The wild bootstrap to quantify variability in diffusion tensor MRI

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Introduction

Quantifying and presenting variability when analyzing diffusion tensor MRI (DT-MRI) data is difficult when using scalar summaries of the diffusion tensor (e.g., fractional anisotropy or FA). Distribution-based standard errors of the tensor elements, from linear regression theory, are not easily applicable to non-linear functions of the tensor. Estimating variability in DT-MRI is needed to objectively follow disease progression, in therapeutic monitoring and to provide consistent readouts of pathophysiology. Quantifying and visualizing standard errors in the parameters of interest provides immediate insight into potential errors in the data and where subsequent analysis techniques (e.g., tractography) may encounter problems. The naïve bootstrap has been used to explore the variability of the diffusion tensor and derived measures, such as FA, [1] but under the assumption of repeated acquisitions in each direction. The wild bootstrap [2] is shown to produce standard errors when only one scan per direction is available. Bootstrap distributions for the diffusion tensor elements follow Gaussianity, while bootstrap distributions for the eigenvalues and FA exhibit non-Gaussian forms. Simulated data, using the method in [3], and a real data set illustrate the technique. Efficient computation is achieved by formulating the least-squares estimation problem as a multivariate multiple linear regression.

Methods

The wild bootstrap is a method for model-based resampling in heteroscedastic linear regression with an unknown form; i.e., when the errors follow a non-constant variance. This is true when estimating the diffusion tensor since different diffusion weights and gradient directions are used. Instead of resampling from the residuals of the linear regression (only valid in the homoscedastic case), the wild bootstrap samples from a two-point distribution and multiplies this random variable with a rescaled version of the residual using a local estimate of the covariance matrix. Computations are efficiently performed by rewriting the voxel-wise estimation problem as a multivariate multiple linear regression, where the response (signal intensity) is a matrix. Thus, one application of a QR decomposition (or SVD) yields the diffusion tensor estimates for all voxels simultaneously. Analytical eigenvalues [4] are also used to increase efficiency. The simulated data used a ratio of 2:1:1 for the eigenvalues with $\bar{\lambda} = 1.0 \times 10^{-3}$ [3]. Gaussian white noise, at 10% of the signal intensity at $b = 0$, was added to the real and imaginary components of the signal. For the observed data, 70 directions (60 diffusion-weighted + 10 T2) were obtained from a Siemens Trio 3T scanner using an 8 channel head coil. 64 slices were acquired with parameters TR/TE = 9200/89ms, b = 700s/mm^2, gmax = 26mT/m, with an acquisition time of 10'53". The diffusion gradient directions were obtained using the electrostatic repulsion method [5].

Results

Diffusion tensor estimates were obtained for the simulated data and the variability of those estimates, along with the eigenvalues, was investigated using the wild bootstrap. For 1000 iterations, the bootstrap distributions for the eigenvalues (Fig. 1a) are similar to those obtained by Monte Carlo (MC) computer simulation in [4]. The bootstrap distributions do not capture the skewness observed in the MC simulation and slightly underestimate the spread. However, these results are quite encouraging since 100,000 independent realizations were used in the MC simulation, while only a single data set was used in the bootstrap procedure. Estimates of FA were obtained from a single slice of the DT-MRI data (Fig. 1b, left). Bootstrap standard errors for FA, based on 100 iterations, show increased variability in the non-brain voxels not properly masked around the border of the brain (Fig. 1b, middle). Elevated standard errors are also apparent in the anterior portion of the brain and bilaterally posterior to the genu. Established white matter tracts exhibit similar error to voxels with low FA. This is highlighted in the image where FA is normalized by the voxel-wise bootstrap standard errors (Fig. 1b, right). Extremely high FA values, usually at isolated pixels, exhibit large standard errors and are de-emphasized in the normalized FA image. This indicates either that the acquired data was possibly corrupted or the diffusion tensor model may be inadequate to describe the observed diffusion characteristics. White matter tracts with relatively little error remain in the normalized image.

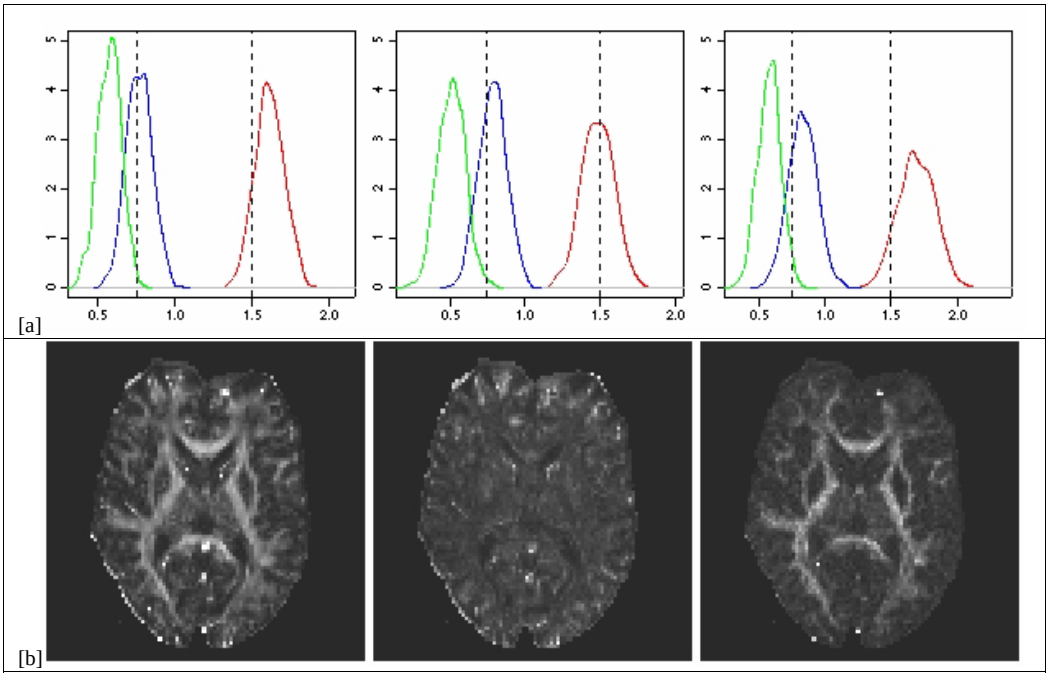

Figure 1: *[a] Bootstrap realizations of the eigenvalues (λ_1, λ_2, λ_3) from simulated data with ratio 2:1:1. Orientations (from left to right) are collinear, non-collinear with (0°,30°,15°) and non-collinear with (0°,170°,60°). [b] Fractional anisotropy (left), bootstrap standard errors of FA (middle) and FA normalized by the bootstrap standard errors (right).*

Discussion

We have provided a method for quantifying variability of non-linear functions of the diffusion tensor using the bootstrap. Measures of the standard error for derived quantities, such as FA, may be estimated rapidly using common computational platforms even when the scanning procedure obtains only a single scan per direction. Results from a DT-MRI analysis can now provide both estimates and measures of their variability, allowing researchers to scrutinize the quality of the data acquired or the validity of the diffusion model used.

References

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