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Toward global tractography

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ABSTRACT

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,

2011). They regularise spherical deconvolution with smoothness constraints modelling the fibrous structure of white matter.

During the last few years, a group from Germany has rediscovered the use of energy-based global tractography in the spirit of our initial proposal, obtaining several successes that lead us to believe that we could have reached a turn of the tide (Kreher et al., 2008; Reisert et al., 2011). In a tractography competition based on a realistic phantom made up from artificial fibres, the global tractography algorithm of Reisert et al. obtained the best results within a group of 10 participants (Fillard et al., 2011). The method is now computationally affordable and distributed to the community. It has been used in a first paper evaluating its contribution to the study of connectivity (Li et al., 2012). Therefore, although the local inverse problem of providing an interpretation of the diffusion profile is still a key issue worthy of further study (Jbabdi et al., 2012; Parker et al., 2012), we think that the community should now put more effort into modelling spatial interactions between diffusion profiles. Although it is probably too early to claim that global tractography will be a straightforward improvement on mainstream approaches, the field is mature enough to explore the concept further.

A key difference between energy-based approaches and the other global tractography methods mentioned above lies in the bottom-up behaviour of the optimization framework. The most consistent pieces of bundle emerge first before merging into complete bundle trajectories in a multi-scale perspective. In our opinion, this is key to the efficient performance of simultaneous tractography of the complete set of fibre bundles. A bottom-up strategy paves the way to focus the computational power on the ambiguous areas. The local inverse problem in these areas can be reconsidered by taking into account the rich constraints provided by the tractography performed in the neighbourhood. This can be achieved with a multi-scale perspective whereby breaks of a single voxel in trajectories are overcome first before wider ambiguous areas are considered.

The bottom-up strategy could probably be embedded into the other frameworks, but it is unclear to what extent this could be done efficiently. A key difference between our past proposals and Reisert's method lies in the modelling of the local inverse problem. In our proposals, the local inverse problem can stem from any independent fibre ODF methodology. The fibre ODF is converted into a diffusion-based pseudo-likelihood. The global energy driving the optimization process uses this pseudo-likelihood to build a local potential measuring the extent to which a piece of bundle is compatible with the local data. This potential has local minima for the directions with highest probability in the fibre ODF. The local pseudo-likelihood is not questioned during the optimization. In Reisert's approach, a generative model converts the set of pieces of bundles located in a given voxel into a diffusion signal that is compared with the measured signal. Hence, tractography can influence the interpretation of the raw data, in the spirit of the Bayesian framework (Jbabdi et al., 2007), which should enable more information to be extracted. Local and global inversions are performed simultaneously.

Let us imagine a configuration where the local inversion failed in one voxel leading to a fibre ODF with a missing peak in the direction of the bundle of interest. The only chance of correcting this mistake lies in the curvature-based energy that will strive to connect the two pieces of the bundle split into this voxel. The wider the gap between the two pieces of bundles, the more difficult the fix, because the pseudo-likelihood potentials will be opposed to the reconnection. This is a pity because most of the time the local inversion is borderline in relation to the recovery of the direction of the bundle. Whenever this potential is replaced by a generative potential, the risk of wrong interpretation is removed. Borderline diffusion data will not be opposed to the reconstruction of the complete bundle.

It should be noted that the energy-based approaches are often derived by means of Bayes's rule, but energy normalisation issues prevent a simple use for model selection, which in return is the strength of the actual Bayesian framework.

A concrete example: spin glass tractography

In order to provide a better understanding of the energy-based paradigm for global tractography, this section provides an overview of an upgrade of our framework presented a few years ago at the MICCAI conference (Fillard et al., 2009). Fibre fascicles are parameterized by small segments, called spins, which are optimised to minimise a twofold global energy: the first models fidelity to the diffusion data and the second models a low curvature prior. This new version called spin glass tractography (SGT) overcomes several weaknesses of the initial scheme (Poupon et al., 2000). Note that the spin glass terminology is only used here to refer to the idea from statistical physics but our model is not a standard spin glass. In the original method spins simply behaved like compass needles, rotating in the centre of the voxels: now SGT lets spins move, rotate and duplicate. Moreover, SGT provides an extension of the initial framework to fibre ODF.

Spins and potentials

In the following a spin s is an oriented particle defined by its position x and its orientation v. A spin can be interpreted as a piece of fascicle living inside white matter. Spins are endowed with three types of energies: *diffusion* potentials, *interaction* potentials and *generative* potentials. The diffusion potentials act as a local non-stationary magnetic field attracting the spin orientations toward the local putative fibre directions. The interaction potentials control how spins associate with neighbours and embed the prior that fibre fascicles have a low curvature. The generative potentials authorise the spontaneous generation of new spins to ensure that fascicles do not end inside white matter.

Within our framework, the minima of the local *diffusion* potential E_d should coincide with the putative fibre directions. The expression of this potential obviously depends on the management of the local inverse problem but follows a straightforward principle: provide low values in the fibre directions and high values in the directions to be penalised. Hence, the simplest choice is the log-likelihood of the probability p of finding a fibre in a given direction: $E_d\ (x,v) = -Log(p\ (x,v))$. In the case of a diffusion tensor model D, the simplest form for E_d is vDv. Note that in the case of multiple orientation maxima for $p(x)$, the local diffusion potential acts as a multi-modal magnetic field attracting a spin toward the closest maximum of p.

The *interaction* potentials E_{int} control how spins interact with each other and encourage them to assemble into long chains. This potential embeds the prior that brain fascicles have a low curvature. For each spin s, the direction v locally splits the spin glass into two sets: backward spins and forward spins. A spin s associates with a unique backward spin s^b and a unique forward spin s^f, located inside a local ball of radius r, in order to get the minimal interaction potential for the trajectory s^b–s–s^f. In the following, the interaction potential is $E_{int}\ (s^b\text{–s–}s^f) = -w/5 \sum Log[(\cos\ \alpha_j - \cos\ \alpha_{\max}) / (1 - \cos\ \alpha_{\max})]$, where w is a constant weighting E_{int} relative to E_d, the angles α_j are defined in Fig. 1, and $\alpha_{\max}$ is the maximum angular deviation allowed. This interaction potential favours low angular changes between neighbour's directions. Beyond the $\alpha_{\max}$ threshold, E_{int} yields an infinite potential which forbids the spin association. When a spin leads outside the tractography domain, the interaction potential is cancelled in that direction.

The *generation* potential plays a particular role: it ensures that fascicles do not end inside white matter, i.e. spin chains do not stop within the tractography domain. There are situations where a spin cannot find a candidate neighbour to associate with, which causes a chain to end prematurely. This is the case when all its neighbours have already been associated, or when available neighbours lead to an infinite interaction potential. In such cases the generation potential triggers the creation of a new spin to complete the broken chain. Otherwise the generation potential is null.

The combination of interaction and diffusion potentials has a competitive influence on the spin orientations and localizations. Hence, the optimal spin glass configuration corresponds to a trade-off between fidelity to the local inverse problem and the low curvature assumption. The generative potential only affects the quantity of spins so that chains do not stop within the glass. The optimal configuration is retrieved via an alternate minimization procedure. For a given spin glass topology, spin positions and orientations are optimised stochastically to minimise the sum of diffusion and interaction potentials. Once the spin glass has reached a stable state, the generative potential is triggered in order to merge compatible spin chains or add new spins at the extremities of broken chains. Finally, the process is iterated until convergence (no more spin association or generation).

In the following, depending on the size of the dataset, 10 to 100 iterations are necessary and a hundred to millions of spins are required. Note that the initial spin concentration is important for balancing the quality of the final reconstruction versus the computation time. In spite of the stochastic optimization, initialization has some influence on the final results because of the generative potentials. In the experiments presented in the following, the spins are positioned randomly inside each voxel, and the initial orientations correspond to the minima of the diffusion potentials, in order to take into account all the clues in favour of fascicle existence.

Experiments

Two toy examples of SGT built from diffusion tensors are proposed in Fig. 2: a synthetic crossing (20 iterations, 230 initial spins, 314 spins after convergence) and a synthetic half-circle (30 iterations, 1000 initial spins, 1450 spins after convergence). For both experiments the parameters are set to $w = 1$, $\alpha_{max} = 45°$ and r = 3mm. The rationale for choosing these parameters is beyond the scope of this paper. The crossing experiment illustrates the general principle in the ideal configuration where fascicles are straight spaghetti. The half-circle experiment shows that the low curvature prior does not prevent curved fascicles being reconstructed. Note how fascicles seem perfectly parallel.

SGT was also illustrated with two actual diffusion datasets: an MR phantom embedding a 45-degree crossing and a real brain dataset. For each dataset, we compared the output of the SGT algorithm with a tensor-based streamline tractography (TBT) and a Q-ball-based streamline tractography (QBT) (Descoteaux et al., 2009). For tensor fitting, we used the Rician noise removal strategy developed in (Fillard et al., 2007). For Q-ball estimation, we used the spherical harmonic decomposition of (Descoteaux et al., 2009) which provides an analytical formulation of the ODF. Note that the diffusion potential of the SGT was derived from the ODF and not from the tensor. Parameters of the spin glass algorithm are the same as for the toy problems. The same angular threshold was used for the TBT and QBT to obtain comparable results.

The crossing phantom was elaborated with hydrophobic fibres strongly tightened within a medium and immersed in a solution of water doped with gadolinium (Poupon et al., 2008). Acquisitions were done on a 1.5T MRI scanner (4000 directions, b-value of 2000 $s \cdot mm^{-2}$, image size: $32 \times 32 \times 3$, resolution: $1 \times 1 \times 1.4$ mm) (Poupon et al., 2006). Results of tractography are shown in Fig. 3. Obviously, TBT was not able to recover a crossing of this low angular difference, since tensors are unable to model the two-fibre compartment inside the crossing area. The QBT algorithm was able to recover part of the crossing but deviates in regions where the ODF peaks are not well defined (mainly because of noise and partial voluming). Indeed, maxima are generally detected by thresholding the ODF to prevent the extraction of small noisy peaks. In our case, the ODF circled in green had only one maximum detected out of the two expected, which caused several erroneous pathways. SGT, initialized in accordance with the maximum selection for QBT, was able to pass the crossing correctly everywhere. Note that the only goal of this experiment was to illustrate the behaviour of SGT. A configuration with straight fibres is not realistic and provides a strong bias in favour of SGT because of the low curvature prior. With more complex configurations, however, the sibling method of Reisert won the fibre cup in the MICCAI context (Fillard et al., 2011).

The brain dataset was acquired on a 1.5 T scanner with two protocols. First, a DT-MRI dataset of 41 directions with a b-value of $700s \cdot mm^{-2}$ was acquired for TBT. Second, a HARDI dataset of 200 directions with a b-value of $3000s \cdot mm^{-2}$ was acquired for QBT and SGT. Note that the b-value used for the DT-MRI dataset was chosen to fit standard clinical acquisitions and was much lower than for the HARDI acquisition. Estimating the tensor from the high b-value dataset had no impact on the result, however. Image size is $128 \times 128 \times 60$, resolution is: $1.8 \times 1.8 \times 2$ mm. Results of tractography are illustrated in Fig. 4. For reasons of clarity, only fascicles passing through a sagittal slice of the corpus callosum (CC) are presented. Fascicles are coloured depending on their localization in the CC (linear colour gradient from the back in red to the front in blue). Nearly all the fascicles reconstructed by the TBT algorithm were classically redirected vertically because of the projection fibres (corona radiata) crossing the callosal fibres. QBT performed slightly better and some fascicles connecting the lateral parts of the frontal and parietal lobes were found, showing that QBT is able to pass the corona radiata. The ODF quality was not sufficient, however, to recover a realistic set of commissural fibres. From this point of view, SGT performs much better. Moreover, the fascicle colouring scheme shows that the topography of the CC is kept until the cortex, which is a consequence of the low curvature assumption. SGT required two million spins to reconstruct the entire brain and three days of computations on a regular PC. Once again, this illustration is not a validation, and most of the reconstructed fascicles are bound to be trapped by a spurious fork in one place or another. The goal of this experiment was to show that global tractography gets closer to the goal than conventional streamline approaches.

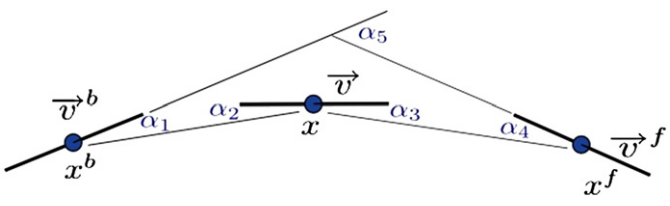

Fig. 1. Angular differences between a spin s and its backward s^b and forward s^f neighbours. A spin position is represented by a circle, and its orientation by a black line. The role of α_{max} is to prevent a spin to create a junction between two incompatible neighbours, which would result in an angular deviation greater than α_{max} for the fascicle.

Where do we go with global tractography?

The concept of global tractography can be developed in a lot of different directions. This section highlights some of them with a focus on the global inverse problem perspective. The future of MR imaging could provide additional features related to axon geometry like axon diameter (Assaf et al., 2008; Zhang et al., 2011). In the context of energy-based approaches, this could lead to new interaction potentials assuming slow variations of such features along the fascicles, which could help in reconnecting bundles broken in ambiguous areas. In addition to longitudinal interaction potentials, it could be of interest to introduce transverse interaction potentials controlling the distance between parallel fascicles. This would help to master the sampling and the inner organisation of large bundles that could be exploited to study the transport of fine-scale topography from one area to another. The future of MR acquisition could also produce data with different spatial resolutions; for instance a very high spatial resolution with tensors and a lower spatial resolution with high angular resolution ODF. The diffusion potentials could easily be tuned accordingly.

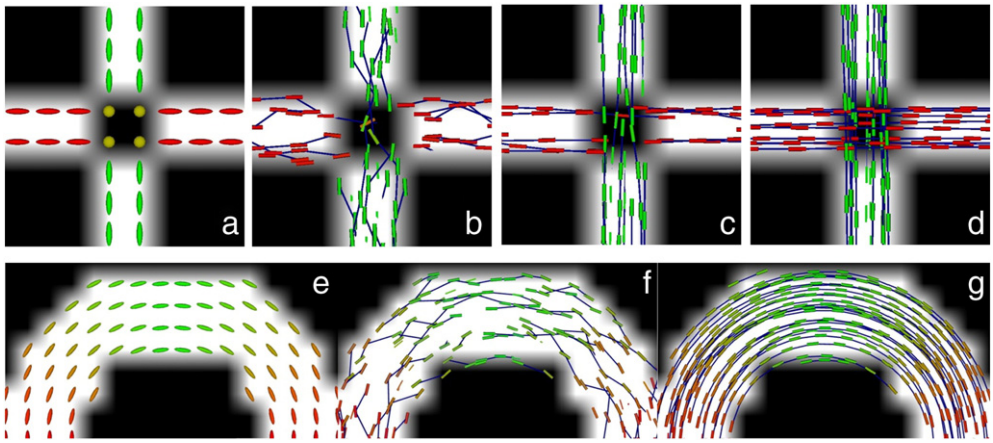

Fig. 2. Toy examples of SGT on synthetic tensor configurations. a) A simulated crossing. b) The initial spin glass: spins (represented by green and red cylinders) were randomly placed and aligned with the first tensor eigenvectors. The blue links represent the spin associations. c) The minimal energy configuration of the spin glass in b). d) After convergence: spin chains have grown and merged to reconstruct the crossing area. e) A simulated half-circle. f) Initial spin configuration. g) After convergence.

As mentioned previously, a key issue when one is designing the energy driving the global tractography is the choice between a generative model of the diffusion signal and the pseudo-likelihood implied by local inverse problems. At first glance, the generative model is the more attractive because it offers the possibility to reinterpret raw diffusion data by taking into account the surrounding tractography information. The generative model, however, misses the sophisticated techniques involved in the local inversion. Although this could be partly overcome if the local inversion is used to initialize the spin glass, complex configurations may require a more advanced strategy because of optimization problems.

Standard stochastic optimization algorithms like simulated annealing are efficient with funnel-like landscapes riddled with shallow local minima, provided that the landscape is explored with an adapted kinetics. Whenever the chains of state transitions to hop from one minimum to another are too long or include systematically a high-energy mountain pass, the underlying Monte Carlo sampling process cannot behave correctly. Intuitively, this difficulty occurs because the actual network of paths allowing navigation between the local minima is too sparse, which often happens when the paths are built only from chains of single spin transitions. The creation of additional reversible transitions that change the state of several spins simultaneously is an efficient solution (Swendsen and Wang, 1987).

When the local inverse problem provides several alternative configurations, for instance a crossing and a kissing configuration, the paths of single spin transitions switching from one configuration to the other are very long and difficult to find during the optimization. The solution is to introduce the knowledge of this alternative through explicit dedicated transitions in the Monte Carlo sampling scheme. Following this idea, the generative models could be used to evaluate the energy and the local inverse problems could be used to design the optimal strategy dedicated to the exploration of the energy landscape.

The existence of alternative local solutions requiring dedicated optimization strategy can stem from the local inverse problem but also from a priori knowledge. For instance, the geometry of white matter inside gyral windows is very problematic for tractography. Indeed the low curvature assumption forbids 90-degree turns occurring when fibres quit white matter to enter the cortical mantle. This is probably one of the reasons why it has been observed that most of the diffusion-based tracts reach the crest of the gyri (Roca et al., 2009). The white matter mask can be preprocessed in order to extract a gyral white matter mask where several modifications of the model could be introduced. For instance, the set of multiple-spin transitions could include the sharp turn alternative to the simpler configuration with parallel fibres going to the gyral crest. The interaction potentials would also have to be modified in order to allow 90-degree turns. Furthermore, a probable future will enrich the framework with accurate diffusion measurements from inside the cortical mantle which may contribute to the detection of the sharp turns (McNab et al., 2013).

In general, revisiting post-mortem staining, acquiring very long post-mortem MR acquisitions (Miller et al., 2012) and exploiting new opportunities like polarised light imaging (Axer et al., 2011a, 2011b) should provide precious spatial priors that will have to be translated into the global or local inverse problems. Some of these new priors will act in specific places, like gyral white matter or thalamus, whereas others may contribute globally. For instance, whenever the bold model about the white matter geometry put forward by Van Wedeen is confirmed (Van Wedeen et al., 2012), the interaction potentials dealing with the low curvature assumption should be strongly modified, in the spirit of what was suggested above to deal with sharp turns in gyral white matter.

The dedicated multiple-spin transitions mentioned above address only groups of spins located in the same voxel. Specificities of the energy landscape could require the definition of multiple-spin transitions on a

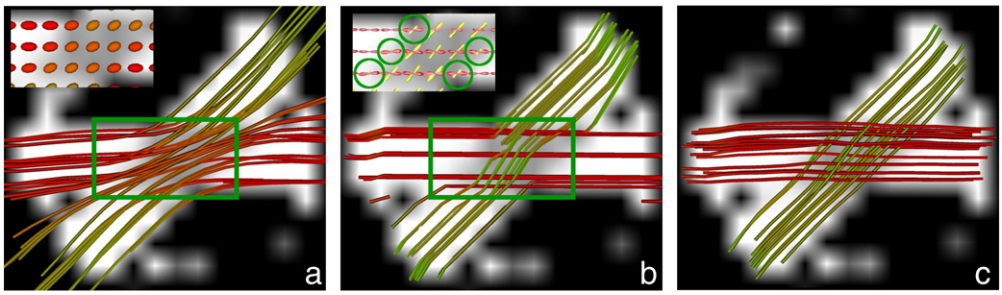

Fig. 3. Tractography of a 45-degree crossing MR phantom. a) Result of TBT. Tensors contained within the green rectangle are displayed. b) Result of QBT. ODF contained within the green rectangle are displayed. Those circled in green had only one maximum detected. c) Result of SGT. The same ODF were used for QBT and SGT.

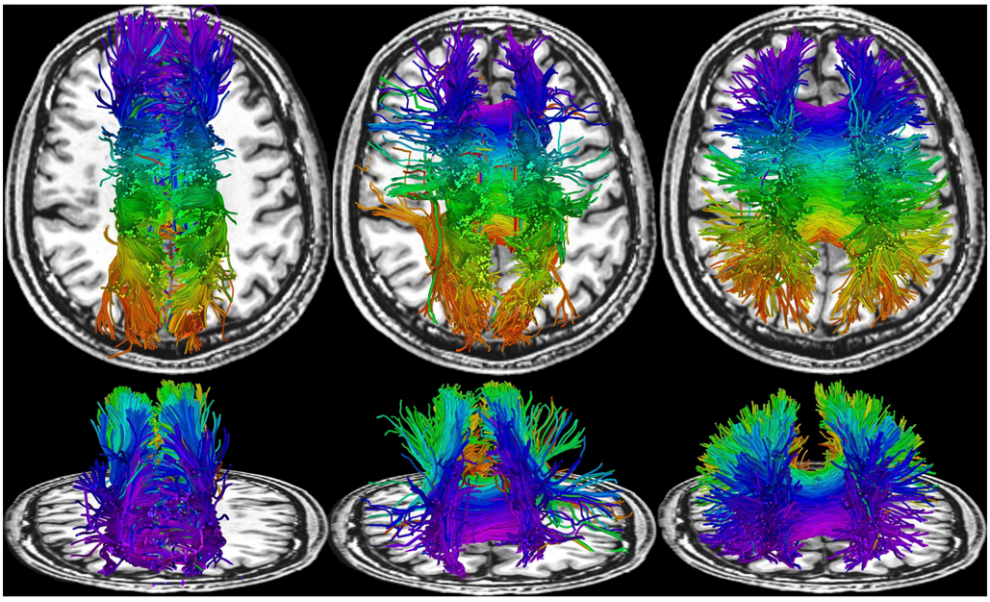

Fig. 4. Reconstruction of callosal fibres by three methods. Left: TBT. Middle: QBT. Right: SGT. All fibres of TBT are redirected vertically because of the surrounding corona radiata. QBT performed slightly better but missed a large part of the callosal fibres. SGT was able to recover the myriad fibres crossing the corona radiata.

larger scale. This could be achieved without combinatorial explosion following a bottom-up strategy. A first minimization of the global energy would lead to the detection of the pieces of bundle distinguished without ambiguity from the diffusion data. This part of the spin glass could be frozen in order to focus the next stage of the minimization in each left-over ambiguous area independently. The goal would be to reconnect the fascicles broken in the area of interest. The geodesic strategy could be a tool of choice for evaluating the optimal trajectories of the different alternatives. Then massive computational power could be used to look for the optimal configuration of the whole area.

In addition to the bottom-up strategy, one should work out a way to implement a top-down strategy. For instance, an atlas of bundles could be used to influence the reconnection of the pieces of fascicles, in the spirit of the Bayesian approach (Jbabdi and Johansen-Berg, 2011). The atlas of Guevara and colleagues, which models the variability of the localization of each bundle in a standard space, could be used to select the reconnections maximising the agreement with the associated prior (Guevara et al., 2012). A lot of additional information stemming from the human connectome project could be used to develop further this top-down perspective, but it should be clear that such top-down priors can only be used to help find the knowledge already described by current atlases. One may, however, consider designing group analyses to performing the global tractography of several subjects simultaneously, which could open the door to top-down priors resulting from the influence of the different subjects on each other.

As observed in the previous paragraphs, future progress depends on the modelling of the priors enhancing the regularisation provided by the global inverse problem framework. It will, however, require treatment of all the situations in which some of these priors have to be relaxed because of non-standard white matter organisation or pathology. This is bound to be the most difficult research programme.

Conclusion

The goal of this paper was to attract more research fellows to the field of global tractography. In our opinion, the domain is at a stage where global modelling can provide qualitative improvements to tractograms. Furthermore, multiple analogies with the problem of contour completion, a fundamental process in computer vision, could provide a rich source of inspiration (MomayyezSiahkal and Siddiqi, 2013; Tupin et al., 1998). Note however that global modelling cannot overcome all the difficulties. Global tractography is bound to make some wrong turns. The hope is that global modelling can decrease the number of such failures in local tractography. The guidelines for future developments may look like a cookbook, but we want to stress the point that global tractography is a very pragmatic framework. Although the modelling of the local inverse problem has reached a very technical stage requiring a lot of expertise, global modelling is still in its infancy. Hence everybody can cook up refreshing experiments that will help us to understand the true potential of this new field of research.

Conflict of interest

None.

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