Orientation and Tractography

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Introduction

Diffusion MRI tractography is an extremely powerful imaging technique, because it is currently the only in vivo method for tracing large-scale neuronal connections. Other techniques for inferring neuronal connectivity include tracer injection in non-human primates, and post-mortem analysis in analysis. Diffusion MRI gives us the possibility to virtually dissect specific fibre bundles noninvasively. To do this, we must first obtain voxelwise estimates of fibre orientation, and then perform additional post-processing to infer intervoxel connectivity. This review will discuss these two aspects of the tractography problem.

Fibre orientations and confidence

Early white matter fibre tractography used the principal eigenvector from standard diffusion tensor imaging [2] as the voxelwise estimate of fibre orientation. The diffusion tensor model assumes that the diffusion displacement distribution is a single anisotropic Gaussian distribution. In general, if we perform the radial integral of the 3D diffusion displacement distribution, we obtain a 2D surface called the diffusion orientation distribution function (ODF). In the case where the voxel contains predominantly one fibre orientation, the principal eigenvector of the diffusion tensor will point along the (single) maximum of the diffusion ODF. However, if the voxel contains two or more fibre orientations, the principal eigenvector orientation will not be sufficient to describe the fibre geometry. If two fibre populations occupy equal volume fractions of the voxel and cross at ninety degrees, the diffusion ODF described by the diffusion tensor will be pancake shaped, and the principal eigenvector will be undefined. In the presence of noise, it will generally end up in a random direction in the plane of the pancake. In the case where the crossing is at less than ninety degrees, the principal eigenvector will lie in the intermediate direction. If the fibre volume fractions are unequal, the principal eigenvector direction will be biased toward the larger fibre population. In the case of smooth, constant, curvature, the diffusion displacement distribution will be more isotropic, and the principal eigenvector will lie along the tangent orientation. This case of constant curvature is indistinguishable on the subvoxel scale from the case of splay or fanning of fibres, in which case there is also a continuous range of fibre orientations.

For the more complex subvoxel fibre geometries described above, techniques that measure or model either the full diffusion displacement distribution or the fibre orientation distribution function without the assumptions of the single tensor model may be preferable. These high angular resolution techniques include spherical deconvolution [33], q-ball imaging [34], diffusion spectrum imaging [37], Combined Hindered and Restricted Model of Diffusion (CHARMED) [1], multi-tensor approaches [14], and other multi-fibre models, such as Behrens’ ball and multi-stick model [3]. They will be discussed in detail in the next lecture.

Given a voxelwise measure of the fibre orientation or orientations, it is important to quantify our confidence in this measure. When performing diffusion tensor reconstruction, for which the minimal acquisition time is much shorter than for high angular resolution reconstruction, it is possible to repeat the measurement many times to infer the uncertainty associated with the principal
eigenvector. Alternatively, one can compute the tensor from multiple subsets of a larger, redundant acquisition, and employ bootstrap statistical techniques [10] to infer the uncertainty in the fibre orientation [19]. Bootstrap and other statistical techniques have been used recently for high angular resolution diffusion MRI reconstruction methods. In this case, acquisition of multiple repeats of sufficient data to reconstruct the probability distribution for the fibre direction is usually not practical. However, inference of the probability distribution for the fibre orientation(s) can be done using a single high angular resolution dataset using techniques such as the residual bootstrap. The residual bootstrap has been used with q-ball imaging [6, 13] and spherical deconvolution [17, 21]. In addition to bootstrap techniques, Bayesian inference has been used for analysis of q-ball imaging data [11] and the Behrens model [3, 4].

It is important to note here that the fibre orientations measured with diffusion MRI are orientations, not directions. The diffusion displacement distribution function we measure is symmetric: we cannot, with this technique, measure gradients in diffusion, nor can we distinguish between afferent and efferent neuronal fibre bundles.

**Fibre tract reconstruction**

Tractography is the process of going from voxelwise measures of fibre orientation, either single or multiple, to global descriptions of fibre architecture. Early diffusion MRI fibre tractography was posed as an integration problem, and existing integration techniques, such as Euler-Lagrange, and second and fourth order Runge-Kutta (RK4), were employed. The resulting lines are called streamlines. Another integration technique, termed Fibre Assignment using Continuous Tracking (FACT), was developed by Mori et al. [23]. FACT integration alleviates some of the problems associated with constant step size integration by using an intuitive variable step size that terminates at voxel borders. Both Euler and Runge-Kutta approaches require interpolation of the fibre direction, a problem that is still not completely solved, and that requires increased computation time. These various integration techniques have been quantitatively compared by various researchers. For instance, Lazar et al. found that RK4 integration has superior performance in non-divergent fibre orientation fields, whereas FACT has superior performance in divergent fields [20]. All of these integration techniques are in use today, in various software packages for diffusion tractography.

Subsequent to the integration techniques, several surface evolution approaches to tractography were investigated, e.g., [8, 26, 32], particularly in the context of probabilistic tractography, which will be discussed below. The current preference of the field is to use streamline techniques instead of surface evolution, even for probabilistic tractography, as the surface evolution approaches appear to suffer from discretization problems and difficulty handling curvature on the appropriate scale. A slightly different approach to tractography is termed “global tractography”, wherein one assumes a connection exists between two regions, and then infers the most likely path. This has been done using simulated annealing [35] and in a Bayesian framework [16]. Other approaches to tractography include particle filtering [40] and completion fields [22].

The integration process in tractography generally follows the orientation closest to the incoming orientation, propagating in this fashion until one of many stopping criteria is reached. Branching and splay are exceptions, where multiple orientations may be followed [22, 29]. The stopping criteria commonly used include constraining the tractography to voxels with fractional anisotropy above a certain value, constraining the tractography to remain outside of cerebral spinal fluid (CSF) using a CSF map based on the mean diffusivity or other imaging contrasts, and constraining the curvature of the tract. The tracts are defined using one or more tract-delineating regions of interest.
(ROIs), which are often called “way points”. All paths that go through all of the tract-delineating ROIs are returned. These ROIs may be as precise or broad as the user desires, and reflect priors about the anatomy to be reconstructed. The user may also define exclusion ROIs to remove tracts that pass through specific regions. The integration can be started in one tract-delineating ROI, or in all voxels, retaining only the pathways that pass through the tract-delineating ROIs [9]. The latter approach is often called “brute force” tractography, and while more computationally expensive, it will result in a superset of the former approach, because the integration result is sensitive to direction of propagation. It is also common to seed the streamlines at more than one point within each start voxel [7], thus facilitating branching. This can be done on a subvoxel grid, or in the case of the single tensor, on the plane perpendicular to the principal eigenvector orientation.

Tract delineating ROIs can be defined manually using a well-defined protocol guided by our prior knowledge of the neuroanatomy [15, 36]. Alternatively, they can be defined with the assistance of functional MRI (fMRI). This is particularly helpful in cases where the anatomy and function may be significantly altered by pathology, and has been performed for the purpose of pre-surgical mapping [30]. Often, fMRI activated ROIs are extended either manually [28] or automatically [30] in order to include some white matter as well as the activated grey matter, as the fibre orientation is poorly defined in grey matter at typical diffusion imaging resolution. Tract delineation, both ROI placement and tracking itself, can be guided by atlases created from previously acquired populations [12, 39]. Fully automated tract delineating ROI placement has recently been explored [25].

Diffusion MRI fibre tractography has a high rate of both false negative and false positive results [8]. There are many reasons for this. Use of an inappropriate model of the subvoxel fibre geometry is one cause of both types of error: the wrong fibre direction, or only a subset of the fibre directions, could be inferred, as discussed above. Spatial resolution of the diffusion weighted images is also a problem. If the resolution is such that certain fibre pathways always occupy a small volume fraction of the voxels they pass through, it will be difficult to reconstruct these pathways, even with high angular resolution reconstruction techniques. An example of this is a common false negative: reconstructions of the cortical spinal tract robustly reconstruct the most medial connections, but often miss the more lateral connections. Yamada et al. report an 80% failure rate when tracking from the motor hand region to the peduncle using single tensor tractography. This may be due to partial volume averaging with fibres of the corpus callosum and/or superior longitudinal fasciculus, and is not completely solved by using a multi-tensor approach [38]. A common source of false positives is jumping from one tract system to another proximal one. At typical imaging resolutions, it is very easy for the voxelwise measures of fibre direction to suggest a smooth pathway that jumps from one fibre tract to another, as fibre pathways in the human brain lie very close to each other and/or interleave. An example of this is one very robust false positive result: seeding in the centre of the corpus callosum will often track down the cortical spinal tract, a connection that does not exist. The incorporation of anatomical priors, e.g., exclusion masks, can remove this artifact. One point to note as well is that fibre tractography cannot distinguish between mono- and multi-synaptic connections.

**Fibre tract confidence measures**

Ideally, the uncertainty in the voxelwise fibre orientation estimates obtained in diffusion MRI is propagated to the fibre tractography results to quantify the confidence in connectivity between various regions of interest in the anatomy, given the underlying data. Tract propagation using a single
definition of the fibre orientation(s), with no quantification of confidence, is termed “deterministic tractography”, while propagation using a probability distribution for the fibre orientation(s) is termed “probabilistic tractography”. Note that the confidences in connection, or connectivity indices, obtained from probabilistic tractography reflect strictly the confidence in the data supporting the existence of a given connection: they are not “strengths of connection” in a physiological sense, although the two may be related. Lower confidences in connection often arise because the path of interest occupies a relatively small fraction of the volume of the voxels it passes through, sharing those voxels either with unoriented tissue or other fibre populations. Hence, if a large fibre bundle converges and diverges throughout its trajectory, the tract segments in the bottleneck or convergence may be assigned higher confidence than the tract segments in the area of divergence, where the fibres may occupy only a fraction of the voxels. An example is the corpus callosum: high confidence is often assigned to the medial corpus callosum, and lower confidence to the lateral projections, even if there is no difference between the parts of the axons in these tract segments.

Several measures of confidences in connection have been proposed in the literature. The most common is the “frequency of connection” approach, where streamlines are propagated iteratively from a seed ROI with direction of propagation chosen at random from the probability distribution for the fibre orientation, and the number of times each voxel in the volume is reached by a streamline is counted [4, 27]. Parker et al. have introduced a “weakest link” approach, where each streamline is assigned a confidence equal to that of the segment thereof in which there is the least confidence [26]. This has been modified by slight smoothing along the tract to reduce sensitivity to noise [21]. Voxels are assigned the confidence of the tract of highest confidence that reaches them. This confidence is relative to a specific reference ROI, that need not be the streamline seed ROI. The “weakest link” approach has several possible advantages: it is guaranteed to be monotonic along a pathway, it is independent of the size and shape of the reference ROI, and it is more robust to length-of-tract effects. With frequency of connection techniques, voxels near the seed region will be assigned higher probabilities of connection, because the finite voxel size means that streamlines will pass through them for a broad range of propagation directions. To alleviate the length-of-tract bias in frequency of connection measures, and to give the results more statistical meaning, Morris et al. have introduced a connectivity index derived by comparison to a null distribution [24]. Probabilistic tractography results can be visualised as scalar maps, as streamlines colour-coded for confidence, or as maximum intensity projections.

Application of tractography

Diffusion MRI fibre tractography can be used in various contexts in neuroscience research and clinical diagnosis and treatment. It has been applied to nearly every common neurological disorder, and to studies of normal anatomy, development, and aging. It has been used for surgical planning and analysis of the outcome of surgery and other therapies. Due to the large number of false positive and false negative results, it is more difficult to characterise unknown or changed anatomy than to use tractography as a user-guided tool to extract all or parts of known pathways for analysis. Tractography is most often used as a tool to extract the voxels that contain specific pathways in order to then investigate scalar quantities in these tracking-defined ROIs. Tractography can also be used to segment grey matter structures based on differences in their connectivity profiles [5, 18]. Additionally, tractography can be used to investigate tract geometry itself, e.g., tract length, tract volume, tract asymmetry, and more complex network properties. While investigation of neuronal anatomy is the most common use of diffusion MRI tractography, the technique can be applied to
any tissue with coherently oriented fibres that restrict water diffusion on the scale of microns, such as muscle, e.g., skeletal muscle [41] and myocardium [31].

References


