

# An Approach To Validation of Diffusion MRI-based White Matter Tractography

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## Purpose:

The validation of diffusion MRI-based white matter tractography in the human brain is a major challenge. No comparable non-invasive technique exists for cross-validation, and diffusion coefficients change almost immediately after death, making ex-vivo validation problematic. We sought to overcome this by devising a knowledge-based macroscopic validation strategy. This approach draws on the existing knowledge of neuroanatomical connectivity in humans to build a matrix of over 1500 regions of expected connectivity between various brain areas as designated by an expert neuroanatomist based on classical literature-based descriptions of white matter connectivity. This matrix can then be used as a “truth table” to examine various approaches to white matter connectivity. We patterned our approach after a publicly available database of macaque brain connectivity (www.cocomac.org) that in a similar way lists what is known about connectivity of the primate brain. We tested four different streamline-based connectivity approaches to determine their overall accuracy compared to the “truth table”.

## Methods:

In a manner similar to the databases listed for the macaque on cocomac.org, we first constructed a “truth table” by creating a 48 x 48 matrix of brain regions, with each region (e.g., V1, V2, etc.) listed along one axis. The expert neuroanatomist then marked each box in the connectivity matrix with “1” for connected, “0” for not connected, or “unknown” if the connectivity is not yet understood per classical methods in humans. Three human normal subjects underwent MR imaging after approval by our institutions committee on human research approved the study protocol. Each subject had MRI scanning on a 3.0T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) including diffusion tensor imaging (DTI) acquired at 2mmx2mmx2mm resolution and anatomic imaging (MP-RAGE) at 1mm isotropic resolution. The anatomic imaging data from each of the three brains were segmented using a manual segmentation technique similar to previously described technique [1]. This allowed parcellation of the brain into the 48 different cortical and subcortical areas. These segmentations were co-registered with the DTI data. This segmentation of the DTI data was then used for generating the seed regions of fiber connectivity determination.

Connectivity was determined using software that generated fibers based on regions of interest (ROIs) as seed points. Each ROI could be specified manually, or, for the purposes of this study, the 48 segmented portions of the brain were each sequentially used as seed ROIs. Cortical ROIs were grown by 1 pixel for purpose of connectivity determination. Once an ROI was used, fibers from this ROI to other locations in the brain were generated according to the connectivity algorithm under study. The presence or absence of connectivity to the other 47 other regions was then determined by whether or not the fibers passed through that region. In addition to a binary (yes/no) connectivity determination, a threshold approach was also evaluated whereby the determination for connectivity was varied depending on the number of fiber bundles generated by the connectivity algorithm. A receiver-operating-characteristic (ROC) curve was then generated to characterize the performance of the various connectivity algorithms across a range of thresholds, and compared using the “area under the curve” (AUC) metric for each ROC curve.

Four different streamline-based connectivity approaches were tested: the original FACT approach [2], the fixed step-length (interpolated) approach [3] with step length of ¼ voxel size, 2<sup>nd</sup> order Runge-Kutta approach and Tensor Deflection (Tensor-line) approach [4]. Each of the four connectivity approaches also had its performance measured as key thresholds were set in the individual algorithm, such as the threshold of fractional anisotropy (FA) at which a fiber was deemed to terminate, or the degree of curvature allowed for a fiber to maintain connectivity.

## Results:

Figure 1 shows ROC curves for the performance of the four connectivity algorithms tested from one of the three datasets. Each approach yielded substantially similar results, by covering different part of a similar ROC curve, with accuracy at the optimal operating point of the ROC curve of about 70%. However, each algorithm did show markedly different characteristic. For example, from Figure 1, FACT approach cannot reach high sensitivity area even at angle threshold of 60 degree and FA threshold of 0.04. That may suggest that it might be sensitive to low anisotropic or fiber crossing areas and noise. Interpolated fixed step-length approach improves in that aspect. Also, Tensor Deflection shows very low sensitivity to angle threshold, which matches its “incoming vector rules” nature.

## Conclusions:

This approach appears to provide a standardized method for the validation of DTI connectivity algorithms.

## References:

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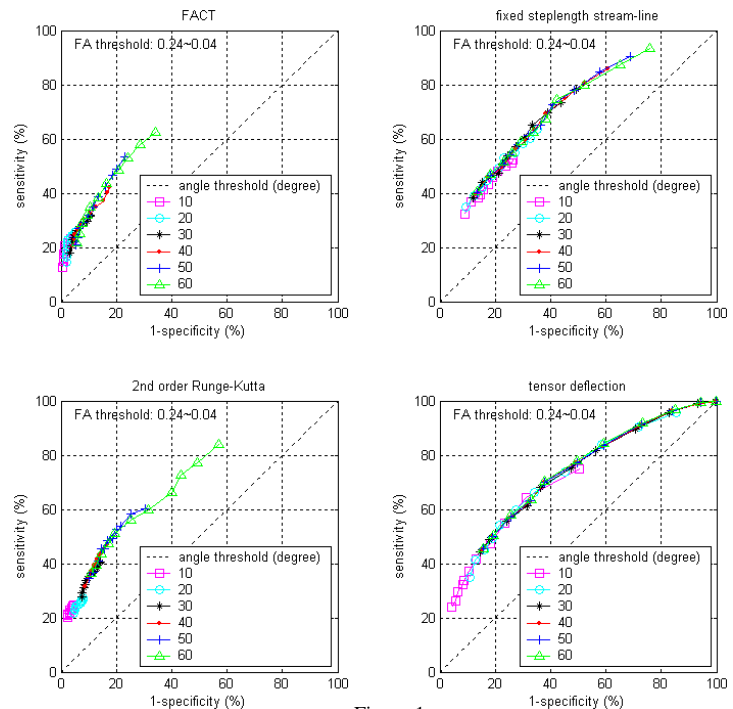


Figure 1