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1 | INTRODUCTION

Diffusion MRI (dMRI) uses a specific type of MRI sequence that is sensitive to the random microscopic motion (or diffusion) of water molecules. The coherent arrangement of fibers in brain tissue introduces a directional dependence to this motion, as water molecules are less hindered along the fibers than in their perpendicular orientation. By measuring the dMRI signal for each imaging voxel along a number of non-collinear orientations, the local fiber orientations can be assessed throughout the tissue of interest. These local fiber orientations can then be pieced together to infer long-range pathways connecting distant regions of the brain, a process that is most often called fiber tracking or fiber tractography.

The ability of dMRI-based fiber tractography to delineate the white matter fiber pathways of the brain non-invasively has raised possibilities for clinical applications and offers enormous potential for the study of brain anatomy, development, and even function. To understand how the brain operates as a whole, not only do we need to understand what cortical regions are active; it is also important that the physical connections that mediate information transfer between the regions are mapped out.

The ability of fiber tractography to delineate non-invasively the white matter fiber pathways of the brain raises possibilities for clinical applications and offers enormous potential for neuroscience. In the last decade, fiber tracking has become the method of choice to investigate quantitative MRI parameters in specific bundles of white matter. For neurosurgeons, it is quickly becoming an invaluable tool for the planning of surgery, allowing for visualization and localization of important white matter pathways before and even during surgery. Fiber tracking has also claimed a central role in the field of “connectomics,” a technique that builds and studies comprehensive maps of the complex network of connections within the brain, and to which significant resources have been allocated worldwide. Despite its unique abilities and exciting applications, fiber tracking is not without controversy, in particular when it comes to its interpretation. As neuroscientists are eager to study the brain’s connectivity, the quantification of tractography-derived “connection strengths” between distant brain regions is becoming increasingly popular. However, this practice is often frowned upon by fiber-tracking experts. In light of this controversy, this paper provides an overview of the key concepts of tractography, the technical considerations at play, and the different types of tractography algorithm, as well as the common misconceptions and mistakes that surround them. We also highlight the ongoing challenges related to fiber tracking. While recent methodological developments have vastly increased the biological accuracy of fiber tractograms, one should be aware that, even with state-of-the-art techniques, many issues that severely bias the resulting structural “connectomes” remain unresolved.

KEYWORDS
brain, connectivity, diffusion MRI, fiber tracking, global, probabilistic, quantification, white matter

Abbreviations used: 3D, three dimensional; dMRI, diffusion MRI; dODF, diffusion orientation distribution function; DTI, diffusion tensor imaging; FA, fractional anisotropy; fODF, fiber orientation distribution function; ODF, orientation distribution function; ROI, region of interest; SNR, signal-to-noise ratio; TDI, track density imaging; uODF, uncertainty orientation distribution function
In the last decade, fiber tracking has become the method of choice to investigate quantitative MRI parameters in specific bundles of white matter for a wide range of diseases, including, but not limited to, Alzheimer’s disease, schizophrenia, stroke, and epilepsy. For neurosurgeons, fiber tractography is quickly becoming an invaluable tool for the planning of surgery, allowing for visualization and localization of important white matter pathways before and even during surgery.6 Fiber tracking has also claimed a central role in the field of “connectomics,” a technique that builds and studies comprehensive maps of the complex network of connections within the brain,7 and to which significant resources are allocated worldwide.8,9

Despite its unique abilities and exciting applications, fiber tracking is not without controversy.10-13 On the one hand there are the enthusiasts, who are eager to apply this appealing technique to better understand the human brain. Typically, these people use fiber tracking software, and often as a black box. On the other hand, there are the so-called cynics,6 who say that many of the findings obtained with fiber tracking should be taken with a grain of salt. These people are very well aware of the potential pitfalls and limitations of fiber tracking and feel that fiber tracking is frequently abused or that fiber tractography based results are often misinterpreted. Interestingly, these cynics are often the same people who actually developed the fiber tracking tools in the first place. In light of this ongoing controversy, this paper will provide an overview of the key concepts of tractography, the technical considerations at play, and the different types of tractography algorithm, as well as the common misconceptions and mistakes that surround them. We will also highlight the ongoing challenges related to fiber tracking.

We understand that, by focusing on the challenges and limitations of fiber tracking, our views in this review article may come across as pessimistic to some readers. However, our hope is that it will open many eyes and urge people to reflect on the intrinsic limitations of tractography. At the same time, we hope that the naked truth presented here will be an inspiration for developing the next generation of fiber-tracking algorithms.

2  KEY CONCEPTS AND TERMINOLOGY

This section formally introduces fiber tracking and its most fundamental terminology. It also establishes the common nomenclature related to white matter nerve fibers that will be used throughout this review.

2.1  White matter fibers

Although fiber tracking can be performed on various fibrous tissue types such as cardiac muscle,14 skeletal muscle,15 ligaments,16 peripheral nerves,17 and renal pyramids,18 its primary application has been the central nervous system and more particularly the brain’s white matter. Given the topic of this special issue, we will focus on brain fiber tracking in this review.

The brain’s white matter is composed predominantly of bundles of myelinated nerve fibers. A nerve fiber (or axon) is a long, threadlike extension of a nerve cell (or neuron) that connects specific brain regions and relays information by means of electrical impulses. These fibers are tightly packed together into fiber tracts, fiber bundles, or fasciculi, which share a common origin and destination.

The full wiring diagram of the brain, in all its complexity, is often called the connectome.19,20 Capturing the full connectome can be regarded as the holy grail of fiber tractography (and perhaps even of the whole of neuroscience for that matter), as it will provide us with unprecedented insight into the brain’s architecture and, ultimately, the functioning of the brain.

2.2  Fiber tractography

In its most straightforward form, fiber tractography assumes that each imaging voxel is characterized by a single predominant fiber orientation and pieces together these local orientations to infer global fiber trajectories (see Figure 1). Mathematically, the set of local fiber orientations can be considered as a three-dimensional (3D) vector field and the global fiber trajectories as its streamlines.21-23 A streamline is any curve that along its trajectory is tangent to the vector field and that can be represented as a 3D space curve \( r(s) \), parameterized by its arc length \( s \). In order for a streamline to align with the vector field, the tangent at arc length \( s \) has to be equal to the vector at the corresponding position:

\[
\frac{dr(s)}{ds} = v[r(s)],
\]

where \( r(s) \) denotes the 3D position along the streamline and \( v \) is the 3D vector field. Note that the above equation is a differential equation that can be solved by means of integration:

\[
r(s) = \int_{s_0}^{s} v[r(s)] ds.
\]

where \( r(s_0) = r_0 \) represents the starting point of the streamline, which is often referred to as the seed point. The above process of integrating stepwise orientations into streamlines is generally referred to as streamline tracking or tractography, and the resulting trajectories are often called tracks or pathways. The ensemble of tracks generated using tractography is sometimes called a tractogram.

Some might argue that the term realists would be a better fit.
At this point it should be clear that, while the white matter “fibers” in our brain are physical objects, “fiber tracks” or “streamlines” obtained with fiber tracking are virtual entities that encompass no physical volume and that are related only indirectly to the nerve fibers. For this reason, and for reasons outlined in this review, the terms “connectome” and “tractogram” should not be interchanged freely without proper context. While it is the ultimate goal of fiber tracking to map the human connectome, different tracking approaches will produce very different tractograms given the same connectome, and even the most advanced tracking algorithms are bound to produce only very crude approximations to the actual connectome.

3 | TECHNICAL CONSIDERATIONS

In this section, the main technical considerations when designing a fiber-tracking approach are reviewed.

3.1 | Local fiber orientation estimation

One of the most defining and challenging aspects of designing a tracking algorithm is choosing the underlying model that relates the raw dMRI images to the local fiber orientations. These models all rely on one fundamental assumption: when a number of nerve fibers align themselves along a common orientation, the diffusion of water molecules will be hindered to a greater extent across this orientation than along it. It is important to realize that, in contrast to several imaging techniques such as (polarized)-light microscopy and electron microscopy, where individual fibers can be visualized directly, dMRI can probe white matter fiber orientations only indirectly by looking at the associated average diffusion pattern of the water molecules.

Given that a single white matter voxel can contain hundreds of thousands of fibers, as well as other microstructural tissue constituents, the mapping from diffusion signal to fiber orientations is ill posed. This means that distinctly different fiber configurations such as bending, fanning, crossing, and kissing of fibers can all give rise to the same MRI measurements, making it impossible to distinguish between these cases at the local voxel level. Consequently, it should be clear that fiber tracking can do no more than to make an educated guess at the local fiber orientation(s). As such, tractography results should always be interpreted with extreme caution. A full review of the local fiber models underlying tractography is beyond the scope of this paper; for the technical details, the reader is referred to Reference 3. In the following paragraphs, however, we briefly discuss the main difference between a multi-fiber and a single-fiber model in the context of fiber tractography.

To date, one of the most widely used models for characterizing fiber orientation in terms of measured diffusion signal is the diffusion tensor. Diffusion tensor imaging (DTI) requires only a limited number of raw dMRI images to be acquired, and estimating the diffusion tensor typically requires modest computing resources. However, the diffusion tensor is only capable of distinguishing a single fiber population per voxel (see Figure 2, left). In voxels of complex fiber architecture (e.g. crossing fiber populations or partial volume effect between adjacent fiber populations)
the diffusion tensor is often a poor representation of the underlying fiber orientations,\textsuperscript{28-30} causing false negatives, in which tracking can terminate prematurely,\textsuperscript{31,32} or false positives, in which tracking can switch to an unrelated adjacent tract.\textsuperscript{32,33}

Over the last decade, a range of so-called “higher-order” fiber modeling methods have been proposed, with the capability of estimating the orientations and relative contributions of multiple fiber populations within each voxel, without any explicit assumption regarding the number of underlying fiber populations.\textsuperscript{3,30,34} These methods often represent fiber orientations as a continuous function of the sphere, known as the fiber orientation distribution function (fODF)\textsuperscript{35} (see Figure 2, right). By using the fODF as a propagator, tracking can be performed even in white matter regions with complex fiber architecture.\textsuperscript{32,36} While initially the adoption of “higher-order” models was hampered by unacceptably long scan times and limited software availability, nowadays higher-order fiber-tracking methods have been integrated into a plethora of software packages and can be readily used on clinically feasible data sets.

Although there seems to be a growing consensus in the dMRI community that diffusion tensor tractography should be deprecated,\textsuperscript{6,34,37,38} this wisdom does not seem to have been fully translated into clinical practice. Farquharson et al. found that roughly 98% of the 160 neurosurgical tractography studies published to date reported the use of DTI-based tractography.\textsuperscript{6} Recent studies have shown that DTI-based tractography can result in systematically unreliable and clinically misleading information, while higher-order tractography approaches, using the same dMRI data, clearly demonstrate fiber trajectories that are biologically much more plausible.\textsuperscript{32,36} It should be noted that even the most advanced higher-order models are still only models, i.e. simplified approximations of the physical reality, and that some of the assumptions behind these models might not always hold. As such, even advanced fiber-tracking approaches will still be subject to modeling errors. For a more in-depth discussion on this topic the reader is referred to Reference 3.

### 3.2 | Integration methods

Once the fiber orientations are obtained for each voxel in the brain, the next challenge is linking them together to form the long-range fiber trajectories. The most intuitive way to perform the numerical integration of Equation 2 is by starting at a given seed point $r_0$, obtaining the corresponding local fiber orientation $v(r_0)$, and then following that direction for a short distance $\Delta$, called the step size, to obtain the next point $r_1 = r_0 + v(r_0)\Delta$ on the streamline.\textsuperscript{21} This method, known as Euler integration, can reconstruct the entire pathway by iteratively performing this procedure:

$$r_{i+1} = r_i + v(r_i)\Delta.$$  \hspace{1cm} (3)

Note that Euler integration is a first-order integration method and assumes that the orientation $v(r)$ is constant at the length scale of step size $\Delta$, which will make this method highly susceptible to overshoots in highly curved regions, especially for larger step sizes (see Figure 3). Higher-order numerical integration schemes, such as Runge-Kutta integration, take into account the variations of $v$ between $r_i$ and $r_{i+1}$ and are much less susceptible to these integration errors.\textsuperscript{23,29} It should be clear at this point that, even when using higher-order integration methods, the sheer
step-by-step nature of such a procedure makes streamline fiber tracking extremely susceptible to error propagation: indeed, even small local errors can accumulate along the way, causing tracks to veer off course and jump to unrelated adjacent tracts or to stop prematurely.

3.3 Interpolation methods

From the right-hand sides of Equations 2 and 3 it is clear that the integration process requires that the local fiber orientations are available at arbitrary positions in space, which do not necessarily align with the regular grid of acquired voxel positions. Therefore, a method for interpolating the discrete measurements into continuous space is needed. The simplest method to obtain an estimate of the local fiber orientation at any location is to use nearest-neighbor interpolation.22,40 This method approximates the desired fiber orientation by that of the nearest voxel. However, this approach leads to much greater interpolation errors than approaches that perform a smooth interpolation between grid points39 (see Figure 4). Smooth interpolation methods assume that the fiber orientations between grid points contain contributions from each neighboring point. Most algorithms use trilinear interpolation, where the local fiber orientations are calculated as a weighted sum from the eight voxels nearest to the point of interest, with the weight of each neighboring voxel determined by its distance from the point of interest.21 Some implementations perform trilinear interpolation on the raw diffusion-weighted data and recompute the local fiber orientations based on the interpolated data.21,32 Another approach is to directly interpolate the local fiber orientation
While the latter approach can save a lot of computation time, special care has to be taken if the relationship between the diffusion data and the local fiber orientation information is not linear.41-43

### 3.4 Seed point selection schemes

In general, the integration procedure is performed by starting from a number of seed points that define a specific region of interest (ROI). Typically, these ROIs are defined by the user. This task requires anatomical knowledge and is subject to inter-operator variability. To reduce the operator dependence, ROIs can also be defined from atlas labels, or they can be obtained from cortical activation maps measured with functional MRI. While this latter approach is particularly appealing as it allows for correlation analyses between structural and functional connectivity, it may suffer from ill-defined fiber orientations present in gray matter regions.

An alternative to ROI-based tractography is the use of whole-brain tractography, where tracking is initiated from seed points placed throughout the brain. Whole-brain tractograms are the bread and butter of connectomics, where one wants to study the connections in the brain as a whole. Note that whole-brain tracking can be achieved either by seeding from all white matter voxels or by seeding solely from those voxels that are close to the gray matter-white matter interface, as this is where fibers are known to originate from (see Figure 5). The former strategy has the advantage that the tracking is guaranteed to probe the whole of the white matter. Note, however, that this approach will typically result in an overdefinition of long large white matter bundles, as they are probed by many more seed points.44-46 The overrepresentation of long bundles can be reduced by seeding at the gray matter-white matter interface; however, it is not guaranteed that these trajectories will be able to cover the whole of the white matter, as tracks typically end prematurely due to errors.

![Whole-brain tracking](image)
3.5 | Track termination and acceptance criteria

A final aspect of streamline tractography is choosing when to stop the tracking process. Two criteria are commonly used: local fiber orientation probability and curvature. For example, in DTI tractography it is common to stop a streamline when the fractional anisotropy (FA) falls below a certain threshold value. The rationale behind this criterion is that regions of low FA tend to be associated with high uncertainty in the principal diffusion direction, and therefore a large potential error for the next streamline step. For tractography methods based on high-order reconstruction algorithms, tracking is usually terminated when the local fiber densities as characterized by the IODF along the current tracking orientation fall below a certain threshold, as this indicates a low probability that the local fiber orientation is supported by the data.32,36,47

The curvature threshold imposes a maximum local curvature of the tracks: if the angle between two successive steps is above a predefined threshold, the track is terminated. Since it is unusual to find bends in white matter bundles that have radii of curvature on the scale of an imaging voxel, any sudden change in trajectory is assumed to be caused by artifacts such as noise or model imperfections.

Apart from termination criteria, fiber-tracking algorithms often also employ acceptance/rejection criteria. The most commonly used criterion is that of minimal track length, rejecting short, often spurious, tracks. More advanced criteria are based on anatomical priors, and reject tracks that terminate in cerebrospinal fluid or within white matter and only accept tracks that connect different gray matter regions.44,46

3.6 | Virtual dissection

Specific fiber tracts can be isolated from a whole-brain tractogram by means of track selection.21,48,49 In practice, track selection is performed by defining ROIs through which the tract of interest is known to pass (also referred to as inclusive ROIs or “AND” gates). Tracks that enter these regions are deemed anatomically plausible, and all other tracks are discarded. It is also possible to define regions through which the tract is known not to pass and discard any tracks that enter these regions (also referred to as exclusive ROIs or “NOT” gates). This technique has been successfully used to isolate many different fiber tracts and as such it is sometimes referred to as virtual dissection (see Figure 6). While this technique is very powerful, it relies heavily on prior anatomical knowledge. Alternatively, ROIs obtained from atlases can be combined to automatically extract specific bundles.50

Virtual dissection is particularly useful to study tract shape or for the purpose of tractometry, a set of techniques where quantitative metrics (from either dMRI or other imaging modalities) are extracted in specific fiber tracts.52 In its simplest and most widely used form, tractography-defined ROI analysis, metrics are averaged across all voxels covered by a specific tract,53-57 but more advanced techniques such as profilometry study metrics as a function of arc length along tract-specific exemplar tracks.58-60

4 | FIBER-TRACKING ALGORITHMS

Since its introduction in 1998,61,62 a multitude of papers introducing new tracking algorithms have been published. It is beyond the scope of this paper to review every published technique. Instead we will give a brief overview of families of tracking algorithms based on their most distinguishing features.

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FIGURE 6  Multiple fiber bundle trajectories (right) are virtually dissected from a whole-brain tractogram (left), using tract selection. As an example, part of the cingulum bundle pathways (green) is dissected from the whole-brain tractogram using two circular “AND” gates (white)
4.1 Deterministic versus probabilistic approaches

Deterministic tractography algorithms assume a unique fiber orientation estimate in each voxel, and as such provide a single pathway emanating from each seed point. However, the local fiber orientation estimates are subject to errors due to imaging noise and artifacts, and also due to local model inaccuracies and streamline integration errors, all of which will be reflected in the final global fiber tracks.39,63-65 These errors are especially important in the context of streamline tractography, as measurement uncertainty can propagate.

To characterize this uncertainty, probabilistic tractography algorithms generate a large collection or distribution of possible trajectories from each seed point (see Figure 7). Brain regions that contain higher densities of the resulting trajectories are then deemed to have a higher probability of “connection” with the seed point.66,67 Probabilistic streamline results are, therefore, often quantified by generating visitation count maps of the number of trajectories that traverse each voxel, which can then be analyzed and compared more readily. By treating the problem in a probabilistic fashion, it also becomes possible to track through regions of high uncertainty, where deterministic techniques would usually stop, acknowledging, however, that the probability of “connection” beyond this region is lower.

Typically, probabilistic tractography algorithms build on the deterministic streamline approach described in the previous section, and as such are subject to the same limitations. The fundamental difference is that the orientations for track propagation are drawn at random from a local orientation distribution function (ODF). Note that the exact definition of probabilistic fiber tracking is somewhat contested. Some authors prefer to restrict the usage of the term “probabilistic tractography” to cases where the distribution of tracks emanating from a given seed point is dictated solely by the statistical uncertainty of the local fiber orientation estimates. They typically assume discrete fiber orientations that are subject to noise and model errors, resulting in a distribution of possible fiber orientations (also known as the uncertainty ODF or uODF). Other authors assume that each voxel contains a continuous distribution of fiber orientations (also known as the fiber ODF or fODF) and typically ignore noise and model uncertainty. Here, random samples are drawn from the fODF during track propagation to build a tractogram that aims at reflecting anatomical distribution rather than statistical uncertainty. The implications of these choices will be further discussed in section 5.2.

4.2 Local versus global approaches

The streamline approach described previously is the prime example of a local tractography approach. Tracking is performed in small successive integration steps by following the local fiber orientations that have previously been extracted independently from each other using an appropriate model. An individual integration step is not affected by the previous steps or by other tracks passing the same region (see Figure 8). Local methods are fast and used widely but have important drawbacks. The most apparent is probably that minor errors in the local fiber orientations can accumulate and significantly affect the final result. Another, lesser-known downside is that streamline tractograms are typically a very poor predictor of the dMRI data that was actually measured, resulting in fiber tracks that have little to no quantitative or biological meaning (this issue is further discussed in section 5.4).
Global methods, on the other hand, try to reconstruct all tracks simultaneously by finding the configuration that best describes the measured dMRI data\textsuperscript{68-73} (see Figure 9). In general, this problem has many solutions and selecting a suitable one requires prior knowledge about the expected properties of the trajectories such as local smoothness. Global tracking promises a better stability with respect to noise and imaging artifacts and a better agreement with the actual dMRI data that was acquired. The main problem with global methods is that they rely on stochastic optimization procedures and consequently do not guarantee convergence to a globally optimal solution.\textsuperscript{74} A further problem is the arbitrariness in defining prior knowledge. Specification of prior knowledge that is too strong might lead to inconsistencies with the actual data, potentially resulting in non-existent fiber trajectories. On the other hand, specification of prior knowledge that is too weak might lead to fiber tracks that perfectly match the underlying data, but that make little sense anatomically.

Closely related to global tracking is the concept of filtering a whole-brain tractogram.\textsuperscript{45,74-77} While global fiber tracking uses a bottom-up approach, where a tractogram is directly constructed in one global optimization routine to match the measured dMRI data, tractogram filtering adopts a top-down approach, starting from a dense whole-brain tractogram that was obtained using a local tracking technique and subsequently removing or reweighting tracks in order to match the local track densities to the measured dMRI data.

In between the purely local and purely global methods is the category of "shortest-path" methods, including front evolution, simulated diffusion, geodesic, and graph-based approaches.\textsuperscript{78-87} These methods construct globally optimal pathways from a given seed point, which do not necessarily always align with the locally estimated fiber orientation. However, they do not consider the pathways from all seed points simultaneously, setting them apart from the purely global methods. While these frameworks are often mathematically elegant, they are not widely adopted in software packages and their use in practical studies has been limited.
5 | COMMON MISCONCEPTIONS AND MISTAKES

There are many misconceptions that surround fiber tracking, and not recognizing its many technological pitfalls can easily lead to big mistakes, in particular when it comes to interpretation of fiber-tracking results. For the neuroscientist watching gorgeous 3D shaded renderings of dense fiber tractograms, it is extremely tempting to forget about the virtual nature of fiber tractograms and to start dreaming about quantification. In this section, we will highlight common misconceptions and mistakes and highlight the many pitfalls when it comes to quantification of fiber-tracking results.

5.1 | Taking the path of least hindrance

Fiber tracking is sometimes phrased as “the process of following the path of least hindrance to diffusion.” While this is true to some extent, it implies that the amount of diffusion in a particular direction is directly proportional to the underlying proportion of white matter fibers along that direction. However, due to the nature of diffusion, the proportion of diffusion as a function of orientation (diffusion orientation distribution function, dODF) does not necessarily reflect the underlying fODF. Although water molecules are most likely to diffuse along the fiber orientation, diffusion along other, even perpendicular, orientations is still common. As a consequence, diffusion from closely aligned fiber orientations will be blurred together, implying that only a single fiber population is present. Additionally, the overlapping of diffusion from different fiber populations is known to introduce a bias in the orientations of least hindrance. These issues can only be addressed properly by the introduction of a suitable model for diffusion in white matter.

Nevertheless, the dODF is sometimes credited as a model-free and thus unbiased estimator for intra-voxel fiber orientations, making it the method of choice for fiber tracking propagation. While the dODF is indeed model free, in the sense that it does not assume any model to relate diffusion to white matter fibers, it has been demonstrated repeatedly that it is biased in the way it assesses fiber orientation. Recently, the perceived superiority of dODF tracking was further facilitated by its use in a high-profile paper and by the introduction of the term “high-definition fiber tracking.” However, the sole high-definition aspect of many dODF tracking approaches is that they rely on lengthy acquisitions involving many diffusion directions and very high diffusion weighting strength. On the same data, however, they are unlikely to outperform fODF tracking approaches. For a more in-depth discussion of the dODF in relation to the fiber orientation estimation, the reader is referred to Reference 3.

5.2 | The distinct flavors of probabilistic fiber tracking

Researchers new to the field of fiber tracking are often confused as to how they should interpret probabilistic tractograms and their visitation count maps. This is further complicated by the fact that there are two fundamentally different “schools” of probabilistic fiber tracking. The difference between the two approaches is frequently underappreciated even by researchers who have been in the field for a long time.

The first “school” assumes that a limited number of dominant fiber orientations is present in each voxel. These local fiber orientations are subject to noise and model errors, resulting in a distribution of possible fiber orientations also known as the uODF. By drawing random samples from the uODF, a distribution of fiber tracks can be generated, reflecting this uncertainty. A notable example of this approach is FSL’s probtrackx. Probabilistic uODF tracking will provide an indication of how precise the fiber-tracking results are, with more reproducible fiber trajectories exhibiting higher visitation counts. It should be noted at this point that, while probabilistic uODF tracking gives an indication of the precision of the tracking result, it says nothing about accuracy: even the most reproducible fiber pathways can be highly inaccurate.

The second “school” assumes that each voxel contains a continuous distribution of fiber orientations, also known as the fODF, and ignores the effects of noise and model errors. By drawing random samples from the fODF, this approach is trying to capture the dispersion of fibers within a voxel due to the underlying microstructure. A notable example of this approach is MRtrix’s probabilistic fODF tracking. In a sense, this approach can be regarded as providing more biophysically meaningful tractograms, as it is driven by anatomical dispersion rather than noise characteristics and model inaccuracies.

The difference between the two approaches is most evident when looking at how their visitation count maps should be interpreted. When seeding from Region A and counting the tracks reaching Region B, disregarding all tractography biases, the uODF approach allows its users to assess the probability that Region B is on the dominant pathway. Under the same circumstances (disregarding all tractography biases) and when additionally ignoring the effects of noise, the fODF tractography approach tries to assess the proportion of white matter fibers that reach Region B. It should be clear that, while each “school” aims at providing distinctly different information, they are also highly complementary. As previously suggested by Behrens et al., combining the two approaches could potentially provide both types of information simultaneously. However, convincing results based on this combination have not been published to date.

5.3 | Practical consequences of integration errors and error propagation

When tracking a specific fiber tract, newcomers to the field are often surprised to see that streamline fiber-tracking results differ substantially based on where along the tract they place their seed points (see Figure 10 for an example in the cingulum bundle). This is due to the completely localized, step-wise fashion by which fiber tracking is most often performed. Related to this issue is the fact that fiber tracking is typically non-
5.4 | The slippery slope of quantification

As demonstrated succinctly by Jones et al., both deterministic and probabilistic fiber tracking are more likely to reconstruct tracks that are short and straight and that do not encounter regions of complex fiber configuration (such as crossing and fanning). Indeed, it is easy to see that, as tracks grow longer, the chance of encountering local tractography errors as well as the extent of error accumulation increases, making it more likely for trajectories to terminate prematurely. In curving bundles, integration errors can accumulate to the point at which tracks will stop prematurely.
making it less likely for them to occur than their straight counterparts. It is also easy to see that increased architectural complexity will increase the local fiber orientation uncertainty, resulting in fewer tracks making it from start to finish. These simple issues prohibit straightforward quantification of both deterministic and probabilistic fiber-tracking results. In the following subsections, we will further discuss the two most commonly attempted methods of quantification: voxel-wise track counts and point-to-point connection strengths.

### 5.4.1 Voxel-wise track counts

**Track count mapping or track density imaging (TDI)** starts from a dense whole-brain tractogram and counts the number of tracks passing through each imaging voxel. TDI can provide maps with high anatomical contrast, and when combined with a super-resolution voxel grid can potentially resolve sub-voxel anatomical details. It is only natural that many researchers have been tempted to use track density as a surrogate measure of fiber density. However, there are some serious pitfalls that make track density an unreliable quantitative measure.

First, as TDI is based on fiber tracking, it is very sensitive to noise, the accumulation of noise-induced errors, and model imperfections. However, track-density maps typically appear to be of high signal-to-noise ratio (SNR), even when calculated from low-quality data. This is achieved by starting fiber tracking from a huge number of seed points (of the order of millions) distributed across the brain. In a sense, TDI is hiding the noise present in the raw dMRI images, giving the impression of very high-quality images. However, this approach does not necessarily yield accuracy, and some structures observed in TDI have been shown to be caused by noise rather than anatomy.

Second, TDI is sensitive to the previously mentioned biases towards simple fiber trajectories, potentially artificially reducing fiber densities near high-curvature or high-complexity regions.

Finally, and most importantly, the seeding procedures associated with whole-brain tracking are known to cause overrepresentation of long fiber tracks and underrepresentation of short fiber tracks. It is easy to see that, when seed points are distributed uniformly throughout the brain, longer tracks will be sampled by a larger number of seed points, artificially increasing their local track counts. Conversely, short tracks will be sampled by only a limited number of seed points, artificially decreasing their local track counts.

These issues can be somewhat suppressed by what is called "short-track TDI," where fiber tracking is allowed to continue only for a short distance from the seed point, potentially reducing the problems of error accumulation and tractography biases and reducing the issue of overrepresentation of long fiber tracks. However, the fundamental problem remains: in general, there is no mechanism in place that will ensure that local virtual fiber counts are consistent with the actual local raw dMRI signal. Indeed, for local track densities to make any sense quantitatively, it should be possible to map them back onto the raw dMRI data using a model that relates the fibers to the dMRI signal with minimal residuals (up to a global scaling factor). This requirement can be met either by using a global tracking approach, which satisfies this requirement by its very definition, or by applying filtering approaches that will remove or weight fiber tracks, such that the sum of their contributions fits the measured dMRI signal best.

Figure 11 shows voxel wise track densities obtained from whole-brain probabilistic fiber tracking both with and without prior filtering of the tractograms, as well as apparent fiber densities obtained directly from the raw dMRI data without any help from tractography. When comparing the standard probabilistic fODF track densities (top row) with the apparent fiber densities (bottom row), the highly non-quantitative nature of track-density images is immediately obvious: long, thick, and coherent bundles are vastly overrepresented while the fibers close to the cortex are very much underdefined. It is also clear that filtering can significantly improve the quantitative characteristics of TDI (middle row). However, one could ask oneself "why go through all this trouble to approach something that we could obtain directly from the dMRI data in the first place?" Indeed, while filtering techniques or global tracking can significantly improve the quantitative characteristics of TDI, Calamante et al. recently demonstrated that apparent fiber densities obtained directly through local modeling, without any fiber tracking, are still vastly superior in terms of inter- and intra-subject variability compared with track-density estimates obtained with fiber tracking.

### 5.4.2 Connection strength(s)

Even more than quantifying local fiber densities, probabilistic fiber tracking is now also being used to obtain metrics for structural brain connectivity that can assess how strongly distant brain regions are connected. While there are many possible definitions of connection strength, one typically assumes that it directly relates to the proportion of white matter fibers connecting different regions, with regions that are connected by a larger proportion of fibers deemed to be more strongly connected. It is clear that researchers have been tempted to derive such metrics from fiber tracking. But can it really provide reasonably accurate quantitative estimates of brain connectivity?

When adopting the uODF approach of probabilistic fiber tracking, the answer is clearly "no," as, by definition, it reconstructs only the dominant pathways and their spread is dictated to a large extent by uncertainty and data quality, rather than belief that fibers are actually spreading out.

When adopting the fODF approach, at least in theory, we are closer to an actual measure for quantification; however, in practice we still have to curb our enthusiasm, as pretty much exactly the same limitations that plagued local track counts come into play.

Noise and its unintuitive, long-distance manifestation in fiber tractograms remains cumbersome, even more so since we now want to obtain an accurate representation of fibers over large distances, rather than just at the individual voxel level. Also, when studying connection strengths for the entire brain (aka connectomics), whole-brain seeding will potentially overrepresent long fibers, which will result in biased connectivity matrices with little biophysical meaning. As explained earlier, these issues can be addressed to a large extent by means of global tractography or by means of filtering techniques that will ensure that the tractogram can predict the dMRI signal properly.
The biggest issue with the quantification of connection strengths lies in the well-known bias of tractography towards simple trajectories. As long and curving tracks or tracks that encounter more complex fiber architecture are more likely to terminate, how can long-range connection strengths ever be used reliably in a quantitative fashion? Unfortunately, tractogram post-processing techniques or the concept of global tracking cannot come to the rescue this time, as they only address local track-density issues. In order to prevent tracks from stopping prematurely, the only available mechanism is to introduce strong biologically realistic priors. An interesting approach to this respect is that of Smith et al., where fibers are not allowed to terminate inside the white matter or cerebrospinal fluid, but only at known terminals such as the cortical or deep gray matter. If
an implausible connection does occur, it is either backtracked or rejected. Such simple, but very strong, biological priors have been shown to massively increase the plausibility of long-range fiber connections, especially when used together with filtering techniques or global tracking that ensure that the fiber tractogram accurately predicts the raw dMRI signal.

Figure 12 shows whole-brain tractograms as well as density maps of the tracking endpoints, for different tractography approaches. With conventional tracking, significant numbers of fiber tracks are terminating prematurely within white matter (e.g. in regions of complex fiber architecture) or at the interface with cerebrospinal fluid (left column). Such connections make no sense biologically and are symptomatic of the many fiber-tracking biases. Post-processing of this tractogram does not remedy these issues (middle column). However, by introducing anatomical constraints during fiber tracking, the resulting fiber trajectories no longer stop prematurely within white matter, but evenly cover the white matter-gray matter interface.

Unfortunately, using anatomical constraints does not necessarily mean that we can now rely on fiber tracking to provide connection strengths. While rejecting biologically implausible connections avoids these clearly false connections, it is not guaranteed that this strategy will provide us uniquely with true connections. In fact, a recent simulation study has shown that fiber tracking will produce non-existing fiber bundles (that were never part of the set of ground-truth fiber bundles) even with biological priors in place. What is alarming is that these artificial bundles approximate true anatomical structures very well: they connect cortical areas and appear to be dense and well structured. This leads us to the inconvenient truth that current fiber-tracking techniques cannot be used to reliably quantify long-range structural connectivity.

FIGURE 12 Axial slab visualizations of whole-brain tractograms (top) and their corresponding endpoint density maps (bottom) for standard probabilistic fODF tracking (left), probabilistic fODF tracking + filtering (middle), and anatomically constrained fODF tracking + filtering (right). Although all tractograms appear great, inspection of the tracking endpoints reveals numerous biologically implausible terminals (left). In particular, trajectories end prematurely in regions containing complex white matter configurations (green arrows) or at the cerebrospinal fluid interface (cyan arrows). Filtering the tractogram makes the distribution of endpoints more uniform, but does not prevent the many implausible terminals (middle). Clearly, the issue can only be addressed by imposing anatomical constraints (right).
6 | ONGOING CHALLENGES AND CONTINUING HEADACHES

6.1 | Proper treatment of ambiguous local geometries

Despite the clear advantages of "high-order" models for fiber tracking, distinctly different local fiber geometries, such as crossing, kissing, bending, and fanning, can give rise to the same MRI measurements, making it impossible to distinguish between these cases purely at the voxel level. However, each of these geometries may require different decisions to be taken during track propagation, and failing to distinguish between these cases could adversely affect fiber-tracking outcomes. For example, when tracking through a region with complex local geometry, fiber-tracking algorithms may need to pick a candidate fiber population along which to propagate the current trajectory. A commonly used heuristic is to opt for the fiber population whose orientation is closest to the current tracking direction. While this approach makes perfect sense in a true crossing configuration, in the case of kissing fibers or a sharp bend it will potentially result in both false-positive and false-negative trajectories. Matters become even more complicated in the case of fanning fiber configurations, as one should also take into account the polarity of the fanning. For example, fibers typically diverge as they move towards the cortex, but they converge when tracking in the opposite direction. Failing to account for this asymmetry could lead to a fanning-out of the trajectories in both directions, potentially introducing false positives as fibers move away from the cortex.

While there is no information in the voxel-wise data to disambiguate these local geometries, it is possible to test whether they are supported by the local neighborhood and use this information to make better-informed decisions during fiber tracking. Note that this local support or continuity does not have to be based purely on the trajectories themselves (i.e. geometric), but can also be based on the microstructural features underlying the current trajectory. For example, by assuming that fiber densities and/or axon diameters remain consistent along their trajectory, one can potentially disambiguate e.g. crossing and kissing fibers (assuming that each of the interacting fiber bundles exhibits a significantly distinct microstructural signature). Despite promising in silico results, it remains to be seen whether the fiber bundles constituting ambiguous fiber configurations in vivo exhibit sufficient microstructural contrast to disambiguate them. In general, techniques that disambiguate local fiber geometries do not seem to have found their way into popular fiber-tracking software yet and remain inaccessible to most researchers.

In theory, global tractography methods should already be able to resolve these local ambiguities by their very definition, as they search for the set of continuous trajectories that best explain the full dMRI data, in particular when they are combined with microstructural continuity priors. However, there is currently no clear experimental evidence to support the superiority of global tracking with respect to ambiguous geometries.

6.2 | Tracking near the cortex

Initially, fiber tracking focused on mapping the major deep white matter tracts, leaving the white matter close to the cortex and in the cortical folds as mostly uncharted territory. With a growing interest in connectomics, where the long-range connections between different cortical regions are studied, an accurate mapping of the origins/terminals of the fiber bundles within the cortex has become more important than ever. However, reliable tracking near the cortex and in the cortical folds is challenging. More specifically, fiber-tracking algorithms have a hard time penetrating into the gyri, and if they do manage they tend to propagate more often towards the crowns of the gyri than towards the gyral walls.

The inability of fiber tracking to properly penetrate the gyri can mostly be ascribed to large modeling errors in the local fiber orientation estimation as one approaches the gray matter. While most high-order local fiber models can provide high-quality fiber orientation estimates in voxels containing pure white matter, in voxels partially containing grey matter tissue these models may no longer be appropriate and are known to produce unreliable, noisy fiber orientation estimates. To address this issue, the fiber-tracking community has started to embrace local models that go beyond modeling white matter tissue or axons, and that try to account for the presence of other tissue types or microstructural compartments. This advancement has been made possible by using data acquired with multiple diffusion weighting strengths or b-values (the so called "multi-shell" scheme) and exploiting the unique b-value dependences of the different tissue types or microstructural compartments to tease them apart. While multi-shell data were rarely acquired for the purpose of fiber tracking in the past, these schemes have become increasingly popular in recent years, and can be acquired nowadays within clinically feasible scan times on current MRI hardware. Recent studies have shown that, by simply extending a commonly used white matter model with a gray matter and cerebrospinal fluid component, local fiber orientation estimation and subsequent fiber tracking within the cortical folds can be dramatically improved (see Figure 13).

The tendency of fiber tracking to reach the crowns, rather than the walls, of the gyri is mostly caused by failing to account for ambiguous local geometries. Indeed, as fibers enter the gyrus, the geometry of the cortical folds requires fairly sharp turns for them to cover the whole of the cortical surface and, as explained before, when faced with the option of continuing a straight path or taking a sharp turn, most fiber-tracking algorithms will favor the straight option.

6.3 | Spatial resolution

It should be clear that the above issues of local modeling errors and ambiguous local geometries are closely tied to the spatial resolution available in dMRI. High-definition 3D renderings of dense fiber tractograms have featured on the cover of high-impact neuroscience journals, and they have adorned many scientific presentations and grant proposals. While gazing at these stunning high-resolution visualizations, it is easy to forget that the actual resolution of the MRI data on which the tractograms are based is anything but high definition. To put things into perspective, a typical
96 × 96 dMRI slice amounts to only 0.009 megapixels, which is minuscule compared with your 2 megapixel full-HD computer screen. As voxels become larger, their tissue or microstructural content will become more heterogeneous, requiring more complex models to extract the fiber orientations reliably. In addition, large voxels will also cause larger discontinuities in the field of local fiber orientation estimates, complicating the process of distinguishing between different complex geometries. Currently, obtaining diffusion-weighted images covering the whole brain with a clinical scanner within a reasonable scan time for routine use limits the resolution to at best 2 mm³; to characterize the fine structures of the white matter, and particularly the intricate folding patterns of the cortical surface or the small structures near the deep gray matter (nuclei, brainstem), clearly, a higher spatial resolution is required. Increasing spatial resolution is challenging, as it typically goes hand in hand with either a significant drop in SNR or a significant increase in acquisition time, resulting in either poor-quality data or impractically long scan times. Ongoing improvements in hardware (e.g. increased gradient strength⁸,¹¹⁴-¹¹⁵) as well as clever pulse sequences and matching reconstruction techniques (e.g. simultaneous multi-slice¹¹⁶-¹¹⁷ and super-resolution reconstruction¹¹⁸-¹²¹) have resulted in faster diffusion imaging with limited loss of SNR, allowing dMRI data sets to be acquired at much higher resolutions (see also Figure 13).

6.4 | Angular resolution limits

It is important to realize that the spatial accuracy of fiber tracking is determined not only by the spatial resolution of the data, but also by what is known as angular resolution or ability to resolve small inter-fiber angles. When the angle between two fiber populations drops below a certain threshold, local fiber orientation models can no longer distinguish the distinct fiber populations and fiber trajectories will tend towards the average of the two populations, effectively creating an angular black hole. Such effects can potentially veer a track off course and create completely artificial fiber trajectories.

The angular resolution of an acquisition scheme is determined by the diffusion weighting strength or b-value and by the number or unique diffusion encoding gradient orientations. Experimental evidence suggests that the angular frequency content of the dMRI signal in the brain white matter levels off at a b-value of approximately $b = 3000 \text{s/mm}^2$, suggesting that this b-value achieves the highest practically available angular resolution.¹²² Given this b-value, the minimal number of unique diffusion encoding gradient orientations to fully characterize the angular frequency
content (disregarding noise and artifacts) was estimated to be just 45. This goes to show that, despite terms such as “high-angular-resolution diffusion imaging,” the angular resolution of practical dMRI experiments is fairly limited. As a consequence, even with state-of-the-art high-angular-resolution diffusion imaging and cutting-edge fiber orientation estimation techniques, inter-fiber angles below 30° are rarely resolved, and are a potential source of inaccurate and/or completely artifactual fiber trajectories.

6.5 | False positives

As mentioned earlier, tractography is an ill-posed problem. Locally, many different fiber configurations can lead to the same voxel-wise dMRI signal (branching, kissing, crossing, bottleneck, ...). This also means that, globally, many different track configurations can explain the dMRI signal very well. As shown in References 12 and 13, this leads to important numbers of false-positive tracks and bundles that are thick and “look real.” Out of 96 tractograms submitted to the ISMRM 2015 Tractography Challenge using state-of-the-art methods from 21 international groups, there were on average four false-positive bundles for every valid bundle recovered. While most methods did find the existing true bundles, it is striking to see how current methods produce a number of invalid connections that is much larger than the number of valid ones. The next generation of tractography algorithms is no longer to simply find existing valid connections but to control for the many false-positive connections polluting the tractograms. This is a clear open challenge from tractography and connectomics in general.

6.6 | Sheetography

The question “Sheet happens?” has been a topic of debate in the diffusion imaging society since Wedeen et al. proposed that brain white matter is organized as parallel sheets of interwoven fiber pathways.96 While considered controversial by many researchers,123,124 recent work by Tax et al.125 proposed a mathematical framework to quantify the presence of sheet structure in the brain and demonstrated that several white matter regions indeed show a significant degree of sheet structure. In analogy with streamline tracking one could now consider developing “sheetography” approaches to propagate surfaces in regions where such sheet structure is supported by the underlying dMRI data (Figure 14).

7 | CONCLUSION

It should be clear that fiber tracking is a complicated endeavor involving many steps (local fiber orientation modeling, interpolation, integration/propagation, seeding, masking, stopping criteria, etc.), each incurring potential errors. As these errors tend to accumulate, it is imperative that developers try to tick all the boxes by thoughtfully implementing each of these steps. In the past, new tracking tools have sometimes focused on what sets their implementation apart from other approaches (e.g. local modeling), paying less attention to equally important but less exciting steps (e.g. integration). However, it is more important that also the users are (made) aware of the underlying steps and the corresponding limiting factors, given that they will actually use/interpret the fiber tractograms. As such, in-depth knowledge of the terminology, inner workings, and limitations of fiber tracking is key.

Even using the latest-and-greatest methods and with state-of-the-art data acquisition, fiber tracking is still limited when it comes to quantification and biological interpretation. As stated by Jbabdi and Johansen-Berg, “One frustrating thing about tractography is that it takes a quantitative acquisition method and makes it less quantitative.”88

FIGURE 14  Schematic representation of “sheetography,” the surface-based reconstruction of fiber pathways that are organized as sheets (courtesy of Chantal Tax)
Fiber tracking has delivered truly impressive qualitative delineations of many of the large white matter structures that could not be obtained by any other in vivo imaging technique. Such qualitative delineations are particularly useful for tractography-defined ROI analysis, where quantitative metrics are studied within the voxels spanned by specific fiber tracts, or for more advanced tractometry, where these metrics are studied along tract-specific exemplar tracks. The value of qualitative fiber bundle delineations is also evident in the field of neurosurgery. Especially when using state-of-the-art high order approaches, fiber tracking can be an extremely useful method to guide complicated neurosurgery, as long as the neurosurgeons are aware of the limitations and potential inaccuracies of fiber tracking.

When it comes to quantifying connection strengths and performing connectomics with fiber tracking, one is skating on thin ice. Without a proper high-order model, without anatomical constraints, and without enforcing fidelity of the fiber tracks to the raw dMRI data, quantifying connections using fiber tracking is the equivalent of opening Pandora's box: the resulting "connectomes" will be riddled with false positives and false negatives and the connection strengths will be severely biased by the size, shape, and complexity of the underlying fiber bundle configuration, to such an extent that the biological accuracy of the connectomes becomes highly questionable. By using a proper high-order model, by applying realistic anatomical priors, and by ensuring fidelity of the tractograms to the data, the biological accuracy can be vastly increased and one could potentially start to derive useful connectivity information. While recent comparisons of tractography-created cortical connectomes with data from neuroanatomical tracers have shown that state-of-the-art tractography performs much better than chance, fiber tracking is still far from perfect in detecting neuroanatomical pathways and their corresponding connection strengths. One should be aware that, even using the state-of-the-art techniques and high-quality data, many issues that could potentially bias the resulting "connectomes" remain unresolved, and one has to proceed with extreme caution.

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