Microstructure Tracking (MicroTrack): An Algorithm for Estimating a Multiscale Hierarchical White Matter Model from Diffusion-Weighted MRI

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Introduction: MicroTrack combines whole-brain global tractography and local tissue microstructure estimation. The algorithm simultaneously estimates macrostructure (tract cross-section and connectivity) and microstructure (average axon radii and axon volume fraction) parameters for a white matter connectome using a mutliscale forward model. To date, tractography algorithms and microstructure parameter estimation operate entirely independently. However, connectivity and microstructure estimates have great potential to inform one another because 1) microstructural features (axon radii) tend to remain consistent along the length of fiber tracts and 2) these features vary between different tracts. In particular, simultaneous estimation provides a solution to the well-known kissing-versus-crossing ambiguity that confounds traditional tractography. MicroTrack can resolve the ambiguity by determining the configuration that maximizes microstructural consistency along each tract. Here we demonstrate this specific benefit using synthetic data. The connectivity estimate also benefits microstructure parameter estimation, because it provides knowledge of the fibre orientation distribution in each voxel, which confounds the axon radius estimate [1]. We demonstrate improved spatial consistency of microstructural parameter estimation with MicroTrack compared to voxel-by-voxel fitting in post-mortem monkey-brain data.

Method: As detailed in Sherbondy et al. [2], our connectome model is a set of streamlines sampled from a large database of candidates obtained by running various traditional tractography algorithms from every possible starting voxel in the image. To achieve physical plausibility, each streamline has a cross-section radius and microstructure parameters, such as average axon radius, volume fraction, and diffusivity. Each voxel in the image may be intersected by multiple portions of streamline cross-sections yielding voxel compartments with various orientations and microstructure parameters. We predict the voxel's MRI signal using a local diffusion model for each compartment of the voxel intersected with a streamline and sum the contributions from each. Remaining voxel space is filled with an isotropic diffusion compartment. This gives a minimal model of white matter diffusion (MMWMD) exactly as in [1], which is similar to the CHARMED [3] and Stanisz [4] multi-compartment models of white matter.

MicroTrack searches over parameters across spatial scales defining connectivity and microstructure in order to minimize a global error. The error (E) balances the difference between predicted and observed MRI signals with the physical integrity (no overlap) of the estimated tracts [5]. A differential evolution (DE) genetic search algorithm is used to optimize these parameters with respect to E. Although this optimization strategy cannot guarantee convergence on the global minimum for this problem, in practice we are able to produce good, if suboptimal, solutions in a reasonable time (16 hours on 30 2.3GHz CPUs).

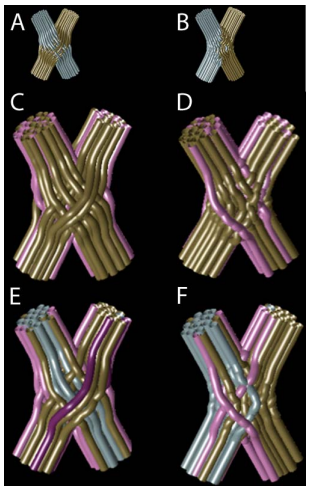

Fig. 1: Crossing (A) and kissing (B) synthetic data. 40% false connections (pink) without microsructure (C,D) and 14% with MicroTrack (E,F).

Imaging and synthetic data: We use a multi-shell HARDI protocol tuned for simultaneous sensitivity for axon radii of 0.5, 1 and 2.5 μm with a maximal gradient strength (G_{max}) of 300 mT/m [6]. The 360 measurements of the optimized protocol include three unique b-values [2421, 4609, 11329] s/mm^2 with [102, 105, 82] diffusion weighted gradient directions and 71 b=0 s/mm^2. Images from a 32 month perfusion fixed Vervet monkey brain were acquired on experimental 4.7T Varian Inova scanner using a conventional (pulse-gradient) spin-echo sequence with single-line readout [7]. The dataset includes 30 sagittal slices covering the midsagittal plane of corpus callosum (CC), isotropic 0.5 mm voxels, TR=2500ms and TE=39.1 ms. All ethical rules for care and handling of live animals were followed. To demonstrate the potential improvements for connectivity estimates we created two synthetic volumes that demonstrate the well-known kissing versus crossing ambiguity. The synthetic volumes were carefully constructed so that the white matter in the oblique crossing configuration overlaps the white matter volume in the kissing configuration as much as possible. The volumes were synthetized using the multi-shell HARDI protocol and a modification of the Numerical Fiber Generator (NFG) software [8].

Results: The two synthetic datasets (Fig. 1) capture the classic crossing versus kissing ambiguity. The tracts contain either axon radii of 1 μm (blue) or 5 μm (brown). When microstructure parameter estimation is turned off and MicroTrack is reduced to solving only connectivity, we show a false positive (Fig. 1C,D pink curves) rate of 40% on average. When MicroTrack optimizes over the joint distribution of connectivity and microstructure (axon radii), false positives are reduced nearly 3 fold to 14% (Fig. 1D,E), because MicroTrack leverages the microstructure signature to improve connectivity estimates.

In the corpus callosum of the fixed brain dataset, we can compare MicroTrack estimates of average axon radius within each voxel to estimates from the voxel-by-voxel fitting algorithm in [1]. As previously reported, estimates of axon radii in the midsagittal section of the corpus callosum (Fig. 2A), from splenium to midbody to genu, go from low to high to low, which agrees with histology [9]. However, the pattern changes markedly just two millimeters away from the midsagittal plane (Fig. 2B). We hypothesize this estimation error is due to a conflation of microstructure information and fascicle curvature (Fig. 2C, blue arrow). By simultaneously optimizing over microstructure and tract geometry, MicroTrack estimates a pattern of axon radii that matches the common assumption that the histological pattern does not deviate this close to the midsagittal section (Fig. **2**D-F); low-high-low pattern persists.

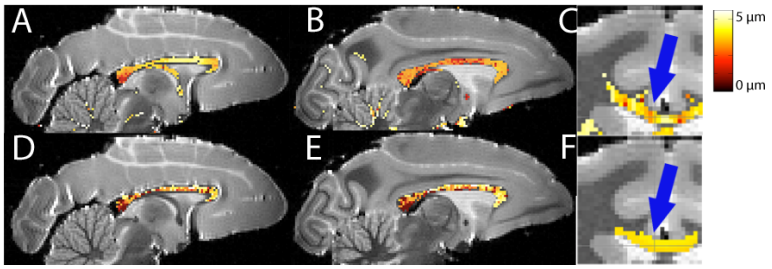

Fig. 2: MicroTrack solves for connectivity and microstructure and maintains consistent axon radii estimates in regions of fascicle curvature.

Discussion and conclusion: MicroTrack is a new algorithm that optimizes parameters across spatial scales defining connectivity and microstructure parameters. In the postmortem brain, the feasibility of measuring microstructural features within previously prohibitive regions of complex fascicle architecture is demonstrated. Further, the simple synthetic experiment demonstrates the possibility of disambiguating crossing versus kissing configurations using microstructure contrast.

References: 1. Alexander et al NIMG '10, 2. Sherbondy et al MICCAI '10, 3. Assaf et al NIMG '05, 4. Stanisz MRM '97, 5. Sherbondy et al MICCAI '09, 6. Dyrby et al ISMRM '10, 7. Dyrby et al HBM '10, 8. Close et al NIMG '09, 9. Lamantia et al J Comp Neuro '90