

Optimizing diffusion weighting scheme by Cramer-Rao Lower Bound Analysis and Monte Carlo Simulation

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Introduction:

Diffusion tensor imaging (DTI) has been successfully applied to detect central nervous system (CNS) tissue injury. Increased radial diffusivity λ_{\perp} and decreased axial diffusivity λ_{\parallel} have been shown to reflect demyelination and axon injury respectively [1]. One crucial yet less frequently addressed factor affecting all diffusion measurements is the complex environment surrounding the axon in physiological (partial volume effect of gray matter and CSF) or pathological (cell infiltration, edema, and axonal loss) conditions. A novel multiple-tensor analysis, diffusion basis spectrum imaging (DBSI) [2], was recently developed to resolve both the crossing-fiber and partial volume effects due to increased cellularity or CSF/gray matter contaminations. Although DBSI has demonstrated its feasibility and capability in both phantom and in vivo animal studies [2], the prototype DBSI diffusion scheme is not yet optimized. This study employed Cramer-Rao lower bound (CRLB) [3] analysis to compare the precision of DBSI solution using a multiple-shell diffusion scheme [3] vs. the grid scheme used in DSI [2]. Monte Carlo (MC) [3] simulation was further employed to examine the effects of signal-to-noise ratio (SNR), diffusion weighting strength, and distribution of diffusion weighting vectors on the accuracy and precision of DBSI.

Method: Multiple Shell Diffusion Scheme vs. Grid Diffusion Scheme: Multiple shell diffusion scheme [3] is composed of three-fold tessellated icosahedric gradient directions, 184 total directions, on two shells: $b_1/b_2 = 1000, 3500 \text{ s/mm}^2$. Multiple grid diffusion scheme is composed of 99 uniformly spaced Cartesian grid direction, an inner subset of the scheme used in DSI. The maximal b value of the multiple-grid scheme is 3200 s/mm^2 .

Cramer-Rao Lower Bound Analysis and Monte Carlo Simulation:

CRLB analysis was employed to evaluate the theoretical lower-bound of the variance of model parameters. CRLB analysis provided the precision of DBSI modeling. In addition, MC simulation was performed to examine the potential bias of DBSI solution and determine whether the theoretical lower bound of parameters can be effectively reached by DBSI. With maximal b value fixed at 3200 s/mm^2 , diffusion direction numbers fixed at 99 (out of 500 candidate directions uniformly distributed on a sphere), an optimized diffusion scheme was designed by minimizing total CRLB on all DBSI derived indices using global pattern search technique [4].

In Silico Phantom: The phantom with two crossing fibers and a non-restricted isotropic component examined in the previous study [3] was employed in this study to compare the multiple shell diffusion scheme and grid diffusion scheme. A second phantom with one fiber, simulating *in vivo* mouse spinal cord white matter tract diffusion properties at the peak of experimental autoimmune encephalomyelitis (EAE) ($\lambda_{\parallel} = 1.8 \mu\text{m}^2/\text{ms}$, $\lambda_{\perp} = 0.24 \mu\text{m}^2/\text{ms}$, fiber fraction 55%), one isotropic restricted component (infiltrating cells at EAE, $\text{ADC} = 0.17 \mu\text{m}^2/\text{ms}$, cell fraction 26%), and one isotropic non-restricted component (edema, $\text{ADC} = 1.8 \mu\text{m}^2/\text{ms}$, 19%) was built to investigate the effects of SNR, diffusion weighting strength, and spatial distribution of diffusion weighting vectors on the accuracy and precision of DBSI.

Results and Discussion:

Consistent with the previous study [3] with multiple shell diffusion scheme at $\text{SNR} = 25$ (Fig. 1), the relative CRLB ($r\text{CRLB}$) $> 15\%$ was indeed observed for axial diffusivities ($\lambda_{1\parallel}, \lambda_{2\parallel}$) of both crossing fibers, and the volume ratio (f_2) and radial diffusivity ($\lambda_{2\perp}$) of the second fiber. Since $r\text{CRLB}$ is dependent on SNR, a SNR dependent $r\text{CRLB}$ analysis was also performed (Fig. 1). Our results show that the precision of measurements improves linearly with increasing SNR. We performed the same SNR dependent CRLB analyses using multiple grid 99-direction diffusion weighting and max b -value of 3200 s/mm^2 (Fig. 1, red bars). Our data indicate that the $r\text{CRLB}$ of $\lambda_{1\parallel}, \lambda_{2\parallel}, f_2$, and $\lambda_{2\perp}$ are all $< 15\%$ at $\text{SNR} = 25$, an approximately 40% improved precision comparing with the two-shell scheme. Our results strongly suggested that the multiple-grid scheme provides a better precision for DBSI derived parameters. We further performed both MC simulation and CRLB analysis on the phantom with one fiber, one isotropic restricted component, and one isotropic non-restricted component. MC simulations indicate that all parameters can be estimated accurately at $\text{SNR} = 40$, a typical quality of our *in vivo* mouse spinal cord measurements, with the bias $< 15\%$ (Fig. 2). MC simulation and CRLB derived variances agreed with each other, and improved with increasing SNR. A theoretical analysis was conducted on minimizing CRLB to optimize diffusion scheme and b -value selection for the model under $\text{SNR} = 40$ (Fig. 3, blue bar). Preliminary assessments suggest that a significantly improved precision of DBSI is achievable by appropriately distributing diffusion weighting vectors (Fig. 3, red bar). With increased maximal b -values, DBSI precision can be further improved (Fig. 3, green bar).

References: [1] Song, SK. *et al. Neuroimage*. 2002; 17:1429. [2] Wang, Y. *et al. Brain*. 2011; In Press. [3] Caan, MW, *et al. IEEE Trans Med Imaging*. 2010; 29:1504. [4] Lewis RM, *SIAM Journal on Optimization*. 1999; 9:1082

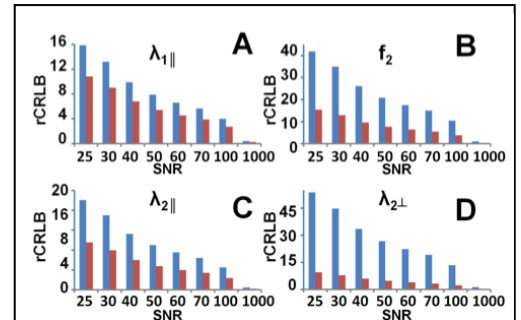


Figure 1. SNR dependent CRLB of multiple shell (blue) and multiple grid (red) diffusion schemes. The comparison was conducted for the DBSI derived axial diffusivity $\lambda_{1\parallel}$ of the first fiber (A), the volume ratio f_2 (B), axial diffusivity $\lambda_{2\parallel}$ (C), and radial diffusivity $\lambda_{2\perp}$ (D) of the second fiber.

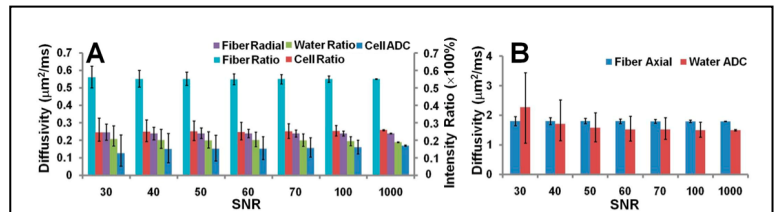


Figure 2. MC simulation derived fiber ratio, water ratio, cell ratio, cell ADC, fiber radial diffusivity (A), and fiber axial diffusivity, water ADC (B) are shown as bar plots, using the current multiple grid 99-direction scheme with max $b = 3200 \text{ s/mm}^2$. Precision is displayed as the error bars: positive bar = MC simulation derived variances; negative bar = CRLB derived variances.

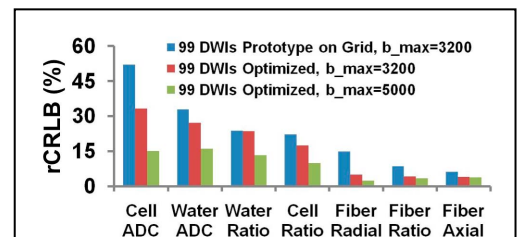


Figure 3. By fixing $\text{SNR} = 40$ and total number of multiple grid diffusion weighting gradients at 99, we performed a preliminary CRLB based optimization on the one-fiber and two isotropic diffusion model. Results suggest that with CRLB optimization at the same max b -value the precision can be improved by optimizing diffusion directions ($\sim 40\%$ improvement than the prototype DBSI). The optimized directions with increased max b -value ($= 5000 \text{ s/mm}^2$) yielded $\sim 140\%$ improvement than the prototype DBSI.