The Variance of DTI-derived Parameters via First-Order Perturbation Methods

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Introduction: In typical applications of diffusion tensor MRI (DTI), DT-derived quantities are used to make a diagnostic, therapeutic or scientific determination. In such cases, it is essential to characterize the variability of these tensor-derived quantities. Parametric [1] and empirical methods (e.g., Monte Carlo [2] and Bootstrap [1]) have been proposed to estimate the variance of the estimated DT, and quantities derived from it. The former method is not general since a parametric distribution cannot be found for all DT-derived quantities. The bootstrap requires oversampling diffusion weighted imaging (DWI) data. Statistical perturbation methods [3-5] represent a hybrid between parametric and empirical approaches and overcome the primary limitations of both methods. Here we use 1st-order perturbation method to obtain analytic expressions for the variance of DT-derived quantities, such as the Trace, FA, eigenvalues and eigenvectors for a given experimental design. Monte Carlo simulations of DTI experiments are performed to test these formulae, and to determine the range of applicability for different experimental design parameters, e.g., SNR, diffusion gradient sampling scheme, and number of DWI acquisitions. This information should be useful in designing DTI studies or for assessing the quality of inferences drawn from them.

Method: Let $\mathbf{y} = \{\ln(S_1),\ldots, \ln(S_N)\}^T$, where S_i is the intensity measurement in a DTI acquisition, and $\boldsymbol{\alpha} = \{D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}, \ln(A_0)\}^T$ contains the DT model parameters. To 1st order, the log linear model [6] can be written as $\mathbf{y} = \mathbf{B}\boldsymbol{\alpha} + \mathbf{e}$, where $\mathbf{B}$ is the b-matrix with the jth row equals $-\{b_{xxj}, b_{yyj}, b_{zzj}, 2b_{xyj}, 2b_{xzj}, 2b_{yzj}, -1\}$ and $\mathbf{e}$ is the error vector. The covariance matrix of $\mathbf{e}$ is a diagonal matrix with $(\Sigma_{\mathbf{e}})_{ii} = \sigma_i^2 / S_i^2$. The weighted least squares solution of $\boldsymbol{\alpha}$ is given by $\boldsymbol{\alpha} = \left(\mathbf{B}^T \tilde{\Sigma}_{\mathbf{e}}^{-1} \mathbf{B}\right)^{-1} \left(\mathbf{B}^T \tilde{\Sigma}_{\mathbf{e}}^{-1}\right)\mathbf{y}$, while the covariance matrix of the estimated tensors is given by $\boldsymbol{\Sigma}_{\boldsymbol{\alpha}} = \left\langle \boldsymbol{\alpha}\boldsymbol{\alpha}^T \right\rangle \approx \left(\mathbf{B}^T \tilde{\Sigma}_{\mathbf{e}}^{-1} \mathbf{B}\right)^{-1}$ assuming that $\tilde{\Sigma}_{\mathbf{e}} \approx \Sigma_{\mathbf{e}}$. Let $\boldsymbol{D_0}$ be a real, symmetric 3×3 unperturbed tensor matrix and the estimated tensor $\boldsymbol{D} = \boldsymbol{D_0} + \Delta\boldsymbol{D}$, where $(\Delta \boldsymbol{D}_{ii})^2 = (\boldsymbol{\Sigma}_{\alpha})_{i,i}$ and $(\Delta \boldsymbol{D}_{ij})^2 = (\boldsymbol{\Sigma}_{\alpha})_{i+j+1,i+j+1}$ [3]. Using 1st order matrix perturbation analysis [7-9], one can compute the uncertainty for each eigenvalue $\langle (\Delta\lambda_i)^2 \rangle = \langle (\boldsymbol{\varepsilon}_i^T \Delta \boldsymbol{D} \boldsymbol{\varepsilon}_i)^2 \rangle$, where λ_i is the ith eigenvalue and $\boldsymbol{\varepsilon}_i$ is its eigenvector. The uncertainty of other tensor derived quantities such as Trace and FA can be computed by applying the error propagation theory [10]. If we assume $\boldsymbol{D_0}$ comes from the biological tissue with high diffusion anisotropy, i.e., $\lambda_1 > \lambda_2$ and $\lambda_1 > \lambda_3$. It can be also shown the perturbation of the eigenvector associated with the largest eigenvalue is given by $\Delta\boldsymbol{\varepsilon}_1 = \sum_{i=2}^{3} \frac{\boldsymbol{\varepsilon}_1^T \Delta \boldsymbol{D} \boldsymbol{\varepsilon}_i}{\lambda_1 - \lambda_i} \boldsymbol{\varepsilon}_i$. Using small angle approximation, the root mean square of perturbed angle is $\theta_{RMS} = \sqrt{\left\langle \theta^2 \right\rangle} \approx \sqrt{\left\langle \| \Delta\boldsymbol{\varepsilon}_1 \|^2 \right\rangle} = \sqrt{\sum_{i=2}^{3} \frac{(\Sigma_{\alpha})_{2+i,2+i}}{(\lambda_1 - \lambda_i)^2}}$.

Simulations: Monte Carlo simulations were performed to test the proposed approximations. We simulated cylindrically symmetric anisotropic DTs with diffusivity in the x direction set to 3, 5, and 7 times the diffusivity in the y and z directions. The Trace was representative of that in brain parenchyma (2.1 x 10^{-3} mm^2/sec). According to Jones [11] at least 30 unique sampling orientations are required for rotationally invariant statistical properties of the estimated DT-derived quantities. Therefore, we tested the 30 direction scheme [12] with 35 b-values (5 with b=0, and 30 with b=1000 s/mm^2) and SNR ranged from 5 to 100. We also tested the same scheme but with 2, 4, and 8 replicates (70, 140, and 280 b-values). For each pre-defined DT we created synthetic DW data conforming to the DTI model [1]. Gaussian distributed noise was then added in quadrature to the synthetic noise-free signal to achieve various SNRs in the non-diffusion weighted (b=0) data. To assess the precision and accuracy of the estimated uncertainty using the proposed analytic formulae in clinical DT-MRI brain data, we acquired DWIs from a health volunteer using a high angular scheme. Robust tensor fitting [13] was also used to obtain the DT estimates. Those pre-computed DT volume data combined with an assumed set of standard b-matrices are then used to back-project a DWI data set using the linear tensor model [6] for an assumed experimental design with a 30-direction sampling scheme with b=1000 and 5 non-diffusion weighted images with SNR=10.

Results and Discussion: Figure 1 shows the computed θ_{RMS} using both Monte Carlo (MC) methods and the analytical formulae (AF) for various given anisotropic DTs at different SNRs. The uncertainty decreases as the anisotropy or SNR increases. The trends in the AF and MC are consistent. Both empirical and analytical methods predict a power law scaling relationship: $\theta_{RMS} \propto SNR^{-1}$. This result is empirically given by the MC method, but is analytically derivable from the formulae given above. Figure 2 shows the estimated θ_{RMS} decreases as more DWIs are used and, again, the trends for the AF and MC are consistent. Both approaches also predict a power law scaling relationship: $\theta_{RMS} \propto N^{-1}$, where N is the number of DW replicates. Figure 3 shows the estimated standard deviation of FA using AF and MC. This result demonstrates that the estimated uncertainty of FA using AF and MC is similar in most of the brain regions and is over-estimated by AF in the low anisotropic regions.

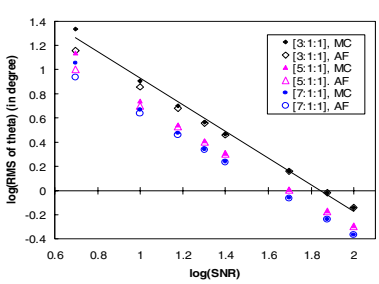

Fig. 1 The logarithmic (base 10) transformed θ_{RMS} computed using MC and AF for different SNRs and various predefined anisotropy [λ_1:λ_2:λ_3] (with Trace= 2100 μm^2/sec).

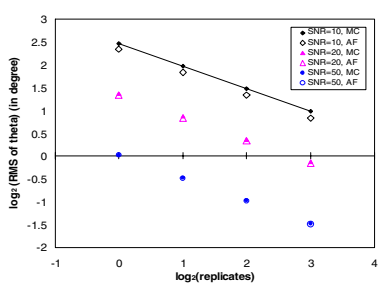

Fig. 2 The logarithmic (base 2) transformed θ_{RMS} computed using MC and AF for different SNRs with different number of replicates. The predefined tensors α are [1500, 300, 300, 0, 0, 0] μm^2/sec.

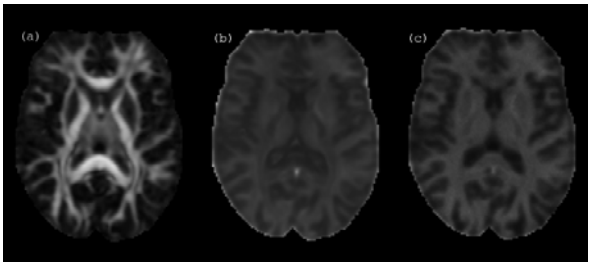

Fig. 3 The uncertainty map (here we show the standard deviation of estimated FA) calculated using AF (b) and MC (c), images were scaled between 0 and 0.5. The FA map (a) is shown here for the reference (scaled between 0 and 1).

Conclusion: We have validated the proposed analytic formulae using Monte Carlo methods. The analytic error propagation approach is a powerful tool in the DT-MRI data analysis and experimental design in estimating the uncertainty in diffusion tensor and its derived quantities, particularly when studying Regions of Interest (ROI). The proposed formulae provide a quick, accurate estimate of the uncertainty for a given tensor and SNR. This information should be helpful in selecting an optimal experimental design for longitudinal and multi-center DTI studies.

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