

# Bundle-specific tractography with incorporated anatomical and orientational priors

Francois Rheault, Etienne St-Onge, Jasmeen Sidhu, Klaus Maier-Hein,

Nathalie Tzourio-Mazoyer, Laurent Petit, Maxime Descoteaux

# ▶ To cite this version:

Francois Rheault, Etienne St-Onge, Jasmeen Sidhu, Klaus Maier-Hein, Nathalie Tzourio-Mazoyer, et al.. Bundle-specific tractography with incorporated anatomical and orientational priors. NeuroImage, 2019, 186, pp.382-398. 10.1016/j.neuroimage.2018.11.018 . hal-02063638

# HAL Id: hal-02063638 https://hal.science/hal-02063638

Submitted on 13 Nov 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Bundle-Specific Tractography with incorporated anatomical and orientational priors

Francois Rheault<sup>a,\*</sup>, Etienne St-Onge<sup>a</sup>, Jasmeen Sidhu<sup>a</sup>, Klaus Maier-Hein<sup>c</sup>, Nathalie Tzourio-Mazoyer<sup>b</sup>, Laurent Petit<sup>b</sup>, Maxime Descoteaux<sup>a</sup>

<sup>a</sup>Sherbrooke Connectivity Imaging Laboratory (SCIL), Université de Sherbrooke, Canada <sup>b</sup>Groupe d'Imagerie Neurofonctionnelle, IMN, UMR5293, CNRS, CEA, Université de Bordeaux,

Groupe à Imagerie Neurofonctionnelle, IMN, UMR5293, UNRS, CEA, Université de Bordeaux, France

<sup>c</sup>Division of Medical Image Computing, German Cancer Research Center (DKFZ), Heidelberg, Germany

# 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

# 1 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,

<sup>4</sup> 2010; Jbabdi and Johansen-Berg, 2011; Maier-Hein et al., 2017]. In Maier-Hein et al.

<sup>5</sup> [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

Email address: Francois.M.Rheault@USherbrooke.ca (Francois Rheault)

Preprint submitted to Neuroimage

November 13, 2018

<sup>\*2500,</sup> boul. de l'Université, Sherbrooke (Québec) Canada, J1K 2R1

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

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

<sup>40</sup> 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 (ii)), 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.

<sup>41</sup> conclusions. At the tract-based analysis level [Dayan et al., 2016; Cousineau et al., 2017;
<sup>42</sup> Yeatman et al., 2012, 2018], the spatial extent of bundles (in cm<sup>3</sup>) is a measurement

often used to investigate morphological group differences, such as atrophy or asymmetry
[Catani et al., 2007; Song et al., 2014; Chenot et al., 2018]. At the connectome-level, the
number of streamlines in WM bundles connecting all possible pairs of cortical regions
is usually used [Sotiropoulos and Zalesky, 2017]. However, because of a combination of
local and global differences in brain geometry and WM configurations, certain subjects
may have easier-to-track bundles than other subjects, which results in WM bundles
that fill-up in spatial extent before others and thus have artificially larger number of

streamlines. Two strategies exist to attempt overcoming these issues: 1) a whole brain
 tractography with millions of streamlines followed by manual, clustering or advanced
 filtering techniques, 2) a tailored ROI-based tractography.

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

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

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

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

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

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

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

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

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

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

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

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

#### 155 2. Methods

<sup>156</sup> 2.1. Bundle-Specific Tractography

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

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

Our BST approach can be applied to any bundle of interest with the previous 3 steps. We now detail each of these steps before describing the datasets and how it was applied 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.

<sup>171</sup> Building the templates of streamlines

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

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

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

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

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

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

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

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

# 222 Anatomical priors: Tractography map creation

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

# 236 Orientational priors: Enhancing fiber orientations

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

To achieve this "prioritization" of FOD lobes, the local orientation histogram from nearby segments of streamlines is computed at every voxel. This method is based on a TOD map estimated from the template of streamlines, as originally introduced [Dhollander et al., 2014]. Improvements related to the FOD field aiming to constraint tractography spatially were proposed in the past [Portegies et al., 2015; Reisert and Kiselev, 2011].

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

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

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

# 278 2.2. DWI Datasets

For this work the templates and experiments were performed with the BIL&GIN database [Mazoyer et al., 2016]. The datasets are composed of T1-weighted and diffusionweighted 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
- sphere for averaging, on a single shell ( $b = 1000 \ s/mm^2$ ) with a 2 mm isotropic resolution.
- $_{\tt 284}$   $\,$  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

of order 6 Tournier et al. [2008]; Descoteaux et al. [2009].

# 287 2.3. Template creation

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

# 305 2.4. Experiments, Evaluation, and Statistical analysis

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

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

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

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

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

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

### 367 3. Results

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

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

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

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

392



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	Magle	Bundle	Dies inder	Average	% of valid	Efficiency
	model	Mask	vol. $(cm^3)$	Dice index	length (cm)	streamlines	(%)
1.	FOD	WM	$9.80 \pm 3.42$	$0.63\pm0.12$	$12.58\pm0.38$	$0.29\pm0.20$	$1.30\pm0.92$
2.	FOD	BOI	$14.70 \pm 4.00$	$0.71 \pm 0.10$	$12.66 \pm 0.32$	$0.67\pm0.38$	$4.01 \pm 2.45$
3.	E-FOD	BOI	$27.95 \pm 6.24$	$0.86 \pm 0.06$	$12.16 \pm 0.30$	$3.92 \pm 1.95$	$11.73 \pm 6.49$

#### Right Pyramidal Tract

	Local	Mask	Bundle	Dice index	Average	% of valid	Efficiency
	model		vol. $(cm^3)$		length (cm)	streamlines	(%)
1.	FOD	WM	$6.56 \pm 2.74$	$0.51\pm0.15$	$12.03\pm0.32$	$0.14 \pm 0.10$	$0.58\pm0.42$
2.	FOD	BOI	$11.08 \pm 3.42$	$0.64\pm0.13$	$12.07\pm0.26$	$0.38\pm0.22$	$2.21 \pm 1.32$
3.	E-FOD	BOI	$25.27 \pm 5.33$	$0.83 \pm 0.06$	$11.59\pm0.24$	$2.42 \pm 1.19$	$7.26 \pm 3.95$

Corpus Callosum

	Local	Mask	Bundle	Dice index	Average	% of valid	Efficiency
	model		vol. $(cm^3)$		length (cm)	streamlines	(%)
1.	FOD	WM	$25.78 \pm 6.58$	$0.65\pm0.11$	$11.25\pm0.37$	$0.72\pm0.33$	$2.89 \pm 1.39$
2.	FOD	BOI	$49.51 \pm 7.40$	$0.78\pm0.07$	$11.49 \pm 0.31$	$2.68\pm0.85$	$14.09 \pm 5.17$
3.	E-FOD	BOI	$87.23 \pm 7.71$	$0.86\pm0.06$	$11.53 \pm 0.26$	$12.20\pm3.46$	$30.32 \pm 9.96$

#### Left Arcuate Fasciculus

	Local	Mask	Bundle	Dice index	Average	% of valid	Efficiency
	model		vol. $(cm^3)$		length (cm)	streamlines	(%)
1.	FOD	WM	$54.21 \pm 9.49$	$0.70\pm0.08$	$10.61 \pm 1.30$	$1.23 \pm 0.45$	$4.92 \pm 1.94$
2.	FOD	BOI	$56.27 \pm 10.06$	$0.70\pm0.08$	$10.78 \pm 1.26$	$1.48\pm0.55$	$7.99 \pm 3.28$
3.	E-FOD	BOI	$110.03\pm10.23$	$0.75\pm0.06$	$12.29\pm0.72$	$9.74 \pm 2.80$	$32.26 \pm 11.14$

#### Right Arcuate Fasciculus

	Local	Mask	Bundle	Dice index	Average	% of valid	Efficiency
	model		vol. $(cm^3)$		length (cm)	streamlines	(%)
1.	FOD	WM	$35.89 \pm 9.97$	$0.58\pm0.13$	$9.35 \pm 2.44$	$0.77\pm0.36$	$2.71 \pm 1.60$
2.	FOD	BOI	$37.99 \pm 10.26$	$0.59\pm0.13$	$9.55 \pm 2.37$	$0.95\pm0.44$	$4.62 \pm 2.69$
3.	E-FOD	BOI	$81.84 \pm 12.99$	$0.80\pm0.06$	$11.60\pm0.82$	$5.95 \pm 2.46$	$18.89 \pm 9.15$

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.

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

The reproducibility across datasets was measured by the Weighted-Dice coefficient. Tractography without priors poorly performed with values between 0.5 (PT right) and 0.7 (AF left). In Figure 8 b), an increase in overlap for all BOI is observed when E-FOD are used, with Weighted-Dice values all more or less 0.8. Similarly to the volume, the AF are the only bundles with no significant increase between methods 1 and 2, while the overlap significantly increases when enhanced FOD are used. For methods 2 and 3, the standard deviation of the Weighted-Dice coefficient is decreasing as the average coefficient is increasing. For all bundles, except the left AF, the Weighted-Dice increases by 20% when method 3 is used instead of the classical tracking.



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

408

Figure 8: Quantitative measures for each BOI across the 3 tracking algorithms. Results from global tractography is added to provide more context, but comparaison 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

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

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

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

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

# 436 4. Discussion

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

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

# <sup>462</sup> Template creation needed for Bundle-Specific Tractography

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

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

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

with specific needs can easily customize the pipeline and the configuration file and obtainexactly what they need.

# 500 Bundle volume and spatial coverage

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

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

#### 521 Reproducibility

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

# 537 Computational Performance

Immediately stopping any streamline getting out of the bundle of interest region using a priori imposed dilated masks directly reduces the number of tractography iterations and saves computation time without altering the resulting dissection. Such stopping criteria also decreases the rate of false positives, as streamlines must follow a reasonable path to be considered valid. The efficiency of BST is also increased since streamlines
follow the main direction of the BOI instead of leaving prematurely the tracking mask
without reaching ROI endpoints. By following the appropriate direction in the crossing,
the streamlines have more chance to respect all the bundle definitions, resulting in a
higher amount of valid streamlines.

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

# 551 Future Work

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

#### 560 5. Conclusion

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

### 574 Acknowledgements

Thank you to Philippe Poulin and Jasmeen Sidhu for their insights which helped shape this paper. A special thank you to the funding sources for this work, the FRQNT and CREATE-MIA programs. Thank you to the Neuroinformatics Chair of the Sherbrooke University which helped push forward neurosciences research.

#### 579 References

Avants, B.B., Epstein, C.L., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration
 with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Medical

image analysis 12, 26–41.

- Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J., Aldroubi, A., 2000. In vivo fiber tractography using
   dt-mri data. Magnetic resonance in medicine 44, 625–632.
- Behrens, T.E., Berg, H.J., Jbabdi, S., Rushworth, M.F., Woolrich, M.W., 2007. Probabilistic diffusion
   tractography with multiple fibre orientations: What can we gain? Neuroimage 34, 144–155.
- Benedictis, A., Petit, L., Descoteaux, M., Marras, C.E., Barbareschi, M., Corsini, F., Dallabona, M.,
   Chioffi, F., Sarubbo, S., 2016. New insights in the homotopic and heterotopic connectivity of the
   frontal portion of the human corpus callosum revealed by microdissection and diffusion tractography.
   Human brain mapping 37, 4718–4735.
- Calamante, F., Smith, R.E., Tournier, J.D., Raffelt, D., Connelly, A., 2015. Quantification of voxel-wise
   total fibre density: investigating the problems associated with track-count mapping. Neuroimage 117,
   284–293.
- Catani, M., Allin, M.P., Husain, M., Pugliese, L., Mesulam, M.M., Murray, R.M., Jones, D.K., 2007.
   Symmetries in human brain language pathways correlate with verbal recall. Proceedings of the National Academy of Sciences 104, 17163–17168.
- 597 Catani, M., De Schotten, M.T., 2008. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. cortex 44, 1105–1132.
- Catani, M., Howard, R.J., Pajevic, S., Jones, D.K., 2002. Virtual in vivo interactive dissection of white
   matter fasciculi in the human brain. Neuroimage 17, 77–94.
- Chamberland, M., Scherrer, B., Prabhu, S.P., Madsen, J., Fortin, D., Whittingstall, K., Descoteaux,
   M., Warfield, S.K., 2017. Active delineation of meyer's loop using oriented priors through magnetic
   tractography (magnet). Human brain mapping 38, 509–527.
- Chamberland, M., Whittingstall, K., Fortin, D., Mathieu, D., Descoteaux, M., 2014. Real-time multi peak tractography for instantaneous connectivity display. Frontiers in neuroinformatics 8, 59.
- <sup>606</sup> Chekir, A., Descoteaux, M., Garyfallidis, E., Côté, M.A., Boumghar, F.O., 2014. A hybrid approach
   <sup>607</sup> for optimal automatic segmentation of white matter tracts in hardi, in: Biomedical Engineering and
   <sup>608</sup> Sciences (IECBES), 2014 IEEE Conference on, IEEE. pp. 177–180.
- Chenot, Q., Tzourio-Mazoyer, N., Rheault, F., Descoteaux, M., Crivello, F., Zago, L., Mellet, E., Jobard,
   G., Joliot, M., Mazoyer, B., et al., 2018. A probabilistic atlas of the human pyramidal tract in 410
   healthy participants. bioRxiv, 251108.
- <sup>612</sup> Christiaens, D., Reisert, M., Dhollander, T., Sunaert, S., Suetens, P., Maes, F., 2015. Global tractog <sup>613</sup> raphy of multi-shell diffusion-weighted imaging data using a multi-tissue model. Neuroimage 123,
   <sup>614</sup> 89–101.
- Côté, M.A., Girard, G., Boré, A., Garyfallidis, E., Houde, J.C., Descoteaux, M., 2013. Tractometer:
   towards validation of tractography pipelines. Medical image analysis 17, 844–857.
- Cousineau, M., Jodoin, P.M., Garyfallidis, E., Côté, M.A., Morency, F.C., Rozanski, V., GrandMaison,
   M., Bedell, B.J., Descoteaux, M., 2017. A test-retest study on parkinson's ppmi dataset yields
   statistically significant white matter fascicles. NeuroImage: Clinical 16, 222–233.
- Daducci, A., Dal Palú, A., Descoteaux, M., Thiran, J.P., 2016. Microstructure informed tractography:
   pitfalls and open challenges. Frontiers in neuroscience 10, 247.
- pitfalls and open challenges. Frontiers in neuroscience 10, 247.
   Daducci, A., Dal Palù, A., Lemkaddem, A., Thiran, J.P., 2015. Commit: convex optimization modeling
- for microstructure informed tractography. IEEE transactions on medical imaging 34, 246–257.
- Dayan, M., Monohan, E., Pandya, S., Kuceyeski, A., Nguyen, T.D., Raj, A., Gauthier, S.A., 2016.
   Profilometry: a new statistical framework for the characterization of white matter pathways, with
   application to multiple sclerosis. Human brain mapping 37, 989–1004.
- Dell'Acqua, F., Simmons, A., Williams, S.C., Catani, M., 2013. Can spherical deconvolution provide
   more information than fiber orientations? hindrance modulated orientational anisotropy, a true-tract
   specific index to characterize white matter diffusion. Human brain mapping 34, 2464–2483.
- Descoteaux, M., Deriche, R., Knosche, T.R., Anwander, A., 2009. Deterministic and probabilistic
   tractography based on complex fibre orientation distributions. IEEE transactions on medical imaging
   28, 269–286.
- Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale,
   A.M., Maguire, R.P., Hyman, B.T., et al., 2006. An automated labeling system for subdividing the
- human cerebral cortex on mri scans into gyral based regions of interest. Neuroimage 31, 968–980.
  Dhollander, T., Emsell, L., Van Hecke, W., Maes, F., Sunaert, S., Suetens, P., 2014. Track orientation
- density imaging (todi) and track orientation distribution (tod) based tractography. NeuroImage 94, 312–336.
- Di Tommaso, P., Chatzou, M., Floden, E.W., Barja, P.P., Palumbo, E., Notredame, C., 2017. Nextflow
   enables reproducible computational workflows. Nature biotechnology 35, 316–319.
- <sup>641</sup> Fernández-Miranda, J.C., Wang, Y., Pathak, S., Stefaneau, L., Verstynen, T., Yeh, F.C., 2015. Asym-

metry, connectivity, and segmentation of the arcuate fascicle in the human brain. Brain Structure
 and Function 220, 1665–1680.

- Forkel, S.J., de Schotten, M.T., Kawadler, J.M., Dell'Acqua, F., Danek, A., Catani, M., 2014. The
   anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography.
   Cortex 56, 73–84.
- Friston, K.J., Glaser, D.E., Henson, R.N., Kiebel, S., Phillips, C., Ashburner, J., 2002a. Classical and
   bayesian inference in neuroimaging: applications. Neuroimage 16, 484–512.

Friston, K.J., Penny, W., Phillips, C., Kiebel, S., Hinton, G., Ashburner, J., 2002b. Classical and
 bayesian inference in neuroimaging: theory. NeuroImage 16, 465–483.

- Garyfallidis, E., Brett, M., Amirbekian, B., Rokem, A., Van Der Walt, S., Descoteaux, M., Nimmo Smith, I., 2014. Dipy, a library for the analysis of diffusion mri data. Frontiers in neuroinformatics 8,
   8.
- Garyfallidis, E., Brett, M., Correia, M.M., Williams, G.B., Nimmo-Smith, I., 2012. Quickbundles, a
   method for tractography simplification. Frontiers in neuroscience 6, 175.
- Garyfallidis, E., Côté, M.A., Rheault, F., Descoteaux, M., 2016. Quickbundlesx: sequential clustering of
   millions of streamlines in multiple levels of detail at record execution time. ISMRM2016 (Singapore)
   .
- Garyfallidis, E., Côté, M.A., Rheault, F., Sidhu, J., Hau, J., Petit, L., Fortin, D., Cunanne, S., Descoteaux, M., 2017. Recognition of white matter bundles using local and global streamline-based registration and clustering. NeuroImage .
- Ghaziri, J., Tucholka, A., Girard, G., Houde, J.C., Boucher, O., Gilbert, G., Descoteaux, M., Lippé, S.,
   Rainville, P., Nguyen, D.K., 2015. The corticocortical structural connectivity of the human insula.
   Cerebral cortex 27, 1216–1228.
- Girard, G., Fick, R., Descoteaux, M., Deriche, R., Wassermann, D., 2015. Axtract: microstructure-driven
   tractography based on the ensemble average propagator, in: International Conference on Information
   Processing in Medical Imaging, Springer. pp. 675–686.
- Girard, G., Whittingstall, K., Deriche, R., Descoteaux, M., 2014. Towards quantitative connectivity
   analysis: reducing tractography biases. Neuroimage 98, 266–278.
- Guevara, P., Poupon, C., Rivière, D., Cointepas, Y., Descoteaux, M., Thirion, B., Mangin, J.F., 2011.
   Robust clustering of massive tractography datasets. NeuroImage 54, 1975–1993.
- Hau, J., Sarubbo, S., Houde, J.C., Corsini, F., Girard, G., Deledalle, C., Crivello, F., Zago, L., Mellet, E.,
   Jobard, G., et al., 2017. Revisiting the human uncinate fasciculus, its subcomponents and asymmetries
   with stem-based tractography and microdissection validation. Brain Structure and Function 222,
   1645–1662.
- Hau, J., Sarubbo, S., Perchey, G., Crivello, F., Zago, L., Mellet, E., Jobard, G., Joliot, M., Mazoyer,
   B.M., Tzourio-Mazoyer, N., et al., 2016. Cortical terminations of the inferior fronto-occipital and
   uncinate fasciculi: anatomical stem-based virtual dissection. Frontiers in neuroanatomy 10, 58.
- Jbabdi, S., Johansen-Berg, H., 2011. Tractography: where do we go from here? Brain connectivity 1,
   169–183.
- Jeurissen, B., Descoteaux, M., Mori, S., Leemans, A., 2017. Diffusion mri fiber tractography of the brain. NMR in Biomedicine .
- Jeurissen, B., Leemans, A., Tournier, J.D., Jones, D.K., Sijbers, J., 2013. Investigating the prevalence
   of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging.
   Human brain mapping 34, 2747–2766.
- Jones, D.K., 2010. Challenges and limitations of quantifying brain connectivity in vivo with diffusion
   mri. Imaging in Medicine 2, 341.
- Kreher, B., Mader, I., Kiselev, V., 2008. Gibbs tracking: a novel approach for the reconstruction of
   neuronal pathways. Magnetic Resonance in Medicine 60, 953–963.
- Kurtzer, G.M., Sochat, V., Bauer, M.W., 2017. Singularity: Scientific containers for mobility of compute.
   PloS one 12, e0177459.
- Maier-Hein, K.H., Neher, P.F., Houde, J.C., Côté, M.A., Garyfallidis, E., Zhong, J., Chamberland, M.,
   Yeh, F.C., Lin, Y.C., Ji, Q., et al., 2017. The challenge of mapping the human connectome based on
   diffusion tractography. Nature communications 8, 1349.
- Mangin, J.F., Fillard, P., Cointepas, Y., Le Bihan, D., Frouin, V., Poupon, C., 2013. Toward global
   tractography. Neuroimage 80, 290–296.
- Mazoyer, B., Mellet, E., Perchey, G., Zago, L., Crivello, F., Jobard, G., Delcroix, N., Vigneau, M.,
   Leroux, G., Petit, L., et al., 2016. Bil&gin: a neuroimaging, cognitive, behavioral, and genetic
   database for the study of human brain lateralization. Neuroimage 124, 1225–1231.
- Meola, A., Comert, A., Yeh, F.C., Stefaneanu, L., Fernandez-Miranda, J.C., 2015. The controversial

- existence of the human superior fronto-occipital fasciculus: Connectome-based tractographic study
   with microdissection validation. Human brain mapping 36, 4964–4971.
- Mori, S., Crain, B.J., Chacko, V.P., Van Zijl, P.C., 1999. Three-dimensional tracking of axonal pro jections in the brain by magnetic resonance imaging. Annals of Neurology: Official Journal of the
   American Neurological Association and the Child Neurology Society 45, 265–269.
- Mori, S., Wakana, S., Van Zijl, P.C., Nagae-Poetscher, L., 2005. MRI atlas of human white matter.
   Elsevier.
- Mori, S., van Zijl, P., 2002. Fiber tracking: principles and strategies-a technical review. NMR in
   Biomedicine 15, 468–480.
- Moyer, D., Thompson, P.M., Steeg, G.V., 2018. Measures of tractography convergence. arXiv preprint arXiv:1806.04634 .
- Neher, P.F., Stieltjes, B., Reisert, M., Reicht, I., Meinzer, H.P., Fritzsche, K.H., 2012. Mitk global
  tractography, in: Medical Imaging 2012: Image Processing, International Society for Optics and
  Photonics. p. 83144D.
- O'donnell, L.J., Golby, A.J., Westin, C.F., 2013. Fiber clustering versus the parcellation-based connectome. NeuroImage 80, 283–289.
- Pestilli, F., Yeatman, J.D., Rokem, A., Kay, K.N., Wandell, B.A., 2014. Evaluation and statistical
   inference for human connectomes. Nature methods 11, 1058.
- Portegies, J.M., Fick, R.H.J., Sanguinetti, G.R., Meesters, S.P., Girard, G., Duits, R., 2015. Improving
  fiber alignment in hardi by combining contextual pde flow with constrained spherical deconvolution.
  PloS one 10, e0138122.
- Raffelt, D.A., Tournier, J.D., Smith, R.E., Vaughan, D.N., Jackson, G., Ridgway, G.R., Connelly, A.,
   2017. Investigating white matter fibre density and morphology using fixel-based analysis. Neuroimage
   144, 58–73.
- Reisert, M., Kiselev, V.G., 2011. Fiber continuity: an anisotropic prior for odf estimation. IEEE
   transactions on medical imaging 30, 1274–12 83.
- Reisert, M., Mader, I., Anastasopoulos, C., Weigel, M., Schnell, S., Kiselev, V., 2011. Global fiber
   reconstruction becomes practical. Neuroimage 54, 955–962.
- Renauld, E., Descoteaux, M., Bernier, M., Garyfallidis, E., Whittingstall, K., 2016. Semi-automatic
   segmentation of optic radiations and lgn, and their relationship to eeg alpha waves. PloS one 11, e0156436.
- Rheault, F., Houde, J.C., Descoteaux, M., 2017. Visualization, interaction and tractometry: Dealing
   with millions of streamlines from diffusion mri tractography. Frontiers in neuroinformatics 11, 42.
- Rheault, F., Roy, M., Cunnane, S., Descoteaux, M., 2018. Bundle-specific fornix reconstruction for
   dual-tracer pet-tractometry. bioRxiv , 423459.
- Rozanski, V.E., da Silva, N.M., Ahmadi, S.A., Mehrkens, J., da Silva Cunha, J., Houde, J.C., Vollmar,
   C., Bötzel, K., Descoteaux, M., 2017. The role of the pallidothalamic fibre tracts in deep brain
   stimulation for dystonia: a diffusion mri tractography study. Human brain mapping 38, 1224–1232.
- Smith, R.E., Tournier, J.D., Calamante, F., Connelly, A., 2012. Anatomically-constrained tractography:
   improved diffusion mri streamlines tractography through effective use of anatomical information.
   Neuroimage 62, 1924–1938.
- Smith, R.E., Tournier, J.D., Calamante, F., Connelly, A., 2015a. The effects of sift on the reproducibility
   and biological accuracy of the structural connectome. Neuroimage 104, 253–265.
- Smith, R.E., Tournier, J.D., Calamante, F., Connelly, A., 2015b. Sift2: Enabling dense quantitative
  assessment of brain white matter connectivity using streamlines tractography. Neuroimage 119, 338–
  351.
- Song, J.W., Mitchell, P.D., Kolasinski, J., Ellen Grant, P., Galaburda, A.M., Takahashi, E., 2014.
   Asymmetry of white matter pathways in developing human brains. Cerebral cortex 25, 2883–2893.
- Sotiropoulos, S.N., Zalesky, A., 2017. Building connectomes using diffusion mri: Why, how and but.
   NMR in Biomedicine .
- St-Onge, E., Daducci, A., Girard, G., Descoteaux, M., 2017. Surface-enhanced tractography (set).
   NeuroImage .
- Tournier, J., Calamante, F., Connelly, A., et al., 2012. Mrtrix: diffusion tractography in crossing fiber
   regions. International Journal of Imaging Systems and Technology 22, 53–66.
- Tournier, J.D., Yeh, C.H., Calamante, F., Cho, K.H., Connelly, A., Lin, C.P., 2008. Resolving crossing
   fibres using constrained spherical deconvolution: validation using diffusion-weighted imaging phantom
   data. Neuroimage 42, 617–625.
- Voineskos, A.N., O'donnell, L.J., Lobaugh, N.J., Markant, D., Ameis, S.H., Niethammer, M., Mulsant,
   B.H., Pollock, B.G., Kennedy, J.L., Westin, C.F., et al., 2009. Quantitative examination of a novel

- clustering method using magnetic resonance diffusion tensor tractography. Neuroimage 45, 370–376.
  Wang, R., Benner, T., Sorensen, A.G., Wedeen, V.J., 2007. Diffusion toolkit: a software package for
- diffusion imaging data processing and tractography, in: Proc Intl Soc Mag Reson Med, Berlin.
  Wassermann, D., Makris, N., Rathi, Y., Shenton, M., Kikinis, R., Kubicki, M., Westin, C.F., 2016. The
- white matter query language: a novel approach for describing human white matter anatomy. Brain
   Structure and Function 221, 4705–4721.
- Wasserthal, J., Neher, P., Maier-Hein, K.H., 2018a. Tractseg-fast and accurate white matter tract
   segmentation. arXiv preprint arXiv:1805.07103 .
- Wasserthal, J., Neher, P.F., Maier-Hein, K.H., 2018b. Tract orientation mapping for bundle-specific
   tractography. arXiv preprint arXiv:1806.05580.
- Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C.,
   Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in fsl. Neuroimage 45,
   S173–S186.
- Yeatman, J.D., Dougherty, R.F., Myall, N.J., Wandell, B.A., Feldman, H.M., 2012. Tract profiles of
   white matter properties: automating fiber-tract quantification. PloS one 7, e49790.
- Yeatman, J.D., Richie-Halford, A., Smith, J.K., Keshavan, A., Rokem, A., 2018. A browser-based tool
   for visualization and analysis of diffusion mri data. Nature communications 9, 940.
- Yeh, F.C., Tseng, W.Y.I., 2011. Ntu-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. Neuroimage 58, 91–99.
- Yendiki, A., Panneck, P., Srinivasan, P., Stevens, A., Zöllei, L., Augustinack, J., Wang, R., Salat, D.,
  Ehrlich, S., Behrens, T., et al., 2011. Automated probabilistic reconstruction of white-matter pathways
  in health and disease using an atlas of the underlying anatomy. Frontiers in neuroinformatics 5, 23.
- Zhang, F., Wu, W., Ning, L., McAnulty, G., Waber, D., Gagoski, B., Sarill, K., Hamoda, H.M., Song,
   Y., Cai, W., et al., 2018. Suprathreshold fiber cluster statistics: Leveraging white matter geometry
- 784 to enhance tractography statistical analysis. NeuroImage .
- Zhang, Y., Zhang, J., Oishi, K., Faria, A.V., Jiang, H., Li, X., Akhter, K., Rosa-Neto, P., Pike, G.B.,
   Evans, A., et al., 2010. Atlas-guided tract reconstruction for automated and comprehensive examina-
- tion of the white matter anatomy. Neuroimage 52, 1289–1301.

# 788 Appendix A. Anatomical Definition

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

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

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

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

# <sup>819</sup> 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)

# <sup>821</sup> Appendix B.2. Results from all tractography algorithms

In this section results from all tractography type are shown, comparaison to global tractography from the Medical Imaging Toolkit (MITK) [Neher et al., 2012; Kreher et al., 2008] was added. The tracking was performed with the original FOD and WM mask, default parameters and 1x10<sup>8</sup> iterations. For a fair comparaison, each subject whole brain tractogram was filtered to be similar to the classic tractography. Tractogram was forced to end in the BOI adapted interface, subsampled to the same number of streamlines and 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.