EFFECT OF DTI BOOTSTRAP BIAS ON THE DTI UNCERTAINTY MEASUREMENTS AND PROBABILISTIC TRACTOGRAPHY

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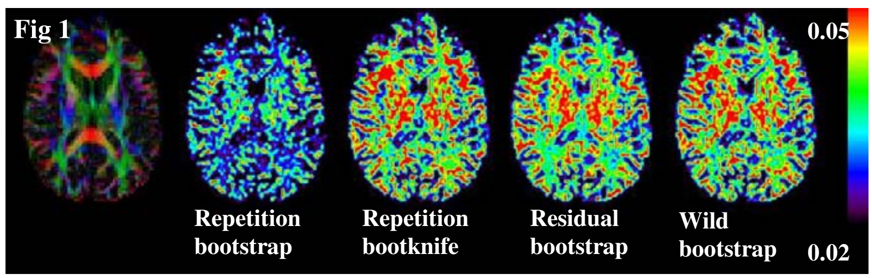
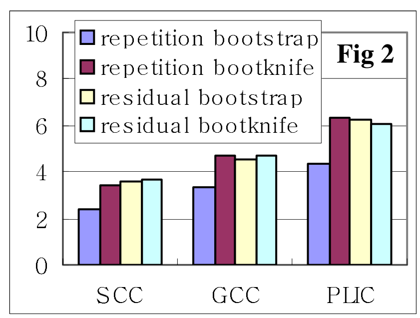
INTRODUCTION: Bootstrap analysis is a powerful tool for estimating the uncertainties inherent in diffusion MR data. Multiple bootstrap algorithms exist, and a prior study described four different bootstrap algorithms for DTI and investigated the accuracy of bootstrap estimation using Monte Carlo simulation experiments [1]. In this study, we examine whether different properties of different bootstrap methods, especially bias, can be observed *in vivo* as well. Estimates of uncertainty in specific ROIs are compared among four bootstrap methods. In addition, bootstrap probabilistic tractography was performed with each bootstrap method on the human data.

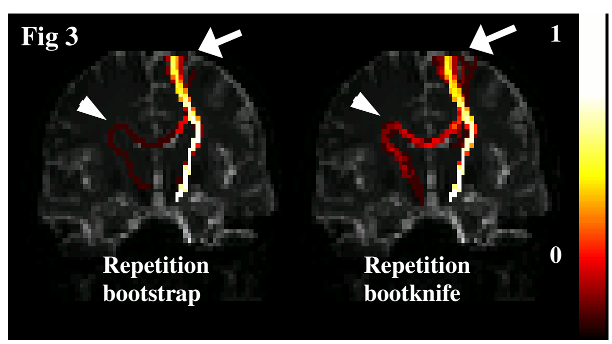
THEORY: Bootstrap is a non-parametric data resampling technique, mainly used for the estimation of uncertainties when more traditional parametric statistical tools are not readily applicable. For DTI, four different bootstrap algorithms was described extensively [1] and here we briefly summarize their operation. Four algorithms can be classified as either repetition-based (or stratified) or model-based resampling methods. Repetition-based methods, including repetition bootstrap and repletion bootknife, resample data from different diffusion directions separately (thus 'stratified'). Repetition bootknife is a modified version of repetition bootstrap (conventional bootstrap in the DTI [2]) to reduce the downward bias of repetition bootstrap. Model-based methods, including residual bootstrap and wild bootstrap, depends on the fact that diffusion tensor (DT) is calculated via multiple regression, and resample residuals, not the raw data directly. While residual bootstrap resample residuals freely from all the data with different diffusion directions, wild bootstrap is more constrained, only modifying the residuals without relocating them.

METHODS: *Acquisition*: Whole-brain DTI was acquired for a healthy volunteer using single-shot spin-echo EPI sequence on a Philips Intera 3T MRI system with 33 mT/m gradients and 8-channel SENSivitiy Encoding (SENSE) head-coil. Diffusion weighted images were acquired on 32 non-collinear directions with the diffusion weighting of b=1000s/mm2, isotropic voxels of 2.5 mm, 55 contiguous slices without gap and SENSE reduction factor of 2. A single acquisition (NEX=1) is sufficient for model-based resampling, but in order to compare the model-based methods with repetition-based methods using same dataset, two sets of DTI were acquired with a10 minute scan. *Analysis*: DTI parameters (such as primary eigenvectors and FA) were calculated in conjunction with each of the four bootstrap methods to estimate uncertainties [1]. Bootstrap resampling was iterated 200 times to create with 200 DTI volumes that were used for calculating standard error maps. Probabilistic tractography was performed by repeating fiber tracking on all of the generated volumes and combining the results to produce a probabilistic track distribution map. ROI analyses on a few selected white matter structures were performed to compare uncertainties from different bootstraps. Fiber tracks were launched from a single voxel seed placed in the middle of the cerebral peduncle.



RESULTS & DISCUSSION: Figure 1 shows the color anisotropy map and standard error (SE) of FA map calculated by four bootstrap methods on the same slices. While repetition bootknife, residual bootstrap and wild bootstrap have comparable SE range, repetition bootstrap has generally lower SE values. The underestimation bias is in repetition bootstrap is consistent with the previous simulation studies. This bias was confirmed with ROI analysis. Figure 2 shows the 95 percentile confidence interval angle (degrees) in three anatomic locations, splenium of corpus callosum (SCC), genu of corpus callosum (GCC) and posterior limb of internal capsule (PLIC). SCC has the smallest uncertainty, and PLIC the largest of three, but regardless of the structures, repetition bootstrap estimated uncertainties are only about 70% of the others. Figure 3 shows the maximum intensity projection of bootstrap probabilistic track map for repetition bootstrap and repetition bootknife. Repetition bootknife fiber tracks tend to diverge more, especially near the cortex (arrow), and to branch out more (arrowhead). Model-based resampling based tractography showed similar results to repetition bootknife (not shown). Fewer diverging tracks with repetition bootstrap is consistent with the fact that repetition bootstrap underestimates the uncertainty of the primary eigenvector orientation.





CONCLUSION: This bootstrap analysis of *in vivo* data is consistent with prior theoretical and simulation experiments showing that if the number of repeated scans is low, repetition bootstrap is downward biased while other methods are generally unbiased. These results suggest that for optimal uncertainty estimation, either model-based resampling or repetition bootknife (when stratified resampling is preferred) should be used to avoid bootstrap estimation bias.

REFERENCES:

[1] Chung S et al. *NeuroImage* 2006; 33: 531-41.

[2] Pajevic S et al. J Magn Reson 2003; 161: 1-14