Bias in Diffusion Tensor-Derived Quantities Depend on The Number of DWIs Composing The DT-MRI Dataset

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Introduction

Diffusion tensor eigenvalues and anisotropy indices derived from them, such as the fractional anisotropy (FA), are common metrics used in clinical MRI research. Understanding how experimental factors affect the statistical properties of these quantities is important for proper statistical analysis of DTI data. Mathematical simulations have shown that noise in the diffusion weighted images (DWIs) produces biased mean values of FA and of the eigenvalues, while the Trace of the diffusion tensor, Trace(D), is relatively immune from bias [1]. Measurements in isotropic media are more affected than those in anisotropic media [1]. Noise tends to increase apparent anisotropy when signals are still higher than the noise floor, and then results in artifactually reduced anisotropy at very high b-values [2]. It has been shown that the variance of tensor-derived quantities shows an undesirable dependence on directions if fewer than about 20-30 directions are sampled [3]. Here we explore the effect of the number of images comprising the DTI dataset on the statistical properties of DT-derived quantities. We hypothesize that reducing the number of DWIs composing the dataset will lead to an overall noisier experimental design that will produce consequences on the diffusion tensor derived quantities similar to those previously described in [1] by lowering the SNR of the individual DWIs: i.e., in isotropic media increased variance of Trace(D) and biased mean values for FA and the eigenvalues 1 and 3.

Methods

This investigation was prompted by the need to analyze DWI data collected with a heterogeneous protocol in a large multicenter DTI study: the NIH Pediatric Neuroimaging Study of Normal Brain Development (www.nih-pediatricMRI.org). By analyzing diffusion measurements that were collected on an isotropic water phantom over 2.4 years in this study, we found no temporal dependence of the results but overall systematic between-site and within-site differences in FA but not in Trace(D). These differences appeared to depend on the number of DWIs composing the DTI dataset. To validate this hypothesis, for one of the sites, we partitioned each DTI dataset into four subsets and computed tensor-derived quantities for each subset and the original complete set. We then used a paired t-test to compare the average of the values obtained by the four subsets with the corresponding values obtained from fitting the complete set. If varying the number of DWIs in the DTI dataset would result in statistical bias, we expect to find statistically significant differences using the t-test. Additionally, we performed Monte Carlo simulations similar to what that was proposed in [1] but in our case keeping SNR constant and varying the number of DWIs in the dataset. We defined isotropic diffusion tensors with Trace(D) = 2400 x 10^{-6} mm^2/s, and a fixed SNR = 20 in the b=0 images. The basic set of DWIs was collected with the direction scheme proposed in [4] using 7 b-matrices (1 b=0 and 6 b=1000 s/mm^2). The effect of varying the number of DWIs was simulated by adding replicates of this basic set up to 140 images.

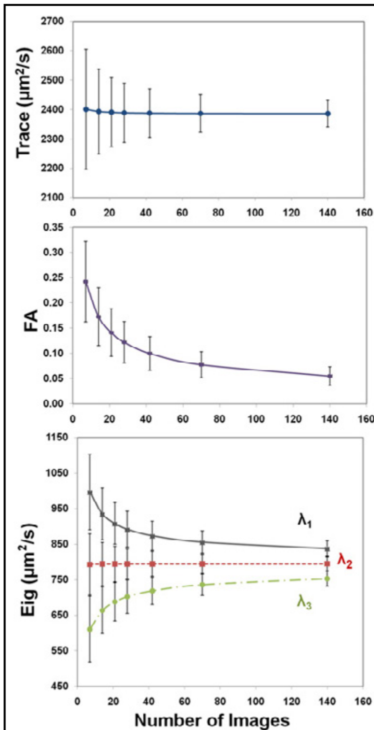

Fig.1. Monte Carlo simulation of the effect of the number of DWIs in the DTI dataset on the accuracy of diffusion tensor parameters in an isotropic medium. Bars indicate one standard deviation.

Set/Measure	Trace	FA	Eig1	Eig2	Eig3
Mean of Subsets	6696 ± 174	0.15 ± 0.0103	2575 ± 82	2215 ± 58	1906 ± 42
Complete Set	6655± 168	0.08 ± 0.0074	2391 ± 72	2222 ± 61	2042 ± 38

Table 1. Phantom DTI data analysis results (mean ± SD, SD computed over all time points).

Results

Paired t-tests of the isotropic phantom data showed significant differences for Trace(D), FA, Eig1, and Eig3 ($p<0.0001$) between the mean values of the four subsets vs. the complete set. As illustrated in Table 1. Trace(D) and FA are significantly higher for the mean values of subsets compare to the complete set. While there is no significant bias in Eig2 ($p=0.164$), there is a positive bias for Eig1 and negative bias for Eig3. Fig. 1 summarizes the results of Monte Carlo simulations showing an underestimation of Eig3 and an overestimation of FA and Eig1 as the number of images in DTI estimation is reduced. Surprisingly there is a small underestimation of Trace(D) as the number of DWIs increases.

Discussion and Conclusions

To the best of our knowledge the observation that bias in tensor-derived quantities can be modulated by varying the number of DWIs from which the diffusion tensor is estimated has not been reported previously. For some tensor-derived quantities, in particular for FA, the level of bias is remarkably high even when using a large number of DWIs. This effect shows striking similarities to what has been described by varying the SNR of DWIs in previous studies [1,3]. A unifying interpretation, could be that rather than considering the SNR of the individual images, one should consider the SNR of the entire experiment. Koay C.G et al. [5] reported that the level of bias in tensor-derived quantities is affected by the tensor fitting algorithm used to estimate the tensor. Here we used a conventional non-linear least square fitting strategy. In the future it would be important to evaluate how the dependence of bias on the number of DWIs in the dataset is affected by different fitting strategies.

References **1.** Pierpaoli C., et al. Magn Reson Med. 36:893-906 (1996), **2.** Jones D.K., et al. Magn Reson Med. 52:979-993 (2004) **3.** Jones D.K., et al. Magn Reson Med. 51:807-815 (2004), **4.** Pierpaoli C., et al. Radiology. 201:637-648 (1996)**, 5.** Koay C.G., et al. JMR. 182 (2006) 115-125.