Numeric Simulations for Optimization of Wild Bootstrap Technique as a Robust Estimator of DTI Measurement Uncertainty

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Introduction: As an empirical non-parametric statistical method, bootstrap (BS) has been introduced to diffusion tensor imaging (DTI) for quantification of measurement uncertainty associated with tensor derived metrics, such as Fractional Anisotropy (FA), Mean Diffusivity (MD) [1] and Cone of Uncertainty (CU) for principle eigenvectors [2]. However, prolonged scan time associated with the required multiple acquisitions for the use of bootstrap makes its application for clinical study often impractical. Recently, wild bootstrap (WBS) method was introduced as an alternative technique [3] to provide equivalent uncertainty estimation as BS but does not require multiple acquisitions. Quantitative comparisons between WBS and BS [4] as well as WBS based tractography [5] have also been reported. In this study, we performed numeric simulations under different combinations of real DTI parameters, such as SNR, unique diffusion gradient number (UDG) and number of WBS iterations (N_WRS). By assessing WBS performance in comparison to "Gold-standard" Monte Carlo (MC) simulation, an optimized WBS setting is proposed.

Methods: *DTI parameter selections*: (1). SNR: from 10 to 40 with increment of 5; (2). UGD: Four DTI protocols with UGD= 6, 21, 31, 61, adapted from human brain measurements on a GE 1.5T scanner; Data were scaled so that the effective SNR for each protocol are approximately same. (2). N_WBS ranging from 500 to 2000 with increment of 500. (4). DTI_Ratio, the ratio between total number of DWI images and total number of non-diffusion weighted images, equal to 1:1 and 1:6 were used. *MC simulation*: Noise-free synthetic prolate diffusion tensor as well as noisy tensor data under different SNR level were generated following the routine by Jones et.al [2], with constant MD value of $0.7\text{x}10^{-3}$ mm^2/s, FA value ranging between [0.1,0.9], and $\text{b}=1000\text{s/mm}^2$. For each combination of DTI parameters discussed above, MC simulation was performed 10,000 times. Summary statistics, such as standard deviation of FA, MD (Std_FA, Std_MD) as well as 95% CU, were calculated. This procedure was then repeated 966 runs, each run with different spatial orientations of tensor which are evenly distributed in the hemisphere. Standard errors of Std_FA, Std_MD and 95%CU (SE_FA, SE_MD and SE_CU) over these 966 runs were also calculated. Both SE_(FA,MD) and Std_(FA,MD) serve as the "gold-standards" to assess the wild bootstrap performance under the same DTI parameter selection. *WBS simulation*: The same procedures for synthetic tensor data as in MC section were applied for WBS simulation. *Evaluation Criteria*: Performance of WBS as a robust estimator for DTI measurement uncertainty was evaluated from two perspectives. First, WBS performance on estimation of standard deviation of DTI metrics at fixed tensor orientation, such as [0,0,0], was evaluated. WBS simulation were repeated 1000 runs with fixed orientation, each run including N_WBS iterations to calculate Std_FA, Std_MD and 95%CU. SE_FA, SE_MD and SE_CU of WBS over 1000 runs were collected. Additionally, Bias (= |*Mean_Std_FA_WBS* – *Std_FA_BS*|, as example of FA) was also calculated. Secondly, dependence between tensor orientation and WBS performance was evaluated. To serve this purpose, WBS simulation was performed at 966 orientations, each orientation with N_WBS iterations. Two quantitative metrics, Bias and Standard Errors discussed above, calculated over all orientations were used for evaluation. For each DTI metrics, both Bias and Standard Errors from WBS estimation were normalized by Monte Carlo estimation of standard deviation (such as Std_FA_BS).

Results: Performance of WBS with comparison to MC as gold-standard is illustrated in ***Figs.1*** to ***3***. (For all the plots, X coordinates are the FA value while Y coordinates represents SNR level. Only Results from the strategy two with DTI_Ratio=6 are displayed). SNR level plays important role in WBS performance. With increase of SNR, both bias and standard error of WBS estimation decrease, which is indicated in plots of ***Fig.1*** as the color turns from red to blue along the Y axis. When all the other parameters are kept the same, with more diffusion gradient directions, WBS tends to have more uniform performance at different anisotropic levels, as illustrated in ***Fig.1.B***. With comparison to MC results, WBS has equivalent performance, as showed in ***Fig.3***, in terms of dependence between tensor orientations and uncertainty estimation. The difference of WBS performance between 500 iterations (***Fig.2***) and 2000 iteration (***Fig.1.A***), although detectable, are fairly small, thus results from 500 are acceptable for WBS applications. The overall WBS performance for strategy one (with DTI_Ratio = 1), although worse than the results showed here, is comparable to the strategy two.

Fig1. *3D map of Normalized Bias and Standard Error of FA uncertainty estimation from wild bootstrap at different levels of FA(X axis) and SNR SNR (Y axis). Results are normalized by Std_FA_BS. The warmer the color, the larger absolute value of Bias or SE. (**A**).Results for protocol with 21 directions, DTI_Ratio = 6; (**B**). Results for protocol with 61 directions, DTI_Ratio = 6. WBS iteration number is 2000;*

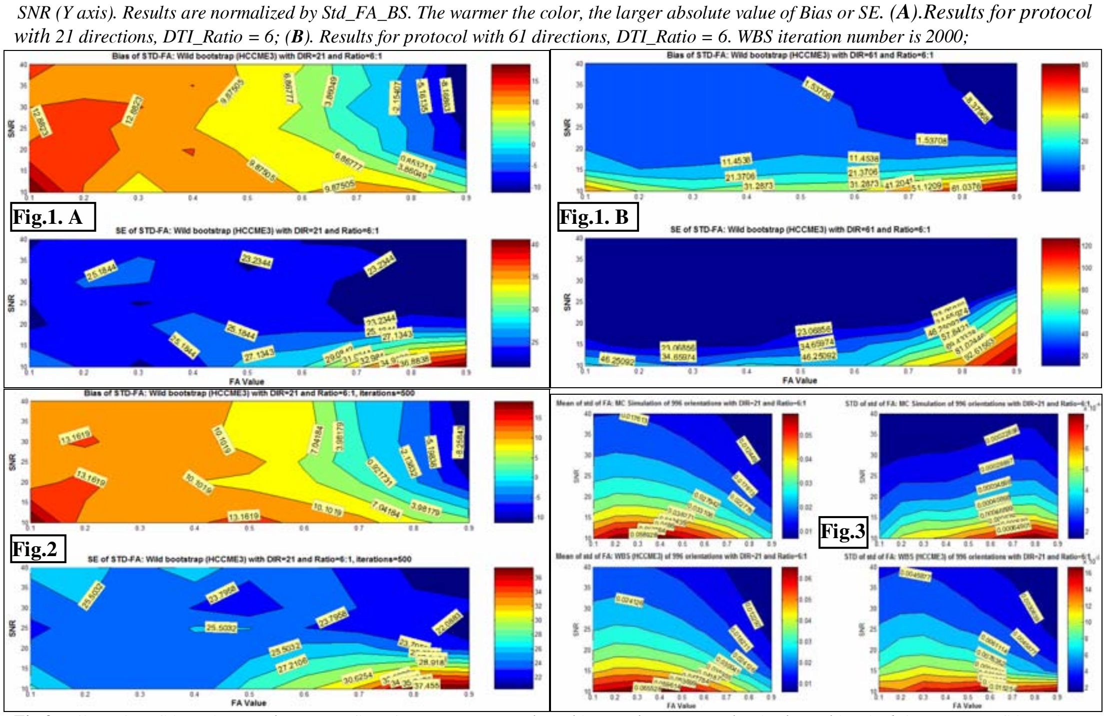

Fig.2. *Effect of WBS iteration number on WBS performance. Protocol used is exactly same as what is showed in Fig.1.A, except WBS iteration here is 500.* ***Fig.3***. *Dependence between tensor orientations and uncertainty estimation. Top row: MC simulation; Bottom row: WB . Left column: Mean value of Std_FA from 996 simulations with different orientations. Right column: Standard errors of Std_FA from 996 simulations.*

Discussions: Performance of wild bootstrap as a robust estimator of DTI measurement uncertainty was assessed by numeric simulations at different combinations of clinical DTI parameters. Optimized setting from simulation results requires at least 500 wild bootstrap iterations, SNR level better than 25 and more diffusion gradient directions (>20) applied. The study also indicates that even with the optimal setting, there are cases when WBS underestimates measurement uncertainty at high anisotropy levels (as showed in upper right corner of ***Fig.1.A***), for which more careful interpretation of WBS results is required.

References: [1]. Pajevic S et.al. JMR 2003; 161:1-14; [2]. Jones DK. MRM 2003; 49(1):7-12; [3]. Whitcher B et.al. Proc. ISMRM 13th Annual Meeting. Miami, 2005;1333. [4]. Chung S et.al. Neuroimage 2006; 33(2):531-41; [5]. Jones DK. Proc. ISMRM 14th Annual Meeting, Seattle. 2006;435. **Acknowledgements**: This project was support by a grant from the Schmitt Foundation.