Analytic Expressions for the Uncertainty of DTI-derived Parameters and their Validation Using Monte Carlo Methods

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Introduction:

Monte Carlo (1) and Bootstrap (2) methods provide powerful statistical tools for determining the effects of background noise in diffusion weighted imaging (DWI) data on DTI-derived parameters, and for optimizing the design of DTI experiments. While these empirical methods do not provide analytical relationships between the variance of the distribution of noise in the DWI data and the variance of DTI-derived parameters, some progress has been made in this area: Skare et al. employed error propagation analysis to determine how noise in DWI data affects the uncertainty in the estimated ADCs (3) and in diffusion anisotropy measures (4). Matrix perturbation methods have also been used to propagate errors in estimated DTs themselves to determine the uncertainty in various quantities derived from the DT, such as its eigenvalues and eigenvectors (5,6), and its Trace (6). Analytic error propagation formulas to estimate uncertainties in DTI-derived quantities, such as the variation in the direction of the largest principal diffusivity, due to background noise have been derived elsewhere (7). Here Monte Carlo simulations of DTI experiments (1) are performed to validate these formulae, and to determine their applicability over a broad range of experimental design parameters (e.g., SNR, number of diffusion gradient directions, number of DWI acquisitions, etc.).

Analysis:

Let $\mathbf{y} = \{\ln(S_1), \ldots, \ln(S_N)\}^T$, where S_i represents the i^{th} measurement in a DTI acquisition, and $\mathbf{a} = \{D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}, \ln(A_0)\}^T$ are the DTI model parameters. To first order, the log linear model is written as $\mathbf{y} = \mathbf{Ba} + \mathbf{e}$, where the j^{th} row of $\mathbf{B}$ contains b-matrix entries of the j^{th} DWI acquisition $-\{b_{xxj}, b_{yyj}, b_{zzj}, 2b_{xyj}, 2b_{xzj}, 2b_{yzj}, -1\}$, and $\mathbf{e}$ is the error vector. The covariance matrix of $\mathbf{e}$ is $(\Sigma_\mathbf{e})_{ii} = \sigma_i^2 / \langle S_i \rangle^2$, where $\langle u \rangle$ denotes the expectation of random variable u. Measured $\mathbf{y}$ data is assumed independent, i.e., $(\Sigma_\mathbf{e})_{ij} = 0 \quad \forall i \neq j$. The weighted least squares solution is $\mathbf{a} = \left(\mathbf{B}^T \tilde{\Sigma}_\mathbf{e}^{-1} \mathbf{B}\right)^{-1} \left(\mathbf{B}^T \tilde{\Sigma}_\mathbf{e}^{-1}\right)\mathbf{y}$, with covariance matrix for $\mathbf{a}$ given by $\Sigma_\mathbf{a} \approx \left(\mathbf{B}^T \tilde{\Sigma}_\mathbf{e}^{-1} \mathbf{B}\right)^{-1}$. Let $\mathbf{R}\Sigma_\mathbf{a}\mathbf{R}^T = \Xi$ be the covariance matrix of the parameters rotated onto the principal diffusivity axis. Then the root mean square (RMS) estimate of the angle of deviation of the measured principal direction can be approximated by: $\theta_{RMS} = \sqrt{\sum_{i=2}^{3} \frac{(\Xi)_{2+i,2+i}}{(d_1 - d_i)^2}}$, where d_1, d_2 and d_3 are the eigenvalues of the true diffusion tensor (7).

Monte Carlo Methods:

Monte Carlo simulations were performed to validate the proposed formulae. We simulated cylindrically symmetric anisotropic diffusion tensors with diffusivity in the *x* direction set to 3, 5, and 7 times the diffusivity in the *y* and *z* directions. The Trace of the DTs was representative of the Trace in brain parenchyma (2100 μm2/sec). A recent study by Jones (8) showed that at least 30 unique sampling orientations are required for rotationally invariant statistical properties of the estimated DT-derived quantities. Therefore, we tested the 30 diffusion sampling direction scheme (9) with 35 b-values (5 with b=0, and 30 with b=1000 s/mm2). We also tested the same scheme but with 2, 4, and 8 replicates (70, 140, and 280 bvalues). For each pre-defined DT we created synthetic DW signal intensity data conforming to the DTI model. Gaussian distributed noise was then added in quadrature to the synthetic noisefree signal to achieve various SNRs in the non-DW (b=0) data.

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, but they differ by a factor of about 2. 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 DWI are used and, again, the trends for the AF and MC are consistent, differing by a factor of about 2. Both approaches also predict a power law scaling relationship: $\theta_{RMS} \propto 1/N$ where N is the number of DW replicates.

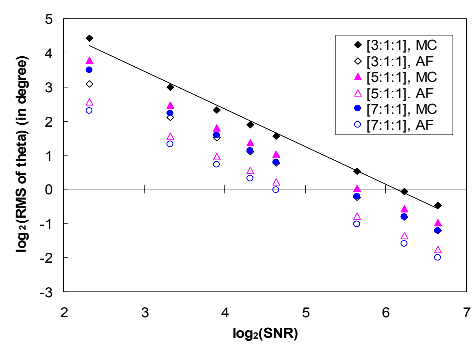

Fig. 1 The root mean square (RMS) of θ, θ_{RMS}, computed using Monte Carlo (MC) methods and Analytical Formulae (AF) for different SNRs with various predefined anisotropic diffusion tensors and 35 b-values.

Conclusion:

The analytic error propagation framework complements the empirical MC and Bootstrap approaches for estimating variability in DT-MR data. Its utility is in providing functional dependences between the uncertainty of DT-derived parameters on various experimental parameters, such as the SNR, number of DWI acquisitions, underlying DT, etc. The proposed formulae provide a reasonable estimate of uncertainty for θ_{RMS} to within a factor of 2. Moreover, they can easily be generalized for other DT-derived quantities of interest. Finally, they provide a way of testing noise sensitivity among different possible experimental designs.

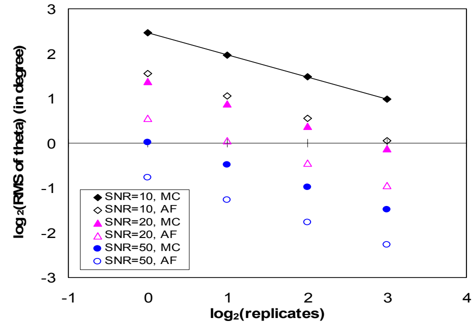

Fig. 2 The root mean square (RMS) of θ, θ_{RMS}, computed using Monte Carlo (MC) methods and Analytical Formulae (AF) for different numbers of replicates. The eigenvalues of the predefined cylindrically symmetric DT are in the ratio 5:1:1.

Bibliography:

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