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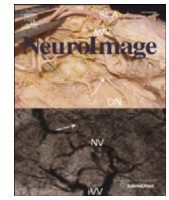

Toward global tractography

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Diffusion-based tractography is an ill-posed problem, because the step-by-step reconstruction of a fibre bundle trajectory cannot afford any serious mistake in the evaluation of the local fibre orientations. Such evaluation is difficult, however, because the myriad fibres passing through a single voxel follow different directions. Modelling tractography as a global inverse problem is a simple framework which addresses the ill-posed nature of the problem. The key idea is that the results of tractography in the neighbourhood of an ambiguous local diffusion profile can help to infer the local fibre directions. This paper provides an overview of past achievements of global tractography and proposes guidelines for a future research programme in the hope that the potential of the technique will increase the interest of the community.

Introduction: the ill-posed nature of diffusion-based tractography

In the early days of MR diffusion-based tractography, the potential impact of the technique was so uplifting that the neuroscience community was comfortably blind to the 'ill-posed' nature of the problem: the step-by-step reconstruction of a fibre bundle trajectory cannot afford any serious mistake in the evaluation of the local fibre orientations. This major risk was difficult to deal with because it does not exist in the well-known invasive techniques used with animals: a marker injected in a neuron is trapped inside the axon except when it can be transmitted into another neuron via synaptic connections. Hence invasive methods are not at risk of losing a bundle during tracking. Unfortunately, apart from the large bundles of deep white matter where axons are parallel, the evaluation of local fibre orientations in diffusion data is difficult. Indeed the myriad axons passing through a given MRI voxel usually have different orientations. Numerous ambiguities arise when one gets close to grey matter because of crossing, kissing and more exotic configurations (Jbabdi and Johansen-Berg, 2011). Considering the over-simplistic tensor models used at the beginning of the field, it is easy to understand why the first tractograms were full of spurious forks leading to barely exploitable connectivity maps.

Rapidly realising these failures, the methodological community has come to the conclusion that the solution should stem from a better understanding of the link between the diffusion profiles and the underlying fibre geometry. Since the 2000s, the rate of development of new models dedicated to this local inverse problem has been very impressive (Jbabdi and Johansen-Berg, 2011). As a result, the quality of the estimated fibre Orientation Distribution Functions (ODF) and of the related tractograms has largely improved. Furthermore, the new acquisition techniques developed in the context of the human connectome project are on the verge of increasing the richness of the diffusion profile maps, which will boost the research programme dedicated to the local inverse problem (Van Essen and Ugurbil, 2012; Van Essen et al., 2012). Yet, "adopting the diffusion profile as a proxy for white matter local geometry is an imperfect model" (Jbabdi and Johansen-Berg, 2011). Several alternative local geometries can give rise to the same diffusion profile. Distinguishing fibre crossing from fibre fanning is especially problematic. Modelling fibre spreading requires a continuous fibre ODF which is challenging for some configurations. In fact, the purely local perspective of the mainstream approaches is bound to provide problematic fibre ODF for some of the voxels of the superficial white matter. Therefore, in spite of the considerable progress achieved by the tractography algorithms exploiting local fibre ODF, for instance using probabilistic approaches to take into account uncertainty (Behrens et al., 2007), we still face the ill-posed nature of the tractography problem mentioned above.

The term 'ill-posed' usually refers to difficult problems in which the solution depends discontinuously upon the data. A slight modification of the acquisition noise can lead to a significant change in the solution. In return, for the ideal well-posed problems, the solution hardly changes when there is a slight change in the data. Ill-posed problems need to be reformulated for numerical treatment in order to reach well-posedness. Typically this involves additional assumptions, such as the smoothness of the solution. This process is known as regularisation. In the case of tractography, ill-posedness means that two different acquisitions of the same brain will lead to two very different fibre bundle reconstructions, each of them being far from the actual white matter geometry. When tensor models are used, this weakness is straightforward because of the impossibility of representing complex fibre configurations. Each fibre crossing or fanning leads to a flat tensor whose first eigenvector direction may be unpredictable and can largely depend on acquisition noise. More

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sophisticated fibre ODF models provide much better representations of white matter geometry. A single ambiguous voxel anywhere along one actual white matter bundle is sufficient, however, to disturb the tracking. Evaluating the number of ambiguous voxels is beyond reach and is largely dependent on the quality of the local inverse problem management, but most of the U-fibre fascicles are bound to cross such ambiguous areas. Moreover, the width of gyral white matter is close to the spatial resolution of diffusion acquisitions. In such areas ambiguous voxels may even change with the subject position relative to the grid of acquisition voxels because of partial volume between grey and white matter.

Global tractography

A recent paper by Jbabdi and Johansen-Berg (2011) provides a clear-cut overview of the current situation. Tractography can be a very useful technique for neuroscience provided that its limitations are clearly understood. Unfortunately, one of the current limitations is our inability to determine the precise transversal localization of connections in the cortex, which is largely related to the ill-posedness mentioned above. They suggest that spatial interactions between local modelling and tractography would improve the method. Indeed, the local estimate of fibre orientation at a given voxel can be informed by estimated orientations in that voxel's spatial neighbourhood. This is the essence of global tractography which is the subject of this paper wherein we advocate a shift toward a global inverse problem perspective, namely the global reconstruction of the geometry of the complete white matter.

In fact, we had suggested this global perspective in the earliest stages of tractography (Cointepas et al., 2002; Mangin et al., 2002; Poupon et al., 1998, 1999, 2000, 2001). Global tractography provides simple ways to 'regularise' the problem. Our global tractography framework amounts to setting up a kind of collaboration between the pieces of bundles arising from unambiguous diffusion profiles in order to disentangle ambiguous areas. In this model, regularisation stems from the optimistic hypothesis that axons tend to run in organised fascicles that bend rather gently. Hence, whatever the noise in the ambiguous areas, the interpretation of the configuration is enforced by the reliable pieces of bundle located around it. They connect with each other to explain diffusion data while minimising their curvatures. Note that the idea of using a low curvature assumption to somewhat help tractography has been around implicitly in a lot of algorithms and is essential for their robustness.

We have shown that Markov Random Fields (MRF), a standard image processing tool inspired by statistical physics (Geman and Geman, 1984), can be used to model the interactions between nearby bundles at different scales. A Markov Random Field is a network of random variables with only neighbourhood-based dependencies, a kind of extension of Markov chains to higher dimensions. An MRF is equivalent to a Gibbs Random Field, which means that the underlying probability distribution can be built upon a set of local energy potentials modelling the dependencies inside the cliques of neighbours. Hence the reconstruction of white matter geometry is modelled as an energy-based optimization problem: looking for the regular spaghetti plate providing the best explanation for the map of diffusion profiles. Curvature-based regularity is achieved via minimising the energy provided to cook the spaghetti. This global perspective, however, looked over-complex at a time when the local inverse problem still relied on tensors and the idea almost sank into oblivion. It should be noted that addressing image reconstruction as a global inverse problem may have looked far-fetched in the field of MRI where Fourier transform is the rule, but this kind of approach is usual in other imaging fields (PET, MEG).

Several other forms of global tractography have been proposed during the last decade, without raising much interest in relation to neuroscience applications. A first category of approaches defines the bundle trajectories as shortest paths for a distance between points of grey matter induced by the white matter map of diffusion profiles (Campbell et al., 2005; Jbabdi et al., 2008; Parker et al., 2002). The underlying metrics embed models of the link between diffusion profile and fibre ODF. These geodesics can be efficiently computed by means of front propagation algorithms. In ambiguous locations where the trajectory of an actual white matter bundle is no longer supported by the diffusion data because of the failure of the local inverse problem, the global search for the shortest path between the two extremities of the bundle can potentially overcome the ambiguity. As long as the number of ambiguous locations remains reasonable, the length of the exact trajectory remains shorter than the length of spurious trajectories. These elegant approaches can overcome some of the local uncertainty in the estimation of fibre orientations but, in the current stage, they do not try to improve the interpretation of ambiguous local data, which would probably require dealing with interactions between the geodesics crossing in the same voxel. A key issue is that there is a geodesic between any pair of points of grey matter, but a tiny number of geodesics correspond to actual bundles. Hence, an unsolved problem lies in the selection of the geodesics to be taken into account in neuroscience applications by using a kind of diffusion-based likelihood integrated along the tracts. The estimation of this geodesic-based likelihood would probably benefit from a better interpretation of ambiguous local data thanks to retroaction from the geodesic trajectories to the local inverse problem.

A second category of approaches involves an explicit sampling of the space of the putative bundle trajectories. One of them is inspired by the voting procedure of the popular Hough transform (Aganj et al., 2011). The set of trajectories is parameterized by polynomials of the arc length modelling the two polar angles of the tangent vector. The voxels cast votes for the curves accounting for the local compatibility of their diffusion profiles. The winners make up the final tractogram. Here, restricting the space of acceptable global trajectories provides a regularisation overcoming local uncertainty. The definition of this space is however questionable with regard to current knowledge about white matter geometry and the method suffers from the high dimensionality of reasonable spaces. A more ambitious proposal builds a global Bayesian framework for tractography (Jbabdi et al., 2007). Assuming the existence of a connection between a pair of regions of interest allows inferences on the localization of the bundle and on the local fibre ODF simultaneously. Hence, this approach goes one step further than the geodesic approach thanks to an explicit retroaction from the trajectories to the interpretation of the diffusion profiles. As far as we are aware, however, although the framework allows simultaneous manipulation of a large set of connections, only one connection at a time was trialled. In fact the focus of the method is on model selection in order to choose between connecting and non-connecting configurations. Testing several connections simultaneously would probably lead to combinatorial difficulties. A key issue, in line with the problem occurring with Hough transform, is the initialization of the connection trajectory, which is modelled with piece-wise cubic splines. The high dimensionality of the spline space requires a heuristic that is sufficient for simple bundle shapes but could fail with complex trajectories.

It should be noted that the post-processing of diffusion-based data can include global modelling before the tractography stage. Spatial regularisation of diffusion tensor fields was suggested to make the tensor estimates less sensitive to noise (Coulon et al., 2004; Tschumperlé and Deriche, 2002). This regularisation is performed by means of variational approaches amounting to optimization of a global function. In a way, deterministic tractography applied after such global regularisation embeds some global tractography flavour. This is all the more true in that the proposed regularisation schemes are anisotropic in order to take into account estimates of the fibre organisation. These sophisticated schemes are mandatory for dealing correctly with the preservation of the numerous discontinuities occurring at the edge between fibre bundles. The most advanced regularisation techniques have been designed for the ODF fields (Goh et al., 2011; Otto et al., 2013; Reisert and Kiselev,