Towards a Marriage of Deterministic and Probabilistic Tractography Methods: Bootstrap Analysis of Fiber Trajectories in the Human Brain

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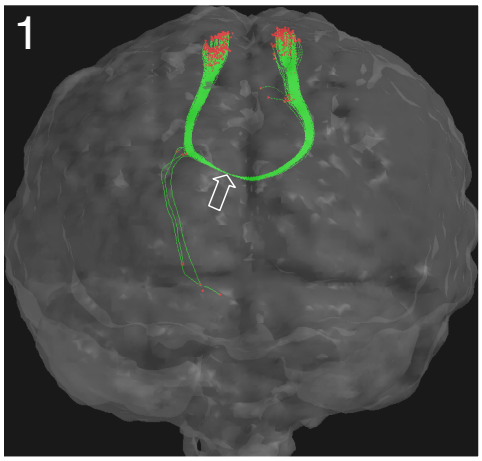
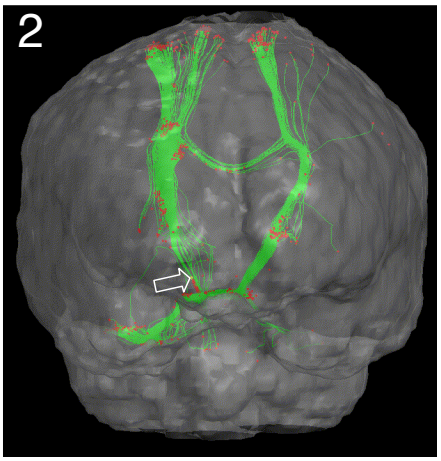
Introduction: The bootstrap method[1] is a non-parametric statistical procedure that enables one to determine the uncertainty of a given statistic, or its probability density function (PDF). It makes no *a priori* assumptions concerning the distribution of the statistic and is therefore an extremely powerful technique when the sources of variability cannot be modeled. However, despite its strengths, with one exception[2], its use in DT-MRI tractography remains virtually unexplored. In this work we highlight the use of the bootstrap and show how it can provide a qualitative 'probabilistic' insight into a deterministic approach and we underline the important effect of local white matter architecture on the reproducibility of tractography.

Methods: Two complete volumes of peripherally gated DT-MRI data (2. 5 mm isotropic resolution) were collected from a healthy volunteer using a gradient sampling scheme consisting of 7 non diffusion-weighted (DW) images and 64 DW images ($b \approx 1300$ s mm^{-2}) in which gradients were uniformly distributed over the sphere[3]. To generate the jth bootstrap sample for a particular slice, one of the two images acquired with each b-matrix was randomly selected (with replacement) to produce a data set consisting of 71 DW images. In this way, 1000 bootstrapped volumes were generated. Two seedpoint voxels were then selected, one in the corpus callosum and one in the cerebral peduncle, such that both had approximately the same uncertainty in fiber orientation. For each of the 1000 bootstrapped volumes, streamline tractography was performed bi-directionally from the two seedpoints using a deterministic tractography approach similar to Basser *et al* [4].

Results: Figs. 1 and 2 show representative tracking results from seeds placed in the corpus callosum and cerebral peduncle respectively. The arrows show the locations of the seedpoints. The endpoints of each reconstructed tract are represented via a red dot, while a subset of the reconstructed tracts is represented by the green streamlines. The fractional anisotropy computed from the entire set of images was smoothed and volume rendered to form a frame of reference for the tracking results.





Discussion: The reproducibility of the tractography result from a seedpoint clearly differs in Figs. 1 and 2. We can understand the importance of white matter architecture for reproducibility by considering that the trajectories are reconstructed by a streamparticle that traces out a streamline. In white matter regions such as the corpus callosum (Fig. 1), where there is a locally coherent organization of white matter fasciculi (i.e. tracts run in parallel over a wide distance), a small perturbation of the computed trajectory from the actual fiber trajectory will take the streamparticle to an adjacent tract – whose pathway runs parallel to the tract that it was originally on. If no other pathways are encountered, (such as in the callosal fibers), then the consequences of noise perturbation are minimal and the majority of the bootstrapped tracts terminate in approximately the same anatomical location. Conversely, in regions where different pathways pass close by, even small perturbations of the streamparticle from its true path can be catastrophic. In Fig. 2, small perturbations of the streamparticle from its original tract result in a wide range of trajectories. Some tracts that project inferiorly from the seedpoint continue through the cerebellar peduncle, some cross the pons and track down the contralateral cerebellar peduncle, or project up the contralateral peduncle. Likewise, the tracts that project superiorly from the seedpoint begin to flair out. Some project up to the ipsilateral cortex, while others cross the corpus callosum and project up to the contralateral cortex. Many of these "connections" are inconsistent with known anatomy. A single streamline approach would only reveal one of these many trajectories and there would be no indication of its reliability. By viewing the bootstrapped results as above, one gains an impression of the reliability of the tracking result. The bootstrap has been used previously to compute uncertainty in fiber orientation in each voxel[5], but it is clear from Figs. 1 and 2 that depicting uncertainty alone is insufficient to predict the variety of pathways that can result under repeat tractography experiments. What *is* important is not only the uncertainty in fiber orientation, but also the *architectural milieu*. In other words, the trajectories of neighboring tracts, when the tracking result veers off-course, play a dominant role in determining the reproducibility of the tracking result.

One of the main strengths of the bootstrap is that makes no *a priori* assumptions regarding the form of the PDF in fiber orientation. Other groups have proposed *ad hoc* PDFs, assuming a relationship between anisotropy and fiber uncertainty[6,7] or have attempted to obtain it from the data directly[8]. Monte Carlo style approaches are then used to propagate pathways based on the assumed PDFs. A limitation of these approaches is that they cannot account for the variability due to physiological noise (e.g. subject motion, cardiac pulsation). Assessing the inherent reproducibility of tractography *in vivo* can be problematic since it normally requires scanning subjects on multiple occasions and careful co-registration of the data sets. In contrast, the bootstrap approach generates many tractography results from the same data set and, by definition, represents the intra-scan variability.

Conclusion: The bootstrap is a powerful technique that remains largely unexplored in DT-MRI tractography. Not only does it allow any deterministic tractography algorithm to be used in a probabilistic fashion, but also its model-free inclusion of *all* sources of variability means it provides the most realistic approach to probabilistic fiber tractography.

References: 1. Efron B & Tibishirani RJ. *An Introduction to the Bootstrap*: Chapman and Hall, 1993; **2.** Lazar M *et al*. Proc ISMRM 2001, p. 1527; **3.** Jones DK *et al*. *MRM* 1999; 42: 515-525. **4.** Basser PJ *et al*. *MRM* 2000; 44: 625-632. **5.** Jones DK *et al*. *MRM* 2003; 49: 7-12. **6.** Parker GJM *et al*. Proc ISMRM 2002, p. 1165; **7.** Tournier J-D *et al*. *NeuroImage* 20: 276-288 (2003). **8.** Behrens TEJ *et al*. Proc ISMRM 2002, p. 1160.