|\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}| > a) = 0$ and $\hat{\boldsymbol{\theta}} \xrightarrow{d} \mathcal{N}_7(\boldsymbol{\theta}, I^{-1}(\boldsymbol{\theta}))$, where covariance matrix $I^{-1}(\boldsymbol{\theta})$ is the inverse of the Fisher information (FI). The ijth entry of the FI is $I_{ij}(\boldsymbol{\theta}) = -\mathrm{E}\left[\frac{\partial^2}{\partial\theta_i\partial\theta_j} l(\boldsymbol{\theta}|S)\right]$. The upper left 6x6 part of the FI is $\frac{1}{\sigma^2}\mathbf{X}'\tilde{\mathbf{S}}^2\mathbf{X}$, where $\tilde{\mathbf{S}}$ is a nxn matrix of zeros except for the main diagonal that is $S_0(\exp(-\mathbf{X}_1\boldsymbol{\beta}), \ldots, \exp(-\mathbf{X}_n\boldsymbol{\beta}))$, where $\mathbf{X}_k$ denotes the kth row of the matrix. The 7th diagonal of the FI is $n/(2\sigma^4)$. 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 inverse of the FI, which is extracted by applying a contrast matrix C to give $\hat{\boldsymbol{\beta}} \xrightarrow{d} \mathcal{N}_6(\boldsymbol{\beta}, \mathbf{C}I^{-1}(\boldsymbol{\theta})\mathbf{C}')$.

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 $g(\hat{\boldsymbol{\beta}})$, where FA expressed in terms of the tensor elements is $g(\boldsymbol{\beta}) := \mathrm{FA} = \left[\frac{3}{2}\left(1 - \frac{(\mathrm{tr}\mathbf{D})^2}{3\,\mathrm{tr}(\mathbf{D}^2)}\right)\right]^{\frac{1}{2}}$. Then, $g(\hat{\boldsymbol{\beta}}) \xrightarrow{d} \mathcal{N}_1(g(\boldsymbol{\beta}), \mathbf{B}\mathbf{C}I^{-1}(\boldsymbol{\theta})\mathbf{C}'\mathbf{B}')$, where $\mathbf{B} := \left(\frac{\partial \mathrm{FA}}{\partial D_x}, \frac{\partial \mathrm{FA}}{\partial D_y}, \frac{\partial \mathrm{FA}}{\partial D_z}, \frac{\partial \mathrm{FA}}{\partial D_{xy}}, \frac{\partial \mathrm{FA}}{\partial D_{yz}}, \frac{\partial \mathrm{FA}}{\partial D_{xz}}\right)$. These partial derivatives are $\frac{\partial \mathrm{FA}}{\partial D_i} = -\frac{1}{2\mathrm{FA}}\left[\frac{\mathrm{tr}\mathbf{D}\,\mathrm{tr}(\mathbf{D}^2) - (\mathrm{tr}\mathbf{D})^2 D_i}{(\mathrm{tr}(\mathbf{D}^2))^2}\right]$, $i = x, y, z$ and $\frac{\partial \mathrm{FA}}{\partial D_j} = \frac{(\mathrm{tr}\mathbf{D})^2 D_j}{\mathrm{FA}(\mathrm{tr}(\mathbf{D}^2))^2}$ $j = xy, yz, xz$. To apply this result, evaluate the FI at the value of $\hat{\boldsymbol{\theta}}$ to give an estimator for the variance of FA, i.e., $\hat{\mathrm{Var}}(g(\hat{\boldsymbol{\beta}})) = \mathbf{B}\mathbf{C}I^{-1}(\hat{\boldsymbol{\theta}})\mathbf{C}'\mathbf{B}'$. Estimate the error variance σ^2 by RSS/(n-6), where RSS is the residual sum of squares.

To validate this method for obtaining the asymptotic distribution of FA, we simulated diffusion measurements for three tensors with FA=0.3578, 0.7840, and 0.9623 and 6, 12, and 252 directions for each level of FA. The goal of the simulations was to determine how many encoding directions are required before the distribution of FA is closely approximated by its asymptotic distribution. The SNR was set to 10, S_0=1000, b=1114 s/mm^2, and 50000 data sets were simulated for each of the 9 FA/direction combinations. The NLSE estimate of the tensor and an FA estimate were computed for each data set. The empirical distributions of the FA estimates were compared to a normal distribution and the sample variance of FA was compared to the variance of the asymptotic distribution.

RESULTS



Simulation Results

# Directions	6	12	252
True FA=0.3578			
Sample Mean	0.3601	0.3589	0.3579
Sample Variance	4.806×10^{-4}	2.014×10^{-4}	9.983×10^{-6}
Asymptotic Variance	4.827×10^{-4}	2.054×10^{-4}	9.981×10^{-6}
True FA=0.7840			
Sample Mean	0.7844	0.7840	0.7840
Sample Variance	1.531×10^{-4}	4.961×10^{-5}	2.370×10^{-6}
Asymptotic Variance	1.526×10^{-4}	4.957×10^{-5}	2.360×10^{-6}
True FA=0.9623			
Sample Mean	0.9625	0.9623	0.9623
Sample Variance	1.440×10^{-5}	9.608×10^{-6}	4.544×10^{-7}
Asymptotic Variance	1.431×10^{-5}	9.622×10^{-6}	4.535×10^{-7}

The three plots above show that the empirical distribution of the 50000 FA estimates is very close to normal for as little as 6 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 FA in all nine simulations. As the number of directions increases, the sample mean gets closer to the true FA. 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 variance as the measure of variability in tensor estimates. The results of this study depend on the differentiability of the function of the tensor. 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

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