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# Bundle-Specific Tractography with incorporated anatomical and orientational priors

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## Abstract

Anatomical white matter bundles vary in shape, size, length, and complexity, making diffusion MRI tractography reconstruction of some bundles more difficult than others. As a result, bundles reconstruction often suffers from a poor spatial extent recovery. To fill-up the white matter volume as much and as best as possible, millions of streamlines can be generated and filtering techniques applied to address this issue. However, well-known problems and biases are introduced such as the creation of a large number of false positives and over-representation of easy-to-track parts of bundles and under-representation of hard-to-track.

To address these challenges, we developed a Bundle-Specific Tractography (BST) algorithm. It incorporates anatomical and orientational prior knowledge during the process of streamline tracing to increase reproducibility, sensitivity, specificity and efficiency when reconstructing certain bundles of interest. BST outperforms classical deterministic, probabilistic, and global tractography methods. The increase in anatomically plausible streamlines, with larger spatial coverage, helps to accurately represent the full shape of bundles, which could greatly enhance and robustify tract-based and connectivity-based neuroimaging studies.

*Keywords:* Diffusion MRI, White Matter, Tractography, Tractometry, Connectivity

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## 1. Introduction

Tractography algorithms are currently challenged by several important open issues and biases that need to be addressed to improve brain connectivity mapping [Jones, 2010; Jbabdi and Johansen-Berg, 2011; Maier-Hein et al., 2017]. In Maier-Hein et al. [2017], it was recently shown that whole-brain tractography can recover most existing true positive bundles but that these are poorly recovered in terms of spatial extent. In the

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7 simulations of 25 human-like synthetic white matter (WM) bundles, an average spatial  
 8 extent recovery of only 30% is reported [Maier-Hein et al., 2017, Fig. 3]. We propose  
 9 to term this tractography issue as the “*poor-spatial-extent*” challenge. Techniques that  
 10 have better spatial extent recovery always generate more invalid streamlines, and thus  
 11 fall into the usual *sensitivity-specificity curse*. In the current context, the notion of  
 12 invalid streamlines refers to anatomically improbable streamlines, meaning their path  
 13 is not reflective of known WM pathways. The quality of WM bundle reconstruction  
 14 using tractography is influenced by many variables: i) global geometry of the bundle like  
 15 curvature, thickness, length, ii) local crossing regions it traverses, position of the bundle  
 16 with respect to other bundles, and iii) extent and shape of cortical endpoints. As a result,  
 17 some WM bundles are harder-to-track than others, which leads to the poor-spatial-extent  
 18 challenge.

19 Why are some bundles more difficult to reconstruct than others? Complex local fiber  
 20 regions, even if well recovered locally in terms of fiber orientation distributions, can lead  
 21 to invalid tractography streamlines that respect the underlying local diffusion signal but  
 22 make clear invalid pathways at the global brain level [Maier-Hein et al., 2017]. Despite  
 23 the fact that almost all WM regions contain crossing fiber populations [Jeurissen et al.,  
 24 2013], some are well-know pitfalls for tractography methods and could be tackled with  
 25 better prior information. As an illustration, the *centrum semiovale*, as seen in Figure 1  
 26 and Figure 2, was and still is a major difficulty for tractography algorithms. Three major  
 27 WM pathways: i) the pyramidal tract, ii) the mid-body of the corpus callosum (anterior  
 28 and posterior), and iii) the arching streamlines connecting the frontal to the temporal  
 29 lobes, are crossing almost orthogonally in the most ventral part. At such an intersection,  
 30 even with multiple fiber techniques, tractography algorithms most often follow the easiest  
 31 path available. Bundles can seem to cover a large spatial extent and have an appropriate  
 32 amount of fanning when millions of streamlines are used. However, the density is far from  
 33 uniform within a bundle, even if it cannot be perceived visually, as seen in Figure 2. The  
 34 amount of crossing regions, overall length and curvature of the bundle will influence the  
 35 probability of a streamlines to reach its expected destination. Moreover, it is common  
 36 to observe streamlines abruptly changing direction to either switch to a different bundle  
 37 or follow an erroneous path, but end up in the right location. Crossing can become even  
 38 harder to distinguish as the main direction of the fiber populations kiss or come into a  
 39 bottleneck [Maier-Hein et al., 2017, Fig.7].

40 A partially reconstructed WM bundle could lead to erroneous interpretations and

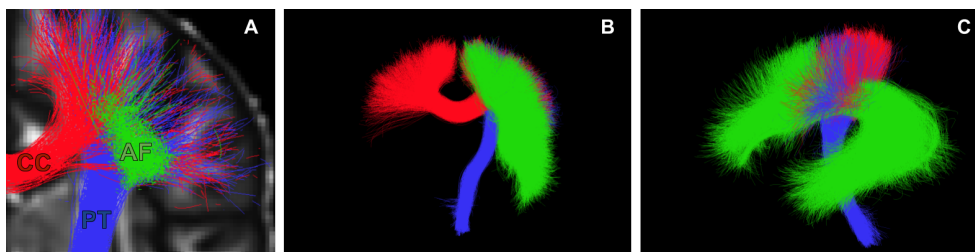


Figure 1: Crossing region of the Corpus Callosum (red), the Arcuate Fasciculus (green) and the Pyramidal Tract (blue) in the centrum semiovale. A) Coronal cross-section, B) coronal 3D view and C) sagittal 3D view.

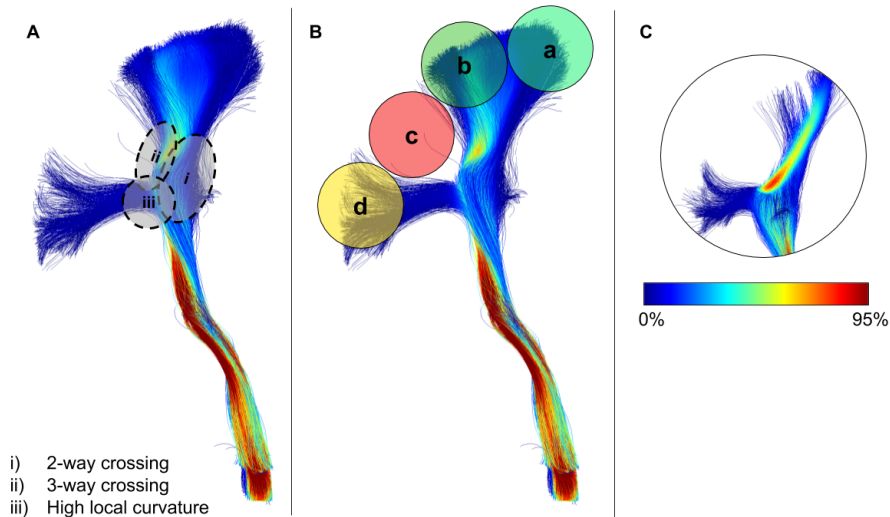


Figure 2: Reconstruction of pyramidal tract (PT) streamlines illustrating some of the challenges of tractography, seen on panel A, i) 2-way crossing ii) 3-way crossing, and iii) high curvature. In panel B, regions *a* and *b* encounter less difficulties in reconstruction due to only being subject to a 2-way crossing limitation, as illustrated in Panel A (i), leading to a higher proportion of streamlines reaching the cortex in these general regions. Conversely, region *c* in Panel B encounters 2 and 3 way crossings (Panel A (i) and (ii)), whereas, region *d* in Panel B encounters 2-way crossing and high-curvature limitations (Panel A (i) and (iii)), leading to a lower proportion of streamlines successfully reaching the cortex. Streamline coloring represents the local streamlines density (at the voxel-level), segments in red shows regions where a large proportion of streamlines pass through a bottleneck as opposed to segments in blue. Panel C illustrates that the majority of streamlines traverse through the core of the PT.

41 conclusions. At the tract-based analysis level [Dayan et al., 2016; Cousineau et al., 2017;  
 42 Yeatman et al., 2012, 2018], the spatial extent of bundles (in  $\text{cm}^3$ ) is a measurement  
 43 often used to investigate morphological group differences, such as atrophy or asymmetry  
 44 [Catani et al., 2007; Song et al., 2014; Chenot et al., 2018]. At the connectome-level, the  
 45 number of streamlines in WM bundles connecting all possible pairs of cortical regions  
 46 is usually used [Sotiropoulos and Zalesky, 2017]. However, because of a combination of  
 47 local and global differences in brain geometry and WM configurations, certain subjects  
 48 may have easier-to-track bundles than other subjects, which results in WM bundles  
 49 that fill-up in spatial extent before others and thus have artificially larger number of  
 50 streamlines. Two strategies exist to attempt overcoming these issues: 1) a whole brain  
 51 tractography with millions of streamlines followed by manual, clustering or advanced  
 52 filtering techniques, 2) a tailored ROI-based tractography.

53 *Whole-brain tractography followed by filtering, clustering or manual dissection.* In the  
 54 first strategy, millions of streamlines are typically reconstructed using a whole-brain de-  
 55 terministic, probabilistic, or global fiber tracking algorithms to fill-up the whole WM  
 56 volume and be able to capture a large spatial extent of all bundles [Wassermann et al.,  
 57 2016; Jeurissen et al., 2017; Moyer et al., 2018; Calamante et al., 2015; Smith et al.,  
 58 2015b]. With more streamlines, a larger extent of bundles is reconstructed (higher sensi-  
 59 tivity) but also more false positive bundles created (lower specificity) [Côté et al., 2013;

60 [Maier-Hein et al., 2017](#)], thus leading to the *sensitivity-specificity curse* mentioned before.  
61 Generation of millions streamlines is often considered a brute force approach with a heavy  
62 computational burden. All *iterations* leading to false positive are considered wasted. Re-  
63 ducing such iterations increases the computational efficiency of a method, meaning that  
64 less effort is required while maintaining an acceptable sensitivity-specificity ratio.

65 Moreover, when millions of streamlines are desired in a whole brain tractogram, mil-  
66 lions of seeds and hundreds of millions of 3D points are generated, which can be an  
67 important computational and memory limitation [[Rheault et al., 2017](#)]. In the case of a  
68 specific tract-based application, where only a single to a few WM bundles are desired,  
69 this whole brain strategy can be sub-optimal both in terms of bundle reconstruction  
70 quality and computational efforts. Increasing the number of streamlines to 10M or 100M  
71 would fill-up more of this hard-to-track fanning space, but would potentially never reach  
72 full extent coverage. Generating more streamlines will artificially increase the density of  
73 the central, easy-to-track part of the bundle and generate a large number of false positive  
74 streamlines. Advanced filtering techniques such as SIFT, LIFE, COMMIT [[Smith et al.,](#)  
75 [2015a](#); [Pestilli et al., 2014](#); [Daducci et al., 2015](#)] are able to filter some false positives and  
76 reduce the density bias by making sure streamlines explain the desired diffusion signal,  
77 but at the cost of removing some hard-to-track valid streamlines as well [[Maier-Hein](#)  
78 [et al., 2017](#)].

79 *ROI-based tractography.* In the second strategy, a ROI-based tractography strategy uses  
80 different masks, filtering ROI pass-ways and varying tractography parameters (step size,  
81 curvature, anisotropy thresholds) [[Chamberland et al., 2014, 2017](#)] to enhance the quality  
82 of results based on neuroanatomical prior knowledge. A ROI-based seeding strategy is an  
83 efficient way to quickly target a bundle of interest by removing unnecessary computations  
84 needed in whole brain tractography. Such strategy has already been used in multiple  
85 research projects to avoid generating unwanted streamlines [[Basser et al., 2000](#); [Catani](#)  
86 [et al., 2002](#); [Mori and van Zijl, 2002](#); [Behrens et al., 2007](#); [Ghaziri et al., 2015](#); [Renauld](#)  
87 [et al., 2016](#); [Rozanski et al., 2017](#); [Chamberland et al., 2017](#)], mainly using manual  
88 delineations, or ROIs obtained from a segmentation tool such as FreeSurfer [[Desikan](#)  
89 [et al., 2006](#)], or the JHU template [[Mori et al., 2005](#)].

90 Here, ROI-based tractography can be more efficient but not necessarily lead to better  
91 spatial extent recovery. The poor-spatial-extent problem is temporarily “hidden” because  
92 one can now afford to launch millions of seeds just to reconstruct a single bundle. How-  
93 ever, the same issues illustrated in [Figure 2](#) remain, i.e. hard-to-track fanning regions are  
94 hard to reach and easy-to-track regions are amplified. Also, because of the ROI-based  
95 filtering process, all the false positive streamlines generated are thrown out and excluded  
96 from the result, but, computational efforts are still deployed to track them. Hence, over-  
97 all, a ROI-based approach still suffers from poor efficiency, incomplete spatial-coverage  
98 and a similar underlying trade-off between sensitivity and specificity.

99 To address these issues, tractography needs the injection of more information and  
100 priors into the streamline tracing process itself. In [Maier-Hein et al. \[2017\]](#), it was clearly  
101 shown that following local orientations alone cannot resolve all the potential ambiguity  
102 and biases of fiber tracking. Bottlenecks are not tractable using directional information  
103 alone.

104 Several approaches have been proposed to inject more prior knowledge. An automated  
105 method called TRACULA [[Yendiki et al., 2011](#)] was proposed to include anatomical

106 priors from anatomical labeling. Pathway labels are used to initialize and constrain  
107 the probabilistic tractography algorithm. However, this approach uses a conservative  
108 reconstruction model (FACT, [Mori et al., 1999]) and strict anatomical definitions as  
109 training sets, which limits the spatial extent of bundles. Further, probability maps are  
110 computed instead of streamlines potentially limiting tract-based analyses. More recently,  
111 Wasserthal et al. [2018a] proposed a method to directly segment the volume occupied  
112 by bundle of interests. However this method does not rely on tractography and does  
113 not produce streamlines. Features of the raw diffusion signal are learned and regions  
114 of interests segmented where the characteristics of the signal match with bundles of  
115 interests.

116 On the other hand, global tractography algorithms [Kreher et al., 2008; Mangin et al.,  
117 2013; Christiaens et al., 2015; Neher et al., 2012] can sometimes overcome difficult lo-  
118 cal crossing regions, but resulting tractograms do not always represent the expected  
119 anatomical complexity of fasciculi. Global tracking algorithms are promising but are  
120 known to have their share of open challenges such as heavy computational needs, the  
121 generation of a large number of broken streamlines, and difficulty to impose anatomical  
122 priors [Maier-Hein et al., 2017; Jeurissen et al., 2017].

123 Other approaches exist to overcome fiber crossing difficulties. Chamberland et al.  
124 [2017] proposed a magnetic tracking (MAGNET) tool to manually influence directions  
125 in strategic regions, improving the reconstruction of the optic radiations bundle. MAG-  
126 NET essentially pulls tractography towards the occipital lobe with an orientation prior,  
127 allowing fiber tracking to perform a “U-turn”-like reconstruction needed to fully recon-  
128 struct Meyer’s loop. Moreover, Dhollander et al. [2014] also suggested a method to  
129 sharpen orientations based on streamline distributions, called *Track-Orientation Distri-*  
130 *butions (TOD)*. TOD can help enhance tractography to cover longer distances along  
131 WM structures and address some of the biases of fiber tracking. However, since stream-  
132 lines density is not uniform across a tractogram and does not represent the underlying  
133 anatomy, using such a method iteratively across WM will increase the density bias in  
134 easy-to-track regions. More recently, Wasserthal et al. [2018b] proposed an approach  
135 using bundle-specific orientation maps learned from multiple datasets to select a single  
136 fiber orientation distribution (FOD) peak in each voxel, thus improving reconstruction of  
137 bundles by simplifying regions with complex WM configuration. To the best of our knowl-  
138 edge, these techniques are the only existing methods trying to inject orientational prior  
139 knowledge into the tractography process. Other approaches have proposed to include  
140 an orientation-based regularization term in the local reconstruction of fiber orientations,  
141 but to our knowledge, not in the tractography procedure itself [Reisert and Kiselev, 2011;  
142 Portegies et al., 2015].

143 Tractography is therefore currently blind to the anatomy and does not have access  
144 to the anatomical knowledge accumulated over the past several hundred years by the  
145 neuroanatomy community. This neuroanatomical information, when available, could  
146 enhance tractography. For instance, priors could capture the “where” and “how” of  
147 bundles. That is where should the origin and target region of bundles be, and how dif-  
148 ficult crossing, fanning, bending regions should be traversed. Our novel Bundle-Specific  
149 Tractography (BST) algorithm is designed to directly incorporate these anatomical and  
150 orientational priors in the tractography process itself. The main contribution is a novel  
151 methodology enhancing local fiber orientation distribution based on WM bundle priors  
152 coming from templates of streamlines. BST is fully automatic and yields better spatial

153 coverage, increases quality in the fanning extents and produces more plausible shape  
154 reconstructions of bundles in the centrum semiovale.

## 155 2. Methods

### 156 2.1. Bundle-Specific Tractography

157 Our novel bundle-specific tractography (BST) approach is composed of three steps.  
158 For each bundle of interest to be reconstructed, one needs to:

- 159 1. Build a *template of streamlines* that represents the shape and position of each  
160 bundle, covering as much geometric variability as possible (see first row of Figure 3  
161 and Figure 4).
- 162 2. Build the *anatomical priors* by incorporating dilated versions of endpoints and  
163 spatial coverage maps defined from the template of streamlines in 1) (see second  
164 row of Figure 3).
- 165 3. Build the *orientation priors* by generating a field of enhanced fiber orientation  
166 distributions (E-FOD) from the track-orientation distribution of the template of  
167 streamlines in 1) (see Figure 4).

168 Our BST approach can be applied to any bundle of interest with the previous 3 steps.  
169 We now detail each of these steps before describing the datasets and how it was applied  
170 to bundles intersecting in the centrum semiovale seen in Figure 1.

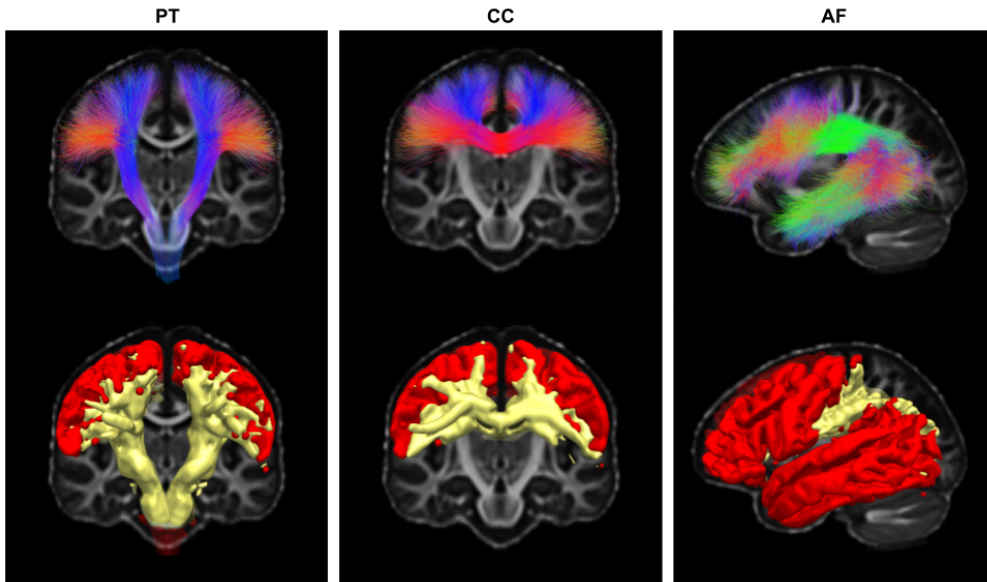


Figure 3: The first row shows streamlines from the template on top of the FA template. In the second row, tracking masks (yellow) and seeding endpoints masks (red), automatically extracted from the template of streamlines of the first row.

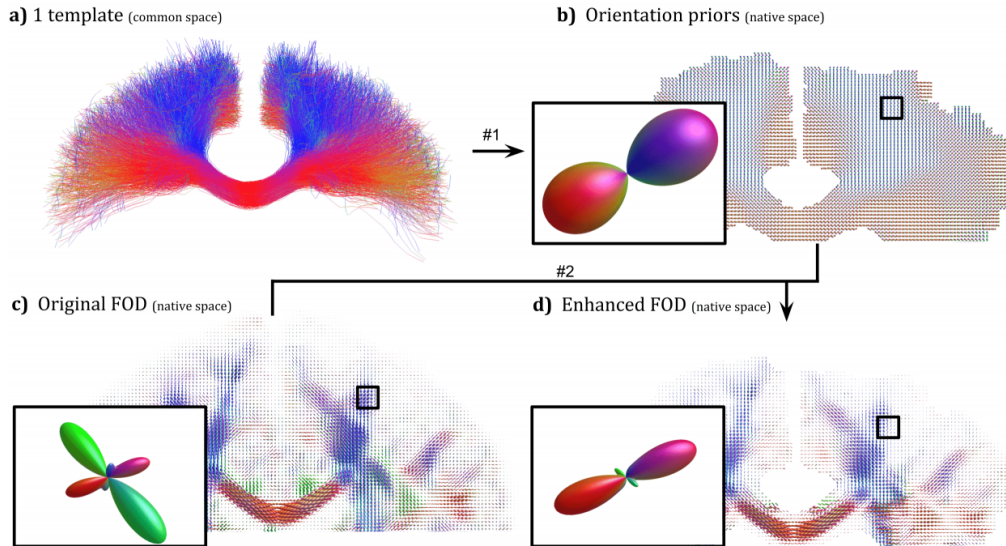


Figure 4: a) Template in a standard space, b) orientation priors in native space, c) initial FOD from CSD, d) pre-computed enhanced FOD.

171 *Building the templates of streamlines*

172 This initial step is crucial since the template of streamlines affects all additional  
 173 orientational and anatomical priors used by the BST algorithm. It involves four technical  
 174 steps (see Figure B.9):

- 175 (i) Run a whole-brain or ROI-based tractography technique on the selected subjects.
- 176 (ii) Segment the bundles of interest.
- 177 (iii) Merge all streamlines of each bundle and each subject in a common space.
- 178 (iv) Adjust the density bias of streamlines distribution.

179 *i) Initial tractography.* Our approach works in combination with any existing whole-brain  
 180 streamline-based or iterative tractography algorithm [Jeurissen et al., 2017]. BST will  
 181 enhance the initial tractography algorithm and retain the properties of the chosen initial  
 182 algorithm. Global tracking and graph-based/geodesic techniques could also be casted in  
 183 a BST setting but this is outside the scope of the current paper and will be discussed  
 184 later.

185 *ii) Segmentation of bundles.* Bundles of interest needed for a particular study are usually  
 186 well-defined in terms of anatomical regions they traverse or connect to [Catani et al.,  
 187 2002; Catani and De Schotten, 2008]. Moreover, the shape of the bundle is generally  
 188 agreed upon by various experts [Catani and De Schotten, 2008; Hau et al., 2016] or have  
 189 often been established from *ex vivo* Klingler blunt dissections [Fernández-Miranda et al.,  
 190 2015; Benedictis et al., 2016; Hau et al., 2017]. Hence, this segmentation step of bundles  
 191 is either done manually or with a semi-automatic filtering or clustering approach. Of



192 course, if the number of subjects is large, a manual approach can be tedious and prone  
193 to human error. Using ROIs defined by in WM and GM atlases to specify a sequence of  
194 rules describing a pathway can be a good alternative [Wassermann et al., 2016]. Another  
195 segmentation method is to select or discard streamlines based on shape of cluster using  
196 models or anatomical *a priori* [Voineskos et al., 2009; Guevara et al., 2011; O’donnell  
197 et al., 2013; Chekir et al., 2014; Garyfallidis et al., 2017; Zhang et al., 2018].

198 *iii) Bring streamlines to a common space.* A common space needs to be chosen. The  
199 usual MNI space is a possibility or a tailored template space defined for a specific group of  
200 subjects. Each subject is nonlinearly warped to that common space and the deformation  
201 field used to move each bundle of interest from each subject into the common space. The  
202 deformation involves transforming each point (vertex) of each streamline, using *tract-*  
203 *math* [Wassermann et al., 2016] or a in-house tool. Once aligned to a common space,  
204 bundles of interest are concatenated together into single track file, as seen in Figure 3.  
205 The intention of these templates is to represent the general shape and position of bundles.

206 *iv) Correct for the density bias.* An individual subject tractogram generally has low  
207 density in crossing regions, while extremely dense in regions of one fiber population  
208 (easy-to-track parts). The overall shape of a bundle influences this density, i.e. straight  
209 bundles will be denser than curved bundles. Since the concept of tract density (stream-  
210 lines count) in tractography can be a major pitfall that does not accurately represent the  
211 underlying WM structure [Jones, 2010; Jbabdi and Johansen-Berg, 2011; Daducci et al.,  
212 2016], this non-uniform density bias needs to be removed from the template of stream-  
213 lines as only the orientation is of interest for our priors. A smart streamline subsampling  
214 method based on hierarchical clustering algorithm and minimal direct flip (MDF) dis-  
215 tance [Garyfallidis et al., 2012, 2016] is used to overcome this issue. A streamline within  
216 2mm of its neighboring streamlines do not carry new information and is removed, without  
217 altering the general shape of the template.

218 As mentioned before, the template of streamlines essentially captures the a priori  
219 knowledge of “*where*” and “*how*”, i.e. where is the bundle originating from, where is  
220 going to, and how is it supposed to traverse complex crossing/kissing/branching/fanning  
221 regions.

#### 222 *Anatomical priors: Tractography map creation*

223 The streamlines in the template can now be displaced using the same point-wise  
224 method from the template creation (using the inverse deformation field). Once the  
225 template of streamlines is in the subject space, a new tracking mask is automatically  
226 generated from the voxels intersected by the template streamlines. The streamlines end-  
227 points can also be used to generate a ROI seeding mask. To reduce gyral bias effects  
228 and to cover the potential variability across subjects, the seeding and tracking regions  
229 are all dilated by 5mm, as seen in Figure 3. These masks are used to generate prob-  
230 abilistic exclusion and inclusion maps as well as an interface GM-WM map needed for  
231 anatomically-constrained tractography [Smith et al., 2012; Girard et al., 2014]. To pre-  
232 vent streamlines from being generated outside of the white matter, all tracking masks  
233 were constrained by the subject’s white matter mask. This ensures that our method does  
234 not enforce its priors over a subject tissue segmentation, and only the general position  
235 within the white matter.

236 *Orientational priors: Enhancing fiber orientations*

237 During tractography, streamlines are generated by taking steps using the fiber orien-  
238 tation distribution (FOD) to choose the next direction [Jeurissen et al., 2017]. The value  
239 of the FOD is used to weigh the probability of picking a direction. The proposed BST  
240 approach uses orientation priors estimated from the template of streamlines to modify  
241 the weighting according to the general, or more global, *a priori* bundle direction. If a  
242 streamline is following a specific fiber population, the most well-aligned FOD lobe needs  
243 to be prioritized.

244 To achieve this “prioritization” of FOD lobes, the local orientation histogram from  
245 nearby segments of streamlines is computed at every voxel. This method is based on a  
246 TOD map estimated from the template of streamlines, as originally introduced [Dhol-  
247 lander et al., 2014]. Improvements related to the FOD field aiming to constraint trac-  
248 tography spatially were proposed in the past [Portegies et al., 2015; Reisert and Kiselev,  
249 2011].

250 Then, at each voxel, a point-wise multiplication of the FOD and TOD orientation  
251 priors is performed, followed by a normalization. As a result, when a lobe is well-  
252 aligned with the directions of the priors, the values stay the same. This is observed  
253 in Figure 5, where the top row shows TOD maps associated to the pyramidal tracts,  
254 the corpus callosum and the arching streamlines respectively. The bottom row shows the  
255 corresponding enhanced FOD (E-FOD) associated with each bundle intersecting through  
256 the centrum semiovale. Therefore, when a streamline reaches this crossing region, the  
257 probability of choosing an appropriate direction is increased. The orientational prior will  
258 amplify the desired direction present in the TOD map, and thus improve the directionality  
259 of streamlines at the crossing. This concept of using *a priori* information as well as the  
260 observed signal to increase anatomical validity of the decision is borrowed from Bayesian  
261 statistics, which is common in neuroimaging [Woolrich et al., 2009; Friston et al., 2002b,a].

262 If the template of streamlines have crossing or complex fanning, the TOD map will  
263 correctly capture this and an appropriate weighting will be achieved. This can be seen in  
264 the zoomed picture of Figure 4. On the contrary, lobes that are perpendicular decrease in  
265 value as seen in Figure 6, It is important to note that other lobes are not removed, they  
266 are simply decreased in amplitude as this information was still present in the diffusion  
267 data. As the aim is not to enforced our orientation priors, but simply re-weighting the  
268 FOD amplitude, these two scenarios show the impacts in a extreme case and a typical  
269 situation.

270 To ensure that non-existent or erroneous information is not created, a minimal lobe-  
271 value threshold is set on the sphere for the orientational priors. This is to ensure that if  
272 there is no well-aligned lobe with an amplitude high enough compared to the others, the  
273 operation will not increase the values in that direction. A similar threshold was used in  
274 Raffelt et al. [2017] to exclude orientations that do not likely represent a fiber population,  
275 and used to perform peak extraction on FOD, also to exclude unlikely fiber populations  
276 [Tournier et al., 2012; Chamberland et al., 2014; Dell’Acqua et al., 2013]. In our case,  
277 we set a relative amplitude threshold to 0.2 (or 20%).

278 *2.2. DWI Datasets*

279 For this work the templates and experiments were performed with the BIL&GIN  
280 database [Mazoyer et al., 2016]. The datasets are composed of T1-weighted and diffusion-  
281 weighted images from 39 healthy subjects. The dMRI acquisition consists of 21 gradient

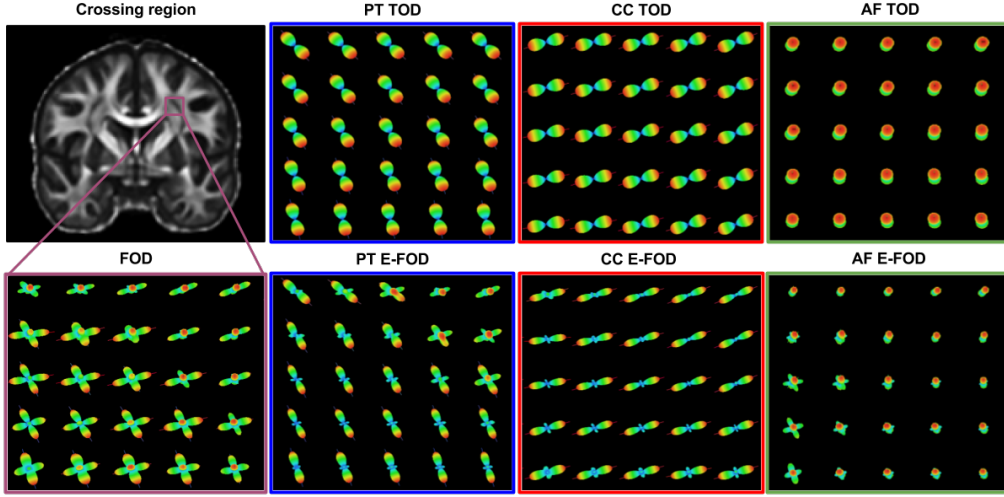


Figure 5: Orientation distribution of the crossing section presented in Figure 1. The first row illustrates the track orientation distribution (TOD) maps generated from the different template (Pyramidal tract, corpus callosum, Arcuate Fasciculus). In the second row, the first FOD vignette presents the original fiber orientation distribution (FOD) in the crossing region followed by enhanced FOD (E-FOD), a combination of the associated template TOD (from the first row) and the original FOD.

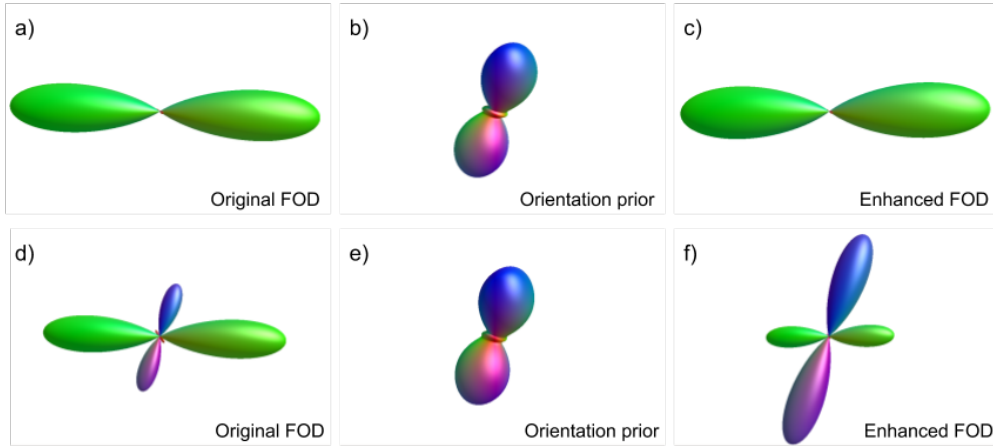


Figure 6: The first row represents a voxel where the FOD (a) does not have any lobe aligned with the orientation prior (b), which results in an enhanced-FOD (c) almost identical to the original. The second row represents a voxel where a FOD (d) with a lobe of sufficient size (above the minimum relative amplitude threshold) globally aligned with the orientation prior (e), which results in an enhanced-FOD (f) with a increase amplitude for that lobe.

282 directions on half a sphere, the same direction were acquired on the other half of the  
 283 sphere for averaging, on a single shell ( $b = 1000 \text{ s/mm}^2$ ) with a  $2 \text{ mm}$  isotropic resolution.  
 284 This scheme was acquired twice for averaging to increase SNR. At each voxel, the FOD  
 285 was computed using constrained spherical deconvolution (CSD) with spherical harmonics

286 of order 6 [Tournier et al. \[2008\]](#); [Descoteaux et al. \[2009\]](#).

### 287 2.3. Template creation

288 For each subject, a whole brain tractogram was reconstructed using the anatomically-  
289 constrained probabilistic particle filtering tractography (PFT), with recommended de-  
290 fault parameters [[Girard et al., 2014](#)]. Each tractogram was then segmented using an  
291 automatic ROI-based method to extract five bundles of interest, these five bundles will  
292 simply be referred to as the left/right pyramidal tract (PT), the corpus callosum (CC)  
293 and the left/right arcuate fasciculus (AF). The complete anatomical definitions used  
294 by the neuroanatomy expert can be found in the [Anatomical Definition](#) Section. We  
295 built our own tailored anatomical template using the fractional anisotropy (FA) maps  
296 of the 39 subjects with ANTS Multivariate Template Construction script [[Avants et al.,](#)  
297 [2008](#)]. This group average template was used as a common space for the template of  
298 streamlines. Subsequently, the 5 bundles of interest, from each subject, were moved into  
299 that common space using the nonlinear deformation field from ANTS. Once BOI are  
300 concatenated across subject, any redundant streamlines, up to a 2mm MDF distance  
301 threshold, are discarded. [Moreover, in this work, a leave-one-out approach was used to](#)  
302 [ensure that the template streamlines generalize to independent datasets. Any experi-](#)  
303 [ment using a template performed on a particular subject did not use the subject itself](#)  
304 [in that template.](#)

### 305 2.4. Experiments, Evaluation, and Statistical analysis

306 Probabilistic (Prob) and deterministic (Det), with or without PFT [[Girard et al.,](#)  
307 [2014](#)] were compared, as well as global tractography from *MITK Diffusion* [[Neher et al.,](#)  
308 [2012](#)]. GM-WM interface seeding was performed, with 5 seeds per voxel, adapted to each  
309 bundle of interest (BOI) seeding region (BOI map). Three main sets of parameters were  
310 used to compare between classical tracking algorithm and the proposed BST method. To  
311 distinguish the impact of improvements from bundle-specific tracking anatomical prior  
312 masks and orientational prior enhanced-FOD, three tractography reconstructions were  
313 performed:

- 314 1. Original FOD with the original exclude/include maps
- 315 2. Original FOD with bundle-specific exclude/include maps
- 316 3. Enhanced FOD with bundle-specific exclude/include maps

317 Item 1 corresponds to classical HARDI tracking [[Tournier et al., 2012](#); [Jeurissen et al.,](#)  
318 [2017](#)]. The last item is the full BST method, while item 2 is a point of comparison to  
319 help separate the contributions of the anatomical and orientation priors. Finally, we  
320 also run global tractography [[Kreher et al., 2008](#); [Neher et al., 2012](#)] to test against the  
321 proposed BST methods. Detailed descriptions of the experiments are available in the  
322 [Annexes](#) Section. These lead to five bundles, two tracking evolution approaches (Prob  
323 and Det), two algorithm (PFT/no-PFT), and the three compared method (classical, BOI  
324 map and BOI & E-FOD), for a total of 60 tractography files plus one global tractography  
325 result per subject. With these 2379 tractograms (61 tractograms times 39 subjects), the  
326 automatic bundle segmentation method mentioned earlier ([Anatomical Definition](#)) was  
327 applied to obtain each bundle.

328 Evaluation and statistical analysis were performed using the following measures: bundle  
329 volume, weighted-Dice coefficient, average streamlines length, percentage of valid  
330 streamlines and computational performance. The volume was obtained by computing a  
331 binary mask of every voxel intersected by streamlines, in a 1mm isotropic grid [Rheault  
332 et al., 2017]. The weighted-Dice was introduced by Cousineau et al. [2017] to obtain  
333 a value representing spatial agreement that takes account streamlines density. Using  
334 the Dice coefficient as a spatial agreement metric will be severely penalized for spurious  
335 streamlines. The overall shape of bundles of interests were expected to be similar across  
336 subjects. The strict anatomical definitions lead to comparable bundles across subjects  
337 once registered in a common space, especially for major WM pathways. In addition, an  
338 intra-subject approach would not have provided direct information regarding the quality  
339 of a bundle reconstruction. Lack of fanning reaching the cortex could be reproducible  
340 and the spatial agreement high without showing improvement compared to the expected  
341 shape. Since the bundles of interests in this project (AF, CC, PT) are major WM  
342 pathways, they are generally anatomically comparable across subjects, i.e. the spatial  
343 agreement is expected to be high, without necessarily reaching a perfect score.

344 The percentage of valid streamlines is the proportion of generated streamlines re-  
345 specting the anatomical definition of a bundle from the expert (see [Anatomical Defini-](#)  
346 [tion](#) Section) and a length threshold compared to the total amount of streamlines that  
347 were originally generated. All outputs from tractography have to respect the algorithm  
348 constraints (tracking mask, angular threshold, spherical function threshold), however the  
349 length threshold was applied only for bundles. segmentation. In the context of our ex-  
350 periments, the notion of valid and invalid streamlines vary with the bundle of interest  
351 investigated. A valid streamline for a particular BOI will be considered invalid for all  
352 other BOI. For example, a BOI interface of 100 voxels with 5 seeds per voxel would launch  
353 500 streamlines, if 25 streamlines are segmented (considered valid), this would amount  
354 to 5% of valid streamlines. Computational performance (efficiency), represents the total  
355 number of tractography iterations, i.e. tracking steps, leading to valid streamline points.  
356 This is slightly different than the previous percentage of valid streamlines measure, es-  
357 pecially with the BOI tracking mask, because most invalid streamlines end up having  
358 less than 50 steps while valid streamlines end up with more 500 steps. This metric is  
359 better than streamlines count to represent the improvement in terms of computational  
360 performance.

361 For statistical analysis, all subjects and bundles were analyzed separately. Then, to  
362 highlight general trends, results were averaged. The analysis was performed with all  
363 streamlines registered in the FA template space. This alignment, allowed to compute  
364 overlaps between subjects and to normalize the values obtained for the volume and  
365 average length. This procedure ensures that variations in volume or length does not  
366 come from disparities in brain size of the subject but rather from the tracking itself.

### 367 3. Results

368 To simplify reading of tables, graphs and figures, the focus will be on probabilistic  
369 tracking with particle filter tractography (PFT), but all evaluation data, graphs and  
370 figures are available in the [Annexes](#) Section. Observations and trends are similar and  
371 as expected. Moreover, MITK Global tractography was also benchmarked on the same  
372 measures to ensure an adequate comparison to state-of-the-art tractography algorithms.

373 Figure 7 shows segmentations of PT, CC, and AF bundles of interest with a prob-  
 374 abilistic PFT algorithm, comparing the use of original FOD and PFT maps to the pro-  
 375 posed BST approach using the enhanced FOD with the modified PFT maps. The re-  
 376 constructed bundles of interest from the classical tracking show some degree of fanning,  
 377 but the number of streamlines generated was not sufficient to fully recover the spatial  
 378 extent of bundles. All bundles reconstructed using the masking priors and the enhanced  
 379 FOD show an increase in both bundle coverage and quality of the fanning. For the PT,  
 380 the lateral portions of the pre- and post-central gyri are better covered while they are  
 381 almost non-existent with standard PFT. Similarly, the CC has the fanning fully covering  
 382 the pre-central and post-central gyri. As for the AF, the spatial extent in the frontal  
 383 and temporal lobes is increased, but streamlines are also reaching more laterally into the  
 384 gyri. The quantitative impact of the improved fanning directly impacted the volumes of  
 385 the reconstructed bundles, as seen in the first column of Table 1.

386 Figure 8 shows the trends for each measures of the analysis, where each graph  
 387 represents the changes of all bundles across the three sets of tractography parameters.  
 388 The impacts are not the same for each bundle, as the shape, size and the underlying  
 389 anatomy are inherently different. Error bars in the histograms represent the average  
 390 values and their standard deviation across 39 subjects. As the histograms can be hard  
 391 to compare, values are also shown in Table 1.

392 In Figure 8 a), an increase in volume for all bundles is measured when the priors

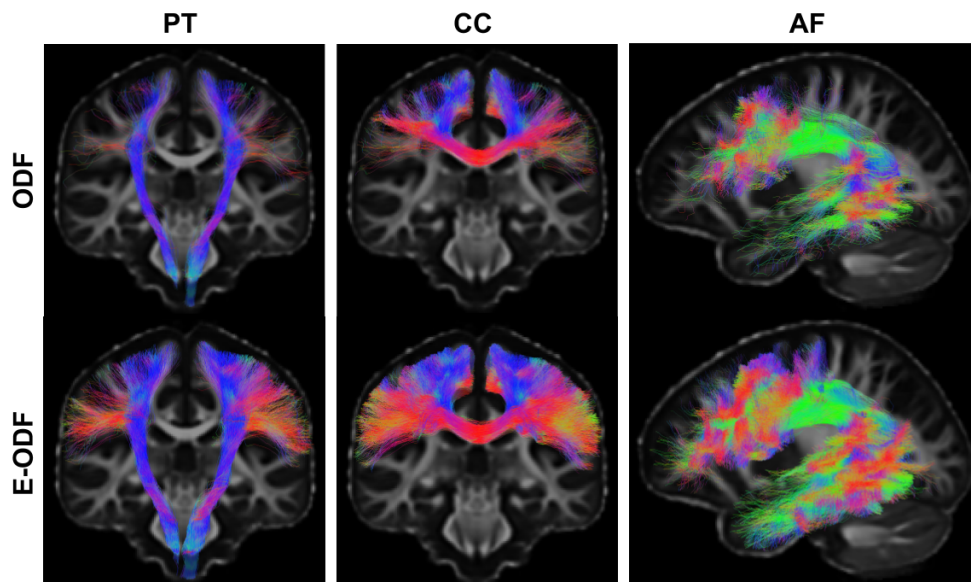


Figure 7: Examples of resulting PFT and BST algorithms for a single subject. The first row shows results from standard tracking of the PT, CC and AF, while the second row shows results from the proposed bundle-specific tracking. Of note, at no point tracking is allowed outside of the initial white matter tracking mask. It involves that no streamline travel in gray matter or CSF and the impression of going over the sulci which can be observed in the second row is due to coronal view lacking perspective.

## Left Pyramidal Tract

	Local model	Mask	Bundle vol. ( $cm^3$ )	Dice index	Average length (cm)	% of valid streamlines	Efficiency (%)
1.	FOD	WM	9.80 $\pm$ 3.42	0.63 $\pm$ 0.12	12.58 $\pm$ 0.38	0.29 $\pm$ 0.20	1.30 $\pm$ 0.92
2.	FOD	BOI	14.70 $\pm$ 4.00	0.71 $\pm$ 0.10	12.66 $\pm$ 0.32	0.67 $\pm$ 0.38	4.01 $\pm$ 2.45
3.	E-FOD	BOI	<b>27.95 <math>\pm</math> 6.24</b>	<b>0.86 <math>\pm</math> 0.06</b>	12.16 $\pm$ 0.30	<b>3.92 <math>\pm</math> 1.95</b>	<b>11.73 <math>\pm</math> 6.49</b>

## Right Pyramidal Tract

	Local model	Mask	Bundle vol. ( $cm^3$ )	Dice index	Average length (cm)	% of valid streamlines	Efficiency (%)
1.	FOD	WM	6.56 $\pm$ 2.74	0.51 $\pm$ 0.15	12.03 $\pm$ 0.32	0.14 $\pm$ 0.10	0.58 $\pm$ 0.42
2.	FOD	BOI	11.08 $\pm$ 3.42	0.64 $\pm$ 0.13	12.07 $\pm$ 0.26	0.38 $\pm$ 0.22	2.21 $\pm$ 1.32
3.	E-FOD	BOI	<b>25.27 <math>\pm</math> 5.33</b>	<b>0.83 <math>\pm</math> 0.06</b>	11.59 $\pm$ 0.24	<b>2.42 <math>\pm</math> 1.19</b>	<b>7.26 <math>\pm</math> 3.95</b>

## Corpus Callosum

	Local model	Mask	Bundle vol. ( $cm^3$ )	Dice index	Average length (cm)	% of valid streamlines	Efficiency (%)
1.	FOD	WM	25.78 $\pm$ 6.58	0.65 $\pm$ 0.11	11.25 $\pm$ 0.37	0.72 $\pm$ 0.33	2.89 $\pm$ 1.39
2.	FOD	BOI	49.51 $\pm$ 7.40	0.78 $\pm$ 0.07	11.49 $\pm$ 0.31	2.68 $\pm$ 0.85	14.09 $\pm$ 5.17
3.	E-FOD	BOI	<b>87.23 <math>\pm</math> 7.71</b>	<b>0.86 <math>\pm</math> 0.06</b>	11.53 $\pm$ 0.26	<b>12.20 <math>\pm</math> 3.46</b>	<b>30.32 <math>\pm</math> 9.96</b>

## Left Arcuate Fasciculus

	Local model	Mask	Bundle vol. ( $cm^3$ )	Dice index	Average length (cm)	% of valid streamlines	Efficiency (%)
1.	FOD	WM	54.21 $\pm$ 9.49	0.70 $\pm$ 0.08	10.61 $\pm$ 1.30	1.23 $\pm$ 0.45	4.92 $\pm$ 1.94
2.	FOD	BOI	56.27 $\pm$ 10.06	0.70 $\pm$ 0.08	10.78 $\pm$ 1.26	1.48 $\pm$ 0.55	7.99 $\pm$ 3.28
3.	E-FOD	BOI	<b>110.03 <math>\pm</math> 10.23</b>	<b>0.75 <math>\pm</math> 0.06</b>	<b>12.29 <math>\pm</math> 0.72</b>	<b>9.74 <math>\pm</math> 2.80</b>	<b>32.26 <math>\pm</math> 11.14</b>

## Right Arcuate Fasciculus

	Local model	Mask	Bundle vol. ( $cm^3$ )	Dice index	Average length (cm)	% of valid streamlines	Efficiency (%)
1.	FOD	WM	35.89 $\pm$ 9.97	0.58 $\pm$ 0.13	9.35 $\pm$ 2.44	0.77 $\pm$ 0.36	2.71 $\pm$ 1.60
2.	FOD	BOI	37.99 $\pm$ 10.26	0.59 $\pm$ 0.13	9.55 $\pm$ 2.37	0.95 $\pm$ 0.44	4.62 $\pm$ 2.69
3.	E-FOD	BOI	<b>81.84 <math>\pm</math> 12.99</b>	<b>0.80 <math>\pm</math> 0.06</b>	<b>11.60 <math>\pm</math> 0.82</b>	<b>5.95 <math>\pm</math> 2.46</b>	<b>18.89 <math>\pm</math> 9.15</b>

Table 1: Quantitative results are shown separately for each bundle of interest from three experiments, measures of the 39 validation subjects were averaged together. Values for average and standard deviation are formatted to simplify interpretation. All measures, except average length, are improved by our approach when compared to classical tractography (approach 1 and 2), the difference is statistically significant ( $p < 0.01$ ). Average length remains stable across method, however it was significantly higher for both arcuate fasciculus.

393 are used. The AF are the only bundles with no significant increase between the tracking  
394 using no *a priori* masking and the tracking using only the *a priori* masking, however the  
395 volume significantly increases when enhanced FOD are used. The standard deviation,  
396 for methods 2 and 3, in proportion to the average, is decreasing. The volume of the  
397 reconstructed PT using method 3 is approximately 400% of the volume obtained from  
398 classical tracking, 300% for the CC and 200% for the AF.

399 The reproducibility across datasets was measured by the Weighted-Dice coefficient.  
400 Tractography without priors poorly performed with values between 0.5 (PT right) and  
401 0.7 (AF left). In Figure 8 b), an increase in overlap for all BOI is observed when E-FOD  
402 are used, with Weighted-Dice values all more or less 0.8. Similarly to the volume, the  
403 AF are the only bundles with no significant increase between methods 1 and 2, while

404 the overlap significantly increases when enhanced FOD are used. For methods 2 and  
 405 3, the standard deviation of the Weighted-Dice coefficient is decreasing as the average  
 406 coefficient is increasing. For all bundles, except the left AF, the Weighted-Dice increases  
 407 by 20% when method 3 is used instead of the classical tracking.

408 The average length and standard deviation was computed to evaluate the shape

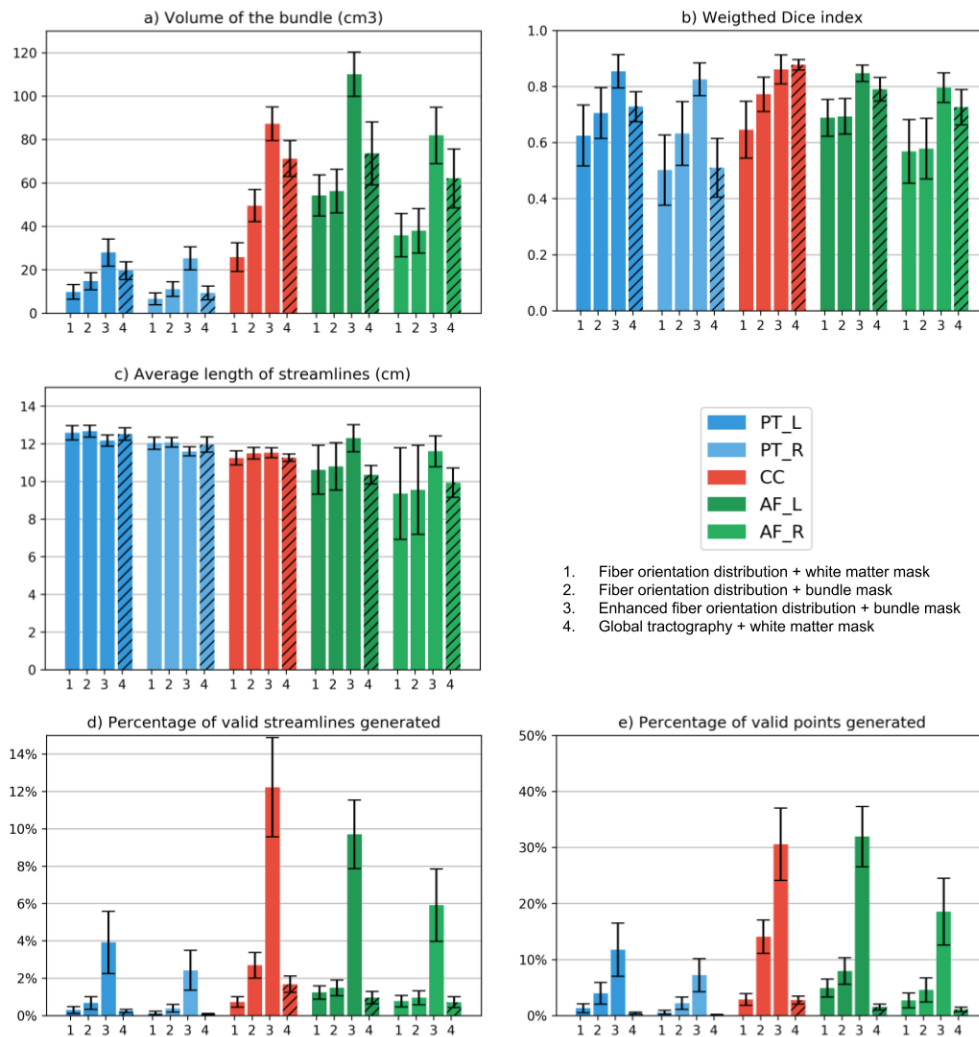


Figure 8: Quantitative measures for each BOI across the 3 tracking algorithms. Results from global tractography is added to provide more context, but comparison is partly “unfair” as many variables cannot be controlled in the same way. The Results are shown for probabilistic tracking with PFT. Graphs for deterministic and probabilistic versions of the algorithms with and without PFT are also available in the [Annexes](#) Section



409 coherence of each bundle. Globally, the average length of most BOI remained similar for  
410 each method, as seen in Figure 8 c). However, for the AF, going from methods 2 to 3,  
411 the average length increased and the standard deviation decreased. This can be observed  
412 more easily in Table 1. As mentioned earlier (Figure 7), this is due to streamlines reaching  
413 further inside the lateral gyri.

414 Finally Figure 8 d) and e) and the last two columns in Table 1 show measures of  
415 efficiency. The use of adapted tracking masks (method 2) is not remarkably influenc-  
416 ing the percentage of valid streamlines. However, integrating enhanced FOD (method 3)  
417 significantly increases efficiency. A tractogram with one million streamlines, each stream-  
418 line with more or less one hundred points, would need one hundred million iterations.  
419 However, not all streamlines have the same number of points depending on their length.  
420 When adapted tracking masks (method 2) are used, most invalid streamlines are quickly  
421 stopped and thus a large number of iterations avoided. Also, it is important to note that  
422 the percentage of valid streamlines and efficiency are improved but that they are still  
423 under 15% and 40% respectively, which leaves plenty of room for further improvements.

424 Similar trends can be observed in the Annexes Section for probabilistic tractography  
425 (without particle filtering). Bundle-specific tractography also improves reconstruction  
426 when using deterministic algorithms, the difference between classical deterministic and  
427 deterministic bundle-specific tractography was statistically significant ( $p < 0.01$ ). This  
428 shows that most algorithms using FOD as an input need orientational priors to better  
429 reconstruct bundle of interest.

430 Results from MITK global tractography [Neher et al., 2012] were overall superior to  
431 all classic tractography algorithms used for the experiments, as seen in Annexes Fig-  
432 ures B.10,B.11,B.12,B.13. However, bundle-specific probabilistic tractography always  
433 generate bundles with higher volume and higher reproducibility across subjects compared  
434 to global tractography. The orientational prior used with probabilistic tractography (with  
435 or without PFT) achieve better results while decreasing computational needs.

#### 436 4. Discussion

437 Our bundle-specific tractography algorithm is designed to address the poor-spatial-  
438 extent challenge and the sensitivity-specificity trade-off of tractography. Contributions  
439 are: i) novel bundle-specific anatomical and orientational priors directly incorporated  
440 in the tractography process to boost streamline tracking in hard-to-track regions, ii)  
441 results that show increased reproducibility, sensitivity, and specificity of PT, CC, AF  
442 bundle reconstructions in the complex centrum semiovale region, and iii) a new BST  
443 algorithm with increased efficiency and reduced overall computation time. The main  
444 methodological innovation is the novel local fiber orientation distribution enhancement  
445 methodology based on white matter bundle priors. These additions were shown to yield  
446 better spatial coverage of the pyramidal tract, corpus callosum, and arcuate fasciculus,  
447 increasing the quality of the extent of fanning reaching the cortex, helping to accurately  
448 represent the shape of each fascicle. Increase in volume is not a direct measure of the  
449 quality of a bundle reconstruction. The use of a strict anatomical definition based on the  
450 literature is fundamental to correctly address this concern. The definition was designed  
451 to reduce as much as possible the number of false positives, meaning that significant

452 increase in volume cannot be accounted by an increase in outliers, spurious streamlines  
453 or contributions from other bundles. As mentioned earlier, tracking is never allowed  
454 outside of the initial white matter tracking mask. Hence, increase in volume cannot  
455 come from “new voxels” added by our algorithm. The increase in volume was observed  
456 in regions that initially lack fanning reaching the cortex, which is a common difficulty  
457 for classical tractography [Girard et al., 2014; St-Onge et al., 2017]. It is important to  
458 note that the FOD enhancement affects the mathematical properties of the FOD. The  
459 E-FOD should not be used to compute FOD metrics such as the AFD [Raffelt et al.,  
460 2017] or even NuFO [Tournier et al., 2008] since lobes amplitude changed and no longer  
461 agree with the DWI signal.

#### 462 *Template creation needed for Bundle-Specific Tractography*

463 The creation of an appropriate template of streamlines is crucial for the proposed  
464 method, as mentioned in the Methods Section. The input bundle of interest of the  
465 template needs to be strictly segmented and cleaned of spurious streamlines, while still  
466 representing all the potential anatomical variability across subjects. We acknowledge  
467 that anatomical definition of WM bundles can vary among experts and that there exist  
468 several open controversies in the WM neuroanatomy literature [Forkel et al., 2014;  
469 Meola et al., 2015; Hau et al., 2017]. However, having a consensus on the definition of  
470 the bundle is not necessary to showcase the potential of our Bundle-Specific Tractogra-  
471 phy. Neuroanatomists can debate and converge on the precise definitions of anatomical  
472 bundles, which can then be adjusted into our BST method.

473 Moreover, the nonlinear deformation of the template to the subject’s native space is  
474 done under the assumption that ANTS performs an adequate registration in-between FA  
475 maps. In the case of a different study, with pathology or large brain alterations, such as a  
476 tumor, cyst, severe atrophy, or missing brain regions, the quality of the alignment would  
477 need to be guaranteed manually. Using a tailored template based on a specific cohort  
478 enables our proposed BST method to be fully automatic without relying on manually  
479 placed ROIs to enforce certain directions and ending regions. Pathological brains already  
480 raise numerous challenges for tissue segmentation, registration, classical tractography  
481 and analysis, which all require case-by-case decisions and tuning. For example, WM  
482 lesions for Alzheimer’s disease, multiple sclerosis, traumatic brain injuries do not have  
483 the same underlying causes and tractography could sometimes be allowed to go through  
484 them or not. When all conditions are met and potential pitfalls related to the pathology  
485 are accounted for, BST can yield interesting results and can have positive impacts for  
486 challenging datasets, as illustrated on the fornix reconstruction in an aging study [Rheault  
487 et al., 2018].

488 As atlases of streamlines become more widely available, such as the one of Yeh and  
489 Tseng [2011]; Wasserthal et al. [2018a], different research groups will be able to use these  
490 without having to build their own. As an attempt to facilitate its use and guarantee  
491 the quality of the anatomical priors for well-known pathways, a WM atlas dedicated to  
492 the BST has been designed. This is a step in the right direction to include anatomical  
493 priors to improve tractography and address some of the challenges raised in Maier-Hein  
494 et al. [2017]. To facilitate future investigations and help other researchers to use our  
495 method, a *Nextflow* pipeline [Di Tommaso et al., 2017] has been developed. By providing  
496 configuration files, a lightweight WM atlases of bundles and a singularity environment  
497 [Kurtzer et al., 2017], this pipeline will simplify the usage of our method. Also, researchers

498 with specific needs can easily customize the pipeline and the configuration file and obtain  
499 exactly what they need.

#### 500 *Bundle volume and spatial coverage*

501 The priors on the regions of interests and local orientations noticeably improve the  
502 virtual dissection results by increasing the total volume and the fanning extent. FOD  
503 enhancement helps to overcome tracking difficulties in the crossing regions, allowing more  
504 streamlines to respect the anatomical definition of the bundle of interest (see [Anatomical](#)  
505 [Definition](#) Section). Difficulties encountered in the crossing region would have required a  
506 higher number of seeds per voxel to obtain an appropriate reconstruction for the classical  
507 method, however this approach does not ensure to fully capture the spatial extent. When  
508 FODs are enhanced to support the main directionality of a bundle of interest, crossing  
509 regions become less disorienting during the tractography, thus increasing the number of  
510 streamlines to be considered during segmentation. All this while being more efficient, in  
511 term of valid streamlines after segmentation.

512 As the fanning component of the bundles represent the majority of their volume,  
513 improved fanning has a quantitative impact on the volume. For example, the fanning  
514 of the PT and CC occurs in the 3-way crossing region (Figure 1), traditionally resulting  
515 in a small preponderance of streamlines reaching lateral portions of the primary motor  
516 and somatosensory cortex. The priors largely impact the volume of the bundles (first  
517 column of Table 1). The use of *a priori* seeding tracking masks increases volume as  
518 particle filtering tractography enforces streamline termination in GM regions. The usage  
519 of enhanced FOD increases the volume even more by reducing the potential confusion in  
520 crossings, as picking a bad direction at each step quickly accumulates in terms of error.

#### 521 *Reproducibility*

522 Bundles of interest considered in this project are known to have anatomical variability  
523 at the micro-scale, but at the macro-scale (on the whole bundle level) the AF, CC  
524 and PT are expected to cover the same regions (once in a common space) after the  
525 segmentation described in the [Anatomical Definition](#) Section. We acknowledge that an  
526 identical coverage is not expected, meaning the weighted-dice should not be expected to  
527 be 1.0. However, poor spatial agreement (inter-subject) with the classical tractography  
528 method mainly comes from poor fanning, a typical solution to this problem is to seed  
529 more until the expected shape is obtained and fanning is adequate. The low weighted-  
530 dice value seen from classical method is influenced by the high variability of the fanning  
531 (CC, PT) or from the early-stop of streamlines in the frontal and temporal lobe (AF).  
532 The goal was not to obtain a value of 1.0. The goal was to reduce the variability in  
533 these regions as they were caused by tractography limitations and not explained by the  
534 underlying anatomy. Intra-subject reproducibility could have hidden this pitfall as a  
535 lack of fanning could be reproducible (intra-subject) and would not have reflected if the  
536 expected anatomical shape was achieved.

#### 537 *Computational Performance*

538 Immediately stopping any streamline getting out of the bundle of interest region using  
539 a priori imposed dilated masks directly reduces the number of tractography iterations  
540 and saves computation time without altering the resulting dissection. Such stopping  
541 criteria also decreases the rate of false positives, as streamlines must follow a reasonable

542 path to be considered valid. The efficiency of BST is also increased since streamlines  
543 follow the main direction of the BOI instead of leaving prematurely the tracking mask  
544 without reaching ROI endpoints. By following the appropriate direction in the crossing,  
545 the streamlines have more chance to respect all the bundle definitions, resulting in a  
546 higher amount of valid streamlines.

547 Performance is not just about number of streamlines. The increase in performance  
548 combined with the increase in volume and overlap between subjects (Table 1) shows that  
549 using the proposed method helps to reach stable results more rapidly, while improving  
550 the quality of the bundle of interest.

#### 551 *Future Work*

552 Since the output of the proposed method is in the form of FOD in a widespread format  
553 (spherical harmonics) and binary masks, any algorithm that accepts such input could be  
554 easily adapted. Other forms of tracking (Dipy [Garyfallidis et al., 2014], FSL [Behrens  
555 et al., 2007], MRtrix [Tournier et al., 2012], Real-time tractography [Chamberland et al.,  
556 2014], even Global tractography [Kreher et al., 2008; Christiaens et al., 2015; Reisert  
557 et al., 2011]) could be tried. Algorithms designed to add more *a priori* could also be  
558 tried alongside enhanced-FOD such as surface-enhanced tractography [St-Onge et al.,  
559 2017] and microstructure-informed tractography (AxTract) [Girard et al., 2015]).

## 560 **5. Conclusion**

561 We developed a new bundle-specific tracking (BST) algorithm incorporating novel  
562 anatomical orientational priors directly into the streamline tracing process to address  
563 the poor-spatial-extent challenge and sensitivity-specificity trade-off of WM bundle re-  
564 construction using tractography. This fully automatic method exploits information ex-  
565 tracted from a template of streamlines of bundles of interest to enhance the local modeling  
566 in the desired direction using the *a priori* fiber orientation distribution. It was shown  
567 that the proposed approach improves the spatial coverage and increases the quality of the  
568 fanning in crossing regions, while reducing computational need. Since a stable volume  
569 and sufficient anatomically valid streamlines are reconstructed faster than with classi-  
570 cal techniques, this method helps the exploration of structural connectivity with more  
571 confidence and less biases in white matter bundles metrics. This could have a posi-  
572 tive impact on the neurosciences community using dMRI tractography tract-based and  
573 connectivity-based analyses.

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788 **Appendix A. Anatomical Definition**

789 The PT was extracted following the anatomical definition proposed by [Chenot et al.](#)  
790 [\[2018\]](#) based on a precise manual positioning of individual subcortical regions of interest  
791 (ROI) along the descending pathway of the PT. Three ROIs were therefore drawn in  
792 each hemisphere within the internal capsule, the midbrain and the medulla oblongata  
793 using both b0 and color FA maps. This was performed with TrackVis [\[Wang et al., 2007\]](#).  
794 Additional anatomical ROIs were used from the JHU template [\[Zhang et al., 2010\]](#) once  
795 warped to the native diffusion space of each subject using ANTS non-linear registration.  
796 Streamlines passing through the 3 ROIs, terminating either in the frontal lobe or the  
797 parietal lobe, and not terminating in the cerebellum were considered to compose the PT.

798 The AF was extracted in each hemisphere from a first set of streamlines with one  
799 termination in the frontal lobe and the other either in the temporal lobe or in the oc-  
800 cipital lobe. Then, streamlines that do not pass through the ventral part of the external  
801 capsule (vEC) were considered as composing the AF. Such streamlines are anatomically  
802 constraint to leave the frontal lobe from the superior part of the external capsule and  
803 then present an arcuate shape defining the AF. The vEC ROI was composed of the region  
804 of the JHU template located in the ventral part of the external capsule, namely the infe-  
805 rior fronto-occipital and uncinate ROIs. Note that frontal, temporal and occipital lobes  
806 were composed of the frontal, temporal and occipital cortical gray matter and superficial  
807 white matter regions of the JHU template, respectively.

808 The CC was extracted from a first set of commissural streamlines with one termination  
809 in each hemisphere. A precentral-postcentral ROI, composed of the gray matter and  
810 superficial white matter part of the precentral and postcentral gyri of the JHU template  
811 was created for each hemisphere. Then, the present CC bundle was composed of callosal  
812 streamlines with one termination in each of the precentral-postcentral ROI and passing  
813 through the corpus callosum.

814 It is important to mention that streamlines considered for segmentation come from  
815 a tractogram generated with certain constraints and conditions. All streamlines are  
816 within the subject white matter, respect the length threshold (20mm-200mm), the an-  
817 gular threshold (45 degrees cone aperture for probabilistic and 20 degrees cone aperture  
818 for deterministic) and the minimum relative spherical function threshold of 0.1)

819 **Appendix B. Annexes**

820 *Appendix B.1. Pipeline overview*

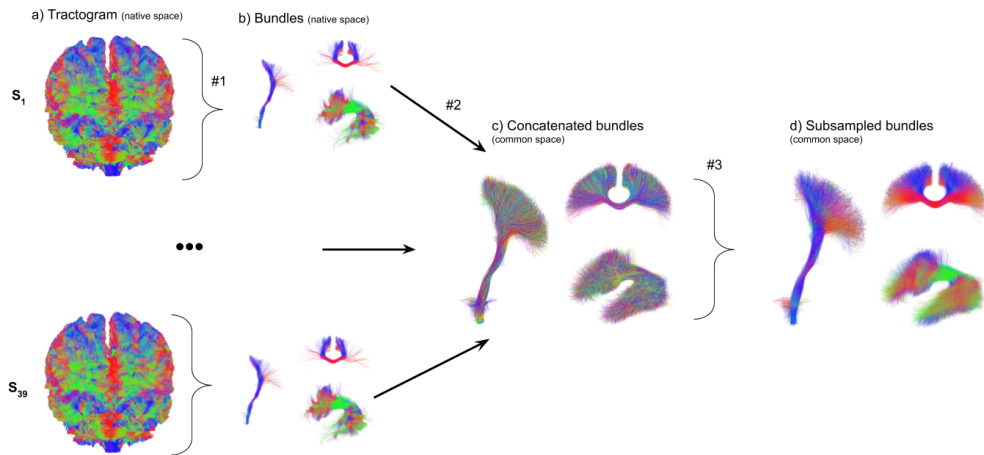


Figure B.9: Overview of the template creation pipeline. From whole brain tractogram (a) bundles are extracted (b) and then warped and concatenated in a common space (c), finally the density bias is reduced by a spatial subsampling (d)

821 *Appendix B.2. Results from all tractography algorithms*

822 In this section results from all tractography type are shown, comparison to global  
823 tractography from the Medical Imaging Toolkit (MITK) [Neher et al., 2012; Kreher et al.,  
824 2008] was added. The tracking was performed with the original FOD and WM mask,  
825 default parameters and  $1 \times 10^8$  iterations. For a fair comparison, each subject whole brain  
826 tractogram was filtered to be similar to the classic tractography. Tractogram was forced  
827 to end in the BOI adapted interface, subsampled to the same number of streamlines and  
828 then segmented using the same automatic method.

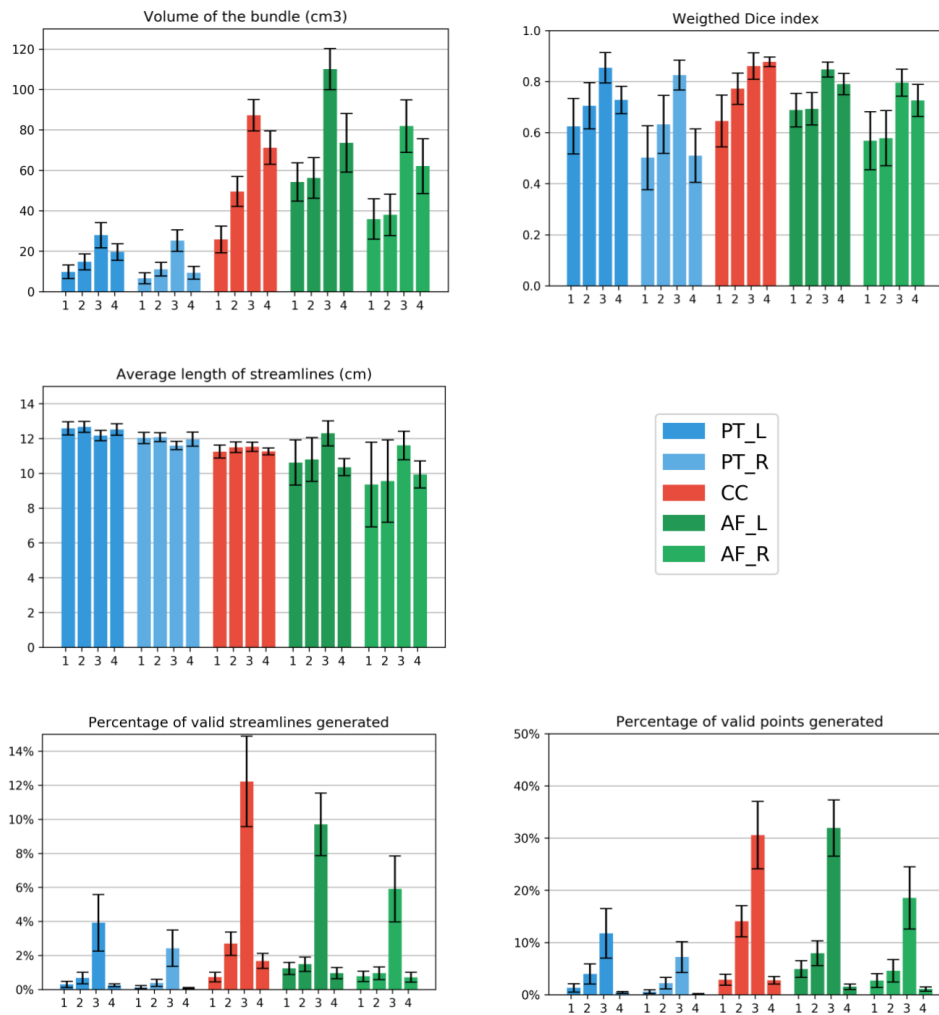


Figure B.10: Results for each BOI across the 4 tracking variations with probabilistic particle filtering tractography, where the fourth method is the global tracking.

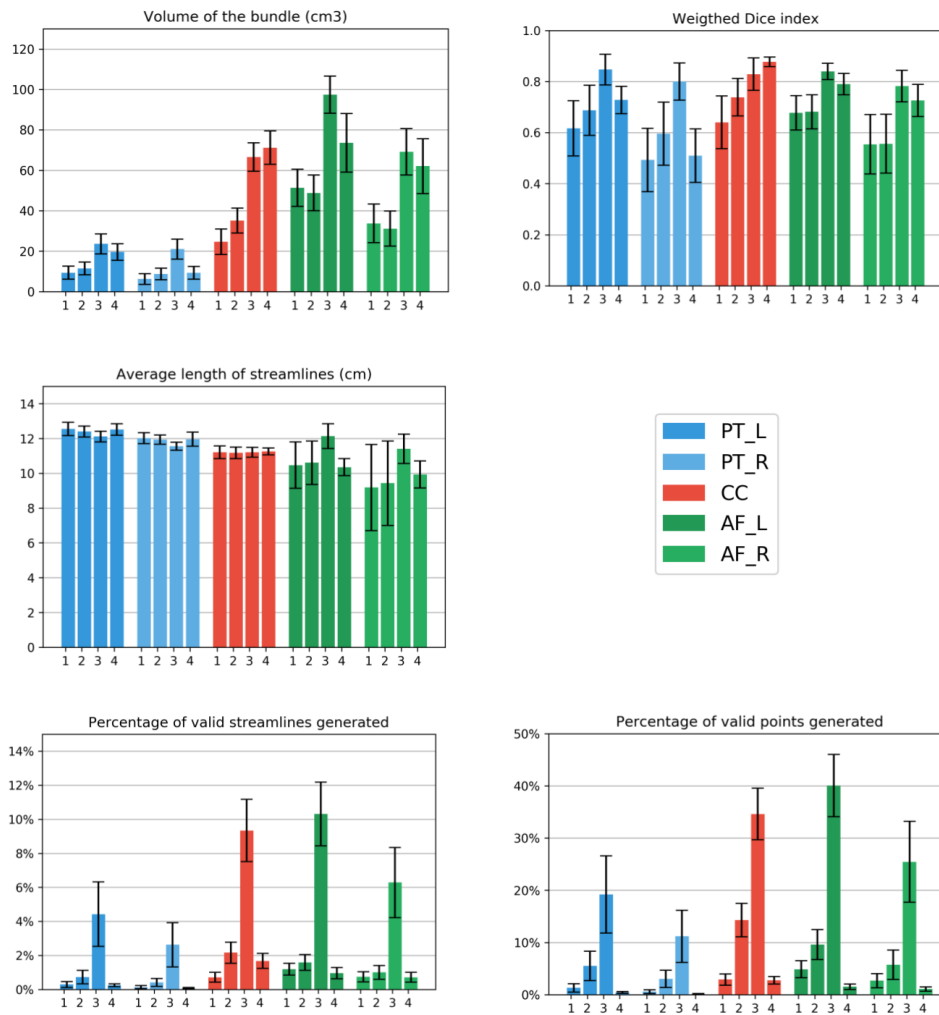


Figure B.11: Results for each BOI across the 4 tracking variations with probabilistic tractography, where the fourth method is the global tracking.

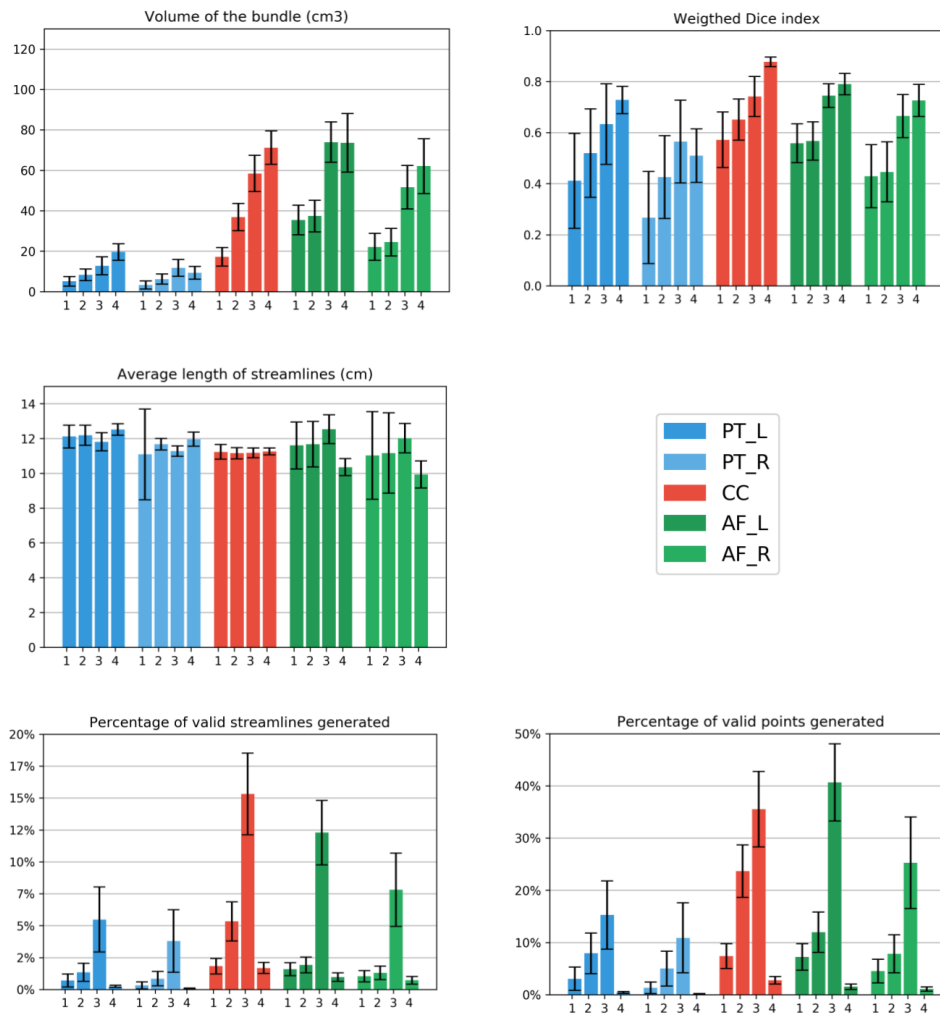


Figure B.12: Results for each BOI across the 4 tracking variations with deterministic particle filtering tractography, where the fourth method is the global tracking.

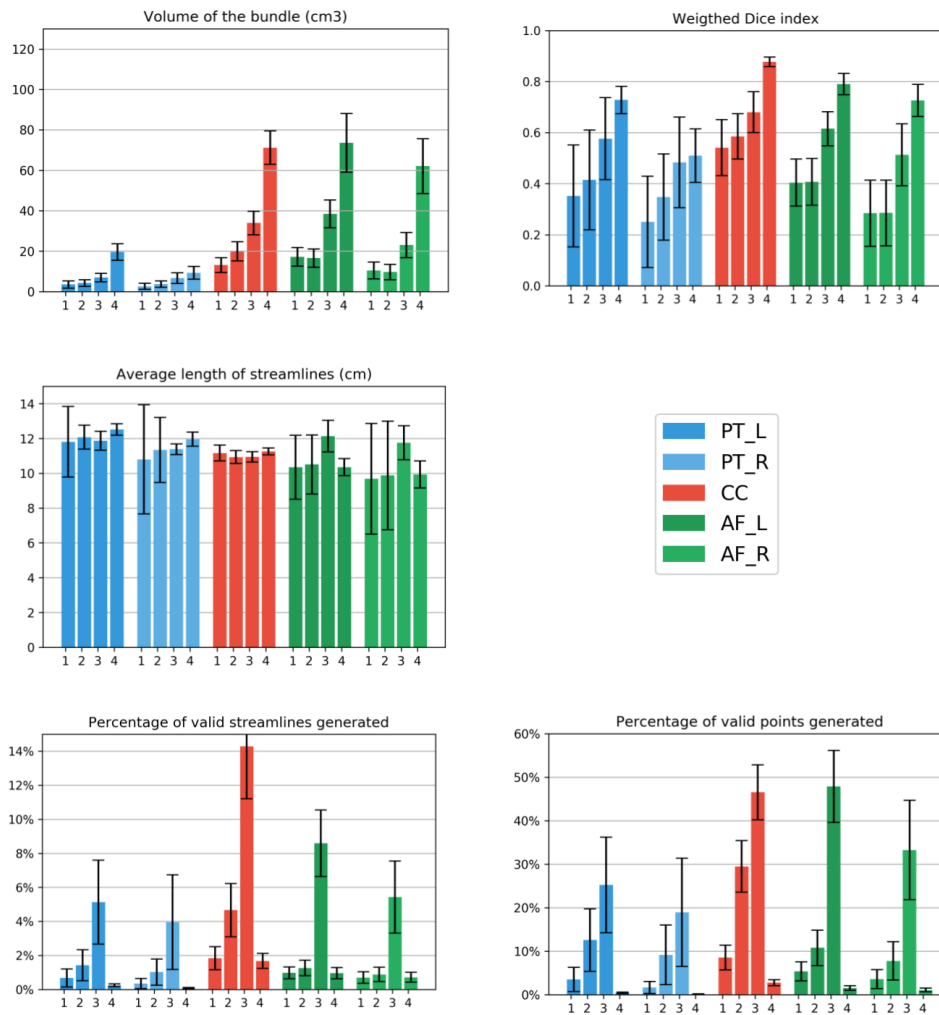


Figure B.13: Results for each BOI across the 3 tracking variations with deterministic tractography, where the fourth method is the global tracking.